THE UNIVERSITY OF HULL

The Effects of Structural and Functional Damage to Limbic Structures on Cognitive Abilities

Being a Thesis submitted for the Degree of Ph.D.

In the University of Hull

By

Satvir Minhas

BSc. (University of Victoria, Canada)
MRes. Diploma (University of Aberdeen, Scotland)

September 2005

Acknowledgments

This thesis is dedicated to my sister Raj. I thank Raj for having been the heart of the family and taking such good care of everybody. I also thank her for giving so incredibly much of herself; and now, for being my Angel.

I would like to thank my parents for their amazing love, patience and prayers throughout my studies. I am eternally grateful for their support, without which I could not have studied abroad. I will never thank them enough for all the extraordinary advice and guidance they have given me as it has shaped the person I am today. Despite our childish interactions, I am also grateful for my brother Gur who also always stood right behind me with understanding.

This thesis could not have been possible without the help of my supervisor Annalena Venneri. It would be hard to overstate how much I benefited from her and for all the effort she made to teach me and bring out the best in me. I thank her for her valuable suggestions and comments on this thesis, as she helped me through several versions to understand and organize the material. I also greatly appreciate having a supervisor who was always so kind and willing to help with any problem and for always being available around the clock.

I would also like to express my deep gratitude to Dr. Mario Liotti for his supervision during my PhD. I will always be indebted to him for introducing me to this topic and inviting me to write a Doctoral thesis. I am also greatly indebted to Gianluca Mingoia for all his hard work in assisting me with the fMRI experiment. I also sincerely thank Dr.'s Jennifer Clelland, Mike Shanks and Alastair Hull for referring the patients who so kindly took part in this study. I am grateful for several people for helping, in one way or another, with the writing of this thesis and would like to express my gratitude to all of them.

I would like to thank my family in Canada for their love, continuous support and encouragement to finish as quickly as possible. Furthermore, I would like to thank my friends in Canada whom I have seen only in person from time to time but for being there with warmth, sensitivity, and understanding.

And finally, I can't thank enough the friends I have made in the UK, particularly those I met in the Departments of Psychology at both Aberdeen and Hull University. My deep appreciation for all the moral and practical support, delightful and mindless chats, and most of all, for the great parties and trips.

Abstract

Functional and degenerative damage to regions of the limbic system are often associated with cognitive impairments in different aspects of memory. Neuroimaging studies in post-traumatic stress disorder (PTSD) and Alzheimer's disease (AD) have reported selective hippocampal atrophy. Neuroimaging studies in panic disorder have also suggested reduced functional activity in the right parahippocampal gyrus. It is unclear whether this hippocampal damage is responsible for the emergence of selective neuropsychological deficits. Abnormal activity in limbic structures has also been reported in PTSD patients exposed to trauma-related stimuli. This thesis was concerned with examining the effects of structural and functional damage to the limbic system on selective cognitive abilities. The limbic structures under investigation included the hippocampus, parahippocampal gyrus, anterior cingulate cortex and amygdala. In order to investigate this issue, a series of neuropsychological and neuroimaging experiments were carried out using groups of patient populations, such as panic disorder, PTSD and AD, known to exhibit abnormalities to the limbic structures. An fMRI study, using the Color Stroop and Emotional Stroop task was also administered to PTSD patients and healthy controls.

Results from the neuropsychological studies showed greater impairments in topographical/spatial memory compared to verbal memory in all groups of patients. In addition, voxel-based correlation analyses found that both PTSD and AD are associated with neuropsychological deficits in the area of visuo-spatial and topographical memory that may be explained by the regional brain atrophy in limbic structures. Abnormalities of the parahippocampal gyri and cingulate cortex and possibly the amygdalae in the fMRI study also suggested a dysregulation in limbic-cortical networks in PTSD. This thesis has demonstrated that damage to limbic structures might contribute to the cognitive abnormalities of panic disorder, PTSD and AD.

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CHAPTER 1 Introduction

Animal and clinical studies as well as work with healthy subjects have provided an enormous array of data outlining the functional and structural role of the limbic system. Damage to limbic structures, such as the hippocampus, produces mainly learning and memory impairments (McEwen, 1999). In addition, dysfunction of limbic structures has also been heavily involved in the aetiology of psychiatric illnesses, such as post-traumatic stress disorder (PTSD) and panic disorder (Kötter, 2003). For example, the limbic structures have been implicated in the pathophysiology of post-traumatic stress disorder (Bremner, Staib, Kaloupek, Southwick, Soufer & Charney, 1999a; Bremner, Narayan, Staib, Southwick, McGlashan & Charney, 1999b; Liberzon, Taylor, Amdur, Jung, Chamberlain, Minoshima et al., 1999). A more detailed review of the structural and functional involvement of the limbic system in the breakdown of skills that can be seen as consequences of degenerative or psychiatric disorders will allow for a more comprehensive understanding of the role these structures play in an array of symptoms that can be observed as a consequence of either functional or structural damage to all or part of its structures. This latter point will be the focus of the studies reported in this thesis. The following introduction will primarily discuss the functional studies of the limbic structures, including the hippocampus, parahippocampal gyrus, amygdala and cingulate cortex. The structural studies of each limbic area will be discussed in detail in chapters 3-5.

1.1 The Limbic System

The term 'limbic' has been based on the seam-like arrangement of cortical structures at the junction of the hemispheres with the diencephalon and brain stem (Kötter, 2003). The limbic system consists of a series of subcortical structures, including the amygdala, hypothalamus, cingulate cortex, anterior thalamus, mammillary bodies, hippocampus and parahippocampal gyrus (Banich, 1997; Kötter, 2003). The subcortical structures included in the limbic system vary among authors. Morgane, Galler & Mokler stated that the limbic system includes the hippocampal formation, amygdaloid complex of nuclei, hypothalamus, nucleus accumbens, cingulate cortex, ventral tegmental area, major areas of the prefrontal cortex and limbic midbrain areas. These authors also suggested that the limbic brain includes these formations as well as their connections to forebrain, midbrain and hypothalamus. It was also suggested that the limbic system encompassed a heterogeneous group of medial and basal telencephalic structures, which together include part of the cerebral hemisphere connected to the hypothalamus (Maclean, 1949 & Nauta, 1958, as cited in Morgane, Galler & Mokler, 2005). Spyer (1997) has stated that the hypothalamus is a central component of the limbic system. The hypothalamus plays an important role in eating, drinking and reproduction and is able to detect changes in homeostatic parameters such as body temperature, blood glucose levels and hormones (Spyer, 1997). The hypothalamus therefore defends the body against physiological disturbances. The limbic system structures have been found to play a prominent role in emotional functions, as well as functions involving motivation, motor control, attention, memory, neuroendocrine control, and sexual behaviour (Banich, 1997; Kötter, 2003; Morgane, Galler & Mokler, 2005). In addition, the limbic system is central to learning, memory and emotion (Banich, 1997).

1.2 Hippocampus

The hippocampus is one of the oldest structures in the human brain (Giap, Jong, Ricker, Cullen, & Zafonte, 2000). It is located dorsally to the thalamus and resides next to the temporal lobe (Gabrieli, 1998). The hippocampal formation is comprised of the hippocampus (CA fields), dentate gyrus and subiculum (Gabrieli, 1998). The dentate gyrus sends projections only to the hippocampus (Fitzgerald, 1996 & Martin, 1989, as cited in Giap et al., 2000). The subiculum sends projections to the septal nuclei, thalamic nuclei, the bed nucleus of the stria terminalis and the nucleus accumbens (Martin, 1989, as cited in Giap et al., 2000). Information from the cingulate gyrus and other parts of the limbic system travel through the entorhinal cortex in the perforant path to the dentate gyrus (Fitzgerald, 1996 & Martin, 1989, as cited in Giap et al., 2000). The hippocampal formation also receives cholinergic inputs from the septal nuclei and from the contralateral hippocampal formation (Martin, 1989 & Shepherd, 1994, as cited in Giap et al., 2000). Perirhinal and parahippocampal cortices provide approximately two-thirds of the input to the entorhinal cortex, which is the main site that provides the majority of the input to the hippocampus (Gabrieli, 1998; Witter & Amaral, 1991, as cited in Davachi, Mitchell & Wagner, 2003). Based on these connections, the hippocampal formation is involved in the integration of vast amounts of information. The hippocampus, deep within the temporal lobe, is primarily involved in memory, particularly with the formation of new long-term memories (Banich, 1997; Robertson, 2002). The hippocampus processes newly learned information for a period of weeks to months and then transfers information to specific areas of the cerebral cortex for more permanent storage (Sala, Perez, Soloff, di Nemi, Caverzasi, Soares et al., 2004; Mishkin, 1982; Rosene & Van Hoesen, 1977; Van Hoesen, 1982, as cited in Horel, 1994; Giap et al., 2000). Therefore, the hippocampus plays a major part in memory consolidation (converting short-term memory into long-term memories, which

are then stored elsewhere in the cortex). Examining the famous case of H.M, Horel (1994) suggested that the hippocampus plays a role in registering and storing memories but not for maintaining or for the long-term storage of memories. After surgery, H.M. was no longer able to record new information, within seconds he would forget newly acquired information (Robertson, 2002; Banich, 1997; Horel, 1994). This patient underwent a bilateral resection of the entire medial temporal lobe to treat his seizures and damage to the hippocampus was the main source of his impairment (Horel, 1994; Robertson, 2002; Banich, 1997; Corkin, Amaral, Gonzáles, Johnson & Hyman, 1997).

The hippocampal and parahippocampal regions are also involved in the response to novelty detection and assessment. This suggestion has been formulated based on the findings of PET and functional magnetic resonance imaging (fMRI) experiments in both normal and brain-damaged individuals (Knight, 1996; Schacter et al., 1995; Stern et al., 1996, as cited in Tulving & Markowitsch, 1997). These findings suggest that long-term storage of memories might therefore, depend on novelty assessment. Tulving, Markowitsch, Craik, Habib, and Houle (1996) stated that novelty assessment represents an early stage of long-term memory encoding and that such encoding varies directly with its novelty (as cited in Tulving & Markowitsch, 1997).

Declarative memory is another important function of the hippocampus (Brewer, 1997; Squire & Zola-Morgan, 1991 as cited in Horel, 1994). The hippocampus, as well as surrounding cortical areas mediates declarative memory (Cohen & Eichenbaum, 1993 & Squire, 1992, as cited in Eichenbaum, Schoenbaum, Young & Bunsey, 1996; Cohen & Squire, 1980, as cited in Eichenbaum, 2003). The ability to retain and recall episodic memory seems to be highly dependent on hippocampal functioning (Vargha-Khadem, Gadin, Watkins, Connelly, Van Paesschen, Mishkin et al., 1997). Declarative memory involves the conscious recollection of facts and events, as well as the acquisition and retention of such knowledge (Cohen & Squire, 1980, as cited in Gabrieli, 1998; Suzuki

& Clayton, 2000; Eichenbaum, 2001). The recollection of factual knowledge is referred to as semantic memory and the recollection of personal events is referred to as episodic memory, and these two forms of memory make up declarative memory (O'Keefe & Nadel, 1978; Eichenbaum, 2001; Eichenbaum, 2003). Various authors have suggested that perhaps the hippocampus is involved with episodic memory and the entorhinal, perirhinal and parahippocampal cortices have a major function in semantic memory (Vargha-Khadem et al., 1997; Mishkin et al., 1997, as cited in Suzuki & Clayton, 2000). The work of Vargha-Khadem et al. (1997) demonstrated that perhaps basic sensory memory functions of the perihinal and entorhinal cortices are capable to support the formation of context-free semantic memories but are not capable to support the formation of context-rich episodic memories. These findings were based on the results from three patients with brain injuries, which occurred at birth, at the age of four and at the age of nine. One patient was born after a difficult delivery and did not have a heartbeat for 7-8 minutes. A couple hours after resuscitation she suffered from sporadic seizures, which occurred for 2-3 days despite being administered anticonvulsant medication. Damage to the brachial plexus resulted in permanent impairment of the right arm and hand due to partial loss of the nerve deriving from the 5^{th} and the cervical nerve roots. The second patient was born prematurely at 26 weeks of gestation and at the age of four, suffered from protracted (1.5 to 2 hours) afebrile convulsions. The third patient accidentally received a toxic dose of theophylline, a drug she used to treat asthma. She suffered from an acute episode of seizures, unconsciousness and respiratory arrest. Although she showed good physical recovery, she was severely amnesic. The common symptoms among these patients, who are between the ages of 14 – 22, include the inability to remember events of daily life. These patients exhibited deficits in three main categories. The first is within the spatial domain, the inability to find their way in familiar surroundings, remember where objects and belongings are usually located or

remember where they have been placed. The second is within the domain resulting in lack of temporal orientation in date and time and they have to be reminded frequently of appointments and the third was in the episodic domain, whereby patients cannot recall daily activities or telephone conversations or messages, stories, television programs, visitors, holidays etc. Results from volumetric measurements showed that bilaterally, the hippocampus was abnormally small in the patients relative to normal healthy controls. The volumes of the patients ranged from 43% to 61% of the mean value of normal subjects. Using T2 relaxometry, the hippocampal water T2 values were found to be elevated bilaterally in the patients, which indicated that the remaining hippocampal tissue was severely compromised. In addition, proton magnetic resonance spectroscopy of the temporal lobe showed signal intensity ratios that were within normal range for one patient bilaterally, whereas the other two patients were normal for the left side but were marginally below normal for the right side. Because of these patients amnesia for everyday life events caused by damage produced so early in life, it would be expected that such early damage should result in impairment of cognitive development. However, these patients have progressed normally in school. The ability to comprehend and express ideas through reading and writing and to learn knowledge about the world is a function of semantic memory, thus it is surprising that such memories were formed after damage to the hippocampus. The patients were also given 12 computerised, two choice and recognition tests, which included the administration of a multi-trial associative recognition for lists of non-word pairs, face pairs, voice-face pairs and object-place pairs. The results showed significant differences between the patients and healthy controls on the voice-face and object-place associations. These findings were similar to those found in primates with hippocampal lesions. It has been suggested that higher order cortical sensory areas and the hippocampus communicate indirectly through the perirhinal and entorhinal cortices, therefore, it is possible for the underlying cortices to

support some forms of memory without involvement from the hippocampus (Suzuki, 1996, as cited in Vargha-Khadem et al., 1997). It has also been suggested that in cases such as H.M., damage to the hippocampus as well as perirhinal and entorhinal cortices produces anterograde amnesia for both episodic and semantic memory. Other authors have hypothesised that episodic memory is an extension of semantic memory (Tulving & Markowitsch, 1998). Although episodic memory is quite similar to semantic memory, these authors suggested that episodic memory has more capabilities.

Eichenbaum, Dudchenko, Wood, Shapiro and Tanila (1999) suggested that the hippocampus plays a role in relational memory, which involves the representation of relationships among independent stimuli or events, information learnt under one set of conditions can be used under a different set of conditions (as cited in Suzuki & Clayton, 2000). These authors also suggested that individual structures within the medial temporal lobes contribute to semantic and episodic memory. In addition, authors such as Eichenbaum (2001) suggested that on its own, the hippocampus does not mediate any form of memory but that the hippocampus and surrounding cortices interact together. Davachi, Mitchell & Wagner (2003) used fMRI to determine whether during episodic encoding, perirhinal cortex, parahippocampal cortex or the hippocampus supports distinct forms of learning, therefore, different aspects of recognition memory. This paper studied 14 right-handed native English-speaking participants. During the eight fMRI encoding sessions, the participants were presented with 200 visually presented adjectives during the Image task and 200 visually presented adjectives were presented during the Read task. During the Read task, the participants were required to pronounce the adjective backwards. During the recognition task (outside of the scanner), the participants were presented with the same words observed during the scanning session as well as 400 new words, which were not presented previously. The subjects were required to indicate whether the word was old or new and if answered old, the subject

was required to state whether the word was encoded during the Image task or the Read task. Using this information, the study examined item recognition (recognised vs. forgotten) and source recollection (source correct vs. source incorrect). The results indicated that there was greater medial temporal lobe activation in the hippocampus, perirhinal and parahippocampal cortex during the Image versus Read encoding as well as during Image encoding relative to the fixation. Examining trials based on whether the item was recognised versus forgotten, activation in the left perirhinal cortex predicted subsequent item recognition. Similar activation was found in bilateral hippocampus and parahippocampal cortices, irrespective of item recognition outcome. In addition, activation was greater during trials if items were later recognised relative to those forgotten, whereas, activation did not differ between the hippocampus or parahippocampal cortex according to subsequent item recognition. The perirhinal cortex showed greater activation during encoding that yielded subsequent item recognition in the absence of source recollection (Item Only) relative to subsequent item forgetting. Neither the hippocampus nor the parahippocampal cortex showed greater activation during item only relative to forgotten trials. Activation was also only found in the hippocampus and parahippocampal cortex when encoding events were segregated into those later recognised with (item and source) or without source recollection (item only). This increased activation also predicted later recollection. Therefore, activation in the perirhinal cortex correlated with subsequent item recollection and not source recollection, compared to activation in the hippocampus and parahippocampal cortex, which did not track later item recognition but correlated with whether recognition was accompanied by successful or unsuccessful contextual recollection. Based on these findings, the authors have concluded that the medial temporal lobe structures mediate different learning mechanisms and that these structures complement each other in declarative memory functioning.

Although there is controversy surrounding the role of the hippocampus in episodic and declarative memory, Eichenbaum (2001) has stated that the two forms of memory are related. Firstly, because declarative memory is formed through daily personal experiences, episodic memory could be the 'conscious gateway' to all memories. Secondly, because many specific episodic memories pertaining to particular events will not be maintained as such but rather be remembered in the context of general knowledge about the world. Semantic memory is, therefore, thought to link items that have lost episodic information to those that have maintained episodic memories.

Human navigation has been proposed to be dependent on cognitive maps and the hippocampus has been proposed to maintain a cognitive map of the spatial layout of previously learnt environments (O'Keefe & Nadel, 1978). These maps are stored as allocentric cognitive maps, representations of environmental information (both distances and directions) independent of the observer. These authors have suggested that an individual's personal experience in an environment or knowledge of an environment is stored in a cognitive map. This stored spatial information and memories are needed to make spatial decisions and to navigate within an environment. The neural system is responsible for way-finding behaviours and cognitive maps are a responsibility of the hippocampus (O'Keefe & Nadel, 1978). Researchers commonly use the term 'cognitive maps' when discussing the role of the hippocampus in learning and remembering topographical information. The two hemispheres are known to have different cognitive capacities (i.e. left verbal, right visuospatial). The left hippocampus contributes more to verbal tasks whereas the right is involved with non-verbal cognitive functions such as spatial tasks (Milner, 1971; Baxendale, 1995; Abrahams et al., 1997). The right hippocampus has also been found to be involved in route planning and recall (Maguire et al., 1998; Abrahams et al., 1997; Maguire et al., 1997, Aguirre et al., 1996). In a PET experiment, two groups of healthy control subjects completed either a mental navigation

task, mental exploration of a representation learnt from an actual walk, or a mental map, a mental exploration of a representation learnt from a map (Mellet, Bricogne, Tzourio-Mazoyer, Ghaëm, Petit, Zago et al., 2000). The results revealed that the right hippocampus was more involved when the route was learnt from a map, whereas the bilateral parahippocampal gyrus was more involved when actually navigating within an environment. Many studies that have examined hippocampal functioning in simulated tasks have not found activation within this region, thus suggesting that hippocampal function might be linked specifically to higher-level spatial manipulation and decision-making (Maguire et al., 1997). Ghaem, Mellet, Crivello, Tzourio, Mazoyer, Berthoz, et al. (1997) studied a group of five healthy control subjects using PET to investigate the functional anatomy of mental simulation of routes. Comparing the mental navigation of routes minus the rest condition, increased blood flow was found in the posterior part of the left and right hippocampal regions and the middle part of the right hippocampal region. The hippocampus appears to be more involved with allocentric space versus egocentric according to a review by Nadel & Hardt (2004). Similar results were also found by Abrahams et al. (1997) who found impairments with allocentric space in patients with damage to the right hippocampus. Maguire, Frackowiak, and Frith (1996a) used PET to measure regional cerebral blood flow (rCBF) while subjects watched and memorised film footage. Examining changes in rCBF associated with episodic memory without a navigation component did not show any activations within the medial temporal region. Examining topographical learning in either of the non-memory tasks showed significant bilateral activation of the hippocampal formation and precuneus. Examining the activity during viewing of the topographical memory film compared with that during the non-navigation memory film viewing showed significant activation of the parahippocampal cortex and hippocampus on the right and also activation of the left parahippocampal gyrus. However, the role of the hippocampus in topographical

learning remains controversial (Turriziani, Carlesimo, Perri, Tomaiuolo, and Caltagirone, 2003). Findings from animal research have shown involvement of the hippocampus in topographical orientation by studying place cells (spatially localised firing) however, there is little evidence to support this role of the hippocampus in human subjects (Morris, Garrud, Rawlins & O'Keefe, 1982; Barnes, 1988; Eichenbaum, 2000; O'Keefe & Dostrovsky, 1971, as cited in Turriziani et al., 2003). Aguirre & D'Esposito (1999) stated that if any topographical difficulties exist, they would be accompanied by memory impairments in other areas. Thus, it might not be likely to see topographical disorientation with lesions limited to the right hippocampus. Using PET, Maguire, Frackowiak, and Frith (1997) found increased activation of the right hippocampus during route recall relative to landmark recall in taxi drivers. It has been found that in mammals and birds, increased hippocampal volume has been found relative to brain and body size (Lee, Miyasato & Clayton, 1998, as cited in Maguire, Gadian, Johnsrude, Good, Ashburner, Frackowiak et al., 2000). Therefore, these authors were interested in examining if differences in brain volume are predetermined or if such differences are a result of the plasticity of the brain in response to environmental stimulation. Using voxel-based morphometry (VBM), these authors examined whether morphological changes in the brain are associated with navigational experience in a group of licensed London taxi drivers. A group of 16 male with greater than 1.5 years experience as London taxi drivers and a group of 50 healthy males who did not drive taxis were included in the study. All the taxi drivers had healthy medical, neurological and psychiatric profiles. Females, individuals below 32 and above 62, left-handed males and those with health problems were excluded from the study. The results indicated that significantly greater grey matter volume was found in the left and right hippocampus of the taxi drivers compared to the healthy controls. This larger rise was not found in any other brain structures. This larger area was located in the posterior hippocampus

bilaterally. The control subjects were found to have greater grey matter density in the anterior hippocampus bilaterally, however this finding did not survive a correction for multiple comparisons. An ANOVA examining group by side on anterior hippocampal volumes showed that the controls had significantly greater volume than the taxi drivers and also a main effect for side with the right greater than the left. Examining the body of the hippocampus only showed a main effect for side, with the right greater again than the left. In addition, the posterior hippocampus volume was found to be significantly greater in the taxi drivers, however no interaction or main effect of side was found to be significant. When length of time spent as a taxi driver was analysed, only the right posterior hippocampus showed a positive correlation. Therefore, the authors suggested that such changes in the right hippocampus are acquired and that plasticity can occur when exposed to environmental stimuli. In addition, they also suggested that the anterior hippocampus might be more involved with the encoding of new environmental layouts, while, the posterior hippocampus might be involved when previously learned spatial information is used. The lack of involvement of the left hippocampus suggested that it might have a role in the storage and retrieval of memories of the people and events that took place while driving a taxi. Maguire, Burgess, Donnett, Frackowiak, Frith and O'Keefe (1998) also used PET to study ten subjects as they navigated through a familiar virtual reality town. The subjects were given an opportunity to explore the complex virtual town to build their own internal representations of the town. During scanning, the subjects were required to navigate to locations within the virtual reality town using these internal representations. The subjects completed two conditions within the navigation task. During one condition, the subjects navigated directly to the specified location. During the other condition, the route was altered intentionally so the subjects would have to navigate to the location using detours. Navigation was compared to a task where subjects moved through the town using a trail of arrows, thus not

requiring the use of internal representations. An additional task administered to the subjects included the identification of features in static scenes from the town. The trials were separated into those where the navigation was successful compared to those in which the destination was not correct. Successful trials compared to the arrows task showed significant activation of the right hippocampus. The comparison of the successful trials with the unsuccessful trials also showed activation of the right hippocampus, in addition to activation of the left hippocampus, left lateral temporal cortex, left frontal cortex and thalamus. In the condition where the subjects were able to navigate directly to the location showed significant increase in rCBF in the right hippocampus for accurate responses. Thus, these results indicate that the right hippocampus is more active during navigation than trial-following but also that the more accurate the navigation, the more active the right hippocampus was. Although the left hippocampus was active during successful navigation, destination did not covary significantly with accuracy of navigation. The authors remarked that the left hippocampus is more involved with the episodic memory for personally experienced events. The left hippocampus might be involved in maintaining and recollecting memories for specific paths taken during learning; these paths however, do not provide the required information for a direct route to a destination.

In addition, the hippocampus is an important brain region responsible for regulating the stress response and a major feedback site for glucocorticoids (Sapolsky, 2000). The hippocampus is an important structure for integrating cognitive responses to stress. Recently, the relationship between the effects of chronic stress to the hippocampus was termed the Stress Hippocampus theory, which suggests that excessive levels of stress impair memory function, as the hippocampus is responsible for learning and memory. Animal and clinical studies have revealed that chronic stress does cause damage to the hippocampus and cause neuronal atrophy. Neuronal atrophy and cell death of the

hippocampus are due to the chronic exposure to the high corticosteroid levels that are released when individuals experience a lot of stress. (Reagan & McEwen, 1997). Loss of hippocampal neurons due to exposure to stress has been reported in animal studies as well as in psychiatric disorders related to stress, such as Post-Traumatic Stress Disorder (see chapter 4 for a more detailed review).

1.2.1 Hippocampal Lesion Studies

Damage to the hippocampus has invariably been shown to cause global amnesia, deficits in memory for facts and personal experiences, which includes both spatial and non-spatial information (Eichenbaum, 2000). Such findings were first evident from the famous case of H.M (Scoville & Milner, 1957). In this patient, damage limited to a small portion of the CA1 field of the hippocampus was sufficient to produce anterograde amnesia. The tissue surrounding the hippocampus is called the hippocampal formation and it has been suggested that this region is responsible for the permanent storage of memories to the cerebral cortex (Robertson, 2002). Damage limited to the hippocampal formation has resulted in the failure to form new long-term memories and damage to the hippocampal formation, the connecting fiber bundles and adjacent cortical tissue impairs new explicit memories (Henke et al., 1999, as cited in Robertson, 2002). The hippocampal formation has also been suggested to be involved during the learning of spatial or novel information (Robertson, 2002). A bilateral lesion to the hippocampal formation has also been found to produce an amnesic syndrome (Zola-Morgan et al., 1986, as cited in Corkin et al., 1997). In addition, lesions to other medial temporal lobe structures along with a bilateral lesion to the hippocampal formation, results in more severe anterograde amnesia and impairs the temporal extent of a retrograde amnesia (Gabrieli, 1998).

Studies have also reported that lesions to the right hippocampus show route learning impairments (Barrash, Damasio, Adolphs & Tranel, 2000). Barrash et al. (2000) suggested that the right hippocampus is more involved in spatial memory consolidation, whereas, lesions to the right parahippocampal gyrus show topographical disorientation, thus contributing to deficits in navigation. Work by Mellet, Bricogne, Tzourio-Mazoyer, Ghaëm, Petit, Zago, et al. (2000) has also provided evidence for specialised roles of the right hippocampus and parahippocampal gyrus in topographical memory. These authors reported finding a dissociation between the right hippocampus and bilateral parahippocampal gyrus. Although the study consisted of only healthy male subjects, the results indicated that involvement of the right hippocampus is sufficient to remember information learnt from a survey perspective. Whereas, additional support from the bilateral parahippocampal gyrus would be needed if a large-scale environment, which includes route information as well as "object" landmarks, requires mental exploration (Mellet et al., 2000, p.598). Turriziani et al. (2003) presented a case study of an individual with bilateral hippocampal atrophy and minor cortical atrophy of the frontal, parietal and dorsal portion of the temporal lobe. The patient's performance was normal on general intelligence, executive function, language, and visual-spatial perceptual abilities when compared to a group of healthy male subjects (N=5) and two pathological control subjects. One of these control subjects had bilateral hippocampal atrophy and hypoxia and the other had Alzheimer's disease with diffuse cortical atrophy. Using the patient, healthy controls and pathologic controls, these authors conducted four experiments: comparison of verbal, visual, and spatial learning; learning of visual, topological, metrical, and vectorial information; maze learning, and topographical retrograde memory. Experiment 1 revealed that the patient's memory for visual and verbal memory was not as impaired as his memory for spatial information. These results also revealed he had a specific difficulty with learning new information. The scores

achieved by the patient from experiment 2 were similar to scores from the healthy controls for learning stimuli using verbal and visual techniques and on the recognition of visual objects test. However, the patient's memory for spatial relations between objects was very poor. Maze learning in experiment 3 had three components, maze learning with "full" landmarks, with "few" landmarks, and "without" landmarks. Similar to the controls, the patient completed the test well in the few and full landmark conditions; however, without any landmarks the patient had remarkable impairments. The landmarks (visual-perceptual information) helped guide the patient to navigate in the simulated environment. Examining topographical retrograde memory in experiment 4 demonstrated that the patient was impaired strictly with learning new topographical information as he performed equally well as the normal subjects. The results of all the experiments suggested that this patient was unable to learn or recall spatial information. Any visual-perceptual information that involved spatial information and spatial relations (i.e. reciprocal position learning, proximity judgement and vector judgement tests) were impaired, whereas, information for verbal or visual information without a spatial aspect was preserved. After becoming familiar with a previously unfamiliar environment, he was able to recognise the landmarks and buildings but these did not provide any directional aides. Although he was able to recall the environmental features, he was unable to recall paths/routes that were taken previously within the same area. Although this specific case demonstrated anterograde topographical disorientation, the lesion site was not in the region of the right PHG, in fact the lesion was located in the fronto-parietal dorsal regions and not situated in the inferior ventral cortex of the right hemisphere. The authors' suggestion that the patient had specific problems with consolidation of spatial memories fits well with previous research examining topographical memory. The parahippocampus gyrus appears to be crucial for integrating visual information with spatial representations of environmental characteristics whereas

the hippocampus is primarily responsible for consolidating spatial memories. The presence of bilateral hippocampus atrophy without a lesion to the region of the parahippocampal gyrus supports the evidence that the hippocampus is indeed responsible for retrieving previously stored spatial representations. One particular study investigating bilateral hippocampal lesions revealed interesting results from spatial memory tests. The findings of this study were based on an individual who suffered from a closed head injury from a motorcycle accident (Rosenbaum et al. 2000). Magnetic Resonance Images of this individual K.C., showed large reductions in hippocampal volume and bilateral parahippocampal volume reductions in comparison to age-matched control subjects. In addition, minor damage to the right parahippocampal cortex was reported. K.C. was found to have spared semantic memory and impaired autobiographical memory. The authors explored whether the hippocampus would support K.C.'s spatial memory performance or show impairment as with his autobiographical memory. The findings indicated that K.C. performed at the same level as the controls in locating features on two global maps for the world and North America. However, when required to locate cities on a map of Canada and of the province of Ontario, K.C. was significantly worse than the matched controls. The major findings were that K.C. was impaired in recognizing city locations and in recognizing and identifying non-salient landmarks within his neighbourhood. This patient's hippocampal damage revealed that remote topographical memory was spared but deficits were present when details were to be retrieved, independent of when the individual learnt the information. Bohbot et al. (1998) carried out a study to characterise the learning and memory deficits that result from lesions to specific structures within the medial temporal lobe. These researchers expected that patients with lesions to the right parahippocampal cortex would be significantly impaired on spatial memory tasks but not on non-spatial memory tasks. The patients were split into groups depending on

the location of their lesion to separate the patients with hippocampal damage including the parahippocampal cortex and hippocampal damage excluding the parahippocampal cortex. The groups of patients studied included the following: epileptic patient controls, back-pain controls, patients with right hippocampus damage, patients with right parahippocampal cortex damage, patients with left hippocampus and amygdala damage. The spatial and non-spatial memory tasks included non-visual spatial exploration, invisible sensor task, object location, eight-arm radial-maze, non-spatial working memory, Rey-Osterrieth complex figure, and the Rey auditory verbal learning task. This study found that the two patient groups with damage to the right hippocampus and to the right parahippocampal cortex had deficits in the object location task and the Rey-Osterrieth after immediate and 30 minute delayed recall. The authors suggested that although the patients with hippocampal damage showed no lesions/damage to the right parahippocampal area, the impaired performance on these tasks in the patient group with damage to the right parahippocampal cortex might reflect a functional hippocampal lesion. It was also suggested that although both structures might be involved, it is the hippocampus that is necessary for completing these tasks successfully. These results were also found in the group of patients without damage to the parahippocampal cortex and the authors suggested that this observation supported the finding that the hippocampus is responsible for learning in visuo-spatial memory tests. The group with right hippocampal lesions did not show deficits on the Rey auditory verbal learning test, the non-spatial working memory, the Invisible Sensor task at a 30-minute delay and the non-visual spatial exploration task. Deficits were, however, seen on the object location test. This test was similar to the non-visual spatial exploration task. Subjects, however, were not able to touch the objects and the duration of encoding between the two tests was different. The right parahippocampal cortex group were also impaired on the invisible sensor task with a 30-minute delay compared

to the groups, with the exception of the amygdala damage group who had no spatial memory impairments. Due to these findings, it seems possible that the right parahippocampal gyrus might be responsible for this task. The left hippocampus group were solely impaired during the long delays of the Rey auditory verbal learning test but not for the short delay. This work supports the role the left hippocampus plays in verbal memory. The overall findings of this study reported that the lesions confined to the hippocampus impair spatial memory but also that spatial memory may be spared with right hippocampus damage. The right parahippocampal cortex might therefore, contribute to right hippocampal functioning if it is already damaged.

Lesions of the temporal lobes severely impair learning and memory for long-term memory but spare short-term memory (e.g. H.M). Lesions of the hippocampus interfere with the storage of new memories, whereas memories of earlier events remain intact. The right parahippocampal gyrus is crucial for maintaining and retrieving associations between objects and their locations but does not play a large role in the encoding of this information (Owen, Milner, Petrides & Evans, 1996). It is not clear whether damage to the hippocampus itself is responsible for topographical deficits or whether the parahippocampal gyrus plays an equal or predominate role in the performance of the selected tasks. It has been shown that the hippocampus is involved in spatial memory, but that the parahippocampal gyrus plays a more specific and defined role in topographical memory abilities.

1.3 Parahippocampal Gyrus

The primary brain structure that has been documented to be responsible for topographical memory is the right parahippocampal gyrus (PHG). This structure is situated within the medial temporal lobe. Although it is not located within the hippocampus, it is immediately underneath and surrounds the hippocampus. Bilateral

activation of the parahippocampal gyrus and right hippocampus in an fMRI study was found while subjects viewed visual scenes. Figure 1 illustrates the close proximity of the these two limbic structures from this neuroimaging by Rombouts, Barkhof, Witter, Machielsen and Scheltens (2001).

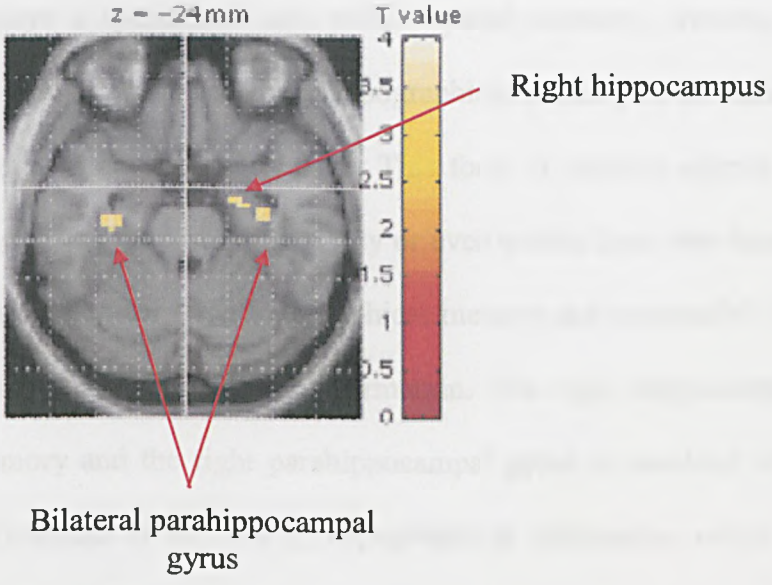

Figure 1.1. Axial image showing activation of the right hippocampus and right parahippocampal gyrus (Rombouts et al., 2001).

The hippocampus and PHG are functionally and anatomically connected very intimately with one another (Aguirre et al., 1996; Suzuki & Clayton, 2000). Thus, it can be difficult to find a focal lesion which does not affect both structures. However, neuro-imaging techniques such as MRI and CT scans are extensively used to more precisely identify the location of lesion sites. Patients may have specific cognitive impairments following focal damage, such as topographical memory, or they may suffer from other cognitive processes as well. For instance, global amnesia, dementia and blindness may also account for topographical memory deficits (Aguirre et al D'Esposito, 1999). Patients with damage to parahippocampal gyrus often experience great difficulty finding their way around novel environments. Experiencing topographical disorientation might

primarily be due to a lesion of the right posterior cerebral artery which in turn, affects the functioning of the right parahippocampal gyrus (Aguirre & D'Esposito, 1999).

As mentioned previously, animal research, neuro-imaging studies and human correlation studies have demonstrated that the right hippocampus and right parahippocampal gyrus are largely responsible for spatial memory. However, the right parahippocampal gyrus plays a specialised role within spatial memory, showing a prominent involvement in topographical memory. Topographical memory is defined as a person's ability to navigate within an environment. This form of memory allows an individual to find their way around in a building, a city or even within their own home. Both types of memory, spatial memory and topographical memory are responsible for encoding, storing and retrieving topographical information. The right hippocampus plays a role in spatial memory and the right parahippocampal gyrus is involved with topographical memory (Abrahams et al., 1997). Topographical information refers to details about different routes, layout plans of homes or buildings, memory for landmarks, buildings, houses, and scenes. This type of memory deals with learning new topographical information as well as remembering previously stored ones. Way-finding (spatial) abilities include aspects such as when an individual plans a journey through an environment (known or unknown) or when an individual has to reorient and re-establish themselves in an environment if they get lost.

Many researchers may refer to an individual's inability to find their way around as a syndrome called 'Topographical Disorientation' (Habib & Sirigu, 1987). This term is most commonly used in situations when an individual has trouble in unfamiliar surroundings (Landis, Cummings, Benson, & Palmer, 1986). However, some patients impairments recognising previous routes and landmarks of places they were once familiar with. For instance, forgetting how to find their way home from a job they had for many years prior to the onset of the impairment. Some researchers have also used

the terms topographical agnosia and topographical amnesia to define a person's topographical memory impairments. The term topographical agnosia is commonly used if the individual has deficits in recognising well known places and buildings, an agnosia for places (Habib & Sirigu, 1987). Visual processing of places, including landmarks, and space exploration are impaired, leaving an individual unable to make the necessary internal representations of an environment. In this type of impairment, patients are unable to estimate distances and have a general difficulty recognizing broad categories of information in the environment (Aguirre & D'Esposito, 1999). Topographical amnesia defines a spatial memory impairment (Aguirre & D'Esposito, 1999). Visual and spatial features of an environment are processed normally but the individual is unable to recall the relevant topographical information that is necessary for navigating in the real world. Authors have also suggested that topographical agnosia results in visual-spatial impairments, whereas patients with topographical amnesia have visual memory impairments (Landis et al., 1986). Although agnosia and amnesia for topographical information are used to categorise topographical disorientation into two subgroups, these terms have been regarded as being quite vague (Aguirre & D'Esposito, 1999).

Landmark agnosia is another term that has been derived from studying patients with topographical disorientation. This selective impairment is a visual recognition deficit of salient environmental characteristics (e.g., buildings and landmarks) that commonly results from damage to the right ventral occipito-temporal cortex (includes the fusiform, lingual, and parahippocampal gyrus) (Aguirre & D'Esposito, 1999). Individuals use many different techniques to navigate within an environment; however, these individuals are unable to use the locations of environmental features such as landmarks to find their way around, a common strategy employed by normal individuals.

Landmark agnosia may also be present in both familiar and unfamiliar environments (Aguirre & D'Esposito, 1999).

In anterograde disorientation, way-finding behaviours are impaired in new environments and spared in old environments that were experienced prior to their lesion. In these cases, patients are not able to form new internal representations of new environments they encounter (Turriziani et al., 2003). The pathological cause of this impairment invariably follows cerebral damage with more right parahippocampal gyrus damage.

Research investigating way-finding behaviour has suggested that we rely on two main processes to travel from one point to another. Egocentric and exocentric representations are the two strategies that are employed to navigate from a starting point to get to the final destination. Egocentric may also be coined as body-centered because the individual relates the location of the object with reference to their own body. This term uses left and right positioning to locate environmental features. For example, they will remember to turn right and left at various locations/streets to get to the desired destination. Exocentric representation is independent of the observer and may also be called, allocentric (Abrahams, Pickering, Polkey, & Morris, 1997). Instead of relying on their body, the individual relies on the spatial relations between the objects within the environment (Aguirre & D'Esposito, 1999). Aguirre & D'Esposito provided an example to describe this term: if an individual walks past a particular building that is to their right, if they turn around, they are aware that the building will now be to their left. Abrahams et al. (1997) examined allocentric and egocentric spatial representations using spatial memory tests in patients with damage to the right hippocampal formation. To test these processes in a laboratory setting, these authors used a test similar to the radial arm maze test. To study allocentric representations, the participant was seated in one of four positions at a square table. There were nine containers placed on the table

that remained constant throughout the test and within these containers were different objects (comb, keychain, coins, paper, etc.). Between the study phase and recognition phase of the test, the subject was required to move to a different position at the table to test for allocentric spatial processes. Moving the subject's position between the study and test phase was intended to encourage the subject to remember the location of the objects in reference to each other and not on egocentric processes that would relate the location of the objects to the individual's body. Using the allocentric spatial representations, it would also be expected that the subject would be using cues (windows, door, picture frames, etc) within the room to remember which containers had objects inside. The patients in this study had either unilateral temporal lobe damage resulting from temporal lobe epilepsy (N = 30: right-sided = 16, left-sided = 14) or temporal lobe resection (N = 47: right-sided = 23, left-sided = 24). In this study, the patients with right sided hemisphere damage showed allocentric spatial deficits. The patients with left temporal lobectomies did not have this impairment. These authors suggested that the lesions that produce topographical disorientation are invariably found to be located in the cortical-subcortical area of the posterior part of the right hemisphere.

1.3.1 Topographical Memory Function in Healthy Subjects

The association between the parahippocampal gyrus and topographical memory function has also been highlighted by neuroimaging studies. Maguire, Frith & Cipolotti (2001) studied twenty healthy participants who took part in one of three experiments. Each experiment differed only in the type of visual stimuli that was presented to the participant. The four different types of visual stimuli were unknown buildings, faces, landmarks, and animals. In Experiment 1, the stimuli were human faces and buildings, in Experiment 2 the stimuli were landscapes and human faces and in Experiment 3, the

stimuli were human faces and animal faces. The results from the PET scan revealed that the encoding of buildings and landscapes activated the PHG bilaterally and the recognition of buildings and landscapes activated only the right PHG. This work supports the fact that the right PHG is crucial for the encoding and recognition of topographically relevant stimuli and that the PHG is an important neural substrate responsible for the memory of buildings and landscapes. Maguire, Frackowiak, and Frith (1996a) studied a group of healthy participants who watched and memorised film footage depicting navigation in an urban environment (topographical memory) compared with a non-navigational film (episodic memory). Patterns of activation found during the topographical memory test were compared with those seen in the episodic memory test and showed significant differences in the medial parietal region, the parahippocampal cortex on the left and right, and the right hippocampus. Maguire et al. (1997) investigated the neural substrates of topographical memory in a PET study of taxi drivers. Eleven subjects participated in six tasks that included topographical (routes and landmarks) and non-topographical tasks (film plots and film frames) and these tasks were either with or without a sequential order. The routes task showed bilateral activity in the extra-striate regions, medial parietal lobe, the posterior cingulate cortex, the parahippocampus gyrus, and the right hippocampus. During the landmarks test, activation was found in the posterior cingulate cortex, medial parietal lobe, occipito-temporal area, and the parahippocampal gyrus. In addition to these regions, the left inferior and middle frontal gyri also showed significant activation in this task. The control tasks that examined film plots and film frames revealed activation only to the left frontal regions, middle temporal gyrus, and left angular gyrus. An interaction was found between the task (topographical vs. nontopographical) and sequential ordering. The area with the greatest activation was the medial parietal area and the right inferior

parietal cortex, with more activation in the topographical task that involved sequencing in the recall of routes.

Aguirre et al. (1996) employed functional magnetic resonance imaging (MRI) to investigate the neuronal contributes of topographical learning. A total of nine participants were tested on their ability to remember a route in a virtual maze. The only brain region that achieved significance during the first learning condition was the PHG. This area was also activated in eight of the nine participants during the last learning trial and for six of the nine subjects during the retrieval phase. The preceding research provides further support for the notion that the PHG plays a crucial role in topographical learning and memory.

1.3.2 Parahippocampal Gyrus Lesion Studies

The right PHG structure plays a key role in the processing of spatial information and is a very important component of the limbic system that supports topographical memory (Maguire, Frith, & Cipolotti, 2001). Human lesion correlation studies have repeatedly shown that damage to the right PHG results in topographical memory impairments. Habib & Sirigu (1987) presented four case studies of individuals suffering from topographical disorientation. Analyses of the four cases determined that the disorientation was related to damage to the right hemisphere and lesions to the PHG. Case 1 was of a 44-year-old man who was taken to the hospital following left-sided hemiparesis and blurred vision. Left hemianopia, mild left hemineglect and a sensory defect with painful sensations in the left limbs were present at the time of admittance. A computed tomography (CT) scan showed a very unspecific hypodensity area in the right temporo-occipital region and a later CT scan revealed an infarct of the right posterior cerebral artery compromising the parahippocampal and lingual gyrus region. This patient could not navigate in an unfamiliar environment, had difficulty drawing a map

of a basic path, and needed help to return to his room. On his own, this individual could find his way back but he did rely on using room numbers. It appeared that the use of major landmarks, such as elevators, helped him navigate. His scores on a battery of neuropsychological tests showed no deficits in verbal memory tests, visual memory, colour vision tests, and the Rey-Osterreith's figure. His score on the Wechsler Memory Scale was above that of normal healthy control subjects. The first few days in the hospital, the patient did have problems recognizing famous faces and completing a Face Learning task. However, after a few days, his ability to recognize famous faces returned and after four months, he was no longer impaired on the Face Learning task. This patient's topographical disorientation deficit in a new surrounding returned to normal after a period of six months. A 26-year-old woman was the second case presented by Habib & Sirigu (1987). She was admitted to the hospital following a fronto-temporal headache and a deficiency in her left visual field, which later was diagnosed as left hemianopia. A CT scan showed hypodensity on the interior portion of the temporal lobe, which was speculated by the authors to include the hippocampal-parahippocampal region. This patient showed no deficits on visuo-constructive or visuo-spatial deficits and geographical knowledge, localization of cities on a map, non-verbal memory and spatial memory were also performed within a normal range. She was unable to find her room, navigate within the hospital corridors, learn a route or draw a route without excluding necessary turns and inaccurately placed landmarks on a map. She was able to find her way around in unfamiliar and previously familiar streets and buildings with a map and although she improved within a year's time, she did not completely recover. Three years prior to going to the hospital for a chronic headache, case 3 had a stroke and left hemiplegia which she partially recovered from. At the hospital, she had proprioceptive ataxia of the left arm along with decreased pinprick sensation on the left limbs and half the face, and severe astereognosis of the left hand. A CT scan showed

hypodensity in the medial region of the right occipital lobe, which may be a result of an infarct in the region of the right posterior cerebral artery. The patient was not impaired in recognizing pictures, objects, buildings and familiar faces; however, occasionally, the patient experienced difficulty recognizing famous people on television. Although she was not significantly impaired on the stylus maze test, the face recognition test, and a spatial location test, her scores were very poor. The patient complained of losing her "sense of direction". As with the previous cases reported, she had difficulty locating her room and relied on landmarks and signs to guide her. Similar to the second case study, this patient showed impairments in familiar and unfamiliar environments. Although she had gradually improved after suffering from an infarct to the right posterior cerebral artery, she did continue to experience topographical disorientation. The final case presented by Habib & Sirigu (1987) was of a man with left hemianopia. An angiogram revealed a defective filling of the right posterior artery and the CT scan showed reduced density within the right posterior cerebral artery. Neuropsychological testing showed no language, general memory, or spatial and constructive deficits. However, face recognition deficits and topographical difficulties were present. This patient was strictly impaired with new faces as she was able to recognize relatives and any individuals she had known prior to her impairment. However, within the city, she also had trouble with streets that were previously familiar. Unfortunately, this patient continued to suffer and did not improve even after ten years. In addition to the work conducted by Habib & Sirigu, the case of an individual with an ischemic stroke to the PHG studied by Luzzi, Pucci, Di Bella, and Piccircilli (2000) also supports the overwhelming evidence of the role of this structure in topographical memory. The patient presented by Luzzi et al. had a left hemiparesis and fully recovered within one month. Five years later, he had a stroke and his CT scan revealed a right parietal malacic lesion. After the stroke, the patient complained that he was having problems finding his way around and was

immediately taken to hospital. The CT scan showed a cortical-subcortical hypodensity in the right parietal region, similar to the previous stroke he suffered and also a malacic lesion to the right parahippocampal gyrus. The patient continued experiencing difficulties navigating in familiar environments and heavily relied on landmarks to navigate. His performance on verbal memory tests (i.e., Digit Span, Prose test, and Rey Auditory Verbal Learning Test) was similar to the performance of healthy control subjects. On spatial memory tests, he performed within the normal range on the Corsi Block Tapping task and had difficulty on the Barbizet 7/24 test and a spatial location memory test. The patient performed extremely well in naming famous buildings; however, he was unable to locate cities on a map of Italy. When asked to draw a floor plan of the apartment he lived at for many years, he was unable to complete the map accurately, excluding all the major landmarks and was unable place the correct rooms on the left or the right. On a recognition task of unknown buildings, he scored very well and received the same score for recognising photographs of his own house. He performed well on a Locomotor Maze test that required him to navigate within a room with landmarks using a map. On the Stylus Maze test, however, he performed significantly worse than the healthy subjects. On a follow-up study six months later, this patient did not show improvement on the neuropsychological tests.

Previous studies have examined topographical memory in simulated environments; however, researchers have found similar results testing individuals in real-world contexts. A functional imaging study carried out by Barrash, Damasio, Adolphs and Tranel (2000), demonstrated that the PHG is critical for rapidly integrating and processing multiple scenes within a large-scale environment. Barrash et al. (2000) studied a group of 127 participants with focal brain lesions to the posterior regions in both hemispheres. Participants were tested on their ability to learn a complex route within a hospital. Subjects were told they would be shown the route to an office and

would return to the starting point via a different route. The subjects were aware that once they returned they would then have to lead the examiner through the same route. Of those participants with lesions to areas thought to be associated with topographical memory impairments (inferior medial occipital and medial temporal (hippocampus and parahippocampal gyrus) area of the right or left hemisphere), 82% experienced severe difficulties. Also, all four subjects who had definite damage to their right PHG and seven subjects with significant unilateral right hippocampal damage showed significant route learning impairments. These authors suggested that the hippocampus plays a critical role in the encoding of an individual's experience of an environment. In addition, it is speculated that after consolidation of memories into long-term storage, the hippocampus might not be needed for the retrieval of topographical memories. Such a speculation is based on the inconsistent evidence of the role of the right hippocampus in the retrieval of previously learned topographical information using functional imaging paradigms, whereas the parahippocampal gyrus is consistently found to play an important part in the learning or recall of topographical information. These authors suggested that both right and left hemispheres are involved in the complexity of topographical information although they believe that the right has a special role in topographical functioning. The right hemisphere is capable of encoding and recalling individual features of scenes/layouts whereas the left hemisphere may be more involved in the ability of subjects with right-sided damage to successfully navigate a route by the use of verbal descriptions that they have generated.

1.4 Amygdala Function in Healthy Subjects

The amygdala is an almond-shaped structure located in the anterior part of the temporal lobe (Gabrieli, 1998). This structure plays a crucial role in emotions and emotional memories (McGaugh, 2000; Cahill & McGaugh, 1998, as cited in Robertson, 2002).

The amygdala is believed to be the site in which 'emotional memory' or 'memory for emotionally arousing events' is formed and permanently stored (Sala et al. 2004, p.395). It has been cited that during highly stressful situations, information travels through the thalamus to the amygdala, which then enables information to flow both ways between the amygdala and the cerebral cortex. However, it should be noted that other regions of the brain are also involved (Robertson, 2002). Neuro-imaging studies involving facial expressions have shown increased activity in the amygdala when an emotional response is made to different facial expressions, for example, seeing a friendly smile (Whalen et al., 1998, as cited in Robertson, 2002). Animal and human studies have also found evidence to suggest that the amygdala is involved in memories associated with emotional arousal and positive emotional reinforcement (Holland & Gallagher, 1999, as cited in Robertson, 2002). The amygdala has been found to be involved in the acquisition and elaboration of learning associations in fear conditioning (Cahill et al., 1999; Davis, 1997; Kapp et al., 1992; LeDoux, 1996, as cited in Rauch, Whalen, Shin, McInerney, Lasko, Orr et al., 2000). In rats, retention of a negative experience is impaired by stimulating or inactivating the amygdala (LeDoux, 2000, as cited in Robertson, 2002). In addition, the amygdala also shows activation with cues that connote a threat, fear conditioning and the general negative effects induced by viewing unpleasant photographs (Buchel & Dolan, 2000, as cited in Robertson, 2002).

Numerous studies support the notion that emotional events elicit specific hormones that increase the activity within the amygdala, which then leads to the long-term memory storage of the event (Robertson, 2002). Emotional experiences are associated with a release of hormones from the hypothalamic-pituitary system (Robertson, 2002). Since the amygdala has connections to numerous other brain areas, it is possible that the amygdala can affect memory processes throughout the cortex (Robertson, 2002). Based on studies that have examined bilateral damage to the amygdala, it is suggested that the

amygdala is strictly not involved in the retrieval of stored information or experiences once the memory is stored, although this structure might also contribute to declarative memory for emotionally disturbing or aversive experiences (Robertson, 2002). Healthy control subjects have shown high levels of memory performance for emotionally disturbing stimuli when compared to emotionally neutral stimuli. There is also evidence that amygdala activation correlates with individual differences in later recall for emotional film clips compared to neutral film clips using PET. Using a similar imaging technique, amygdala activation was also found during retrieval of autobiographical memories that were more likely to have personal emotional salience (Fink et al., 1996, as cited in Gabrieli, 1998). Whalen, Rauch, Etcoff, McInerney, Lee & Jenike (1998) examined brain activity detected with fMRI in healthy subjects to determine if amygdala activation was present during the presentation of backwardly masked facial expressions. This kind of evidence led to the suggestion that the amygdala might automatically process emotional stimuli without awareness. These researchers predicted to find increased signal intensity of the amygdala during masked fearful facial expressions compared to masked happy facial expressions. In addition, this study expected to find isolated activation of the amygdala during the presentation of masked emotional facial expressions in contrast to previous studies that have found amygdala activation as well as other brain areas during the presentation of nonmasked facial expressions. This study involved ten right-handed males between the ages of 19-32. Subjects were presented with alternating 28 epochs of masked pictures of fearful faces, masked pictures of happy faces or a single cross that served as a low-level fixation condition. Immediately following the experiment, the subjects were asked to describe any aspect of the presented faces. Only two of the 10 subjects reported seeing features of the emotional stimuli. When the remaining eight subjects were asked to comment on the emotional expressions of the faces, the subjects only mentioned the neutral masked

stimuli. When asked if any fearful or happy faces were presented, the subjects reported seeing neither of these facial expressions. In addition, when asked to point to which faces had been presented during the experiment, the subjects only selected the neutral faces. The following results are based on the data from those subjects who reported only seeing the neutral faces. Examining the pulse rate changes, no significant differences were found during the presentation of fearful or happy faces when compared to each other or the fixation baseline condition. Signal changes across the whole brain for the eight subjects in response to masked fearful faces versus masked happy faces revealed activation in the right and left amygdala. When examining the direction of signal change, the masked fear versus fixation contrast revealed a significant increase in signal intensity. Compared to the masked happy versus fixation contrast which revealed a significant decrease in signal intensity. Increased activation was also found in the substantia innominata during both the masked fearful and masked happy facial expressions. These findings support previous studies that have shown the involvement of the amygdala in automatically processing emotional facial expressions, suggesting that the amygdala plays a role in the unconscious monitoring of emotional stimuli (Blair, Morris, Frith, Perrett & Dolan, 1999; Sala, 2004).

Blair et al. (1999) examined whether the amygdala has a neural response to sad and/or angry facial expressions while performing a sex discrimination task using PET. Thirteen healthy male subjects free of psychiatric or neurological illness and free of medication were included in this study. During the discrimination task, subjects viewed static grey-scale images of emotionally expressive faces (angry or sad expressions). For all faces, a range of six intensity levels were produced by computer graphical manipulation. The intensity levels ranged from 0 – 100% and increased by increments of 20. During the task the subjects were only required to distinguish between the male and female faces and not to recognise the emotional expressions. Thirty subjects independent of the

experiment classified the category of photographs based on the following expressions, sad, angry, neutral or other. The correct response to 0, 20, 40% sad and angry expression faces was neutral, whereas the correct response to 60, 80, 100% sad and angry expression faces was sad and angry. Ninety-six percent of the subjects scored correctly in the current study. When subjects were asked to rate the intensity of facial expressions on a seven-point scale, the ratings correlated with the proportion of sad or angry expression in the presented face. The amplitude of skin conductance responses also correlated significantly with the proportion of the sad or angry expression in the presented face. When examining the PET scans, contrasts were performed to reveal brain areas sensitive to the emotional intensity of the facial expressions. Significant activations within the left amygdala, right temporal pole, right inferior temporal gyrus and right middle temporal gyrus were found during the presentation of sad faces. During angry faces, significant activations were found within the right orbitofrontal cortex and the anterior cingulate cortex bilaterally. With respect to both facial expressions, the neural responses in these regions correlated with the increasing intensity of the angry and sad expressions. When the two highest intensities of anger expressions were compared to the neutral conditions, activity was found in the orbitofrontal cortex and anterior cingulate cortex bilaterally. However, no significant activity was found in the amygdala to the anger expressions than to the neutral expressions. When examining regions that showed increased activity to the intensity of facial expressions regardless of type, significant activations in the right temporal pole and anterior cingulate cortex were found. These results support previous findings that there are a minimum of two distinct neural systems that process different emotional expressions. The authors have suggested that the left amygdala is involved with sad expressions even if there is explicit requirement for naming sad expressions.

Although the amygdala has been implicated in the encoding and retrieval of emotional

information, Kensinger & Schacter (2005) were interested in determining which brain regions are involved during accurate retrieval. The authors hypothesised that the hippocampus would be involved with correct memory attributions at retrieval and that regions that are important during emotional processing, such as the amygdala and orbitofrontal cortex, would be associated with the accurate retrieval of emotional information. Sixteen right-handed healthy control subjects, free of medications and depression were recruited to take part in an fMRI study. The reality-monitoring task employed in this study consisted of two parts. First, outside of the scanner, the subjects completed a task that required the formation of mental images of objects. The subjects were shown half of a picture of an object that was either of a negative or neutral content. In addition to viewing the photograph, the word for the object was also presented. During the scanning sessions, one or two days after completing the first part of the test, a retrieval task was performed. For each word that was shown, the subjects were asked to indicate whether or not a corresponding photo object had been presented during the study phase of the test. Results from the behavioural data indicated that memory for emotional items was more accurate compared to memory for the neutral items. Conjunction analyses were conducted as the aim of the study was to determine how the emotional content of the stimuli affected the neural process that was associated with accurate memory retrieval. For both the word-only and word-picture objects, conjunction analyses examined which brain regions were related to accurate retrieval. During the retrieval of emotional and neutral items, activity was found in the anterior hippocampus. Retrieval of emotional items was found to be specifically related to amygdala and orbitofrontal cortex with ANOVA showing a significant interaction between response type (correct attribution and misattribution) and emotion (emotional and neutral). Comparing those regions involved in the accurate retrieval of neutral items versus emotional items, activity was found bilaterally in the inferior prefrontal cortex

and right posterior hippocampus. An ANOVA indicated that a significant interaction existed between response type (attribution and misattribution) and emotion (emotional and neutral). The results of this study suggested that involvement of the amygdala during encoding and retrieval might possibly reduce the likelihood of memory distortions. Overall, the findings from this study have demonstrated that limbic structures are related to the accurate retrieval of emotional items while prefrontal and medial temporal-lobe regions are related to the accurate retrieval of neutral items.

1.4.1 Amygdala Lesion Studies

Damage and/or lesions to the amygdala have often been found to be implicated in producing amnesia because of the close proximity of the amygdala to the hippocampal formation (Gabrieli, 1998). Thus, being so close anatomically has posed problems for determining the exact role of these structures. The role of the amygdala in declarative memory for emotionally disturbing or aversive experiences has also been reported in lesion studies. Individuals with lesions to the amygdala exhibit impairments in the identification of fearful or angry facial expressions, which further supports the role of the amygdala in processing negatively salient stimuli (Adolphs, Tranel, Damasio & Damasio, 1994). Lesions to the amygdala have also resulted in deficits in fear conditioning. Gabrieli (1998) reviewed two studies which showed that patients with amygdala resections and the Urbach-Weithe syndrome (a rare congenital dermatological disorder that leads to the mineralisation of the amygdala but spares the hippocampal formation) show little or no fear conditioning (Bechara et al., 1995 & LaBar et al., 1995). The subjects in these studies were exposed to pairings of initially neutral conditioned visual stimuli preceding aversive unconditioned auditory stimuli, (white-noise or boat-horn bursts) that elicited an unconditioned response, which was measured by examining the changes in skin conductance responses. Only the healthy controls

showed fear conditioning by making responses in skin conductance to the conditioned visual stimuli, which was not found in the patients. However, the patients were found to have high levels of performance in declarative memory for the presented stimuli, whereas amnesic patients without amygdala damage showed no deficits in fear conditioning but impaired declarative memory for the presented stimuli (Bechara et al., 1995, as cited in Gabrieli, 1998).

The severity of memory impairments following hippocampal damage is far more extensive compared to memory impairments following damage to the amygdala (Parkin, 1997). Considering the case of H.M., Mishkin (1978) concluded that damage to the amygdala and hippocampus caused global anterograde amnesia (as cited in Murray & Wise, 2004). Damage to the hippocampus also has been demonstrated to produce amnesia, whereas, damage to the amygdala alone affects the processing of emotion (Parkin, 1997). Studies have shown a double dissociation between damage to the amygdala and the hippocampus. For instance, patients with damage to the amygdala do not show a physiological response to stimuli that are paired with an aversive shock. Whereas, patients with damage to the hippocampus do show a physiological response to the stimuli but do not recall that it was paired with the aversive shock (LeBar et al., 1995 & Bechara et al., 1995, as cited in Phelps, 2004). Therefore, it is suggested that these two limbic structures function as independent memory systems. Another function of the amygdala might be to aid the hippocampus in its consolidation process. Phelps (2004) has suggested that consolidation might not occur immediately because the amygdala must first make an emotional reaction to the event in order for appropriate storage of the memory to take place. As suggested by evidence from animal studies, the amygdala might contribute to the consolidation of hippocampal-dependent memories through the action of stress hormones (McGaugh & Roozendaal, 2002, as cited in Phelps, 2004). In addition, studies have also shown correlations between activity in the

amygdala during encoding and later memory for emotional stimuli (Cahill et al., 1996; Canli et al., 2000; Hamann et al., 1999, as cited in Phelps, 2004).

Retrieval of emotional memories, personal autobiographical memories or memories created by the experimenter for pictures of emotional stimuli have been studied using PET. Retrieval of personal autobiographical memories were found to show increased activity in the right prefrontal cortex and in right anterior limbic areas such as the amygdala, hippocampus, temporal pole and insula (Fink et al., 1996, as cited in Hamann, 2001). Post-traumatic stress disorder patients have been studied to examine the brain activity involved with the retrieval of traumatic versus neutral personal memories. The results showed activation of limbic areas mainly in the right hemisphere, such as the amygdala, anterior cingulate, insular and temporal cortices (Rauch, Bessel, van der Kolk, Fisler, Alpert, Orr et al., 1996).

The amygdala also undergoes pathology early in Alzheimer's disease (AD) (Scott, deKosky, Sparks, Knox & Scheff, 1992). Patients with AD who show memory impairments typically have damage in the medial temporal lobe, including the amygdala and hippocampus. Therefore, it can be expected that emotional memory impairments may exist in individuals with AD. To study the role of limbic structures in emotional memory, AD survivors of a massive earthquake were studied using memories of the earthquake as an index of emotionally-loaded event memory. A semi-structured interview 6-10 weeks after the disaster was administered and recall performance was correlated with the amygdaloid complex and hippocampal formation volume acquired using MRI. Thirty-six patients who had been attending the clinic prior to the event and 27 healthy control subjects were included in this study. Behavioural results showed that 31% of the patients recalled the earthquake. The mean total emotional memory score was 4.5 (maximum score = 9). The patients also scored 2.1 on event recall, 2.1 on personal memory, and 0.5 on general knowledge in the assessment of the earthquake.

The results also indicated that the mean amygdaloid and hippocampal formation volumes were significantly smaller in the patient group compared to the healthy subjects. Normalised amygdala volume significantly correlated with the total emotional memory score, the event recall score and the personal memory score in the patient group. These results remained even after the effects of whole brain atrophy and functional/cognitive impairment were controlled for. However, the significant correlation between hippocampal formation volume and the personal memory score was not found when the effect of severity of functional impairment was partialed out. These results indicate that the amygdala plays a critical role in the memorisation of emotional information versus neutral information, as non-personal factual knowledge of the earthquake (also poorly recalled) did not correlate with amygdala or hippocampal formation volume.

The function of the amygdala has also recently been reported in neuroimaging studies of patients with PTSD, however, the findings are not consistent among studies (Rauch et al., 1996; Shin et al., 1997; Shin et al., 1999; Bremner et al., 1999a). Based on evidence from animal fear conditioning paradigms, the role of the amygdala in patients with PTSD is expected to differ from those without PTSD (Tanev, 2003). Findings from the following articles illustrate the abnormal activation of the amygdala in PTSD.

It has also been suggested that PTSD patients have impairments in processing memory associated with traumatic and emotional information (American Psychiatric Association, 1994). This is evident from the cardinal symptoms of PTSD, intrusive memories, recurrent dreams and flashbacks of the traumatic event (Liberzon et al., 1999). Therefore, limbic structures, known to be involved in memory and emotion, are thought to be implicated in this disorder. Neuroimaging studies of subjects with PTSD have revealed increased amygdala activity using symptom provocation and cognitive activation tasks (Hull, 2002). Liberzon et al. (1999) used SPECT to study a group of

PTSD patients and two control groups. Subjects were scanned immediately after exposure to provocative stimuli (e.g. helicopter sounds, small arm fire, etc) and after non-provocative stimuli (white noise). The study included 14 Vietnam veterans with PTSD, 11 Vietnam veterans without PTSD and 14 nonveteran male subjects. Subjects with PTSD were diagnosed according to the DSM-III-R criteria and any subjects with a history of psychotic disorders or dementia were excluded. Head CT scans were performed prior to the study to exclude structural abnormalities. The experiment consisted of two separate sessions that were held on separate days, 48 hours apart in a counter-balanced order. In one session, subjects were exposed to white noise and in the other sessions, subjects were exposed to trauma-related stimuli. Physiologic responses were recorded throughout the session and subjective distress, pre and post-stimulus presentation was measured using 100 mm subjective units of distress scale (SUDS). During the activation scans, a 3 minute audiotape of combat sounds at gradually increasing volume was played and for the baseline scan, white noise with the same frequency was played. The subjects closed their eyes to facilitate imagery. Behavioural results indicated that the PTSD patients had significantly higher heart rates, skin conductance and subjective distress compared to the control subjects. In addition, the PTSD patients had higher heart rates and skin conductance during the combat sounds compared to the white noise condition relative to the healthy control subjects. No differences in physiologic responses were found between the two control groups. The only activation foci that exceeded the set statistical threshold in the a priori limbic area occurred within the PTSD group in the left amygdala. Regions which showed relative increases of activation which were outside the a priori region included the anterior cingulate and medial prefrontal cortex and regions with relative decreases included the right retrosplenial region. Relative activity in the region of the left amygdala was found to be roughly similar between the three groups during the white noise stimulus

presentation; however, rose sharply only in the PTSD group during combat sounds. Activation in the anterior cingulate and medial prefrontal cortex showed similar results in all three groups using the composite image as well as the averaged image from each group. All three groups also showed activation peaks bilaterally in the temporal lobes, however, in the PTSD group, the left temporal lobe activation appeared larger and more dorsal compared to the other two groups. Based on the findings that all three groups exhibited a response in the anterior cingulate and medial prefrontal cortex, the authors stated that responses to combat sounds might not be specific to PTSD. This evidence was interpreted as further support to the hypothesis that structures of the limbic system involving also the amygdala are involved in PTSD symptomatology. Furthermore, activation of the anterior cingulate cortex in all three groups is consistent with the role played by this structure in emotional processing (will be discussed in further detail in section 1.5).

Using the masked-faces paradigm, Rauch, Whalen, Shin, McInerney, Macklin, Lasko et al. (2000) employed fMRI to examine the automatic amygdala responsivity to general threat-related stimuli in PTSD subjects. These authors predicted to find amygdala activation in response to masked-fearful versus masked-happy faces in traumatised subjects with or without PTSD. In addition, it was predicted that PTSD patients would show exaggerated amygdala responses relative to the traumatised control subjects without PTSD. This study consisted of 16 men with a history of exposure to combat-related emotional trauma, eight of which met the DSM-IV criteria for PTSD, whereas, the other eight did not and were included as the other control group. During each of the 28 epochs, subjects were presented with either 56 masked-fearful stimuli or 56 masked-happy stimuli or neutral expression. Comparing the PTSD group to the non-PTSD group, significant activations were found in the left amygdala for the masked-fearful versus masked-happy faces condition. Functional MRI signal intensity differences

corresponding to the masked-fearful versus masked-happy contrast within the amygdala for each subject was examined. The analyses revealed that the PTSD patients, compared to the combat exposed controls, showed significantly greater amygdala responses. A significant between-group difference in the magnitude of amygdala activation was also found. Statistical analyses were also carried out using group-averaged data to examine a direct between-group comparison. As before, this analysis showed significantly greater activation within the amygdala for the PTSD patients. The finding of an exaggerated autonomic response within the amygdala to general threat-related stimuli, with no medial frontal activation, further supports the role of the amygdala in the pathophysiology of PTSD. Additional studies that have shown activation of the amygdala in PTSD patients as well as structural studies of the amygdala are discussed in Chapter 4 in more detail.

1.5 Cingulate Cortex Function in Healthy Subjects

The cingulate cortex provides a connection between subcortical and cortical regions to link emotional and sensory information (Banich, 1997). Thus, the cingulate cortex processes the significance of incoming emotional stimuli to make a motor response to a given situation. The cingulate gyrus makes up a large proportion of the paralimbic belt, which provides a region of cytoarchitectonic transition among the main limbic areas and fronto-parietal neocortex (Mesulam, 2000, as cited in Mesulam, Nobre, Kim, Parrish & Gitelman, 2001). A few animal and clinical studies have also found that damage to the cingulate gyrus produces deficits in spatial attention, also known as contralesional neglect (Mesulam, 1981, as cited in Mesulam, Nobre, Kim, Parrish & Gitelman, 2001). However, the contribution this structure makes in spatial attention has been difficult to understand, as it is rare to find patients with lesions isolated to the cingulate cortex (Mesulam et al.). Other areas of attention that the cingulate gyrus is involved in includes

eye movements, motor control, spatial working memory, selection-for-action, conflict monitoring and performance evaluation (Paus et al., 1993, O'Sullivan et al., 1995, Petit et al., 1996, Botvinick et al., 1999, Carter et al., 2000, MacDonald et al., 2000, Nobre et al., 2000, as cited in Mesalum et al.). Activation in this area has also been reported during overt and covert shifts of spatial attention using fMRI (Gitelman et al., 1996, 1999, Nobre et al., 1997, Kim et al., 1999, as cited in Mesulam et al.). Using fixed effects analyses, the anterior and posterior cingulate have primarily shown activation during tasks of spatial attention (Kim et al., 1999). Mesulam et al. (2001) carried out a study to investigate the association between cingulate activation and performance on spatial attention tasks using a random effects analysis. Sixteen right-handed healthy control subjects took part in this study. The subjects completed one of two tasks of covert attentional shifts in which head and eye movements were not allowed. The subjects were presented with a computer screen that consisted of a central diamond and two peripheral squares and where required to respond as quickly as possible to targets (X) but not to foils (+). In the central expectancy task, directional cues of 100 ms duration were presented in the centre of the visual field, to trigger shifts of visuospatial attention. During these trials, the target appeared on the side indicated by the cue 80% (valid) and 20% for the opposite side (invalid). The second task, spatial priming, a 100 ms change of luminance in a peripheral square provided an exogenous priming cue followed by a target. These targets were presented on one side of the cue 50% of the time (valid) and also 50% were on the opposite side (invalid). Twenty-six experimental sessions were analysed in this study, 14 subjects completed the central expectancy task and 12 completed the spatial priming task. The subjects were 90% accurate for target detection in all sessions and the reaction times varied from 610 – 340 ms. The cue effect was referred to short reaction times to the valid cued targets versus invalid cued targets. The p values for the cue effects ranged from .007 to 0.44. The sessions were divided

into two subgroups based on whether the p values for the validity effect fell above or below the median for the whole group of sessions. The seven subjects who completed the central expectancy task and the six subjects who completed the spatial priming task had p values that fell below the median, which varied from 0.007 to 0.07. These 13 sessions formed the cue effect group, whereas, the remaining 13 sessions that had p values ranging between .17 and .44 made up the non cue-effect group. The cue effect group was found to have significantly shorter reaction times to valid cued targets compared to invalidly cued targets and the reaction times to the validly cued targets were shorter in the cue effect group compared to the non-cue effect group. The reaction times to the invalidly cued targets did not show significant between-group differences and the non-cue effect group did not show significant differences in reaction times to the valid compared to invalid cued targets. The areas that showed activation during the spatial priming task and the central expectancy task included the intraparietal sulcus, frontal eye fields and the cingulate gyrus. Although the precuneus, anterior insula and temporo-occipital areas in the middle and inferior temporal gyri were also activated, the authors only focused on cingulate activation. Data from the central expectancy and spatial priming tasks where compiled due to a lack of significant cingulate activation when the two tasks were compared. Cingulate activation was first analysed in individual sessions because of the large inter-subject variability in reaction times and cue effects. Significant activations were found at the junction of the anterior cingulate sulcus (BA 32) during attentional shifts compared to at rest. Using random effects analysis, significant group activation was found in the anterior cingulate. Six of the 26 sessions also showed posterior cingulate-retrosplenial (BA 23/29/30) activation. This was not found when a random effects analysis was carried out for the group. Behavioural variables were also correlated with signal changes throughout the brain during the active tasks compared to the baseline condition. In this analysis, the posterior cingulate did

appear to correlate with the median reaction time for the entire 26 sessions. The reaction times for the group of six sessions that showed posterior cingulate activation also had significantly shorter reaction times compared to the 20 sessions without posterior cingulate activation. Furthermore, analyses of both the cue effect group and non-cue effect groups revealed that the correlation of posterior cingulate signal change with reaction time was significant only for the cue effect group of sessions (when cued effects were present). The median reaction times to validly cued targets in the cue effect group showed a significant correlation in the posterior cingulate. No significant correlations were found within the posterior cingulate in the non-cue effect group. Magnitude of the cue effect did not correlate with signal changes or activation, which suggested that any changes in signal intensity within the posterior cingulate correlated with reaction times only with the presence of a cue effect. The posterior cingulate was the only part of the brain that showed a significant correlation with reaction times or cue effect. Overall, these results showed that the posterior cingulate activation significantly correlated with the speed of attentional shifts but not when the differences between experimental and baseline conditions were examined. These results are also consistent with previous studies that have found that the posterior cingulate is more responsive to attention-directing cues than the anterior cingulate (Hopfinger et al., 2000, as cited in Mesulam et al., 2001). Furthermore, the posterior cingulate neurons might be responsible for resetting the network of brain regions involved in shifting attention.

The anterior part of the cingulate cortex is involved in the planning and control of motor movements (Banich, 1997). This structure is also implicated in motor commands that require novel or unrehearsed movements (Paus et al., 1993, as cited in Banich, 1997). The anterior cingulate also plays an important role in monitoring and regulating emotional states and responses (Vogt et al., 1999; Devinsky et al., 1995, as cited in Lanius, Williamson, Hopper, Densmore, Boksman, Gupta et al., 2003). The cingulate

cortex has been implicated in processing incoming information to select a response and the anterior part of this structure has been suggested to play a role in selecting an appropriate response (Banich, 1997). It has been shown repeatedly that the anterior cingulate is also involved if multiple responses are available and if the selection of a response is complicated. The Stroop task elicits involvement of the anterior cingulate using techniques such as functional MRI and PET in healthy control subjects. Thus, the role of this structure in attentional control has been quite clearly established. Attentional control is required during this task to inhibit a typical response in order to produce the correct response. For example, the individual must name the color of ink in which a word is printed (e.g. 'red') when the word spells a conflicting color name (e.g. 'blue') (Whalen Bush, McNally, Wilhelm, McInerney, Jenike et al., 1998). Chapter 4 provides a detailed report of the involvement of the anterior cingulate in the Stroop task in healthy control subjects and PTSD patients.

1.5.1 Cingulate Cortex Lesion Studies

The anterior cingulate cortex is part of a network of brain regions involved in regulating behaviour (Ochsner, Kosslyn, Cosgrove, Cassem, Price, Nierenberg et al., 2001). Deficits in visual cognition and attention have also been reported following bilateral anterior cingulotomy. Ochsner et al. (2001) administered eight cognitive tasks, which tapped into attention and visual cognition to a 41-year-old cingulotomy patient. Seven of these eight cognitive tasks were presented in a perception version and imagery version and the eighth task was the classic Stroop task. During the perception version tasks, the participants inspected and compared stimuli presented on a computer screen. Whereas, during the imagery version tasks, the participants generated, transformed and/or manipulated visual mental images of the same type of stimuli. Previous studies have found either no deficits on standard neuropsychological tests following cingulotomy or a range of deficits ranging from visual spatial processing, simple motor

skills, high-level attention, planning or intention[1]. Fortunately, a majority of deficits do gradually disappear weeks or months following surgery. These researchers examined preoperative and postoperative performance to determine whether postoperative performance was abnormal when compared to pre-surgical performance. The patient, M.T., was diagnosed with obsessive-compulsive disorder and co-morbid major depression and had a history of anorexia nervosa that was stable for 4 years prior to the surgery. At the age of five, she had suffered from a loss of consciousness and a grand mal seizure after being struck by an automobile in a pedestrian accident. Although she was on anti-seizure medication until the age of nine, her EEG, CT and MRI scans were normal. She was on medications prior to the surgery and nausea medication post-surgery. The cingulotomy consisted of three lesions per hemisphere. No Talairach coordinates for the lesion were available for this patient. Prior to the cingulotomy, M.T. performed normally on a battery of neuropsychological tests (i.e., WAIS-R, Wechsler Memory Scale, Wisconsin card sorting test, Boston Naming test, Rey-Osterreith figure test and the Rey Auditory Verbal Learning test). Normative data was collected from eight right-handed female participants who were not on medication, did not have a personal or family history of psychiatric illnesses, and who never suffered a head injury resulting in a loss of consciousness. Each test consisted of 16 trials with the choice of a yes or no response made with the index and middle finger of the right hand. Including the Stroop task, the participants completed the letters in a grid task, mental rotation task, size comparison task, picture verification task, facial shape task, word comparison task and the scanning task. Clinical measures of compulsions and depression improved by 55% five years following the cingulotomy. Data were analysed using response times and error rates from the imagery and perception versions of each of the seven visual cognition tasks. Between pre and post operative assessment, there was a significant

[1] Intention refers to attention to action (Bench et al., 1993, as cited in Cohen, Kaplan, Moser, Jenkins & Wilkinson, 1999).

difference in M.T.'s performance only during the imagery version of the letters in grid test compared to the healthy controls. The number of errors made by M.T. were significantly different compared to the controls during the imagery version of the Mental Rotation test. However, no significant differences were observed during the perception version of the task. In the imagery version of the Size Comparison test, M.T.'s response times decreased whereas the response times for the control subjects increased. Error rates in the imagery version of this test were also more frequent for M.T. compared to the control subjects. In the perception version of this task, neither response times nor error rates differed between the groups. The imagery version of the Picture Verification test was more difficult for M.T. after the operation and response times slowed significantly compared to the controls; however, error rates were not different. In the perception version of the task, no differences between-groups were observed for response times or error rates. For the Facial Shape test, response times for M.T. were not significantly decreased in both the imagery and perception versions of this task compared to the controls. Error rates also did not differ in the imagery and perception versions of this task between the two groups. Response times also did not differ between the two groups in both versions of the Word Comparison test. Similar results were found for error rates between the two groups. In the imagery version of the Scanning test, M.T. and controls showed similar response times and error rates. In the perception version of the Scanning test, error rates increased for M.T. in T2 compared to the controls. Results from this test also suggested that perhaps M.T. has deficits in her ability to shift attention. Examination of the error trials revealed that all incorrect responses were made when the arrow cue was far away from the ring.

For the Stroop test, trial type (incongruent, congruent and neutral) was considered the within subjects factor and group was the between-subjects factor. The results indicated that response times were found to be slower for M.T. compared to the controls and that

response times were different for incongruent, congruent and neutral trials. Response times were also found to be longer for incongruent trials than congruent and neutral trials and that congruent response times were longer than neutral trials. A significant three-way interaction between group, time of test and trial type revealed that the change in response times from T1 to T2 was different between the groups. In addition, it was found that although response times during the incongruent condition decreased for the controls, for M.T. the response times were increased. In addition, the decrease in response times for M.T. was far greater compared to the controls during the congruent and neutral condition. In summary, this study found that the bilateral removal of the anterior cingulate produced impairments in the ability to sequence novel cognitive operations necessary to generate multipart images or rotate perceptual stimuli. In addition, post-operatively, the patient was not able to search for, select, or compare images of objects when instructions did not state exactly which objects should be visualised and was impaired in the ability to select a controlled and unpractised response over an automatic one. Therefore, the results of this study support the role of the anterior cingulate cortex in an executive system responsible for controlling behaviour in many domains.

Cohen et al., 1999 examined a group of patients following cingulotomy to determine whether the anterior cingulate is associated with attentional processes involving response intention and production as well as influencing emotional experience. The authors predicted that impairments of attention and executive functions would gradually improve after surgery and impairment of intention and spontaneous responding would not improve. Twelve patients underwent bilateral cingulotomy to treat chronic, intractable pain. Previous attempts for treatment that did not prove effective included pharmacologic interventions, nerve blocks, transcutaneous nerve stimulation or surgical procedures such as laminectomy for peripheral nerve relief. The patients did not have a

history of neurocognitive or neuropsychiatric disorders prior to surgery. The 12 control subjects were also suffering from chronic pain but had opted for a nonsurgical pain intervention. The control subjects were included in the study if their rating of pain, on a ten-point visual analog rating scale, was comparable with the patients. One month before surgery, patients completed a baseline neurocognitive assessment and the controls completed the same battery of tests as part of their Pain Clinic workup. The battery consisted of tests used to measure the functional domains of language, visual integration, learning and memory, executive control, attention, motor control, intellectual functioning, response intention, generation and persistence. The tests administered to both groups included: Wechsler Adult Intelligence Scale-Revised (WAIS-R), Boston Diagnostic Aphasia Exam (Auditory Comprehension, Commands and Repetitions), Boston Naming test, Hooper Visual Organization test, Judgment of Line Orientation, Complex Figure test, Wechsler Memory Scale (WMS), Auditory Verbal Learning, Complex Figure test (immediate and delayed recall), Grooved Pegboard, Finger Tapping test, WCST, Stroop, Trail Making (A and B), Reciprocal Motor Programs, Rampart Figures, Verbal Fluency-Animal Naming, Controlled Oral Word Association test, Letter Cancellation, Digit Span and Adaptive Rate Continuous Performance test (ARCPT). In addition, an index to measure spontaneous verbal response initiation and production was used to examine spontaneous utterances. The task was comprised of a behavioural event recoding method and provided information about the frequency of verbal production without prompts or specific instructions. Design fluency as well as object construction (a modification of the Tinker Toy test) was also administered to the subjects. After surgery, the patients underwent a structured mental status examination and a test of verbal fluency (animal naming) before being discharged from the hospital. The patients were also tested using the same neurocognitive battery used at baseline three months following surgery and 12 months

following surgery. However, the Wisconsin Card Sorting test was not administered three months following surgery. Initial clinical findings revealed that three of the eight patients who underwent the brief mental status evaluation on the day after the surgery had mutism and all patients had greatly reduced Verbal Fluency as measured by Animal Naming. All eight patients also appeared to be akinetic or bradykinetic in their movements. Six patients showed significant blunting of affect, and two patients were lethargic. However, eight of the patients did not show any language comprehension, recognition memory or visual perceptual ability deficits. Examining pre-surgery results from the neurocognitive battery showed no significant group differences in performance between the patients and control subjects. However, the patients had highly significant differences in performance in all three assessments (i.e., baseline, 3-months and 12-months) on the measures of intention and spontaneous response production. Relative to the baseline condition, the patients were significantly impaired across the three assessments at the 3-month and 12-month post-surgical examination, whereas, there was no difference between the 3-month and 12-month assessment. Univariate comparisons indicated significant impairments relative to baseline on the three measures within the intention and spontaneous response production (Spontaneous Utterances, Design Fluency and Object Construction) at 3 and 12 months post-surgery. Performance on executive functioning tasks revealed significant differences across the three assessments. There were significant differences in performance in the patient group in this domain between baseline and 3-month testing and by 12 months, the patients had recovered to the level of functioning of the 3-month assessment; however, still showed marked impairment relative to the baseline assessment. The Stroop and ARCPT-Inconsistency Index performance were impaired following the 3-month assessment but recovered with only minimal deficits at the 12-month assessment. Performance on the digit Symbol subtest, Verbal Fluency-Animal Naming, Trail Making B, and the

ARCPT-False-Positive showed impairments at the 3-month assessment but recovered and did not show any differences between baseline and 12-month assessment. The WCST performance did not differ significantly between baseline and 12-month assessment. On measures of selective attention, the patients also had significant differences in performance across the three assessments. However, this was only evident between baseline and 3-months post-surgery assessment because by 12 months there was no difference relative to the baseline assessment. Tests used to measure selective attention included: Digit Span, Letter Cancellation, Trail Making A and ARCPT-Discrimination. Across the three assessments, performance did not differ significantly on the WAIS-R or WMS tests. Using MANOVA, performance on language, visual, motor and memory functions also did not vary across the three assessments. The patients did not change significantly between baseline and 3-months post-operation on any of these measures, therefore, it is suggested that cingulotomy has minimal initial effect on overall cognitive ability. Results from the ratings of pain indicated that although the patients reported only modest improvement in pain severity, the patients' response to the pain improved dramatically. Prior to the surgery, families commented that the patients were quite irritable, easily frustrated and unable to focus on anything but their pain. Post-operatively, patients tended to show increased passivity, a reduction in emotional tension and a more laid-back attitude with less worry of their pain. Four patients also returned to work after being on disability for many years. The results from this study have demonstrated that the anterior cingulate plays a central part within a larger frontal-subcortical brain system. This was evident from the impairment of executive control and attention with spontaneous response most affected in this group of patients as this is most commonly observed with frontal lobe damage. In addition, the authors stated that the intentional deficits (deficits in spontaneous response production) seen in this group of patient's supports current views of the cingulate cortex being

fundamentally involved in attention, mainly for the processes of intention and response selection and control. Motivation, arousal and physiologic activation are also known to be other factors underlying intention, which has been implicated with cingulotomies (Cohen et al., 1990, Heilman, Valenstein & Watson, 1983, Mesulam, 1993, Cohen, 1993, as cited in Cohen et al., 1999). Using neuroimaging techniques, the anterior cingulate cortex has also been critically involved in modulating responding over time using tasks that have demanded attentional focus (Cohen et al., 1994, as cited in Cohen et al., 1999). Human neuroimaging studies have shown that the prefrontal cortex is most consistently activated by verbal, spatial and object information (Robertson, 2002). The authors have also stated that the anterior cingulate might be implicated in attentional, executive and emotional processes based on the overlapping projections the anterior and posterior cingulate have with other limbic system structures and the lateral frontal and parietal cortices, along with efferent projections from the anterior cingulate to frontal subsystems. In summary, the authors suggested that the functional neuroanatomy of the anterior cingulate and its involvement in attention might clarify how the cingulate improves chronic pain and neuropsychiatric disorders such as obsessive-compulsive disorder.

The anterior cingulate has also been proposed to play an important role in autonomic control (Critchley, Mathias, Josephs, O'Doherty, Zanini, Dewar et al., 2003). Activity within the dorsal and genual regions of the anterior cingulate have also been found to be linked with affective and bio-regulatory processes (including nociception; the physiological response to painful stimuli), respiration and the representation of somatosensory, viscerosensory and autonomic arousal states (Buchel et al., 2002, Rainville, 2002, Liotti et al., 2001, Buchel et al., 2002, Aziz et al., 2000, Athwal et al., 2001, Fredrikson et al., 1998, Critchley et al., 2000a, b, 2001a, b, c, as cited in Critchley et al., 2003). Sympathetic nervous system activity is mainly responsible for the effects

of the low-frequency component of beat-to-beat variability in heart rate. The pyramidal neurons of the anterior cingulate project to subcortical brain regions associated with homeostasis and autonomic control, which includes the hypothalamus, periaqueductal grey and pontine grey matter (Ongur et al., 1998, An et al., 1998, Vilensky & Van Hoesen, 1981, Porrino & Goldman-Rakic, 1982, as cited in Critchley et al.). Previous studies have reported that during effortful cognitive and motor task performance, the anterior cingulate, insula and pons were involved in mediating changes in cardiovascular arousal. In addition, the anterior cingulate has been proposed to control sympathetic electrodermal activity responses, especially the contextual generation of arousal states that are required for the behavioural demands of the task. Using event-related fMRI and electrocardiography (ECG), Critchley et al. examined which brain regions are associated with the control of heart rate variability (HRV) during effortful cognitive and motor behaviours. Using ECG, regressors for low-frequency (LF) and high-frequency (HF) components of HRV were derived to examine differential neural contributions from sympathetic and parasympathetic control processes. Based on previous work carried out by these authors, they predicted that autonomic control would account for variation in neural activity within areas including the dorsal anterior cingulate cortex and insula cortices. The study included six healthy controls and three patients with lesions to the dorsal anterior cingulate cortex. The patients were tested using autonomic function tests including mental stress testing, which involved the pressured performance of mental arithmetic and also completed a formal neuropsychological evaluation. The authors predicted that the patients would show abnormalities in cardiovascular responses, which would be evoked by cognitive and motor effort. In addition, the authors predicted the patients would not show neuropsychological deficits in attention or general cognitive performance but show deficits in autonomic cardiovascular arousal based on the dissociation of autonomic and

nonautonomic components of cognitive work. Six healthy control subjects completed two cognitive tasks and two motor tasks during scanning. The cognitive tasks included the 1-back and 2-back task. During the 1-back task, the subjects made a brief handgrip response if a letter was immediately repeated, whereas during the 2-back task, the subjects responded if the letter was repeated after a single intervening stimulus. During the two motor tasks, the subjects were required to maintain a maximal handgrip squeeze for the duration of the visual presentation of the word 'squeeze' and were required to relax during the visual presentation of the word 'rest'. These two tasks differed in the duration of the epochs, which were either 6 seconds or 11 seconds in duration. During the scanning sessions, electrocardiography measurements were also recorded. Of the three patients, the first patient was tested 3 years following a traumatic intracranial bleed and had a medial prefrontal lesion involving the bilateral anterior cingulate cortex. The second patient was tested 2 years following a partial resection of a bilateral (mostly left-sided) medial frontal oligodendroglioma arising from the anterior cingulate cortex. The tumour extended throughout the dorsal extent of the anterior cingulate cortex posterior to the surgical lesion and might have possibly been infiltrating the adjacent dorsolateral and ventral prefrontal cortices, the medial temporal lobe and the insula. The third patient was tested after removal of a predominantly right prefrontal glioma. This tumour involved most of the anterior cingulate cortex, extending anteriorly towards the frontal pole, posteriorly to the midcingulate and inferiorly to involve the genual region. Results from the comprehensive neuropsychological battery indicated that the patients did not have any impairments in general intellectual functions or focal cognitive deficits. In addition, the patients performed well on tasks of mental arithmetic, speed and attention abilities as well as on tasks examining frontal executive functions. However, the first and second patients performed slightly worse on a couple of tests assessing functioning of the frontal lobes. The autonomic function tests were used to

examine cardiovascular responses to respiratory, postural, cold, mental effort and exercise challenges with simultaneous monitoring of beat-to-beat heart rate and blood pressure changes. The cognitive effort task administered to the patients involved the serial subtractions of the number 7 from 400 while the examiner corrected and encouraged the patient to complete the test as fast as possible. The effortful motor task completed by the patients involved holding a grip of a pneumatic cuff for 3 minutes at 30% of their maximal grip strength. The patient's heart rate and blood pressure responses to this test were compared to normative data from 147 healthy control subjects who were tested using the same protocol by evaluating the same autonomic measures. The tests administered to the patient group differed from those administered to the control subjects during the fMRI scanning sessions. However, comparative data was obtained from 12 healthy controls under identical conditions. The healthy control subjects showed enhanced activity associated with performance on the cognitive tasks in areas that included the dorsolateral, medial and orbitofrontal cortices and medial and lateral parietal cortices. During the effortful motor tasks, performance was associated with activity changes which were greatest in the contralateral sensorimotor cortex and in the straitum, cerebellum and pons. The heart rate variability overlapped with the cognitive and motor-related activity; however, the largest cluster was located bilaterally in the dorsal anterior cingulate cortex. This area was also associated with both cognitive and motor activity. Significant clusters of HRV-related activity were also found in the genual anterior cingulate cortex, bilateral insula, orbitofrontal, retrosplenial, medial parietal, bilateral somatosensory and superior temporal cortices and hypothalamus. Conjunction analyses revealed that for regions such as the dorsal anterior cingulate cortex, medial orbitofrontal cortex, insula, hypothalamus and medial parietal lobe, the HRV-related activity was independent of whether the subject was performing the cognitive or motor task. Analyses using indices of low frequency (LF) and high

frequency (HF) power were entered with task-related regressors to examine activity reflecting changes in sympathetic and parasympathetic output. Group analyses showed activity within the bilateral dorsal anterior cingulate cortex, insula, hypothalamus and inferior parietal and somatosensory cortices associated with increasing LF (sympathetic). These findings show that cortical and subcortical regions are involved in autonomic cardiovascular control and to sympathetic influences on heart rate. The authors suggested that such regulation of autonomic arousal might explain previous findings of anterior cingulate cortex activity during emotional and cognitively demanding tasks and also cingulate responses to respiratory, noxious or visceral stimulation. The results supported the set hypothesis that dorsal anterior cingulate cortex lesions would disrupt autonomic responses integrated with cognitive and motor behaviours when the performance of the patients was compared to the normative data of 147 healthy controls. Three patients were found to show blunted cardiovascular responses during the effortful cognitive task. Whereas the healthy control subjects showed significant increases in systolic blood pressure and heart rate during the mental stress test, this was not found in the patient group. During the effortful motor task, when the patients were required to hold a grip, abnormalities were found in the cardiovascular responses; however, this behaviour was not consistent across patients. Analyses of the ECG data also further supported the findings that lesions to the anterior cingulate cortex impairs autonomic, specifically sympathetic, control of the heart during clinical testing. Using data from two of the three patients, significantly greater variability in heart rate was found during mental arithmetic stress testing relative to the healthy controls. One of these two patients also showed greater HRV during rest and during the motor exercise compared to the healthy controls. Support for the involvement of the anterior cingulate cortex in homeostatic centres was found in the analyses of HF and LF components of HRV. These results revealed abnormalities in sympathetic as well as parasympathetic

influences on heart rate in patients with lesions to the anterior cingulate cortex, which were characterised by relative reductions in sympathetic power in patients during the cognitive effort tasks. Therefore, the authors concluded that the anterior cingulate cortex has a direct link with modulation of cardiac function via the sympathetic output. This region is also responsible for the appropriate generation of autonomic arousal during effortful cognitive and physical work. In addition, these authors also suggested that the findings of satisfactory performance on tests of cognitive functioning and tests used to examine frontal executive dysfunction might indicate that this region plays a limited role in general attentional or executive control of cognitive functions. Tests such as the Stroop task, which involves response conflict, have been found to induce autonomic changes in cardiovascular arousal and this test has been found to reliably show anterior cingulate activation in healthy control subjects (Hoshikawa & Yamamoto, 1997, as cited in Critchley et al., 2003; Bremner, Vermetten, Vythilingam, Afzal, Schmahl, Elzinga et al., 2004).

CHAPTER 2 Aims

This thesis involved testing cognitive functioning in psychiatric disorders known to be associated with damage to limbic structures. Neuropsychological tests that tap into spatial, topographical and verbal memory were used to examine cognitive abilities in groups of patients and healthy control subjects who were matched on age, gender and education. Emotional disorders, such as PTSD and panic disorder show more right hemisphere effects; therefore, greater spatial and topographical memory deficits were predicted than verbal memory deficits. The degenerative disorder, Alzheimer's disease, which in its early stages affects primarily limbic structures was also investigated. This disease in most cases affect verbal more than visuospatial memory in the early stages. Therefore, hypotheses for the behavioural experiments in this thesis were based on the widely known finding that the right hemisphere is largely responsible for spatial memory whereas the left hemisphere plays a significant role in verbal memory. For each of the three patient groups studied, Panic Disorder, Post-Traumatic Stress Disorder and Alzheimer's disease, the experiments within each chapter will first investigate neuropsychological performance. Following the behavioural studies, the post-traumatic stress disorder and Alzheimer's disease experiments will also identify the presence of global atrophy and systematically analyse the relationship between neuropsychological deficits and regional atrophic changes observed in these patient groups using magnetic resonance imaging data. In addition, Correlational analyses will also address the relationship between disease severity and regional atrophy. The following paragraphs will provide details of the experimental work involved in this thesis.

In Chapter 3, panic disorder will be investigated. Panic disorder has been associated with cognitive deficits. However, the exact nature of these deficits has not been studied in a laboratory setting. Based on previous literature it has been found that the right parahippocampal gyrus shows abnormalities in panic disorder patients (Reiman et al., 1986). This hypothesis was based from a background of PET studies that have shown decreased blood flow of the right parahippocampal gyrus during the resting baseline condition in panic disorder patients. Therefore, the cerebral abnormalities in the hippocampus and the right parahippocampal gyrus of patients with panic disorder raises the question of whether specific memory impairments associated with these regions exist in panic disorder. The important role of the right parahippocampal gyrus in topographical memory suggests that panic disorder may be associated with topographical memory deficits. Currently there are no studies of selective deficits in panic disorder. This chapter will focus on topographical memory function in this group of patients building on previous evidence of topographical memory impairments in individuals with damage to the right parahippocampal gyrus. The selection of tests were primarily chosen based on results from animal studies and human studies associating substrates of anxiety with brain regions (hippocampus and right parahippocampal gyrus) linked to neuropsychological functions such as topographical and spatial memory as well as verbal memory.

With reference to the preceding section, the hypothesis of the behavioural studies within this thesis stems from the lateralisation for the right hemisphere of emotional processing. The right hemisphere has a special and dominant influence on the reception and expression of emotions and has a special role in mediating emotional behaviour (Heberlein et al., 2003). Right hemisphere damage might interfere with the development of an appropriate cognitive state (thought to be an essential component of emotion), thereby resulting in emotional flattening in patients with right hemisphere disease or

dysfunction (Heilman, Watson, & Bowers in Hellman & Satz, 1983). Therefore, the right hemisphere has a special role in mediating emotional behaviour, as well as, processing affective stimuli and programming emotional behaviour. However, it also appears to have a special relationship to those subcortical structures important for mediating cerebral arousal and activation. In normal subjects, the right hemisphere has a special and dominant influence on the reception and expression of emotions (Heberlein et al., 2003). Patients with left hemisphere damage appear depressed and patients with right hemisphere lesions appear indifferent or emotionally flattened (Hellman & Satz, 1983; Borod, 1992). Left hemisphere is specialised for speech and language functions, while the right hemisphere is more specialised for visuospatial and other nonverbal processes. Patients with right hemisphere disease often appear indifferent or euphoric, right hemisphere lesion subjects often appear inappropriately "indifferent" (Goldstein, 1948 in Heilman, Watson, and Bowers 1983 in Hellman & Satz). Right hemisphere lesions might have a defect in the comprehension or expression of affect or both. Thus, patients with anxiety disorders such as panic disorder and post-traumatic stress disorder were predicted to show greater deficits on memory tasks associated with right-sided functioning, such as those within the visuospatial domain.

Chapter 4 will focus on post-traumatic stress disorder (PTSD). Although PTSD has been associated with hippocampal atrophy, there has been little work examining memory function in PTSD. There has been evidence that patients with PTSD have explicit memory deficits. This type of memory is defined as the conscious acquisition of knowledge about people, places, and objects (Bremner, Randall, Scott, Capelli, Delaney, McCarthy et al. 1995). Bremner et al. (1993) and Bremner et al. (1995) found that PTSD patients scored significantly lower on short-term memory tests than a comparison group. The patients also performed poorly on logical (verbal) memory component of the Wechsler Memory Scale. Along with finding verbal memory deficits

in PTSD patients, Bremner et al. (1995) also discovered there was a positive correlation between right hippocampal volume and scores on the percent retention subscale on the logical (verbal) component of the Wechsler Memory Scale. No correlation was found between this score and left hippocampal volume. The control subjects were matched to the patients in age, sex, race, handedness, years of education, socioeconomic status, body size, and years of alcohol abuse. It is well known that the right hemisphere is responsible for visuo-spatial memory whereas the left hemisphere is responsible for verbal memory. Although no consistency for hippocampal atrophy in PTSD has been found to date, one particular study investigating bilateral hippocampal lesions revealed interesting results from spatial memory tests. Rosenbaum et al. (2000), reported patient K.C., who had large reductions in hippocampal volume and bilateral parahippocampal volume as well as minor damage to the right parahippocampal cortex. This patient had spared semantic memory and impaired autobiographical memory. The major findings were that K.C. was impaired in recognizing city locations and in recognizing and identifying non-salient landmarks within his neighbourhood.

To gain a better understanding of the neuropsychological performance of the PTSD patients tested in this study, structural MRI scans were used to investigate the presence of atrophy across the whole brain compared to healthy control subjects. Voxel-by-voxel whole brain morphometry was used to examine whether any limbic structures showed atrophy, such as the hippocampus. The results were then used to run correlations between the extent of atrophy and neuropsychological impairment. It was predicted that greater hippocampal atrophy would result in greater impairments on the neuropsychological tests of spatial and verbal memory. Using the Clinician Administered PTSD Scale (CAPS), correlations between severity of disease and neuropsychological impairments were also analysed. Patients with severe forms of PTSD were predicted to suffer from greater topographical memory deficits compared to

those patients with a less severe form of the disorder.

To examine brain activation associated with the presentation of emotional and neutral visual stimuli in PTSD patients, brain activation patterns in response to the colour Stroop and emotional Stroop task were also studied using functional MRI. Given the role of limbic structures such as the anterior cingulate cortex and amygdala, this specific study tested the hypotheses of whether the PTSD patients would show decreased blood flow in these regions in response to traumatic stimuli (during the emotional Stroop task). This functional abnormality in PTSD has been suggested to possibly mediate the distress and arousal symptoms when re-exposed to trauma related stimuli after the development of PTSD (Shin, Whalen, Pitman, Bush, Macklin, Lasko et al. 2001).

In Chapter 5, a novel approach will be used to investigate the relationship between structural and functional deficits, detailing the well-established cognitive decline typical of Alzheimer's disorder (AD). This degenerative disorder is characterised by medial temporal atrophy and progressive cognitive decline (Mizuno, Wakai, Takeda & Sobue, 2000; Pantel, Schönknecht, Essig & Schröder, 2004). A direct consequence of atrophy to structures such as the hippocampus, may likely contribute to the memory impairments, which are predominantly the first signs of this neurodegenerative disorder (Mizuno et al., 2000). As mentioned earlier, the hippocampus structure plays a critical role in learning and memory (McEwen, 1999). The behavioural disturbances evident in AD are quite widespread. However, during the early stages of the disease, deficits are most evident in areas such as memory, language, praxia, cognitive speed, or attention and concentration (Pantel et al., 2004). Yet, many caregivers and Alzheimer's disease patients report difficulties finding their way around (Beatty & Salmon, 1991; Henderson, Mack & Williams, 1989; Hirono, Mori, Ishii, Ikejiri, Imamura, Shimomura et al., 1998; Giannakopoulos, Gold, Duc, Michel, Hof & Bouras, 2000; Cherrier, Mendez & Perryman, 2001; Pai & Jacobs, 2004). However, it is not quite clear whether

this route-finding difficulty arises from normal disease progression that targets the medial temporal region first or due to specific damage to the hippocampus and parahippocampus gyrus. A group of Alzheimer's disease patients were also included in this study, as extensive research has reported that this illness is primarily associated with atrophy to limbic structures (Busatto, Garrido, Almeida, Castro, Camargo, Cid et al., 2003). This group was administered the same battery of neuropsychological tests used to examine cognitive functioning as the panic disorder patients and post-traumatic stress disorder patients. Following the behavioural study, a voxel-based MRI volumetric experiment was carried out to identify regions where grey matter density volume differed significantly between AD patients and healthy control subjects. A correlational analysis between symptom severity (using Mini Mental Status Examination scores) and regional grey matter density was also carried out. In addition, this experiment analysed the association between regional atrophy and different types of memory dysfunction.

CHAPTER 3 Neuropsychological Characteristics of Panic Disorder

3.1 Definition & Characteristics

Feelings of anxiety are a normal part of everyday life; however, some individuals experience anxiety inappropriately. A real or an imagined stimulus may cause individuals suffering from panic disorder, a form of anxiety disorder, to show an inappropriate reaction to fear. Panic disorder is a disabling mental condition characterised by persistent anxiety attacks accompanied with widespread physiological changes. Individuals suffering from panic attacks may experience chest pains, light-headedness, dizziness, nausea, stomach problems, chills, shortness of breath, feeling of choking, tingling, numbness, shaking, trembling, feelings of unreality, terror, a feeling of being out of control or going crazy, blurred vision, temperature sensation, fatigue and weakness, fear of dying, sweating, and a pounding heart (Emmelkamp, Bouman & Scholing, 1992). Many patients cannot predict when an attack will occur, and many patients develop intense anxiety between attacks because of worrying when and where another attack will occur (Emmelkamp, Bouman & Scholing, 1992). However, as the disease progresses an individual will likely learn the cause of their anxiety. The intensity of panic disorder may be mild, moderate, or severe. Experiencing a panic attack once a month with a maximum of four symptoms constitutes mild panic disorder. The term limited symptoms panic attacks is used for patients who report the presence of less than four symptoms and moderate panic disorder falls between the mild and severe category (Emmelkamp, Bouman & Scholing, 1992). A severe panic disorder diagnosis

is given if the person experiences a minimum of eight panic attacks in one month (Emmelkamp, Bouman & Scholing, 1992).

3.2 Diagnostic Criteria

A diagnosis of panic disorder without agoraphobia can be identified by the following criteria developed by the Diagnostic and Statistical Manual of Mental Disorders (1994):

Criterion A (Both 1 and 2 must be present)

1. Recurrent unexpected panic attacks
2. At least one of the attacks must be followed by 1 month (or more) of one (or more) of the following:
    a. persistent concern about having additional attacks
    b. worry about the implications and consequences of the attack
    c. a significant change in behaviour related to the attacks

Criterion B

Absence of Agoraphobia

Criterion C

The panic attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse or medication) or a general medical condition (e.g., hyperthyroidism).

Criterion D

The panic attacks are not better accounted for by another mental disorder, such as Social Phobia, Specific Phobia, Obsessive-Compulsive Disorder, Post-Traumatic Stress Disorder, or Separation Anxiety Disorder.

(p. 402)

3.3 Evaluating Anxiety

Measurements of anxiety may be recorded using questionnaires such as the Hamilton Anxiety Rating Scale, Covi Anxiety Scale, Hospital Anxiety and Depression Scale, and the State Trait Anxiety Inventory. The Hamilton Anxiety Rating Scale and the Covi Anxiety Scale are clinician rated scales, however, the State Trait Anxiety Inventory (STAI), is a patient rated questionnaire (Kennedy et al. 2001; Sesti, 2000). The STAI questionnaire consists of two scales, 20 questions to examine state anxiety (STAI-S) and 20 questions to examine trait anxiety (STAI-T). State anxiety is changeable as it is concerned with how people feel at a particular moment (e.g. situational feelings such as tension and nervousness), whereas trait anxiety is relatively stable and enduring characteristics of people that make them predictable (Kennedy, Schwab, Morris, Beldia, 2001). The STAI Trait scale statements ask people to respond to each question by ticking one of the following: "Almost never," "Sometimes," "Often," "Almost always." Individual items for this component of the scale were taken from scales such as the Taylor Manifest Anxiety Scale and the IPAT Anxiety Scale. Significant correlations found on these anxiety scales indicate they are highly validated measures of individual differences in trait anxiety (Spielberger, 1972). For the STAI State scale questions, individuals must respond to the questions by rating themselves on the following four point scale: (1) Not at all, (2) Somewhat, (3) Moderately so, (4) Very much so (Spielberger, 1972). The fundamental qualities in the STAI State examine feelings of tension, nervousness, worry, and apprehension. While this component of the scale was devised, it was found that such feelings were also highly correlated with the absence of such states (i.e. tension, nervousness, worry, and apprehension). The STAI State scale, therefore, includes 10 questions such as "I feel calm," and "I feel content," to develop a balanced scale. Low scores on the scale indicate calmness and serenity states, intermediate scores represent moderate levels of tension and apprehensiveness, and high

scores indicate states of intense apprehension and fearfulness that approach panic (Spielberger, 1972).

3.4 Genetics

Factors known to increase the risk of being diagnosed with panic disorder include having previous, unexpected panic attacks, depression, alcohol problems, illegal drug use, heavy cigarette smoking, excessive amounts of coffee, medications that may trigger panic attacks, and the heart condition mitral valve prolapse (American Psychiatric Association, 2000). Risk factors for anxiety disorders, such as panic disorder, also include young age, gender (greater risk for women), and family history. Many studies have suggested that a genetic predisposition to the development of panic disorder may exist. Family and twin studies have established that anxiety disorders may be influenced by genetic factors. The risk of developing panic disorder is increased by three to 21 times if there is a family history of panic disorder (Smoller & Tsuang, 1998). Torgersen (1983) studied panic disorder, obsessive-compulsive disorder, and generalised anxiety disorder to determine whether hereditary factors are involved in the development of anxiety disorders. This study involved a group of same-sexed twins from Norway. There were 318 probands (individuals with the disorder under investigation) and of these probands, 85 have had or have an anxiety disorder as their main psychiatric disorder. The 85 twins consisted of 32 monozygotic (MZ) twins and 53 dizygotic (DZ) twins. All subjects completed the modified version of the Present State Examination (PSE), a structured psychiatric interview. However, this interview was modified to include lifetime symptoms instead of recording symptoms from the previous month. In addition, questions pertaining to their developmental history were recorded as well (e.g. relationship with parents, closeness with twin and if childhood environment differed).

The researchers also collected information regarding their social development and the presence of any psychological stresses in adulthood. The administration of either a questionnaire or a blood sample determined zygosity of the twins (monozygotic or dizygotic). If both twins were probands, the pair was counted twice rather than once for the analysis of concordance rates. No monozygotic twins were found to have the same anxiety disorder, however, for the generalised anxiety disorder group; the monozygotic twin concordance rates were higher than the dizygotic twin rates. This difference, however, did not reach significance due to the small sample size. Overall, the monozygotic twins had higher concordance rates than dizygotic twins for each disorder but not for generalized anxiety disorder. These findings were only significant when agoraphobia groups (with and without panic attacks) or all anxiety disorders without generalised anxiety disorder were combined. Therefore, hereditary factors may not be important in the development of generalized anxiety disorder as it may be for panic disorder. Although the twins' childhood or adulthood was not found to be similar, the researcher suspected that the high concordance rate for the monozygotic twins might be due to them having lived in a similar environment. It was suggested that monozygotic twins are likely to spend more time together than dizygotic twins are because they are quite similar to each other.

Noyes, Crowe, Harris, Hamra, McChesney and Chaudhry (1986) carried out a study to examine the relationship between panic disorder and agoraphobia. Usually the lives of many people suffering from panic disorder become quite restricted. Individuals with this disorder often fear having another attack and eventually begin avoiding normal, everyday activities. They ultimately avoid any situation that they fear would make them feel helpless if another panic attack occurs. When a patient feels this restricted by their condition, a diagnosis of panic disorder with agoraphobia is given. When this work by Noyes et al. was completed, there was controversy as to whether agoraphobia should be

considered as a separate disorder. These researchers carried out this study to provide evidence to support the idea that agoraphobia is a feature of anxiety states and panic disorder should be identified as either uncomplicated or complicated by limited or extensive agoraphobia. This would result in removing agoraphobia from the DSM-III as a separate category. Panic disorder was first categorised in the DSM in 1980 and since then, the DSM-IV does classify agoraphobia as being a separate disorder from panic disorder. Noyes et al. carried out a family study to examine the relationship between panic disorder and agoraphobia as well as provided support for revision of the DSM-III. Forty probands with agoraphobia were matched for age and gender with 20 probands with panic disorder. All probands were given a structured interview to screen for medical and psychiatric conditions and the panic disorder diagnosis was made using the DSM-III. For a definite proband diagnosis of agoraphobia, a history of phobic avoidance, diagnosis of a panic disorder, and a history free of any phobic avoidance was required. Fourteen panic disorder probands and 19 agoraphobia probands were diagnosed with a secondary major depression diagnosis, in addition, three panic disorder probands and 12 agoraphobia probands had a secondary diagnoses of alcohol or a sedative drug use diagnosis. Three control probands also had major depression, simple phobia, and adjustment disorder with mixed features. Two panic disorder patients received no treatment, 17 received psychiatric treatment, and 21 received psychiatric treatment. The relatives of the probands received the same structured interview as the probands, with the addition of the Symptom Checklist-90, Eysenck Personality Inventory, Fear Survey Schedule, and Agoraphobia Symptom Rating Scale. The relatives of the probands were also interviewed to obtain information regarding their family history and interviews were carried out that also identify anxiety disorders, affective disorders, and alcohol disorders. The relatives of the anxiety disorder probands had a greater prevalence of anxiety disorders compared with the relatives of the control

probands. The same results were found for the agoraphobia and panic disorder families. An increased prevalence of panic disorder and agoraphobia was found for the panic disorder and agoraphobia families respectively. No significance was found between the prevalence of alcohol disorders among the panic disorder probands and their relatives compared to the control families, however, significance was found for agoraphobia. A greater prevalence was not found for primary affective disorders for either the relatives of panic disorder or agoraphobia probands. The relatives of the agoraphobia group had the greatest prevalence for all disorders; half of these relatives were diagnosed with a psychiatric disorder. Calculations were computed to determine age-corrected morbidity risks for anxiety disorders, affective disorders, and alcohol disorders. The relatives of the agoraphobia probands had a combined risk of 19.9% for panic disorder and agoraphobia and the relatives of panic disorder probands had a 19.2% risk. The female relatives had the greatest risk for anxiety disorders and the risk was the greatest for female siblings of agoraphobics. When examining the risk factor for the female relatives in each disorder it was found that female relatives had a three times greater risk compared to male relatives of the agoraphobia probands and this risk was two times greater in the female relatives compared to the control probands of panic disorder. The risk of alcohol disorder was the highest among the male relatives of agoraphobia (30.8%), the second highest for panic disorder (14.4%) and 9.9% among the relatives of the control probands. Secondary depression was reported in the highest proportion by the relatives of the agoraphobia with anxiety disorders with a percentage of 26.8% compared to the anxious relatives of panic disorder which was 17.7%. In the control probands there was a 13.3% chance of developing secondary depression. The finding that the agoraphobia relatives had the highest proportion of secondary depression may be due to panic disorder and agoraphobia families having a larger increase in primary disorders. Overall, this study found that relatives of agoraphobia probands were at an

increased risk of both agoraphobia and panic disorder, while relatives of panic disorder probands only had an increased risk of panic disorder.

As seen above, investigation of the role of genetics in panic disorder has involved the examination of family and twin studies. A recent meta-analysis studied the genetic epidemiology of anxiety disorders, the consistency between differing results by testing for heterogeneity across studies and compiled data from the major studies completed. Hettema, Neale & Kendler (2001) carried out a meta-analysis using operationalised diagnostic criteria. This analysis, however, excluded studies that examined only anxiety symptoms or anxiety neuroses, systematic ascertainment of probands and relatives, direct interviews with the patients, diagnostic examination of relatives by investigators that are blind to proband affection status, and comparison group studies. Numerous primary studies were rejected if they met these exclusion criteria. The outcome of having a relative diagnosed as either affected or unaffected was the main measure of interest for the family studies. As a vast majority of data is available for panic disorder and obsessive-compulsive disorder, the aggregated risk was calculated by combining the raw data from each of these studies. A total of five family studies were examined in this meta-analysis and three twin studies met the inclusion criteria. Only two large twin samples met the criteria set out by these researchers. Data were obtained from the Virginia Twin Registry and the Vietnam Era Twin Registry. The Virginia Twin Registry collected data from panic disorder, phobia, and generalised anxiety disorder and the Vietnam Era twin Registry studied panic disorder and generalised anxiety disorder. The researchers carried out this meta-analysis using panic disorder and generalised anxiety disorder data. The results revealed a significant association between panic disorder in the patients and panic disorder in first-degree relatives. The results indicated that there was homogeneity for the five studies that were analysed. The summary odds ratio revealed a value of 5.0, which indicates that a familial component

does exist in the development of panic disorder. Two separate analyses were also completed for the twin studies. When incorporating the three smaller studies the results indicated that genetic factors are involved in the aetiology of panic disorder. In addition, the two larger twin studies that used different samples and males/females attributed to 30%-40% of the variance in liability to additive genetics and the remaining variance was due to the individual's specific environment. However, the studies did not find that a family environment plays a role in the aetiology of panic disorder. This genetic evidence has been found to be the strongest in panic disorder compared to generalised anxiety disorder, phobias and obsessive compulsive disorder. However, this may be the case because much more data were available for running an analysis for panic disorder. The larger twin studies also support the finding that familial risk involves genetics to a substantially greater degree in the aetiology of panic disorder than environmental factors.

Woo, Yoon & Yu (2002) examined catechol O-methyltransferase (COMT) genotypes and the relationship between COMT polymorphism and the clinical characteristics of panic disorder. The sample of patients consisted of 51 patients and 45 gender and age matched control subjects. The panic disorder patients in this study were not diagnosed with other mental illnesses and all patients had been treated with the anti-depressant paroxetine for more than three months at the time of the study. The standard phenol-chloroform technique was used to extract the genomic DNA from peripheral blood leukocytes. Treatment response was also investigated in this study using the Clinical Global Impression test. The COMT(H) allele was associated with high activity and the COMT(L) allele was associated with low activity. The genotype frequency was either H/H, H/L, or L/L. The results of this study found that the frequency of COMT(L) allele and L/L genotype frequency was significantly higher in the panic disorder patients compared to the control subjects. In addition, panic disorder patients with the L/L

genotype were found to have a poorer treatment response to their medication compared to those patients with the H/L and H/H genotype. Overall, the three different genotypes did not differ significantly in age of onset, gender, family history of panic disorder, presence of agoraphobia, and pre-treatment severity of the illness. The results of this study demonstrate that COMT activity may be a determining factor in the development of panic disorder. Compared to the healthy control subjects, the patients had significantly higher COMT(L) allele and L/L genotype. The researchers mentioned that these results may however be based on ethnic or sample size differences as previous studies have shown inconsistencies in results. The allele and genotype frequencies have been found to be different among Caucasians, Han Chinese, and for Japanese panic disorder patients.

3.5 Biological Basis

The investigation into the pathophysiology of panic disorder is ongoing and the discovery of what causes this anxiety disorder is not yet established. The existing literature published to date has associated brain and biochemical abnormalities in panic disorder (e.g. increased activity in the adrenergic system, hippocampus, locus coeruleus, and abnormalities in benzodiazepine receptors) (Gratacòs et al., 2001; Uchida, Del-Ben, Santos, Araújo, Crippa, Guimarães et al., 2003). In addition, anxiety disorder researchers have hypothesised that panic disorder is associated with physiological abnormalities.

Experimental work from the 1960's and repeated studies from the 1970's demonstrated that anxiety disorders can be induced in a laboratory setting with lactate infusions and carbon dioxide administration. However, since this initial work, the list of provocative agents has increased to include caffeine, yohimbine, serotonergic agents (m-chlorophenylpiperzine), and neuropeptide cholecystokinin. One interesting finding from

the lactate-induced and carbon dioxide inhalation induced panic attacks was that those patients, who had frequent panic attacks, were more likely than the healthy controls to hyperventilate during an attack (Griez & Schruers, 1998; Reiman, Raichle, Butler, Herscovitch & Robins, 1984). Such findings led researchers to believe that perhaps a respiratory abnormality may cause this disorder. As the research progressed, a new theory developed proposing that lactate infusion and carbon dioxide inhalation shared a common pathway, a hypercapnic acidosis[2] in the sensitive areas of the central nervous system (Griez & Schruers, 1998). It was also proposed that both lactate-infusion and carbon dioxide inhalation triggered a suffocation alarm. Therefore, panic attacks may have been false alarms in individuals with an oversensitive suffocation detector. However, the basis of this theory dismissed the fundamental characteristic of panic disorder, attacks occur from un-expected and repeated episodes of intense fear (Klein, 1993, as cited in Davis, 1999). After extensive work it was determined that panic disorder is not caused by physiological abnormalities in the mechanisms that control breathing.

Using brain-imaging techniques, specific brain structures have been implicated in the regulation of anxiety and fear. In the event of danger, an emotional feeling of fear causes an automatic and rapid protective response that occurs without the need for conscious thought (Davis, 1999). For example, when faced with danger, heart rate increases, hands sweat and bodies will tremble to list a few physiological changes that may be experienced. Animal studies and human studies indicated that the body's fear response is coordinated by the amygdala (Davis, 1999). The symptoms of fear arise from the central nucleus of the amygdala relaying the sensory information it receives onto the hypothalamic and brainstem areas that mediate signs of fear and anxiety. The sensory information is initially received by the lateral and basolateral nuclei that project

[2] Excessive amounts of carbon dioxide in the body, primarily caused by decreased breathing.

to the central nucleus. It was proposed that the amygdala is the neuroanatomical substrate that is responsible for the underlying cause of panic disorder. Prolonged fear of danger may make the amygdala more reactive to succeeding stress. Davis (1999) suggested a priming effect such as this might cause the development of psychiatric illnesses. In addition, the projections from the central nucleus to the parabrachial nucleus may be responsible for the respiratory changes exhibited during fear. Therefore, this structure may be involved with the hyperventilation reported in panic disorder patients in the previous studies mentioned. It seems far more likely that the response to fear may activate the amygdala, which would result in hyperventilation rather than the argument that respiratory abnormalities in individuals with panic disorder may cause panic attacks (Davis, 1999).

Findings from one particular genetic study supported the hypothesis that the locus coeruleus may be involved in the aetiology of panic disorder. Although no gene linkage evidence was found, the α_2 receptor was tested in panic disorder because it is known to regulate the locus coeruleus activity through the negative feedback loop (Wang et al., , as cited in Davis, 1999). This theory proposed that through the sympathetic nervous system, an individual is likely to experience panic attacks due to increased efferent activation from the locus coeruleus (Davis, 1999).

Researchers have also speculated that panic disorder might be caused by a disturbance of neurotransmitter levels. An alteration in the levels of the neurotransmitters from the GABAergic system may be liable for the onset of panic disorder. Anxiety symptoms and panic attacks may be stopped using these neurotransmitters that work as agonists of the benzodiazepine receptors. Anxiety and panic attacks return once these neurotransmitters are not administered. A SPECT study was carried out to quantify the benzodiazepine receptors and to compare the distribution of receptors. The findings indicated that the left hippocampus and precuneus had a reduced number of receptors in

the panic disorder group compared to the comparison group (Bremner, Innis, White, Fujita, Silbersweig, Goddard et al., 2000). In addition, a positive correlation was found; increased anxiety from panic attacks was associated with decreased binding in the frontal cortex.

The highest density of cholecystokinin (CKK) containing neurons have been found in the cerebral cortex, amygdala, and hippocampus. However, these neurons are also located in the midbrain, including the periaqueductal grey, substantia nigra, and raphe nuclei. The administration of this neuropeptide is an excitatory neurotransmitter when delivered ionophoretically[3], whereas, CKK-4-8 works as a stimulant for action potentials in the dentate gyrus of the hippocampus. Low benzodiazepine doses also suppress the activation of hippocampal neurons. Patients with panic disorder are known to have an anxiogenic effect to CKK- 4. In addition, the CKK levels in the cerebral spinal fluid of patients are reported to be lower than in normal healthy subjects, indicating that these receptors might be compensating without having an enhanced function (Davis, 1999).

3.5.1 A) Regional Blood Flow Studies

It has been demonstrated that a functional brain abnormality is present in individuals with panic disorder and that this abnormality may play a role in the pathophysiology of panic disorder (Reiman, Raichle, Butler, Herscovitch & Robins, 1984). Positron Emission Tomography (PET) has been employed to identify the brain abnormalities of patients with panic disorder. Various investigators have documented abnormalities in regional cerebral blood flow (rCBF) in the distinct cortical region of the parahippocampal gyrus (PHG), specifically in the right hemisphere. Reiman et al.

[3] A process of transportation of ionic molecules into the tissues by passage of electric current through the electrolyte solution containing the ionic molecules using a suitable electrode polarity.

(1984) reported this focal brain abnormality in patients with panic disorder and those vulnerable to lactate-induced anxiety attacks using PET. Regional CBF was measured by an intravenous injection of ^{15}O-labelled water. The following study found that panic disorder patients had a positive response to lactate-infusion and that these anxiety attacks did not occur in normal healthy controls that were also given a lactate-infusion. Reiman et al. studied a group of six healthy controls and 10 patients. The panic disorder patients were further divided into three groups: Group 1, seven patients with a history of panic disorder and a positive response to lactate infusion, Group 2, three patients with panic disorder and a negative response to lactate infusion, and Group 3, six healthy control subjects with no history of psychiatric disorders. The authors in this study used the DSM-III criteria for panic disorder as well as the diagnostic criteria outlined by Feighner (1972). No significant differences emerged between the groups when examining CBF in the whole brain, left hemisphere, right hemisphere or comparing the left to right ratio of CBF. The seven patients from group 1 that had a positive response to lactate infusion had a significantly lower left to right ratio in the parahippocampal gyrus compared to group 2 or group 3 when the analysis examined seven areas of interest. The other six areas, hippocampus, inferior parietal lobule, anterior cingulate gyrus, hypothalamus, orbito-insular gyri and amygdala did not show any significant regional asymmetries. The researchers stated that because the absolute CBF values fell within the normal range of values, it is not possible to determine if the PHG asymmetry is due to a decrease in the left parahippocampal gyrus or an increase in the right parahippocampal gyrus. The results did not reveal any other abnormal asymmetries. The researchers carried out another analysis with a group of 20 neurologically normal volunteers to replicate the previous findings. Only one of the 20 volunteers did not show the same ratio of parahippocampal blood flow that was identical to the original group of volunteers. This volunteer had the same ratio that fell within the numbers of those from

the panic disorder patients and a detailed assessment revealed that this volunteer met the criteria for a diagnosis of panic disorder. These results suggest that a predisposition to panic attacks may be associated with an abnormality of the parahippocampal gyrus in the right hemisphere.

To elaborate on the previous study, Reiman, Raichle, Robins, Butler, Herscovitch, Fox et al. (1986) investigated the abnormal hemispheric asymmetry of blood flow in the parahippocampal gyrus. Sixteen patients (9 patients with limited phobic avoidance and 7 without phobic avoidance) and 25 healthy control subjects were included in this PET study. For data analysis purposes, the researchers separated the patients into groups depending on whether they were prone to lactate-induced anxiety attacks; however, the data was collected in the resting, non-panic state. Eight patients with panic disorder that were sensitive to lactate-infusions were placed in group 1. The eight patients with panic disorder who were not vulnerable to lactate-infusions formed group 2 and the 25 healthy control subjects were in group 3. At approximately ten-minute intervals before and during lactate infusions, the subjects reported the presence of anxiety and rated the severity of those anxiety symptoms using a 21 item inventory. The results of this study confirmed earlier findings. Patients in group 1 had a significantly lower ratio of left-right parahippocampal blood flow, left-right parahippocampal blood volume and left-right parahippocampal metabolic rate for oxygen compared to group 3 and even lower for group 2. Right parahippocampal blood flow was also significantly higher in group 1 than the other two groups. Although not significant, group 1 also had higher whole brain blood flow than group 2, and had higher whole brain blood flow than group 3. However, group 2 (patients not vulnerable to lactate-infusion) had significantly lower whole brain blood flow measurements than the other groups. It is also worth noting that group 1 and 2 had a significantly higher number of anxiety symptoms, however, group 1 reported experiencing a typical anxiety attack during lactate infusion, which was not

reported by groups 2 or 3. These findings support the involvement of the right parahippocampal gyrus in anxiety. In addition, this work also suggested that a parahippocampal gyrus abnormality may predispose an individual to anxiety attacks.

Reiman, Raichle, Robins, Mintun, Fussleman, Fox et al. (1989) carried out a study to examine the neuroanatomical correlates of a lactate-induced anxiety attack. Thirty-one patients were separated into three distinct groups as mentioned in the previous study. Group 1, eight panic disorder patients sensitive to lactate-induced anxiety attacks, Group 2, nine panic disorder patients who were not sensitive to lactate-induced anxiety attacks, Group 3, 15 healthy control subjects. After completing PET scans, the subjects reported whether any anxiety symptoms were present during the scan and reported the severity of the symptoms. The subjects were also required to report whether the attack was a severe or unequivocal anxiety attack, a mild or equivocal anxiety attack, or that no anxiety attack was experienced. If the subject reported a minimum of 15 symptoms from a 21-item inventory or if they reported an equivocal anxiety attack, the researchers concluded from these reports whether the lactate-infusion produced the anxiety attack. To support the above subjective ratings of anxiety, heart rate, arterial pH and hematocrit levels were also monitored during the anxiety attack. The values of all variables used to distinguish an anxiety attack were greater in group 1 compared to groups 2 and 3. Group 1 had a significantly greater number of anxiety symptoms that were also more severe than the other groups, higher systolic blood pressure and a significant reduction in arterial PCo_2. Compared to the other two groups, seven patients in group 1 had significant bilateral regional blood flow increases in the temporofrontal cortex, insular cortex, claustrum or lateral putamen in or near the superior colliculus, and in or near the left anterior cerebellar vermis during the lactate-induced anxiety attack. However, no significant decreases in blood flow were found in any other brain regions. As expected, no regional blood flow increases or decreases were found in the non-panic patients or

the healthy controls. As with the previous findings from Reiman et al., the main area of the brain that was involved in the anxiety attacks was the bilateral temporal poles. Therefore, these results support the initial finding that this region of the brain is responsible for generating anxiety.

Mathew & Wilson (1990) attempted to replicate the study by Reiman et al. (1984) but found inconsistencies in the results due to differences in methodology and CBF measurement techniques. These researchers measured CBF with a ^{133}xenon inhalation technique in nine subjects with generalized anxiety disorder, whereas, Reiman et al. (1984) studied subjects with panic disorder using PET scans to measure CBF. These investigators, however, were able to replicate the finding that panic disorder patients at rest, during their baseline condition have an abnormal asymmetry of blood flow in the PHG. In a subsequent study, Reiman, Fusselman, Fox and Raichle (1989) confirmed earlier findings by studying anticipatory anxiety. Similar to patients with panic disorder who develop panic attacks during lactate infusions, anxiety caused by the anticipation of an electric shock also resulted in a significant increase of blood flow in the bilateral temporal poles. The S-Anxiety scale of the State-Trait Anxiety Inventory was completed by the patients before, during, and after the administration of a painful electric shock to obtain a subjective measurement of anxiety during each of the PET scans. In addition, physiological measurements were recorded to examine anxiety, e.g., heart rate and electro-dermal activity. As expected, during each shock, all subjects displayed an increase in the physiological variables measured. Significant increases in regional blood flow in the bilateral temporal poles were observed during anticipatory anxiety but no significant decreases were found.

Cerebral blood flow changes during sodium-lactate infusion were also examined by Stewart, Devous, Rush, Lane and Bonte (1988). The patient group consisted of 10 individuals with panic disorder; however, some of the patients were also diagnosed with

agoraphobia. Patients that have never been medicated with tricyclic antidepressants, monoamine oxidase inhibitors, or alprazolam were selected to take part in the study. Seven patients in this study had never taken any medication to treat their panic disorder symptoms, however, two patients had been on oxazepam up to 48hours before the study and one patient was taking cloarapate up to 24hours before the baseline study. The comparison group consisted of five healthy control subjects. The baseline condition was either a resting state and/or a saline infusion. The subjects were initially evaluated using the Hamilton Rating Scale for Anxiety, the 17-item Hamilton Rating Scale for Depression, the Sheehan Patient-Rated Anxiety Scale, the Phobia Scale, and a checklist to monitor panic symptoms. After two scans, the patients were assessed using the Hamilton Anxiety scale, the Sheehan Patient-Rated Anxiety Scale and with a symptom checklist. Six of the ten patients panicked during the lactate-infusion, four patients did not panic and none of the control subjects experienced any anxiety during the infusion. Blood flow alterations for the frontal, temporal, parietal, occipital, and superior temporal regions of the brain were determined between the baseline and sodium-lactate infusion conditions. The results showed that the percent change in total CBF in the left hemisphere was significantly greater than that of the right hemisphere. The control subjects and those patients who did not panic after the lactate-infusion had significantly greater change in blood flow in the left hemisphere compared to the patients who did experience panic attacks. For the right hemisphere the same findings were obtained, however, the results nearly approached significance level. The patients who experienced a panic attack had a significantly greater increase in regional CBF for the left and right occipital regions compared to the healthy controls and the patients who did not experience panic attacks. In addition, no correlations between severity of panic attacks and change in blood flow for either the right and left hemisphere and occipital lobe were found for the three groups. The investigators of this study referred to results from other

researchers to support their findings of increased CBF in the right occipital region. While experiencing anxiety, it has been suggested that the right occipital area might have a higher density of benzodiazepine receptors (Buchsbaum et al. 1985, as cited in Stewart et al., 1988). In addition, unlike the other studies that have indicated regional blood flow changes in areas such as the right parahippocampal gyrus, this area of the brain could not be seen using the single photon emission computed axial tomography technique that was employed in this study. Previous studies have also shown an increase in regional blood flow during a lactate infusion in control subjects and panic disorder patients who did not panic in response to lactate-infusions. It is suspected that such increases may be a result of having a sodium-lactate-induced increase in serum bicarbonate, increased plasma volume, and hemodilution (Stewart et al.).

Cristofaro, Sessarego, Pupi, Biondi and Faravelli (1993) also studied drug-free lactate sensitive patients to investigate brain perfusion in panic disorder. Of the nine out-patients, two patients had no other comorbid psychiatric disorders, two patients had agoraphobia and five patients also had phobic avoidance. No patient had used tricyclic antidepressants or monoamine oxidase inhibitors, however, some had periodically taken benzodiazepines. In addition, those patients on medications had not been taking any medication at least two weeks prior to the study. The five controls that were recruited for this study were also free of any medications. Seven days after the SPECT study, which involved the injection of HMPAO, all patients were given a sodium lactate infusion. Of these nine patients, seven experienced an anxiety attack. The panic disorder patients did score higher on the Acute Panic Inventory scale than the control subjects but none of the patients experienced an anxiety attack during the HMPAO injection. Of all the regions studied, the hippocampal area was the only area that showed the greatest reduction in the uptake of HMPAO. An increase in brain perfusion was reported on the right side as indicated by the asymmetry index (AI) averages in the frontal cortex. The

mean values in this area were significantly greater for the panic disorder patients compared to the controls. The greatest variability was found in the cerebellum for the patients. When perfusion indices (PI) were examined, the left and right hippocampal areas were significantly lower in the panic disorder group whereas these values were significantly higher in the region of the left occipital cortex. A tendency toward increased perfusion indices in the right occipital cortex, right inferior frontal cortex and the left temporal pole were also found in the patients compared to the controls. These findings are also similar to those found by Nordhal et al. (1990) that will be reported later (see page 20). This study by Cristofaro et al. did not find any regional blood flow changes in the hippocampal region, while Reiman et al. (1984) had found an abnormal asymmetry of blood flow in the parahippocampal region. The authors suggested that the differences in findings may be due to the different way in which brain regions were examined. Instead of localising brain structures using axial slices, the researchers in this study used sagittal slices. The method employed in this study examined both the hippocampus and parahippocampal gyrus versus just the hippocampal region.

Lucey, Costa, Adshead, Deahl, Busatto, Gacinovic et al. (1997) examined brain blood flow in a group of 46 outpatients with a diagnosed DSM-III-R anxiety disorder using a single photon emission tomography technique (SPECT). There were 15 obsessive-compulsive disorder (OCD) patients, 15 panic disorder with agoraphobia (PA) patients, and 16 post-traumatic stress disorder (PTSD) patients. Schizophrenia, major depression, organic disease and/or substance abuse patients, patients with axis I disorders and those who had a personal or family history of tic-spectrum movement disorder were not included in the study. Substance abuse was also taken into consideration to determine whether this factor had any influence on the symptoms. Before 99mTcHMPAO imaging, the patients current drug and alcohol use was recorded, in addition, at the time of scanning, OCD syndrome severity, concurrent low mood, avoidance, and subjective

anxiety was rated. A group of 15 healthy subjects with no personal or family history of mental disorders were used as a comparison group. The SPECT analysis revealed no significant group differences for whole brain blood flow. However, examining rCBF a significant main difference for diagnostic group and a significant effect of cerebral region was found. No interaction was found between diagnostic group and region or group by region by side. Post-hoc analysis looking at rCBF differences between groups, region by region, revealed significant group differences in the area of the superior frontal cortices and in the caudate nuclei. There were significant group differences in the left superior frontal cortical rCBF. Mean left superior frontal rCBF in PTSD and OCD were found to be significantly lower than in healthy controls. The PTSD group also had significantly lower right superior frontal cortical rCBF compared to the healthy controls. In addition, significant subcortical rCBF differences were found in the caudate nuclei. Correlations between anxiety and depression scores from clinical rating scales were also found with rCBF. The Visual Analogue Scale correlated positively with whole brain blood flow and the Beck's Depression Inventory correlated negatively with left and right caudate rCBF. Scores from the Yale-Brown Obsessive Compulsive Scale and the Fear questionnaire measuring avoidance did not show any significant correlations. However, the scores from the Impact of Events Scale, completed by the PTSD group, did correlate negatively with the left and right caudate. Overall in this study it was found that 99mTcHMPAO revealed significantly reduced rCBF in OCD and PTSD. This finding was not observed in the healthy controls or for the PA group. The investigators have proposed that perhaps PA symptoms are different from those in OCD and PTSD. It is also possible that the mental activity, obsessive thinking, intrusive imagery and resistance found in PTSD and OCD is associated with the caudate rCBF reduction.

The studies reporting regional cerebral blood flow abnormalities have been a foundation for work investigating the pathophysiology of panic disorder. Osuch, Ketter, Kimbrell, George, Benson, Willis et al. (2000) studied the relationship between the severity of anxiety and regional cerebral metabolism in 52 mood disorder patients using PET scans. The investigators planned to identify changes in regional cerebral glucose metabolism (rCMRglu) associated with the severity of anxiety symptoms. It was expected that associations between anxiety and rCMRglu in frontal, insular, and temporal areas would be present but the authors did not give an a priori hypothesis of the direction of the correlations. Of the 52 patients with a primary affective disorder, 25 had unipolar disorder and 27 patients had bipolar disorder. The sample of patients consisted of treatment refractory inpatients as well as 18 unipolar less refractory outpatients that were free of medication for a minimum of two weeks prior to the study. During the same week of the PET session, the patients completed a modified version of the Spielberger Anxiety-State Scale (SAnx) that measured comorbid anxiety symptoms and the Hamilton Depression Rating Scale (HAMD). The scores from the SAnx and HAMD scales did not differ between the bipolar and unipolar patients. A direct correlation was found between SAnx scores and rCMRglu in the right parahippocampal gyrus and left anterior cingulate gyrus near the callosum (analysis covaried for age, gender, and HAMD scores). In addition, SAnx inversely correlated with rCMRglu in the left fusiform gyrus, left superior temporal region, left angular gyrus, left insula, and bilateral lateral cerebellum. Running the same analysis after covarying for age, gender, and SAnx, HAMD scores correlated directly with rCMRglu in bilateral medial frontal, right anterior cingulate, and right dorsolateral prefrontal cortices. No significant inverse correlations between rCMRglu and HAMD were found. When the two groups of patients were analysed separately an inverse correlation for the bipolar group was found between SAnx and rCMRglu in the left superior temporal region, left insula, and

bilateral lateral cerebellum. A positive correlation for the unipolar group was present in the inferior anterior cingulate gyrus and an inverse correlation in the right cerebellum. This work by Osuch et al. (2000) supported evidence already present in the literature that the right PHG is an important neural substrate related to anxiety. Furthermore, these findings support Reiman et al.'s finding that a functional brain abnormality exists in individuals with panic disorder, even though the sample studied by Osuch et al. (2000) consisted only of women. Osuch et al. (2000) observed the same hippocampal and parahippocampal abnormalities as Reiman et al. (1986), but in opposite hemispheres. Although the researchers cannot precisely determine why a difference was found, they justified this discrepancy as due to differences in the methodology used in each study.

Bisaga and colleagues (1998) explored glucose metabolism in six women with panic disorder (with and without agoraphobia) who were medication free and sensitive to lactate-infusion and six healthy control subjects. Psychoactive medication was stopped one month before testing and enzyme-inducing agents were stopped one week before the study. In addition, the subjects restrained from having caffeine and alcohol for 24 hours and fasted for 8hours before the PET scan. Patients with co-existing psychiatric disorders and with a score above 15 on the HAMD scale were excluded from the study. The healthy control subjects did not have any psychiatric disorders and did not have a family history of anxiety disorder. The panic disorder patients had a relative increase of glucose metabolism in the left hippocampus and in the parahippocampal region compared to the values in these regions in the healthy control group. In addition, a decrease was found in the right inferior parietal and right superior temporal brain regions in the panic disorder patients compared to those values found for the healthy control group. No other significant differences were found in the regions of interest analyses between the two groups. In addition, no correlation between severity of panic disorder, severity of lactate-induced panic attacks or scores from the clinical variables

on the psychometric scales was found. These researchers stated that the PHG plays a key role in mediating affective states because of its neural inputs from the sensory structures and its outputs to the amygdala, hypothalamus, and brain stem.

Nordahl, Stein, Benkelfat, Semple, Andreson, Zametkin et al. (1998) examined unmedicated panic disorder patients and imipramine-treated patients to determine whether the same regional cerebral metabolic asymmetries were present as those found in previous studies that examined unmedicated panic disorder patients. There were nine patients treated with imipramine, 12 unmedicated panic disorder patients, and 43 healthy control subjects recruited to take part in the study. Of the 12 patients in the unmedicated patient group, one patient had never been on medication and one patient had been off medication for over one year. At the time of the study, the other patients had stopped all medications for a duration of 11-110 days. After the PET study, the subjects completed the Spielberger state anxiety scale (SSAS). The medicated panic disorder patients were also assessed using the Sheehan Patient Related Anxiety Scale (SPRAS). The results showed no significant differences between the medicated panic disorder patients and the healthy control subjects when glucose metabolism rates were examined. Furthermore, glucose metabolic rates for the two patient groups were not significantly different. The researchers divided the results from the regional asymmetries into three regions. The first region of interest was the hippocampus and posterior inferior prefrontal cortex. The left and right posterior inferior prefrontal cortical and hippocampal regional cerebral metabolic rate for glucose (rCMRglc) was found to be lower in the medicated group than the healthy control subjects. The second region taken into consideration was the orbital frontal cortex. Significance differences were present in rCMRglc between the medicated and unmedicated panic disorder patients. The medicated patients had significantly lower posterior orbital frontal rCMRglu compared to the healthy controls. The medicated patients also had lower

posterior orbital frontal rCMRglc compared to the unmedicated patients. For the third region, parieto-occipital cortex, the medicated patients and healthy controls did not differ in rCMRglc for the left Rolandic region, and the left mid and inferior parietal cortex. The two patient groups (with medication and without medication) were different in the left Rolandic region, left midparietal and the left inferior parietal. The medication group was found to have a significantly higher regional cerebral metabolic rate of glucose. There were no differences in the three groups when compared amongst each other for rCMRglc in the midoccipital region. Examination of the Spielberger State Anxiety Scale scores after completion of the PET scan revealed a significant difference between the medicated patients and the healthy controls. Examination of the same scores following the PET scan was also significantly different between the unmedicated and medicated patient groups. The SSAS and the SPRAS scores did not correlate with any region of interest. However, post-hoc analyses revealed positive correlations between SSAS and rCMRglc for the midparietal and the Rolandic region. In addition, an inverse correlation between SPRAS and the left posterior orbital frontal cortex was found for the medicated panic disorder patients. The finding that both groups exhibited abnormal hippocampal and posterior inferior prefrontal asymmetry of regional cerebral glucose metabolic rates (rCMRglc) is compatible with the work by Reiman et al. (1984) who found that panic disorder is associated with a trait abnormality.

Similar to the other studies that have been presented, Eren et al. (2003) also examined rCBF. These researchers were interested in studying whether there is a correlation between rCBF asymmetry and severity of panic disorder. Thirteen of the patients met the criteria for a panic disorder with agoraphobia diagnosis. All patients were included in the study if they experienced an attack two weeks prior to the study and if they had been free of medication for at least 15 days before the SPECT study. The patients were not included in the study if they had a diagnosis of other psychiatric disorders, a history

of alcohol or drug abuse, chronic neurological or physical illness (determined with physical and neurological examinations, electrocardiogram, laboratory tests for renal, hepatic, hematologic and thyroid functions), and also if the patient or their first degree relatives had schizophrenia and schizophreniform disorder. The patient group completed the Panic and Agoraphobia Scale (PAS), and the Hamilton Depression Rating Scale (HDRS). The patients were required to score lower than 17 on the HDRS to be included in the study. The findings indicated that, compared to the healthy control subjects, the panic disorder patients had significantly lower rCBF in the inferior frontal regions bilaterally. Whereas, compared to the control group, the patients had significantly higher rCBF in the right medial and superior frontal regions. Only the finding of lower rCBF ratio in the inferior frontal cortex remained significant after a correction for multiple comparisons. Although the rCBF asymmetry index values were significantly higher for the medial frontal region, this significance did not hold after the correction for multiple comparisons was completed. No significant correlations were found between disease severity (using PAS scores) and rCBF ratio values. There was a positive correlation found between PAS scores and lateral temporal, superior temporal and parietal region rCBF asymmetry index values. However, after correcting for multiple comparisons, the correlations were no longer significant. No other articles presented in this section have reported decreased bilateral inferior frontal perfusion however; these findings may partially be explained by differences in the medication status of the patients in this study. Unlike the previous studies, these patients were drug-free. In addition, the authors also suggest that the differences in some of their results might be due to the heterogeneity of panic disorder. The authors have also suggested that the decrease in the inferior frontal region may be present because of activation of the amygdala or because of the involvement of the locus ceruleus in panic disorder. The

locus ceruleus may cause vasoconstriction from the stimulation it produces when innervating the small veins of the brain.

3.5.2 B) Regional Brain Volume Studies

Massana, Serra-Grabulosa, Salgado-Pineda, Gastó, Junqué et al. (2003) studied grey matter density of the PHG using voxel-based morphometry with a sample of 18 panic disorder patients. Fifteen of the 18 patients had panic disorder with agoraphobia. The left PHG was the only region of the brain that showed any significant differences in the patient group compared to the healthy control subjects when the data were corrected for multiple comparisons. The grey matter density in the left PHG was significantly lower in the panic disorder patients relative to the healthy control subjects. The left cuneus, right middle temporal gyrus, right inferior temporal gyrus, hypothalamus, right parahippocampal gyrus, right thalamus, and left and right cerebellum all showed significant increases in grey matter concentration in the control group compared to the patient group using uncorrected p values. The patient group also had a greater concentration of grey matter in the left middle temporal gyrus and left angular gyrus compared to the healthy controls. The investigators stated that these findings further support the involvement of the parahippocampal area in the pathophysiology of panic disorder.

Using MRI, Vythilingam, Anderson, Goddard, Woods, Staib, Charney et al. (2000) demonstrated that panic disorder patients had smaller temporal lobe volumes but not significantly lower hippocampal volumes. There were 13 outpatients with panic disorder included in this study. Nine had panic disorder with agoraphobia and four without agoraphobia. One of the four patients without agoraphobia, had social phobia, simple phobia, bulimia, major depression and a past history of major depression and polysubstance dependence. Another patient had a current and past history of simple

phobia, one had a past history of major depression and polysubstance dependence and another patient met the lifetime criteria for bulimia but was not currently experiencing any symptoms. The 14 control subjects in this study did not have any Axis 1 disorders based on the Structured Clinical Interview for DSM-III (SCID), history of current alcohol or drug abuse or dependence, meningitis, traumatic brain injury, loss of consciousness for more than ten minutes, or any neurological disorders. The data from patients with comorbid psychiatric disorders and without comorbid disorders were considered together and compared to healthy control subjects as their temporal lobe volumes were not significantly different. Results from an ANOVA indicated that the patients had significantly smaller bilateral temporal lobe volumes compared to the control subjects. Subsequent univariate analyses revealed smaller left and right temporal lobe volumes in the patient group as well as a main effect for side, however, no interaction between side and diagnosis was found. Using an ANCOVA to control for differences in whole brain volumes between the two groups, the patient's temporal lobe volumes were significantly smaller. No side differences were found in L/R hippocampal volumes between the two groups. In addition, no main effect diagnosis and no significant side by diagnosis interaction were found. Panic disorder patients, however, did have smaller whole brain volume compared to the healthy control subjects. Although hippocampal volumes were not found to be smaller in this group of panic disorder patients, the authors suggested that the overall reduction in the temporal lobe volume does indicate that anatomical changes in this brain area may be a risk factor for panic disorder.

Vythilingam et al. (2000) were the first researchers to use a quantitative MRI technique to examine whether any anatomical abnormalities exist in panic disorder. However, as mentioned above, these researchers were not able to localise the entire hippocampus to report whether any significant differences exist in this area. A similar study was carried

out by Uchida et al. (2000) who designed a group comparison between patients and healthy controls, particularly focused on the investigation of the amygdala and hippocampal volumes in panic disorder patients. Eleven patients that met the DSM-IV criteria for panic disorder and completed the SCID were selected to take part in the study. With the exception of major depression and dysthymia (often associated with panic disorder), all patients with other comorbid psychiatric disorders were excluded from the study. Six patients had a diagnosis of panic disorder with agoraphobia, five patients had a history of major depression and one met the criteria for dysthymia. The patients were matched with eleven healthy control subjects for sex, age, socioeconomic status, years of education, and handedness. The patients and healthy control subjects had no history of head trauma, electroconvulsive shock, major medical illness or substance abuse. Eight of the patients were taking pharmacological medications at the time of testing (four of which were taking a selective serotonin reuptake inhibitor, three were taking clomipramine, and one was taking a benzodiazepine). The anatomical landmarks, as specified by Watson et al. (1992) (as cited in Uchida et al., 2003), defined the temporal lobe to include the amygdala, hippocampus and inferior horn of the lateral ventricle. The temporal lobe volume of the patient group was found to be significantly smaller compared to the control subjects. In addition, compared to the healthy subjects, the patients had significantly smaller right temporal lobe, right amygdala, left amygdala, and left hippocampal volumes. In addition, the right temporal pole, left temporal pole, and right hippocampus were not found to be significantly different between the patients and healthy control subjects. A correlational analysis between hippocampal volume and time course of panic disorder showed a positive relationship between duration of illness and left hippocampal volume. Recent cases showed greater hippocampal reduction than older cases. Although the authors expected to find greater hippocampal volume reduction in older cases, based on the Stress Hippocampus Theory (see chapter 4) this

work needs to be replicated as it is the only study that has correlated hippocampal volume and duration of disease in panic disorder.

The extensive literature that has been presented here has advanced our understanding of the neuroanatomical and neurochemical substrates of panic disorder. For example, the results of the lactate infusion studies using neuroimaging have suggested that a trait abnormality may indeed be present in patients with panic disorder. The right parahippocampal gyrus (PHG) has shown abnormalities in activation, metabolism rate, blood volume, and rCBF during resting, baseline conditions. Although the anatomical abnormalities of panic disorder have not shown consistent findings across studies, structures of the limbic system (e.g. amygdala, hippocampal formation, and parahippocampus gyrus) show the strongest involvement in the pathophysiology of panic disorder.

3.6 Memory Function

Imaging techniques such as PET have provided evidence of a trait abnormality in brain regions associated with laboratory induced anxiety in panic disorder patients, as well as during resting, baseline conditions (Reiman et al., 1984; Reiman et al., 1986). Use of SPECT has also reported similar regional cerebral blood flow abnormalities as those reported using PET (Cristofaro et al., 1993). In addition, increased atrophy in the temporal region on MRI has been reported (Vythilingam et al., 2000). The prominent area showing abnormalities is the medial temporal region, particularly in the area of the right parahippocampal gyrus. However, no studies to date have examined whether selective deficits in these regions are associated with specific cognitive impairments in panic disorder.

3.7 Aims

Reports of concentration and attention difficulties in panic disorder patients have provided anecdotal evidence for possible cognitive deficits in panic disorder (Lautenbacher, Spernal, and Krieg, 2001). However, the exact nature of these deficits has not been studied in a laboratory setting. The findings of rCBF abnormalities in the right PHG as well as significantly smaller right temporal lobe volumes, although not unanimous, suggests, however, that specific memory impairments might exist in panic disorder. The important role of the right PHG in topographical memory suggests that panic disorder might be associated with greater topographical memory deficits, compared to sparing of left hippocampal dependent memory (verbal). The hypothesis of this study stems from the large number of studies that have reported topographical memory impairments in individuals with damage to the right PHG as well as from similar results found in healthy control subjects (See Chapter 1 for more details).

The battery of neuropsychological tests administrated in this study were selected from behavioural animal studies and human PET studies. Using the Nine Box Maze test, Abrahams et al. (1997) demonstrated that damage to the right hemisphere produces significant spatial memory deficits compared with damage to the left hemisphere. Using a selection of tests that are suitable for testing spatial memory as well as other aspects of memory function, the current study expects panic disorder patients to perform poorly on the topographical memory tests compared to the non-topographical memory tests. In contrast to many of the previously mentioned studies, this study will not measure topographical memory using simulated environments or videos depicting routes around a buildings, cities, or parks. The Route Learning task based on work conducted by Barrash et al. (2000) will require participants to learn a route within a real-life environment with actual corridors and stairwells of a building. The other neuropsychological tests administered to the participants include a Topographical

Localisation task and a Visual Picture Recognition test, Non-Topographical stimuli: Faces & Dogs, Topographical stimuli: Buildings & Landscapes (Maguire et al., 2001). Controls task employed in this study include the Visual Word Recognition test (Maguire et al., 2001), Buschke Selective Reminder Test (Bushke & Grober, 1987), and the General Semantic Knowledge test (WAIS-III). In addition, anxiety will be evaluated using the State-Trait Anxiety Inventory (Form Y-1) (Speilberger, 1983) and the Visual Analogue Anxiety Scale.

3.8 EXPERIMENT 1: Neuropsychological Study of Memory Function in Panic Disorder

3.8.1 Method

3.8.1.1 Participants

Seven right-handed out-patients (3 Females and 4 Males) were recruited from NHS specialised clinical psychology clinic at Royal Cornhill Hospital and the Trauma Research Centre, University of Aberdeen, Scotland (M age = 44, SD = 13.51). The Grampian Health Board and the University of Aberdeen joint ethics committee, Scotland, granted Ethical approval prior to conducting this experiment. The control participants were recruited from the Department of Psychology, University of Aberdeen Research Volunteer Panel. A total of seven healthy control subjects matched for gender, age, handedness and education were selected to take part in the study (3 Females and 4 Males; M age = 45, SD = 13.42). All patients were diagnosed with panic disorder with agoraphobia except for one patient who had panic disorder only. All patients had no other psychiatric comorbidity. Three patients were taking medications for depression (Citalopram, Mirtazapine, and Prozac), three patients were taking medications to treat

their anxiety symptoms and depression (Prozac and Inderal'LA, Seroxat & Inderal, and Seroxat & Inderal and Diazapam), and one patient was not taking any medications. The initial causes of anxiety attacks for some of the patients in this sample include: work problems, symptoms of a viral infection, crowds, and pregnancy (previously had miscarried an earlier pregnancy). Following these situations and triggers, some of the patients began to avoid crowded places, which led to the development of a diagnosis of panic disorder with agoraphobia.

3.8.1.2 Materials/Procedure

3.8.1.2.1 Cognitive Evaluation

3.8.1.2.1.1. Visual Stimuli Recognition Test (Maguire et al., 2001)

Word Recognition Task

The list of words used for the Word Recognition test came from an unpublished test (Sutherland, 1997). Each word was assessed for frequency of occurrence. The words selected in this test were half high frequency words and the other half were low frequency words (Hofland & Johnson, 1982). The words were also matched for word length. The experiment was designed using the software SuperLab. This test consisted of an encoding stage and a recognition stage. During the encoding stage, participants viewed two lists of words, each containing eleven words. In the recognition stage of the experiment the two lists of words were randomly mixed in with 20 words not presented in the lists previously seen and the participants were required to distinguish between the old words and the new words. The participants were instructed to press on the keyboard the letter 'N' for words that were new and the letter 'B' for words that they had seen

before. The number of correct responses was analysed along with analysis of d' and β scores calculated using the principles of the signal detection theory. The words were presented in Arial black with a font size of 20, against a white background for 3 seconds followed by an inter-stimulus interval of 1.5 seconds before the next word was shown. During the recognition stage the words were presented for 5 seconds followed by an inter-stimulus interval of 1 second. The order of presentation was randomised for each participant.

Picture Recognition Test

Four categories of colour photographs were designed and presented using the software SuperLab. A 160 photographs were used in this test, forty for each of the following categories; Faces, Landscapes, Buildings and Dogs. Forty photographs of Faces taken from Lundqvist & Litton (1988) and Landscapes (Benson, 2000, personal communication, December 2001) were used. The 40 photographs of Dogs were gathered from various websites and the 40 photographs of Buildings were taken from the following website; . The outline of the Buildings, Faces, and Dogs were traced and viewed against a white background. The Landscape photographs were also viewed against a white background. The pictures of Faces consisted of an even number of male and female adults with neutral emotional expressions who were all wearing identical grey shirts. These photographs did not include any distinct characteristics such as, jewellery, eyeglasses, beards and moustaches. The Faces were an average of 7 x 9 cm when displayed on the computer screen. The Landscape photographs varied between lakes, fields, and oceanic scenery and did not include any manmade landmarks or buildings. These photographs were 15.5 x 11.5 cm when displayed on the computer screen. The Buildings were single skyscraper type buildings and were an average of 4.5 x 7 cm when displayed on the

computer screen while the photographs of Dogs were an average of 6.5 x 5 cm. All stimuli were presented to the participants facing forward in the middle of the computer screen.

During the encoding stage of the experiment, participants viewed 20 photographs of a particular category of visual stimuli (e.g. Dogs, Buildings, Faces, and Landscapes). The photographs were presented for 3 seconds followed by an inter stimulus interval of 1.5 seconds before the next photograph was presented. In the recognition phase, the same 20 photographs were randomly mixed in with 20 photographs that were not shown before. During this stage, the photographs were presented for 5 seconds with an inter stimulus interval of 1 second. As with the word recognition task, the participants were instructed to press the key 'N' for a photograph they had not seen before and the letter 'B' for a photograph that had been shown previously. After the completion of one category of stimuli the next category was shown until the participant viewed all four types of stimuli. The order of presentation of stimuli was randomised for each participant. This test was scored for total correct responses in each category, d' and β values computed using the principles of signal detection theory were also calculated and analysed.

3.8.1.2.1.2. Topographical Localisation Task (Lezak, 1997)

The Topographical Localisation Task was designed from a map of the United Kingdom taken from the following website, www.about.com. The participants were given a map of the United Kingdom with a list of seven cities. The participants were first instructed to place the four compass directions on the map (e.g. North, South, East, and West) and then asked to mark the location of the seven cities on the map by writing down their assigned number. During the test, participants were not given immediate feedback as to whether they had placed the cities in the correct locations on the map. The test was

scored by measuring the difference in centimetres between the actual location of the city and the location of where the participant had placed the number of the city on the map. The scores for the cities within England and within Scotland were added up separately and together as one total map score.

3.8.1.2.1.3. Route Learning Task (Barrash et al., (2000)

A route was designed within the corridors and stairwells of the MacRobert building at the University of Aberdeen, Aberdeen, Scotland. The route was carefully selected to avoid verbal cues but was full of visual cues. The participants were informed that they would be tested on their ability to remember a route. They were told that they would be shown the route to a researcher's office and would be taken back to the starting point through a different route. At the beginning the participants were instructed to pay close attention because they would be required to lead the way through the same route as soon as they returned to the starting point. The participants were instructed that they would have to lead the way through the route for three consecutive test trials if they made errors during the first two trials. If no errors were made during the first two trials the test was successfully completed. Throughout the trials the examiner followed the participant and corrected each error immediately after it occurred and then lead them in the correct direction.

3.8.1.2.1.4. General Semantic Knowledge Test (WAIS-III) (Weschsler, 1997)

Seven questions were taken from the General Semantic Knowledge test (WAIS-III). The participants were required to respond orally to questions examining factual knowledge. The participants were told they would have to answer seven questions. Each

question was read aloud to each participant in a standardised way. If the response to a question was unclear or incomplete the examiner asked the participant to explain what they meant or was asked to tell them more about their answer. It was not allowed to ask the participant leading questions or spell out words. Questions were only repeated when the examinee's response suggested that they might have misunderstood the meaning or misheard the question. A score of one was given for each correct answer and a score of zero for each incorrect answer or if the participant was unable to answer the question.

3.8.1.2.1.5. Buschke Selective Reminder Task (Buschke & Grober, 1987):

In the Buschke Selective Reminder Task, participants were required to recall as many words as possible from a list of words that was read to them. The participants were told this test assessed how quickly they can learn a list of words. The examiner explained to them that a list of twelve words would be read to them and that they must listen carefully because after the words are read they must recall as many of the words as possible. The words did not have to be recalled in any particular order. Once the participants recalled as many words as they could, the examiner repeated the words that they did not recall from the list. The participant was then required to recall the entire list of words again. There were twelve trials and each time the participant has to try to recall all twelve words. The list of words was read at a rate of 2 seconds and the words were always read in the same order, beginning with the top of the list and working to the bottom. The words that were recalled correctly from the previous trial were not read to the participant during the subsequent trial. When the participant was able to recall all twelve words correctly for three consecutive trials, the rest of the trials were discontinued. However, the remaining trials did contribute to the participants score on the test. This test provides a score for the following five variables: Items Total Recall, Long-Term Retrieval, Short-Term Retrieval, Long-Term Storage, Consistent Long-

Term Retrieval, Random Long-term Retrieval, Reminders, Intrusions and Perseverations.

3.8.1.2.1.6. Nine Box Maze (Abrahams et al., 1997):

The Nine Box Maze was a spatial memory task that consisted of nine identical cylindrical containers with detachable lids that stood at a height of 10cm with a diameter of 5cm. The containers were fixated in a circular formation on a round board (diameter of 90cm) that was on top of an empty round table (diameter of 107cm) with four chairs situated around the sides. The containers were placed 40 degrees apart from each other. The test was located in a room with another table, a desk, filing cabinets, and windows. The table remained in the same position throughout the test for all the participants. The ten objects used as testing material were lipstick, a cigarette, lighter, ring, money, paperclip, marker, highlighter, toothpaste tube, and keys. A picture booklet was also used during the object recognition phase of the test that contained nine pages of photographed pictures of the ten objects. Each object was photographed to scale and each page displayed the objects in different sequences. This test consisted of three stages: A) object familiarisation and free recall, B) the two box maze (practice trial), and C) the nine box maze. The National Adult Reading Test was administered as a delay task during the test.

A) Object Familiarisation. The participants were presented with 10 objects, each for 5 seconds. They were instructed to name each object aloud as it was presented and were required to state whether or not they would carry it everyday in their pockets or handbag. After a one-minute delay, the participant had to recall as many objects as possible. Throughout all three stages of this test all delays were filled using the National Adult Reading Test (NART) (Nelson, 1980).

B) Two-Box Maze. Of the ten objects that were introduced to the participant during the object familiarisation stage, nine of the 10 objects were used for the remainder of the experiment. For this component of the test two objects and two containers were used. The participant was informed that two objects would be placed into two containers. They were required to remember what two objects were used and what two containers were chosen (four pieces of information), instead of having to remember which object was in which container. After the objects were placed into two containers there was a one-minute delay, during which the participants were asked to change their seat to one of the three other chairs situated around the table. The participant always moved positions in a clockwise manner. For the remainder of the time the participants were given the NART. After the delay the participants performed the object recognition test. The participants viewed a colour photograph of the nine objects and were instructed to point to the objects that were used. During each trial the participant saw a different photograph of the nine objects arranged in different positions to avoid an association between the object and spatial location. The participants were given immediate feedback if they were correct or wrong. After a wrong response, they were instructed to try again and were given a maximum of ten choices. If the participant repeated a choice of an incorrect object they were informed that their response was wrong but not told they had previously selected that object. The repetitions of errors were scored as wrong responses and the repetition of correct responses were ignored. After the object recognition test, the participant performed the location memory test by pointing to the two containers that were used during each trial. The participant was also given a maximum of ten responses to guess the correct containers. After the completion of each trial, the participant remained in the new seat for the next presentation of objects and locations. The participant always moved location at the beginning of the one-minute

delay. At the end of the entire test, the participant had experienced all four views of the board during the object recognition test and the location memory test.

C) Nine Box Maze. For the remaining nine trials, the participants were informed that instead of using two objects and two containers, four objects would be placed in four containers (eight pieces of information). They were also told that if they successfully recalled all eight pieces of information during four consecutive trials the test would be over and they would not need to complete all nine trials. The one-minute delays were the same throughout the entire test. For the first part the participant would change their seating position and for the remainder of the time were given the NART. Throughout all the trials the objects and containers were randomly selected prior to the experiment.

3.8.1.2.2 Anxiety Evaluation

3.8.1.2.2.1. State-Trait Anxiety Inventory (Form Y-1) (Spielberger, 1983)

This self-evaluation questionnaire was administered to the patients at the beginning of the testing session to measure the patient's subjective state anxiety (Spielberger, 1983). The instructions for responding to the questionnaire were placed at the top of the page. The patients were asked to read 20 statements (questions pertaining to how they felt at that time) and to provide a score for each questions using a four-point scale (1 = not at all, 2 = somewhat, 3 = moderately so, 4 = very much so).

3.8.1.2.2.2 Visual Analogue Anxiety Scale

This scale presented to the patient group was administered before and after the testing session. The patients were asked to rate how they were feeling at that moment by marking the corresponding number on the line. The numbers for each of the four scales ranged from 1 – 7. The first scale of the questionnaire, the word 'tired' was on one end

of the line and was marked as number one and the word 'energetic' was at the other end of the line marked as number seven. The patients were required to mark a number between 1-7 depending on how they were feeling, numbers closer to the number one indicated tiredness, whereas, marking numbers closer to seven indicated they were more energetic than tired. The following scales (Sad-Happy, Relaxed-Tense, and Calm-Anxious) were set up in a similar manner.

3.8.2 Data Analysis

Scores on the neuropsychological tests were used as the dependent variables and group membership (Panic disorder patients and healthy control subjects) was the independent variable in the statistical analyses. Most data were analysed using One-Way and Repeated Measures ANOVA, with test scores as the within factor and group membership as the between subjects factor. Scores obtained from the Visual Picture Recognition test were analysed using a Repeated Measures ANOVA. Reaction time scores obtained from the Visual Picture Recognition test were also analysed using an Independent Samples T-test. Number of correct responses were analysed in a One-Way ANOVA for the General Semantic Knowledge test, Buschke Selective Remainder test. An Independent Samples T-test was used to analyse the error scores obtained from the Route Learning test and the Nine Box Maze test. The combined scores (England and Scotland scores) from the Topographical Localisation test were analysed using an Independent Samples T-test and a Repeated Measures ANOVA was used with Region (England and Scotland) as the within factor and group as the between factor.

3.8.3 Results

3.8.3.1 Word Recognition Test

A One-Way ANOVA using the percent correct scores (F (1, 12) = .139, ns, partial eta^2 = .01), the d' scores (F (1, 12) = .540, ns, partial eta^2 = .043), and β scores (F (1, 12) = 1.74, ns, partial eta^2 = .127) revealed no significant differences in performance between the two groups. A graphical depiction of the percent correct scores for both groups is shown in Figure 1. Performance scores on this test are also shown in Table 1.

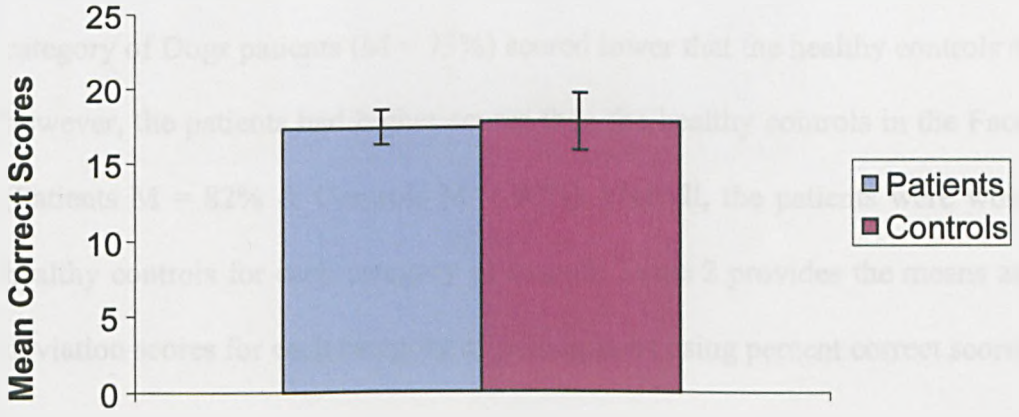

Figure 3.1. Mean (SD) percent correct scores on the Recognition of Words Test achieved by the patients and healthy control subjects.

Table 3.1. *Means (SD) on the Word Recognition test achieved by the patients and healthy control subjects.*

Group	Mean (SD)
Patients	17.4 (2.2)
Controls	17.7 (3.8)

3.8.3.2 Visual Picture Recognition Test

The Visual Picture Recognition test required participants to encode and recall unfamiliar photographs of four different types of visual stimuli (Buildings, Landscapes, Faces, and Dogs). The proportion of correct responses across the four categories were compared using a 2 x 4 Repeated Measures ANOVA with type of stimuli (buildings, landscapes, faces, and dogs) as a within factor and group (patients and controls) as a between factor. No significant difference between the two groups was found, ($F(1, 11) = 1.41$, ns). Although no significant differences were found between the groups, the patients did score poorly for the category of Buildings (Patients M = 72% & Controls M = 76%) and Landscapes (Patients M = 67% & Controls M = 79%) as predicted. In the category of Dogs patients (M = 73%) scored lower that the healthy controls (M = 79%); however, the patients had higher scores than the healthy controls in the Faces category (Patients M = 82% & Controls M = 80%). Overall, the patients were worse than the healthy controls for each category of stimuli. Table 2 provides the means and standard deviation scores for each category of photographs using percent correct scores.

Table 3.2. *Mean and SD scores for all categories of stimuli on the Visual Picture Recognition test.*

	Patients	**Controls**
Visual Picture Recognition	**Mean (SD)**	**Mean (SD)**
Dogs	73% (5.3)	79% (7.9)
Buildings	72% (7.4)	76% (9.9)
Landscapes	67% (9.2)	79% (10.6)
Faces	82% (6.4)	80% (7.0)

A significant effect of stimuli category was found, ($F(3, 33) = 4.14$, $p < 0.05$) however, no interaction was found, $F(3, 33) = 2.48$, ns. When each individual category was analysed using one-way ANOVA's, only a significant difference was found between groups for the landscape category, ($F(1, 13) = 5.10$, $p < .05$). No other category reached significance (Figure 2).

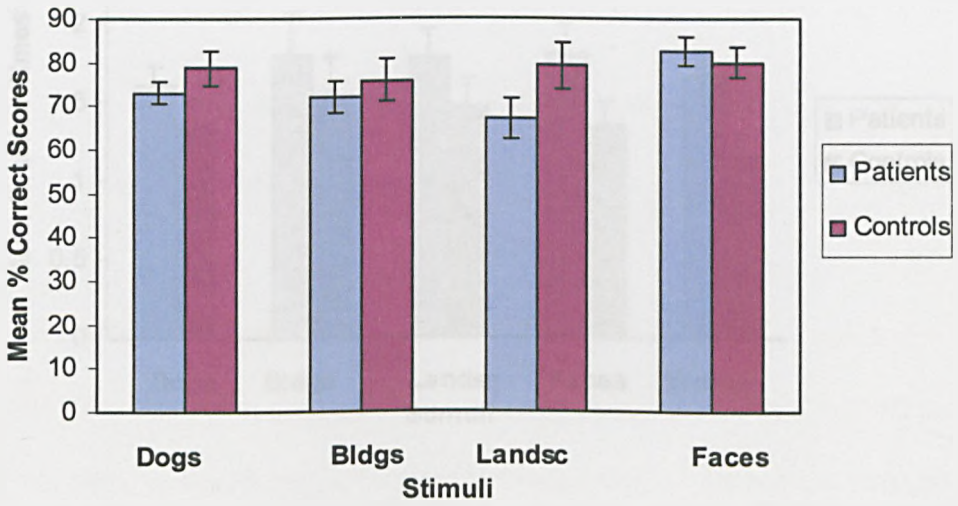

Figure 3.2. Mean percentage correct scores for all stimuli in the Visual Picture Recognition test.

A Repeated measures ANOVA using d' scores also did not reveal a significant difference between the groups, $F(3, 33) = .576$, ns. A main effect for type of stimuli was found, ($F(3, 33) = 4.04$, $p < .05$). There was, however, no significant interaction ($F(3, 33) = .255$, ns).

Independent Samples T-test, were also carried out using the reaction times collected from both groups in response to the four categories of visual stimuli. It was expected that the patients would be significantly slower at recognising the stimuli that were dependent on hippocampal functioning (e.g. Buildings and Landscapes) compared to the Dogs and Faces stimuli. Although the patients were slower for the Buildings,

Landscapes and Dogs stimuli, the results were not significantly different between the two groups of participants. A difference, however, was found between the performance of the two group's for Faces ($t(12) = 2.49$, $p < .05$), and Words ($t(12) = 3.27$, $p < .05$), with the patients being significantly slower than the healthy controls (Figure 3).

Figure 3.3. Mean reaction time scores for all stimuli in the Visual Recognition test.

3.8.3.3 Topographical Localisation Test (Lezak, 1997)

A 2 x 2 Repeated measures ANOVA was used to analyse the performance of the groups using separate Scotland and England scores obtained from the test and an Independent Samples T-test was used to analyse the combined score (England and Scotland). No significant difference emerged between the groups on this test, ($F(1, 12) = 1.53$, ns). Figure 4 illustrates the mean error score (total map score) in centimetres for both the patient group and control group.

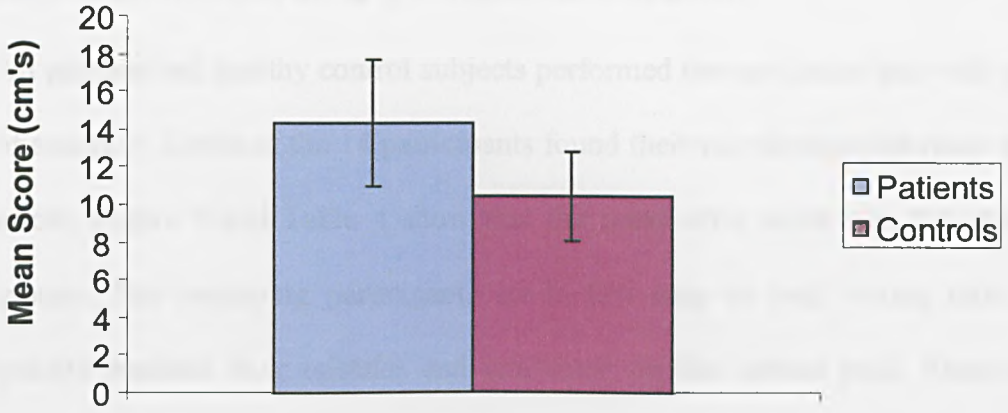

Figure 3.4. Combined mean (SD) scores achieved on the Topographical Localisation task by patients and healthy control subjects.

A main effect for region was found, ($F(1, 12) = 30.54$, $p < .001$), but there was no significant interaction ($F(1, 12) = .099$, ns). Analysis using the combined scores also did not show a significant difference in performance between the two groups, ($t(12) = 1.23$, ns) (partial eta^2, Scotland = .179; England = .041; Combined = .113). Table 3 shows the mean scores obtained by the patient and healthy control subjects. The patients did not show greater difficulties in locating cities on a map of the United Kingdom.

Table 3.3. *Mean and Standard Deviation (SD) error scores by both patients and controls on the Topographical Localisation test.*

	Patients	**Controls**
Topographical Localisation	**Mean (SD)**	**Mean (SD)**
Combined Score	14.3 (6.9)	10.4 (4.7)
Scotland	4.4 (3.5)	2.2 (1.4)
England	9.9 (4.3)	8.2 (4.2)

3.8.3.4 Route Learning Test (Barrash et al. 2000)

All patients and healthy control subjects performed the navigation test with a high level of accuracy. Seven of the 14 participants found their way through the route without any errors. Figure 5 and Table 4 show that the mean error score was the same for both groups. The remaining participants made few (one or two) wrong turns, but very quickly realised their mistake and continued on the correct path. Results from the Independent Samples T-Test showed no significant difference between the two groups, ($t(12) = .00$, ns, partial $eta^2 = 0$). The patients did not have a greater difficulty learning the route compared to the healthy controls.

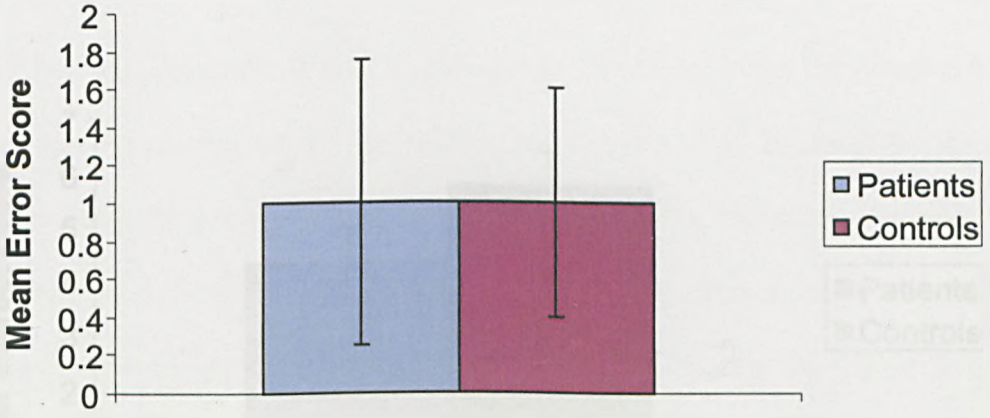

Figure 3.5. Mean number of errors on the Route Learning Test by Panic disorder patients and healthy control subjects.

Table 3.4. *Patient and Healthy Control Subject's Mean (SD) error scores on the Route Learning Test.*

Group	Mean (SD)
Patients	1.0 (1.5)
Controls	1.0 (1.2)

3.8.3.5 General Semantic Knowledge Test (WAIS-III)

An Independent Samples T-test did not reveal a significant difference between the two groups' means, (t (12) = 1.94, ns, partial eta^2 = .239). Figure 6 and Table 5 show the mean correct scores for the patients and healthy control subjects.

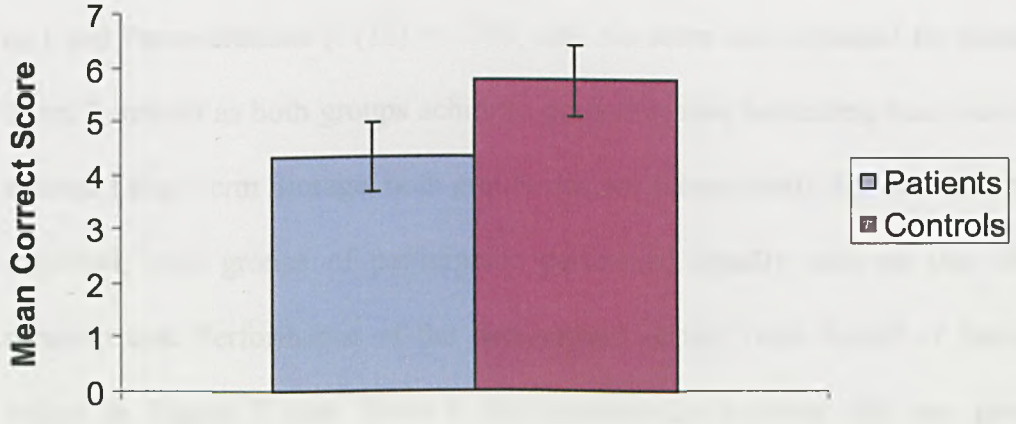

Figure 3.6. Mean correct values obtained by the patients and healthy controls on the General Semantic Knowledge test.

Table 3.5. *Mean (SD) correct scores on the General Semantic Knowledge test.*

Group	Mean (SD)
Patients	4.29 (1.5)
Controls	5.71 (1.25)

3.8.3.6 Buschke Selective Reminder Test

An Independent Samples T-test showed that the two groups did not differ from each other on the five variables produced from this test, Items Total Recall (t (12) = -.472, ns, partial eta^2 = .018), Long-Term Retrieval (t (12) = -.031, ns, partial eta^2 = 0), Short-Term Retrieval (t (12) = -.367, ns, partial eta^2 = .011), Long-Term Storage (t (12) = .044, ns, partial eta^2 = 0), Consistent Long-Term Retrieval (t (12) = -.782, ns, partial eta^2 = .048), Reminder (t (12) = .250, ns, partial eta^2 = .005). Intrusions (t (12) = -1.91, ns.) and Perseverations (t (12) = -.303, ns). No score was obtained for Random Long-Term Retrieval as both groups achieved perfect scores, indicating that once a word had entered Long-Term Storage, both groups did not subsequently fail to recall the word. As expected, both groups of participants performed equally well on this verbal recall memory test. Performance of the two groups on the Total Recall of Items is shown below in Figure 7 (see Table 6 for performance between the two groups on all variables).

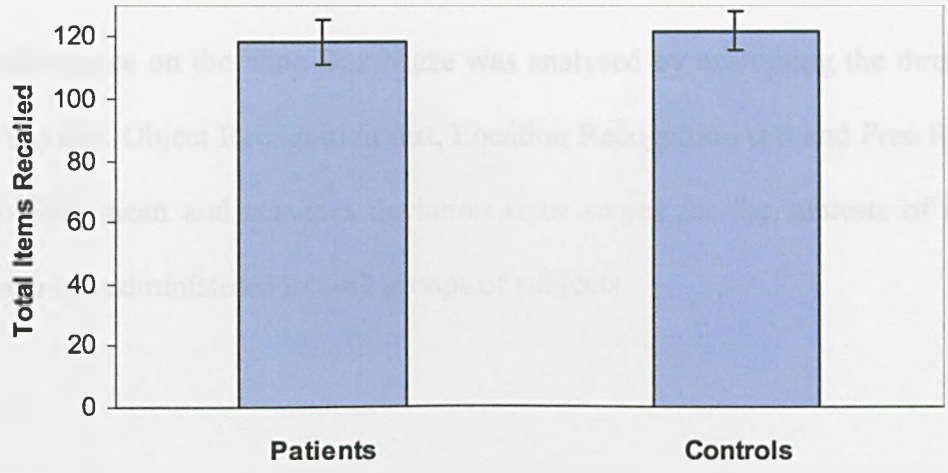

Figure 3.7. Mean scores for the Total Items Recalled on the Buschke Selective Reminder Test by the patients and healthy controls.

Table 3.6. *Mean (SD) scores achieved on the Buschke Selective Reminder test by panic disorder patients and healthy controls.*

	Patients	**Controls**
Buschke Selective Reminder Test	**Mean (SD)**	**Mean (SD)**
Items Total Recall	118.29 (14.85)	121.71 (12.20)
Long-term Retrieval	90.14 (27.71)	90.57 (23.84)
Short-Term Retrieval	28.43 (13.48)	31.14 (14.18)
Long-term Storage	102.57 (23.95)	102.00 (24.19)
Consistent Long-Term Retrieval	71.29 (44.06)	86.86 (28.86)
Reminder	37.00 (13.94)	35.29 (11.66)
Intrusions	0 (0)	2 (2.77)
Preservations	1.71 (1.70)	2.14 (3.34)

3.8.3.7 Nine Box Maze

Performance on the Nine Box Maze was analysed by examining the three components of the test: Object Recognition test, Location Recognition test and Free Recall. Table 7 provides mean and standard deviation error scores for the subtests of the Nine Box Maze test administered to both groups of subjects.

Table 3.7. *Mean (SD) error scores and percentage on the components of the Nine Box Maze Test for the patients and healthy control subjects.*

	Patients	**Controls**
Nine Box Maze	**Mean (SD)**	**Mean (SD)**
Object Recognition	8.3 (5.4)	8.0 (5.8)
Location Recognition	10.6 (4.5)	10.3 (7.9)
Recall	.86 (.69)	.86 (.38)

For the non-topographically relevant tests (object recognition and recall) neither analysis approached significance (object recognition test, t (10) = .319, ns, partial eta^2 = .008; recall test, t (10) = -1.58, ns, partial eta^2 = .172). The location memory test that examined topographically relevant stimuli also revealed no significant differences between the groups, (t (11) = -3.29, ns, partial eta^2 = .474). Judging from their performance, the patients did not find any of the subtests of this spatial memory test more difficult than the non-spatial components (See Figures 8-10).

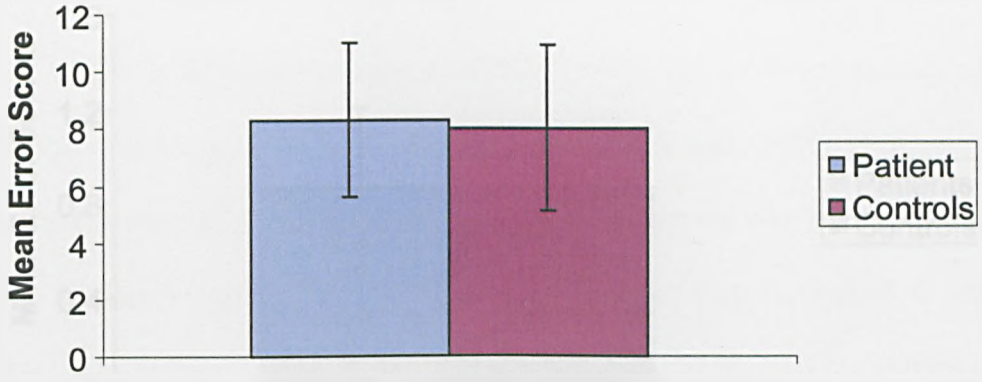

Figure 3.8. Mean (SD) error scores on the Object Recognition subtest of the Nine Box Maze test for the patients and healthy control subjects.

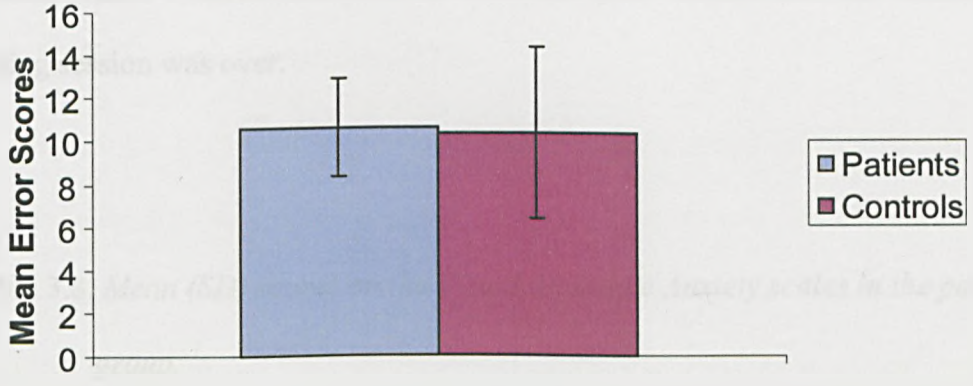

Figure 3.9. Mean (SD) error scores on the Location Recognition subtest of the Nine Box Maze test

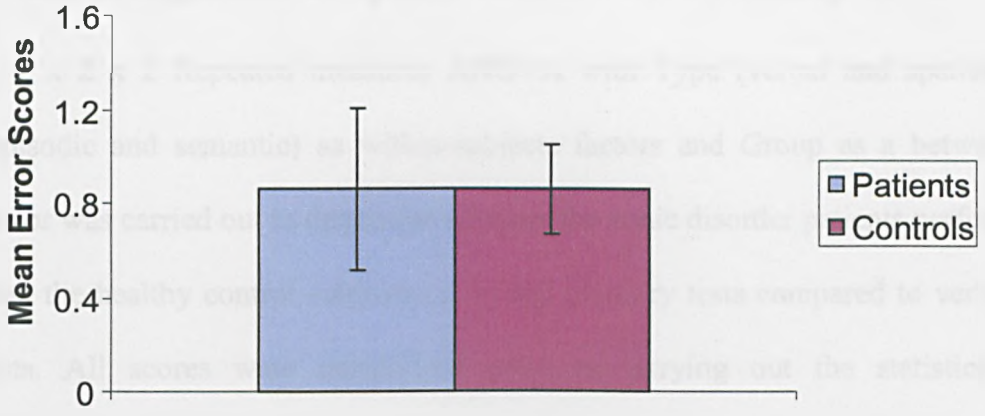

Figure 3.10. Mean and (SD) scores on the Recall subtest of the Nine Box Maze test achieved by the patients and healthy control subjects.

3.8.3.8 Anxiety Scale

Overall, the patients showed the same level of tiredness before and after the testing session. Table 8 shows that patients were also more relaxed and less anxious after the testing session was over.

Table 3.8. *Mean (SD) scores on the Visual Analogue Anxiety scales in the patient group.*

	Before	**After**
Scales	**Mean (SD)**	**Mean (SD)**
Scale 1 (tired - energetic)	3.49 (1.09)	3.50 (1.26)
Scale 2 (sad - happy)	3.94 (.472)	4.50 (.764)
Scale 3 (relaxed - tense)	5.26 (1.41)	4.26 (1.50)
Scale 4 (calm - anxious)	5.07 (1.37)	4.36 (1.49)

3.8.3.9 Comparison of Spatial Versus Verbal Memory Tests

A 2 x 2 x 2 Repeated measures ANOVA with Type (verbal and spatial) and Test (episodic and semantic) as within-subjects factors and Group as a between-subjects factor was carried out to determine whether the panic disorder patients performed worse than the healthy control subjects on spatial memory tests compared to verbal memory tests. All scores were normalised prior to carrying out the statistical analysis. Normalised data was calculated by dividing the individual score by the mean score for for each test and multiplying by 100. There was no difference in performance between the two groups of subjects for the verbal and spatial memory tests, $F(1, 12) = .07$, ns. No main effect for type was found to be significant, ($F(1, 12) = 3.02$, ns), and no interaction was found, ($F(1, 12) = 2.82$, ns). No significant main effect for test, ($F(1, 12) = .33$, ns), and no interaction was found between type and group, ($F(1, 12) = .31$, ns).

3.8.3.10 Correlational Analyses

No significant correlations emerged using Pearson correlation calculations to examine the relationship between the patient anxiety scores on the STAI scale and the performance on the neuropsychological tests. STAI with the d' scores from the Visual Picture Recognition Test revealed the following results: Building, $r = -.55$, ns, Landscapes d' scores, $r = .091$, ns, and Words d' scores, $r = .397$, ns. The following non-significant correlations were found for the Route Learning test, $r = .273$, ns, Topographical Localisation test: England scores, $r = .359$, ns, and Scotland scores, $r = .203$, ns.

3.8.4 Discussion

The battery of neuropsychological tests administered in this pilot study were designed to assess different aspects of memory functioning. The results of this study found no statistically significant group differences between panic disorder patients and healthy control subjects in performance on the verbal and visuospatial tasks. However, results from the Recognition of Visual Stimuli test gives indication for further investigation into tests measuring topographical and spatial information. Analysing the categories of stimuli presented in the Recognition of Visual Stimuli test revealed a significant difference between the two groups for the category of Landscapes. The results of the present test illustrate the importance of the parahippocampal gyrus for topographical memory as discussed by Maguire et al. (2001) and Aguirre, Zarahn, and D'Esposito (1998). Studying a group of healthy control subjects, Maguire et al. (2001) found that the encoding of both buildings and landscapes was associated with activation of left and right parahippocampal gyri compared to the control group of faces and animals photographs. In addition, the recognition of buildings and landscapes gave rise to activation of the right parahippocampal gyrus, right posterior cingulate cortex, and right inferior frontal gyrus compared to the control task. Although these researchers demonstrated that buildings and landscapes activate a similar set of brain regions, the deficits in recognising Landscapes but not Buildings (also dependent on topographical memory) in this study may be due to the complexity of the Landscape stimuli compared to Buildings. The absence of a significant group difference on the Route Learning test might be attributed to a ceiling effect. Designing a more complex route might have resulted in a greater difference in performance between the patient and control group.

The patients performed within the same level of accuracy as the healthy control subjects on the verbal memory tasks (dependent on left hemisphere functioning). These findings

support the hypothesis of the study that patients with panic disorder might have deficits associated with right hemisphere functioning and not of left hemisphere functioning.

The battery of tests selected in this study was taken primarily from studies that examined patients with lesions to the hippocampal region. Therefore, using spatial and topographical tests taken from lesion studies may not be capable of detecting subtle damage that may be present in panic disorder patients. Unfortunately, due to the nature of a MRI scan, none of the seven panic disorder patients were able to complete an entire scanning session. Therefore, no imaging data were available for these patients. Obtaining structural imaging data could have determined whether these patients did have any structural abnormalities as reported in previous studies and also if there were any group differences between the subjects. As no imaging data was obtained from this group of panic disorder patients, it cannot be determined whether they exhibit regional brain atrophy. In addition, imaging data might have established whether atrophy of the right PHG and surrounding areas contributed to the impairment in recognising Landscapes.

A major limitation of this study is the small sample size that was examined, despite being a pilot study. A larger sample of subjects could have improved the statistical power of the analyses, which could have increased the likelihood of detecting any subtle deficits associated with panic disorder. Further studies should also include a control test to match for task difficulty. As mentioned earlier, the deficits found for the Landscape category could possibly be due to the complexity of the photographs compared to the other stimuli. In addition, the tests in the current study were not all standardised tests (e.g., General Semantic Knowledge, Visual Picture Recognition, and Route Learning test). It is also important to acknowledge that the group of panic disorder patients studied were on maintenance medication. Greater impairments in learning and recall of topographical behaviour may be observed if these patients were not on medication. It is

also possible that the extent of the impairment may be related to the severity of symptoms. Therefore, further studies need to examine the influence of medication status, as well as, symptom severity. The Spielberger (1983) STAI scale administered to the patients measured subjective anxiety before the testing; however, a measure of symptom severity was not obtained.

It is also unclear whether a more appropriate comparison group could be a likely explanation as to why these patients did not show significant impairments on the other tasks that measured spatial and topographical memory (e.g. Topographical Localisation task, Route Learning Task, Buildings stimuli, and the Nine Box Maze test). Perhaps including other psychiatric disorders will explain whether deficits observed in the current study are specific to panic disorder or implicated in psychiatric illnesses. For example, a control group of medicated patients with depression could have controlled for overall illness effect and medication status. In addition, individuals with depression may have shown a different pattern of impaired performance, as there is evidence that clinically depressed patients might have rCBF abnormalities in the prefrontal cortex and anterior cingulate (Dolan et al., 1994; Awata et al., 1998). Future studies should also take into consideration that the effects of drugs vary depending on whether anti-depressants or anxiolytics are administered, since most panic disorder patients respond to anti-depressants (i.e. serotonin reuptake inhibitors).

Despite the small sample size, this study has given insight into future directions that will perpetuate further research to gain a better understanding of the neuropsychological markers of panic disorder. In addition, this study has provided the earliest line of evidence that the findings of temporal lobe reduction and PHG abnormalities in panic disorder might conceivably contribute to memory dysfunction, supporting previous evidence that these limbic structures are very sensitive and their function may be easily

disrupted by severe anxiety disorders such as those experienced by patients who develop panic disorder.

CHAPTER 4 Post-Traumatic Stress Disorder

4.1 Definition

Vast majorities of people are exposed to life threatening assaults (sexual assaults, physical attack, robbery, and mugging), accidents, natural disasters, war, and diagnosis of a life threatening illness or other very stressful events. For example, road traffic accidents and/or witnessing death or serious injury to others have often resulted in a diagnosis of Post-Traumatic Stress Disorder (PTSD), it is estimated that 90% of the American population experiences at least one traumatic event in their life (Breslau, Kessler, Chilcoat, 1998). Many individuals can overcome their exposure to a traumatic event; however, others develop PTSD, a form of anxiety disorder.

In the United States, however, it is estimated that only 9-15% of the population develop PTSD following life threatening or horrifying traumatic events and approximately one-half of these individuals develop chronic PTSD (Breslau et al., 1998; Kessler et al., 1995). Acute PTSD sufferers experience symptoms within the first three months of the event; however, chronic PTSD symptoms may last several years or possibly an entire lifetime (American Psychiatric Association, 1994). The prevalence rates for traumatic events are as follows: Vietnam combat veterans 31% for males, 37% for females, Civil Violence 23%, Major Flood 44%, Major Transportation disaster 54%, Road traffic accidents 10%, burns 35%, and Rape and sexual assault of women 57% (Hull, 2004).

Similar to other anxiety disorders, the symptoms of PTSD interfere with normal daily life activities and impair cognitive, emotional and behavioural functions (Joseph, Williams, and Yule, 1997). Symptoms of this devastating condition occur through

nightmares and flashbacks, numbing of general responsiveness and withdrawal from other people, and hyperarousal (irritability, sleeping problems, fearfulness, nervousness and agitation) (Joseph, Williams, and Yule, 1997). Flashbacks are re-occurring, involuntary vivid recollections of the traumatic experience. The following are considered the main symptoms of PTSD; intrusive phenomena, avoidance and numbing symptoms, and hyperarousal symptoms (Hull, 2004). The category of intrusive phenomena is comprised of recurrent distressing recollections, nightmares, flashbacks, distress with reminders and physiological reactions of either fight or flight. Avoidance and numbing symptoms involve the patient avoiding reminders of the event, avoiding thinking or talking about the event, psychogenic amnesia, loss of interest, detachment, emotional numbing and the sense of a foreshortened future. Hyperarousal symptoms affect the patient's sleep, cause irritability and anger, concentration difficulties, hypervigilance, and an exaggerated startle response. Other symptoms of PTSD include headaches, gastrointestinal discomfort, immune system problems, poor memory, instability, dizziness, chest pain, and discomfort in other areas of the body (Clayer, Bookless-Pratz, & Harris, 1985). The symptoms must be present for one month and may interfere with early detection of PTSD. Many patients may complain of these physical symptoms without being aware that the onset occurred after the exposure to a traumatic event. Often patients do not disclose such information unless the physician asks the individual.

4.2 Diagnostic Criteria

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) (1994) the following six categories need to be present for a diagnosis of PTSD:

1. The person has been exposed to a traumatic event in which both of the following were present: the person experienced, witnessed, or was confronted with an event or

events that involved actual death or serious injury, or a threat to the physical integrity of self or others. The person's response involved intense fear, helplessness, or horror.

2. The traumatic event is persistently re-experienced in one (or more) of the following ways:

(a) recurrent and intrusive distressing recollections of the event, including images, thoughts or perceptions.

(b) recurrent distressing dreams of the event.

(c) acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated.

(d) intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

(e) physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

3. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:

(a) efforts to avoid thoughts, feelings, or conversations associated with the trauma

(b) efforts to avoid activities, places or people that arouse recollections of the trauma

(c) inability to recall an important aspect of the trauma

(d) markedly diminished interest or participation in significant activities

(e) feeling of detachment or estrangement from others

(f) restricted range of affect (e.g., does not expect to have a career, marriage, children, or a normal life span)

4. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:

(a) difficulty falling or staying asleep

(b) irritability or outbursts of anger

(c) difficulty concentrating

(d) hypervigilance

(e) exaggerated startle response

5. Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month)

6. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

Acute: if duration of symptoms is less than 3 months

Chronic: if duration of symptoms is 3 months or more

Specify if:

With Delayed Onset: if onset of symptoms is at least 6 months after the stressor (American Psychiatric Association, 1994: DSM IV, p.427).

4.3 Prevalence

Some authors have suggested that an individual's experience of a traumatic event is quite idiosyncratic; what one individual might class as being very disturbing may not hold true for another individual that experiences the same event. However, the following traumatic events have been the most common for generating PTSD symptoms: natural disasters, technological disasters, combat, sexual assault, childhood sexual abuse, political violence, and being a refugee. It is likely that any individual that experiences a serious life-threatening event or an event that causes serious injury will result in the development of PTSD. It was found that 80% of females who were raped, experienced life-threat or physical injury developed PTSD (Kilpatrick et al., 1989, as cited in Joseph, Williams & Yule, 1997). From these findings, the authors have suggested that the intensity and the nature of the event are strong factors that play a role in the individual's response to the event. Wounded Vietnam veterans had a 20% prevalence rate whereas; those veterans that were not wounded had a small 3.5% prevalent rate (Helzer, Robins, & McEvoy, 1987, as cited in Blake, Weathers, Nagy, Kaloupek, Gusman, Charney, et al., 1995). The prevalence rate for veterans exposed to heavy combat was 27% compared to a prevalent rate of 19% for all veterans. A total of 25-50% of Veterans with minimal exposure to combat met the full criteria for PTSD compared to the 70% of veterans that were exposed to very high levels of combat (Foy

et al., 1987, as cited in True, Rice, Eisen, Heath, Goldberg, Lyons et al., 1993). The authors also found the following factors to be crucial in the onset of PTSD: being wounded, witnessing of deaths of non-veterans, and exposure to carnage. In addition, the probability of developing PTSD is 13 times greater in veterans that have experienced very intense events when measured 45 years later compared to those individuals who were non-combat veterans (Spiro, Schnurr, & Aldwin, 1994).

However, data from community-based studies have shown that 1-14% of the population has a lifetime prevalence rate for PTSD. However, examining individuals at risk (e.g., combat veterans, victims of volcanic eruptions or criminal violence) have shown rates ranging from 3-58% (American Psychology Association, DSM-IV, 1994). Perkonigg, Kessler, Storz and Wittchen (2000) reported a lifetime prevalence rate for females of 12.3% from a telephone survey in the United States conducted by Resnick et al. (1993). Breslau, Davis, Andreski and Peterson (1991) reported that 10.4% of females and 6% of males had a lifetime history of PTSD. Rates for males were found to be 5% and 10.4% for females in the United States National Comorbidity Survey. The authors also reported that the lifetime prevalence for PTSD of the population of the United States between the ages of 15-55 was 7.8% (Perkonigg et al., 2000). Surveys have also indicated that at an early age, individuals may experience traumatic events and the probability of developing PTSD is extremely high among the 15-24 year age range (Kessler et al., 1995). The prevalence of PTSD in this age group is 2.8% for males, and 10.3% for females. Breslau et al., (1991) and Breslau et al., (1998) found that traumatic events peak between the ages of 16-20 years of age.

4.4 Consequences of PTSD

This mental condition is associated with changes in physiology and neurobiology. Patients may experience symptoms relating to cognitive functions, circulatory,

neuromuscular, digestive, and respiratory symptoms, as well as various other conditions (Clayer, Bookless-Pratz, & Harris, 1997). Some neurological symptoms include dizziness, headaches, change of consciousness, depersonalization, derealisation, blurred vision, and pupillodilation. Circulatory impairments include a pounding heart, irregular beats, tachycardia, angina, and pallor. Neuromuscular symptoms of this disorder may consist of any or all of the following: paresthesia, tremor, tetany, bruxism, temporomandibular pain, tension headache, fibromyalgia, intercostals muscle pains, sudden exhaustion, and muscle weakness. Digestive complaints may include any of the following: difficulty swallowing, esophageal spasms, bloating and belching, nausea and vomiting, abdominal pains, and acute diarrhoea. Respiratory problems experienced by PTSD patients include: breathlessness, irregular breathing, sighs, breath-holding incidents, and hyperventilation. Other symptoms may include, urge to urinate, erections, ejaculations, piloerection, perspiration, skin exanthema, and acute fever. Other reported health problems include: tiredness, renal disorders, infectious diseases and problems of the immune system (Clayer, Bookless-Pratz, & Harris, 1997). During an examination, a medical doctor may also find any of the following signs or symptoms: fearful eyes, sharp blood pressure changes, ischemic electrocardiographic changes, leucocytosis, hypokalemia.

There are also physical consequences to experiencing a traumatic event. A patient's own subjective ratings of their physical health are much lower prior to PTSD and these patients are more likely to seek medical help after the onset of PTSD (Joseph, Williams, & Yule, 1997). Social relationships may also be impaired after the exposure to a traumatic event. After a 1983 Australian bushfire, the social interactions between 183 families were compared to 497 families not affected by the bushfire. Eight months and 27 months after the event, there was increased irritability, fighting, withdrawal, and decreased enjoyment from shared activities in the families exposed to the event

(McFarlane, 1987, as cited in Joseph, Williams & Yule, 1997). The results of this study have suggested that PTSD may be associated with poor interpersonal functioning. Goenjian (1996, as cited in Radant, Tsuang, Peskind, McFall & Raskind, 2001) found similar findings from individuals involved in the Armenia earthquake. Marital problems, intrafamilial and interpersonal violence was present in the group of civilians that were studied. There was also an increased probability of having other psychiatric disorders in individuals with diagnosed PTSD. The comorbidity rate in PTSD with other mental disorders varies from 62-92% (Helzer, Robins, & McEvoy, 1987; Shore, Vollmer, & Tatum. 1989, as cited in Perkonigg et al., 2000; Breslau et al., 1991). Most commonly, this disorder is associated with anxiety, affective and substance abuse disorders (Kessler et al., 1995). The most common comorbid disorders in men with PTSD are alcohol abuse or dependence, major depression, conduct disorder and drug abuse and dependence. The prevalent disorders women have along with PTSD are major depression, simple phobias, social phobias, and alcohol abuse and dependence. Perkonigg et al. (2000) in their sample of 3021 participants with PTSD found that 87.5% suffered from at least one other mental disorder and 77.5% also had two or more disorders along with PTSD. Simple phobias were found to be present in 71.4% of the sample prior to the traumatic event and 85.7% of the sample were diagnosed with this disorder before the onset of PTSD. In addition, panic disorder without agoraphobia was found to occur at roughly the same time of the PTSD diagnosis, whereas, major depression and substance abuse disorders occurred after the onset of PTSD. Other interesting findings from this study were that primary substance abuse disorders also increased the risk of developing future traumatic events. For example, alcohol use disorders significantly increased this risk. In addition, primary anxiety disorders, in particular social and simple phobia and panic attacks increased the risk of secondary traumatic events, but also increased the risk of developing secondary PTSD.

Psychosocial impairments are also known to be associated with PTSD (Ford, Ruzek & Niles, 1996). Studies of Vietnam veterans with PTSD have been found to have problems with their relationships with family members and other interpersonal relationship problems with employment and were found to be involved in more criminal activities.

Changes in neurobiology include alterations of brainwave activity, decreased hippocampal volume and abnormal activation of the amygdala. The hormones involved in the body's response to stress, glucocorticosteroids are also reported to be abnormal with the onset of PTSD. Responses to combat videotapes viewed by eight Vietnam veterans with PTSD and eight Vietnam veterans without a mental disorder were compared using the point biserial statistical analysis (Mason et al. 1986). Over a two week period, the subjects viewed a 14 minute neutral videotape followed by a 15 minute combat video as well as another 30 minute neutral videotape. The session was completed twice, with an approximately two week interval between the two sessions. During one session, the subjects were given an intravenous placebo and in the other session the subjects were given intravenous naloxone. During the videotape, autonomic responses, emotional self reports and blood reports were collected. There was a significant correlation found between the two groups when examining norepinephrine in response to the combat videotapes. The control subjects showed a larger mean norepinephrine response to the combat videotapes than the PTSD subjects. In addition, there was also a significant difference found between heart rate, emotional dimensions (arousal, valence, pleasantness and dominance), and emotional states (happiness, sadness, fear, surprise, anger, disgust, and guilt). Mason et al., (1986) found that norepinephrine and epinephrine were higher, cortisol levels lower and the norepinephrine levels were elevated in PTSD patients compared to other groups of patients tested using urinary samples.

Various other studies have examined the neurochemical changes associated with PTSD and have found alterations in cortisol levels. Researchers have primarily found lower cortisol levels in patients with PTSD; however, it was only evident after exposure to traumatic events and was found to be higher in individuals with exposure to stress (Yehuda, Keefe, Harvey, Levengood, Gerber, Geni et al., 1995; Mason et al., 1986). These findings are quite intriguing as the body releases cortisol in response to stress. It would be expected that cortisol would also be higher in PTSD after exposure to a traumatic event as these events are known to produce high levels of stress (Yehuda, 2002). Many years of research involving different populations of control groups who have experienced stress, has indicated that perhaps PTSD occurs as a response to traumatic events and not as a response to stress. It is suggested that the cortisol receptors in PTSD may be more sensitive, thus, cortisol levels may be lower due to a greater negative feedback inhibition of cortisol. Individuals with this disorder are known to be quite sensitive and may react to non-threatening stimuli as well as threatening stimuli. The sympathetic nervous system and the hypothalamic-pituitary-adrenal axis (HPA) are involved in the body's endocrine response to stress. Therefore, a consequence of inhibition of the negative feedback will be a significant decrease of corticoids at the end of a stressor (Yehuda, 2002). McFarlane, Atchison, and Yehuda, (1997) found that cortisol was lower in individuals who went on to develop PTSD immediately following a traumatic event compared to those who did not develop PTSD after exposure to a traumatic event (as cited in Yehuda, 2002). Cortisol levels were measured approximately one to two hours after a motor vehicle accident and also six months after the accident. The findings do suggest that cortisol levels do change immediately following a traumatic event. Resnick et al. (1995) found that rape victims had lower cortisol levels if they had a history of rape or assault compared to women who had been raped with no such history (as cited in Horner & Hammer, 2002). Low

cortisol levels may be due to the women's past traumatic exposure or to other factors that precede the traumatic event. Bonne, Gilboa, Louzoun, Brandes, Yona, Lester, et al. (2003) studied 11 survivors of civilian-related traumatic events who met the criteria for PTSD, 17 trauma-exposed (Non-PTSD), and 11 nontrauma-exposed healthy control subjects. All trauma survivors were free of medication. All participants had SPECT and MRI scans done within one week after the traumatic event. The patients had cortisol levels drawn between 8:00 am and 9:00 am on the morning of a SPECT scan, 20 minutes after placement of an intravenous (IV) catheter, and immediately before HMPAO injection. Cortisol levels were not taken from the nontrauma-exposed healthy control subjects. The results revealed that cortisol levels were similar between groups and were within a normal range. No significant correlation was found between cortisol and rCBF when all trauma survivors were analysed. However, a significant correlation between cortisol levels and rCBF was found for PTSD patients and control subjects (trauma exposed and without PTSD). Correlations were found between cortisol and rCBF in medial temporal and prefrontal regions. Medial temporal lobes and fronto-cingulate cortex were analysed in detail using the region of interest approach. A highly significant positive correlation was found between mean rCBF in the left medial temporal lobe as well as the right medial temporal lobe. Significant negative correlations were found between mean rCBF in the fronto-cingulate transitional cortex and both left and right amygdalae. In addition, average rCBF in the right medial temporal lobe was significantly higher in the left medial temporal lobe. Although the findings of greater rCBF in the right medial temporal lobe are inconsistent with other studies, the authors have suggested this might be explained by the group of PTSD patients in this study. These patients were also the patients who were studied by Bonne, Brandes, Gilboa, Gomori, Shenton, Pitman et al. (2001), who did not show any progressive hippocampal atrophy after one week of experiencing a traumatic event to

six months following the event. Greater reductions in right sided hippocampal volume may be more evident in cases of severe PTSD.

4.5 Susceptibility

Several factors have been shown to influence the occurrence of PTSD; it is not clearly understood, however, why only a small population of people develop PTSD following exposure to a traumatic, stressful event(s). One possibility is that some individuals are perhaps more vulnerable to developing PTSD whereas others are more resilient to developing PTSD. There may be pre-existing characteristics that contribute to PTSD vulnerability. A genetic predisposition in several disorders, such as panic disorder, suggests that genetics may also have a role in PTSD (Finn and Smoller, 2001). Connor and Davidson (1997) examined 11 studies of World War I or II PTSD patients, five studies included a control group. The studies that examined a control group revealed that the PTSD relatives suffer from psychiatric problems (i.e. nervousness, alcohol abuse, neurocirculatory asthenia and epilepsy). Family studies also examined the risk of children developing PTSD if a parent was diagnosed with the disorder. The authors found that the children's probability of developing PTSD increased by five times if one parent was diagnosed with PTSD (Sack, Clarke & Seeley, 1995). A family background of depression is associated with a twofold increased risk of PTSD compared to control subjects (Breslau, Davis, Andreski, & Peterson, 1991). The presence of anxiety disorders in a family is associated with a 2.4-3.0 higher chance of developing PTSD (Breslau et al., 1991). In addition, psychosis is associated with a 3.89% higher chance, and personality disorder with a 2.4-3.0 higher chance when compared to the control subjects, however, there is no increased risk of PTSD if alcohol abuse or other substance abuse runs in the family (Breslau et al., 1991).

Twin studies using a sample of 2,224 monozygotic and 1,818 dizygotic male twins of Vietnam War Era United States Veterans discovered that some of the PTSD symptoms

of the Veterans are inherited (True, Rice, Eisen, Heath, Goldberg, Lyons et al., 1993). Examining the difference in exposure to trauma between the sets of twins showed 30% of the variance in PTSD symptoms to be due to genetics. Stein, Jang, Taylor, Vernon and Livesley (2002) carried out a second study examining monozygotic and dizygotic twins with PTSD. This work extended the study by True et al. (1993) to examine the data from a population of females as the previous authors exclusively studied male twins. Stein et al. (2002) tested 174 female monozygotic twins and 48 male twins along with 117 dizygotic female twins and 27 male twin pairs. Correlations between the groups using assaultive trauma data revealed that the correlations between monozygotic twins exceeded the correlations between dizygotic twins. This finding suggests that genetics may have a role in the development of PTSD. Examining nonassaultive trauma data, the correlations between the monozygotic twins and dizygotic twins were roughly the same. By comparing intrapair correlations between the twins (sister-sister pairs only and with sister-sister and brother-brother pairs), the magnitude of genetic and environmental effects was the same for both genders. When opposite-sex dizygotic pairs were included in the analysis, a significant drop in the correlation between dizygotic twins was found. These results suggested that although the magnitude of genetic and environmental effects are the same for both genders, they are gender specific. Further analysis with 139 monozygotic twins and 88 dizygotic twins revealed that assaultive trauma was mostly due to additive genetic and nonshared environmental influences whereas an environmental model best explained the variance in nonassaultive trauma. Although this study does provide analysis with a group of female PTSD patients, some drawbacks of the study include the small sample size and the use of self-report questionnaires to diagnose PTSD within the sample.

Other factors that play a role in the development of PTSD may be categorized into three groups: stressor (strength, duration and circumstances of occurrence), personality (age,

previous experience, social support, and history of psychiatric disorders) and organic factors (effects of autonomic nervous system and neurobiology of the brain). Hull (2004) suggested the following categories of risk factors for PTSD: patient-related factors, trauma-related factors, and environmental factors. Factors in the patient-related category include acute stress reaction, serious physical injury, coping styles, personality traits, family or personal history of mental disorder, intelligence, socioeconomic status and level of education. Trauma-related factors include sudden and unexpected events, natural disasters or man-made trauma, prolonged exposure, perceived threat to life, multiple deaths and/or mutilation, personally relevant factors (involvement of a child) or proximity of the trauma. Environmental factors may include ongoing life stresses, reactions of others, economic resources and the absence of a support network or the inability to use a support network when available. Coexisting stressful life events and social environments that create shame, guilt, stigmatisation and self-hatred also contribute to the development of PTSD (Stein et al., 2002; Maes, Delmeire, Mylle & Altamura, 2001; Hull, 2004). Perkonigg et al. (2000) studied a sample of 3021 Munich residents between the ages of 14-24. From this sample it was found that the risk of developing PTSD was greater for older females with a low socioeconomic status who were residing in the metropolitan area of Munich. In addition, in this sample, exposure to sexual abuse and rape, the number of traumatic events experienced and being younger than 12 years when experiencing a traumatic event were found to be significantly associated with PTSD (Perkonigg et al., 2000). The number of traumatic events and the type of trauma were also found to be associated with PTSD using univariate and multivariate analyses. O'Toole, Marshall, Schureck and Dobson (1998) studied a group of 641 males to identify risk factors for PTSD in Australian Vietnam veterans. Examining pre-Vietnam factors, the researchers reported that the only difference between the two groups was that men with PTSD were generally born in later

years than men without PTSD. The other differences that emerged between the two groups of participants were their emotional life at home. Compared to men with no PTSD, men with PTSD reported having bad relationships with their mothers but not their fathers, or brothers or sisters. Fathers of men with PTSD were more affected by their war service versus the men without PTSD. These men with PTSD also reported that their fathers had suffered from emotional problems during childhood. There were significant differences found between the groups on education, school life and scores on cognitive tests. Men with PTSD were more likely to leave school earlier, were at a lower class, and were more likely to have not completed school. On self-reports, these PTSD men regarded themselves as being more involved in extracurricular activities and having a better social life and more girlfriends, but rating themselves worse on conduct and behaviour than males with no PTSD. The PTSD group did not further their education immediately after high school nor did they enter the workforce shortly after completing their education. These men were not employed and often enlisted in the army after spending time travelling. Therefore, these men had a longer gap between finishing school and joining the army. Prior to enlistment, the PTSD men encountered traumatic events such as assaults or muggings but did not experience any events such as death in the family or threat to life or a major accident to themselves or a loved one, divorce or separation, or other unpleasant events. While looking at Vietnam and army service factors, it was reported that these PTSD males were more likely to end their relationship with a girlfriend or a wife while in Vietnam than men without PTSD. Examining combat stress factors revealed that while serving in the war these men experienced more combat exposure (measured by combat exposure scales) and were more likely to be a casualty. In addition, their exposure to traumatic events and the traumatic events they had experienced were more severe than the exposure to traumatic events experienced by non-PTSD males.

Another approach to testing the susceptibility factors in PTSD research is to examine the presence of structural abnormalities. Gilbertson, Gurvits, Lasko, Orr and Pitman (2002) studied a group of 17 pairs of monozygotic twin and 23 pairs of monozygotic twins without PTSD to determine whether smaller hippocampal volume predicted a vulnerability to trauma. The Vietnam Era Twin (VET) Registry determined zygosity and combat status in all twin pairs. A standardised 18-item combat exposure measure was used to assess combat severity and a clinical psychologist diagnosed PTSD status of combat-exposed twins and overall PTSD symptom severity was measured using the Clinician Administered Post-Traumatic Stress Disorder Scale (CAPS). All subjects also underwent a Structured Clinical Interview for DSM-IV (SCID) to determine whether other Axis I mental disorders were present. Subjects were also excluded if they met the criteria for a psychotic or bipolar disorder or non-combat-related PTSD. Because of the high comorbidity of major depression and substance abuse in PTSD, subjects with these disorders were not excluded from the study. A stressful life event checklist that tallied the lifetime number of non-combat events that could have met the DSM-IV PTSD A (stressor) criteria was completed by all subjects, as well as, the Michigan Alcoholism Screening Test (MAST). The results revealed a significant negative correlation between the CAPS score and hippocampal volume for the PTSD twins exposed to combat. A negative correlation between hippocampal volume in unexposed twins and PTSD severity in their exposed PTSD brothers was also found. These results indicate that although the unexposed twins were not exposed to combat (and without PTSD), their smaller hippocampal volumes are in fact related to greater PTSD symptom severity in their combat exposed brothers. PTSD severity remained to be significantly associated with hippocampal volume after adjusting for whole brain volume in the PTSD exposed twins and in unexposed brothers of PTSD combat veterans. Combat severity was not significantly related to hippocampal volume in any of the subjects and alcohol abuse (as

measured by the MAST) was associated with only right hippocampal volume in exposed PTSD twins, this was not found in unexposed brothers of PTSD exposed twins. Brain volume differences in the twin pair groups revealed that the severe PTSD cases, (CAPS > 65) in comparison with non-PTSD cases showed a significant main effect of diagnosis in total hippocampal volume. The exposed and unexposed twin pairs had smaller hippocampal volumes in cases when the combat-exposed brother had greater PTSD severity, however, combat or PTSD status revealed no differences in hippocampal volume between the brothers. The findings from this study suggested that smaller hippocampi might increase the risk of developing PTSD symptoms. The authors of this study suggested that heredity might explain the results observed in PTSD combat veterans and their twins.

4.6 Stress Hippocampus Model

In the last decade, stress has been classified as being dangerous to our physical health. According to Walton Cannon's Fight or Flight theory, the body would not prepare itself for dangerous situations without a release of hormones in a stressful situation. Although stress is a normal response of the body that aids survival, excessive stress has been found to be dangerous to the hippocampus and could result in impaired memory function. Stress also occurs as a result of many disorders and researchers are beginning to study cortisol levels to examine whether a relationship exists between stress and mental disorders. For instance, Alzheimer's disease has been investigated and it has been observed that this disorder is associated with greater cortisol release (Lupien, DeLeon, DeSanti, Convit, Tarshish, Nair et al., 1998, as cited in Lupien & Lepage, 2001). These authors proposed that understanding the relationship between stress and hippocampal damage will perhaps develop methods to monitor cortisol levels in individuals at risk of chronic stress. Early detection of high cortisol levels might prevent

memory impairments that are associated with stress-related damage to the hippocampus. Studies have examined the changes in hippocampal morphology caused by stress and have found that adrenal steroids, particularly glucocorticoids released during a stress response, have adverse effects on the nervous system when released in excessive amounts. Sapolsky (2000) stated that excessive levels of these glucocorticoid hormones kill the CA3 neurons in the hippocampus. These effects, particularly on the hippocampus, can be detrimental because of the critical role this structure plays in encoding, integrating and retrieving memory (McEwen & Sapolsky, 1995).

The clinical studies mentioned in the previous section (section 4.4, Consequences of PTSD) reported chronic stress to be directly associated with PTSD. The aforementioned work has stemmed from animal research that found excessive levels of stress release glucocorticoid steroids, which in turn have been found to cause neuronal atrophy of the hippocampus. Anxiety disorders such as PTSD cause a lot of stress for individuals. The hippocampus is the main area of the brain that mediates stress and has the highest density of receptors for corticosteroids, therefore, is the most affected by excessive stress (McEwen et al., 1986, as cited in Bremner, 1999; Lupien & Lepage, 2001). Recent research has referred to this relationship between stress and memory function as the Stress-Hippocampus Model (Lupien, Gaudreau, Tchiteya, Maheu, Sharma, Nair et al., 1997).

Although it is not certain whether neurological disorders are the underlying cause of stress, or if high stress levels facilitate the occurrence of some neurological disturbances, the hippocampus has been found to play a key role in stress-related psychiatric disorders. Mental disorders such as post-traumatic stress disorder, depression, and schizophrenia have also been reported to show selective atrophy of the hippocampus and right hemisphere dysfunction in some cases. (Sapolsky, 2000; Garcia, 2002; Altschuler et al., 1991, as cited in Bremner et al., 1995). Various studies

exploring hippocampal atrophy in PTSD have revealed significant hippocampal volume differences compared to controls without PTSD (Sapolsky, 2000). Bremner, Randall, Scott, Bronen, Seibyl, Southwick et al. (1995) carried out a study involving 26 male Vietnam combat veterans with PTSD recruited from the inpatient unit of the National Center for PTSD. The patients had no history of meningitis, traumatic brain injury, neurological disorder, HIV-positive diagnosis, current alcohol or substance abuse, lifetime schizophrenia, or any other condition that would complicate the results from the MRI scans. The patients also stopped all psychotropic medication three weeks prior to testing. The researchers hypothesised that PTSD patients would have smaller hippocampal volumes than the 22 control subjects matched for age, education, sex, race, handedness, height, weight, socioeconomic status, and years of alcohol abuse. Results from repeated measure ANOVA indicated significantly smaller (8%) right hippocampal volume in the PTSD patients compared to the healthy controls whereas the left hippocampal volume was smaller (3.8%) but there was not a significant difference between the groups. When years of education and years of alcohol abuse were covaried using ANCOVA, significant difference in volume was found between the patients and the comparison group in the right hippocampal region. Gurvits, Shenton, Hokama, Ohta, Lasko, Gilbertson et al. (1996) measured the hippocampal volume of seven combat-related PTSD patients, seven combat controls subjects without PTSD, and eight normal controls. Patients with organic mental, bipolar, or psychotic disorders, alcohol or other substance dependence or abuse within the past year (as determined by the Structured Clinical Interview for DSM-III-R), neurologic disorders, and history of major head trauma were excluded from the study. The seven PTSD patients did however, have comorbid current or past lifetime Axis 1 disorders (all psychiatric disorders are listed as Axis 1, expect for personality disorders and mental retardation, which are reported on Axis II). In detail, there was one patient with bipolar II, four with

major depression, two had dysthymia, two with panic disorder, one with a simple phobia disorder, one with a social phobia disorder, one with obsessive compulsive disorder and four with generalised anxiety disorder. There were a total of three combat control veterans that had major depression. Their findings revealed that both left and right hippocampal volumes were significantly smaller in the PTSD group. No significant differences emerged between the other two groups. Similar results were obtained using ANCOVA's. Age and whole brain volume covariates revealed significant differences for left hippocampal volume and for right hippocampal volume. No group effect remained for right hippocampal volume after adjusting for lifetime months of excessive drinking and adjusting for combat exposure by adding the Combat Exposure Scale Score as a covariate. The results of this study support previous work that has shown that severe stress from combat service damages the hippocampus. It is still however unclear whether hippocampal atrophy is a risk factor for exposure to combat or whether combat exposure is a vulnerability factor for the onset of PTSD. Recent work however, by Gilbertson, Shenton, Ciszewski, Kasai, Lasko, Orr et al. (2002) found both trauma-exposed and unexposed twin pairs had significantly smaller hippocampi than non-PTSD twin pairs. Therefore, this study suggests that small hippocampal volumes might precede trauma exposure and might be related to an increased vulnerability to develop PTSD. Stein, Koverola, Hanna. Torchia and McClarty (1997) examined 21 women who developed PTSD from childhood sexual abuse and 21 women with no childhood sexual abuse. Participants were selected on a voluntary basis from notices in community women's health care clinics. Severe childhood sexual abuse was determined by a 20-30 minute telephone interview. The healthy controls were free from experiencing any trauma or childhood abuse, as well as Axis I pathology. A total of 15 of the women with a history of childhood sexual abuse met the criteria for PTSD and 15 met the criteria for a dissociative disorder (dissociative

amnesia, N = 1, dissociative identity disorder, N = 5, and dissociative disorder not otherwise specified, N = 9). There were 13 women who had PTSD and a dissociative disorder and six women who met the criteria for major depression, along with one with social phobia and one with obsessive-compulsive disorder. The right hippocampus volumes were found to be 2.9% smaller in the women with childhood sexual abuse compared to the control subjects, whereas, the left hippocampal volume was 4.9% smaller compared to the control group. Repeated measure ANOVA showed there was also a significant main effect of hippocampal size, larger on the left side. Post-hoc analysis (Dunnett's T test) revealed that there was no significant difference in right hippocampal volumes between the groups but the difference reached significance for left hippocampal volume. Scores from the Dissociative Experience Scale (DES) correlated with left hippocampal volumes in the group with childhood sexual abuse. No correlations were found using the clinician administered post-traumatic stress disorder scale (CAPS) score or with the Beck Depression Inventory scores. As with previously mentioned studies, these authors have also stated that hippocampal damage may have been present prior to when the trauma was experienced and/or may be a factor that predisposes development of PTSD after such trauma.

In addition, there are also no consistent findings suggesting that the observed hippocampal atrophy in PTSD may be linked to strictly one hemisphere. Results to date have found either substantial right hippocampal atrophy or substantial left hippocampal atrophy or atrophy of both hemispheres (Bremner et al. 1995; Gurvits et al. 1996; Stein et al. 1997). Some researchers have attributed this lateralisation to when PTSD was developed in the individual. It is speculated that PTSD arising from adulthood results in right hippocampal atrophy whereas, PTSD arising from childhood results in greater left hippocampal atrophy (Bremner et al., 1999). The investigators have stated that a likely explanation for these findings is that the hippocampus continues to develop after birth.

It is speculated that damage to the hippocampus at different stages of development may possibly have different effects on the hippocampus. A more plausible explanation to support lateralisation of atrophy in PTSD might come from work that has suggested that emotional disorders, (i.e., anxiety disorders) show cerebral abnormalities. The right hemisphere has been reported to show hyperactivation, whereas the left shows hypoactivation (Vasterling, Rogers & Kaplan, 2000). It has been documented that anxiety disorder patients show a negative withdrawal emotion (as mentioned previously, symptoms of PTSD include: avoidance, emotional detachment and numbing of responsiveness), therefore, the relationship between PTSD and hyperactivation of the right hemisphere support previous literature that the right hemisphere is involved in emotional processing (Borod, 1992).

Although there is no clear evidence suggesting that stress-related atrophy should be lateralised, Hull (2002) explained these findings as a result of not studying a sufficiently broad variety of PTSD patient populations. The studies that have been completed to date may not accurately represent the broad spectrum of PTSD patients but rather focus on selected few, i.e., veterans and abuse-related victims. The enormous amount of data that has been collected from combat veterans have also included only male subjects, whereas, the literature on childhood sexual abuse victims and rape victims consists mainly of samples of women. In addition, it is important for researchers to take into account that this disorder has also been found to be associated with alcohol abuse and as mentioned earlier, co-morbidity with other psychiatric disorders is also prevalent in most cases. It is important, therefore, to identify other factors that may cause hippocampal atrophy. The studies that have investigated hippocampal atrophy in PTSD have not always used appropriate control groups for comparison (Hull, 2002). It is especially important to use control groups that have also experienced trauma but did not go on to develop PTSD as this will determine whether the differences observed are due

to trauma exposure or PTSD itself (Hull, 2002). Other factors, such as methodology should also be taken into account {e.g., diagnostic tools, type of trauma, and type of symptom provocation (i.e., personalised trauma scripts or trauma-related sounds or pictures)}.

Another important question asked by many researchers is whether hippocampal atrophy and smaller hippocampal volumes are a predisposition for PTSD or if hippocampal atrophy and smaller hippocampal volumes occur after exposure to trauma. Bonne, Brandes, Gilboa, Gomori,Shenton, Pitman, et al. (2001) studied hippocampal volume in trauma survivors with PTSD using MRI one week and again six months after exposure to the trauma compared to trauma survivors that did not develop PTSD. Any subjects who suffered from a head injury or physical injury requiring hospitalisation or surgery were excluded. In addition, subjects with a history of neurological disorders, psychotic disorders, PTSD, or substance abuse were not recruited into the study. After 48hours of being admitted to the hospital, the subjects were contacted by a research psychologist who determined whether the subject met the DSM-IV diagnostic criteria A.1[4] and A.2[5] for PTSD. A total of 44 subjects completed the study and a total of 37 completed both MRI sessions. This study did not find reductions in hippocampal volumes between one week and six months after the initial exposure to the traumatic experience. Results also showed that the PTSD symptoms were not significantly different between one week and six months after the onset of PTSD and after exposure to a traumatic event. Three way ANOVAs examining diagnosis (PTSD versus No PTSD), time (1 week versus 6 months), and side (left versus right) as within-subject independent variables and

[4] the development of characteristic symptoms following exposure to an extreme traumatic stressor involving direct personal experience of an event that involves actual or threatened death or serious injury, or other threat to one's physical integrity; or witnessing an event that involves death, injury, or a threat to the physical integrity of another person; or learning about unexpected or violent death, serious harm, or threat of death or injury experienced by a family member or other close associate.

[5] The person's response to the event must involve intense fear, helplessness, or horror (or in children, the response must involve disorganized or agitated behaviour).

hippocampal volume as a dependent variable did not show any significant main effects of diagnosis, time or side.

A significant effect of side was found when the dependent variable was amygdala volume, however, no significant main effect was found for diagnosis and time and no significant interactions were found. Similar results were obtained when using relative volumes and when examining the female subjects separately. Based on these findings smaller hippocampal volumes were not a risk factor for developing PTSD. The findings of this study also indicated that no progressive reduction in hippocampal volume was found between 1 week and 6 months of diagnosis. Importantly, the authors have however stated that such atrophy may be found in chronic or complicated cases of PTSD. Their findings, however, should be taken together with work of Gilbertson et al. (2002) who addressed this issue as they studied monozygotic twin pairs in which one twin was a Vietnam combat veteran and the identical twin had no combat exposure. The results from their study suggested that smaller hippocampal volumes may precede exposure to trauma and represent a vulnerability factor for a pathological response to stress. The results of the study by Gilbertson et al. are consistent with the well established Stress-Hippocampus model (glucocorticoids released in chronic stress responses cause hippocampal atrophy) as their subjects had severe PTSD symptoms (CAPS > 65) whereas overall the participants in the Bonne et al. (2001) study did not have such high CAPS scores (57.90).

Bonne et al. (2003) also examined the relationship between PTSD symptoms and severity and depression symptoms with rCBF using the Clinician Administered PTSD Scale (CAPS), the Mississippi Scale for PTSD (civilian trauma version), Impact of Events Scale – revised (IES), and the Beck Depression Inventory (BDI). Resting state hexamethylpropyleneamineoxime single photon emission computed tomography and magnetic resonance imaging sessions took place six months after trauma. Twenty-eight

survivors of civilian traumatic events (11 with PTSD) and 11 healthy control subjects were examined. The majority of the trauma was caused from motor vehicle accidents, subjects who suffered head injury or physical injury requiring hospitalisation or surgery were excluded. Subjects with trauma exposure were free of any medications and underwent routine physical and blood examinations. In addition, subjects were free from DSM-IV Axis I psychopathology and current or past neurological disorders. Positive correlations between PTSD severity were found with rCBF in the cerebellum/midbrain, right cerebellum, and left occipital gyrus (BA 18; 19). Positive correlations were also found for PTSD symptoms using the Mississippi Scale for PTSD in the right lingual gyrus (BA 19) and middle/left cerebellum. Similar positive correlations were found using the BDI with rCBF in the left occipital gyrus (BA 18; 19) and middle/right cerebellum. The authors have stated that the CAPS correlation with midbrain activation may also represent an increase in locus coeruleus activity in PTSD.

4.7 Neuropsychological Studies and Neuroimaging Studies

Although the preceding studies have shown that PTSD is associated with immediate memory impairments, the literature examining cognitive functioning in PTSD is quite limited and the few studies published show inconsistencies in the results. These differences are commonly attributed to factors such as: comorbidity, trauma aetiology, medication status and methodology. The following section will introduce the studies that have examined memory functioning in PTSD and those studies that have investigated the relationship between hippocampal function and memory performance in PTSD.

Current studies have reported that PTSD is associated with immediate memory deficits. Studies by Bremner, Scott, Delaney, Southwick, Mason, Johnson, et al. (1993) and Bremner, Randall, Scott, Capelli, Delaney, McCarthy, et al. (1995) found PTSD

patients to score significantly lower on short-term memory tests than healthy control groups. Bremner et al. (1995) compared the memory function of adult survivors of childhood sexual and physical abuse to healthy control subjects. A sample of 21 patients was selected based on their scores from the Early Trauma Inventory (ETI) scale, presence of an Axis 1 disorder determined by a semi-structured interview, the Schedule for Affective Disorders and Schizophrenia Lifetime version (SADS-L). The patients were excluded if they had a history of exposure to combat trauma, schizophrenia diagnosis, alcohol or substance abuse as determined by SADS-L, history of traumatic brain injury or neurological disorder, use of benzodiazepine medication, or a history of unconsciousness for longer than 10 minutes. At the time of the study some patients were on antidepressant medication. Twenty control subjects were matched with the patients for age, gender, race, handedness, height, weight, years of education, years of parental education, and years of alcohol abuse. As with the patients, the controls were excluded if they had history of any of the following conditions: a history of traumatic brain injury, meningitis, neurological disorder, current alcohol abuse determined by DSM-III-R, physical illness, psychiatric disorder, or a history of loss of consciousness for more than 10 minutes. All patients were diagnosed with PTSD and many patients were also diagnosed with an affective disorder (major depression, lifetime dysthymia). Some patients also had comorbid anxiety disorders (current and lifetime panic disorder with agoraphobia, current and lifetime panic disorder without agoraphobia, current and lifetime social phobia, current and lifetime generalised anxiety disorder, and current and lifetime simple phobia). Other diagnoses included bulimia, current and lifetime anorexia and lifetime anorexia. Among these patients, 78% had been diagnosed for alcohol dependence, 6% for alcohol abuse, 17% for sedative/hypnotic/anxiolytic dependence and 6% for abuse, 50% for cannabis dependence and 11% for abuse, 39% for stimulant dependence and 11% for abuse, 28% for opiate dependence and none for abuse, 56% for

cocaine dependence and none for abuse, 6% for hallucinogen/phencyclidine dependence and 11% for abuse, 22% for polydrug dependence and none for abuse. Childhood and physical abuse were determined by the use of self-reports in this study. Both groups of subjects completed four subtests of the Wechsler Adult Intelligence Scale (WAIS-R) that examined arithmetic, vocabulary, picture arrangement, and block design. Two subtests of the Wechsler Memory Scale were administered according to the Russell revision, Russell, 1975 which included Logical Memory, the free recall of two story narratives, and Figural Memory. The Verbal Selective Reminding Test (VeSRT) and the Visual Selective Reminding test (ViSRT) were also administered to both groups. A series of T-tests was carried out and the results revealed that adult survivors of abuse performed poorly on verbal short-term (immediate and delayed) recall but not for percent retention that was measured by the logical memory component in the Wechsler Memory Scale. There was also a significant difference between the adult survivors and the normal subjects in verbal recall (VeSRT). There were no differences in performance on the visual short-term memory test (ViSRT), IQ scores, WAIS-R verbal IQ test and full scale IQ test for the adult survivors of severe childhood physical and sexual abuse and controls. The adult survivors did, however, score lower than the healthy controls. Pearson's product-moment correlations between scores on neuropsychological tests and abuse severity scores (combined physical, sexual and emotional abuse scores) revealed a significant relationship with verbal short-term recall deficits as measured by the WMS Logical immediate recall subcomponent. A correlational analysis revealed that severity of abuse (sum of physical, sexual, and emotional abuse) was related to deficits in short-term verbal recall, as measured by the WMS Logical immediate recall subcomponent, in the PTSD patients. Correlational analyses were carried out using just severity of sexual abuse scores, related to deficits in verbal short-term memory, as measured by the WMS Logical immediate recall subcomponent. No difference was found in IQ between the

early trauma patients and healthy control subjects, there was a relationship found between abuse and IQ. The summed severity scores correlated with decreased performance IQ and severity of physical abuse correlated with decreased performance IQ. Yehuda, Keefe, Harvey, Levengood, Gerber, Geni, et al. (1995) carried out a study of combat veterans and found that although their group of patients performed within normal range on tests of immediate memory, they exhibited specific deficits in the monitoring and regulation of memory information as measured by the California Verbal Learning test. In this study, a total of 20 male combat veterans and 12 control subjects matched for gender, age, race, and years of education were studied. Control subjects with past or current psychiatric assessment as measured by the Schedule for Affective Disorder and Schizophrenia (SADS) were excluded. Any subjects with PTSD or other psychiatric disorders, using psychotropic medications, severe illnesses, neurological disorders, history of head trauma or loss of consciousness were excluded from the study. A team of four clinicians used the Combat Exposure Scale, the Mississippi Scale for Combat-Related PTSD, clinical history and the CAPS score to diagnose PTSD. The Wechsler Adult Intelligence Scale (WAIS) and the California Verbal Learning test were administered to both patients and control subjects. The two groups studied in this experiment did not differ in IQ, age, and years of education. The California Verbal Learning test was comprised of two components, short-term delay and long-term delay. During the first (initial) and last trial (cumulative) there were no group differences for learning List A of 16 words. There was also no significant difference in the acquisition of learning and performance for remembering words from List B. There was, however, a significant decline from learning trial 5 to short-delay free recall (retroactive interference) between the groups with the patients having greater difficulty with recalling of words. The patients were beginning to recall fewer words from word List A after the long delay compared to the controls. The results indicated that patients seemed

to have cognitive deficits as a result of retroactive interference. The second word list that was presented was poorly retained and recalled by the patients perhaps because they were not able to concentrate on the new list of words or perhaps were blocking out the first list.

Bremner et al. (1993) studied a sample of 26 male Vietnam veterans with PTSD who were diagnosed using the DSM-III-R and a sample of 15 male controls. The subjects were assessed using the Addiction Severity Index interview to determine lifetime alcohol abuse, Mississippi Scale for Combat-Related Posttraumatic Stress Disorder that measured current PTSD symptom severity, and the Combat Exposure Scale which is also a self-report questionnaire such as the Mississippi Scale for Combat-Related PTSD. The neuropsychological tests that were administered to both groups included the four subtests of the Wechsler Adult Intelligence Scale-Revised (arithmetic, vocabulary, picture arrangement, and block design tests), and two subtests of the Wechsler Memory Scale that included logical and figural memory tests (Russell version, 1975). Furthermore, both groups completed two components of the Selective Reminding Test and the visual component test of the Selective Reminding test. The PTSD group scored significantly lower on the immediate and delayed recall component of the Wechsler Memory Scale logical (verbal memory) component. The patients scored lower on the figural component of the test (visual memory), but this difference did not reach significance. Taking alcohol abuse into account as a covariate, there was a significant difference for the immediate and delayed recall on the logical component; however, there was also a difference found between the groups in percent retention after multiple comparisons were controlled for. The PTSD patients scored significantly worse on most areas of the verbal and visual component of the Selective Reminding test (areas of total recall, long-term storage, long-term retrieval, continuous long-term retrieval, and delayed recall for both components). The results were also similar again using

ANCOVA with alcohol abuse taken into account. In addition, percent of retention for the Wechsler Memory Scale figural test correlated with the current level of PTSD symptoms.

Gilbertson, Gurvits, Lasko, Orr and Pitman (2001) studied a broad range of cognitive functions (memory, attention, visual spatial skills, and executive function) in a group of combat-exposed veterans with and without PTSD. This study attempted to determine whether poor performances on neuropsychological tests are due to trauma exposure or to the development of PTSD by incorporating a group of non-PTSD combat veterans. A sample of 19 PTSD combat veterans and 13 non-combat veterans took part in this study. The veterans were placed in either current PTSD and non-PTSD groups using the SCID, which was also administered to determine comorbid Axis I diagnoses. The participants were recruited from the Manchester NH Veterans Affairs Medical Center out-patients, a Vietnam Veterans Outreach Center, and from advertisements in the media. The following exclusion criteria was used to obtain a group of participants without any confounding factors known to interfere with performance on neuropsychological tests: history of head trauma and loss of consciousness greater than 10 minutes, brain tumour, epilepsy, cerebrovascular accident, free of psychotropics or other medications with confounding neurological or cognitive effects for at least two weeks prior to examination. The veterans were also excluded if they had a past diagnosis of PTSD, lifetime bipolar or psychotic disorders, alcohol/substance abuse or dependence within the last year. The following are the comorbid Axis I disorders and self-reported developmental problems in the PTSD group: 12 had major depression, 1 had dysthymia, 2 had panic disorder, 1 had agoraphobia, 3 had social phobia, 1 had simple phobia, 2 had generalised anxiety disorder, 1 had somatoform disorder, 9 had past alcohol dependence, 7 had past drug dependence, and 10 had a history of developmental problems or repeated grades. The following are the comorbid Axis I disorders and self-

reported developmental problems in the non-PTSD participants: 1 had major depression, 1 had a social phobia, 4 had past alcohol dependence, 2 had past drug dependence, 1 had a history of developmental problems or repeated grades. In addition to completing a battery of neuropsychological tests, the participants also completed the CAPS assessment, the Combat Exposure Scale (CES), the Beck's Depression Inventory (BDI), and the Michigan Alcoholism Screening Test (MAST) (although participants were excluded who had a current substance abuse/dependence). Four different statistical analyses were conducted in this study, t-test comparisons, a step-wise discriminative analysis, a multivariate regression analysis, and a univariate analyses. The t-test comparisons revealed significant differences between the PTSD combat veterans group and the non-PTSD combat veterans group on all components of the Wechsler Memory Scale (all subscales), the scores on the copy section of the Rey-Osterreith Complex Figure, Form B of the Trail making Test, Symbol Digit Modalities, and on the Wisconsin Card Sorting Test. No significant differences emerged between the two groups on the immediate and delayed recall components of the Rey-Osterreith Complex figure and Trails A on the Trail-making test. However, the poor performance on the memory and IQ tests by the PTSD combat veterans group may be due to the above-average performance of the non-PTSD group. The step-wise discriminant analysis carried out to differentiate PTSD veterans from non-PTSD veterans reported that the Digit Span test (examining Attention) and the General Memory Index subscale of the Wechsler Memory Scale-Revised were significant predictors for differentiating PTSD veterans from non-PTSD combat veterans. The multivariate regression analysis was carried out to determine if factors such as the scores on the CAPS, CES, BDI, and MAST contributed to the performance on the neuropsychological tests as the PTSD combat veterans did score higher on these assessments (higher scores indicate greater symptom severity). The regression variables were eight summary scores taken from the

neuropsychological tests and CAPS, CES, MAST, and BDI scores were used in the analysis as the simultaneous dependent measures. The multivariate model and three of the four separate regression models were found to be significant (CAPS, CES, and MAST). Further stepwise regression analyses, using each of the dependent variables in the multivariate model indicated that the Wechsler Memory Scale-Revised, General Memory component and Digit Span, were the best predictors of PTSD symptom severity (accounting for roughly 58% of model variance). CES was best predicted by performance on the Digit Span test (accounted for 44% of that variable). Past alcohol use, as measured by MAST, was only found to be related to Symbol Digit Modalities (accounted for 47% of the model variance). Overall, CES was related to Attention as indicated by both the multivariate and univariate analyses. A significant negative correlation was found between the BDI scores and performance on the Wechsler Memory Scale-Revised General Memory component and with Attention. There was a significant relationship found between MAST scores and General Memory. Only the univariate analysis revealed a significant relationship to General Memory, Attention, and PTSD severity. The relationship between General Memory and PTSD severity also showed significance after controlling for the effects of IQ. Using the same analyses for Attention yielded similar results. Significant differences between the PTSD combat veterans and non-PTSD combat veterans were found for General Memory and Attention after co-varying for the presence/absence of learning disorder history. This significance remained after removing all subjects with a history of a developmental disorder or repeated grades from the sample. In summary, this study found that PTSD combat veterans demonstrated explicit memory impairments, as measured by the Wechsler Memory Scale-Revised compared to the non-PTSD combat veterans. Significant differences between the groups are also evident after controlling for attentional disturbances and comorbidity. These findings also suggest that such performance on the

memory tests are due to PTSD symptoms and not due to intellectual ability. In addition, PTSD symptom intensity was found to be related to both memory and attention and combat exposure was only found to be related to attention. Therefore, the authors proposed that attentional differences may be due to exposure to trauma and differences in explicit memory may be due to PTSD development.

Nixon, Nishith, & Resick (2004) also carried out a study to examine the impact of prior traumatic experience on neuropsychological performance (short term and delayed verbal memory). The difference of this work from the other literature mentioned is the use of a sample of adult rape victims on treatment, as opposed to combat veterans who are commonly studied. Participants were excluded if they met current criteria for substance abuse/dependence, had a history of head injury associated with loss of consciousness or neurological impairment or psychosis. Of the 73 PTSD participants, 67 had current PTSD and six had subthreshold PTSD. Within the sample, 18% were on psychotropic medications, 39% met the criteria for alcohol dependence, 22% had other drug dependence, and 1% had polysubstance dependence. PTSD was measured using CAPS and Major Depressive Disorder Scale (MDD) and Alcohol and substance dependence was assessed using the SCID. The Sexual Abuse Exposure Questionnaire (SAEQ) and the Assessing Environments-III-Physical Punishment Scale (AE-III-PP) was used to measure the frequency of childhood trauma exposure. In addition, the Quick Test was used to measure general intelligence and Logical Memory I (LM-I) and Logical Memory II (LM-II), taken from the Wechsler Memory Scale-Revised (WMS-R) were used to test verbal memory. Interview questions were also used to determine alcohol use and self-report questionnaires such as the PTSD Symptom Scale (PSS) and the Beck Depression Inventory (BDI) were used to measure PTSD symptom severity and severity of depression respectively. A significant association between memory performance and frequency of high-impact stressors was found and the occurrence/non-

occurrence of childhood rape also correlated significantly with memory performance. The results indicate that performance on Logical Memory was related to estimated IQ, but not for age, education, PSS, BDI, use of psychotropic medication, any alcohol or substance use measures, or any other traumatic experiences. A hierarchical regression analysis revealed that estimated IQ and prior trauma exposure predicted immediate recall on the LM-I (with roughly 27% of the variance in scores being accounted for). Adult trauma exposure was found to predict performance on the delayed recall (LM-II), which accounted for roughly 20% of the variance in scores. Participants who experienced rape as adults compared to those who had not and participants who experienced child rape to those who had not both showed significantly poorer performance on the LM-I and LM-II tests. The findings of this study suggest that experiencing prior trauma in childhood and adulthood do influence short term and delayed verbal memory abilities. Therefore, the authors suggested that the accumulation of stress throughout an individual's life does have an influence on neuropsychological performance, specifically verbal memory.

Memory, attention, function, and mood was assessed in a group of 36 chronic PTSD veterans and a group of 18 age, gender, and education matched controls (Sachinvala, Scotti, McGuire, Fairbanks, Bakst, McGuire et al. 2000). The Posttraumatic Stress Diagnostic Scale (PDS), Hamilton-D Depression Rating Scale, and the Cognitive Evaluation Protocol (CEP) was administered to the PTSD group. The control subjects were only evaluated using the Hamilton-D Depression Rating Scale. The CEP was a computer-based evaluation instrument that consists of 14 subtests that examined short-term and extended memory, attention, functional capacities, and mood (mainly depression). The other two measurements were paper and pencil based tests that assessed PTSD symptom severity and severity of depression. The patients were included in this study based on the following conditions: met the DSM-IV criteria for

PTSD, absence of second Axis 1 diagnosis with the exception of depression, and absence of associated Axis II disorders or substance abuse. Diagnosis of chronic PTSD was given to individuals with persistent signs and symptoms of PTSD over a three year period and without much change in symptoms over the previous year. The authors have stated that a majority of the PTSD subjects were currently taking anti-depressants, none were taking anti-psychotics and six subjects were taking anti-anxiety medication. The results were based only on those tasks that were completed by the subjects as four of the PTSD subjects and one control subject did not complete the entire series of testing. Significant differences were found between the two groups on the Attention tests (Attention – Simple, Double, Reverse), Memory tests (Numbers Recall, Words Recall, Extended Memory), Functional Tests (Clocks, Associations, and Judgment), Mood Tests (Mood Assessment, and Face Test), and on the other category of tests (Reaction Time). The PTSD subjects, however, did not perform significantly worse than the healthy controls on one of the Memory tests, Forms Recall test and on one of the tests in the other category which was the Lexicon-Search. A correlational analysis revealed that the depression scores of the PTSD subjects had an effect on performance on the memory subtest but not on attention. The Hamilton-D Depression Rating Scale scores and the CEP Mood Assessment scores were inversely correlated with performance specifically on the Numbers Recall test and Extended Memory test. Test-retest scores also showed very little change in performance in the PTSD group when tested for the second time (based on the data collected from 25 of the subjects who completed two trials of the CEP). However, on the Attention tests, significantly better performance was found on the Attention-Double test and more accurate performance was found on the Clocks test. This study demonstrated that PTSD is related to cognitive functioning impairments as indicated by the Cognitive Evaluation Protocol that assessed attention, memory, function and mood.

An MRI study by Bremner et al. (1995) mentioned earlier also examined short-term memory deficits in their group of PTSD patients who were found to have significantly smaller right hippocampal volumes compared to a group of healthy controls. The patients performed worse than the controls on the Wechsler Memory Scale logical memory component for the subscales of immediate recall, delayed recall and percent retention compared to the controls. There were no differences reported for the figural component on immediate recall, delayed recall, and percent retention. The researchers did, however, find a positive correlation between right hippocampal volume and score on the percent retention subscale of the Wechsler Memory Scale component. Therefore, smaller hippocampal volume was associated with lower scores on this verbal memory test. There was no correlation between verbal memory scores and left hippocampal volumes, bilateral caudate or temporal lobe volumes or between left or right hippocampal volume and scores on the Wechsler memory Scale figural component (visual memory) subscales. Right hippocampal volume and verbal memory deficits have been correlated by Incisa dello Rochetta, Gadian, Connelly, Polkey, Jackson, Watkins et al. (1994). These researchers found that minor damage to the left hippocampus along with lesions to the right hippocampus results in verbal memory deficits. Richardson, Strange, Duncan and Dolan (2003) studied a group of patients with unilateral left hippocampal sclerosis and healthy control subjects. The patient group was subdivided into two groups according to the presence or absence of additional left amygdala pathology (those with normal left amygdala and those with abnormal left amygdala). These researchers predicted that left medial temporal lobe pathology would result in verbal encoding functions to be transferred and performed by the right medial temporal lobe. A total of 12 right handed controls and 24 right handed patients took part in this study. The patients had temporal lobe epilepsy and had undergone MRI scans to identify left hippocampal sclerosis and normal right hippocampus. The patients had an

IQ greater than 80; however, IQ scores were not obtained from the control subjects. The psychological test that was administered to the subjects during the MRI session was a recognition task. The subjects saw 255 words which included 36 emotionally aversive words (e.g., cancer, terrorist, murder, and rape), after the presentation of each word, using their right hand, the subject had to identify, using a key press whether the word indicated a living or nonliving entity. Ninety minutes after scanning, the subjects were given a surprise recognition memory test. The words were presented in a similar manner to that used during scanning. The 255 words the subjects saw during scanning were randomly mixed with 170 neutral foils and emotional foils. Using a right-hand button press, the subjects had to respond using the R key if they remember seeing the word, K if the word seemed familiar and N if the word was new. Analysis revealed that the right and left hippocampal volumes were significantly different in the patient group. The hippocampal sclerosis group had normal left amygdala T2 – weighted images, and the second group with hippocampal and amygdala sclerosis (HSAS) had abnormally elevated left amygdala T2. There was also a tendency for the HSAS patients to have larger left hippocampi than the HS patients. Thus, the HS patients had normal left amygdala but smaller left hippocampus in contrast to the HSAS patients who had larger, though still abnormal, left hippocampus and left amygdala. During the encoding phase of the recognition test, both patient groups showed greater activity in the right hippocampus and parahippocampal gyrus compared to the healthy controls. The patients with abnormal left amygdala showed increased activation in the right amygdala compared to the patients with a normal amygdala when encoding emotional versus neutral words. Therefore, the authors could confidently state that those patients with left medial temporal lobe pathology successfully encoded and recognised both neutral and emotional words using right medial temporal lobe structures. In further support of this finding, healthy controls have also shown increased activation of the right hippocampus

in a word stem completion task using PET (Squire, Ojemann, Miezin, Petersen, Videen, & Raichle, 1992). In this study the regional cerebral blood flow of 18 healthy controls was examined using ^{15}O labelled water while engaged in a verbal memory task. The test consisted of four conditions, eight participants completed the conditions randomly, whereas, ten participants completed the study in the same order as stated below. However, prior to the testing session, the subjects were presented with a list of 15 common English words. The subjects were instructed to rate each word on a 5 point scale according to how much they liked the word. During each scan subjects saw 20 word stems (three letter word beginnings) that could form 10 English words. In the first condition the subjects made no responses. They viewed word stems and made no response and none of the stems could form words. During the second condition, which was the baseline condition, the subject said the first word that came to their mind and as before, none of the stems could form words. The third condition was the priming condition in which the subjects were required to say the first word they thought of and half of the stems viewed during this condition had been presented earlier. The fourth condition was a memory condition during which the subjects used the word stems to recall words aloud from the list that had been presented before. However, only half of the word stems produced words previously seen before. The results indicated that the largest blood flow change during the memory condition was located in the right medial temporal lobe in the area of the hippocampus and parahippocampal gyrus. This area of activation in the right was significantly greater than that of the left medial temporal lobe. These results referred to only 14 subjects, as data sets for four subjects were not included for analysis due to excessive movement artifacts. There was also no area of significant activation in the area of the amygdala, right or left amygdala. The authors suggested that this work supported research that considered the amygdala as a separate structure from the rest of the medial temporal lobe. During the priming condition, the

right hippocampal area was also activated but not to the same extent as it was during the memory condition. This finding may be because the subjects were able to link the word stems to the words that were seen previously, and the task became more of a visual recognition test. There were 15 subjects who completed the priming condition and the baseline condition without moving and the analysis revealed that there was a significant reduction in the right posterior cortex in the region of the lingual gyrus. This area was also found to show reduced activation during the memory condition. This finding may be explained because both the priming task and the memory condition were quite similar and priming may have taken place during the memory condition. In addition, the memory condition when subtracted from the baseline condition revealed activation of the right prefrontal cortex. This area was found to be inversely correlated with the number of correct matches between word stems and words during the memory condition. However, no similar correlation was found for the right hippocampus. These researchers did find activation in areas of the left hippocampus during the no response condition when the subjects simply viewed words. Changes were also observed bilaterally in the occipital cortex, left prefrontal cortex, left temporal cortex, and right cerebellum. Although it is widely agreed that the left hemisphere mediates verbal memory, these results suggested that the visual form of words may trigger a greater involvement of the right hemisphere rather than the phonetic or semantic analysis of words for which the left hemisphere shows more involvement.

Pederson, Maurer, Kaminski, Zander, Peters, Stokes-Crowe et al. (2004) also carried out a study with trauma survivors with and without PTSD to delineate the effect of PTSD on hippocampal volume and function. These researchers also incorporated a group of healthy control subjects. There were 17 participants in each of the three groups (PTSD and abuse, abuse only and healthy controls). The PTSD group had been abused prior to adolescence for at least five years and developed PTSD and the abuse group

were also abused for five years preadolescence, however, did not develop PTSD. Subjects were excluded from the study if they had attention deficit disorder or learning disabilities. After evaluating medical history and childhood abuse status via a telephone interview, all eligible participants completed the demographic questionnaire, Childhood Trauma Questionnaire (CTQ), Trauma Symptom Inventory (TSI), and Millon Clinical Multiaxial Inventory-3rd Edition (MCMI-III). Each of the participants scored at a level of clinical significance on the alcohol dependence, drug dependence, bipolar, delusional, and thought disorder subscales of the MCMI-III. The classification (PTSD and abuse versus abuse only) was based on whether the participant qualified for the Severe to Extreme category on the CTQ for emotional, physical and/or sexual abuse. This placement was then confirmed using the CAPS scale. All participants also completed the Wechsler Memory Scale-3rd Edition (WMS) and the Wonderlic Personnel Test (Wonderlic, 1998, as cited in Pederson, 2004). The results showed no significant differences in age-adjusted scores for the five WMS factors across the groups. No significant differences were found for hippocampal volume and no significant relationship was found between the CAPS severity score and the memory or hippocampal variables. Based on the findings from this study, the authors speculated that PTSD status might not be sufficient to show deficits in memory performance and hippocampal volume. The researchers suggested their results may be attributed to the young age of the participants (approximately 20 years younger) compared to other studies, less severe PTSD symptoms, lack of high scoring on any MCMI-III scale for Axis I psychiatric disorders, and absence of group differences on confounding factors such as substance abuse.

In an attempt to answer the question of whether deficiencies in hippocampal function is related to PTSD, Bremner, Vythilingam,Vermetten, Southwick, McGlashan, Nazeer, et al. (2003) recently carried a study, using MRI and PET, to examine the structure and

function of the hippocampus. This study tested three groups of subjects, a group of women with childhood sexual abuse and PTSD (n = 10), women with childhood sexual abuse without PTSD (n = 12), and women with no childhood sexual abuse or PTSD (n = 11). To measure memory functioning, the participants completed a verbal declarative memory task while being scanned using PET. PTSD diagnosis was made using the SCID and a medical and physical examination was completed to exclude any participants with existing conditions that may affect brain structure and function. The Early Trauma Inventory was used to obtain information regarding the history of childhood abuse and PTSD symptom severity was assessed using the Civilian Mississippi Scale. In addition, the Clinician-Administered Dissociative States Scale was used to measure the severity of dissociative states. The participants in this study, with the exception of the non-abused and non-PTSD participants, had comorbid diagnoses of lifetime history of major depression (n = 11), past history of dysthymia (n = 1), lifetime history of panic disorder with agoraphobia (n = 3), lifetime history of panic disorder (n = 1), past history of alcohol and/or substance abuse disorders (included past alcohol dependence (30%), polysubstance dependence (10%), marijuana dependence (18%), and cocaine dependence (18%), marijuana abuse (n = 1)), or dependence disorder (n = 4), , lifetime obsessive-compulsive disorder (n = 1), lifetime generalised anxiety disorder (n = 1), lifetime anorexia (n = 1). The subjects with abuse and with or without PTSD underwent four PET scans while completing verbal declarative memory and control tasks over the course of one day. During the first two scans, participants listened to two different paragraphs and were instructed to count the number of times they heard the letter 'd'. The participants were then instructed to form an image in their mind and to recall as much information as possible for one of the two different paragraphs presented earlier. The remaining two scans were then completed while the participants listened to one of the two paragraphs again. Free recall of the paragraph then took place

five minutes following the last two scans. Structural MRI scans of the hippocampus revealed (using repeated measures ANOVA with side as the repeated measure) that there was a significant difference in left and right hippocampal volumes between the three groups of participants (abused women with PTSD, abused women without PTSD, and women without abuse and PTSD). No significant differences emerged between the abused women with and without PTSD on the paragraph recall task (number of correctly recalled items was used in the analysis). The group consisting of women with abuse and without PTSD were found to have increased blood flow in the left hippocampus during verbal memory encoding in comparison to the control task, whereas the abused women with PTSD showed no left hippocampal activation. No significant difference in blood flow was found during the control task between the groups. Women without PTSD were found to have a significantly greater increase in blood flow during the verbal memory encoding task relative to the control task compared to women with PTSD. The authors suggested that this lack of activation in the abused PTSD women may not be secondary to smaller hippocampal volume in these patients, as indicated by results showing similar statistical differences after adjusting for left hippocampal volume. The following areas were also found to be activated during the verbal memory encoding in women without PTSD: right superior temporal gyrus (Brodmann's area 22), right inferior frontal gyrus (Brodmann's area 45), bilateral somatosensory cortex (Brodmann's areas 40, 43, 4), and cerebellum. Areas of decreased blood flow in the same group of participants included: left superior and middle frontal gyrus (Brodmann's area 8 and 9), anterior cingulate (Brodmann's area 32), left fusiform and left inferior temporal gyrus (Brodmann's area 20). Increased blood flow in the PTSD group included: bilateral middle (Brodmann's areas 10, 44, 45) and inferior (Brodmann's areas 45, 46) frontal gyrus, anterior cingulate (Brodmann's area 32), left inferior parietal lobule (Brodmann's area 40), left superior temporal gyrus (Brodmann's

areas 39, 21, 22), and right visual association cortex (Brodmann's area 19). Women with PTSD showed decreased blood flow in the orbitofrontal cortex (Brodmann's area 11), right superior frontal gyrus (Brodmann's area 10), and cerebellum. Between group contrasts revealed that women without PTSD also had greater blood flow increases in the cerebellum and in the bilateral inferior frontal gyrus (Brodmann's areas 44, 45) during memory encoding relative to the control condition. This is in addition to showing greater hippocampal activation during the same memory encoding condition. Linear regression analysis revealed that measures of higher dissociative symptom level, as measured with CAPS, were correlated with smaller left hippocampal volume and measures of PTSD symptom severity correlated with smaller right hippocampal volume. In summary, the results indicated that abused women with PTSD had 16% lower mean hippocampal volume than abused women without PTSD and 19% lower mean hippocampal volume than women without abuse or PTSD. Based on the group of participants selected for this study, the findings strongly suggested that the hippocampal dysfunction found in the performance on the declarative verbal memory task is associated with the development of PTSD and not due to trauma (childhood sexual abuse). In addition, failure to find significant differences in performance on the paragraph recall component task between the women with and without PTSD was attributed to the small number of subjects in this study. However, women with PTSD did perform worse than the non-PTSD women and this might have reached significance using a larger sample size.

4.8 Clinician-Administered PTSD Scale

The Clinician-Administered Post-Traumatic Stress Disorder Scale (CAPS) is a structural interview used to assess PTSD diagnostic status and symptom severity (Blake, Weathers, Nagy, Kaloupek, Gusman, Charney, et al., 1995). This scale

measures core and associated symptoms, frequency and intensity of each symptom as well as providing a continuous measure of symptom severity and dichotomous (presence or absence of symptoms) scores for current and lifetime PTSD symptoms. Frequency and intensity of individual symptoms are recorded on a five-point (0-4) rating scale and these may be summed to create a nine-point (0-8) severity score for each symptom (Weathers, Keane, & Davidson, 2001). With these rating scores, the CAPS test is quite flexible in scoring in that the administrator may focus on the frequency, intensity or severity ratings for each symptom, for the three PTSD symptom clusters (re-experiencing, avoidance and numbing, and hyperarousal), and for the PTSD syndrome as a whole (Weathers et al., 2001). This test starts with an initial phrased prompt question that targets each symptom and also follow-up prompt questions to clarify an inquiry if there is any confusion regarding the PTSD criteria. CAPS includes the 17 symptoms presented in the DSM-IV, along with eight associated symptoms of guilt and dissociation, the impact of symptoms on social and occupational functioning, improvement in PTSD symptoms since the last CAPS assessment, overall response validity and overall PTSD severity is assessed. The current version of the CAPS also assesses Criterion A (exposure to a traumatic event), Criteria B-D (core symptom clusters of re-experiencing, numbing and avoidance, and hyperarousal), Criterion E (chronology), and Criterion F (functional impairment) specified by the DSM-IV manual for a diagnosis of PTSD.

4.9 Aims

Given the establishment that PTSD is associated with atrophy in limbic structures, such as the hippocampal regions, predominantly in the right hemisphere, the following set of experiments will address the question of whether selective memory impairments exist in PTSD and whether it is directly related to the regional brain atrophy. In experiment 1,

spatial and topographical memory functioning in PTSD patients and healthy controls will be examined using a battery of neuropsychological tests. In experiment 2, using voxel-based morphometry (VBM), grey matter density volumes of both patients and healthy controls will be examined to determine whether any reductions in whole brain volume are present in the PTSD group. In experiment 3, a correlational study examining behavioural scores and grey matter density volumes was examined to determine whether structural alterations in PTSD are associated with deficits in cognitive functioning.

4.10 EXPERIMENT 2: An Investigation of Topographical Memory in PTSD

The literature introduced in chapter 1 and this present chapter provides strong support for the role of the hippocampus in verbal memory and spatial memory. However, these findings also demonstrate that it is difficult to localise verbal and spatial memory to either the left or right hemisphere. The studies mentioned above support the enormous body of research that suggests that both hemispheres are involved in the processing of verbal and spatial information. The right hemisphere, however, is more specialised for spatial information while the left is more responsible for manipulating and processing verbal information (See Chapter 1). Lesion-correlational data and functional imaging studies have specifically implicated the right hippocampus and right parahippocampal gyrus (PHG) in spatial and topographical memory (Maguire et al., 2001; Rosenbaum et al., 2000; Barrash et al., 2000; Aguirre, Detre, Alsop, and D'Esposito, 1996; Aguirre et al., 1998). Individuals with lesions to these specific areas of the brain invariably demonstrate spatial and topographical memory deficits (Maguire, Burke, Phillips, and Staunton, 1996; Aguirre, Zarahn, & D'Esposito, 1998; Rosenbaum et al., 2000; Luzzi et al., 2000). In addition, animal studies and most recently, clinical studies, have provided

overwhelming evidence to support the Stress-Hippocampus Model. This model has found that the hippocampus undergoes severe structural and functional damage as a result of excessive levels of glucocorticoids released during a stress response. MRI morphometry studies in PTSD have also reported atrophy to be selectively confined to the hippocampus. To investigate if any memory deficits exist in PTSD and if these impairments are lateralised to one hemisphere, a series of tasks that examined topographical, spatial, and verbal memory were selected. The rational of this study also stems from findings that the right hemisphere shows cerebral abnormalities in anxiety disorders. Therefore, this study predicted that any abnormalities or atrophy associated with PTSD might affect hippocampal function dependent on the right hemisphere more so than the left hemisphere, as a result of stress-related atrophy. The selection of neuropsychological tests was based on a number of studies that have been discussed in Chapter 1 and on the few of those studies used in Experiment 1.

The following experiment was carried out to determine whether PTSD, a form of anxiety disorder, might result in specific memory deficits to gain a better understanding of the cognitive functioning of the hippocampus in PTSD and to identify if specific visuo-spatial and topographical memory impairments exist in PTSD relative to control tasks of similar difficulty, in particular verbal memory tasks.

4.10.2 Method

4.10.2.1 Participants

Fifteen right-handed PTSD patients (mean age = 48, SD 13.6) and an equal number of healthy control subjects (mean age = 48, SD 13.86), matched for age, sex, handedness and education took part in this study (PTSD mean education = 16.73, SD 1.94; Controls = 18.2, SD 3.23). There were seven females and eight males in each group. The study

received ethical approval by the joint Grampian NHS health board and University of Aberdeen Ethics committee. The patients were recruited from the Trauma Research Centre at Royal Cornhill Hospital, Aberdeen, Scotland and the control participants were recruited from the University of Aberdeen Psychology Volunteer Panel. All control subjects were healthy without any history of neurological or mental health disorder. The patients were diagnosed using the DSM-IV criteria for PTSD and also had been assessed using the Clinician Administered Post-Traumatic Stress Disorder Scale (CAPS) (see section 4.8). The patients also completed an Impact of Events Scale revised version (IES-R) which is a self-report measure designed to assess current subjective distress for any specific life event. Five patients had comorbid diagnoses, four of depression and one with lifetime diagnosis of harmful alcohol misuse, but currently abstinent. Altogether eight of the patients were taking antidepressants for symptomatic relief. Only one patient had suffered head injury and for another patient it was uncertain whether they had had a head injury. Onset of PTSD in this patient group developed after exposure to Road Traffic Accidents (RTA) in eight patients, three cases had had industrial accidents, one witnessed an industrial accident, one patient experienced combat exposure, one suffered assault and robbery, and one had been involved in a helicopter crash (See Appendix A for more detailed patient information).

4.10.2.2 Materials/Procedure

4.10.2.2.1 Recognition Task:

Word Recognition Test

The list of words used for the Word Recognition Task came from an unpublished test which included words that were controlled for frequency and word length (Sutherland,

1997; Hofland & Johnson, 1982). A computer program was devised for this experiment using the software Presentation (Version 0.76, www.neurobs.com). The test consisted of an encoding stage and a recognition stage. During the encoding stage participants viewed a list of ten words. In the recognition stage of the experiment the list of words from the encoding stage were randomly mixed in with 10 new words not presented in the previous list. The participants were required to distinguish between the old words and the new words. The participants were instructed to press the letter 'L' for words that were new and the letter 'A' for words that they had seen before in the encoding phase. The percentage of correct responses was analysed. Further analyses were carried out using d-prime (d') and beta (β) scores derived using the principles of the Signal Detection Theory. The words were presented in black arial with a font size of 20 and presented against a white background for 3 seconds. During the recognition stage the words were presented for 5 seconds. The order of presentation was randomised for each participant.

Picture Recognition Test

There were four categories of colour photographs used for the Picture Recognition Task that was also devised in computerised form using the software Presentation. A total of 80 photographs of Faces, Landscapes, and Dogs were used. Twenty photographs of Faces (Lundqvist & Litton, 1988) and Landscapes (Benson, 2000) were selected from among those used in other published studies. There were 20 photographs of Dogs gathered from various websites. The photographs of Houses were taken from the following website, . The outline of the Houses, Dogs, Faces, and Landscapes were traced and viewed against a black background. The pictures of Faces consisted of an even number of male and female adults with neutral

emotional expressions who were all wearing identical grey shirts. These photographs did not include any distinct characteristics such as jewellery, eyeglasses, beards and moustaches. The Faces were an average of 7 x 9cm when displayed on the computer screen. The Landscape photographs varied between lakes, fields, and oceanic scenery and did not include any manmade landmarks or buildings. These photographs were 15.5 x 11.5cm when displayed on the computer screen. The photographs of Dogs were 6.5 x 5cm and the House photographs were 4.5 x 7cm when displayed on the computer screen. All stimuli were presented to the participants facing forward in the middle of the computer screen. During the encoding stage of the experiment participants viewed 10 photographs of a particular category of visual stimuli. The photographs were presented for 3 seconds before the next photograph was presented. In the recognition phase, the same 10 photographs were randomly mixed in with 10 photographs that were not shown before. During this stage, the photographs were presented for 5 seconds. As with the word recognition task, the participants were instructed to press the key 'L' for a photograph they had not seen before and the letter 'A' for a photograph that had been shown previously. After the completion of one category of stimuli the next category was shown until the participant viewed all four types of stimuli. The order of presentation of stimuli was randomised for each participant. This test was scored for total correct responses in each category; d' and β values computed using the principles of signal detection theory. These values were also analysed.

4.10.2.2.2 Topographical Localisation Task (Lezak, 1997):

The Topographical Localisation Task consisted of a map of the United Kingdom obtained from , in which participants had to localise seven cities. The following cities were chosen: Aberdeen, Bristol, Liverpool, Glasgow, Birmingham, Manchester, and Edinburgh. The participants were given a map of the United Kingdom

with the list of seven cities written on the left hand side of the sheet. The participants were first instructed to place the four compass directions on the map (North, East, South, and East) and then asked to mark the location of the cities on the map by writing down their assigned number. During the test, participants were not given immediate feedback as to whether they had placed the cities in the correct locations on the map. The test was scored by measuring the difference in centimetres between the actual location of the city and the location of where the participant had placed the number of the city on the map. The scores for the cities within England and within Scotland were added up separately and together as one total map score.

4.10.2.2.3. General Semantic Knowledge Test (WAIS-III):

A total of seven questions were taken from the general information section of the verbal part of the Weschsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997). The participants were asked to orally respond to these questions which investigated factual knowledge. The participants were told they would have to answer seven questions verbally. Each question was read aloud to each participant in a standardised way. If the response to a question was unclear or incomplete the examiner asked the participants to explain what they meant or asked them to tell more about it. Leading questions or spelling out words was not allowed by the examiner. Questions were only repeated when the examinee's response suggested that they might have misunderstood the meaning or misheard the question. A score of one was given for each correct answer and a score of zero for each incorrect answer or if the participant was unable to answer the question.

4.10.2.2.4. Corsi Block Test:

Participants were presented with a board with nine 1.5 inch blocks fastened to it in a random order (Milner, 1971). The experimenter tapped a sequence of eight blocks with approximately two seconds between each tap. After each trial the participant was required to tap the same sequence of blocks as was shown by the experimenter. This continued until the participant was able to complete two consecutive trials without errors or after completing five trials.

4.10.3 Results

4.10.3.1 Recognition Test

Word Stimuli

One way analysis of variance using percent correct scores and d' scores revealed significant differences in performance between the two groups, $F(1, 28) = 6.91$, $p < .05$ and $F(1, 28) = 6.59$, $p < .05$ (for percent correct and d' scores) (See Figure 1 & 2). No significant difference in performance was observed using β scores, $F(1, 28) = 1.03$, ns. The performance of the patients and controls on this test are shown in Table 1.

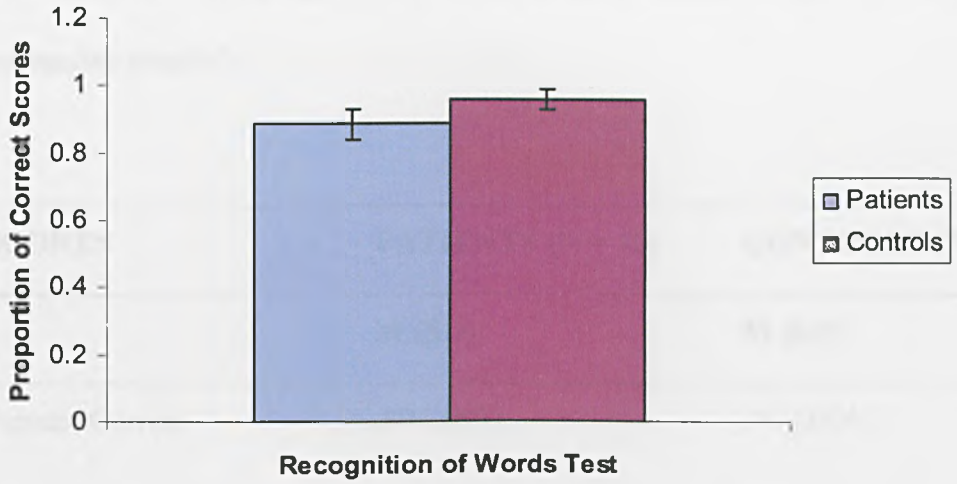

Figure 4.1. Mean Percent scores achieved by the patients and healthy controls on the Recognition of Words test.

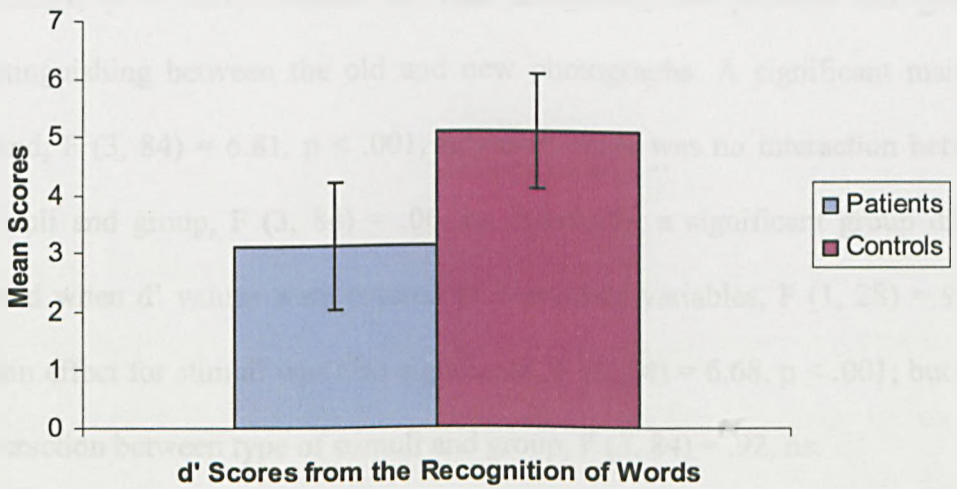

Figure 4.2. Mean d'scores for both patients and healthy controls on the Recognition of Words test.

Table 4.1. *Mean (SD) performance scores on the Recognition of Words test by patients and healthy controls.*

SCORES	PATIENTS (N = 15)	CONTROLS (N=15)
	M (SD)	M (SD)
Percent Correct	.89 (.093)	.96 (.054)
d'	3.10 (2.20)	5.06 (1.96)
β	4.45 (13.20)	1.00 (.000)

Picture Stimuli

A repeated measures ANOVA showed a significant difference between patients and healthy controls using proportion of correct scores from the Recognition test ($F(1, 28) = 12.51$, $p < .001$). Across all four categories, the patients had greater deficits distinguishing between the old and new photographs. A significant main effect was found, $F(3, 84) = 6.81$, $p < .001$; however, there was no interaction between type of stimuli and group, $F(3, 84) = .06$, ns. Similarly, a significant group difference was found when d' values were entered as dependent variables, $F(1, 28) = 9.58$, $p < .05$. Main effect for stimuli was also significant, $F(3, 84) = 6.68$, $p < .001$; but there was no interaction between type of stimuli and group, $F(3, 84) = .92$, ns.

Post-hoc, one-way comparisons for each individual category showed a significant difference in d' scores for Landscapes, ($F(1, 28) = 10.31$, $p = .003$) between the groups, with the patients having greater difficulties in distinguishing between the old and new photographs. There were no significant differences between the groups performance for

the remaining categories, (Dogs, F (1, 28) = 2.27, ns; Faces, F (1, 28) = 4.25, p = .05; Houses, (F (1, 28) =2.14, ns). (See figure 3).

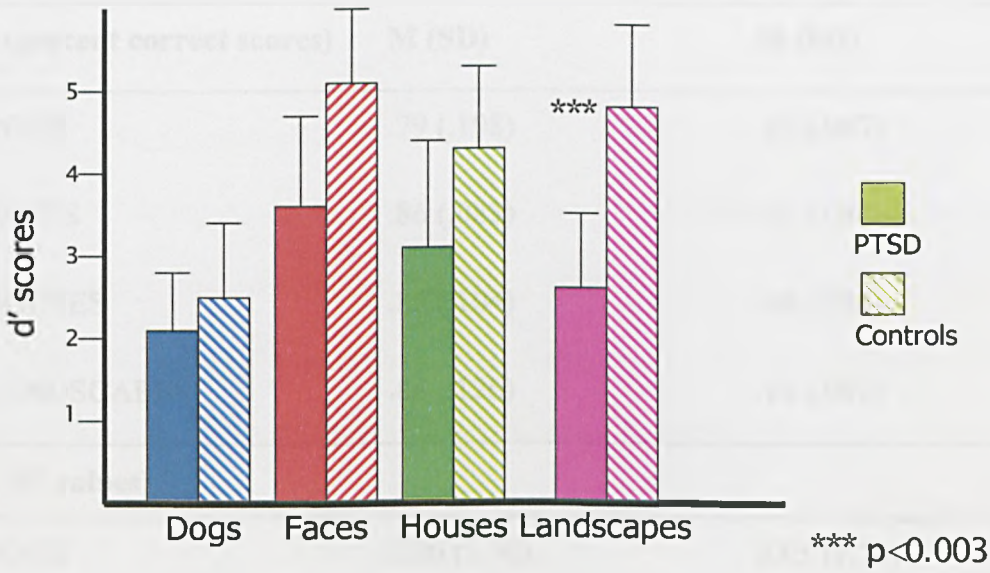

Figure 4.3. d' scores for the 4 categories achieved by the patient and healthy controls on the Recognition test.

Repeated measures ANOVA using β scores did not show a significant difference between the two groups (F (1, 28) = 3.58, ns). Also, there was no significant main effect of type of stimuli (F (3, 84) = 1.45, ns) nor was there a significant interaction between group and type of stimuli, (F (3, 84) = 138.49, ns). Table 2 provides the mean and standard deviation scores for the proportion of correct scores, d' and β values for the patients and healthy control subjects.

Table 4.2. *Mean (SD) scores for (a) percent correct scores, (b), d' scores and (c) β values for patients and controls.*

	PATIENTS (N = 15)	**CONTROLS (N = 15)**
a (percent correct scores)	**M (SD)**	**M (SD)**
DOGS	.79 (.108)	.85 (.067)
FACES	.86 (.083)	.94 (.084)
HOUSES	.86 (.104)	.94 (.054)
LANDSCAPES	.84 (.126)	.92 (.092)
b (d' values)		
DOGS	2.06 (1.50)	2.95 (1.74)
FACES	3.67 (2.16)	5.15 (1.77)
HOUSES	3.13 (2.34)	4.32 (2.09)
LANDSCAPES	2.61 (1.83)	4.88 (2.03)
c (β values)		
DOGS	4.44 (13.20)	1.00 (.000)
FACES	11.25 (21.17)	1.00 (.000)
HOUSES	1.00 (.000)	1.00 (.000)
LANDSCAPES	7.82 (18.00)	4.41 (13.21)

4.10.3.2 Topographical Localisation Test

The separate England and Scotland scores were analysed using a 2 x 2 Repeated measures ANOVA with region as the within subjects factor and group as the between subjects factor. A significant group difference was found, $F(1, 28) = 12.14$, $p < .05$. The patients demonstrated greater difficulties in locating cities within Scotland and England on a map of the United Kingdom. A main effect was found for region, $F(1, 28) = 99.24$, $p < .001$ and an interaction between region and group was found, $F(1, 28) = 7.55$, $p < .05$. A Univariate Analysis of Variance showed a significant difference between the two groups using the combined map score, $F(1, 28) = 12.14$, $p < .05$, the Scotland scores, $F(1, 28) = 8.22$, $p < .05$, and also England scores, $F(1, 28) = 10.89$, $p < .05$. Therefore, the PTSD patient group performed worse on all three components on the Topographical Localisation task compared to the healthy controls (see Table 3 and Figure 4).

Table 4.3. *Mean (SD) scores for England and Scotland and the combined scores achieved by the patients and healthy controls on the Topographical Localisation test.*

Topographical Localisation test	**PATIENTS (N = 15)**	**CONTROLS (N = 15)**
	M (SD)	**M (SD)**
England	9.63 (4.08)	5.41 (2.81)
Scotland	2.68 (1.41)	1.46 (.853)
Combined Score	12.31 (5.06)	6.87 (3.31)

Figure 4.4. Mean combined score on the Topographical Localisation test by patients and healthy controls.

4.10.3.3 General Semantic Knowledge Test (WAIS-III)

The performance of the patients and healthy control subjects on the General Semantic Knowledge test showed no significant difference in performance, F (1, 28) = 2.53, ns. Mean performance scores are shown in Table 4 and Figure 5.

Table 4.4. *Mean (SD) scores achieved by the patients and healthy controls on the General Semantic Knowledge test.*

General Semantic Knowledge Test	Mean (SD)
Patients	.585 (.162)
Controls	.675 (.148)

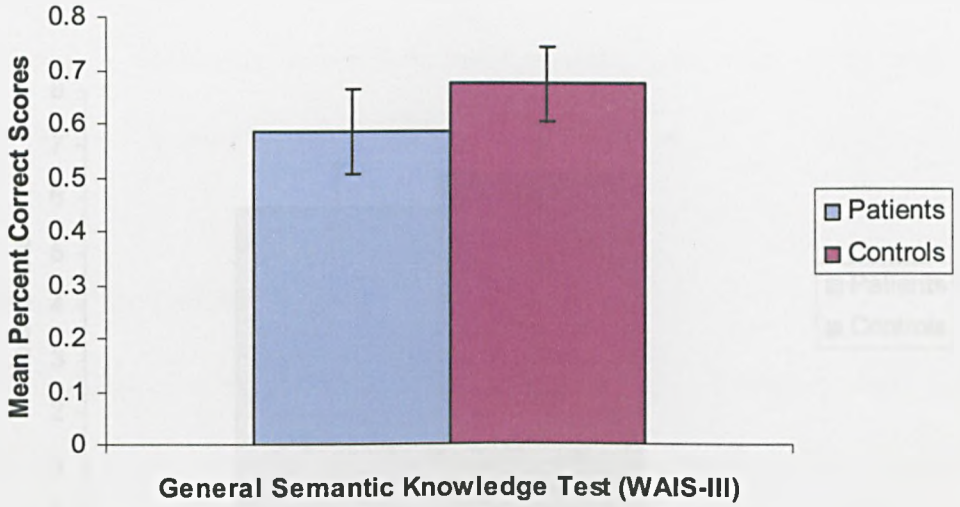

Figure 4.5. Mean scores on the General Semantic Knowledge test by the patients and healthy controls.

4.10.3.4 Corsi Block Test

One way analysis of variance revealed that scores of patients and healthy control subjects were not significantly different on the Corsi Block test, F (1, 28) = .95, ns. Table 5 and Figure 6 show the performance on this test by the patients and healthy control subjects.

Table 4.5. *Mean score (SD) on the Corsi Block test by the patients and healthy control subjects.*

Corsi Block Test	**M (SD)**
Patients	5.84 (1.57)
Controls	6.44 (1.80)

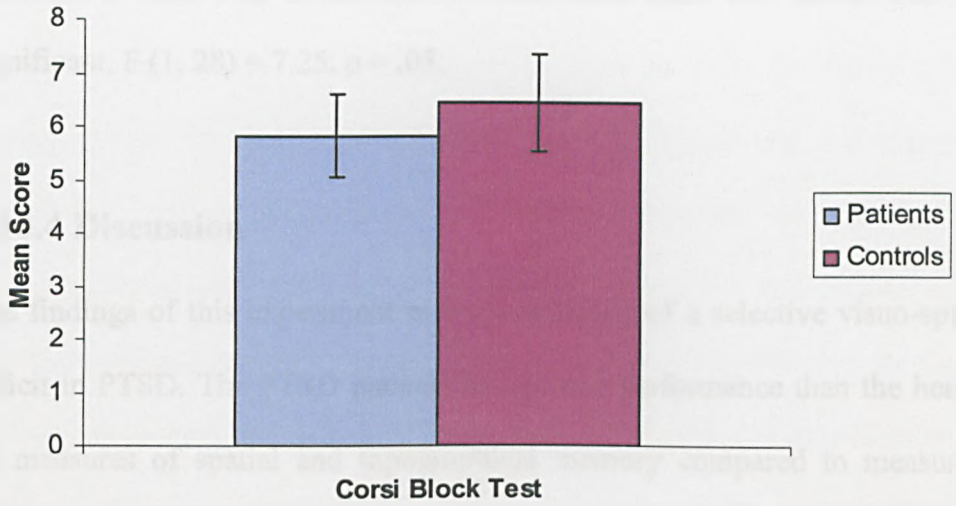

Figure 4.6. Mean scores on the Corsi Block test by the patients and healthy controls.

4.10.3.5 Comparison of Spatial Versus Verbal Memory Tests

A statistical analysis using a 2 x 2 x 2 Repeated Measures ANOVA was computed for Test (spatial and verbal memory) by Type (semantic and episodic) as within subject factors and by Group (PTSD and healthy control subjects) as the between subjects factor. The Corsi Block Test and Topographical Localisation task were the spatial tests administered and the verbal memory tests were the General Semantic Knowledge test and the Word Recognition test. The General Semantic Knowledge test and the Topographical Localisation task examined semantic memory and the Word Recognition test and the Corsi Block test examined episodic memory. All scores were normalised prior to carrying out the statistical analyses. A significant difference was found between the groups, $F(1, 28) = 13.38$, $p < .001$. A main effect for Type of Test, $F(1, 28) = 308.22$, $p < .001$ and a main effect for Test was found, $F(1, 28) = 390.85$, $p < .001$. An

interaction between type and group, $F(1, 28) = 7.90$, $p < .05$ was found and an interaction between test and group was also significant, $F(1, 28) = 7.99$, $p < .05$. In addition, a three-way interaction between test, type, and group was found to be significant, $F(1, 28) = 7.25$, $p = .05$.

4.10.4 Discussion

The findings of this experiment provide evidence of a selective visuo-spatial memory deficit in PTSD. The PTSD patients had poorer performance than the healthy controls on measures of spatial and topographical memory compared to measures of verbal memory. These results are in line with earlier reports linking PTSD with memory impairments (Bremner et al., 1993; Bremner et al., 1993; Yehuda et al., 1995; Gilbertson et al. 2001; Sachinvala et al. 2000). More importantly, these results support the hypothesis that PTSD is associated with greater hippocampal impairments dependent on right hemisphere functioning compared to left hippocampal functioning. The PTSD patients had a remarkable difference in performance on the Landscape category compared to the healthy control subjects on the Visual Picture Recognition test. These findings follow similar patterns to the impairment found in K.C., the individual with extensive bilateral hippocampal volume reductions studied by Rosenbaum et al. (2000). These authors suggested that the hippocampus and adjacent cortex is responsible for providing a rich representation of spatial information, memory for details, regardless when these memories are formed. The photographs of the Landscapes presented to the PTSD patients may have contained many details that the patients were not able to remember during the recognition phase of the test. The non-significant results for the category of Houses in this study may be explained by the same findings as photographs of houses are quite general and rarely very unique, as environmental landscapes can be. The patients may have successfully completed this

task by paying attention to details such as door colours or other obvious features of the house. Future studies should carefully match experimental and control tasks for task difficulty.

To further support the findings by Rosenbaum et al. 2000, the results obtained for the topographical localisation test are also similar to a map test that was given to their patient K.C. Patient K.C. did not have difficulty locating major bodies of water and continents on a map of the world and performed equally well as the control subjects. However, when required to locate cities on a map of Canada and for the Province of Ontario, the patient had deficits. In this study, the PTSD patients did show impairments locating cities on a map of the United Kingdom. Rosenbaum et al. suggested that the hippocampus and surrounding cortex is important for storing and retrieving detailed topographical information, regardless of when the information is learned. This task however reflects semantic topographical information and there is evidence that the hippocampus is also important in the retrieval of semantic information as well as episodic (Vargha-Khadem et al., 1997 & Squire & Zola, 1998).

The Corsi Block test, a spatial memory test, did not show a significant difference between the groups. The PTSD patients were able to retain the sequence of targeted movements immediately after the experimenter had demonstrated the movements. These findings may be attributed to the PTSD patients using a verbal strategy to navigate within the board. The patients may have mentally directed themselves around the board by remembering to go up and down and left and right to repeat the same sequence of blocks tapped.

The patients did not show difficulties on the General Semantic Knowledge test. However, as reported by other studies, a Word Recognition test, examining verbal memory function, did show a significant difference in performance between the two groups. The neuropsychological studies examining PTSD have primarily focused on

verbal short-term memory, working memory and declarative memory. Bremner et al. (1993) found that PTSD was associated with verbal short term memory deficits in their study conducted with 26 Vietnam combat veterans and 15 control subjects. The neuropsychological tests administered in that study were the Wechsler Memory Scale (WMS) Logical Component, for immediate and delayed recall as well as percent retention and the verbal Selective Reminding Test (vSRT). The patients showed deficits in short-term verbal memory as measured by the vSRT. In addition, deficits were found in paragraph recall as measured by the WMS, Logical Component, for both immediate and delayed recall, as well as percent retention. In addition, other groups of PTSD patients have also shown memory impairments. For example, abuse related PTSD have exhibited immediate and delayed recall and percent retention on the WMS, logical memory component and also on the vSRT and long term retrieval.

The results suggest that this sample of PTSD patients might have hippocampal atrophy of the right and left hemisphere, as indicated by their performance on the Landscapes test and Recognition of Words test. Findings from the analysis comparing verbal and spatial memory tests suggest greater right-sided atrophy, however, the nature of the neuropsychological deficits observed in this study will be better understood using neuroradiological techniques such as MRI. Statistical analyses using MRI data might identify whether atrophy (if at all present) of the left hippocampus contributed to the deficits of verbal memory and whether atrophy of the right hippocampus contributed to impairments of spatial memory, or whether atrophy of both hemispheres are implicated with the neuropsychological impairments seen in PTSD. This hypothesis can be studied by morphometric analysis of the brain of patients and controls. For example, using voxel-based morphometry, correlational analyses of the relationship between the behavioural test scores and regional grey matter density may be examined to determine whether the neuropsychological deficits observed are the direct consequences of atrophy

of the hippocampus in the PTSD patients included in this experiment. A morphometric analysis of PTSD and control subjects and the correlation between volumetric measurements and neuropsychological performance will be the topic of the following 2 experiments.

4.12 EXPERIMENT 3: A Voxel-Based Morphometric Study to Examine Differences in Grey Matter Density between PTSD Patients and Healthy Controls

4.12.1 Voxel-Based Morphometry Methods

The following experiments will use the voxel-based morphometry (VBM) technique. To clarify the use of this novel approach, the following section will provide details of the VBM methodology.

Structural magnetic resonance images can differ in many ways among subjects (Ashburner & Friston, 2001). VBM, a relatively new technique is sensitive to such differences and is capable of disregarding positional and other large-scale volumetric differences in gross anatomy (Ashburner & Friston, 2001). This neuro-imaging technique is an objective and automatic procedure that identifies regional differences in grey matter and white matter density in structural MRI scans (Ashburner & Friston, 2001; Salmond, Ashburner, Vargha-Khadem, Connelly, Gadian & Friston, 2002). This procedure allows every area of the brain to be considered in an unbiased way, with no a priori regions of interest (Salmond, Ashburner, Vargha-Khadem, Connelly, Gadian et al., 2002). Therefore, important differences will not be overlooked due to difficulties in defining separate regions using the labour-intensive method of manual volumetry (Allen, Bruss, Brown & Damasio, 2005). Importantly, this procedure is useful because

it can show regions where grey matter concentration differs significantly between groups.

The first step in VBM involves normalising the MRI data. During this procedure, the images are spatially normalised into the same stereotactic space to remove unwanted differences to enable analysis of the data. The grey matter, white matter and cerebrospinal fluid are extracted from the normalised images and then data are spatially smoothed. The optimum smoothing kernel typically corresponds to the size of the effect that is anticipated.

It is the spatial normalisation step within VBM that removes any positional and volume differences that may exist in the data. A high resolution warping method is also applied to the data during spatial normalisation. A series of images are warped to fit the standardised template, however, because all brains are different from one another, it is very likely that the volumetric differences will incur as a result of this process. Ashburner & Friston (2001) give an example of this, if the temporal lobe of one subject is half the volume of the standardised template, then its volume will be doubled during the spatial normalisation step. Thus, statistical analysis will be carried out on data that will appear to have double the number of grey matter voxels when in fact it does not. To overcome this problem, VBM multiplies the relative volume of the images before and after warping (Ashburner & Friston, 2001). It is also possible that structural differences may be considered to be grey matter (or significant) when in actual fact they are not. For instance, although the aim of spatial normalisation is to provide a "good global match between brain images", sometimes due to differences in ventricle sizes, this is not always possible (Ashburner & Friston, 2001, p. 1242). To make an exact match, volume of the surrounding tissue is changed in order to make the ventricles of the individual subjects the same size. The major problem with this is that if the ventricles are enlarged then grey matter is also enlarged during spatial normalisation. Therefore, this problem

can be corrected by carrying out the spatial normalisation step on segmented grey matter (Ashburner & Friston, 2001). However, it should be emphasised that VBM does not attempt to match every cortical feature precisely but corrects for global brain shape differences (Ashburner & Friston, 2000). More importantly, if the images were matched exactly, no significant differences would emerge. In addition, it is important that the chosen template should also have been registered with the same accuracy of the spatial normalisation technique (Ashburner & Friston, 2000).

Using a modified mixture model cluster analysis technique, the spatially normalised images are segmented into grey matter, white matter, cerebrospinal fluid and three other background classes.

Following spatial normalisation and segmentation but before carrying out statistical analyses on the processed data, the images are spatially smoothed. It is has been stated that the main reason why the images are smoothed is to use the "Matched Filter Theorem to sensitise subsequent statistical tests to differences of a particular spatial scale" (Ashburner & Firston, 2001, p.1242). Thus, if the data are smoothed by 8mm, the statistical tests will be sensitive to regional differences in structures that are approximately 8mm. In addition, spatially smoothing the data corrects for inaccurate spatial normalisation. According to the central limit theorem, smoothing also makes the data more normally distributed, which increases the validity of parametric statistical tests (Ashburner & Friston, 2000). Furthermore, each voxel of smoothed data is considered to represent a local concentration of tissue and in VBM, the logit transformation is also carried out prior to conducting statistical tests on these voxels to make the data more normally distributed.

The statistical analysis that is carried out to examine regional grey matter concentration uses the general linear model. This flexible framework allows for the use of group comparisons as well as identifying whether grey matter volume is associated to

covariates such as disease severity or age. The standard parametric statistical procedures, such as t tests and F tests, are used to test the hypotheses of the study. Corrections for multiple comparisons are made using the theory of Gaussian random fields (Friston, et al., 1995a, b; Worsley et al., 1996, as cited in Ashburner & Friston, 2001).

In order for VBM to be used as a valid technique it is important that the steps within this process are completed correctly. For example, the segmentation should accurately identify and separate grey matter, white matter and cerebrospinal fluid. To determine whether this process is completed successfully it is possible to superimpose the extracted grey matter and white matter on an image to visualise the segmentation. Secondly, it is important to compare groups of subjects whose images were acquired using the same scanner. Another important issue that should not be overlooked when using VBM is to make sure that the data are normally distributed (Ashburner & Friston, 2000).

The use of VBM is advantageous when examining small-scale differences that are not as readily identified using classic volumetry. Many brain areas are not investigated due to a lack of clear boundaries that are typically needed in manual volumetry studies that examine regions of interest. Thus, VBM is capable of identifying small, localised regions. In conclusion, VBM is an important statistical tool in assessing anatomy throughout the brain of individuals and groups. The following experiments in this chapter as well as Chapter 5 will use this technique to identify grey matter volume differences of PTSD and AD patients from healthy control subjects. Experiment 3 will include a voxel-based morphometric group comparison between the PTSD patients and healthy control subjects to identify whether any regional brain differences exist between the two groups. In addition, Experiment 4 will establish if a relationship exists between symptom severity by correlating regional grey matter density with CAPS scores.

Furthermore, using voxel-based morphometry, Experiment 5 will examine whether regional brain atrophy may explain the observed neuropsychological deficits in spatial and verbal memory tests. Although there is strong evidence that PTSD is associated with hippocampal atrophy, no previous study has investigated regional brain atrophy and neuropsychological function in the same group of patients. Therefore, no such work examining regional brain atrophy and specific memory deficits are present, more importantly, voxel-based techniques have not been previously used to examine whether memory impairments correlate with brain atrophy in PTSD (Bremner et al., 1995; Bremner et al., 1999; Sapolsky, 2000; Gilbertson et al., 2002).

4.12.2 Aims

The findings from Experiment 2 demonstrated that PTSD affects memory performance with greater impairments in topographical tasks compared to verbal tests. Previous work has shown that the brain region responsible for mediating topographical and spatial memory is the hippocampus and more importantly, the parahippocampal gyrus in the right hemisphere. To elaborate on the findings from the previous experiment, a subgroup of the same PTSD patients completed a structural Magnetic Resonance Imaging (MRI) session. Using a voxel-by-voxel MRI morphometric technique with Statistical Parametric Mapping software, 1999 version (SPM99), grey matter density volumes of PTSD patients will be compared to healthy normal controls, to verify the hypothesis that PTSD is associated with greater regional grey matter density deficits in the right limbic/temporal regions (Wellcome Department of Imaging Neuroscience, London).

4.12.3 Methods/Procedure

4.12.3.1 Participants

The group comparison analysis consisted of ten patients, three females and seven males (Mean age = 46, SD = 14.37). The sample of ten patients were taken from Experiment 1, however, due to the confinement of a MRI scanner only ten patients were able to complete this study. The following traumatic events were the initial triggers that led to the development of PTSD in this sample: road traffic accidents (N = 4), an industrial accident (N = 3), witness of an industrial accident (N = 1), combat veteran (N = 1), robbery/assault (N = 1), and a helicopter incident (N = 1). Eight healthy control subjects matched for gender and education agreed to take part in the study. The time since the trauma ranged from one year to five years, however the combat veteran's traumatic event dated back to 1964. One patient did suffer a mild head injury; however, it is not known whether one of the road traffic victims experienced a head injury. At the time of the study, seven patients were taking anti-depressants (e.g. nefazodone, sertraline, mirtazapine and reboxetine). For two patients, it was however not known at the time of testing if they were prescribed anti-depressants but were definitely not taking any other medications. None of the other patients were taking other drugs. The University of Aberdeen ethics committee and the Grampian Health Board granted ethical approval for this study.

4.12.3.2 MRI Imaging

3D MRI brain scans were performed at the MRI Centre, of the University of Aberdeen, Scotland. Subjects were scanned using a 1.5 Tesla GE MRI system acquiring T1-weighted images using a SPGR imaging sequence. The voxel dimensions were 2.56 x

2.56 x 1.24, in plane resolution, field of view 240mm (pixel size 0.9375mm) with a slice thickness of 1.6mm. Before carrying out statistical analyses, images were normalised onto a standardised anatomical space, segmented into grey matter, white matter and cerebrospinal fluid. The grey matter images were then spatially smoothed using a full width at half maximum (FWHM) kernel of 4mm. The amount of smoothing was determined by the a priori hypothesis predicting hippocampal atrophy. Therefore, smoothing greater than 4mm might not detect differences in smaller brain structures such as parts of the hippocampus, or nearby regions.

4.12.3.3 Data Analysis

Data were analysed using the image analysis SPM99 software (Wellcome Department of Imaging Neuroscience). The comparison between PTSD and control subjects was performed using ANCOVA, with age used as a covariate. Only clusters surviving corrected cluster probability levels were considered as significant.

4.12.4 Results

A volumetric group comparison was performed using ANCOVA because some patient and volunteer images/scans were lost during data collection and thus the groups were no longer matched for age. However, this small difference was accounted for by covarying for age. No significant difference between the groups was found using a height threshold corrected for multiple comparisons on the whole brain. However, when a small volume correction was adopted, this analysis revealed significant differences in grey matter density in the right fusiform gyrus (BA 20), middle frontal gyrus (BA 46), postcentral gyrus (BA 5), inferior temporal gyrus (BA 20), lingual gyrus (BA 18), and

superior frontal gyrus (BA 6). In addition, left middle temporal gyrus (BA 21), inferior parietal lobule (BA 40), postcentral gyrus (BA 3), inferior occipital gyrus (BA 18), parahippocampal gyrus, and medial frontal gyrus (BA 6) (Table 6 & Figure 7) Small volume corrections was adopted because of an a priori hypothesis predicting atrophy in the hippocampal region.

Table 4.6. *Brain regions, corresponding Brodmann's areas, Talairach coordinates, Z-scores, and Cluster sizes and corrected cluster probability levels of the difference observed between the two groups*
(R = right; L = left).

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
L middle temporal gyrus (BA 21)	149	.008	3.94	-51	-12	-15
L inferior parietal lobule (BA 40)	175	.005	3.76	-55	-53	36
R superior frontal gyrus (BA 6)	284	.001	3.68	12	11	60
R lingual gyrus (BA 18)	175	.005	3.62	14	-76	4
L postcentral gyrus (BA 3)	140	.010	3.47	-50	-18	36
R inferior temporal gyrus (BA 20)	243	.001	3.43	59	-2	-35
L inferior occipital gyrus (BA 18)	723	.000	3.42	-38	-84	-11
L parahippocampal gyrus	144	.009	3.29	-30	-24	-16
L medial frontal gyrus (BA 6)	118	.016	3.24	-2	-12	65
R postcentral gyrus (BA 5)	281	.001	3.15	24	-41	68
R middle frontal gyrus (BA 46)	107	.021	3.15	40	32	21
R fusiform gyrus (BA 20)	140	.01	3.06	38	-38	-20

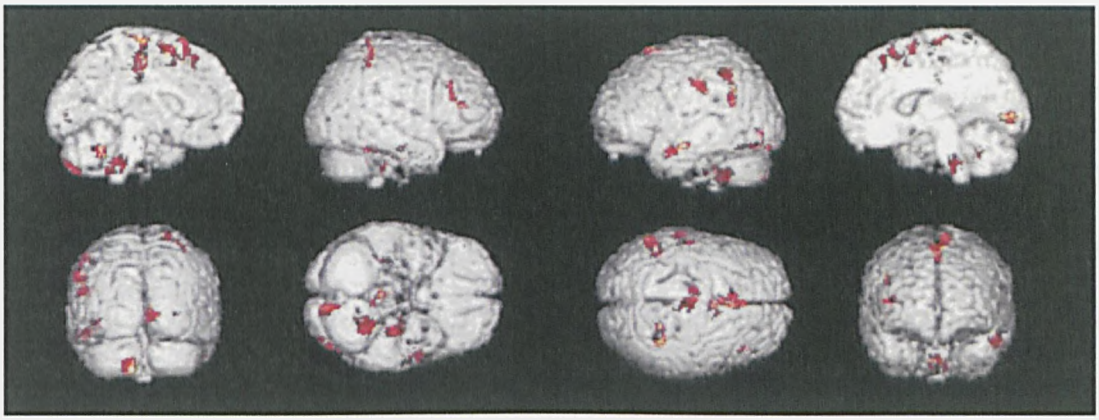

Figure 4.7. Observed frontal, occipital and temporal brain atrophy of PTSD patients compared to healthy normal controls (height threshold $p < .05$).

4.12.5 Discussion

In this study, PTSD patients when compared to healthy controls showed atrophy in the following areas of the right hemisphere: fusiform gyrus (BA 20), middle frontal gyrus (BA 46), postcentral gyrus (BA 5), inferior temporal gyrus (BA 20), lingual gyrus (BA 18), and superior frontal gyrus (BA 6). In addition, brain regions that showed atrophy in the left hemisphere included the middle temporal gyrus (BA 21), inferior parietal lobule (BA 40), postcentral gyrus (BA 3), inferior occipital gyrus (BA 18), parahippocampal gyrus, and medial frontal gyrus (BA 6). Although the current study did not find atrophy confined to the hippocampus or to the right parahippocampal gyrus, many of the observed regions presenting grey matter volume reductions are within the medial temporal regions (i.e., fusiform gyrus, inferior temporal gyrus, middle temporal gyrus and parahippocampal gyrus). Gurvits et al. (1996) examined hippocampal volume of combat-related PTSD patients, combat control subjects without PTSD, and normal controls. Their findings revealed that both left and right hippocampal volumes were significantly smaller in the PTSD group. Bremner et al. (1995) found a significant difference between Vietnam veterans with PTSD and healthy controls in the area of the right hippocampus. This difference emerged when years of education and years of

alcohol abuse were statistically controlled for using ANCOVA. Similar results were found by Stein et al. (1997) who examined women with childhood sexual abuse PTSD and control subjects with no history of childhood abuse. The right hippocampus volumes were found to be 2.9% smaller in the women with childhood sexual abuse compared to the control subjects. Left hippocampal volume was also found to be 4.9% smaller compared to the control subjects. Bremner et al. (2003) recently studied three groups of subjects, a group of women with childhood sexual abuse and PTSD (n = 10), women with childhood sexual abuse without PTSD (n = 12), and women with no childhood sexual abuse or PTSD (n = 11), using MRI and PET. The results indicated that abused women with PTSD had 16% lower mean hippocampal volume than abused women without PTSD and 19% lower mean hippocampal volume than women without abuse or PTSD. This present study is the first one to analyse patients with PTSD by using voxel-based morphometry. Therefore, this might be a possible reason for the differences in the observed structures showing reduced grey matter density volumes. This technique allows the investigation of grey matter density over the whole brain, while the region of interest approach used by other studies investigated only a limited number of areas.

Evidence of grey matter density volume in right and left medial temporal regions raises the question of whether the differences between the groups are directly related to the diagnosis of PTSD. Correlating symptom severity scores with grey matter density might address whether the observed atrophy appeared as a consequence of the disorder and if it is at all linked to the severity of the symptoms. The following experiment will correlate disease severity scores (CAPS) with grey matter density volumes.

4.13 EXPERIMENT 4: A Voxel-Based Morphometric Correlational Study of PTSD Symptom Severity and Cortical Grey Matter Density Volumes

4.13.1 Aims

The influence of symptom severity on regional brain atrophy will be examined using voxel-based morphometric correlational analysis, to determine whether the difference in grey matter density detected between PTSD patients and controls in experiment 3 is linked to the severity of the PTSD symptoms.

4.13.2 Methods/Procedure

4.13.2.1 Participants

Same ten PTSD patients as in the group comparison analysis (see Experiment 2).

4.13.2.2 Materials

All PTSD patients completed the Clinician Administered PTSD Scale (CAPS). As mentioned in Chapter 4, Section 4.8, this structured interview assesses PTSD diagnostic status and symptom severity (Blake et al., 1995). The CAPS test can measure both the frequency and intensity of individual PTSD symptoms using five-point rating scales. The symptoms of PTSD are classified into 3 categories, re-experiencing, avoidance and numbing and hyperarousal. The CAPS test can also assess these 3 symptom clusters as well as the PTSD syndrome as a whole using rating scales, which makes this test very flexible in scoring (Weathers, Keane & Davidson, 2001). The CAPS also assesses all the DSM-IV criteria for PTSD, exposure to a traumatic event, core symptom clusters of

re-experiencing, numbing and avoidance and hyperarousal, chronology, functional impairment, and the associated symptoms of guilt and dissociation. The assessment includes questions which require the individual to describe the traumatic events they have experienced and/or witnessed, how they responded emotionally to the event (i.e., anxious, frightened, horrified, helpless). The assessment also includes questions regarding the occurrence of unwanted or unpleasant memories and flashbacks. Individuals are also asked if anything reminds them of the event or if these reminders trigger bad feelings related to the traumatic event. Physical reactions after the event and if the individual has ever tried to avoid thoughts or feelings are assessed, as well as if the individual now avoids certain activities they once enjoyed. Memory, concentration and social and occupational functioning is also examined.

4.13.2.3 MRI Methods

See Experiment 2.

4.13.2.4 Data Analysis

A simple regression analysis (conducted within SPM99), correlating cerebral grey matter volumes with a measure of PTSD severity expressed as scores from the Clinician Administered PTSD Scale. Only clusters surviving corrected cluster probability levels were considered as significant.

4.13.3 Results

Severity of PTSD symptoms correlated negatively with grey matter density volumes in the right parahippocampal gyrus (BA 30), right paracentral lobule (BA 31), middle temporal gyrus (BA 21), and the right fusiform gyrus (BA 37). Figure 8 shows a coronal

image of the significant negative correlation between CAPS scores and the right parahippocampal gyrus atrophy.

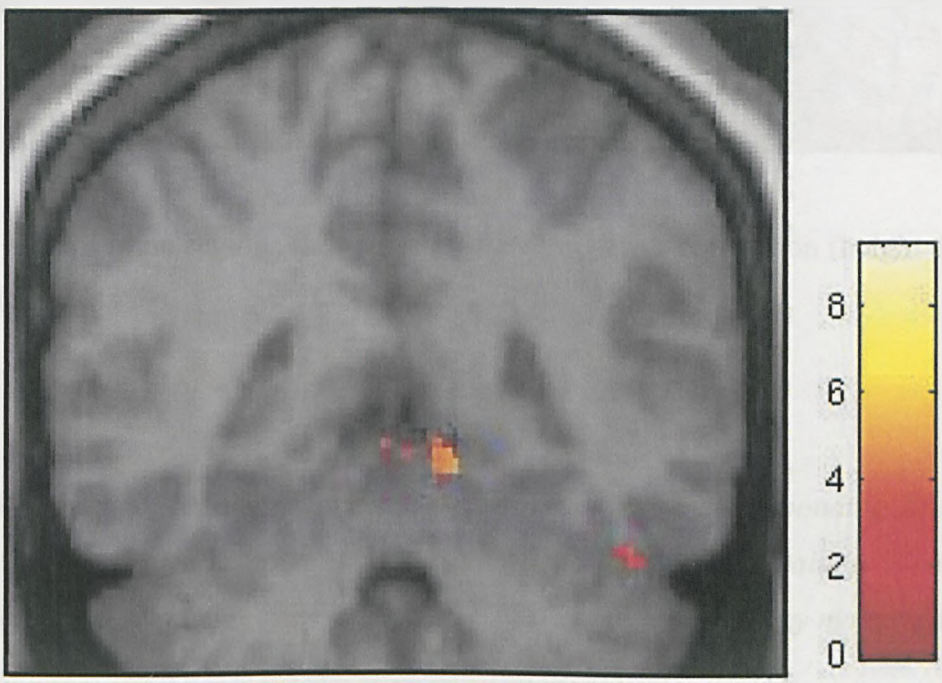

Figure 4.8. Coronal slice showing atrophy of the right parahippocampal gyrus when correlated with the CAPS scores (height threshold $p < .02$).

The left inferior frontal gyrus (BA 47) also correlated negatively with severity of symptoms. Figure 9 illustrates a rendered image showing all the brain regions in which a significant negative correlation with the CAPS scores was found. Table 7 lists the brain regions, along with corresponding Brodmann's areas, cluster sizes, Z-scores, p-values, and Talairach coordinates.

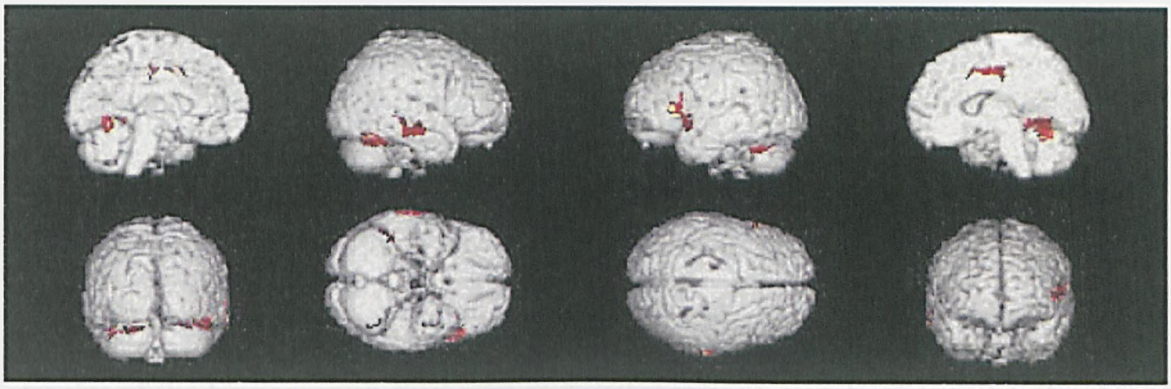

Figure 4.9. All brain regions showing significant negative correlation (height threshold, $p < .02$).

Table 4.7. *Areas of Significant Negative Correlation (with corresponding Brodmann's areas, Cluster sizes and corrected cluster probability levels, p-values, Z-scores and Talairach coordinates) between severity of PTSD symptoms and grey matter density.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
R parahippocampal gyrus (BA 30)	312	.000	4.36	10	-43	-6
L inferior frontal gyrus (BA 47)	255	.001	3.78	-48	23	3
R fusiform gyrus (BA 37)	147	.044	3.69	44	-59	-14
R paracentral lobule (BA 31)	145	.048	3.67	8	-13	43
R middle temporal gyrus (BA 21)	161	.024	3.43	69	-12	-11

4.13.4 Discussion

Symptom severity scores as measured by CAPS correlated negatively with grey matter density volumes in the right parahippocampal gyrus (BA 30), right fusiform gyrus (BA

37), right paracentral lobule (BA 31), and right middle temporal gyrus (BA 21). In addition, grey matter density volumes in the left inferior frontal gyrus (BA 47) also correlated negatively with CAPS scores. Results of the CAPS analysis suggests that PTSD symptom severity plays an important role in the atrophy observed in this disorder. Although right hippocampal atrophy was not found, the fusiform gyrus and parahippocampal gyrus, located within the medial temporal region, are closely connected to the hippocampus. Additional studies using larger sample sizes might find atrophy of the hippocampus that is in line with previous reports of specific atrophy of the hippocampus in PTSD. However, not many studies to date have correlated grey matter density volume with symptom severity scores and none of these studies have used the voxel-based morphometry technique, which is more precise in detecting regional brain differences than the method of using regions of interests. Gurvits et al., 1996 found that total hippocampal volumes were highly correlated with combat exposure and symptom severity as measured by the CAPS in their sample of seven combat-related PTSD patients. Gilbertson et al. (2002) also reported that hippocampal volume was smaller with greater severity of PTSD symptoms in PTSD twins exposed to combat. PTSD severity remained to be significantly associated with hippocampal volume after adjusting for whole brain volume. Combat severity was also not significantly related to hippocampal volume in any of the subjects. Stein et al. (1997) examined the relationship between the subscales within the CAPS (re-experiencing, numbing, arousal and the total score) and total and left-sided hippocampal volume. The correlations ranged between 0.4-0.5, however, these did not fall below the P level of 0.003 after adjusting for multiple tests. Bonne et al. (2001) correlated hippocampal volume (left or right) and PTSD symptoms, as measured by the CAPS, after one week from the traumatic event and six months after developing PTSD. No statistically

significant correlation was found between symptom severity scores and hippocampal volumes.

Results of the present study provide strong evidence that severity of PTSD is related to the degree of atrophy of the medial temporal regions, particularly of the right hemisphere. These results support the hypothesis of the current study but also provide support for the Hippocampus-Stress model, which states that exposure to stress results in hippocampal neurotoxicity (Bremner, 1999; Sapolsky, 2000). Increased levels of glucocorticoids released in a stress response induce neuronal damage in the hippocampus. Based on the findings from Experiment 2 and 3, the following experiment will identify whether such regional brain atrophy contributes to neuropsychological deficits, based on the well-established role of the limbic structures in learning and memory.

4.14 EXPERIMENT 5: A Voxel-Based Morphometric Correlational Study with Neuropsychological Performance

4.14.1 Aims

Voxel-based MRI volumetric correlational analyses will also be carried out to explore whether low grey matter density volumes in medial temporal regions is associated with poor neuropsychological performance.

4.14.2 Methods/Procedure

4.14.2.1 Participants

A total of nine patients completed the neuropsychological testing and had undergone a MRI session. There were three females and six males (Mean age = 47, SD = 14.45). The sample is the same as those who completed Experiment 3 & 4; however, one of the road traffic accident victims did not take part in the neuropsychological testing. All other patient characteristics are the same as those in Experiment 3 & 4.

4.14.2.2 MRI Methods

See Experiment 2.

4.14.2.3 Data Analysis

This correlational study consisted of a series of simple regression analyses. Scores from the Topographical Localisation Task and Corsi Block Test, as well as the D' scores from the Landscapes and Words category of the Recognition of Visual Stimuli test were correlated with grey matter density volumes. Only clusters surviving corrected cluster probability levels were considered as significant.

4.14.3 Results

4.14.3.1 Words (Recognition of Visual Stimuli Test)

A correlational analysis using the D' scores from the Words category revealed no areas of significant correlation with grey matter density in any region of the brain.

4.14.3.2 Landscapes (Recognition of Visual Stimuli Test)

A significant negative correlation was found between the D' scores from the Landscapes category and right parahippocampal gyrus grey matter density values. Poor performance on this task was associated only with atrophy of this brain region (Figure 10 and Table 8).

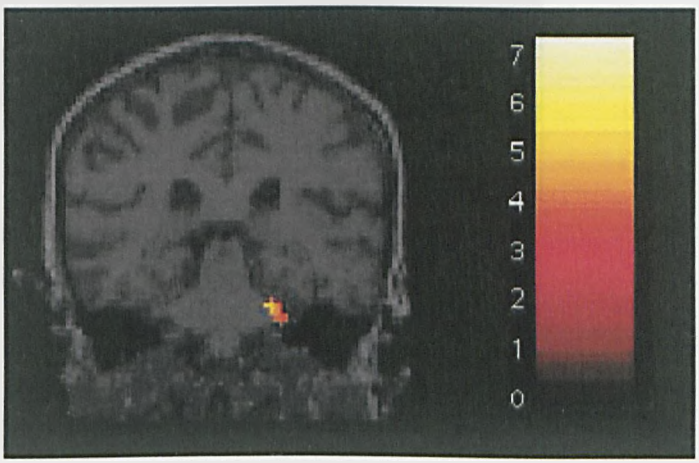

Figure 4.10. Coronal view of the atrophy associated with the D' scores from the Landscape category of the Recognition of Visual Stimuli test (height threshold, $p < .001$).

Table 4.8. *Areas of significant negative correlation (corresponding Brodmann's area, Talairach coordinates, z-score and cluster size and corrected cluster probability levels) between the D' scores achieved of the Landscapes stimuli and grey matter density.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
R parahippocampal gyrus (BA 36)	50	.001	2.78	26	-26	-30

4.14.3.3 Topographical Localisation test

A significant negative correlation was also found between the performance on the Topographical Localisation Test and atrophy in the left thalamus and hypothalamus, (Figure 11 and Table 9).

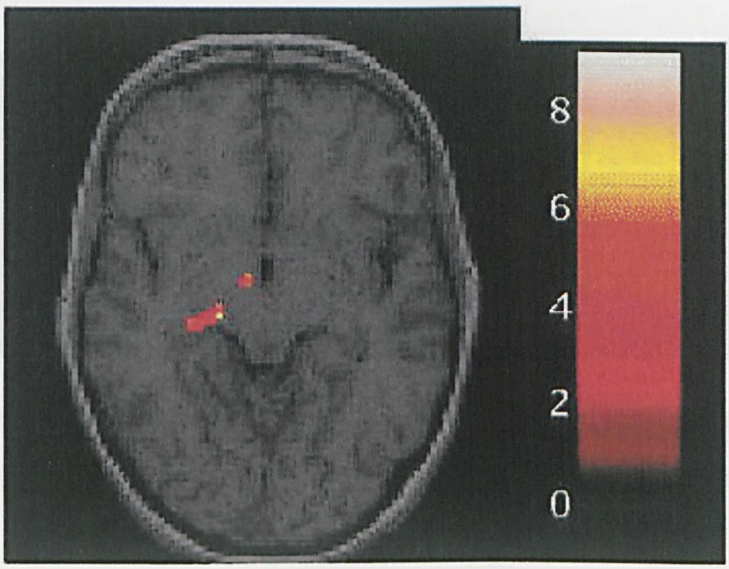

Figure 4.11. Axial image showing left thalamus and left hypothalamus atrophy correlated to performance on the Topographical Localisation test.

Table 4.9. *Stereotaxic coordinates, cluster sizes and corrected cluster probability levels, p-values, and Z-scores of the areas of significant correlation between the scores achieved on the Topographical Localisation test and grey matter density volumes.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
L Thalamus	675	.000	3.91	-14	-24	0
				-12	-10	-0
L Hypothalamus			3.49	-4	-5	-7

4.14.3.4 Corsi Block Test

A significant negative correlation was found between the scores on the Corsi Block test and brain atrophy in the left hippocampal region, right medial posterior temporal cortex (BA 19 & 37), and left thalamus (Figure 12 and Table 10).

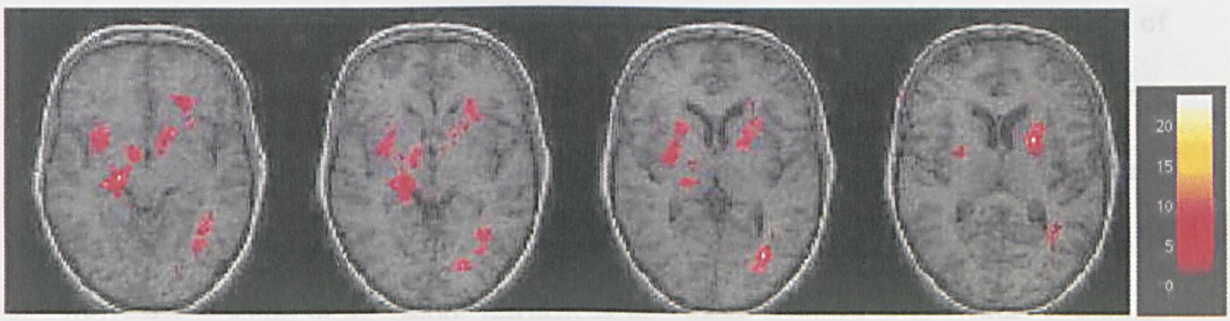

Figure 4.12. Axial image of the areas showing regional atrophies showing significant negative correlation with the Corsi Block Test performance (height threshold, $p < .03$).

Table 4.10. Areas of *significant negative correlations between grey matter density volumes and scores on the Corsi Block test (including Brodmann's areas, number of voxels in cluster and corrected cluster probability levels, p-values, Z-values, and Talairach coordinates.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
R Lingual Gyrus (BA 19)	75	.000	5.09	30	-68	6
R Fusiform Gyrus (BA 37)			3.15	36	-50	-6
L Ventral Post Lateral Nucleus	117	.000	4.33	-18	-18	4
L Hippocampus			9.88	-26	-22	-6
L Ventral Lateral Nucleus			9.16	-14	-14	4
L Middle Frontal Gyrus (BA 8)	94	.000	4.09	-50	28	46
L Inferior Frontal Gyrus (BA 46)			9.44	-54	42	14

4.14.4 Discussion

The results from this experiment clearly demonstrate medial temporal atrophy contributed to the memory deficits observed in Experiment 2. Carrying out a simple regression analysis with patients D' scores on the Landscape category of the Visual Picture Recognition test and grey matter density showed atrophy in the right parahippocampal gyrus (BA 36). The finding of atrophy of the right parahippocampal gyrus (PHG) being specifically associated with poor performance on a test of topographical memory is not surprising as extensive literature has demonstrated its role in scene recognition and navigation within environments. Structural and functional neuroimaging studies have implicated the PHG in topographical memory (Maguire et al., 2001; Rosenbaum et al., 2000; Barrash et al., 2000; Aguirre et al. 1996, Zarahn & D'Esposito, 1998). Maguire et al., 2001, examined the neural systems for the encoding and recognition of topographical information in healthy control subjects. These researchers found that the right PHG showed increased activation in the encoding and recognition stage of Landscape photographs. The results of this present study also suggest that the Visual Picture Recognition test of Landscapes, devised to be a similar test as that used by Maguire et al. (2001), is a sensitive test to measure topographical memory functioning and is particularly sensitive to detect even subtle parahippocampal damage.

Based on the consistent evidence that the right parahippocampal gyrus and hippocampus are important for topographical learning, the significant negative correlation between left thalamus atrophy and poor performance on the Topographical Localisation test might be difficult to interpret. However, Barrash et al., (2000) found that the right and left medial temporal regions correlated with a route learning impairments, but also found similar associations with the left and right thalamus. Right thalamus was also found to be activated when successful navigation trials were

compared to a task involving a trail of arrows (Maguire et al., 1998). Along with activation of the right thalamus using PET, right hippocampus and the left tail of the caudate nucleus were also activated. The preceding studies that found involvement of the thalamus along with medial temporal regions such as the hippocampus, is consistent with animal studies that have established that the thalamus is involved in spatial memory. Such studies have found that unilateral thalamic lesions can cause impairments on visuospatial tasks when there is damage to at least one of the temporal lobes in the opposite hemisphere (Ridley, Baker, Mills, Green & Cummings, 2004). Aggleton, Neave and Hunt, (1995) and Warburton, Baird, Morgan, Muir, and Aggleton (2001) also found that animals showed more severe impairments on spatial memory tasks when hippocampal and thalamic lesions were in the contralateral hemispheres compared to animals who had lesions in the same hemisphere. The connection of the hippocampus to the thalamus in PTSD has not been studied, thus, it is difficult to determine why hippocampal atrophy, along with atrophy of the thalamus was not found in the current study. One explanation for the association between poor performance on the Topographical Localisation test and the thalamus could be that although the hippocampus and connecting structures are responsible for spatial/topographical memory, lesions confined to the thalamus might presumably be sufficient to produce the deficits observed on the Topographical Localisation test. Golob & Taube (1997) lesioned hippocampi of rats to determine whether episodic spatial information can be stored and maintained over time without the hippocampus by examining head direction cells[6] in the postsubiculum and anterior thalamus. The findings of their study did suggest that extra-hippocampal structures in rats can encode spatial features of an environment, independent of the hippocampus.

[6] neurons that fire only when an animal orients its head in a certain direction. These cells are found in several different brain areas, with different neurons selective for different head orientations; they are influenced by landmarks as well as motor and vestibular information concerning how the head moves through space.

Peru & Fabbro (1997) examined a patient with a bilateral thalamic lesion caused by venous infarction. The patient initially suffered from verbal and spatial memory deficits, however, months afterwards when the lesion was confined to the left thalamus, verbal memory deficits remained, while performance on spatial memory tasks were within normal ranges. Therefore, the semantic nature of the Topographical Localisation task might provide an explanation for the finding of atrophy to the left hemisphere of the thalamus rather than the right thalamus.

A significant negative correlation was found between the scores on the Corsi Block test and brain atrophy in the left hippocampal region, right lingual gyrus, right fusiform gyrus, left ventral posterior lateral nucleus, left middle and inferior frontal gyrus. These regions are common brain structures related to spatial and topographical memory (Aguirre & D'Esposito, 1997; Johnsrude, Owen, Crane, Milner, and Evans, 1999). Atrophy of the left hippocampal region in this analysis may be explained by the use of a verbal strategy by the patients to navigate around the pegs of the Corsi board. This is a very likely explanation as the objective of this test is to remember the spatial temporal sequence of blocks tapped by the experimenter. The Corsi Block test, a test of visuospatial memory span is strongly linked to greater impairment following right-sided damage compared to left hemisphere (Kessels, de Haan, Kappelle, & Postma, 2001). Although no right hippocampal atrophy was observed, atrophy to right medial temporal and frontal regions are known to be involved in spatial memory (e.g. lingual gyrus and fusiform gyrus). Aguirre & D'Esposito (1997) used fMRI to study the appearance of a place (landmark knowledge) versus the location of a place (survey knowledge). Left inferior parietal lobule and premotor cortex were activated in the position task. During the appearance task, bilateral activation of the parahippocampus, fusiform and lingual gyrus and right middle occipital gyrus was found. In the PTSD group, it was expected that verbal memory impairments would be associated with left hippocampal atrophy,

however, no significant correlation was found using the D' scores from the Words recognition test and any region of the brain.

Few studies have examined memory functioning in PTSD and those that have, have primarily focused on attention, immediate memory and short-term verbal memory. Only a very limited number of studies have correlated neuropsychological performance with grey matter density. A MRI study by Bremner et al. (1995) examined short-term memory deficits in their group of PTSD patients who were found to have significantly smaller right hippocampal volumes compared to a comparison group of healthy controls. No significant difference between PTSD and control subjects in the left hippocampal volume was found. Short-term verbal memory as measured by the percent retention subscale of the Wechsler Memory Scale logical component was reported to be associated with right hippocampal volume reduction only in PTSD subjects compared to the control group. Gurvits et al. (1996) found significant correlations between hippocampal volume and performance on a summary index of attention (Wechsler Memory Scale-Revised), Arithmetic subtest of the WAIS-R, and the Benton Visual Retention test in a sample of seven Vietnam veterans and seven combat control subjects (i.e., lower total hippocampal volume correlated with more impairment). In addition, Bremner, Randall, Vermetten, Staib, Bronen, Mazure et al. (1997) studied a sample of 17 adult survivors of childhood abuse and found no significant correlation between scores on the Wechsler Memory Scale (immediate or delayed recall) and left or right hippocampal volume. As mentioned earlier, this is the first study investigating verbal and topographical memory using a voxel-based morphometric approach, therefore, further studies using this technique and using larger sample sizes should be carried out to gain a clearer understanding of the neuropsychological deficits associated with this disorder.

4.14.5 General Discussion

The findings from the present study showed that selective atrophy in the right and left medial temporal regions correlated with disease severity scores and with specific memory deficits in PTSD, but only for spatial memory tasks. Previous literature examining PTSD have addressed a number of questions that remain unanswered regarding the relationship between hippocampal atrophy and PTSD. Hippocampal volume reduction has been reported in various studies; however, many researchers remain unclear as to whether such atrophy is a cause of PTSD or an effect of PTSD (Horner & Hamner, 2002). Before PTSD is fully understood, neuroanatomically and behaviourally, authors such as Horner & Hamner (2002) and Hull (2002) have raised certain issues surrounding the existing literature on PTSD. For example, these researchers suggested that PTSD studies need to include a variety of PTSD populations as a vast majority of the work has involved combat veterans and sexual abuse victims. Studies should also attempt to include different PTSD populations within each study to determine whether findings are related to the exposure to specific traumatic events. The results of many studies reported in the Introduction of this chapter control for confounding factors. Many studies however, do not covary for factors such as psychiatric comorbidity, treatment effects, and alcohol and/or substance abuse. It is important to control for and take such factors into consideration as these factors have been reported to influence hippocampal morphology (Horner & Hamner, 2002). Although there are limitations in this current study, a heterogeneous sample of PTSD patients was studied and seven of the ten patients included in the group comparison did not have a second diagnosis. Only one patient had a lifetime diagnosis of harmful alcohol misuse, which is quite uncommon in the papers that have studied combat veterans. However, prior to the neuropsychological testing and MRI scanning session the patient was abstinent. A total of seven patients were, however, taking anti-

depressant medications. Severity of depression was not measured in this sample of PTSD. Future studies should attempt to control for depression symptoms. In addition, a group of depression patients or other psychiatric disorder groups should have been studied to delineate whether the memory deficits and hippocampal atrophy is specifically related to PTSD or if it is a general finding of psychiatric disorders. Vakili, Pillay, Lafer, Fava, Renshaw, Bonello-Cintron et al., (2000) did not find that major depression was associated with hippocampal volume. Their results suggested however, that disease severity, gender, and treatment response might influence hippocampal volume.

Another potential weakness of this study could be the small sample size of PTSD patients. Using a larger sample size might have showed selective atrophy of the right hippocampus in the group comparison or on tasks such as the Corsi Block Test and Topographical Localisation test. A larger sample size would also provide greater statistical power to detect impairments associated with PTSD in future studies.

In conclusion, this voxel-based correlational study has demonstrated that regional anatomical changes are associated with neuropsychological deficits in PTSD. More importantly, these regional changes have been found to be related to the severity of the PTSD symptoms suggesting that the relationship between hippocampal atrophy and PTSD produces spatial and topographical memory impairments.

4.15 EXPERIMENT 6: An Functional MRI Study of Susceptibility to Trauma Related Stimuli in PTSD

4.15.1 Introduction

The hippocampus, amygdala, anterior cingulate and medial prefrontal cortex are involved in conditioned fear responses (Bremner, Vermetten, Vythilingam, Afzal, Schmahl, Elzinga et al., 2004 & Sala, Perez, Soloff, Ucelli di Nemi, Caverzasi, Soares et al., 2004). Exposure to threatening stimuli activates the amygdala, which instantly performs the necessary behavioural and neuroendocrine response to threat. Threatening information also activates cortical structures and the hippocampus, which also projects to the amygdala. This network of brain areas not only plays a role in the modulation and extinction of fear responses, but also in the stress response (Bremner et al., 1999 & Brewin, 2001). For example, the medial prefrontal dopaminergic system is an extremely sensitive area that reacts to even mild stressors (Bremner et al., 1999). In addition, the hippocampus has the highest density of glucocorticoid receptors in the brain and evidence from animal and clinical studies have shown the greatest damage to this structure during chronic, excessive exposure to stress (McEwen et al., 1986, as cited in Bremner, 1999). Importantly, this structure has also been associated with atrophy in PTSD patients. In addition, fMRI studies of PTSD patients exposed to traumatic stimuli have reportedly shown changes in blood flow within limbic and frontal areas (Rauch, van der Kolk, Fisler, Alpert, Orr, Savage et al., 1996). Previous work has reported increased blood flow in limbic regions (i.e., right insula/amygdala and anterior cingulate) and decreased blood flow in frontal and temporal regions. The following section will introduce the current work that has been found in PTSD patients during

exposure to traumatic stimuli, primarily focussing on activations within the anterior cingulate cortex.

Using the emotional Stroop task in functional MRI (fMRI) studies, researchers have examined whether the affective division of the anterior cingulate (ACad) would be activated in healthy subjects when presented negative words to the same group of healthy subjects who demonstrated ACcd (cognitive division) activation during the counting Stroop (Whalen, Bush, McNally, Wilhelm, McInerney, Jenik et al., 1998). Thus, one of the aims of the study carried out by Whalen et al. (1998) was to determine whether fMRI could be used as a valid probe of ACad function in anxiety disorders. The emotional Stroop task is based on the classic colour Stroop interference paradigm. In the emotional Stroop, subjects are presented with words relevant to their condition and are required to press the button corresponding to the colour of the word (for example, word 'panic' in blue ink; answer blue). Interference in the classic Stroop occurs in the incongruent condition (word 'red' printed in yellow; the subject must answer yellow), in the emotional Stroop, interference occurs when disorder-relevant words are viewed. Most fMRI studies have modified the emotional Stroop task to the counting Stroop (cStroop) to avoid the head movements produced by speech. During the cStroop, words appear on the screen one to four times. Subjects are required to press the number on a key press corresponding to the number of times the word was presented. The nine healthy control subjects who participated in the study were free of medications, and also neurological, major medical, and psychiatric disorders. All subjects completed two runs of the emotional counting Stroop (ecStroop). Each run consisted of four 30 second blocks of neutral words (i.e. household items) and four blocks of negative words (e.g., murder, however half of the words in this study were general negative words, (danger & murder) and other half were specific to obsessive-compulsive disorder). Reaction time data revealed no significant main effect or

interaction when condition X block was analysed using an ANOVA. General negative words and obsessive-compulsive disorder words were compared. No significant differences in reaction times were found. Examination of the negative versus neutral words using the fMRI data revealed significant activation within the left ACad (BA 32) when the first two negative blocks were compared to the two neutral word blocks. Comparison of initial negative versus neutral blocks also showed activation of the left superior parietal lobule (BA 7). No other significant activation to negative versus neutral words within other limbic areas such as the amygdala, sublenticular substantia innominata, insular cortex, or orbitofrontal cortex was found. In addition, no significant difference in ACad activation to general negative versus obsessive-compulsive disorder specific words was found. The ACad signal intensity during task performance (both neutral and negative blocks) was found to be significantly lower than during the baseline fixation blocks that preceded and followed stimulus presentations. Examining the Fixation versus Task (all neutral and negative blocks) contrast, significant deactivation was found during task performance over a large portion of the ACad and frontal cortical regions (the subgenual AC (BA 25) and the orbitofrontal cortex were not visible in this study due to signal dropout). The results of this study found that the ecStroop task activated the more dorsal ACcd and also that the ACad showed a decrease in signal intensity when cognitive versus emotional information were compared. In this study, the authors stated that the ACad signal intensity appears to be modulated by processing word presentations during the cStroop and ecStroop. The authors have also suggested that lower signal intensity during stimulus presentations might indicate inhibition of the limbic area in an attempt to allocate resources for efficient cognitive performance. In addition, based on these findings, it is evident that normal anterior cingulate functioning can be studied in patient populations using the ecStroop. Regional blood flow increases have also been found in the amygdala, orbitofrontal cortex,

anterior temporal poles, insular cortex, and posterior cingulate cortex during exposure to reminders of trauma in PTSD patients (Bremner, Staib, Kaloupek, Southwick, Soufer, & Charney, 1999a; Bremner, Narayan, Staib, Southwick, McGlashan & Charney, 1999b; Liberzon, Taylor, Amdur, Jung, Chamberlain, Minoshima et al., 1999; Rauch et al. 1996).

The cingulate cortex is a part of each hemisphere that is situated in the midline above the corpus callosum. This region is separated into subdivisions that subserves cognitive, emotional, motor, nociceptive and visuospatial functions (Bush, Phan, & Posner, 2000). The anterior cingulate cortex is considered as being executive in function whereas the posterior cingulate cortex is characterised as evaluative (Bush et al., 2000). Based on anatomical tracing studies, the anterior cingulate cortex can be divided into separate cognitive and emotional regions (Whalen et al., 1998; Bush et al.). The cognitive division (ACcd) is within the dorsal areas (Brodmann's Areas 24b′-c′ and 32′) and the affective division (ACad) is within the rostral-ventral areas (Brodmann's Areas 24a-c and 32 and ventral areas 25 and 33 (Bush et al., 2000; Vogt et al. (1992) & Devinsky et al. (1995); as cited in Whalen et al., 1998). Evidence from imaging studies have also found the ACcd to have strong interconnections with the lateral prefrontal cortex (BA 46/9), parietal cortex (BA 7) and premotor and supplementary motor areas (Devinsky et al., 1995; as cited in Bush et al.). Some of the functions of this cognitive division include modulation of attention or executive functions by influencing sensory or response selection (or both); monitoring competition, complex motor control, motivation, novelty, error detection and working memory; and the anticipation of cognitively demanding tasks (Bush et al.). The affective division of the anterior cingulate has connections with the amygdala, periaqueductal grey, nucleus accumbens, hypothalamus, anterior insula, hippocampus and orbitofrontal cortex (Devinsky et al., 1995; as cited in Bush et al.). The main role of the ACad involves assessing the salience

of emotional and motivational information and the regulation of emotional responses (Whalen et al., 1998; Devinsky et al., 1995; as cited in Bush et al.).

Using an Emotional Stroop task, functional MRI (fMRI) studies have also found increased activation of the anterior cingulate cortex (ACC) during emotional words compared to neutral words in healthy subjects, but not in PTSD patients (Shin et al., 2001). The ACC is activated during the processing of emotional information. It might be predicted, therefore, that anxiety disorders such as PTSD, might be associated with decreased activation in the ACC in response to trauma-related words. Shin et al. (2001) used the Emotional Counting Stroop (ecStroop) in an fMRI study to examine the rostral ACC. Eight Vietnam combat veterans with PTSD and eight without PTSD were enrolled to take part in the study. The PTSD group had higher scores on the Combat Exposure Scale (CES) and CAPS. Select PTSD patients also met the criteria for current comorbid diagnoses of major depression, dysthymia, specific phobia, social phobia, panic disorder, generalised anxiety disorder, and obsessive compulsive disorder. All subjects in the study were free of metallic implants, neurologic and major medical conditions, and psychotropic and cardiovascular medications. During the ecStroop task, the subjects viewed a set of identical words (1-4 words were presented per trial) and were required to count the number of words presented and pressed a button corresponding to that number. The stimuli consisted of three different types of words: neutral words that names household items, generally negative words unrelated to combat, and also combat-related words. All subjects completed two 5-minute runs that consisted of ten 30-second blocks. In each run, there were four blocks of neutral words, alternating with two blocks of general negative words and two blocks of combat-related words. The fMRI data was collected using a General Electric Signa 1.5 Tesla high-speed imaging scanner. Response time data indicated that the PTSD group had longer response times than the non-PTSD group across all conditions. No main effect of word

type or interaction between word type and group was found. Analysing error rates also revealed that the PTSD group had significantly greater error rates than the non-PTSD group across all conditions. Main effect of word type or an interaction between word type was not found to be significant.

Within the combat versus general negative contrast, the non-PTSD group showed significant increases in the right rostral ACC and significant decreases in the left insular cortex. Within the PTSD group, significant increases were found bilaterally in the anterior insular cortex and in the dorsal ACC. In the combat versus neutral contrast, the non-PTSD group showed significant increases in the left anterior insular cortex. The PTSD group showed significant increases in the right anterior insular cortex. Within the general negative versus neutral contrast, the non-PTSD group showed significant increases in the medial frontal cortex, right mid-cingulate cortex, left hippocampus, and left parahippocampal gyrus. The PTSD group exhibited no increases in any region. The following areas showed significantly greater increases in the non-PTSD group compared to the PTSD group in the combat versus general negative condition: right anterior insular cortex and a region of ACC just posterior to the posterior boundary of rostral ACC. Within the same condition but within the PTSD group relative to the non-PTSD group, significant increases were found in the left anterior and bilateral posterior insular cortex and dorsal ACC. Same results were found when the combat condition was compared to the neutral condition except that the activation in the ACC was not significantly greater in the non-PTSD group than the PTSD group. Although previous studies have reported increases in activation in the rostral ACC in PTSD patients, this was only found in the non-PTSD group when the combat versus general negative condition was analysed. The authors stated that their results were consistent with previous studies. The PTSD patients in this study did not exhibit significant activation of the rostral ACC but did show significant activation in a dorsal region of ACC. The

increase in activation in the rostral ACC might play a role in allocating resources during a task involving interference between the meaning of the emotional word and counting the words presented (Mayberg, 1997; as cited in Shin et al. 2001). The authors have suggested that an increase in the cognitive processing load and an increase in behavioural interference might have activated a dorsal region of the ACC, which has been shown to be involved in interference paradigms (e.g. standard colour Stroop).

Bremner et al. (2004) hypothesized that the Stroop task would be associated with a lack of anterior cingulate activation in a group of abuse-related PTSD patients. This study assessed 12 PTSD patients whose diagnosis was made using the Structured Clinical Interview for DSM-IV. All patients were free of major medical illness on the basis of history and physical examinations, laboratory testing, and electrocardiogram and patients were not abusing substances or alcohol (a minimum 6 months). Subjects with a medical or neurologic illness, comorbid psychotic disorders, retained metal, a history of head trauma, a loss consciousness, cerebral infectious disease or dyslexia were excluded from the study. All patients and nine healthy control subjects (history of abuse with no PTSD) were not taking any medications. Childhood trauma was assessed using the Early Trauma Inventory (ETI). The patients and healthy control subjects completed the colour and emotional Stroop task and a control task during a PET scanning session. During the control condition, the subjects were required to name coloured X's that were presented randomly in red, yellow, green and blue. During the PET scans, psychophysiological measures were also obtained, such as, heart rate and blood pressure. Correctly naming the coloured words and emotional words resulted in lower scores than in the control condition. Patients with PTSD named fewer words across conditions, however, no significant interaction was found. Heart rate was also found to be higher within the PTSD group during the baseline tasks. Heart rate was also found to have increased in both groups to an equal degree in all of the tasks. No difference was

found in response time to emotional versus colour Stroop in the PTSD group compared to the healthy controls. Comparing the colour Stroop with the control task revealed a non-specific increase in anterior cingulate blood flow in both groups. During the colour Stroop, a direct comparison of the two groups showed no difference in activation in the anterior cingulate. The emotional Stroop was found to be associated with decreased blood flow in the anterior cingulate in only the PTSD group when compared to the colour Stroop. Comparing the emotional Stroop to the control condition, the non-PTSD group showed increased blood flow in the anterior cingulate. This difference however, was not significant when the two groups were directly compared. The non-PTSD group also showed increased activation during the colour task compared to the control task in the cerebellum, right middle temporal gyrus and left fusiform gyrus. Decreased blood flow was found in the left anterior frontal cortex and cuneus. The PTSD patients during the colour Stroop showed increased blood flow in the cerebellum, left inferior and middle frontal gyrus, right superior temporal gyrus, cerebellum, right supplementary motor area and right amygdala. Decreased blood flow was found in the right visual association cortex, precuneus and right inferior parietal lobule. Greater increases within the non-PTSD group was found during the colour Stroop in the right visual association cortex, cuneus, and right inferior parietal lobule. Greater decreases were found in the right superior temporal gyrus and orbitofrontal cortex. Comparing the emotional Stroop to the colour Stroop revealed a decrease in left inferior parietal lobule within the healthy control subjects. Within the PTSD patients, the emotional Stroop showed increased blood flow in the left precuneus, right cuneus, and right lingual gyrus. Decreased blood flow was found in the left middle frontal gyrus, left inferior frontal gyrus, right anterior frontal cortex, cerebellum, insula, uncus, right hippocampal region, midbrain and left superior temporal gyrus. A comparison between the non-PTSD subjects and PTSD patients revealed greater increases in blood flow during the emotional Stroop in the left

insula, pons, cerebellum, and left middle frontal gyrus and decreased blood flow in the precuneus.

Comparing the emotional Stroop to the control condition revealed increased blood flow in the anterior cingulate and decreased blood flow in the orbitofrontal cortex and right inferior parietal lobule in the healthy controls. The PTSD patients in the emotional Stroop showed increased blood flow in the left inferior frontal gyrus, cerebellum, hypothalamus and subthalamic area. Decreased blood flow was also found in the PTSD group in the precuneus, right inferior parietal lobule, uncus, right hippocampal region, midbrain and superior/middle temporal gyrus. The non-PTSD patients compared to PTSD patients had greater increases in blood flow within the emotional Stroop versus the control condition in the right hippocampus and right inferior temporal gyrus and decreased blood flow in the precuneus and posterior cingulate. The colour Stroop task resulted in a non-specific activation of the anterior cingulate in both non-PTSD women and PTSD women. The authors suggested that the anterior cingulate dysfunction in PTSD is specific to the neural circuitry of processing emotional stimuli. Similar to the previous study, deficits of the anterior cingulate functioning might be associated with PTSD.

Bremner et al. (1999) also hypothesised that combat veterans with PTSD relative to combat veterans without PTSD would show greater activation in cortical and subcortical brain areas implicated in memory, emotion and fear response when exposed to traumatic pictures and sounds. The following areas were predicted to result in greater activation using PET: amygdala, hippocampus and adjacent cortex, cingulate and prefrontal and parietal cortex. A total of 10 combat veterans with PTSD and 10 without PTSD were included in the study. Subjects in this study were screened for emotional and psychophysiological reactivity to specific traumatic stimuli. The subjects who met the criteria for current combat-related PTSD as assessed by the Structured Clinical

Interview (SCID) for DSM-IV were included in the study. Those subjects who did not meet this criteria and did not have an Axis I disorder based on the SCID were included as the control group. Subjects were excluded if they had any medical illnesses based on a history and physical examination, lab testing, and electrocardiogram and were not actively abusing substances or alcohol (minimum of 6 months) and were free of medications for at least 4 weeks before the study. However, subjects were not taken off medication solely for the purpose of participating in the study. Subjects were also excluded from the study who had major medical or neurological illness, organic mental disorders or comorbid psychotic disorders, current, alcohol and/or substance abuse or dependence (past 6 months), metal implants, a history of head trauma, loss of consciousness for greater than 10 minutes, cerebral infectious disease or dyslexia. All subjects completed four scans on a single day. The Subjective Units of Distress Scale (SUD's) was administered to the subjects every 5 minutes until three successive ratings were unchanged, which indicated that the subjects had adapted to the study's settings. Baseline subjective ratings were also collected as well as a 17 item PTSD symptom scale, the Panic Attack Symptom Scale (PASS), Clinician Administered Dissociative States Scale (CADSS), another SUD's scale and a visual analogue scale (0 to 100) to assess fear. In addition, baseline heart rate and blood pressure was also measured. Subjects completed PET scans during neutral (winter scenes with nonverbal music) and traumatic (combat slides) conditions with the exclusion of any rest scans where no stimuli was presented as this was reported to increase frontal lobe activity. An ANOVA revealed a significant main effect for diagnosis indicating that the PTSD patients had higher diastolic blood pressure than the controls, however, no main effect was found for time of presentation. The combat veterans with PTSD were also found to have relatively greater increases while viewing traumatic slides than the combat veterans without PTSD (significant time by diagnosis effect), for PTSD, anxiety, dissociative symptoms, and

subjective distress and fear. Significant increases in blood flow during the traumatic pictures and sounds was found in the PTSD group within the cerebellum, right inferior frontal gyrus and midbrain. The control subjects had increased blood flow in cerebellum, right anterior cingulate, left visual association cortex, left middle frontal gyrus and right middle temporal gyrus. Decreased blood flow within the PTSD group while viewing traumatic pictures and sounds was found in bilateral medial prefrontal cortex (BA 25), adjacent areas of left anterior cingulate, left thalamus, left visual association cortex, and superior temporal and left middle temporal cortex. The controls showed decreased blood flow in left superior temporal cortex, left precentral (motor) cortex, left inferior parietal lobule, mid-cingulate, cerebellum, and right lingual gyrus. A significant difference in the pattern of cerebral blood flow response to traumatic pictures and sounds was found between the combat veterans with PTSD relative to those without PTSD in the following areas: the left inferior parietal lobule, posterior cingulate (BA 23), left motor cortex (precentral gyrus), and the right lingual gyrus. Areas involved also consisted of a region, which included the dorsal pons and lateral cerebellum and portions of the parahippocampal gyrus (i.e., significant interaction between condition and diagnosis). The significant interaction was related to a pattern of either an increase in the PTSD group and a decrease in the non-PTSD group or a combination of both. There were also significant differences in the pattern of cerebral blood flow response to traumatic pictures and sounds between the PTSD and non-PTSD group in bilateral medial prefrontal cortex (subcallosal gyrus, BA 25) and bilateral middle temporal gyrus, which was mainly caused by a deactivation in the PTSD group. The significant difference in the medial prefrontal cortex was immediately adjacent to and merged into the anterior cingulate (BA 24 and 32). The authors have stated that this difference between groups was due to activation in the non-PTSD combat veterans. The results of this study have supported the stated hypothesis that combat veterans with PTSD relative

to combat veterans without PTSD would show significant differences in cerebral blood flow response to traumatic pictures and sounds in cortical and subcortical areas involved in memory, visuo-spatial processing, and emotion. Overall, the PTSD group showed increased blood flow, whereas the non-PTSD group showed significant decreases in blood flow. The decrease observed within the PTSD group was found in the medial prefrontal cortex (BA 25), middle temporal gyrus, and a region immediately adjacent to the right anterior cingulate (BA 24 & 32).

As mentioned in the Introduction of this thesis, Liberzon et al. (1999) measured regional cerebral blood flow using SPECT to examine the neurobiologic role of the limbic brain areas (including the amygdaloid complex, hippocampal formation, and limbic cortex which includes the orbitofrontal and anterior cingulate regions) in PTSD. The patient sample included 14 Vietnam veterans, 11 combat controls, and 14 normal control subjects. During the presentation of the stimuli (white noise and combat sounds), the subjects closed their eyes to facilitate imagery during the session. Compared to the control groups, only the PTSD group showed activation within the left amygdaloid. Regions that showed relative increases of activation which were outside the a priori region included the anterior cingulate / medial prefrontal cortex and regions with relative decreases included the right retrosplenial cortex. Relative activity in the region of the left amygdala was found to be roughly similar between the three groups during the white noise stimulus presentation but rose sharply only in the PTSD group during combat sounds. Activation in the anterior cingulate / medial prefrontal cortex showed similar results in all three groups using the composite image as well as the averaged image from each group. All three groups also showed activation peaks bilaterally in the temporal lobes, but in the PTSD group, the left temporal lobe activation appeared larger and more dorsal compared to the other two groups. Based on the findings that all three groups exhibited a response in the anterior cingulate/medial prefrontal cortex, the

authors stated that responses to combat sounds might not be specific to PTSD. This evidence was interpreted as providing further support to the hypothesis that structures involving the limbic and amygdala are involved in PTSD symptomatology. Activation of the amygdala supported existing evidence that this brain area is involved in emotion (Liberzon et al.). Furthermore, activation of the anterior cingulate cortex in all three groups is consistent with the role of this brain structure in emotional processing.

In addition to the anterior cingulate showing functional abnormalities in PTSD, a recent study, the first published of its kind, has also reported a structural abnormality of the anterior cingulate using VBM. This study investigated victims of the Tokyo subway sarin attack caused by terrorists. A total of 36 participants were recruited from a group of victims and of those 36, nine individuals with PTSD and 16 victims without PTSD took part in the study. These individuals were recruited on the basis that they received no psychiatric treatment for PTSD caused by the attack and had no history of alcohol and substance abuse. Of three of the nine PTSD victims, one also had comorbid current major depression, one had current panic disorder and one had a history of panic disorder with agoraphobia. The PTSD victims and non-PTSD victims did not differ from each other in age, gender, education, socioeconomic status and parental socioeconomic status. The comparison of regional grey or white matter between victims with and without PTSD revealed less grey matter density in victims with PTSD in the left anterior cingulate cortex. These results also remained after controlling for age and gender in the PTSD group versus the non-PTSD group. A negative correlation between total CAPS score was also found within the left anterior cingulate cortex. The authors have stated that this work supports previous studies which have also failed to show hippocampal atrophy following recent traumatic events, but showed deficits in frontal lobe tasks (Uddo et al., 1993; Vasterling et al., 1998, as cited in Yamasue, Kasai, Iwanami, Yamada, Abe, Kuroki et al., 2003). These results also support existing

evidence that the anterior cingulate is involved in regulating fear responses to traumatic events in PTSD patients. The absence of hippocampal atrophy in these PTSD patients may be explained by the following explanations by the authors. Firstly, previous studies that have found hippocampal atrophy studied combat veterans or survivors of sexual and/or physical abuse. An earlier study by Bonne et al. (2001) also did not find such atrophy in a group of patients one week or 6 months following the traumatic event. The patients presented in this paper by Yamasue et al. also included patients who had recently experienced the traumatic event, suggesting that smaller hippocampal volume may be present in chronic cases of PTSD. Also, it is likely that the comorbid depression and alcohol abuse often seen in PTSD might also be associated with hippocampal atrophy. Overall, this structural abnormality of the anterior cingulate cortex also suggests, along with the reported functional abnormalities, that a dysfunction in this region contributes to the pathology of PTSD.

4.15.2 Aims

The purpose of the present study was to use fMRI to compare brain activation between PTSD and healthy control subjects during exposure to disorder-specific stimuli. The emotional Stroop task was used as it is a standardised and well-established paradigm to examine brain areas involved in processing emotional information (Bremner et al. 2004; Shin et al. 2001; Whalen et al. 1998). Based on previous studies and the observed atrophy of the right medial temporal region, this study will examine changes in brain activation in the PTSD group during the Emotional Stroop and the Colour Stroop task.

4.15.3 Methods/Materials and Procedure

4.15.3.1 Participants

Replicated from Experiments 3 – 5.

4.15.3.2 Colour and Emotional Stroop Task

All participants performed the Colour and Emotional Stroop task during the fMRI data acquisition. During the congruent condition of the Colour Stroop task, the participants were required to name the colour of words (e.g. red, blue, green, and yellow). During the incongruent condition, the semantic context of the word was a colour name that was incongruent with the colour (e.g., the word green presented in red ink). During all conditions, participants viewed the words displayed simultaneously on a screen and pressed a button which corresponded to the colour in which the word was presented (i.e., Blue, Red, Green, Yellow). The participants were also presented with emotional (Threat) and neutral words. The participants viewed the words (30 words per block) displayed simultaneously on a screen and pressed the button which corresponded to the colour of the presented word. Threat/neutral and congruent/incongruent blocks were randomly presented across participants. Behavioural data, (i.e. response times) was collected during task performance.

Stimuli

In each of the four conditions, 75% of the stimuli were relevant to that condition and 25% were for the appropriate controlled condition (i.e., Congruent: 75% congruent and 25% incongruent, Incongruent: 75% incongruent and 25% congruent. Emotional: 75% threat and 25% neutral, Neutral: 75% neutral and 25% threat). This strategy was

adapted to control for a response bias. The emotional and neutral words were matched for length and frequency of usage (Kucera & Francis, 1967).

4.15.3.3 Data Analysis

Response times (for correct responses only) were averaged within each session for the incongruent and congruent condition as well as for the emotional and neutral conditions. Behavioural data from three patients was lost due to incomplete log files (technical difficulties) and due to poor performance.

4.15.3.4 Functional MRI Method

Functional MRI data were collected using an echo planar imaging technique with a 1.5 Tesla GE MRI system (TR = 2500, TE = 33ms, flip angle $\alpha = 90°$, voxel size = 1.88 x 1.88mm in plane resolution). Two hundred and four sets of 24 contiguous 5mm thick axial images were acquired. Stimuli were presented with a program devised using the software Presentation. The stimuli were projected via an Epson LCD projector onto a screen viewable with a mirror attached to a standard head coil. A block design was used with the alternation of threat/neutral and congruent/incongruent conditions. Each condition represented a 30 second epoch. Each complete set of four conditions was repeated twice in each session, for a total imaging time of 8 minutes and 32 seconds per session. Three sessions were recorded for each participant.

4.15.3.5 Functional MRI Data Analysis

Data were analysed using the SPM99 software (Wellcome Department of Imaging Neuroscience). Images were realigned and spatially normalised onto a standardised

anatomical space and then smoothed using a Gaussian filter set at 8mm. One sample and two sample t-tests were conducted using a random effects analysis procedure. Comparisons were made between the incongruent and congruent conditions and threat and neutral conditions and their interactions.

4.15.4 Results

4.15.4.1 Behavioural data

Repeated measures ANOVA revealed no significant differences between the PTSD patients and healthy control subjects in response times between the threat and neutral conditions ($F(1, 12) = .204$, ns) or accuracy scores between the groups, $F(1, 12) = .159$, ns). In addition, no main effect or interaction was significant comparing the response time data and accuracy scores between the PTSD patients and healthy control groups (Table 11).

Table 4.11. *Mean (SD) response times and accuracy scores (%) for threat and neutral conditions for both patient and healthy controls.*

Group	**Response Time**		**Accuracy Scores**	
	Threat	**Neutral**	**Threat**	**Neutral**
Patients	893.34 (216.2)	890.34 (207.4)	97.57 (1.9)	98.29 (1.7)
Controls	858.5 (169.6)	833.74 (165.4)	97.93 (2.0)	96.96 (3.6)

A repeated measures ANOVA revealed no significant differences between the PTSD patients and healthy control subjects in response times between the incongruent and

congruent conditions ($F(1, 12) = .363$, ns) or accuracy scores between the groups, $F(1, 12) = .037$, ns). However, a main effect of condition (incongruent and congruent) was found for the response time data and accuracy scores ($F(1, 12) = 33.52$; $p < .001$; $F(1, 12) = 8.40$; $p < .05$). No significant interactions were found to be significant when comparing the response time data and accuracy scores between the PTSD patients and healthy control groups ($F(1, 12) = 1.17$, ns; $F(1, 12) = 3.09$, ns) (Table 12).

Table 4.12. *Mean (SD) response times and accuracy scores (%) for congruent and incongruent conditions for both patient and healthy controls.*

Group	Response Time		Accuracy Scores	
	Congruent	**Incongruent**	**Congruent**	**Incongruent**
Patients	860.15 (128.77)	1009.37 (204.25)	86.51 (22.90)	82.46 (26.51)
Controls	805.34 (175.09)	953.54 (195.50)	84.20 (16.78)	80.40 (18.36)

4.15.4.2 Functional MRI data

Incongruent Vs. Congruent

Within the healthy control group, a one-way ANOVA revealed significant activations in the right middle occipital gyrus (BA 19), cuneus (BA 30), precuneus (BA 7), inferior temporal gyrus (BA 37), fusiform gyrus (BA 37), and supramarginal gyrus (BA 40) during the incongruent condition. Areas of significant activations within the left hemisphere were located in the precentral gyrus (BA 6), cingulate gyrus (BA 24), and

anterior cingulate (BA 32) (Figure 12). Full details can be found in Table 13. Only clusters surviving corrections for multiple comparisons were included as significant.

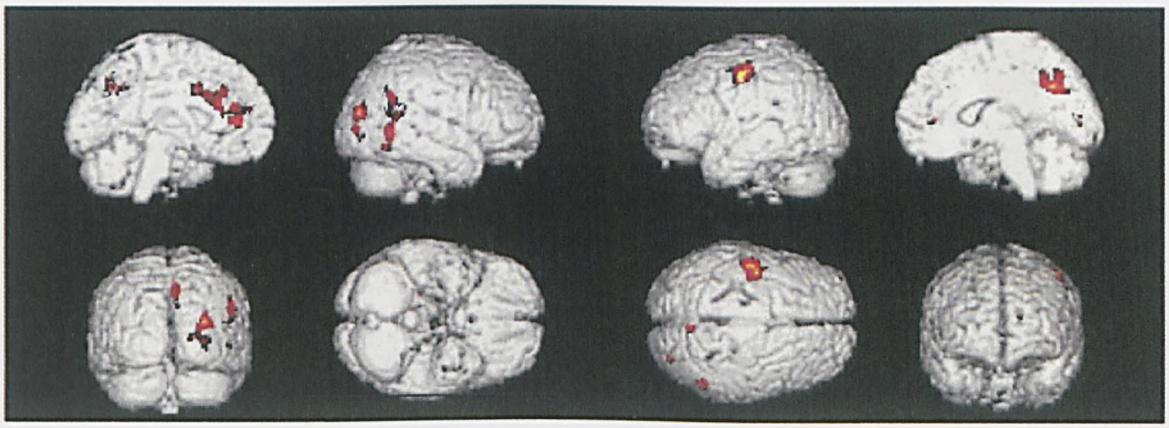

Figure 4.12. Areas of significant activations in the healthy control participants relative to the patients in the incongruent versus congruent condition (images are presented in the neurological convention) (threshold $p < 0.03$ corrected).

Table 4.13. *Brain regions of significant activations in the control group in the incongruent condition compared to the congruent condition.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
R middle occipital gyrus (BA 19)	308	.002	5.27	30	-82	18
R Cuneus (BA 30)			9.85	26	-74	6
R precuneus (BA 7)	366	.001	5.11	8	-60	36
			4.14	8	-66	42
			9.51	16	-54	44
L precentral gyrus (BA 6)	399	.000	4.67	-40	-10	46
L postcentral gyrus (BA 3)			9.80	-48	-16	48
L cingulate gyrus (BA 24)	587		4.31	-14	8	34
L anterior cingulate (BA 32)			4.14	-8	40	8
R inferior temporal gyrus (BA 37)	382		4.23	50	-56	-2
R fusiform gyrus (BA 37)			9.67	42	-58	-14
R supramarginal gyrus (BA 40)			9.51	52	-54	28

Within the PTSD group, areas of significant activations were found in the right subcallosal gyrus (BA 47), right parahippocampal gyrus, left medial frontal gyrus (BA 10), left insula and left transverse temporal gyrus (BA 41). See Figure 13 and Table 14.

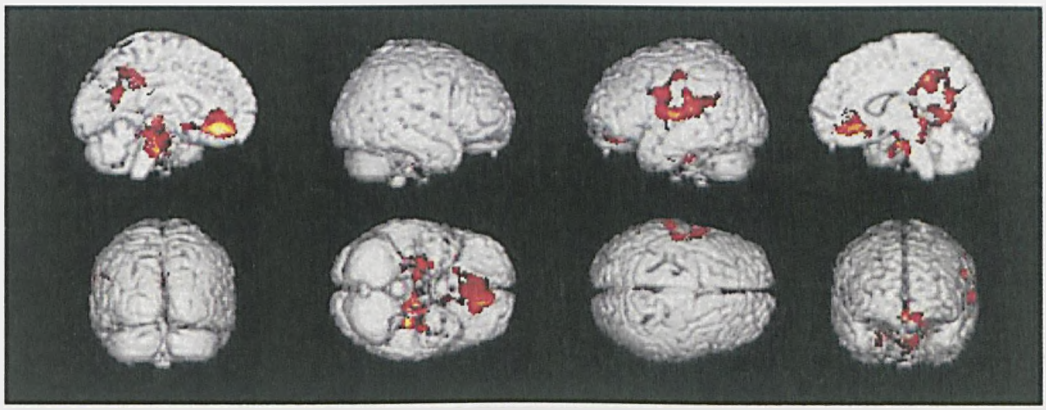

Figure 4.13. Areas of significant activation in the PTSD group in the incongruent versus congruent condition (threshold $p < 0.03$).

Table 14.14. *Areas of increased activations within the PTSD group in the incongruent vs. congruent condition, including Brodmann's areas, number of voxels in cluster, Cluster sizes and corrected cluster probability levels, Z-values, and Talairach coordinates.*

Area	Number of voxels in cluster	Uncorrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
R Subcallosal gyrus (BA 47)	1254	.000	4.30	20	15	-14
L Medial frontal gyrus (BA 10)			3.03	-8	38	-7
L Insula (BA 13)	1861	.000	4.26	-44	-15	6
L Transverse temporal gyrus (BA 41)			3.89	-32	-27	12
R Parahippocampal gyrus	2431	.000	3.89	26	-32	-15
L Posterior cingulate	665	.002	3.54	0	-57	21
R Cingulate gyrus (BA 31)			3.29	4	-37	33
L Precuneus (BA 7)			2.57	-2	-43	43

Within the PTSD group, areas of significant deactivations were found in the right inferior parietal lobule (BA 40), cingulate gyrus (BA 31), middle frontal gyrus (BA

6/8), and inferior frontal gyrus (BA 9). In addition, significant deactivations were also found in the left superior parietal lobule (BA 7). See Figure 14 and Table 15. Only clusters surviving correction for multiple comparisons were considered significant.

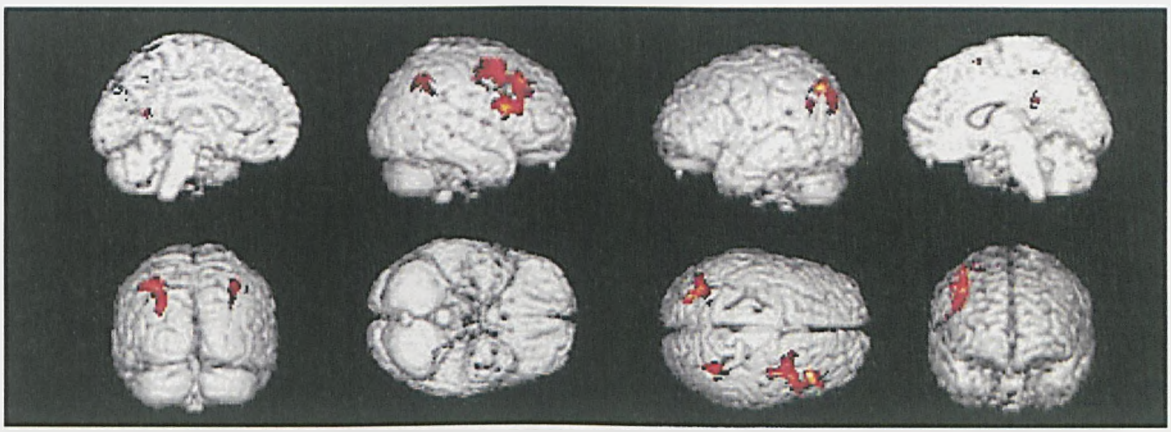

Figure 4.14. Areas of significant deactivation in the PTSD group in the incongruent versus congruent condition (threshold $p < 0.03$).

Table 4.15. *Areas of decreased activations within the PTSD group in the incongruent vs. congruent condition, including Brodmann's areas, number of voxels in cluster, Cluster sizes and corrected cluster probability levels, Z-values, and Talairach coordinates.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
R parietal lobule (BA 40)	853	.01	3.99	32	-52	38
L superior parietal lobule (BA 7)			9.06	-24	-58	44
R cingulate gyrus (BA 31)	1000	.005	3.54	26	-40	26
R middle frontal gyrus (BA 8)	1517	.000	3.41	40	24	46
R inferior frontal gyrus (BA 9)			9.20	54	8	24
R middle frontal gyrus (BA 6)			9.01	42	10	58

Group Comparisons

Healthy controls relative to patients in the incongruent versus congruent condition revealed significant areas of activation in the right middle occipital gyrus, left posterior cingulate (BA 29), left ventral lateral nucleus, left lateral posterior nucleus, left cingulate gyrus (BA 32), right precentral gyrus (BA 6), and right inferior frontal gyrus (BA 9). (Figure 15 and Table 16).

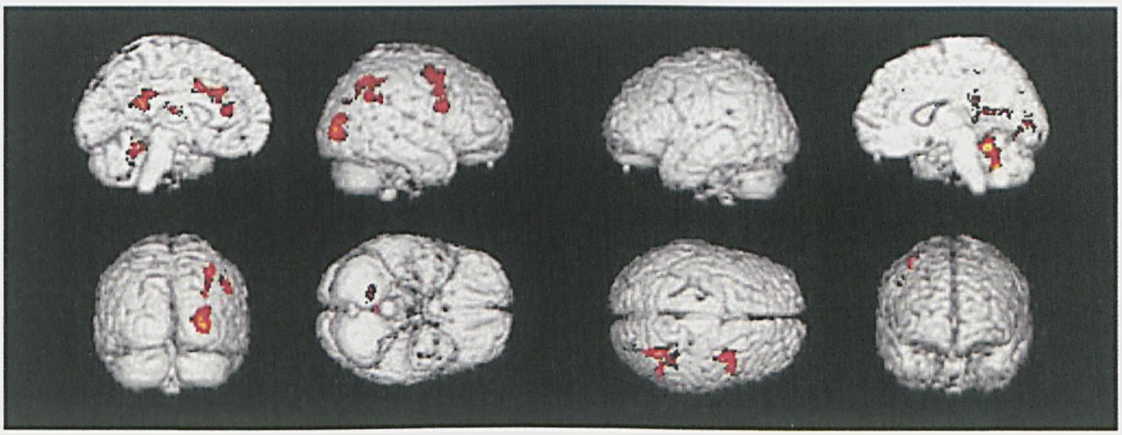

Figure 4.15. Areas of significant activation in the healthy controls relative to the patients in the incongruent versus congruent condition (threshold $p < 0.01$ corrected).

Table 4.16. *Areas of increased activations within the healthy controls compared to the patient group in the incongruent compared to congruent condition, including Brodmann's areas, Cluster sizes and corrected cluster probability levels, Z-values, and Talairach coordinates.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
R middle occipital gyrus	1899	.000	4.45	28	-86	2
R culmen	468	.02	4.54	14	-46	-18
L posterior cingulate (BA 29)	601	.005	4.12	-12	-42	20
L ventral lateral nucleus -			3.92	-18	-12	14
L lateral posterior nucleus -			9.79	-22	-18	18
L cingulate gyrus (BA 32)	541	.009	3.94	-14	24	32
R precentral gyrus (BA 6)	632	.003	3.77	34	4	24
R inferior frontal gyrus (BA 9)			9.95	52	8	26

A significant interaction between patients and healthy controls in the incongruent versus congruent condition also revealed significant deactivations in the left cingulate gyrus (BA 32) (See Table 17). As can be seen in Figure 16, in the PTSD group the cingulate gyrus showed decreased activation during the incongruent words and increased activation during the congruent words. The healthy controls showed an opposite pattern, with increased activation during the incongruent words and decreased activation during the congruent words.

Table 4.17. *Area of decreased activation in the patient group compared to the controls in the incongruent task relative to the congruent task.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
L cingulate gyrus (BA 32)	541	.041	3.94	-14	24	32

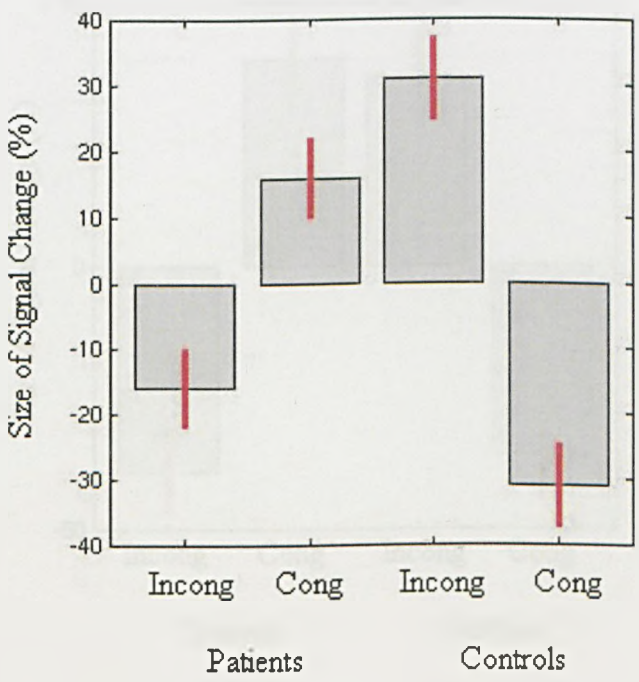

Figure 4.16. Size and direction of signal changes in the left cingulate gyrus (BA 32) in the PTSD patients and healthy control subjects (threshold $p<0.01$ corrected).

A significant interaction showing decreased activation was also found in the patients compared to healthy controls in the incongruent versus congruent condition in the right middle occipital gyrus (Table 18). Figure 17 illustrates the significant deactivations during the incongruent words and increased activations in the congruent words for the PTSD group and also shows the increased activation in the incongruent task and decreased activation in the congruent task for the healthy control subjects.

Table 4.18. *Area of decreased activation in the patient group compared to the controls in the incongruent task relative to the congruent task.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local	Talairach coordinates		
R middle occipital gyrus	1899	.000	4.45	28	-86	2

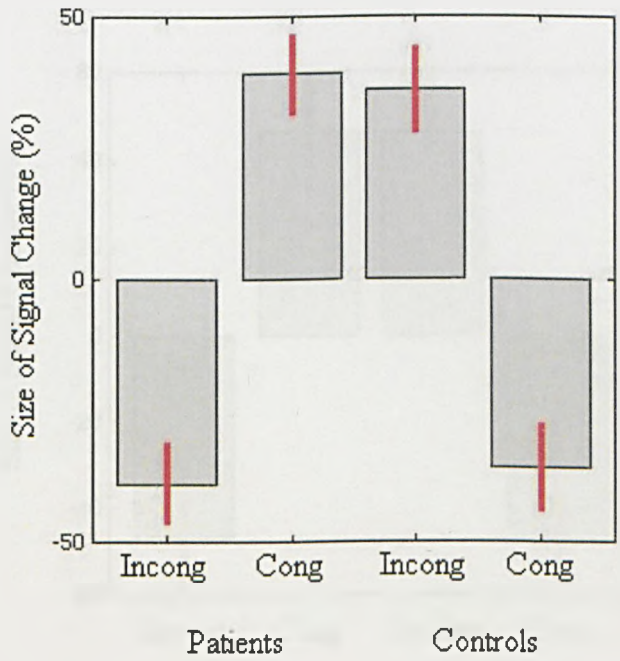

Figure 4.17. Size and direction of signal changes in the right middle occipital gyrus in the PTSD patients and healthy control subjects (threshold $p<0.01$ corrected).

A significant interaction also revealed significant decreased activation of the right precentral gyrus (BA 6) in the patients relative to the healthy controls in the incongruent condition compared to the congruent condition (Table 19). The PTSD patients showed decreased activation during the incongruent condition and an increased activation in the congruent task. The healthy controls were found to have increased activation within the right precentral gyrus (BA 6) during the incongruent condition and decreased activation in the congruent condition (Figure 18).

Table 4.19. *Area of decreased activation in the patient group compared to the controls in the incongruent task relative to the congruent task.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local	Talairach coordinates		
R precentral gyrus	632	.000	3.77	34	4	24

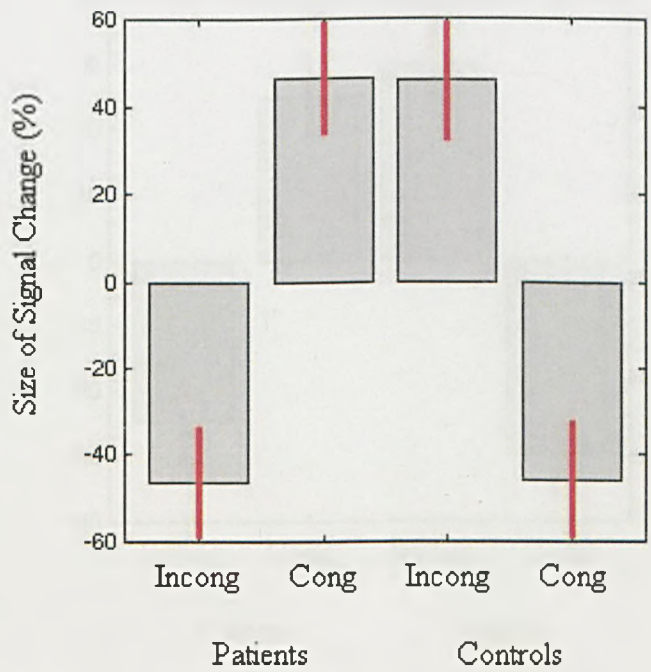

Figure 4.18. Size and direction of signal changes located within the right precentral gyrus (BA 6) in the patient and control group (threshold $p<0.01$ corrected).

An interaction between the patients and healthy controls was found in the incongruent and congruent condition which revealed decreased activation of the posterior cingulate (BA 29) (Table 20).

Table 4.20. *Area of decreased activation in the patients in the incongruent versus the congruent condition, including Cluster sizes and corrected cluster probability levels, z value, and Talairach coordinates.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
L posterior cingulate (BA 29)	601	.000	4.12	-12	-42	20

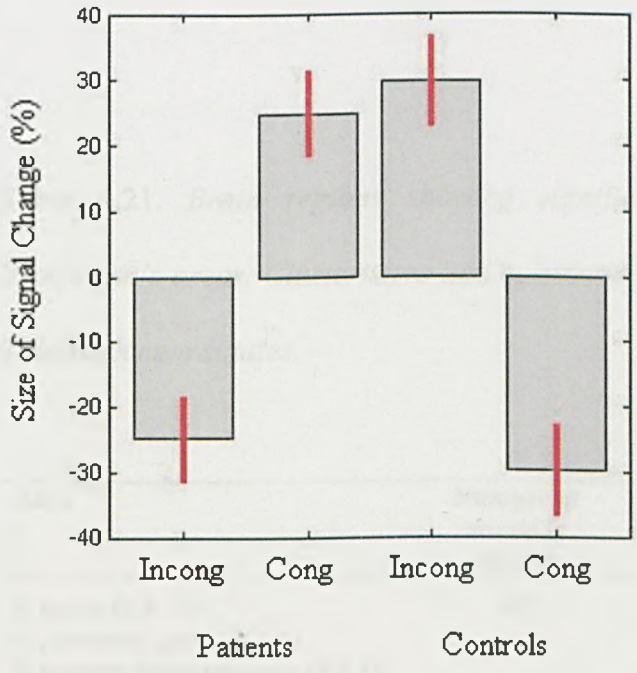

Figure 4.19. Size and direction of signal change of the left posterior cingulate (BA 29 in PTSD patients and healthy control subjects (threshold $p<0.01$ corrected).

Emotional Vs Neutral

Results from a one-sample t-test indicated that the healthy control subjects showed significant deactivations in the emotional condition (Threat words) compared to the neutral condition in the right insula (BA 13), right precentral gyrus (BA 4), and right superior temporal gyrus (BA 22) (Figure 20 and Table 21).

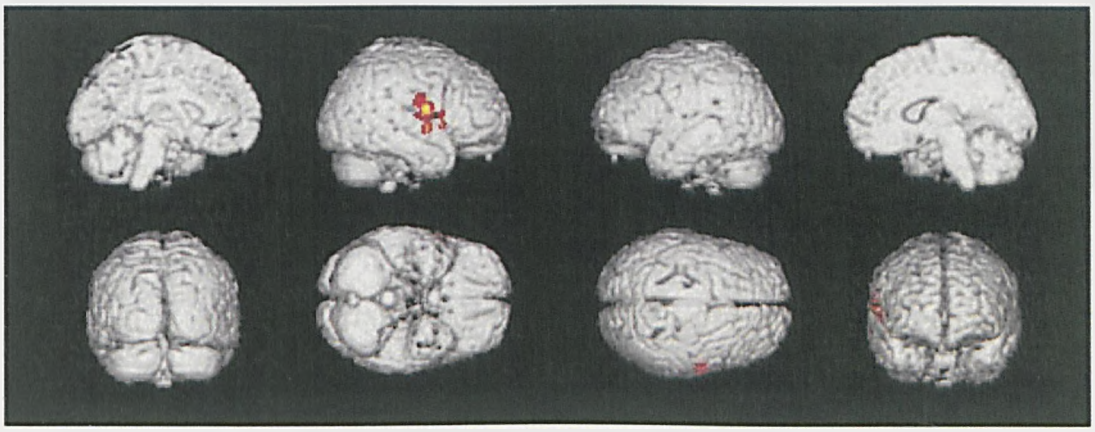

Figure 4.20. Areas of decreased activation in the healthy control subjects in the emotional words condition (threshold $p < 0.01$ corrected).

Table 4.21. *Brain regions showing significant deactivations and corresponding Brodmann's areas, Cluster sizes and corrected cluster probability levels, Z values, and Talairach coordinates.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
R insula (BA 13)	487	.032	3.53	40	-12	4
R precentral gyrus (BA 4)			9.48	60	-2	16
R superior temporal gyrus (BA22)			9.91	48	-2	-2

The PTSD group showed significant activations in the emotional condition compared to the neutral condition in the left dentate and right pons (Figure 21 and Table 22).

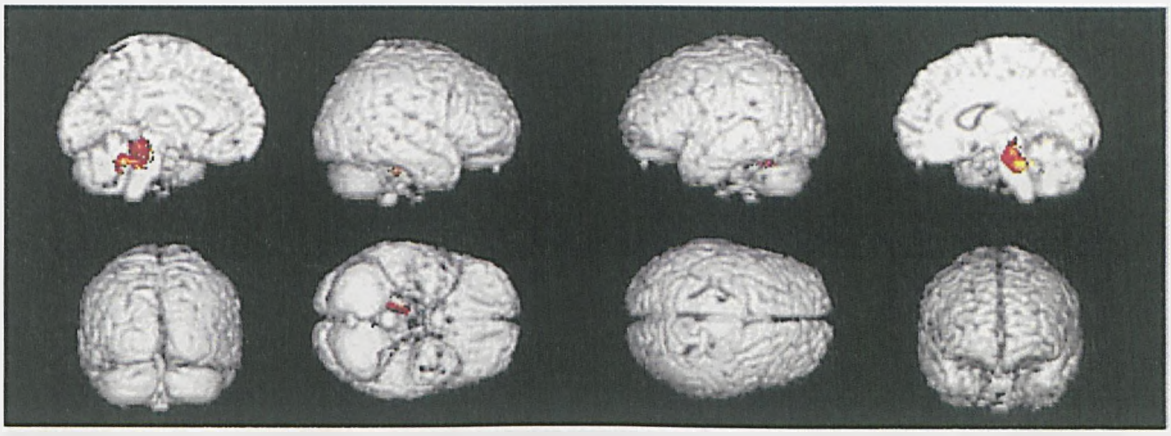

Figure 4.21. Areas of increased activation found in the PTSD patients during the emotional words condition (threshold $p < 0.03$ corrected).

Table 4.22. *Areas of increased activation in the patients in the emotional versus the neutral condition, Cluster sizes and corrected cluster probability levels, z value, and Talairach coordinates.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
L dentate	1022	.008	4.01	-10	-48	-26
R pons			9.28	10	-26	-24

Within the PTSD group, significant deactivations were found in the left medial frontal gyrus and left middle frontal gyrus (BA 46) during the emotional words condition (See Figure 22 and Table 23).

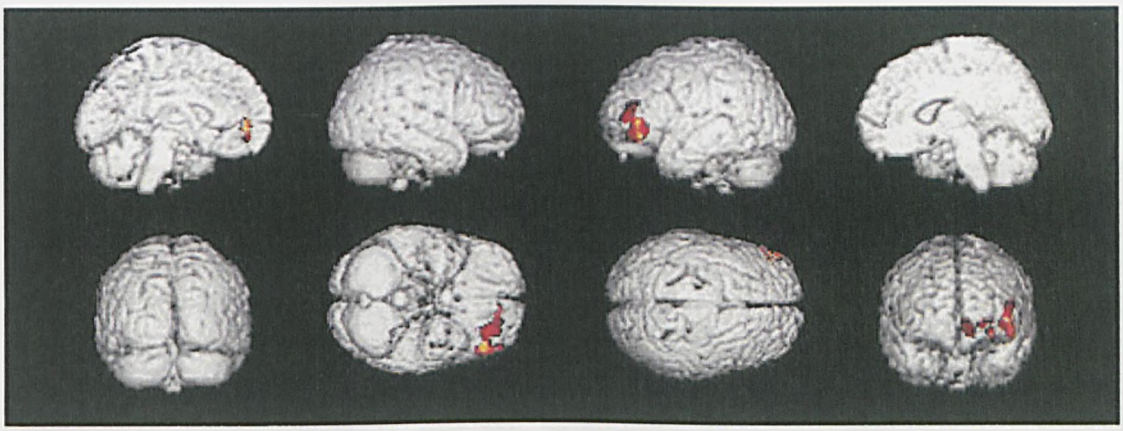

Figure 4.22. Areas of significant deactivations in the PTSD patient group within the emotional condition (threshold $p < 0.03$ corrected).

Table 4.23. *Areas of significant deactivations in the PTSD group within the emotional condition compared to the neutral condition.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
L medial frontal gyrus	808	.03	4.10	-8	48	2
L middle frontal gyrus (BA 46)			9.49	-44	48	16
			9.19	-48	42	20

Group Comparison

A two sample t-test comparing the patient group to the healthy controls in the emotional condition compared to the neutral condition revealed significant activations in the right middle temporal gyrus (BA 21), right substania nigra, and bilateral activation within the pons (See Figure 23 and Table 24).

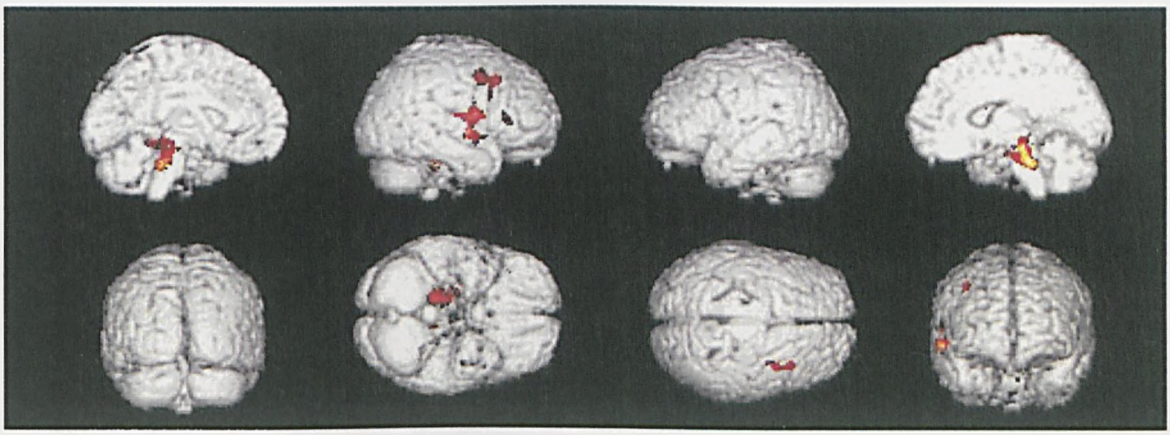

Figure 4.23. Areas of significant activations in the PTSD patient group relative to the healthy controls in the emotional condition compared to the neutral condition (threshold $p < 0.05$).

Table 4.24. *Areas of significant activations within the PTSD patient group compared to the healthy controls in the emotional versus neutral condition.*

Area	Number of voxels in cluster	uncorrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
R middle temporal gyrus (BA 21)	1149	.005	3.41	60	-2	-4
R pons	914	.01	3.18	10	-26	-24
R substania nigra			2.82	12	-28	-14

Figure 24 represents a significant condition by group interaction in the right middle temporal gyrus (BA 21). This figure illustrates the increased activation within the right middle temporal gyrus (BA 21) during the emotional condition in the PTSD group compared to decreased activation in the neutral condition. In addition, the healthy controls showed decreased activation in the right middle temporal gyrus (BA 21) during the emotional condition and increased activation during the neutral condition.

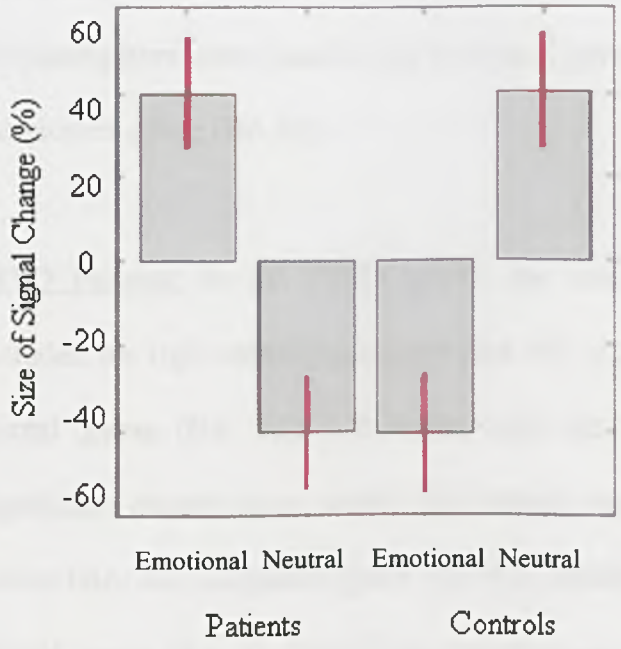

Figure 4.24. Size and direction of signal change in the right middle temporal gyrus (BA 21) in the PTSD patients and healthy control subjects.

4.16 Discussion

The present study aimed to use fMRI to compare brain activation between PTSD and healthy control subjects during exposure to disorder-specific stimuli. Use of emotional

and neutral words enables the ecStroop to be used as a neuroimaging probe of brain function in anxiety disorders such as post-traumatic stress disorder.

Incongruent Versus Congruent Condition

Healthy Participants: The results of the present study showed activations within the healthy control participants in the right middle occipital gyrus (BA 19), cuneus (BA 30), precuneus (BA 7), inferior temporal gyrus (BA 37), fusiform gyrus (BA 37) and supramarginal gyrus (BA 40) during the incongruent condition. Activations within the left hemisphere were found in the precentral gyrus (BA 6), cingulate gyrus (BA 24) and anterior cingulate (BA 32).

PTSD Patients: In the PTSD group, the areas that showed significant activations included the right subcallosal gyrus (BA 47), right parahippocampal gyrus, left medial frontal gyrus (BA 10), left insula and left transverse temporal gyrus (BA 41). Significant deactivations within this cohort were found in the right inferior parietal lobule (BA 40), cingulate gyrus (BA 31), middle frontal gyrus (BA 6/8) and inferior frontal gyrus (BA 9). Significant deactivations were also found in the left superior parietal lobule (BA 7).

Group Comparison: The healthy control subjects, relative to the PTSD patients in the incongruent versus congruent condition were found to have significant activations in the right middle occipital gyrus, left posterior cingulate (BA 29), left ventral lateral nucleus, left lateral posterior nucleus, left cingulate gyrus (BA 32), right precentral gyrus (BA 6) and right inferior frontal gyrus (BA 9). When comparing the PTSD patients to the healthy control subjects, a significant interaction revealed significant deactivations in

the left cingulate gyrus (BA 32), right middle occipital gyrus, right precentral gyrus (BA 6), and posterior cingulate (BA 29).

Emotional Versus Neutral Condition

Healthy Participants: The healthy control subjects showed significant deactivations during the emotional condition relative to the neutral condition in the right insula (BA 13), right precentral gyrus (BA 4) and right superior temporal gyrus (BA 22).

PTSD Patients: The PTSD patients showed significant activations in the emotional condition compared to the neutral condition in the left dentate and right pons. Significant deactivations were found in the left medial frontal gyrus and left middle frontal gyrus (BA 46).

Group Comparison: When the PTSD patients were compared to the healthy participants during the emotional condition relative the neutral condition, significant activations were found in the right middle temporal gyrus (BA 21), right substantia nigra and bilateral activation was found in the pons.

Neuroimaging studies using symptom cueing paradigms in PTSD have shown involvement of the anterior cingulate cortex (ACC). Previous studies have either reported activation of the ACC (Rauch et al., 1996), shown no involvement of the ACC (Pissiota, Frans, Fernandez, von Knorring, Fishcher, Fredrikson et al., 2002), increases within the ACC of both controls and PTSD (Liberzon et al., 1999), or greater increases in the controls than PTSD subjects (Bremner et al., 1999a, 1999b; Lanius, Williamson, Densmore, Boksman, Gupta, Neufeld et al., 2001). There have been many

inconsistencies regarding the involvement of the ACC during symptom provocation in PTSD patients.

In the comparison of incongruent versus congruent word conditions, the controls exhibited significant activation in the left anterior cingulate, but no significantly activated regions were found in the PTSD patients during this condition. These findings are consistent with Pissiota et al. (2002). Using PET, these researchers carried out a symptom provocation study in a group of PTSD patients who had experienced recent combat exposure. Their findings included rCBF increases in the right sensorimotor cortex (BA 4/6), the cerebellar vermis and the periaqueductal grey matter adjacent to the pons and decreased rCBF in the right retrosplenial cortex (BA 26/29/30) and rCBF was significantly higher in the right amygdala but not the left amygdala.

Within the PTSD group, significant deactivations in the incongruent versus congruent condition included the right parietal lobule (BA 40), left superior parietal lobule (BA 7), right cingulate gyrus (BA 31), right middle frontal gyrus (BA 6/8) and right inferior frontal gyrus (BA 9). Anterolateral prefrontal cortex (superior and middle frontal gyri) have been reported to be involved in mediating visuospatial processing, which is important for survival in life threatening situations (Bremner et al.,1999b). This area is also interconnected with the medial prefrontal cortex to play a role in the stress response. Using PET, decreased metabolism was also found at baseline within the temporal and prefrontal cortex in PTSD subjects and also in the parietal cortex of PTSD subjects with comorbid substance dependence (Semple et al., 1996, as cited in Bremner et al., 1999b). Decreases in the inferior frontal cortex have also been found in PTSD subjects in studies utilising traumatic scripts as well as trauma-related mental imagery (Rauch et al., 1997 & Shin et al., 1997, as cited in Bremner et al., 1999b). The inferior frontal gyrus plays a role in the encoding and processing of verbal material (Bremner et al., 1999a). Memory encoding and retrieval in patients with PTSD have been reported to

be different from those without PTSD (Charney et al., 1993 & Orr et al., 2002, as cited in Gilboa, Shalev, Laor, Lester, Louzoun, Chisin et al., 2004). Decreased activation of the right middle frontal gyrus (BA 6/8) found in this group of PTSD subjects supports previous studies as this area is involved in the strategic retrieval of episodic memory (Gilboa et al., 2004). Consistent with other studies, the PTSD group also showed increased activation in a medial prefrontal region, right subcallosal gyrus (BA 47), which plays a role in autonomic control (Giloboa et al., 2004; Shin et al., 1997, as cited in Shin et al., 2001). Increased activation within the PTSD group in the incongruent versus congruent condition was also found in the right parahippocampal gyrus, an area involved in visuospatial memory as well as anxiety. The parahippocampal gyri, along with the posterior cingulate and parietal cortex have been suggested to work together to mediate the cognitive functions that are required to cope with threat. Using p values uncorrected for multiple comparisons, the results also showed increased activation of the posterior cingulate. In addition, increased activation was also found in the left medial frontal gyrus (BA 10), left insula (BA 13) and left transverse temporal gyrus (BA 41). Bremner et al. (1999b) studied PTSD subjects while listening to scripts of childhood sexual abuse and found increased activation in the PTSD group in the following areas: posterior cingulate, anterolateral prefrontal cortex (BA 6/9) and motor cortex. In addition, the authors also found decreased activation within the subcallosal gyrus region of the anterior cingulate (BA 25), failure of activation in adjacent areas of the anterior cingulate (BA 32), decreased activation in the right hippocampus, fusiform/inferior temporal gyrus, supramarginal gyrus and visual association cortex. Bremner et al. (1999a) also found decreased activation in the ventral portions of ACC (subcallosal gyrus, BA 25). Bremner et al. employed PET to measure CBF during exposure to combat-related and neutral pictures and sounds in Vietnam veterans with PTSD and without. Similar to the current study, Shin et al. (2001) also found increases

within the PTSD group when the combat versus general negative condition was compared in the insular cortex, bilateral medial frontal gyrus and bilateral parahippocampal gyrus. Activation of the right insula was also found in PTSD subjects when exposed to traumatic scripts (Bremner et al., 1997, as cited in Bremner et al., 1999b). Similar to the medial prefrontal cortex, the insula plays a role in the response to fear (Bremner et al., 2004). Within PTSD, excessive recruitment of the brain areas involved in visuospatial processing, attention and memory might be seen as due to dysfunction of the brain's response in coping with stress and threat (Bremner et al., 1999a).

The current study differed from other published studies that found decreased activation of the amygdala and anterior cingulate. No brain areas showed increased activation in the PTSD subjects relative to the healthy controls in the incongruent versus congruent condition. Examining the incongruent versus congruent condition showed increased activation in right middle occipital gyrus, right culmen, left posterior cingulate (BA 29), left ventral lateral nucleus, left lateral posterior nucleus, left cingulate gyrus (BA 32), right precentral gyrus (BA 6) and right inferior frontal gyrus (BA 9) in the healthy controls relative to the PTSD subjects.

Of interest is the presence of significant interactions between the groups and conditions. Significant interactions were found in the PTSD subjects relative to the healthy controls in the incongruent condition compared to the congruent condition. The PTSD subjects showed decreased activation in the left cingulate gyrus (BA 32), right middle occipital gyrus, precentral gyrus (BA 6) and left posterior cingulate (BA 29) during the incongruent condition and increased activation of these areas during the congruent condition. The controls showed the opposite pattern in these areas during the incongruent versus the congruent condition. Visual association cortex (BA 19) and cuneus are involved in making visual associations and processing visual imagery and

memory. Dysfunction of these areas might represent a neural correlate of alterations in visual imagery in PTSD (Bremner et al., 2004). Although not predicted, activation of the precentral gyrus (BA 6) could prepare an individual for action during a stressful situation, thus, authors have suggested this area might be involved in the motor aspect of such memories (Squire and Zola-Morgan 1999 & Lang et al., 1983, as cited in Bremner et al., 1999a). Bremner et al. (1999a) stated that the posterior cingulate and inferior parietal cortex mediate visuospatial processing, which plays an essential element in the preparation of coping with a physical threat. Increased activation of the posterior cingulate has also been found using PET in victims of bank robbery while watching films depicting bank robbery (Fischer et al., 1996, as cited in Bremner et al., 1999a). These findings support the role this structure has in emotional processing of distressing material.

The healthy control subjects showed decreased activation in the right insula (BA 13), right precentral gyrus (BA 4) and right superior temporal gyrus (BA 22) in the emotional condition compared to the neutral condition. The PTSD group showed significant deactivations in the left medial frontal gyrus and left middle frontal gyrus (BA 46) within the emotional condition compared to the neutral condition. In addition, increased activation within the PTSD subjects during the emotional versus neutral condition was found in the left dentate and right pons. The group comparison examining the emotional condition to the neutral condition in the PTSD subjects relative to the healthy controls showed significant activations in the right middle temporal gyrus (BA 21), right pons and right midbrain. Along with the anterior cingulate, the middle temporal cortex is involved in the extinction of fear through inhibition of the amygdala (Jarrell et al., 1987 & Romanski & LeDoux, 1993, as cited in Bremner et al., 1999a). These previous studies have found decreases within the middle temporal gyrus, whereas this study found an increase in this region. An increase in right middle temporal gyrus is

also consistent with the work by Shin et al. (2001). Exposure to threat words also showed increased activation in areas such as the right middle temporal gyrus, an area involved in memory and visuospatial processing (Bremner et al., 1999a). Decreases in the middle temporal gyrus has also been suggested to play a role in verbal declarative memory tasks (Tulving et al., 1994, as cited in Bremner et al., 1999a). A major site of noradrenergic neurons that has projections throughout the cortical and several subcortical regions are found in the dorsal pons. This network plays a role in stress and coping with threat and the pons is an area that might possibly participate in PTSD symptomatology, however, not many studies have found unequivocal results (Tanev, 2003). This study is consistent with increased activation of the pons in PTSD and also the increased activation of the right midbrain in the emotional versus neutral condition (Bremner et al., 1999a). Unlike other studies, this study did not find a difference in response times to emotional words in the PTSD subjects compared to the healthy controls. The mean response times were slower than the controls, however, it might have reached significance with a larger sample size.

Amygdala activation has been found in PTSD symptom provocation studies but unlike prior studies, increased or decreased activation of the amygdala was not found in the current study. Abnormal activation of the amygdala and anterior cingulate cortex has been reported in PTSD patients exposed to trauma-related stimuli (Gilboa et al., 2004; Liberzon et al., 1999; Rauch et al., 1996). The medial prefrontal cortex has been implicated in the failure of emotional regulation and the inability of fear extinction (through impairment of the ability to inhibit the amygdala) in PTSD (Bremner 2002 & Pitman 2001, as cited in Bremner et al., 2004). Located in the anterior part of the temporal lobe, the amygdala is involved in the fear response and emotional processing (Bremner et al., 2004). Although not consistently observed, it is speculated that within PTSD, the anterior cingulate cortex fails to inhibit a hyperresponsive amygdala, which

would explain why PTSD subjects are not capable of extinguishing the fear response when exposed to traumatic cues and reminders (Bremner et al., 2002; Bremner et al., 1999b). Some investigators have suggested that within PTSD, the amygdala responds to threat-related stimuli independent of medial frontal activation (Rauch et al., 2000). Similar to this study, Bremner et al. (2004) also did not find activation of the amygdala in the emotional-colour Stroop task. These authors have suggested that the processing of emotional words in PTSD is not associated with increased amygdala activation. The equivocal findings of amygdala activation in PTSD subjects might be due to the nature of the trauma (Hull, 2002). The amygdala might be more responsive to personal narratives of traumatic events compared to those studies that have used commonly used traumatic pictures (Rauch et al., 1996) and combat sounds (Bremner et al., 1999a).

The initial predictions of this study were only partly supported by the results and activity was seen in a more general neural network than predicted. However, this failure to observe activation or deactivation in the predicted areas should not be confused with previous findings of activation and deactivation because this present study has a few limitations that need to be addressed. The PTSD subjects included in this study did not have a similar history of trauma. Previous studies have always included groups of combat veterans or sexually abused victims, no investigators have included patients with a mixed aetiology of PTSD. Therefore, these studies are also able to include a control group of healthy subjects who have also been exposed to similar trauma but did not develop PTSD. Investigators are then able to determine whether such findings are a cause of trauma or PTSD. The lack of activation and/or deactivation of the anterior cingulate and amygdala in this study and also across other studies which show inconsistencies might also be attributed to factors such as study design (personal trauma script or generalised traumatic words and sounds) and imaging techniques (PET, SPECT, fMRI). It can be expected that perhaps employing a larger sample size could

demonstrate specific patterns of activations. However, it is also possible that different PTSD symptoms correlate with different activation. Several different clusters of symptoms are present within PTSD and not all PTSD subjects may experience the same cluster of symptoms. It is speculated that perhaps instead of just one PTSD neurocircuitry, different clusters of symptoms activate different neural circuits. These interpretations will require additional studies. In conclusion, this study suggests that symptom provocation in PTSD does correlate with brain regions involved in memory (as well as visuospatial memory) and emotion and that a dysfunction in limbic-cortical networks exists in PTSD.

CHAPTER 5 Alzheimer's Disease

5.1 Early Onset Alzheimer's Disease

Alzheimer's disease (AD) is a degenerative disorder of the brain that is chronic and progressive and inevitably leads to death (Busatto et al., 2003; Adelstein, Kesner & Strassberg, 1992). The incidence of dementia rises exponentially with age (40-64) (Jorm, 1990, as cited in Hunter, 1997). By the age of 40 the incidence of dementia is 1 in a 1000 and 3 – 4 of 1000 show signs of cognitive impairment, although not severe enough to require further investigation. Before the age of 65, men are more affected by dementia compared to women (Hunter, 1997). AD is categorized into two groups, early onset AD refers to individuals who are diagnosed before the age of 65 and late onset AD refers to individuals who develop the disease after the age of 65 (Hunter, 1997). Early onset AD is rare among the general population of AD patients and has been found to have a genetic determinant (Hunter, 1997). Early onset AD patients usually have a family history of dementia, which is caused by AD (Breitner et al., 1988, as cited in Hunter, 1997).

The symptoms of early onset AD can be divided into two groups, cognitive and behavioural. However, these groups of symptoms are not seen independent of each other (Hunter, 1997). Cognitive deficits include memory, intellect and reasoning associated with disturbances in consciousness and attention. Hallucinations, delusions, disturbances in mood and wandering are typical behavioural symptoms observed in early onset AD (Hunter, 1997). AD is also associated with brain abnormalities such as, medial temporal lobe atrophy, neurofibrillary tangles, and senile plaques (O'Brien et al. 1997; Mizuno et al., 2000). Researchers have also found that long before such

behavioural and cognitive symptoms are seen in AD patients, the pathological process of AD (atrophy of brain structures) is already present (Wolf, Grunwald, Kruggel, Riedel-Heller, Angerhöfer, Hojjatoleslami et al., 2001; Fox & Schott, 2004).

5.2 Diagnostic Criteria

The following criteria for the diagnosis of probable AD, possible AD and definite AD have been determined by The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria (McKhann et al., 1984).

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

- dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
- deficits in two or more areas of cognition;
- progressive worsening of memory and other cognitive functions;
- no disturbance of consciousness;
- onset between ages 40 and 90, most often after 65; and
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease include:

- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);
- impaired activities of daily living and altered patterns of behaviour;
- family history of similar disorders, particularly if confirmed neuropathologically; and
- laboratory results of:

- normal lumbar puncture as evaluated by standard techniques;

- normal pattern or nonspecific changes in EEG, such as increased slow-wave activity; and

- evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

- plateaux in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;
- other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
- seizures in advanced disease; and
- CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

- sudden, apoplectic onset;
- focal neurologic findings such as hemiparesis, sensory loss, visual fields deficits, and incoordination early in the course of illness; and
- seizures or gait disturbances at the onset or very early in the course of illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

- may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;

- may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and
- should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable causes.

VI. Criteria of DEFINITE Alzheimer's disease are:

- the clinical criteria for probable Alzheimer's disease and histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

- familial occurrence;
- onset before age of 65;
- presence of trisomy-21; and
- coexistence of other relevant conditions such as Parkinson's disease.

5.3 Morphometry Studies

The medial temporal lobe is generally the first region of the brain that shows the most volume reduction in Alzheimer's disease (Karas, Burton, Rombouts, van Schijndel, O'Brien, Scheltens et al., 2003; Frisoni, Testa, Zorzan, Sabattoli, Beltramello, Soininen et al., 2002; Baron, Chételat, Desgranges, Perchey, Landeau, de la Sayette et al., 2001; Rombouts, Barkhof, Witter & Scheltens, 2000; Braak & Braak, 1991). Studies by investigators such as Dickerson, Goncharova, Sullivan, Forchetti, Wilson, Bennett et al. (2001) have been carried out to compare the extent of MRI-derived hippocampal atrophy as well as entorhinal atrophy in very mild and incipient AD in order to identify the areas that show pathology early in the disease process. These researchers studied 34 healthy elderly control subjects (NC), 28 patients who reported cognitive complaints but did not meet the criteria for dementia (ND) and 16 patients with very mild probable AD

(AD). The clinical diagnosis of probable AD was determined by the criteria of the National Institute for Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA). Exclusion criteria for the AD and ND patients included evidence of other neurological, psychiatric or systemic conditions that could cause cognitive impairment, such as, stroke, alcoholism, and major depression. As determined from the results of the neuropsychological test battery, the ND patient group included 13 patients with isolated memory impairment, two members with attention deficits, one patient with language deficits and 12 patients without any evidence of a cognitive impairment. However, no patients in this group had a cognitive impairment in more than one domain. In this study, manual segmentation was used to compute volumes of regions of interest with a PC image analysis program. The results indicated that the three groups did not differ in age or level of education, however, significant group effect for MMSE scores did emerge. Both the ND and AD patients differed from the controls but did not differ from each other. Results from the ANOVA revealed significant group and hemisphere effects for hippocampal volume, however, the interaction was not significant. In this analysis, the two patient groups differed in total hippocampal volume from the controls but also from each other. The total hippocampal volume showed the greatest atrophy in the very mild AD group. In addition, these investigators also found significant group and hemisphere effects for entorhinal volume but also no significant interaction was found between the groups. Additional analyses were also carried out to determine whether hippocampal and entorhinal volume could predict group membership using logistic regression analysis. These results indicated that hippocampal volume could differentiate AD patients from the ND patients, whereas, entorhinal volume was more accurate when differentiating healthy control subjects from ND patients. These results not only support previous literature showing hippocampal atrophy in AD, but also demonstrates how

early hippocampal atrophy is affected in the process of the disease as this study included very mild AD patients.

Many of the earlier studies that have reported medial temporal lobe atrophy have used the classic volumetry method. This technique takes the sum of multiple regions of interest, which are drawn from a series of contiguous brain slices on a computer screen (Baron et al., 2001; Karas et al., 2003). This technique is quite time consuming, unreliable and observer dependent (Baron et al., 2000; Rombouts et al., 2000). In addition, classic volumetry is not suited to investigate whole brain volume therefore; the number of brain areas that can be studied is very limited. Although, temporal lobe atrophy has consistently been reported, other brain areas have not been studied due to the lack of appropriate methods to analyse MRI data. Recently, voxel-based morphometry (VBM), an automated technique to analyse the entire brain has been developed to investigate regional grey matter density (see chapter 4 for further details).

The first study to employ the VBM technique using AD patients was carried out by Rombouts et al., (2000). A group of seven AD patients, as diagnosed by the NINCDS-ADRDA participated in this study. The seven elderly control subjects that participated in this study did not suffer from any medical problems or complained of memory disturbances. Bilateral grey matter volume reductions were found in the hippocampus, as expected by the authors. Bilateral reductions were also found in the head of the caudate nucleus and the insula. Grey matter density reductions were also found in the right middle temporal gyrus, lateral part of the right precentral gyrus, medial part of the left precentral gyrus, left fusiform gyrus and the left posterior postcentral gyrus.

Baron et al., (2001) also used the voxel-based morphometry technique to examine if any differences in grey matter density volumes were present in a group of mild AD patients and healthy control subjects. Mild severity for the clinical presentation of probable AD was established on the NINCDS-ADRDA criteria. The diagnosis of probable AD was

also reached using a neuropsychological battery of tests: Mattis Dementia Scale, Wechsler's Memory Scale, the Story and Figure Recall tests from Signoret's battery, verbal span (forward and backward), verbal working memory (Brown-Peterson paradigm), verbal fluency (letter and category), and a copy of Rey's Figure. The Mini Mental State Examination (MMSE) was also administered to the AD patients. The comparison group consisted of 16 healthy control subjects matched for gender. These controls subjects were not taking any medications, did not show any signs of vascular lesions on MRI and were screened for the presence of cerebrovascular risk factors, mental disorders, substance abuse, head trauma, significant MRI or biological abnormality, and incipient dementia using a memory test battery. High-resolution T1-weighted volume MRI scans were obtained for each participant using a 1.5-Tesla scanner. Raw images were processed, spatially normalised, segmented, smoothed (12 mm), and statistically analysed using Statistical Parametric Mapping, version 1999 (SPM99). The authors also analysed the grey matter density volumes using the Proportional Scaling routine. In this type of analysis, only decreases in relative grey matter density is examined, which is achieved by normalising the images. A threshold of $p < 0.001$ (uncorrected) was used for this analysis. The results revealed significant clusters of reduced grey matter density in the following structures (symmetrical reductions), in decreasing order of statistical significance: amygdala, anterior hippocampus, entorhinal cortex areas, posterior cingulate cortex and adjacent precuneus, perisylvian areas, temporoparietal association neocortex (left-sided predominance), posterior hippocampus, anterior hypothalamus and thalamus, prefrontal cortex (left-sided predominance), caudate nucleus and putamen. The group comparison analysis revealed that AD patients were found to have a significant reduction in the total amount of grey matter compared to the healthy controls. However, as expected, no reductions were found in the healthy controls relative to the AD patients. Results from

the second analysis, using normalised images, were similar to the previous results using non-normalised images, however, the extent of the clusters and the Z-scores of the peak voxels were greatly reduced. The anterior cingulate showed a significant reduction in grey matter density in the analysis using normalised images; however, in the main analysis grey matter density differences in this structure were marginally below the selected threshold value. The data were reanalysed using age as a covariate (the controls were seven years younger than the patients on average) and the results from this third analysis were surprisingly similar to the main analysis, indicating that the previous results were not due to age-related effects. Between these two groups, AD patients showed significant grey matter density volume reductions in the limbic/paralimbic structures, posterior parietal cortex (angular gyrus) and the dorsal frontal cortex. These results indicated that mild AD is also associated with minimal grey matter density reductions in the frontal lobe.

Frisoni, Testa, Zorzan, Sabattoli, Beltramello, Soininen et al. (2002) carried out a study to investigate the use of voxel-based morphometry to detect the presence and severity of regional grey matter density reductions in Alzheimer's disease. These authors compared a group of mild AD patients to a group of gender and education matched control subjects. Dementia in the 29 patients was assessed using standardised medical history, laboratory examinations, physical and neurological examination, neuropsychological assessment and computed tomography scans. The patients were diagnosed for Probable AD using NINCDS/ADRDA criteria. The 26 healthy control subjects did not have any cognitive deficits and were also given the MMSE and clinical dementia scale. Based on these scores, the patients had mild to severe dementia. Exclusion criteria included physical diseases such as heart failure, renal failure, and cirrhosis; however, patients with hypertension, diabetes and other known risk factors were not excluded from the study. Images were processed and analysed using SPM99. Statistical analysis was

conducted using segmented grey matter density volumes, which had also undergone the normalisation process and smoothed with 8mm filter. Three patients within the highest range of the MMSE distribution of scores were considered as having very mild AD and were also studied separately from the analysis that compared the 29 patients with the 26 healthy controls. Three statistical models were examined in this study. The first model compared decreases in grey matter density in the patients compared to the controls, using age as a covariate. The second model, using only the three very mild AD patients, had a significance threshold set at 0.0001 uncorrected to compensate for the small sample size. For the third model, MMSE was used as a nuisance covariate. Regional grey matter density reduction in the mild to moderate AD patients compared to the healthy controls showed the greatest areas of reduction bilaterally in the hippocampus (including head and tail), amygdala, and the uncus. Atrophy was also present in the frontal gyrus. A further analysis with a sub-sample of 17 of the 29 patients and 17 of the 26 healthy controls who were matched for age revealed that the most significant clusters were also in the left hippocampal head, posterior amygdala and right anterior amygdala. Analysing the three patients with the highest MMSE scores also showed the largest reductions in the bilateral medial temporal regions. Smaller regions of grey matter density reductions were also found to be significant in the temporal and frontal gyrus, and one voxel was significant in the precentral gyrus. Correlating grey matter density with MMSE scores showed the greatest volume reductions in the temporoparietal cortex, involving the superior and inferior temporal gyrus and parietal lobule (mainly on the right side), and the precuneus. Results from the first analysis revealed that the greatest reductions were in the right hemisphere and the results of the correlational analysis, using MMSE scores, showed significant voxels in the right and left temporoparietal regions. The findings of this study provide evidence for the use of VBM in detecting grey matter density reductions in medial temporal regions even in

very mild AD patients. Grey matter density reductions were also found outside of the medial temporal regions suggesting that atrophy of the frontal regions might also occur very early in the course of the disorder.

Using the VBM technique, the studies reported above have demonstrated reductions in brain volumes within the medial temporal regions. In addition, this technique has also demonstrated that minimal atrophy of the frontal lobes might also be present in mild AD patients. Karas, Burton, Rombouts, van Schijndel, O'Brien, Scheltens et al. (2003) stated that a possible problem using VBM in samples of AD populations lies within the normalisation process in VBM image processing. The normalisation step in VBM, particularly in SPM99, involves registering the images to a standardised brain template of young healthy controls. As AD patients typically have enlarged ventricles and displacement of structures, a standardised template might not be suitable to investigate atrophy in AD patients. Karas et al. (2003) examined AD patients using a template created specifically for patients with dementia. Twenty-five 25 AD patients (diagnosed using NINCDS/ADRDA) were compared to 25 healthy elderly subjects matched for age. All AD patients underwent a neuropsychological test battery and completed the Cambridge Mental Disorders of the Elderly Examination (CAMCOG), which also included the MMSE. To exclude those patients who might have had major depression, the Montgomery Asberg Depression Rating Scale (MADRS) was also administered to the patients (Montgomery, 1975; as cited in Karas et al., 2003). The control subjects were also assessed to exclude those who might have dementia, depression, and neurologic, physical, and psychiatric disorders. A 1.0 Tesla scanner was used and the images were processed and analysed within SPM99. The template utilised in this study was created by averaging the scans of the patients and controls that took part in the experiment. The images in the study were smoothed with a 10mm kernel and the analysis was performed using grey matter segments. The analyses first involved

examining mean grey matter images in both groups. This examination did show an increased ventricle size when the mean images of the patient group was compared to the controls. The areas that showed significant reductions in grey matter in the AD patients compared to the controls included the cerebral cortex (insula), hippocampal and temporal pole, and grey matter around the Sylvian fissure. Examination of the statistical maps indicated that the medial temporal lobe of the left hemisphere had greater atrophy compared to the right hemisphere in the AD patients. Using a technique referred to as morphological opening[7], significant atrophy of the caudate nucleus and medial thalamus were also observed. Because no "spreading" of structures (over a wider area) was observed in the mean images viewed, it can be assumed this is in fact atrophy and not due to variation of ventricle sizes as it would have been had the images been spatially normalised onto a standard template of young controls. The results of this study also support other studies that have shown occipital, cerebellum, and sensorimotor cortex sparing in the early and mid stages of AD (Braak et al., 1991; Brun and Englund, 1981, Fox et al., 2001, Samuel et al., 1991, as cited in Karas et al., 2003). More importantly, the results of this study were in agreement with previous VBM studies which have used templates of young controls.

Busatto, Garrido, Almeida, Castro, Camargo, Cid et al. (2003) attempted to replicate previous studies that have found medial temporal volume reductions and also examined the topographic distribution of grey matter changes across the separate gyri of the lateral temporal cortex. Similar to Karas et al. (2003), these researchers used a specific elderly template for the spatial normalisation stage. Fourteen patients met the NINDS/ADRDA criteria for probable AD. Patients were also interviewed with the Cambridge Mental Disorders of the Elderly Examination (CAMDEX). Assessment also included full blood

[7] Enlarged ventricles are frequently observed in AD and due to partial voluming the tissue intensity can be greatly increased, thus resembling grey matter. The Bayesian segmentation process, then considers these voxels as grey matter and creates a thin rim of grey matter voxels around the lateral ventricular system in both groups. Morphological opening is therefore used to remove this thin rim of grey matter (Baron et al., 2001; as cited in Karas et al., 2003).

count, liver, renal and thyroid function tests; Vitamin B_{12} and folate levels, syphilis serology, urinalysis, and cranial computed tomography. Patients who scored greater than four on the Hachinski Ischemic Scale (Hachinski et al. 1975; as cited in Busatto et al. 2003) or had gross hearing deficits were excluded from the study. Eleven patients were classified as mildly impaired (MMSE $\geq$ 20) and three patients were moderately impaired (MMSE 14-18). Patients also completed the Montgomery-Asberg depression rating scale (MADRS). The 14 healthy control subjects (matched for age, gender, handedness, and education) completed the CAMDEX and were found to be free of physical and mental disorders, obtained MMSE scores of above 28, and had scores above four on the Hachinski Ischemic Scale. Both groups were assessed using a neuropsychological test battery which included language comprehension, praxis, remote memory and recent memory from the CAMDEX section examining cognitive function (including verbal fluency, the Fuld object-memory evaluation, FOME, and an auditory verbal learning test). The AD patients relative to the controls had significant reductions in grey matter volume bilaterally over the temporal and parietal cortices, the lateral prefrontal and sensorimotor cortices, and the precuneus, as well as in the left anterior and posterior cingulate cortex, and in the right thalamus. Within the medial temporal region, significant clusters were located in the right amygdala and entorhinal cortex and bilaterally in the posterior parahippocampal gyrus. Significant reductions of the bilateral posterior parahippocampal gyrus remained when the analysis included a correction for multiple comparisons, however, the right amygdala and entorhinal showed a trend toward significance. Corrections for multiple comparisons also showed reductions in the left inferior temporal and fusiform gyrus and a cluster in the right anterior superior temporal gyrus showed a trend towards significance. Performing a correction for multiple comparisons using only mild AD patients (MMSE scores $\geq$ 20, n = 11) revealed significant clusters in the left posterior inferior temporal gyrus and fusiform

gyrus. Carrying out an ANCOVA with global grey matter differences controlled for the sum of the intensity values of all voxels from the segmented grey matter images, showed reductions in the temporal lobe. The clusters were located in the right and left posterior parahippocampal gyrus, the right amygdala and entorhinal cortex, the left posterior inferior temporal gyrus and fusiform gyrus (BA 20/37), the anterior portion of the left middle temporal gyrus (BA 21), and the right posterior superior temporal gyrus (BA 22). These results indicated that the reductions in grey matter volume in the temporal lobe foci surpassed the global grey matter loss in the AD patients. Replicating this analysis using only the mild AD patients showed reductions in the left posterior inferior temporal gyrus/fusiform gyrus (corrected for multiple comparisons). The findings of atrophy in bilateral medial temporal regions in this study are also consistent with previous reports that did not use the VBM technique. The results of this study also showed grey matter reduction in non-limbic, lateral portions of the temporal lobe, such as left posterior inferior temporal gyrus/fusiform gyrus, anterior and posterior borders of the superior temporal gyrus bilaterally, and in the anterior portion of the left middle temporal gyrus.

5.4 Neuropsychological Studies

As mentioned above, one of the first regions of the brain to show atrophy in AD is the medial temporal area (De Leon, George, Golomb, Tarshish, Convit, Kluger et al., 1997). Relative to age-matched control subjects, hippocampal atrophy in AD has been reported consistently in the growing AD literature (De Leon et al., 1997). In addition, hippocampal volume reduction in AD has been found to increase as the disease progresses (De Leon et al., 1997). Extensive research examining memory impairments have been carried out in Alzheimer's disease, as it is the earliest and most striking

symptom of this degenerative disorder (Hodges & Patterson, 1995). Progression of AD can be characterised by a gradual deterioration of behaviour and cognition (Venneri, Turnbull & Della Sala, 1996; Pai & Jacobs, 2004). The early stages of AD are generally associated with mild cognitive impairments, typically confined to a few cognitive domains, such as memory and language (Fox et al. 1998; Venneri, Turnbull & Della Sala, 1996; Hodges & Patterson, 1995). However, the magnitude of studies addressing language deficits is far greater than those examining spatial memory. Although AD patients typically tend to wander and get lost, not much work has been devoted to studying visuospatial memory in AD. Cherrier, Mendez and Perryman, (2001) stated that 39% of AD patients suffer from topographical disorientation. Authors, Henderson, Mack and Williams (1989) suggest that this might be due to the large variability of symptoms among AD patients. The following section will address a number of studies that have investigated spatial and topographical memory functioning in AD.

Topographical disorientation in unfamiliar environments has been commonly reported during the early stages of Alzheimer's disease and in familiar environments (e.g., in their home or neighbourhood) as the disease progresses (Cherrier, Mendez & Perryman, 2001). Pai and Jacobs (2004) examined topographical disorientation in a sample of 112 AD with a mean age of 74 years and disease duration of 37 months. Patients were selected from a dementia clinic in a referral national university medical centre. Patients were excluded if they met the following criteria: institutionalised, visually impaired, or experiencing cardiopulmonary, orthopaedic, or other physical problems that prevented ambulation. Diagnosis of AD was made using the DSM-IV criteria and all patients completed the MMSE as well as the Cognitive Ability Screening Instrument (CASI). The CASI is a validated test that consists of the following sub-tests: long-term memory, short-term memory, attention, concentration/mental manipulation, orientation, visual construction, abstraction and judgment, list-generation fluency and language. To

eliminate floor effects, patients with a score of zero on the CASI test were excluded from the statistical analyses. Topographical orientation was assessed using a semi-structured interview to gather information regarding the patients' navigational skills. However, the interview was administered to the primary caregivers, spouses or cohabitants. The caregiver's report of the first time the patient had difficulty recognising roads, (the ability to find their way competently in an environment without hesitation), determined the onset of topographical disorientation (TD). This first report of a cognitive dysfunction or behavioural disturbance defined TD as an incipient symptom. The caregivers were also asked about the patient's indoor disorientation, out-of-home range disorientation, having been escorted home by others, and if they worried when the patient went out alone. The results indicated that of the 112 AD patients examined, 61 had current TD. Twenty-eight of these patients had TD at a very early stage of the disease and 33 developed TD within the following three years of the study. There were 51 patients who did not go on to develop TD during the course of testing (over the span of 20 months). Those with current TD were more likely to have had TD as an incipient symptom of AD and had a longer duration of AD symptoms. Those with current TD were also reported to have changed their residence significantly more often than those without TD. Between the patients who had current TD or no TD, there were no differences in MMSE scores and CASI scores, or its sub-tests. Alzheimer's disease patients with current TD differed from those without TD because they were more likely to be escorted home by others, to be disoriented when away from familiar territory, to have a smaller familiar territory range, and that the caregiver was more likely to be worried when the patient was out alone. No differences were present in the reports of disorientation that occurred indoors or as a function of the type of residence where the patient lived (i.e., apartment, house, countryside, or other). The following seven variables, all of which showed statistical significance, were entered into a multiple

regression analysis: changes of residence, TD as an incipient symptom, duration of AD, out-of-home range disorientation, having been escorted home by others, worried if out alone, and safety niche. History of residence changes and duration of AD remained significantly associated with TD after performing the analysis and accounted for 47% of the variance associated with the occurrence of current TD. Current TD patients who had to be escorted home by others performed worse on the MMSE, CASI, and its sub-tests of attention, visual construction, language, and orientation compared to those AD patients who had never had to be escorted home by others. These findings proposed that TD is relatively prevalent in early AD patients. While TD was not an incipient symptom for all AD patients, the prevalence rate was not low (25%). These authors suggested it would be useful to devise tests that can detect TD in AD. The authors stated that with the exception of the Money Road Test (Money et al., 1976 as cited in Pai & Jacobs, 2004) and the Washington University Road Test (Hunt et al., 1997 as cited in Pai & Jacobs, 2004), most neuropsychological tests are insensitive to TD. Cherrier, Mendez, and Perry (2001) examined the nature and mechanisms involved in TD in Alzheimer's disease patients. The route learning test administered to the patients and healthy controls measured cognitive abilities associated with navigating and learning a route, which included verbal, visual, and spatial memory (navigation and spatial orientation), and incidental memory. The main hypothesis for this study was that spatial attention and memory for a spatial layout (compared to memory for individual landmarks) would be the best predictors of poor performance on the route learning test, opposed to a primary deficit in visuospatial perception or deficits in recognising landmarks (topographical agnosia). A sample of 16 AD patients and 19 healthy control subjects took part in the study. Those patients who met the diagnostic criteria for probable AD, as outlined by NINCDS/ADRDA were included in the study. Healthy participants who did not have any health problems as assessed by an initial telephone interview, between the ages of

60 and 90 years, were included to take part in the study. The AD patients and healthy controls were excluded under the following conditions: head injury with loss of consciousness for one hour or more, alcoholism or drug abuse, major psychiatric illness (schizophrenia or affective disorder), and learning disability. All subjects in the study also had corrected distant vision better than 20/40. In addition, the AD patients fell within the mild to moderate ranges of dementia with a mean dementia rating scale (DRS) score of 107 (SD = 18) and mean duration of the disease was 3.8 years. The participants were administered the following tests at the West Los Angeles Veterans Administration Medical Center (VAMC): DRS, North American Adult Reading Test, Route Learning Test, New Map Test-revised, Visuospatial Learning Test-revised, Fargo Map Test-revised, Judgment of Line Orientation Test, Money's Standardized Road Map Test of Direction Sense, Figure Matching, and Hooper Visual Organization Test. Although the patients and controls were intended to be matched for DRS scores, a significant difference was found between the groups. The AD patients had visited the VAMC significantly more times than the healthy controls. However, this might have been due to the multiple visits during the assessment process or for other medical care and one patient was a former employee for the VAMC. The route-learning test consisted of a total score as well as sub-scores achieved on the following measures: walking recall, verbal landmark order recall, verbal landmark number recall, picture recognition, incidental memory, and route cues. The AD patients were found to be significantly impaired on the route-learning test as well as on the sub-tests compared to the healthy controls. Using the Pearson correlation statistical test, a significant difference between the groups was also found on the route map recognition test. The AD patients did worse than the healthy controls on a majority of the memory tests, including the Visuospatial Learning Test and New Map Test. A stepwise linear regression analysis with all the tests revealed that only the Money's Standardized Road Map Test of Direction Sense

(MRMT) could significantly predict the Route Learning test total score. The DRS score also correlated with the Route Learning total score, as determined by the Pearson correlation coefficients of the regression analysis. The results of this study indicated that Alzheimer's disease patients were significantly impaired on the route-learning test compared to the healthy controls; despite performing relatively well on tests of visuospatial abilities. Topographical disorientation might be dependent on optic flow because it provides information about self-movement and spatial navigation in natural environments. Tetwesky and Duffy (1999) found an association between optic flow and the ability of AD patients to recall information from a walking route. Cherrier, Mendez, & Perryman (2001) suggested that possible optic flow impairments in their sample of AD patients might contribute to the observed route learning deficits. In addition, poor spatial orientation and spatial reasoning might also be responsible for the route learning difficulties.

Henderson, Mack & Williams (1989) investigated whether damage to the areas of the right hemisphere involved in visuospatial processing are implicated in the spatial disorientation frequently observed in Alzheimer's disease patients (the terms spatial or topographical disorientation are used interchangeably). In particular, poor performance on neuropsychological measures of right inferior parietal lobule deficits would be associated with spatial disorientation, compared to tasks of left hemisphere functioning (verbal tasks). Right parietal dysfunction was operationally defined by the performance on a visuo-constructive task of line drawings taken from the Spatial Quantitative Battery supplement to the Boston Diagnostic Aphasia Examination. The diagnosis of probable AD for the 28 outpatients in this study was determined by the criteria of the NINDS/ADRDA. Behavioural status of the patients was obtained through a 30-item Memory and Behaviour Problems Checklist given to the primary caregivers. Four-items pertained directly to spatial disorientation (i.e., wandering, getting lost indoors, getting

lost on familiar streets, and being unable to recognise familiar surroundings). The Quantitative Battery task administered to the patients required them to draw: 1) the face of a clock showing the numbers and two hands, 2) a house in perspective, showing the roof and two sides, 3) a clock, and 4) a house. Delayed recall for a 5-item address from the Information-Memory Concentration Test measured long-term declarative memory (delayed recall) (Blessed et al., 1968, as cited in Henderson, Mack & Williams, 1989). The backward and forward digit span task measured attention (Wechsler Adult Intelligence Scale-Revised, 1981), the Boston Naming test measured language function and severity of dementia was measured using the MMSE. Of the 28 AD patients, 11 patients had difficulties with three of the four behaviours related to spatial disorientation three or more times per week. The five independent variables: scores on the visuo-constructive test, delayed recall, digit span, Boston Naming test, and MMSE showed moderate simple correlations with spatial disorientation. Using stepwise regression, delayed recall and visuo-constructive performance were found to be significant predictors of spatial disorientation. The strongest significant predictor of spatial disorientation was performance on the delayed recall task. Performance on the delayed recall and visuo-constructive tests accounted for 41% of the variance in spatial disorientation. The findings of the present study supported the authors' hypothesis that tasks that measure focal damage of the right inferior parietal lobe can predict spatial disorientation in Alzheimer's disease patients. The authors suggested that the poor performance on the route-learning test is attributed to the AD patients poor spatial orientation or spatial reasoning.

Topographical memory functioning can also be assessed using tests of geographical information. Beatty & Salmon (1991) examined remote memory for visuospatial information in Alzheimer's disease patients using the Fargo Map Test, which measures geographical knowledge. A group of sixteen patients who met the NINCDS/ADRDA

criteria for Alzheimer's disease and 13 healthy controls took part in this study. Exclusion criteria for AD patients and controls included having a history of drug or alcohol abuse, major psychiatric illness, severe head injury, or central nervous system diseases. To exclude any patients that might have suffered from multi-infarct dementia, those patients with scores above four on the ischemia scale of Hachinski et al. (1975) were not included in the study (as cited in Beatty & Salmon, 1991). Laboratory tests were also completed to exclude those patients and healthy controls that might have developed dementia due to traumatic, metabolic, toxic, and viral causes. The AD patients also completed the Vocabulary Scale from the Wechsler Adult Intelligence Scale-Revised, a shortened version of the Boston Naming test, a test of copying a cube, and the Number Information test. The AD patients and healthy controls completed all five sections of the Fargo Map tests: residential history, the United States map, the California-Nevada (CA-NV) map, San Diego County, California map, and a map of the region of the United States where the subject was born and raised. Both groups did not differ in number of years of residing in the CA-NV region and San Diego County. The results indicated that the AD patients were significantly less accurate in locating cities on the maps of CA-NV and San Diego County than the controls. The AD patients were, however, better at locating cities on a map of the region where they were born and raised, compared to the map of the region where they were currently residing. An ANOVA (a group by region analysis) and t-tests revealed a significant difference in the accuracy of performance on the map where the patient was born and raised and CA-NV maps, however, this was not the case for the control subjects. Further statistical analyses also revealed that accuracy on the US and the two regional maps were significantly correlated. In addition, performance on the three maps was significantly related to global mental status and the strongest correlation was found on the Number Information Memory Concentration test. The magnitude of the temporal gradient (difference in

accuracy between the map where they were born and raised and CA-NV) was significantly correlated with errors on the Information Memory Concentration test and with accuracy on the map of the region where they were born and raised. The negative correlation between the temporal gradient and errors on the Information Memory Concentration test suggested that the temporally graded retrograde amnesia for geographical knowledge might only be present in those AD patients with mild dementia.

Based on the evidence of spatial disorientation in AD, Adelstein, Kesner & Strassberg (1992) were the first to examine whether patients exhibit spatial order impairments. The authors were interested in examining memory for lists of spatial locations and also to examine memory for order spatial recognition memory. Forty-seven participants were placed into three groups, classified based on scores from the Global Deterioration Scale (GDS). This scale gives a measure of functional performance and also assigns participants into specific skill groups (GDS 1, 3, and 4). Sixteen participants were placed into group GDS 1 (mean MMSE score of 28.88), the GDS 3 group consisted of 15 patients (mean MMSE score of 20.8), and the GDS 4 group consisted of 16 patients (mean MMSE score of 16.63). Patients with an MMSE score greater than eight but less than 23 were considered to reflect moderate to severe impairment. The group of participants in GDS 1 were healthy control subjects. Pre-study physical examinations and a history of medical information was obtained from the participants physician. Any participant with a medical or psychological illness that might have affected cognition (e.g., renal failure and/or depression) or any clinical diagnosis or history of other major neurological disease (e.g., stroke, multi-infarct, or tumour) were excluded from the study. A medical geriatrician and neurologist jointly made the diagnosis of Primary Degenerative Dementia of the Alzheimer's Type. Group GDS 3 and 4 also met the DSM-III criteria for Primary Degenerative Dementia of the Alzheimer's Type. The

subjects were also given the Satz-Mogel modification of the Wechsler Adult Intelligence Scale-Revised and the National Adult Reading test. Both these tests were administered to obtain a current and premorbid estimate of verbal intellectual functioning. The Brief Cognitive Rating Scale was also administered to all participants. All participants completed an item (Spatial Recognition memory) and order (Spatial Order memory) test for spatial location on sheets of paper containing 16 squares. Each test consisted of a study and a test phase. During the study phase of the item test, the subject was shown six stimulus sheets with 16 squares and one of these squares contained an 'X' on each sheet. During the test phase, the subject viewed a stimulus sheet with two squares that contained the letter 'X' and had to identify which square had the 'X' in it previously. All sheets consisted of a square (with an 'X') that was seen before and one that was not shown during the study phase. During the test phase of the order test (spatial order memory), the subject was shown a stimulus card with two squares that contained an 'X', both had been seen previously. The participant was required to recall which X had occurred before the other during the study phase sequence. An ANCOVA, covarying for age, was carried out, as there was a significant difference in age between the groups. For the Spatial Recognition memory test a significant effect of age and group effect was found. The GDS 1 group performed significantly better than GDS 3 and 4 groups and the GDS 3 group performed significantly better than the GDS 4 group. The GDS 1 group also performed better than GDS 4 for serial position 1. GDS 3 and GDS 4 performed significantly worse than GDS 1 for serial position 5. In addition, the GDS 1 and GDS 3 groups performed significantly better than GDS 4 for the last serial position (six serial positions in total). The results from this test suggested that the mild AD patients were impaired in recalling the early serial positions compared to the last serial positions. Data from the Spatial Order memory test was also covaried for age, however, the effect of age was not

significant. A significant group effect and a significant group by choice order serial position interaction was found. GDS 1 group and GDS 3 performed significantly better than GDS 4 for serial positions 1-2 and 2-3. Group GDS 1 performed better than GDS groups 3 and 4 for position 3-4, 4-5, and 5-6. Group GDS 3 performed better for serial positions 1-2 and 2-3 compared to positions 3-4, 4-5, and 5-6 choice orders. The healthy controls and group GDS 4 did not have any significant differences across choice orders. The mild (GDS 3) dementia patients showed greater impairments in remembering last choice orders in a list within the spatial order memory test. There was, however, no significant differences between the two groups' performance on the spatial order and spatial recognition tests. Based on impairments observed in animals and humans, the performance of the mild AD patients might be explained by damage in the parietal cortex and hippocampal formation caused by AD.

Grossi, Becker, Smith and Trojano (1993) examined the Visuo-Spatial Scratchpad system (VSSP), within the Working Memory Model in a group of Alzheimer's disease patients. This VSSP is a spatially based system capable of retaining and maintaining in memory visual images for a short time. Within the VSSP is also the pattern-based system, which is thought to maintain spatially arranged stimuli, however, does not contribute to retaining temporal sequences of items presented visually. The authors predicted that AD patients would show visuo-spatial memory impairments within the context of the Working Memory Model. Thirty-nine patients from two separate clinics took part in this study (Italy and United States) and both groups were diagnosed with probable AD using the NINCDS/ADRDA criteria. A total of 62 age and education matched healthy control subjects were selected for the comparison group. Both patients and healthy controls completed the MMSE. An ANOVA revealed that there was no significant group by centre interaction. The participants were administered three tasks; the first task was to eliminate any subjects who could not copy a pattern of stimuli

previously presented to them. During the second task, a Visuospatial Pattern Test, the participants were shown stimulus cards and 2 – 6 squares were blackened in. Immediately afterwards, the participants were shown a blank response card and were required to cross out the squares to match the card that was shown previously. Memory span was determined from the longest list that could be reproduced. A version of the Corsi Block test was also administered to all participants. The subjects were required to immediately repeat the same sequence of blocks tapped as had been shown by the examiner. As with the Visuo-spatial Pattern test, memory span was determined as the longest sequence of blocks that could be successfully replicated. A majority of the control subjects performed at ceiling on the Visuo-spatial Pattern test (42/62), whereas, only 12/39 patients scored the maximum points on this test. Performance on the Corsi test and visual span task was worse for the patients than the healthy controls. Using a two-way ANOVA for the Corsi Block test, the factors group and centre were found to be significant. However, the group by centre interaction was not significant. A one-way ANOVA revealed no significant difference between the centres on the visual span task for the patient group. Comparing the patients' performance on the Corsi Block test and on the Visuo-spatial Pattern test revealed no significant differences. These results suggested that within the context of the Working Memory Model, AD patients do have visuo-spatial impairments. These deficits were found to be present immediately after presentation and the patients were also not able to recall the correct temporal order. Along with the VSSP within the Working Memory Model, there is also the Central Executive System (CES). The CES is responsible for controlling cognitive operations and is responsible for coordinating and scheduling concurrent operations (Grossi et al., 1993). The authors suggested that poor visuo-spatial impairments might be secondary to a defect of the CES. The CES is known to be involved in the overall functioning of the

VSSP and the authors suggested that visuo-spatial impairments might be due to executive functioning deficits.

Caine & Hodges (2001) studied semantic and visuospatial deficits in early AD to understand the cognitive changes associated with the disorder. These authors were interested in investigating whether semantic memory deficits precede visuo-spatial impairments, which would support the current knowledge of the spread of pathology of AD or if visuo-spatial impairments are evident before semantic impairments. The first study of this paper examined whether these patients would have greater verbal and object-based semantic deficits compared to performance on spatially-based perceptual tests. Probable AD diagnosis for 26 patients was made using the criteria of the NINCDS/ADRDA. Twenty-four age and education-matched controls were also included in this study. The patients had either minimal dementia as indicated by their MMSE scores (24-30) or mild dementia (18-23). Patients with isolated progressive nonfluent aphasia, semantic dementia, frontal-type dementia, or visual deficits as their primary symptoms were excluded from the study. Patients with a known or suspected transient cerebral ischemic event or stroke, alcoholism, head injury, or major medical illnesses such as cancer, thyroid dysfunction and other illnesses, as well as major depression were also excluded. The memory tests consisted of the Logical Memory subtest from the Wechsler Memory Scale-Revised and a Recognition Memory test of Words and Faces. The Judgement of Line Orientation test (JLO) was administered to measure visuo-spatial abilities. Object-based perceptual tests consisted of the Object Matching test and the Object Decision test. In addition, the semantic tests administered to the participants included the Picture Naming test, Pyramids and Palm Trees-three-picture version test (PPT), and the Naming in response to verbal descriptions test. The authors examined individual differences among patients rather than studying overall group scores. Patient scores which fell below the 5th percentile of the controls scores

were considered to be impaired on that particular test. All of the patients in this study did have deficits in episodic memory as their primary complaint. Three patients were impaired on tests of episodic memory but showed no impairments on tests of semantic, object-based perceptual function and visuo-spatial tests. Sixteen patients were impaired on both verbal and perceptual semantic tests but showed no impairments on the visual tests. One patient was only impaired on the Object Decision test and another patient was only impaired on the PPT pictures test with performance on the other tests that were within normal ranges. Five patients had marked visual impairment and poor performance on the JLO, however, one of these patients was also impaired on the Object Matching test. These patients could be considered to have greater visual deficits compared to the remainder of the group. Two patients were considered impaired on both visual and verbal tests. One patient was impaired on the PPT pictures and all the semantic tests and one of the visual tests, whereas the other patient was impaired on the Object Decision test and naming to description tests. One patient performed poorly on the perceptually based tests but not on the verbally based semantic tests, which also suggested greater visual processing impairments compared to semantic processing impairments. Another two patients were impaired on the JLO test but had normal performance on all of the semantic tests. Therefore, three patients had pure visual problems compared to spared performance on semantic tests. These results support previous findings of heterogeneity in early AD. In addition, a larger number of patients had deficits on the memory tests together with semantic memory deficits than visual deficits. Thus, the results also suggested that it is possible to discriminate between those who have semantic impairments and not visual impairments and also the opposite in patients with mild AD patients.

The second study in this paper investigated the heterogeneity in AD using highly specific tests in the verbal and visual domain. The word version of the PPT and the

Graded Naming test and a number of subtests of the Visual Object and Space Perception Battery (VOSP) were administered to both the groups (consists of object-based and spatial components). It was hypothesised that performance on the VOSP, Silhouette Naming test (an Object-based test within the VOSP) would be associated with performance on other semantic tests (naming of line drawings and PPT words tests), compared to performance on spatial tests (Dot Counting, Position Discrimination, and Number Location) which would not be associated. A sample of 21 patients and 29 age and education matched controls, who did not take part in the first study, participated in this study. Inclusion and exclusion criteria as well as the MMSE cut-off scores were replicated from the first study. Memory tests were also the same as the first study, however, the Short Recognition Memory test for Words and Faces was also used. The Following VOSP tests were included to measure visuo-spatial skills: Dot Counting, Position Discrimination, and Number Location. The semantic tests included the Graded Naming test, PPT-three-word version, and the Silhouettes test. Data analysis was the same as in the first study. All patients performed poorly on the episodic tests. However, ten of these patients were not impaired on any test of semantic or visual processing. Eight patients were impaired on the semantic tests and had no deficits on the visual tasks. Of these patients, two patients were only impaired on the Silhouette Naming test, a test with a strong perceptual component. These two patients were difficult to classify to a specific domain due to normal performance on the Graded Naming test and PPT words test. From the sample of patients, only two patients had marked deficits exclusively on the visual tests, both of which were impaired on the Silhouette Naming test but not on the semantic tests. In addition, one patient had deficits in both domains and had poor performance on the visual tests and PPT words test. Performance in this study also indicated that a larger proportion of patients had semantic memory impairments compared to visuo-spatial impairments and only a small proportion of

patients had visual impairments without semantic impairments. However, the authors have suggested that visuo-spatial impairments might not have been found because it is possible that the visual tasks, especially in the second study, were much easier than the semantic tests. In addition, navigation, clock-reading or other tasks that tap into spatial relationships and non-perceptual processing such as face or design matching were not examined in this study to measure visuo-spatial abilities in early AD.

Demadura, Delis, Jacobson and Salmon (2001) also predicted their sample of AD patients, who exhibited asymmetric profiles on non-memory, would also show asymmetrical verbal or visual memory impairments. These authors also predicted that although AD patients will show asymmetrical memory performance, both groups would be moderately to severely impaired on both verbal and spatial memory tests. As with the previous studies mentioned, these hypotheses were based on neuro-imaging data that have shown greater medial temporal lobe damage in the early stages of the disease. Sixty-eight AD patients were selected to take part in the study. Any subjects with a history of a past head injury, alcoholism, or serious psychiatric disorders were excluded from the study. Any patients with a score greater than five on the Hachinski Ischemic Scale were also excluded from the study. All patients completed neurological, medical, and psychiatric examinations, the global cognitive screening test (e.g., Mattis Dementia Rating Scale), and the Alzheimer's disease Research Center (ADRC) Core Neuropsychological Battery (assessing basic cognitive domains such as attention, language, and visuo-spatial skills). Only those patients with a score greater than 100 were selected to take part in the study. All patients were diagnosed with probable AD using the criteria set out by the NINCDS/ADRDA. Patients were also selected based on their performance on the Boston Naming Test (BNT) and the Wechsler Intelligence Scale for Children Block Design subtest (WISC-R & BD). The authors used the WISC-R instead of the Wechsler Adult Intelligence (WAIS) test because of the common floor

effect found in the AD patients on the WAIS. From the sample of 124 patients, 68 patients met the criteria for asymmetric cognitive deficits by scoring at least one standard deviation higher or lower on the BNT compared to the BD. Thirty-two of these patients were assigned to the High Spatial group as they scored at least one standard deviation higher on the BD subtest than on the BNT. Thirty-six patients were assigned to the High Verbal group as they performed at least one standard deviation higher on the BNT than the BD test. The High Verbal group were found to have higher scores on the BNT than the High Spatial group, whereas the High Spatial group had higher scores on the BD test. All patients were administered the California Verbal Learning Test (CVLT), the Russell adaptation of the Visual Reproduction subtest of the Wechsler Memory Test, and the Logical Memory subtest of the Wechsler Memory Scale-Revised test. All these tests were incorporated into their annual testing using the test battery of the ADRC. Performance on the CVLT indicated that the High Verbal group did significantly better than the High Spatial on List A Trial 1, List 1 Trials 1-5 Total, Long Delay Free Recall, and on Long Delay Cued Recall. The other components of this test failed to reach significance. The High Verbal AD group recalled significantly more ideas per unit on the immediate and delayed recall conditions of the Logical Memory subtest. The groups failed to reach significance on the Delayed Recall Savings subtest. No significant differences were found on any of the memory measures of the Visual Reproduction subtest (i.e., Immediate Recall, Delayed Recall, or Delayed Recall Savings). As expected, the High Spatial group performed significantly better than the High Verbal group on the Copy measure of the Visual Reproduction subtest. For all the verbal and spatial memory tests, the High Spatial and High Verbal groups were at least two standard deviations below average or lower. Thus, the two AD groups were moderately to severely impaired on all memory tests. On the verbal memory tests, it was found that in general, that the High Verbal patients performed better than the High

Spatial AD group. However, the two groups did not differ on the spatial memory tests. The initial bilateral damage that occurs to the temporal lobes early on in the course of the disease might explain the moderate to severe impairments on all of the memory tests, as suggested by the authors. The High Spatial AD patients in this study might not have shown greater impairments than the High Verbal group on the spatial tests because of verbal and nonverbal strategies that might be involved in the Visual Reproduction subtest. The authors also commented on the possibility that this task might depend on both the right and left hemisphere due to the local (detail) and global (configural) aspects of the test.

5.5 Medial Temporal Atrophy and Memory Impairments in Alzheimer's Disease (Neuroimaging Evidence)

Köhler, Black, Sinden, Szekely, Kidron, Parker et al. (1998) used a volumetric technique to examine the relationship between medial temporal lobe atrophy and specific cognitive impairments in AD. This study addressed whether pathological changes within the medial temporal lobe (particularly the hippocampus) contribute to anterograde episodic memory deficits or whether brain structures outside of the medial temporal lobe also contribute to the memory impairments observed in AD. Twenty-seven AD patients met the criteria for probable AD as specified by the NINCDS/ADRDA. MMSE scores indicated that the AD patients ranged from mild to severe dementia. Thirteen patients were mildly demented (MMS 21-27), twelve were moderately demented (MMS 11-20) and two were severely demented (MMS < 10). Twenty-six control subjects matched for age and education with no presence or history of neurological and psychiatric impairments, based on a detailed health questionnaire took part in the study. The control subjects also completed the Mattis Dementia Rating

Scale to exclude any controls that may have signs of dementia and age-associated memory impairment. All subjects completed the California Verbal Learning test (CVLT), and the Visual Reproduction Test of the Wechsler Memory Scale-R (VRT) and a MRI scanning session. The CVLT and the VRT were part of a larger battery of neuropsychological tests administered to the participants. However, these two tests were the only tests of memory used in the study. The CVLT measured immediate and delayed memory for auditory-presented verbal information, whereas, the VRT measured immediate and delayed recall for visually presented nonverbal information. Based on evidence suggesting that the hippocampus is associated with verbal anterograde memory, the authors measured the hippocampus and parahippocampal gyrus. The hippocampal measurements excluded the subiculum, as it connects the hippocampus to the parahippocampal gyrus. The hippocampus thus included Ammon's horn (CA1-CA4), dentate gyrus, alvenus, and fimbria. The parahippocampal gyrus measurements included the parahippocampal proper (excluding portions inferior to the collateral sulcus), caudal aspects of entorhinal cortex, underlying white matter and medial aspects of the subiculum. The amygdala was not included in either of the two measurements. A single one-step regression model was performed for the neuropsychological scores that correlated significantly with MR volumes. The MR volumetric analysis revealed that the hippocampal and parahippocampal volumes, including both the left hemisphere and right hemisphere volumes, were significantly smaller for the AD group compared to the healthy control subjects. Hippocampal and parahippocampal volumes were also positively correlated in the AD patient group and not for the healthy control group. The scores from the Dementia Rating Scale (DRS) revealed a lower level of cognitive functioning in the AD patients compared to the healthy control subjects. The patients also performed significantly poorer than the control group on the immediate and delayed recall components in episodic memory on the CVLT and VRT. A proportion of

the AD patients were not capable of recalling any items on the CVLT (16 patients) and the VRT (nine patients) after a delay. Delayed recall on the CVLT correlated positively with hippocampal volume and delayed recall on the VRT correlated positively with parahippocampal gyrus volume. Scores on the VRT of zero corresponded to smaller parahippocampal gyrus volumes, whereas, scores above zero did not. Likewise, those patients with scores of zero on the CVLT were found to show smaller hippocampal volumes, whereas, scores above zero did not. Although these results might mean that floor effects may have inflated the size of the correlation, running the same analyses using only those scores, which were above zero, also revealed similar results. Multiple regression analyses (test scores as the dependent variables) indicated that for the CVLT delayed recall score, only the hippocampal volume emerged as a significant predictor. For the VRT delayed recall score, only the parahippocampal gyrus volume emerged as a significant predictor. Right and left medial temporal atrophy was found to be symmetrical in AD, therefore, the authors examined total hippocampal and parahippocampal gyrus volumes. However, to examine laterality, two additional analyses were conducted using both the right hemisphere and the left hemisphere volumes serving as predictors. The right and left sided analyses were significant for the delayed CVLT recall scores. Both models also found that hippocampal but not parahippocampal gyrus volume emerged as a predictor for delayed CVLT recall. Examining right-sided volumes for the VRT scores showed that the volume of the parahippocampal gyrus was significant to predict performance, whereas, the hippocampus did not show similar results. Examining left-sided volumes revealed that the hippocampus and parahippocampal gyrus volumes were not significant predictors of performance for the delayed VRT recall. The right but not the left parahippocampal gyrus showed a positive relationship to behavioural performance on the delayed VRT recall. Delayed CVLT scores did not correlate with the left or right hippocampus or

parahippocampal gyrus. An omnibus test was performed on each matrix of Pearson product-moment correlations between MR volumes and behavioural test scores. Carrying out an omnibus test for the healthy controls showed a significant negative association between hippocampal volume and immediate CVLT recall score. Differences in intracranial capacity, age, sex and education were controlled for in this analysis. The hippocampus and parahippocampal gyrus were not significant in the analysis for the CVLT immediate recall score. However, the CVLT delayed score did reach significance and only the hippocampus was found to be a significant predictor. Overall, the findings of this study found that the hippocampus and parahippocampal gyrus correlated with delayed memory recall but not with immediate memory recall or overall cognitive functioning scores. In addition, a positive correlation with the hippocampus for the delayed recall on the CVLT test was found but not for the VRT scores. More interestingly, the right hemisphere of the parahippocampal gyrus showed a positive correlation with delayed recall on the VRT test but not the CVLT scores. The AD patients showed significant anterograde episodic memory deficits in verbal and non-verbal recall immediately after learning and after a delay. Hippocampal and parahippocampal atrophy in the AD patients was only found to be related to delayed memory impairments. The results of this study have found that atrophy in the hippocampus is associated with a different type of delayed recall task (CVLT) than atrophy in the parahippocampal gyrus (VRT). These findings also suggested that medial temporal atrophy observed in AD affects the hippocampus and surrounding parahippocampal gyrus. The findings also supported previous literature that links the hippocampus with consolidation of verbal information, encoded in a semantic context and the parahippocampal gyrus is linked to the consolidation of non-verbal information in a visual context.

Mori, Yoneda, Yamashita, Hirono, Ikeda and Yamadori, (1997), also examined the relationship between medial temporal structures (amygdaloid complex, hippocampal formation, subiculum, and parahippocampal cortex) and memory deficits. All 46 patients in this study completed routine laboratory tests, standard neuropsychological examinations, EEG, MRI of the brain, magnetic resonance angiography of the neck and head, and cerebral perfusion and metabolism studies by PET or SPECT. The patients were included based on the following information: diagnosis of probable AD using NINCDS/ADRDA criteria, younger than 80 years old and mild to moderate functional impairment (grades of .5 - 2 on the clinical dementia scale). The patients were excluded from the study based on the following criteria: presence of other neurological or systemic diseases, MMSE scores less than 11, presence of focal lesions on MRI, and if informed consent could not be obtained from patients or their relatives. The control subjects consisted of 12 age and gender matched individuals who showed no abnormalities on MRI and scored above 28 on the MMSE. The investigators used a semi-automated segmentation technique that removed the partial voluming and observer's bias often found in traditional volumetric studies. Tests measuring verbal memory included the following: the word recall subtest of the Alzheimer's disease assessment scale (ADAS), the logical memory subtest of the Wechsler memory scale-revised (WMS-R), and the verbal paired associates subtest of the WMS-R. The ADAS test is analogous to a verbal learning test. Subjects are required to recall 10 written words immediately after presentation following each of the three learning trials. Visuospatial memory was measured using the visual paired associates subtest of the WMS-R, the visual reproduction subtest of the WMS-R, and the figure memory subtest of the WMS-R. Only the non-delayed scores of the WMS-R tests were analysed. The results of the comparison between the brain volumes of the AD patients relative to the controls revealed that the total (right and left) volumes of the amygdaloid complex,

hippocampal formation, subiculum, and parahippocampal cortex were significantly smaller. The medial temporal structure did not correlate with age or educational attainment nor did it correlate with gender. Using Student's t test, the memory test scores were significantly different between the groups with the AD patients significantly impaired compared to the healthy controls. Performance on the memory tests also did not correlate with age, educational attainment, or gender. Correlating memory scores with the medial temporal structures revealed that total amygdala volume was significantly correlated with memory performance. The following significant correlations were also found: word recall and logical memory scores correlated with left subicular volume, verbal paired associates scores correlated with right amygdala volume, and the right and left amygdala volume correlated with figure memory scores. Results from the visuospatial test showed significant correlations between the visual reproduction scores and right and left amygdaloid complex. In addition, a significant correlation between right hippocampal volume and visual reproduction scores were also found. Using a stepwise regression analyses, the left subicular volume predicted the scores of the word recall and logical memory, whereas the right amygdala predicted the scores of the verbal paired associates, figure memory, and visual reproduction tests. Although hippocampal volume did not predict severity of memory deficits, the authors suggested that the memory impairments presented after hippocampal damage might be considerably worse following damage to the amygdala proper, its nearby cortices, and the subiculum. The involvement of the left subiculum in verbal memory is not surprising, as other studies with AD patients that have found significant correlations between verbal memory scores and hippocampal volume, have included the subiculum in the volumetric measurements of the hippocampus (Deweer, Lehéricy, Pillon, Baulac, Chiras, Marsault et al., 1995). The subiculum is one of the major output areas for the hippocampus and also provides a major source of cortical input to the hippocampal

formation (Squire & Zola-Morgan, 1991). Therefore, the authors suggested that the subiculum might have a greater role in memory impairment in AD patients than the hippocampus proper.

5.6 EXPERIMENT 7: Neuropsychological Study of Topographical Memory in Alzheimer's Disease

5.6.1 Aims

MRI morphometry studies in Alzheimer's disease (AD) have reported medial temporal lobe atrophy and most of them have observed hippocampal atrophy (Frisoni et al., 2002; Baron et al., 2001;Braak & Braak, 1991). Hippocampal atrophy is associated with alterations in memory function, which is explained by the extensive evidence of the involvement of the hippocampus in memory and learning. In addition, lesion-correlational data and functional imaging studies have implicated the right hippocampus and right parahippocampal gyrus (PHG) in spatial and topographical memory. Memory performance in AD has been studied comprehensively; however, the investigation of topographical and spatial memory performance in AD has not received much attention, albeit that many AD patients wander and get lost. Based on the findings of medial temporal lobe atrophy, the present study predicted that Alzheimer's disease is associated with selective deficits in topographical and spatial memory, in addition to the well-known findings of verbal memory deficits. There is no evidence suggesting that the medial temporal lobe atrophy in AD is greater on one side rather than the other, the current study therefore, was interested in determining whether profound deficits of visuo-spatial processing are present as well as those of verbal memory.

5.6.2 Method

5.6.2.1 Participants

A total of 26 (Male = 14; Female = 12) Alzheimer's disease patients (mean age 78, SD = 8.44) and 22 healthy control subjects (mean age 78, SD = 7.00) (Male = 13; Female = 9) participated in the experiment. No significant differences in age were found between the two groups ($t(45) = .377$, ns), or in education, $t(46) = .356$, ns (Mean education, Patients 16.27, SD = 2.52; Controls 16.05, SD = 1.65) The patients were recruited from the Lochhead Day Centre at Royal Cornhill Hospital and also from the Airyhall Day Centre in Aberdeen, Scotland. The patient sample included eight patients who had minimum cognitive impairment (MMSE scores between 24-30), 13 had mild cognitive impairment (MMSE scores between 19-23), and five had moderate dementia (MMSE 12-18) as determined by their score on the Mini Mental State Examination (Folstein, Folstein & McHugh, 1975). Ethical approval for this study was obtained from the Grampian Health Board and the University of Aberdeen Joint Ethics Committee.

5.6.3 Method and Procedure

The AD patients and elderly control subjects completed the same neuropsychological tests which were administered to the PTSD patients in Chapter 4 (e.g., Recognition task (Word and Picture), Topographical Localisation task, General Semantic Knowledge test (WAIS-III) and the Corsi Block test). Detailed information regarding these tests can be found in the Methods section of Chapter 4. As an additional screening and staging measure, the Mini Mental State Examination was used (for detailed description see below).

5.6.3.1 Mini Mental State Examination:

The Mini Mental State Examination (MMSE) is a widely used method for assessing cognitive mental status (Folstein, Folstein & McHugh, 1975). The evaluation of cognitive functioning is important in clinical settings because of the high prevalence of cognitive impairment in patients such as those with Alzheimer's disease. As a clinical instrument, the MMSE is used to detect impairment, follow the course of an illness, and monitor response to treatment (Folstein, Folstein & McHugh, 1975). While the MMSE has limited specificity with respect to individual clinical syndromes, it represents a brief, standardized method by which to grade cognitive mental status. It assesses orientation, attention, immediate and short-term recall, language, and the ability to follow simple verbal and written commands (Folstein, Folstein & McHugh, 1975). Furthermore, it provides a total score that places the individual on a scale of cognitive function. The maximum test score that can be achieved is 30 and disease severity levels are classified as Minimum (24-30), Mild (19-23), Moderate (12-18) and Severe (0-11). All patients in this current study completed the MMSE before starting the testing session. During this screening test that measures cognitive mental status, the patients performed a number of items that tested verbal and nonverbal abilities.

5.6.4 Results

5.6.4.1 Recognition Test

The four categories of visual stimuli presented in the computerized Recognition test showed significant differences between the two groups using total percent scores, D' scores and β scores. The findings showed that the patients performed more poorly on all

the different categories of stimuli. A one-way ANOVA using the total percent correct scores from the four groups of stimuli produced the following results: Dogs, $F(1, 46) = 31.20$, $p < .001$; Faces, $F(1, 46) = 61.82$, $p < .001$; Houses, $F(1, 46) = 109.96$, $p < .001$; Landscapes, $F(1, 46) = 113.34$, $p < .001$; and Words, $F(1, 46) = 91.91$, $p < .001$. The following results were found after computing a one-way ANOVA using D' scores: Dogs, $F(1, 46) = 15.17$, $p < .001$; Faces, $F(1, 46) = 24.55$, $p < .001$; Houses, $F(1, 46) = 44.38$, $p < .001$; Landscapes, $F(1, 46) = 75.95$, $p < .001$; and Words ($F(1, 46) = 13.61$, $p < .05$). A one-way ANOVA using the β scores revealed that the patient group was significantly different from the healthy controls on the category of Landscapes, $F(1, 46) = 4.33$, $p < .05$. The results for the remaining categories were not significant: Dog, $F(1, 46) = .33$, ns; Faces, $F(1, 46) = 1.61$, ns; Houses, $F(1, 46) = .36$, ns; and Words, $F(1, 46) = 2.74$, ns. Figure 1 shows the mean percent correct scores for both groups across all categories of stimuli. Tables 1 - 3 report the mean and standard deviation scores for all categories of stimuli.

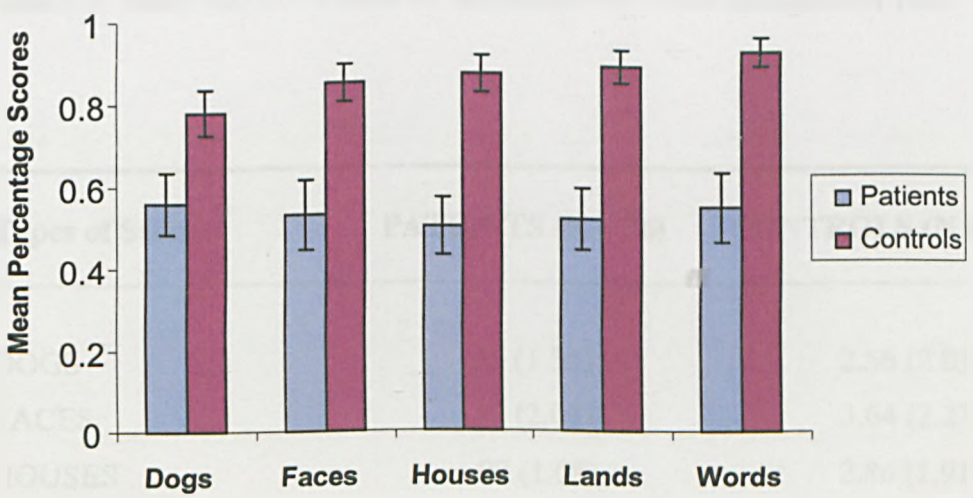

Figure 5.1. Mean Percent scores on all categories of the Recognition Test.

Table 5.1. *Mean (SD) Total Percent Correct Scores for all categories of the Recognition Test.*

Type of Stimuli	PATIENTS (N = 26)	CONTROLS (N = 22)
DOGS	56% (.15)	78% (.11)
FACES	53% (.17)	85% (.09)
HOUSES	50% (.14)	87% (.09)
LANDSCAPES	52% (.15)	89% (.08)
WORDS	55% (.17)	93% (.07)

Table 5.2. *Mean (SD) D' Scores on the categories of the Recognition Test.*

Types of Stimuli	PATIENTS (N = 26)	CONTROLS (N = 22)
DOGS	.55 (1.56)	2.56 (2.03)
FACES	.58 (2.03)	3.64 (2.23)
HOUSES	-.07 (1.08)	2.86 (1.91)
LANDSCAPES	.43 (.90)	4.24 (2.00)
WORDS	1.22 (1.97)	3.43 (2.18)

Table 5.3. *Mean (SD) β Scores on the Recognition Test (Dogs, Faces, Houses, Landscapes, and Words) performed by the AD patients and healthy controls.*

Type of Stimuli	PATIENTS (N = 26)	CONTROLS (N = 22)
DOGS	1.22 (.39)	3.32 (10.91)
FACES	1.07 (.25)	1.01 (.02)
HOUSES	.98 (.14)	1.00 (.00)
LANDSCAPES	1.12 (.28)	1.00 (.00)
WORDS	12.55 (32.70)	1.00 (.00)

5.6.4.2 Topographical Localisation Test

The analysis of the Topographical Localization task revealed significant differences between the groups using the total map scores ($F(1, 45) = 19.15$, $p < .001$) and with the England ($F(1, 45) = 16.26$, $p < .001$) and Scotland scores ($F(1, 45) = 15.79$, $p < .001$) separately (Table 4 and Figure 2).

Table 5.4. *Total mean scores and separate regional mean scores between the AD patients and healthy controls on the Topographical Localisation test.*

Region	PATIENTS (N = 26)	CONTROLS (N = 22)
Map Total	19.66 (11.51)	8.23 (4.44)
England	14.56 (9.08)	6.20 (3.70)
Scotland	5.20 (3.55)	2.03 (1.25)

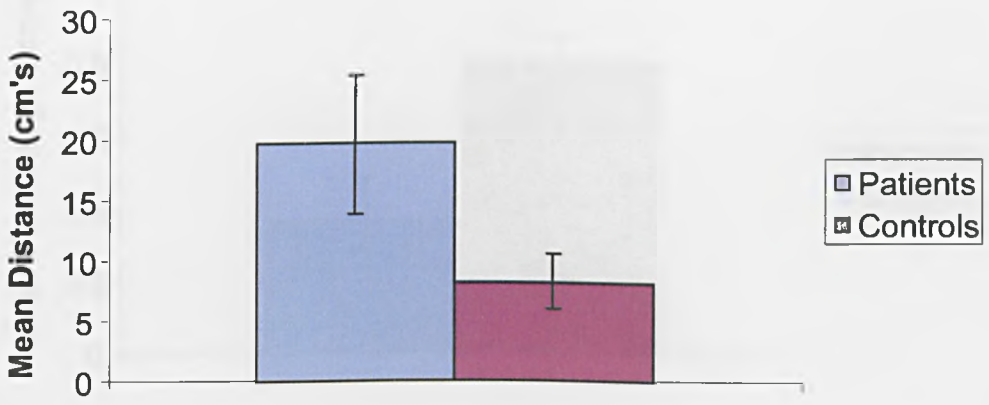

Figure 5.2. Mean distance displacement on the Topographical Localisation test achieved by both the patients and healthy controls.

5.6.4.3 General Semantic Knowledge Test (WAIS-III)

The WAIS test, a test of semantic knowledge also revealed significant differences between the groups using a One - Way ANOVA, $F(1, 46) = 56.94$, $p < .001$ (Table 5 and See Figure 3).

Table 5.5. *Scores obtained by the AD patients and healthy controls on the General Semantic Knowledge test (WAIS-III).*

Group	n	M (SD)
Patients	26	.36 (.25)
Controls	22	.80 (.13)

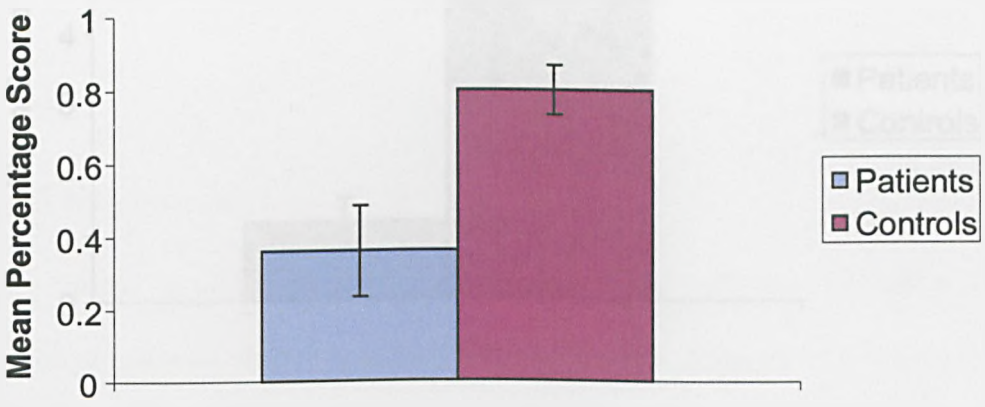

Figure 5.3. Mean percent score obtained by the AD patients and healthy control subjects on the general semantic knowledge test (WAIS-III).

5.6.4.4 Corsi Block Test

Significant group differences emerged between the patient group and healthy control subjects ($F(1, 46) = 84.09$, $p < .001$) with the patients performing worse than the control subjects (Table 6 and Figure 4).

Table 5.6. *Performance (M & SD) achieved by the AD patients and healthy controls on the Corsi Block Test.*

Group	n	M (SD)
Patients	26	1.18 (.72)
Controls	22	4.69 (1.78)

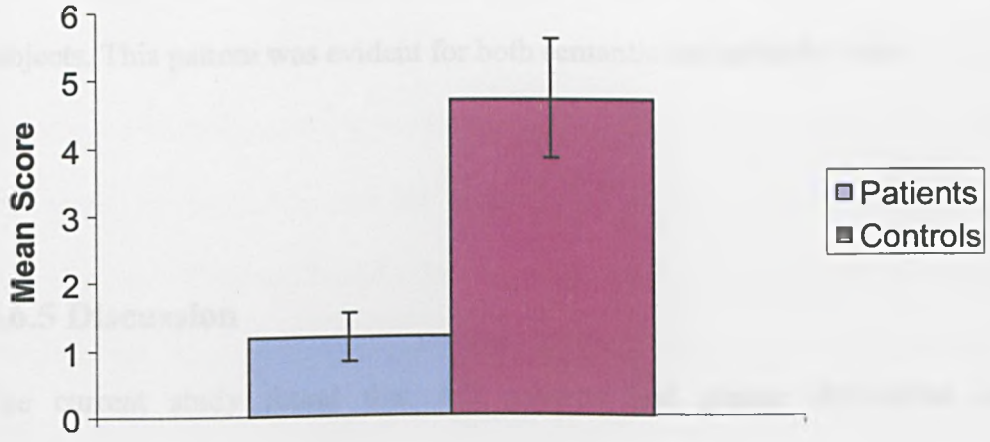

Figure 5.4. Mean scores on the Corsi Block test achieved by AD patients and healthy controls.

5.6.4.5 Verbal Versus Spatial Memory Tests Comparison

A 2 x 2 x 2 ANOVA with Test (Verbal and Spatial) and Type (Semantic and Episodic) as repeated measures and Group as the between factor, was carried out to explore whether AD patients performed significantly worse than healthy control subjects on Spatial memory tests. The following analyses were carried out using normalised data. There was a significant difference in performance between the two groups, $F(1, 45) = 63.49$, $p < .05$. The factor test was significant, $F(1, 45) = 298.34$, $p < .001$. The interaction between Test x Group was also significant, $F(1, 45) = 15.16$, $p < .001$. The factor type ($F(1, 45) = 177.22$, $p < .001$) and the interaction between Type x Group was also significant ($F(1, 45) = 4.82$, $p < .05$). However, the three-way interaction between Test x Type x Group was not significant, $F(1, 45) = 2.78$, ns. The AD patients performed significantly worse on the tests of Spatial memory (Topographical Localisation and Corsi Block Test) than Verbal memory tests (General Semantic

Knowledge Test and Recognition test, Words category) compared to the healthy control subjects. This pattern was evident for both semantic and episodic tasks.

5.6.5 Discussion

The current study found that AD patients had greater difficulties on tests of topographical and spatial memory than the verbal memory tests. However, the AD patients were significantly impaired on all memory tests (Topographical Localisation Test, Corsi Block test, General Semantic Knowledge test, and Recognition Test). Analyses of the d' scores obtained on the Recognition test indicated that the AD patients had greater impairments in distinguishing between the 'Old' and 'New' photographs for all stimuli categories (i.e. Dogs, Faces, Landscapes, Houses, and Words). The analysis using the β scores revealed that the AD patients had a bias for responding 'Old' only to the Landscape photographs. Cherrier, Mendez & Perryman (2001) stated that poor visuospatial attention in AD patients might contribute to deficits in navigation. The landscape photographs were very rich in detail and colour and perhaps contained too much information for the patients to process. The response bias observed thus might be due to the complexity and difficulty of the Landscape photographs.

The results of the current experiment are in agreement with previous studies that have demonstrated that AD patients have problems with topographical information. Pai & Jacobs (2004) studied 112 patients in the early stages of AD and discovered that 61 patients experienced topographical disorientation, 20 of these patients required an escort home, and 28 of these patients first sign of a cognitive dysfunction or a behavioural disturbance was difficulties in navigation. These authors suggested that topographical disorientation might be an early symptom of AD. Cherrier, Mendez & Perryman (2001)

examined the cognitive abilities associated with navigation and route learning in a group of AD patients and healthy control subjects. Their findings indicated that the patients were significantly more impaired than the controls on the route-learning test. The study in this thesis did not assess route learning in AD patients, but there is evidence from Cherrier, Mendez and Perryman who concluded that poor route learning performance is a result of overall poor spatial reasoning or spatial orientation. In this study, AD patients also performed poorly on the topographical localisation task, where patients were required to locate cities on a map of the United Kingdom. Beatty & Salmon (1991) also found that AD patients exhibited deficits in geographical knowledge when asked to locate cities on a map. A group of 16 patients completed sections of the Fargo Map test, which included a residential history, the United States map, the California-Nevada map, San Diego County map and a map of the region of the United States where the subject was born and raised. The patients performed significantly better on a map of where they were born and raised compared to a map of where they were currently residing at the time of testing. The authors claim that these patients might suffer from temporally graded retrograde amnesia, and that this might only be apparent in relatively mild AD patients.

The results of this study do not support the work by Caine & Hodges (2001), who hypothesised that semantic and visuospatial deficits would precede one another or that one group of AD patients would be more impaired on semantic tests and not spatial tests and vice versa. The tests in the current study assessed both verbal and spatial tests and the AD patients showed overall impairments in both spatial and verbal memory tests, with greater deficits in the spatial domain. Based on the heterogeneity of AD symptoms, Demadura et al. (2001) also predicted that a group of AD with high verbal memory would perform better on tests of verbal memory than those with high spatial memory and those with high spatial memory would perform better on tests of spatial memory

than those with high verbal memory. Their results supported the hypothesis; however, these authors also found that these two groups of AD patients did not differ on the spatial memory tests. These studies as well as the current study demonstrate that even during the early stages of AD, it might not be possible to find isolated cases of topographical memory impairment. One explanation for the lack of cases that have reported isolated topographical memory impairment might be because the disease must first cause damage to the mesial temporal-hippocampal structures, to either the right or the left hemisphere (Demadura et al., 2001). However, by the time the disease is diagnosed, sufficient damage has occurred to the right and left mesial temporal structures to cause substantial deficits in both verbal and nonverbal memory. In addition, very few studies have investigated different cognitive domains in isolation (Demadura et al., 2001). If studies examine separate verbal and spatial memory once the patient is diagnosed with AD, asymmetric deficits may not be detected due to floor effects. It has been found that before a clinical diagnosis of AD is made, the pathological process affecting AD has usually been present for years (Wolf et al., 2001). Henderson, Mack & Williams, (1989) suggested that a dysfunction in the neocortical areas of the right hemisphere involved with visuospatial processes was linked with their findings of spatial disorientation in AD patients. In addition, these authors stated their findings could not be explained by general global cognitive decline. Dementia severity did not predict spatial disorientation when scores from other tests were considered. Research has repeatedly found the hippocampus to be involved in memory and learning, and in particular, the right medial temporal regions (e.g. right parahippocampal gyrus) to be involved in spatial memory. Prior to examining whether any atrophy of the medial temporal regions in this group of AD patients contributed to the observed spatial and topographical impairments, the following experiment will examine whether any

significant differences in grey matter density volumes are present between the present group of AD patients and healthy controls using voxel-based morphometry.

5.7 EXPERIMENT 8: A Voxel-Based Morphometric Study to Examine Differences in Grey Matter Density between Alzheimer's Disease Patients and Healthy Controls

5.7.1 Aims

The medial temporal lobe comprised of the hippocampus proper, parahippocampal gyrus and amygdala has been reported to be the first region of the brain in AD that is affected by atrophy (Braak & Braak, 1991; Baron et al., 2001; Frisoni et al., 2002). Numerous studies have also demonstrated that several regions show atrophy (de Leon et al., 2001; Frisoni, 2000, as cited in Karas et al., 2003). However, these studies have used regions of interest analyses, which examine pre-selected structures (Rombouts et al., 2000; Pruessner et al., 2000, as cited in Karas et al., 2002). The VBM technique is capable of carrying out statistical tests between two groups in all areas of the brain and is an unbiased approach to investigate grey matter abnormalities between two groups (Rombouts et al., 2000; Busatto et al., 2003). In addition, MMSE scores will be correlated with grey matter density volume using a voxel-based morphometric correlational analysis.

5.7.2 Methods/Procedure

5.7.2.1 Participants

The group comparison analysis consisted of eight patients (all males) (Mean age = 81.5, SD = 8.44). The sample of patients were taken from Experiment 1, however, due to the nature of a MRI scan and some technical problems only eight patients completed this study. Four patients in this sample had minimum dementia as determined by their MMSE scores (24-26), three patients had mild dementia (20-21), and one patient had moderate dementia (18). Eight healthy control subjects (2 Males and 6 Females) matched for age and education agreed to take part in the study (Mean age = 74.9, SD = 1.55). This study received approval by the joint Grampian Health Board and the University of Aberdeen ethics committee.

5.7.2.2 MRI Imaging

3D MRI brain scans were acquired at the MRI Centre, of the University of Aberdeen, Scotland. Subjects were scanned using a 1.5 Tesla GE MRI system acquiring T1-weighted images using a SPGR imaging sequence. The voxel dimensions were 2.56 x 2.56 x 1.24, in plane resolution, field of view 240mm (pixel size 0.9375mm) with a slice thickness of 1.6mm. Before carrying out statistical analyses, images were normalised onto a standardised anatomical space, segmented into grey matter, white matter and cerebrospinal fluid. The grey matter images were then spatially smoothed using a full width half maximum (FWHM) kernel of 4mm. The amount of smoothing was determined by the a priori hypothesis predicting hippocampal atrophy. Therefore, smoothing greater than 4mm might not detect differences in smaller brain structures such as parts of the hippocampus, or nearby regions.

5.7.2.3 Data Analysis

Data were analysed using Statistical Parametric Mapping 99 (SPM) software (Wellcome Department of Imaging Neuroscience). The comparison between AD and control subjects was performed using ANCOVA, with age used as a covariate. A simple regression analysis using MMSE scores was also completed. Only clusters surviving corrected cluster probability levels were considered as significant.

5.7.3 Results

The comparison of grey matter density volumes between the two groups revealed significant reductions in the AD patients compared to the healthy control subjects. The areas of significant reductions were located bilaterally in the parahippocampal gyrus (BA 19, 30, 35), right middle frontal gyrus (BA 9) and posterior cingulate (BA 30). Figure 5 displays the areas of reduced grey matter density in the AD patients relative to controls. Details about the cluster sizes, p values, z scores, Talairach coordinates and Brodmann's areas are provided in Table 7.

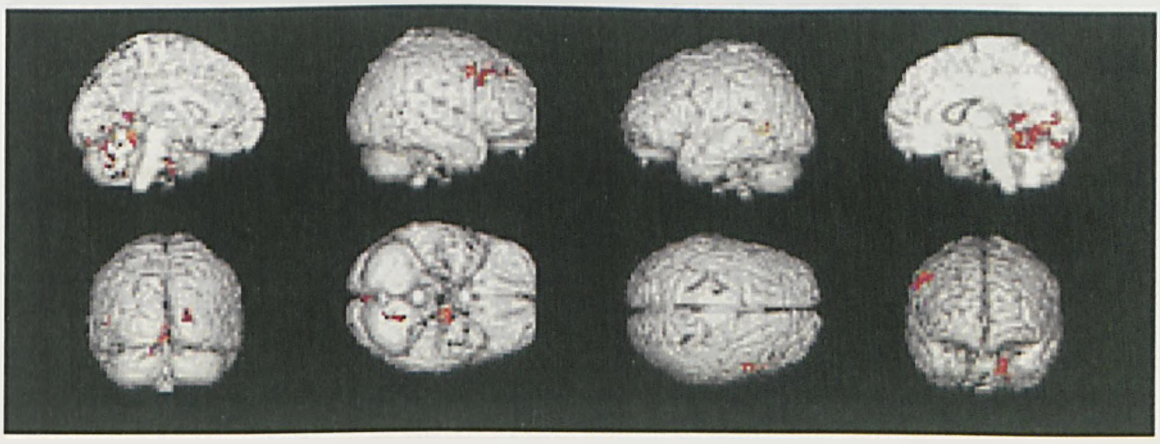

Figure 5.5. Brain regions showing significant reductions in grey matter density volumes in AD patients relative to healthy controls (height threshold, $p < 0.05$).

Table 5.7. *Brain regions, corresponding Brodmann's areas, Talairach coordinates, Z-scores, and Cluster sizes and corrected cluster probability levels of the difference observe between the two groups.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates	
R Post Cingulate (BA 30)	197	.004	4.04	25	-68
L Parahippocampal gyrus (BA 19)	157	.009	3.96	-38	-47
L Parahippocampal gyrus (BA 35)	88	.04	3.26	-16	-13
R Parahippocampal gyrus (BA30)	88	.04	3.40	6	-41
R Middle Frontal gyrus (BA 9)	176	.006	3.22	50	35

(R = right; L = left)

5.7.3.1 Mini Mental State Examination Voxel-Based Correlational Analysis

A significant positive correlation between grey matter density volumes and MMSE scores was found in the left superior frontal gyrus (BA 6), right uncus (BA 38), right postcentral gyrus (BA 5), and left cingulate gyrus (BA 23). Figure 6 shows the brain regions that correlated positively with MMSE scores.

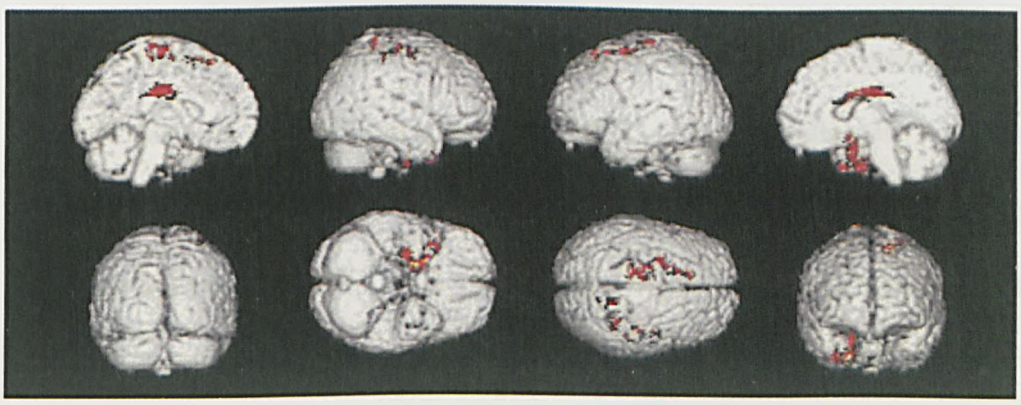

Figure 5.6. Areas of positive correlation with MMSE scores in the AD group (height threshold, $p < .04$).

Table 5.8. *Areas of Significant Correlation (with corresponding Brodmann's areas, Cluster sizes and corrected cluster probability levels, p-values, Z-scores and Talairach coordinates) between MMSE scores and grey matter density volume in the AD group.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
L Superior Frontal Gyrus (BA 6)	408	.005	4.20	-12	32	5
R Uncus (BA 38)	600	.000	3.89	22	6	-3
R Postcentral Gyrus (BA 5)	680	.000	3.53	46	-41	6
L Cingulate gyrus (BA 23)	395	.005	3.49	-4	-22	2

(R= Right, L= Left)

5.7.4 Discussion

This structural MRI study investigated grey matter reductions in AD patients compared to healthy controls using the VBM technique. As predicted, atrophy was observed in the medial temporal lobe and in the parahippocampal gyrus bilaterally (BA 19, 35, 30) in the AD patients relative to the healthy controls. Although VBM has not been extensively employed in AD studies, the findings are consistent with the results of previous studies that have examined atrophy in Alzheimer's disease (De Leon et al., 1997; Busatto et al., 2003; Karas et al., 2003). Galton, Patterson, Graham, Lambon-Ralph, Williams, Antoun et al. (2001) also found bilateral hippocampal atrophy in AD patients relative to controls, with involvement of the amygdala bilaterally and the right parahippocampal gyrus. The parahippocampal gyrus has been found to form a large part of the limbic lobe (Van Hoesen, Augustinack, Dierking, Redman & Thangavel, 2000). In addition, Van Hoesen et al. (2000) have also indicated that the cortical areas that form the parahippocampal gyrus are vulnerable to pathological changes in AD, and its

entorhinal and perirhinal subdivisions are the most seriously damaged cortical areas. Therefore, these areas should be studied further as they might be involved in the initial onset of the disease (Van Hoesen et al., 2000). Although the findings of Busatto et al., (2003) were in agreement with other studies which have also showed temporal lobe atrophy, these authors suggested that such atrophy is not distributed uniformly across the temporal region but limited to specific sub-regions. More importantly, the role of the parahippocampal gyrus, specifically the right side, in spatial and topographical tasks might very well explain the findings of topographical memory impairments reported in Experiment 1. Experiment 3 will address this question further by carrying out a voxel-based correlational analysis with the scores from the topographical memory tests and grey matter density volumes derived from the MRI images.

As mentioned previously, the medial temporal lobe is one of the most prominently affected regions in AD. However, the posterior cingulate has also been found to be atrophic in AD (Baron et al., 2001; Vogt, Hoesen, & Vogt, 1990 & Minoshima et al., 1997, as cited in Frisoni et al., 2002). This study also found grey matter reductions in the right posterior cingulate in the AD patients relative to the healthy controls. The learning and memory impairments observed in early Alzheimer's disease might be of functional importance for the posterior cingulate cortex (Eustache et al., 2000, as cited in Baron et al., 2001). In addition, the posterior cingulate has not only been reported to be one of the first areas to show hypometabolism in AD, it was also reported to have the largest decrement (Valla, Berndt & Gonzalez-Lima, 2001). These authors suggested that such a decrement might contribute to the behavioural symptoms of AD. The use of VBM in this study also identified reductions in grey matter density in the right middle frontal gyrus of the AD patients relative to the healthy controls. Frisoni et al. (2002) reported atrophy of the middle frontal gyrus, although this area was more affected in the left hemisphere, whereas, the current study found the atrophy confined to the right

hemisphere. These discrepancies can be explained by the broad heterogeneity of patterns of impairments which are characteristic of the AD pathology which, although showing common features in most patients, also has a great deal of variability. Many volumetric studies have also shown more general frontal lobe atrophy in AD without remarking on a specific pattern of laterality (Pantel et al., 2004; Halliday, Double, Macdonald & Kril, 2003).

The MMSE scores correlated positively with grey matter density volumes in the left superior frontal gyrus (BA 6), left cingulate gyrus (BA 23), right uncus (BA 38) and right posterior central gyrus (BA 5). Frisoni et al. (2002) are the only other known group of researchers who have correlated MMSE scores with grey matter density volume in AD using VBM. However, Frisoni et al. found a negative correlation with disease severity and grey matter density in the region of the left cingulate gyrus. Other areas included the right inferior temporal gyrus, right superior temporal gyrus, right superior parietal lobule, and the left precuneus. The authors noticed hemispheric asymmetry, with greater atrophy on the right, which was unexpected as the MMSE has been considered to consist of more verbal tasks than nonverbal tasks. However, other authors have also suggested that the MMSE is more affected by lesions to the right hemisphere than to the left hemisphere Grace et al., 1995, as cited in Frisoni et al., 2002).

One aspect of this study that needs to be mentioned is that all the AD patients included were males. Unfortunately, due to technical issues with some of the scans, the only MRI data that was useable were of male patients. With a larger sample size, future studies should also examine atrophy within the different stages of AD using MMSE scores.

5.8 EXPERIMENT 9: A Voxel-Based Morphometric Correlational Study with Neuropsychological Performance

5.8.1 Aims

The findings from Experiment 1 demonstrated that AD patients were significantly impaired on all the memory tasks administered in the study, however, greater deficits in spatial and topographical memory tasks were found compared to verbal memory tests. More importantly, the group comparison carried out in Experiment 2 clearly demonstrated atrophy of the parahippocampal gyrus. Neuro-imaging studies have demonstrated that the hippocampus and parahippocampal gyrus in the right hemisphere are responsible for mediating topographical and spatial memory. In addition, it has been suggested that medial-temporal lesions in humans that include the hippocampus and adjacent regions in PHG produce more severe memory impairments than lesions restricted to the hippocampus, however, the group comparison study did not show any hippocampal atrophy in the AD patients (Rempel-Clower et al. 1996; as cited in Köhler, Black, Sinden, Szekely, Kidron, Parker et al., 1998).

To determine whether atrophy of specific brain structures contributed to the behavioural performance observed in Experiment 7, a subgroup of the same AD patients completed a structural Magnetic Resonance Imaging (MRI) session. Although there is strong evidence that AD is associated with parahippocampal atrophy, no previous study has used voxel-based morphometry, to examine whether poor performance on topographical and verbal memory tests correlate with brain atrophy in this region (Baron et al. 2001; Frisoni et al. 2002; Karas et al. 2002; Busatto et al. 2002). Using voxel-based correlations, Experiment 9 will examine whether regional brain atrophy can explain the observed neuropsychological deficits in spatial and verbal memory tests from

Experiment 7. Therefore, the aim of this study was to examine the neuroanatomical correlates of spatial and topographical memory deficits in AD, as very limited data has been collected to support or challenge this view.

5.8.2 Methods/Procedure

5.8.2.1 Participants

Same as Experiment 2.

5.8.2.2 MRI Methods

See Experiment 2.

5.8.2.3 Data Analysis

This correlational study consisted of a series of simple regression analyses. Scores from the Topographical Localisation Task and Corsi Block Test, as well as the D' scores from the Landscapes and Words category of the Recognition test were correlated with grey matter density. Only clusters surviving corrected cluster probability levels were considered as significant.

5.8.3 Results

5.8.3.1 Word Recognition Test

Scores on the Word category of the Visual Picture Recognition test also did not correlate with any area of the brain, which might be explained by the extremely poor performance of the AD patients on this task.

5.8.3.2 Landscapes D' Scores (Recognition Test)

A significant negative correlation was found on the AD patients' d' scores on the Landscape category of stimuli on the Recognition of Visual Stimuli tests and grey matter density in the right thalamus (Table 9 and Figure 7).

Table 5.9. *Areas of significant correlation (corresponding Brodmann's area, Talairach coordinates, z-score and cluster size and corrected cluster probability levels) between the d' scores achieved on the Landscapes category and grey matter density.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
R Thalamus	83	.000	3.58	8	-27	7

(R= Right, L= Left)

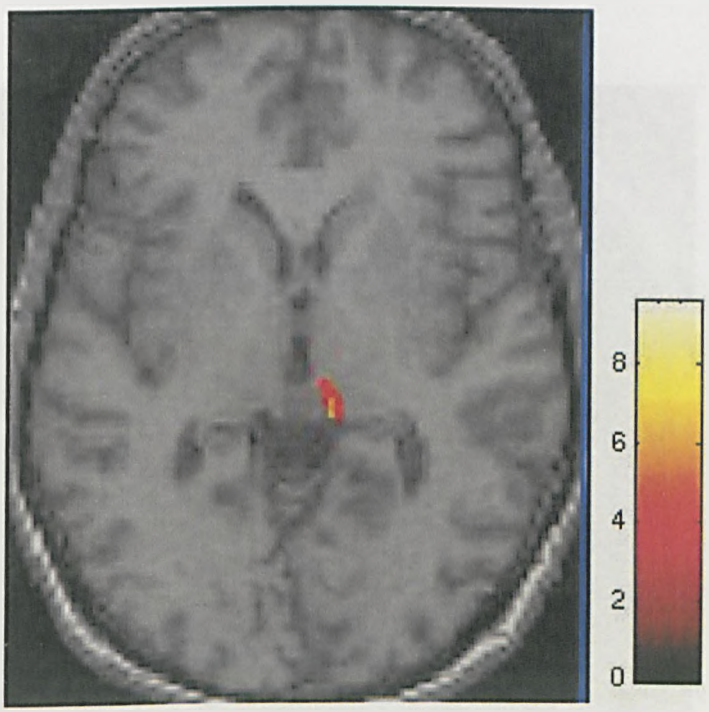

Figure 5.7. Axial view of the right thalamic regions showing significant negative correlation with performance on the landscape category of the Recognition of Visual Stimuli test (height threshold, $p < .01$).

5.8.3.3 Topographical Localisation test

No significant correlation was found between grey matter density volumes in any region of the patients' brain and scores from the Topographical Localisation task. Lack of any significant correlation might be explained by the floor effect observed in the scores of the patients in this group.

5.8.3.4 Corsi Block Test

Significant negative correlations were found between the AD patients' scores on the Corsi Block test and grey matter density in the left fusiform gyrus (BA 19), R cingulate (BA 31), left superior temporal gyrus (BA 22), and left thalamus (Figure 8). Details of the brain regions and corresponding Brodmann's areas, Talairach coordinates, cluster sizes, p values, and Z scores are provided in Table 10.

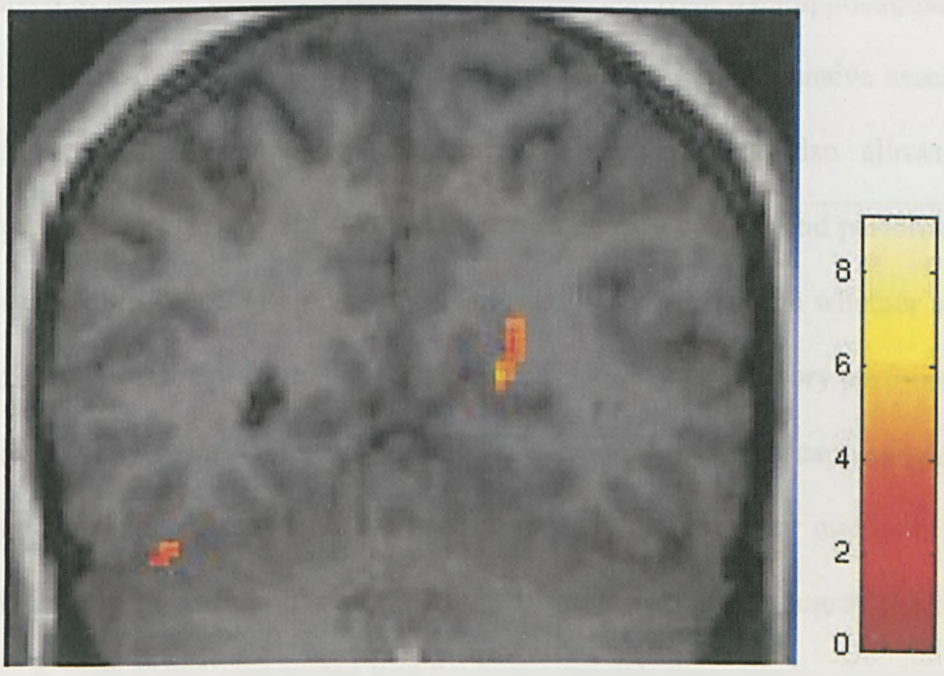

Figure 5.8. Coronal slice showing areas in which significant negative correlations were found with the scores achieved on the Corsi Block test (height threshold, $p < .01$).

Table 5.10. *Significant correlations between grey matter density volumes and scores on the Corsi Block test (including Brodmann's areas, number of voxels in cluster, corrected cluster probability levels, p-values, Z-values, and Talairach coordinates.*

Area	Number of voxels in cluster	Corrected cluster-level p-value	Z value at local maxima	Talairach coordinates		
L Fusiform gyrus (BA 19)	86	.05	3.90	-36	-71	-15
R posterior cingulate (BA 31)	90	.05	3.88	20	-59	20
L superior temporal gyrus (BA 22)	93	.05	3.80	-51	-17	6
L thalamus	78	.05	3.72	-18	-33	7

(R= Right, L= Left)

5.8.4 Discussion

This study focused on the correlations between the brain grey matter volumes and scores achieved by the AD group on neuropsychological tests, which examined visuospatial memory performance. Spatial and topographical memory impairments have been linked to lesions within the right hippocampus and right parahippocampal gyrus in animal and human studies. The use of VBM provides a comprehensive assessment of grey matter densities throughout the brain. This technique also allows for the investigation of a correlation between grey matter density volume and performance on a neuropsychological test. The purpose of this study was to examine whether atrophy of the medial temporal regions in AD contributed to poor spatial memory performance.

The current study found that the AD patients' scores on the Landscape category of the Recognition test correlated with a non-specific reduction of grey matter in the right thalamus. Although the hippocampus might be implicated in topographical memory, Maguire & Frith (2003) suggested that the hippocampal-diencephalic circuit might also be involved in the memory for spatial layouts (as cited in Ridley, Baker, Mills, Green & Cummings, 2004). Della Sala, Spinnler and Venneri (1997) reported verbal and visuo-

spatial long-term memory deficits in a patient with an isolated right thalamic lesion and hypometabolism in the mesial frontal regions. The visuospatial task administered to this patient group was the Corsi Block test. Kubat-Silman, Dagenbach & Absher (2002) also reported deficits on a verbal n-back task, object n-back task, and a spatial n-back task in a group of patients with lesions to primarily to the right thalamus (with the exception of one patient with a left-sided thalamic lesion). Similar to the work by Della Sala and colleagues, these patients did not demonstrate any short-term memory deficits (1997). In addition, Pepin & Auray-Pepin (1993) also found spatial memory deficits following a lesion to the right thalamus (as cited in Della Sala, Spinnler & Venneri, 1997). Ridley et al. (2004) have also found topographical memory impairments after unilateral lesions of the anterior thalamus in a group of macaques. These monkeys were severely impaired in learning tests that required the integration of information about the appearance of objects and their positions in space. In addition, these monkeys were impaired on spatial tests that required the integration of information about the appearance of objects and the background on which objects were situated, irrespective of their positions. In support of the role of the thalamus in memory, research in Korsakoff's syndrome first indicated that damage to the thalamus contributes to amnesia, despite the difficulty in finding isolated lesions of the thalamus (Ridley, Maclean, Young & Baker, 2002). Animal studies involving rats have also found involvement of the thalamus in spatial memory, particularly the anteroventral thalamic nucleus (Mitchell, Dalrymple-Alford & Christie, 2002). Mitchell, Dalrymple-Alford & Christie, carried out the first study to provide evidence that the brainstem's cholinergic innervation to the thalamus influences learning and memory.

Scores on the Corsi Block test correlated significantly with atrophy of the left fusiform gyrus (BA 19), right posterior cingulate (BA 31), left superior temporal gyrus (BA 22), and the left thalamus. It was interesting to see atrophy of the left fusiform gyrus and left

superior temporal gyrus as the Corsi is a spatial test dependent on right-sided functioning. The AD patients might have used a verbal strategy to memorise the order of blocks around the board, which would explain the presence of a significant correlation with scores on this test and left-sided atrophy. The finding of a correlation with atrophy of the right posterior cingulate is consistent with other studies that have also reported topographical memory impairments after a lesion to this area. Katayama, Takahashi, Ogawara, & Hattori (1999) presented a case study of a woman who experienced topographical disorientation after a cerebral infarction involving the isthmus of the right posterior cingulate gyrus. This patient was classified as having topographical amnesia as she was unable to find her way to a rehabilitation room, where she was taken every day and to the lavatory, that was only ten feet away from her room. The patient relied upon visual landmarks and could successfully navigate if given a list of landmarks to indicate the route, but not with a map. Aguirre, Detre, Alsop, and D'Esposito (1996) stated that spatial processing depends on a network of regions that include the posterior parietal cortex, the retrosplenial cortex, the parahippocampus, and the hippocampus. As cited in Katayama et al. (1999), Sutherland & Hoesing (1993) found that the area of the posterior cingulate gyrus, area 29, in rats has the same function as that of the hippocampus on tasks requiring navigation. Therefore, it could be possible that although the hippocampus is largely responsible for memory, other brain regions, such as the right posterior cingulate gyrus could also have specific functions in the memorisation of new routes. Hirono, Mori, Ishii, Ikejiri, Imamura, Shimomura et al. (1998) found that glucose hypometabolism of the posterior cingulate gyrus contributes to time (temporal) and place (locational) disorientation in AD patients. Time and place orientation was examined using the subtests within the Mini Mental State Examination. The posterior cingulate is very closely connected to the medial temporal memory system and the connection between these two regions might be responsible for the role

of the posterior cingulate in orientation (Hirono et al. 1998). In the current study, although grey matter density volumes in the hippocampus or parahippocampus gyrus were not found to correlate with the scores on spatial and topographical memory tests, these regions might still explain the poor performance. However, as the disease progresses, areas such as the thalamus and posterior cingulate might become involved in visuospatial tasks to compensate for the deterioration in functioning of the hippocampus and parahippocampus gyrus. Scores from the topographical localisation test and the word category of the recognition test did not correlate with grey matter volumes in any region of the brain. This negative finding might be the product of a floor effect in the neuropsychological tests. Future VBM studies with a larger sample of AD patients will help improve the current understanding of the neuroanatomical correlates of spatial and topographical memory impairments in AD.

CHAPTER 6 General Discussion

The experiments in this thesis have established that the functioning of the structures of the limbic system can be severely disrupted as a consequence of either a functional (panic disorder or post-traumatic stress disorder) or a degenerative disorder (Alzheimer's disease). The behavioural studies provide overwhelming evidence supporting a vulnerability of individuals with these disorders who primarily show impairments in tasks assessing spatial and topographical memory as well as verbal memory. The correlational studies, using voxel-based morphometry, demonstrate that the observed cognitive impairments are directly linked to reductions in grey matter density volume in structures responsible for such behaviour. For example, deficits in memory for Landscape photographs (topographically relevant information) correlated with atrophy in the right parahippocampal gyrus in post-traumatic stress disorder patients. Findings from the panic disorder study showed selective deficits in topographical memory with relative sparing of verbal memory, supporting previous evidence for the functional role of the parahippocampal gyrus in topographical memory (Aguirre et al., 1998; Maguire et al., 2001). Cerebral blood flow abnormalities in this region, primarily to the right hemisphere, have been implicated in patients with panic disorder (Reiman et al., 1984; 1986). In addition to the observed cognitive deficits in patients with post-traumatic stress disorder and Alzheimer's disease, these impairments are strongly linked with disease severity. Examining brain activation patterns in post-traumatic stress disorder patients also suggest a dysfunction within the limbic system when these patients are exposed to trauma-related stimuli.

Using voxel-based morphometry, this thesis also demonstrates that structural abnormalities are present within the limbic system in post-traumatic stress disorder and Alzheimer's disease. Such structural abnormalities also contribute to the vulnerability of these patient groups' to develop impairments in cognitive abilities. The group comparison between the post-traumatic stress disorder patients and healthy controls support the hypothesis that structural abnormalities within the limbic system exist as atrophy to areas such as the parahippocampal gyrus were found in the patients compared to the healthy controls. A similar analysis within the Alzheimer's disease group also reveal significantly more atrophy to areas such as the right posterior cingulate and parahippocampal gyrus bilaterally.

The use of voxel-based morphometry in clinical neuroimaging studies is very recent. However, the use of the voxel-based correlation technique in patient populations such as post-traumatic stress disorder or Alzheimer's disease to establish associations between regional grey matter density and distinctive cognitive deficits is extremely novel. To date, this is the only study that has used voxel-based morphometry to carry out correlational analyses and only two studies have used this technique in patients with acute post-traumatic stress disorder to evaluate group differences (Yamasue et al., 2003; Corbo et al., 2005). Thus, although voxel-based morphometry is a new approach, the use of this procedure supports the previous structural findings of structural abnormalities in the limbic system in post-traumatic stress disorder and Alzheimer's disease and supports the functional role these structures play in the impairments of memory observed in these disorders. In the following sections, the main findings relating to abnormalities of the different structures of the limbic system will be discussed in detail in relation to findings from previous studies of functional and degenerative disorders. Thus, this discussion will highlight the core contributions that the results of this project provide to better understand the role that abnormalities in the

limbic system play in detecting the cognitive impairments of panic disorder, PTSD and Alzheimer's disease.

6.1 Hippocampus & Parahippocampal Gyrus

The results from the panic disorder study provide strong evidence that memory deficits do exist in panic disorder. The panic disorder patients showed significant impairments on a recognition test of landscape photographs compared to healthy control subjects. Anecdotal evidence has suggested that anxiety disorders do cause attention and concentration difficulties, but, this is the first study to show clear evidence of cognitive deficits in the domain of topographical memory. Unfortunately, due to the nature of the illness, the panic disorder patients were not able to undergo MRI scanning sessions. Thus, although these patients showed significantly worse performance on tests of topographical memory, it is not clear whether explicit damage to the hippocampus and / or parahippocampal gyrus contributed to the memory impairments. Reiman et al. (1984; 1986) found that panic disorder patients showed abnormalities in the right parahippocampal gyrus. Clinical studies as well as studies of healthy control subjects have found that this region is largely responsible for topographical memory. The results from the current study, therefore provide overwhelming evidence to carry out a larger scale study with more patients to investigate topographical memory in panic disorder.

Structural abnormalities in the hippocampus, a part of the limbic system, have been reported in both Post-Traumatic Stress disorder (PTSD) and Alzheimer's disease patients. Selective volumetric studies of the hippocampus in PTSD patients have shown either right or left-sided reductions or bilateral reductions of hippocampal volume (Bremner, Randall, Scott, Bronen, Seibyl, Southwick et al., 1995; Gurvits, Shenton, Hokama, Ohta, Lasko, Gilbertson et al., 1996; Stein, Koverola, Hanna, Torchia & McClarty, 1997; Gilbertson, Shenton, Ciszewski, Kasai, Lasko et al., 2002; Bremner,

Vythilingam, Vermetten, Southwick, McGlashan, Nazer et al., 2003). The importance of the hippocampus in memory formation and consolidation has lead to the question of whether hippocampal atrophy is associated with cognitive impairments in PTSD (Eichenbaum, 2001; Robertson, 2002). Recent studies have investigated whether a link is present between hippocampal atrophy and memory deficits in PTSD. For example, Bremner et al. (1995) found deficits of verbal short-term memory in a group of PTSD with childhood physical and sexual abuse. In addition, Gurvits et al. (1996) found a negative correlation between hippocampal volume and performance on the WAIS-R arithmetic, Wechsler Memory Scale-R attention/concentration index and for the Benton Visual Retention Test 15 seconds delayed recall errors (i.e., lower hippocampal volume correlated with greater impairments). Using a heterogeneous group of PTSD patients, this thesis found evidence of visuospatial deficits using a battery of neuropsychological tests. On a recognition test of visual stimuli, the PTSD patients performed significantly worse than the healthy controls in the category of Landscapes. In addition, on the Topographical Localisation task, the PTSD patients also performed significantly worse than the healthy control subjects. These combined findings strongly suggest that hippocampal dysfunction, primarily to the right side; contributed to the observed deficits as the right hippocampus has been implicated in spatial memory tasks (Abrahams, Pickering, Polkey, & Morris, 1997; Maguire, 1997; Maguire, Frackowiak & Frith, 1997; Bohbot, Kalina, Stepankova, Spacova, Petrides & Nadel, 1998). The left hippocampus is more involved in verbal memory while the right hippocampus is involved in visuospatial memory to a greater extent, thus, right hippocampal dysfunction might explain these findings. Support for this suggestion was revealed after carrying out the correlational analysis using regional brain atrophy and performance on neuropsychological tests. Although the PTSD patients also performed significantly worse than the healthy control subjects in the Word category of the Recognition test of

visual stimuli, no brain region correlated with the patients' scores on this test. Thus, although deficits in verbal memory are expected to correlate with generally left-sided atrophy, the absence of atrophy in any brain region suggests that the poor performance might be attributed to the concentration difficulties often reported by patients suffering with an anxiety disorder. As mentioned in the discussion of Experiment 5, the association between left hippocampal atrophy and scores on the Corsi Block test might be attributed to the use of verbal strategy to navigate among the blocks on the board.

Examination of the group comparison between the PTSD patients and healthy controls using voxel-based morphometry revealed atrophy in medial temporal regions and limbic structures, such as fusiform gyrus and parahippocampal gyrus. However, atrophy was not found localised to the hippocampus. These findings suggest that damage within the limbic system and medial temporal regions might be seen as a vulnerability to functional disorders such as PTSD. Damage to these structures might be a predisposition to developing PTSD. To determine whether atrophy to such brain regions is related to environmental factors such as stress, a correlational study was carried out using scores from the CAPS, which measures symptom severity in PTSD. These results showed strong evidence for a link between stress and hippocampal atrophy. The PTSD patients also showed greater atrophy to limbic structures such as the parahippocampal gyrus that associated with severe forms of the disorder. Although, the CAPS score did not correlate directly with hippocampal atrophy, the parahippocampal gyrus is anatomically and functionally very closely related to the hippocampus (Aguirre et al., 1996; Suzuki & Clayton, 2000).

These results add to the growing literature in support of a relationship between stress and alterations in memory. Many studies have suggested that stress is associated with memory deficits (Lupien, Gaudreau, Tchiteya, Maheu, Sharma, Nair et al., 1997; Bremner, 1999; McEwen, 1999; Lupien & Lepage, 2001). High levels of

glucocorticoids associated with stress result in damage to neurons of the hippocampus (Sapolsky, Uno, Rebert, & Finch, 1990). Secondly, the relationship between regional atrophy and performance on memory tasks suggests that deficits in visuospatial memory are clinically meaningful and relate to symptom severity. Thus, patients with PTSD have a dysfunction within limbic structures and more importantly, memory impairments in areas of spatial and topographical memory are directly related to severity of the disease. As illustrated by the voxel-based correlational analysis using CAPS, reduced grey matter density in the parahippocampal gyrus was significantly related to the severity of the disorder in PTSD subjects.

The Alzheimer's disease patients showed remarkably poor performance on the topographical memory tests as well as the verbal memory tests. Involvement of the hippocampus and parahippocampal gyrus in Alzheimer's disease has been evident for many years now (Van Hoesen, Augustinack, Dierking, Redman, & Thangavel, 2000). During the early stages of Alzheimer's disease, patients characteristically show pathological changes in the medial temporal lobe (Mizuno, Wakai, Takeda, & Sobue, 2000; Rombouts, Barkhof, Witter, & Scheltens, 2000; Baron et al., 2001; Busatto, Garrido, Almeida, Castro, Camargo, Cid et al., 2003). Examination of the group comparison showed atrophy primarily in the limbic structure, parahippocampal gyrus, as well as in the posterior cingulate gyrus and the middle frontal gyrus. These results support the findings that early in Alzheimer's disease, limbic structures such as the hippocampus and parahippocampal gyrus show atrophy. Another cortical area that may be differentially affected by AD pathology is the posterior cingulate, which showed atrophy in the AD patients compared to the healthy control subjects and correlated with performance on tasks of spatial memory. These findings support the evidence that the posterior cingulate is involved in spatial disorientation in AD (Minoshima, Foster & Kuhl, 1994; Hirono et al., 1998; Baron et al., 2001). Therefore, these findings suggest

that alterations of this structure contribute to the deficits of way-finding abilities that are commonly reported in AD. In addition to the involvement of the posterior cingulate in spatial memory in AD, a single case study has reported that a lesion to the right posterior cingulate produced very distinctive topographical disorientation (Katayama, Takahashi, Ogawara & Hattori, 1999).

The positive correlation between regional grey matter density and scores on the MMSE suggests relative sparing of grey matter density in the left superior frontal gyrus, right uncus, right post central gyrus and left cingulate gyrus is associated with greater performance on the MMSE. This supports the view that these regions may be involved later in the cause of the disease process. Although there are well-established findings of significant hippocampal atrophy in AD compared to controls, this current study did not find such clear-cut results. A point to consider is that the AD patients were early in the course of the disease and some degree of atrophy may be present in early ageing.

6.3 Cingulate Cortex & Amygdala

Abnormal activity in the anterior cingulate and amygdala has been reported in PTSD patients exposed to trauma-related stimuli (Bremner, Staib, Kaloupek, Southwick, Soufer, & Charney, 1999a; Shin, Whalen, Pitman, Bush, Macklin, Lasko et al., 2001). Decreased activation of the anterior cingulate cortex was found during the Stroop task in combat-related PTSD and in the emotional Stroop task in PTSD caused by childhood sexual abuse (Shin et al., 2001: Bremner, Vermetten, Vythilingam, Afzal, Schmahl, Elzinga et al., 2004).

The cingulate gyrus as well as the amygdala has been reported to be involved in emotion (Vogt, Finch & Olson, 1992). Within the cingulate cortex, two distinct functions exist. The anterior cingulate cortex has been found to be primarily involved in executive functions related to the emotional control of visceral, skeletal and endocrine

outflow, whereas, the posterior cingulate cortex is involved in evaluative functions, such as, monitoring sensory events and spatial orientation and memory (Vogt, Finch & Olson, 1992). Bremner, Narayan, Staib, Southwick, McGlashan and Charney (1999b) found increased activation in posterior cingulate and motor cortex and a failure of activation in the anterior cingulate in their study of combat veterans with PTSD who were exposed to combat-related slides and sounds. The current study found increased activation of the posterior cingulate and precentral gyrus, with a failure of activation in the ACC in the PTSD group in the incongruent condition compared to the congruent condition. Work with normal healthy subjects has also found that the posterior cingulate is involved in emotional processing (Fischer, Wik & Fredrikson, 1996 and Maddock & Buonocore, 1997, as cited in Bremner et al., 1999b). The posterior cingulate, parietal and motor cortex and cerebellum are all functionally related to the superior and middle frontal gyri (anterolateral prefrontal cortex). Together, these structures are thought to play an important role in mediating visuospatial processing that are vital for coping with life-threatening situations (Vogt, Finch & Olson, 1992; Devinsky, Morrell & Vogt, 1995 and Selemon & Goldman-Rakic, 1988, as cited in Bremner et al.). The posterior cingulate has also been reported to have strong connections with the hippocampus and parahippocampal gyrus and although these structures were not involved in the current study as predicted, abnormality within this network of structures may be responsible for the symptoms of PTSD (Bremner et al., 1999a).

Bremner and colleagues (1999a) suggested that in response to traumatic stimuli, activation of the anterior cingulate should be expected, thus, failure of anterior cingulate activation might be characteristic of PTSD. In addition, "dysfunction of the medial prefrontal cortex may represent a neural correlate of the failure of extinction to fear responding, as well as other pathological emotions in PTSD" (Bremner et al., 1999b, p. 1792). In addition, although the function of the amygdala was predicted to also differ in

PTSD patients compared to healthy controls, this was not found in the present study. However, studies currently examining the amygdala in PTSD have been quite equivocal (Rauch et al., 1996; Lanius et al., 2001; Shin et al., 2001; Pissiota et al., 2002; Rauch, Shin & Wright, 2003). The main differences between the studies, which has made it difficult to determine the exact role of this structure in PTSD include, using different paradigms, imaging techniques, types of stimuli, nature of trauma, study populations and differences in emotional responsiveness to the personal description of the traumatic events often used in symptom provocation studies (Hull, 2002; Tanev, 2003). In addition, it is likely that PTSD patients may not be able to successfully recruit the amygdala when exposed to trauma-related stimuli. Thus, contributing to the emotional dysregulation often seen in PTSD.

In conclusion, the findings of the work within this thesis provide sufficient evidence regarding a distinct association between specific cognitive deficits and either structural or functional abnormalities within the limbic system in both anxiety and neurodegenerative disorders. The panic disorder study showed distinct deficits in topographical memory, suggesting the presence of atrophy and/or functional damage to areas such as the hippocampus and parahippocampal gyrus. The experiments within the PTSD and AD group demonstrated that limbic structures are differentially affected and also contribute to the cognitive deficits observed in these patients. In addition, limbic regions involved in memory and visuospatial processing are likely to play a role in the generation of the symptoms more frequently experienced by PTSD and AD patients (Bremner et al., 1999a). It is expected that larger sample sizes should demonstrate specific patterns of activation as well as regional atrophy within the limbic structures of these groups of patients.

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Appendix

PTSD Patient Information

Nature of Trauma	CAPS	f1i2s65	Secondary Diagnosis	IESR	Anti-Dep.	Drug
RTA	59	no	none	99	no	none
industrial accident	76	Yes	none	99	Yes	nefazodone
Industrial accident	51	no	Lifetime diagnosis harmful alcohol misuse currently abstinent	28	Yes	sertraline
RTA	103	yes	none	61	No	none
RTA	83	Yes	none	37	Yes	sertraline, valproate
RTA	82	Yes	Depressive episode	99	Yes	nefazodone reducing regime
RTA (pedestrian)	67	Yes	Moderate depressive episode, possible post conscussional syndrome	56	Yes	reboxetine
RTA	74	Yes	none	99	uncertain	None
Combat	115	Yes	none	64	Yes	nefazodone, carbamazepine
Industrial accident	53	no	none	26	Yes	sertaline
RTA	82	yes	depressive Episode	99	Yes	nefazodone
RTA	92	yes	none	99	Yes	sertraline
Assault/robbery	70	yes	none	59	Yes	nefazodone, diazepam
industrial (witness of fatal accident)	85	yes	none	99	Yes	mirtazapine but poor compliance
helicopter incident	87	yes	Depressive Episode	57	Yes	nefazodone
RTA	83	yes	none	99	uncertain	possibly

f1i2s65 frequency > or = 1, severity > or = 2 and total severity 65 and above
IESR: Impact of Event Scale-Revised version score (maximum score = 88)