

Visual Processing of Words in a Patient with Visual Form Agnosia: A Behavioural and fMRI Study

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Abstract

Patient D.F. has a profound and enduring visual form agnosia due to a carbon monoxide poisoning episode suffered in 1988. Her inability to distinguish simple geometric shapes or single alphanumeric characters can be attributed to a bilateral loss of cortical area LO, a loss that has been well established through structural and functional fMRI. Yet despite this severe perceptual deficit, D.F. is able to “guess” remarkably well the identity of whole words. This paradoxical finding, which we were able to replicate more than 20 years following her initial testing, raises the question as to whether D.F. has retained specialized brain circuitry for word recognition that is able to function to some degree without the benefit of inputs from area LO. We used fMRI to investigate this, and found regions in the left fusiform gyrus, left inferior frontal gyrus, and left middle temporal cortex that responded selectively to words. A group of healthy control subjects showed similar activations. The left fusiform activations appear to coincide with the area commonly named the visual word form area (VWFA) in studies of healthy individuals, and appear to be quite separate from the fusiform face area. We hypothesize that there is a route to this area that lies outside area LO, and which remains relatively unscathed in D.F.

1. Introduction

Patient D.F. has been one of the most intensively studied cases of visual agnosia in the literature over the past 25 years (Goodale, Milner, Jakobson, & Carey, 1991; Milner & Goodale, 2006; Milner, 1998; Milner et al., 1991). The reasons for this interest have been multiple. First, D.F. is remarkably well preserved, despite her severe carbon monoxide poisoning incident in 1988: she has no problems with motor coordination, and has no serious impairments in intellect, memory, visual perception of colour or texture, or in non-visual perception. Second, despite her profound visual form agnosia, D.F. has well-preserved visually guided movements, including reaching, grasping, saccadic eye movements, locomotion, and obstacle avoidance. There are limits on the visual complexity of the stimuli that can guide her grasping behaviour (Dijkerman, Milner, & Carey, 1998; Goodale et al., 1994; McIntosh, Dijkerman, Mon-Williams, & Milner, 2004), but D.F.'s dissociation between preserved visuomotor control and impaired shape perception is fully consistent with the Two Visual Streams model of Milner and Goodale (2006), and indeed helped inspire the model in the first place. According to that model, the occipito-temporal “ventral stream” of visual areas underlies our perception and recognition of the world, whereas the occipito-parietal “dorsal stream” provides the real-time visual control for our movements. In line with the model, D.F. subsequently turned out to have complete bilateral destruction of the lateral occipital area (LO) in the ventral stream, an area that functional MRI research has linked closely with shape perception (James, Culham, Humphrey, Milner, & Goodale, 2003). Furthermore, despite an absence of any net fMRI responses to visual shape in her ventral stream, D.F. was found still to show responses in her dorsal stream during object grasping in areas associated with visual control of such movements (specifically area hAIP).

The original description of D.F. (Milner et al., 1991) set out in detail her problems in visual perception, but also contains a puzzling discrepancy. Despite her profound difficulty in recognizing and discriminating the simplest of visual shapes, and indeed her equally severe difficulty in recognizing and discriminating single alphanumeric symbols, she nevertheless performs remarkably well when asked to identify whole words. D.F. often responds incorrectly, particularly with less common words, yet her errors are frequently visual in nature, for example *money–honey*, *ring–right*, and *environment–improvement*. Subjectively, D.F. generally says that she is guessing, but her behavioural success is remarkable, typically being better with longer than with shorter (2-3 letter) words. We found these data surprising in 1991, but in hindsight, we now hypothesize that perhaps D.F. retained a preserved “visual word form area” in the left mid-fusiform gyrus of her left hemisphere, a region which anatomical MRI scans suggested remains largely intact. The present study was designed to test this hypothesis, whose plausibility trades on the fact that fMRI activations can be recorded from her “fusiform face area” (Steeves et al., 2006) and her “parahippocampal place area” (Steeves et al., 2004) despite her poor performance on tests of face discrimination or of scene discrimination, respectively.

The history of research on the so-called visual word form area (VWFA) has been a chequered one. The term was first coined by Abdullaev and Posner (1998) in relation to an ERP negativity at around 200 ms post-stimulus in the left occipital region. However activation in this region had been previously recorded in responses to visual words during PET studies many years earlier by Petersen et al. (1988; 1990), who had already argued that the area was concerned with identifying the visual form of printed words. Even earlier, Warrington and Shallice (1980) had postulated the existence of an early system for identifying word form on the basis of their research on reading in patients with “pure alexia”, whose apparent loss of

the ability to perceive whole words required them to depend on a letter-by-letter strategy. Subsequently, Puce and colleagues (1996) reported activation in the left occipito-temporal area associated with letter strings. Puce and colleagues' findings were replicated by Cohen et al. (2000), who also used functional MRI to locate a region responsive to words in the left fusiform gyrus. Since then, regular doubts as to the status of the VWFA have been expressed, starting with the publication of Price and Devlin's critique in (2003), and there is no question that studies using functional MRI have yielded varying results. Some authors have accordingly adopted a less contentious label for the area (e.g. "posterior occipito-temporal sulcus (pOTS)"; Ben-Shachar et al., 2007). Nevertheless the current consensus agrees that the left mid-fusiform gyrus is consistently activated by the presentation of words or pseudo-word letter strings (Cohen & Dehaene, 2004; Cohen et al., 2002; Dehaene & Cohen, 2011; Nestor, Behrmann, & Plaut, 2013), and that patients with pure alexia almost invariably have lesions affecting the left fusiform gyrus or its connections (Cohen et al., 2003; Leff et al., 2001). Therefore in this report we will refer to this area as the "VWFA", which remains the label that is most commonly used in the literature.

Our hypothesis is that D.F.'s partial ability to identify whole words relies on a largely intact VWFA, but that this spared area is subject to severely depleted visual inputs. We assume that the major visual route to the VWFA in the normal brain would provide information from shape processing mechanisms within area LO, an area that is no longer functional in D.F. This would explain her inability to discriminate single letters. We assume however that there must exist a parallel pathway from earlier visual areas to the VWFA, bypassing the lateral occipital complex, and that this may remain largely intact in D.F. The hypothesized parallel pathway to the VWFA could well pass through the inferior longitudinal fasciculus, which DTI analysis has shown to provide the main afferent route to the VWFA (Epelbaum et al., 2008). Of course the functioning of the VWFA would be expected to suffer severely as a result of losing its normal inputs from area LO, and in particular this loss may deprive the VWFA of any residual ability to contribute to the normal phenomenology associated with word recognition. In other words, such impoverished visual inputs to VWFA could explain why it is that D.F. experiences her efforts to identify words as merely "guessing".

Previous investigations (Cohen et al., 2000; Cohen et al., 2002; Hasson, Levy, Behrmann, Hendler, & Malach, 2002) have indicated that the VWFA lies in close proximity to the left FFA in healthy subjects. Structural and functional MRI data from recent studies of D.F. (Bridge et al., 2013; Cavina-Pratesi, Kentridge, Heywood, & Milner, 2010b) indicate that her fusiform gyrus as a whole is structurally intact at a gross level. In particular the tissue lying around the left lateral occipito-temporal sulcus seems to be spared. Thus it is plausible to suppose that the VWFA might indeed be structurally intact in D.F. To test this hypothesis we tested D.F. using an fMRI localizer in which we contrasted the activations elicited by English words against those elicited by strings of digits. We also presented strings of Hebrew characters, random letters and line drawings for comparison (Baker et al., 2007).

Following this localizer study we ran a second experiment in which we attempted to clarify the response characteristics of the area we had tentatively identified as the VWFA in D.F. Dehaene and Cohen (2011) have argued that neurons in VWFA are tuned to fragments of written words. According to his "local combination detector model" (Dehaene, Cohen, Sigman, & Vinckier, 2005), VWFA neurons comprise a hierarchy of receptive fields tuned successively to letters, bigrams (letter pairs), morphemes and small words. Functional MRI studies (Binder, Medler, Westbury, Liebenthal, & Buchanan, 2006; Dehaene et al., 2004; Glezer, Jiang, & Riesenhuber, 2009; Vinckier et al., 2007) have confirmed that VWFA has a

tuning gradient with successive increases in activity from letters to bigrams to words. If therefore D.F.'s putative VWFA responds similarly to these previous observations in healthy subjects, we predicted a similar gradient of activation, with words (e.g. "hardly") > pseudo-words incorporating high-frequency bigrams (e.g. "resone") > random letter strings (e.g. "vkybgq"). In the present study, the pseudo-words were chosen on the basis of the familiarity of their constituent bigrams, since previous fMRI studies have shown that the VWFA is sensitive to bigram frequency (Binder et al., 2006; Vinckier et al., 2007).

In addition, we included a set of real-word stimuli presented in alternating case (e.g. "iNsIdE"). Based on the above evidence about the function of VWFA and its sensitivity to the visual form of letter combinations, we expected that alternating case would produce a reduction in the BOLD signal relative to words written all in lower case. VWFA responds to the form of letter combinations, and the nature of these letter combinations is shaped by our experience of the visual language. Our usual visual experience of words is in single case format, so words in alternating case are more likely to activate populations of neurons tuned to individual letters, which are a less potent stimulus for the VWFA than bigrams and longer letter combinations. In the present study we thus contrasted normal lower-case words against both (a) words printed in alternating case (which have semantic significance but unfamiliar form) and (b) pseudo-words (which retain familiar letter combinations, but have no semantic associations). According to the idea that the VWFA detects familiar letter combinations, these pseudo-words should elicit a higher neural response than real words in alternating case, at least in healthy control subjects. Of course it is possible that D.F.'s putative VWFA behaves differently from normal, depending more on top-down priming by higher-level semantic word representations than on visual input. In this case, her VWFA might show a greater than normal tendency to respond preferentially to alternating-case word stimuli than to pseudo-words.

2. Methods

2.1. Patient

Patient D.F. suffered carbon monoxide poisoning and anoxia in February 1988 while taking a shower fed from a faulty propane gas water heater (Milner et al., 1991). The resulting brain damage was widespread but uneven, being particularly concentrated in certain areas. These areas of dense damage include the lateral occipital area (LO) on both sides of the brain (Bridge et al., 2013; Cavina-Pratesi, Kentridge, Heywood, & Milner, 2010a; James et al., 2003). D.F.'s primary neurological symptom is a profound visual form agnosia (Milner et al., 1991). An inability to distinguish simple shapes, and to recognize objects by virtue of their shape, are diagnostic of this condition (Benson & Greenberg, 1969; Heider, 2000), and these problems are readily explicable as a consequence of D.F.'s bilateral damage to area LO. Her residual ability to recognize objects through their surface properties such as colour and texture are explicable through the sparing of ventro-medial areas in the ventral stream that are critical for distinguishing such features (Cavina-Pratesi et al., 2010a, 2010b; James et al., 2003). In March 2010, when tested in the present studies, D.F. was aged 56.

2.2. Behavioural tests of word recognition

We retested D.F. on a subset of the reading tests that had been administered by our colleague Dr RS Johnston over 20 years previously, as summarized by Milner *et al.* (1991). These

included two standardized reading tests: British Ability Scales Word Reading Test (BAS; Elliott, Murray, & Pearson, 1977), and the National Adult Reading Test (NART; Nelson, 1982), along with the following 5 further word recognition tests:

1. a pseudorandom sequence of 25 single lower-case letters and 24 words;
2. an oddity version of this task in which trios of single letters, 4-letter words or 4-letter non-words arranged along a horizontal line were presented and D.F. asked to say or indicate the odd stimulus;
3. a sequence of 26 single upper-case letters for visual and for tactile recognition,
4. a set of 10 numbers printed either as Arabic digits or as words,
5. a test presenting 18 four-letter words oriented horizontally, vertically (the same words oriented by 90 deg), vertically (as a sequence of correctly oriented letters).

In addition to these retests, we asked D.F. to attempt to read:

6. a set of 60 jumbled 4-to-11 letter words in which two successive consonants were reversed (e.g. *cacnel* and *undertsand*), along with their correctly spelled counterparts (stimuli taken from Velan and Frost, 2007).
7. a series of 20 printed sentences taken from the same study by Velan and Frost (2007). Each sentence contained 3 of the jumbled words (e.g. “*The journey (jounrey) was cancelled (cacnelled) because we forgot (fogrot) our tickets.*”). The same set of 20 sentences was also presented in correct spelling.

2.3. Functional MRI study

2.3.1. Subjects

Patient D.F. (now aged 56 at the time of testing) and 11 control participants took part in the fMRI experiment. Control participants were recruited within the Departments of Psychology at Durham and Hull universities and were all right handed. There were 9 young controls (4 females, age range 22-38, mean age 26.9) and two age-matched controls (both males, aged 54 and 55). All participants (patient and healthy controls) underwent repeated functional scans as well as one anatomical scan during the same session, and gave informed consent before beginning the experiment, which was approved by the Ethics Committees of Durham University and York Neuroimaging Centre (University of York, UK).

2.3.2. Tasks and Stimuli

In the fMRI sessions, D.F. and control participants performed several functional runs, henceforth labelled “Word localizer”, “Face localizer”, and “Lexical decision task”. The localizers were used to delineate the so-called Visual Word Form Area (VWFA) and so-called Fusiform Face Area (FFA), respectively, in individual participants. The experimental runs using the lexical task were then used to examine how the profiles of VWFA activation observed in D.F. and the controls fit with current findings in the literature. In order to investigate this, we asked D.F. and controls to perform a lexical decision task in which they had to decide whether the stimuli presented were words or non-words. D.F. performed only one version of this lexical task, a version henceforth labelled “Easy”. Control participants performed two versions of the task: the same “Easy” version as D.F. and also a “Difficult” version. The latter version was designed to equate task difficulty between D.F. and controls and to check the activation profile for both correct and error trials (since control participants did not make any errors in the “Easy” task).

2.3.2.1. Word localizer and time-course analysis

Participants viewed blocks of images of written words, digit lists, Hebrew symbols, single letters and line drawings (Snodgrass & Vanderwart, 1980) presented on a white background. The words, digits and Hebrew symbols varied in length from 5-7 items per stimulus within a block. The written words were high frequency words (mean HAL log frequency = 11.24) generated from the *English Lexicon Project* database <http://elexicon.wustl.edu/>. All stimuli were presented centrally and subtended a visual angle from 1° (single letters) to 10° (line drawings) depending on the stimulus length/size. Stimuli were presented for 1500ms followed by a blank screen for 500ms. Each block lasted 14s and 7 stimuli were presented in each block with one stimulus repeated. Each run consisted of three blocks of each stimulus type presented in a pseudorandom order to avoid sequential presentations of the same stimulus blocks. Stimulus blocks were interleaved with 16 fixation blocks. During the stimulus blocks participants performed a one-back task, indicating with a key press when a stimulus repeated.

2.3.2.2. *Face localizer*

Participants viewed photographic grey-scale images of faces, outdoor scenes, bodies, hands and tools presented on a white background in blocks of seven stimuli. All stimuli were presented centrally and subtended a visual angle of 10°. In all other respects the procedural details were as described for the Word localizer in section 2.3.2.1.

2.3.2.3. *Lexical decision task (Easy)*

We used an event-related lexical decision task, in which participants indicated whether a letter string was a word or a non-word by making a key press. The experiment consisted of four conditions: High frequency words (W), high frequency words with alternating case (AC), Pseudo-words (PW), and random letter strings (LS). In the word conditions (W and AC) we used 64 high frequency words ranging between 9 and 13 log frequency ($M=10.9$) in the *Hyperspace Analog to Language* corpus (HAL; Balota et al., 2007; Lund & Burgess, 1996). The mean bigram frequency of these words was 2,120 (HAL frequency norms). In the non-word conditions we used 32 pseudo-words with an average bigram frequency of 3,520 generated from the *English Language Project* database, and 32 letter strings using 10 of the least frequently used letters in the English alphabet. In the alternating case condition we included two catch trials per run by changing one letter, thereby creating a non-word. We did this to avoid participants responding to alternating case stimuli based on the appearance of the fonts rather than reading the word. All words and non-words consisted of six black letters in the same font (Courier New) presented centrally against a white background, and subtending 8 degrees of visual angle. Each run lasted 462 s starting with a 14s fixation period. There were 32 experimental trials, with 8 trials from each experimental condition presented in a pseudorandom order (no more than 3 non-word or word stimuli in a row). Each trial lasted 14s, with stimuli presented for 4s followed by a fixation cross for the remainder of the trial.

The choice of bigram frequency was constrained by the design of the lexical task. In designing an ‘easy’ lexical decision task to be used with patient D.F., we chose pseudo-words with lower bigram frequencies than the words, to increase the possibility of finding response differences between these two conditions. In the ‘difficult’ lexical decision task we wanted our control participants to make errors. This meant choosing pseudo-words with relatively high mean bigram frequencies and very low frequency real words. This increased the probability that pseudo-words would be mistaken for real words and real words mistaken for pseudo-words (Rice & Robinson, 1975). There was also the practical constraint that low frequency six-letter words tended to have lower mean bigram frequencies than high

frequency six-letter words. The final choice of words and pseudo words for the difficult lexical task was based on pilot data collected prior to the scans on an independent participant sample.

2.3.2.4. *Lexical decision task (Difficult)*

We created a more challenging lexical decision task to increase the error rates in our control participants, since in the Easy lexical decision task their performance was at ceiling. This “difficult” lexical decision task consisted of four conditions: Low frequency words (W), low frequency words with alternating case (AC), pseudo-words (PW), and letter strings (LS). In the word conditions (W and AC) we used 64 low-frequency words ranging between 0.6 log frequency and 6 log frequency ($M=3.46$) in the HAL corpus. The mean bigram frequency of these words was 1.771. In the non-word conditions we used 32 pseudo-words (PW), with an average bigram frequency of 3,259, and new set of 32 random letter strings using the same letter set described above. The stimulus duration was 300ms and all other parameters were the same as in the “easy” lexical decision task.

2.3.3. *fMRI procedures and parameters*

All participants were tested at York Neuroimaging Centre, using a 3-T whole-body GE *Excite* MRI system. A high-density brain array 8-channel head coil was used in all experiments. BOLD-based functional MRI volumes were collected using optimized T2*-weighted segmented gradient echo planar imaging (26 cm field of view [FOV], with a 64 x 64 matrix size for an in-plane resolution of 3 mm, repetition time [RT] = 2 s, time echo [TE] = 30 ms, flip angle [FA] = 90 deg). Each volume was composed of 40 contiguous slices of 3 mm thickness, angled at approximately 30 degrees from axial, to sample occipital, parietal, posterior temporal, and posterior-superior frontal cortices. During each experimental session, a T1-weighted anatomic reference volume was acquired along the same orientation as the functional images using a 3D acquisition sequence (scan parameters: RT = 7.8 ms, TE = 3 ms, FA = 20 degrees, matrix size = 256 3 256, FOV = 2563256 mm², 176 slices, slice thickness = 1 mm, no gap, and total scan time = 5 min 3 s).

2.3.4. *Data analysis*

2.3.4.1. *Behavioural data collected in the scanner*

Accuracy scores of the age-matched controls in the Experimental tasks (both Easy and Difficult lexical decision) were analysed using repeated-measures analysis of variance (ANOVAs) and paired-comparison t-tests. D.F.’s data were analysed using Chi^2 tests.

2.3.4.2. *Imaging data*

Data were analysed using “Brain Voyager QX” software (version 2.3; Brain Innovation, Maastricht, Netherlands). For each subject, functional data underwent 3D motion correction algorithms. No deviations larger than +/- 2mm translations or 2 degrees rotations were observed in the motion correction output. Functional data were then pre-processed with linear trend removal and underwent high-pass temporal frequency filtering to remove frequencies below 3 cycles per run. Anatomical volumes were transformed into standard stereotaxic space (Talairach & Tournoux, 1988). Functional volumes were then aligned to the transformed anatomical volumes, thereby transforming the functional data into a common stereotaxic space across subjects. The functional MRI (fMRI) data were analysed using a general linear model (GLM), and a random-effects GLM was used for the group average analysis. Different models were used to analyse the four different experiments.

In the word localizer task, the model included 4 experimental predictors (Words, Digit Strings, Hebrew characters, and Letters) and 6 motion correction predictors (x, y, z for translation and for rotation). In the face localizer task, the model included 5 experimental predictors (Faces, Places, Tools, Bodies and Hands) and 6 motion correction predictors (x, y, z for translation and for rotation). For both tasks, the period of fixation (14 s) was used as a baseline. The experimental predictors were modelled as a transient (14-s) epoch where the square-wave function for each phase was convolved with the default Brain Voyager QX “2-gamma” function designed to estimate haemodynamic response properties.

For the experimental lexical decision tasks, the model included 4 experimental predictors (words, alternating case words, pseudo-words, and random letter strings) and 6 motion correction predictors (x, y, z for translation and for rotation). The period of fixation (10 s for the easy experimental run and 12 s for the difficult experimental run) was used as a baseline condition. The experimental predictors were modelled as a transient (4 s for the Easy experimental condition and 2 s for the Difficult experimental conditions) epoch where the square-wave function for each phase was convolved with the default Brain Voyager QX “2-gamma” function designed to estimate haemodynamic response properties. Prior to analysis, the data were z-normalized; thus, beta weights extracted from the active clusters represent an estimate of the magnitude of activation for each condition (constrained by the shape of the expected haemodynamic response function) in units of z scores.

In the averaged voxel-wise group analysis, statistical activation maps were set to reliable threshold levels and cluster volumes ($p < 0.001$, minimum cluster size 225 mm^3) using Monte Carlo simulations (performed using Brain Voyager QX) to verify that our regions of interest were unlikely to have arisen due to chance as a consequence of multiple comparisons. After having identified the areas that were activated by a comparison of interest, we performed post hoc analyses on the percent Bold Signal Change (%BSC) averaged across three data points at peak activity. Percent BSC was extracted for each subject and each condition separately and was analysed using ANOVAs, paired sample t-test (Sidak corrected) and within subject contrasts (linear and quadratic). For single-subject analyses (including D.F.), regions were defined in each individual by contrasting conditions at a threshold of $p < 0.001$, uncorrected. Differences in %BSC between D.F. and control participants were tested using modified t-tests recommended by Crawford and co-workers for single cases analyses. Similarities and differences in amplitude of %BSC were tested using the methods of Crawford and Garthwaite (2002) and Crawford et al. (2010). Similarities and differences in the linear and quadratic trends were tested using Crawford et al. (2004).

3. Results

3.1. Tests of word recognition

Standardized tests of reading. D.F. performed comparably to (or slightly less well than) her performance in 1990, twenty years before the present testing. Thus on the BAS test, she gained a raw score of 31, equivalent to a reading age of 11.2 years (as against 11.1 in 1990). On the NART reading scale she scored only 3 correct (naive, catacomb, thyme) out of 50. Many of her errors, however, were closely visually related to the stimuli, so although she scored 10/50 in 1990, this may have been partly due to “lucky guesses” at that time. Taken together these standardized test results suggest that D.F.’s word recognition has not improved over the intervening 20 years, and may have slightly deteriorated.

Test 1 (single-letter vs word reading): D.F. scored 14 correct words out of 38 (37%), well down on her 1990 performance of 31/38, though she did make six visually-close errors (lawn→dawn, switch→watch, collect→neglect, coat→cat, aborigine→origin, calf→golf). In contrast she only identified 6 out of 25 letters correctly (21%), even fewer than she identified in 1990 (9/25). Although the difference between D.F.’s correct identifications of words and letters had been highly significant in 1990 ($p < 0.001$), there was no significant difference ($Chi^2 = 1.15$, $df = 1$, $p = 0.214$) on the present retest.

Test 2 (oddity): Exactly as in the 1990 testing, D.F.’s performance with letters (10/24) was significantly lower than her performance with words (17/24, $Chi^2 = 4.15$, $df = 1$, $p = 0.04$) or with non-words (17/24, $Chi^2 = 4.15$, $df = 1$, $p = 0.04$). She was little better than chance at discriminating single letters. The odds of D.F. making a correct answer were 3.4 times higher when presented with words or non-words compared to single letters.

Test 3 (tactile vs visual letters): D.F. scored 19/25 through touch (excluding the last trial, which was inaudible on the audio file), as opposed to 5/26 through vision. This difference reached significance ($Chi^2 = 6.12$, $df = 1$, $p = 0.012$), as it did in the 1990 analysis (18 correct tactile, 2 correct visual).

Test 4 (digits vs number words): D.F. failed to identify any of the 10 Arabic digits, whereas she correctly identified 8 out of 10 written number words. This difference was highly significant on a Fisher exact test ($p = 0.001$), just as it was in 1990 (1 digit correct versus 100% written numbers).

Test 5 (horizontal vs vertical words): D.F. successfully identified only one of the 18 four-letter words presented horizontally, though she made numerous visually-close errors (e.g. date→gate, till→still, wake→make, wear→tear, rook→cook), and all except two of the words were at least attempted. In contrast, when words were presented vertically (as a sequence of correctly oriented letters), she was completely unable to offer guesses at their identity, and even when whole words were oriented vertically, only one was attempted (hell→instil). D.F.’s inability to recognize vertical strings replicates closely the original 1990 observations.

Test 6 (singly presented correct vs jumbled words): D.F. performed well at identifying correctly spelt 4-11 letter words (37/60), but significantly less well (20/60) at identifying them when jumbled ($Chi^2 = 8.56$, $df = 1$; $P = 0.0017$).

Test 7 (correct or jumbled words presented in sentences): With the words now presented in context D.F. performed equally well with both correct-spelt (30/60) and jumbled words (32/60).

3.2. Functional MRI data

Our aim was to discover whether or not D.F. exhibits brain activity that is comparable to the visual word form area (VWFA) found in neurologically intact participants, in terms of its anatomical location and profile of response. The VWFA was localized using a word localizer in which we compare words versus digits. This choice of contrast was based on arguments put forward by Baker et al. (2007) in which they maintained that a region selective for words should show greater activation for words compared to strings of symbols or digits. They were concerned that selectivity based on contrasts of words vs. non-words or words vs. line drawings or words vs. checkerboards might be the result of simple visual feature differences. There is also the argument that VWFA might be a general perceptual processing region that responds to any meaningful visual stimulus, as argued by Price and Devlin (2003, 2004). Baker et al (2007) demonstrated in their paper that the VWFA responds more to words than digit strings or symbols. In addition a recent paper by Shum et al. (2013) provides evidence that a region approximating VWFA shows a preferential response to number words and non-number words compared to strings of numerals. We contend that the contrast of words vs. digits controls for the potential confound of simple visual feature differences and meaning, as digit strings are visually similar to words and are also meaningful symbols.

The functional properties of the localized clusters were assessed using behavioural and imaging data. Behavioural data were quantified in terms of accuracy in the lexical decision tasks (section 3.2.2.1). Imaging data were quantified using the peak %BSC for the word localizer and the lexical decision tasks, using the following steps. First, the %BSC for the word localizer was inspected to test whether the selected clusters showed a preference for words as compared to other stimuli such as letters, Hebrew characters, and line drawings (section 3.2.1). Second, %BSC for the lexical decision tasks within the VWFA was analysed to inspect its functional properties. In particular we aimed at disentangling two specific hypotheses. While hypothesis 1 suggests that the activation profile of the VWFA should be driven by semantic content, according to hypothesis 2, the activation profile of the VWFA should be driven by visual familiarity. In separate analyses, we reshuffled the order of the conditions and used trend analyses to test the goodness of fit of the above-mentioned hypotheses (section 3.2.2.2). Third, we used a face localizer task comparing faces versus houses, a standard contrast for localizing the fusiform face area (Kanwisher, McDermott, & Chun, 1997; Mur et al., 2012; Nestor, Behrmann, & Plaut, 2013). This latter analysis was introduced to control for potential overlap between voxels selective for faces and words (Hasson et al., 2002). Differences in the stereotactic Talaraich coordinates and in the activation profile of the lexical decision tasks were used to measure the degree of independence of the two clusters localised within the left fusiform gyrus (section 3.2.3). Importantly, for each step, data were analysed for both controls and patient D.F.

3.2.1. Visual Word Form Area (VWFA) in D.F. and controls

To localize the VWFA in D.F. and in controls we used the word localizer task, within which we compared Word>Digits. Replicating previous findings, we found activations in a series of left hemisphere areas (see Table 1, and Figure 1b). The only two areas that were similarly activated in both controls and D.F. were housed in (a) the left fusiform gyrus (presumably the VWFA) and (b) in the left inferior frontal gyrus (IFG: presumably Broca's area). In consequence, the following analyses are focused on these two areas only.

Percent BSC in the left VWFA and in left IFG in the control participants underwent two separate repeated-measures ANOVAs, using stimulus category (Words, Digits, Hebrew characters, Letters and Line drawings) as a within-subject factor. Results showed that brain activity was affected by the different categories of stimuli in both areas: VWFA

[$F(4,32)=4.49$, $p=0.014$] and IFG [$F(4,32)=8.43$, $p=0.001$]. Post-hoc t-tests showed that the %BSC was higher for words as compared to digit strings (VWFA: $p=0.024$; IFG: $p=0.002$), Hebrew characters (VWFA: $p=0.034$; IFG: $p=0.009$), single letters (VWFA: $p=0.026$; IFG: $p=0.0001$) and line drawings (IFG: $p=0.009$). A one sample t-test showed that %BSC was significantly above baseline for all stimuli in the left VWFA ($p<0.029$ for all stimuli), and for Words only ($p<0.002$) in the left IFG. Higher brain activity for words is not surprising given the way we localized the brain areas (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009), therefore we tested whether the above response profile would be replicated by localizing the VWFA using odd runs and then testing its response profile by using even runs (thus avoiding circularity). By the use of odd runs we localized a cluster of voxels in the left fusiform gyrus ($x=-38$, $y=-48$, $z=-29$), and the time-course extracted from the even runs showed again a higher response for Words as compared to Digits ($p=0.025$), Letters ($p=0.026$), and Hebrew characters ($p=0.028$). These data are shown as striped coloured bars for the data extracted using independent sets of runs in Figure 1e. As before, a one sample t-test showed that %BSC was significantly above baseline for all stimuli ($p>0.027$ for all stimuli).

Brain activity in D.F. (Figure 1a,c) is qualitatively comparable to that of controls (Figure 1b,d) both in terms of location and profile of activity. We compared D.F.'s %BSC against control participant values for each condition in each area using Crawford's modified t-tests. In the VWFA there were no significant differences between D.F. and controls for any condition ($p>0.064$), and the same was true for left IFG in all but one condition ($p>0.072$), the exception being that D.F. showed a higher %BSC for Letters ($p=0.01$).

Previous results have shown that some VWFA voxels may show stronger selectivity for words as compared to line drawings (Baker et al., 2007; Ben-Shachar, Dougherty, Deutsch, & Wandell, 2007; Szwed et al., 2011). We therefore carried out additional analyses looking for voxels in the region of the left VWFA that responded more to words than to line drawings, in each participant separately (including D.F.). By applying a very liberal threshold ($p<0.05$, not corrected) we found a small number of voxels selective for words only, in 4 of the 9 control participants and also in D.F. (averaged Talairach coordinates for control participants: $X=-43.3$, $Y=-38.6$, $Z=-17.9$, D.F. Talairach coordinates: $X=-45.4$, $Y=-48$, $Z=-17.3$).

Please insert Figure 1 here

3.2.2. *Properties of VWFA in D.F. and controls*

In order to investigate the functional profile of the VWFA as localized in D.F. and in the controls, subjects were tested on a lexical decision task, in which they had to decide whether each stimulus presented was a word or a non-word. The word stimuli used in both versions of the task ("easy" and "difficult") consisted of words (W), words with alternating case (AC), pseudo-words (PW), and random letter strings (LS), as described in the Methods section.

3.2.2.1. *Behavioural results*

Accuracy for the Easy lexical decision task was not analysed in controls, as performance was at ceiling, with all participants reaching 100% accuracy (Figure 2b, grey bars). Accuracy scores for the Difficult lexical decision task in controls (grey bars) underwent a repeated measures ANOVA using the different categories of stimuli (W, AC, PW and LS) as the within-subject factor. Accuracy was significantly different across the four stimulus categories [$F(3,24)=65.9$, $p=0.0001$] and post-hoc t-tests showed that the accuracy for LS was the highest, followed by PW, W, and then AC (for all comparisons, $p<0.001$). One sample t-tests

showed that accuracy for W (67%, $p=0.047$), PW (93%, $p=0.001$) and LS (100%, $p=0.0001$), but not for AC (57%, $p=0.37$), were significantly above chance (50%, see Figure 2a).

As shown in Figure 2b (black bars), D.F.'s accuracy was very low for all conditions, except for LS where she reached an above chance accuracy of 71% ($p=0.0065$). This score for LS was significantly higher than for W (50%, $Chi^2=11.42$, $df=1$; $p<0.0001$), PW (38%, $Chi^2=7.63$, $df=1$; $p=0.006$) and AC [38% , $Chi^2=7.63$, $df=1$; $p=0.006$]. Although both control participants and D.F. showed higher accuracy for LS, there was no general bias toward responding "non-word" since if that were the case, accuracy should also be higher for PW (as both LS and PW require a correct response of "non-word"). This was not the case for either control participants or D.F.

Please insert Figure 2 here

3.2.2.2. *Imaging results: controls*

Separate univariate ANOVAs were performed on the peak averaged %BSC for the control participants in the easy and difficult conditions of the lexical task in left VWFA (Figure 3b) and left IFG (Figure 3e), with stimuli (W, AC, PW, LS) as a within-subjects factor. In both brain areas we found a main effect of stimuli for both the easy [VWFA: $F(3,24)=7.8$, $p=0.001$; IFG: $F(3,24)=5.5$, $p=0.005$] and the difficult conditions of the lexical decision task [VWFA: $F(3,24)=3.33$, $p=0.036$; IFG: $F(3,24)=24.3$, $p=0.0001$]. In addition to this comparison across stimulus conditions, we wished to examine on a trial by trial basis how brain activations varied according to whether a response was correct or incorrect. Since the control participants made no errors during the Easy task, no analysis of activations on error trials could be carried out. However we were able to sort trials according to performance on the Difficult task, giving rise to 8 different trial types: W correct (W+), AC correct (AC+), PW correct (PW+), LS correct (LS+), W incorrect (W-), AC incorrect (AC-), PW incorrect (PW-), and LS incorrect (LS-). The peak averaged %BSC in left VWFA (Figure 3c) and left IFG (Figure 3d) was then submitted to separate repeated-measures ANOVAs using trial type as a within-subject factor. A significant main effect of trial type was found in both areas [VWFA: $F(6,48)=4.2$, $p=0.002$; IFG: $F(6,48)=10.4$, $p=0.0001$].

Please insert Figure 3 here

As indicated in the Introduction, there are two possible patterns of data that might emerge from our experimental design. According to *Hypothesis 1*, there should be a superiority of words (even in alternating case) over non-words (which have no semantic content), thus predicting $W>AC>PW>LS$. According to *Hypothesis 2*, there should be a superiority of non-words containing familiar letter bigrams over real words in alternating case (which are visually unfamiliar), leading to the prediction $W>PW>AC>LS$. To decide which of these predictions gave the more accurate match to our data, we therefore ran separate trend analyses based on each hypothesis.

Hypothesis 1. The predicted ordering of conditions $W>AC>PW>LS$ revealed highly significant monotonic trends, as can be seen in Figure 3b. In both activated areas we found a significant linear within-subject contrast for both the easy [VWFA: $F(1,8)=19.9$, $p=0.002$; IFG: $F(1,8)=19.4$, $p=0.002$] and the difficult [VWFA: $F(1,8)=14$, $p=0.006$; IFG: $F(1,8)=26.8$, $p=0.001$] conditions, showing that activity decreased progressively from W to AC to PW to LS stimuli. This suggests that brain activity might be linearly related to the probability of the stimuli being categorized as words (see Figure 2b,e; dotted trend lines). In both areas, brain

activations for W and AC were significantly higher than for LS, during both the easy (VWFA, $p < 0.034$; IFG, $p < 0.034$) and difficult (VWFA, $p < 0.024$; IFG, $p < 0.001$) lexical decision tasks. The main difference between the two areas is that while in the VWFA all conditions are higher than baseline (all $p < 0.026$), PW and LS failed to reach significance in the IFG (for both conditions, $p > 0.066$).

Applying Hypothesis 1 to the trial by trial analysis, we ordered the trial types thus: W+, AC+, PW+, LS+, W-, AC-, PW-. The controls never mistook an unpronounceable non-word for a word, so the LS- condition could not be included in this analysis. A significant quadratic within-subject contrast was found in both areas [VWFA: $F(1,8) = 11.9$, $p = 0.009$; IFG: $F(1,8) = 13.3$, $p = 0.007$], suggesting that brain activity follows a U-shape trend, decreasing from W+ to LS+ and increasing again from W- to PW- (Figure 3c,f; plain trend line). As before, it seems that brain activity in the VWFA may be monotonically related to the probability of the stimuli being categorized as words, with higher activity for correct responses to words – either in uniform or alternating case – as compared to incorrect ones (W+ > W-: $p = 0.009$; AC+ > AC-: $p = 0.009$). Although brain activity was on average higher for PWs erroneously categorized as words (PW-) than for PWs categorized correctly (PW+), the comparison failed to reach significance ($p = 0.56$). As shown above, the main difference between the two areas is therefore that while in the VWFA all conditions are higher than baseline (for all conditions, $p < 0.016$), in the left IFG, LS failed to reach significance (for both conditions, $p > 0.051$).

Hypothesis 2. The ordering of conditions W > PW > AC > LS did not reveal such clear-cut monotonic trends. The VWFA showed a significant linear within-subject contrast only for the easy [$F(1,8) = 11.8$, $p = 0.009$], not for the difficult [$F(1,8) = 3.30$, $p = 0.105$] lexical decision task. This suggests that when the performance of participants does not reach ceiling (i.e. in the difficult condition), the pattern of response in the VWFA fits hypothesis 1 markedly better than hypothesis 2. That is, the VWFA seems to treat words in alternating case as more word-like than normally printed non-words, even though the latter have a greater visual resemblance to real words. In IFG, however, we still found a significant linear within-subject contrast for both the easy [$F(1,8) = 9.40$, $p = 0.015$] and difficult [IFG: $F(1,8) = 32.4$, $p = 0.0001$] lexical decision tasks, suggesting that this area treats both PW and AC stimuli as equally word-like.

Applying Hypothesis 2 to the trial by trial analysis, we ordered the trial types thus: W+, PW+, AC+, LS+, W-, PW-, AC-. In agreement with the previous analysis, a significant quadratic within-subject contrast was found in the IFG [$F(1,8) = 32.58$, $p = 0.0001$], but not in the VWFA [$F(1,8) = 3.92$, $p = 0.083$].

In order to test the strength of our results we compared W+ versus LS+ in control participants to check whether we could localize the same word-related areas found by the use of our localizer task (Word versus Digit). Figure 4b shows overlay activations for Words versus Digits (word localizer, in light blue) and for W+ versus LS+ (Lexical decision task, difficult condition, in green). The Left VWFA, the left posterior middle temporal gyrus (left pMTG), and the left IFG were found to overlap for the two sets of data and comparisons. Additional areas such as SMA, and bilateral insula were active for the Difficult lexical task, but not for the localizer. Details of the activated areas are summarized in Table 2.

Please insert Figure 4 and Table 2 here

3.2.2.3. *Imaging results: D.F.*

The pattern of results in D.F. is shown in Figure 3 (left column). D.F.'s data underwent the same analyses as applied to control participants, and given the specific profile of the response characterized in terms of linear and quadratic trends, we compared D.F.'s and control participants' linear and quadratic correlation coefficients (R^2) using the method introduced by Crawford et al. (2003) for intra-individual measurement of association (i.e. a correlation coefficient) according to each of the two hypotheses.

Hypothesis 1. The linear correlation coefficient for the lexical decision task was computed for D.F.'s correct data (W+, AC+, PW+, LS+) and compared with the linear correlation coefficients computed for each control participant in the easy and difficult lexical decision tasks. Likewise the quadratic correlation coefficient was computed for all D.F.'s data except LS- (i.e. only W+, AC+, PW+, LS+, W-, AC-, and PW-) and compared with the quadratic correlation coefficients computed for each control participant in the difficult lexical decision task. The results (Figure 3a,d,b,e) showed that D.F.'s linear (VWFA: $R^2=0.92$; IFG: $R^2=0.98$) and quadratic (VWFA: $R^2=0.88$; IFG: $R^2=0.96$) values were quite similar to those of the mean values of the controls (VWFA linear $R^2=0.83$, VWFA quadratic $R^2=0.93$; IFG: linear $R^2=0.83$, quadratic $R^2=0.95$). D.F.'s correlations did not differ significantly from those of the controls in the VWFA [linear easy: $t(8)=1.155$, $p=0.281$; linear difficult: $t(8)=1.64$, $p=0.14$; quadratic difficult: $t(8)=0.903$, $p=0.393$], or in the IFG [linear easy: $t(8)=1.649$, $p=0.138$; IFG linear difficult: $t(8)=1.493$, $p=0.174$; IFG quadratic difficult: $t(8)=1.601$, $p=0.148$]. Of course, given that such statistical comparisons should ideally use data gathered from an identical task run in controls and patients, the results should be treated with caution. That said, for the linear correlation coefficient analyses we did keep the experimental stimuli constant (the same easy task in both D.F. and controls), whereas in the quadratic correlation coefficient analyses we kept the degree of difficulty of the tasks constant (the "easy" task for D.F. and the "difficult" task for controls).

Hypothesis 2. A comparison was made between D.F.'s and the control data, this time using the ordering based on hypothesis 2's predictions, that is by comparing the trends from ordering W>PW>AC>LS and W+, PW+, AC+, LS+, W-, PW-, AC- in her data against the same ordering for the controls. Results again showed that the quadratic R^2 values in D.F. did not differ from the ones found in controls in both the VWFA [$t(8)=0.015$, $p=0.988$] and in IFG [$t(8)=0.887$, $p=0.401$].

Just as for the control participants, we tested the strength of our results by comparing W+ versus LS+ in D.F. to check whether we could localize the same word-related areas found by the use of our localizer task (Words versus Digits). Figure 4a shows overlay activations for Words versus Digits (word Localizer, in light blue) and for W+ versus LS+ (lexical decision task, Easy condition, in green) in D.F.'s brain. The left VWFA, the left IFG and left S1/M1 were found to overlap in the two comparisons. Additional areas such as left pMTG, and SMA were active for the easy task, but not for the localizer task.

3.2.3. *VWFA and FFA in D.F. and controls*

FFA was localized in D.F. and the control participants using the Face Localizer task, i.e. by comparing Face vs House stimuli (Kanwisher et al., 1997). The right and left FFAs were successfully localized in all controls and in D.F. (see Table 3 and figure 5a-c, activation highlighted in pink). Percent BSC for the face localizer is plotted in the upper panel of Figure 5d only for completeness (given that both the cluster of voxels and the activation time-course were obtained by using the same data set, i.e. the analysis would be "circular",

Kriegeskorte et al., 2009). We compared D.F.'s %BSC values in each condition with those of the control participants using the Crawford modified t-test, and found no significant differences (for all conditions $p > 0.22$).

Given that both the VWFA and left FFA are housed within the left fusiform gyrus, we wanted to make sure that the VWFA and the FFA were indeed two separate entities. First of all we checked whether or not the two areas overlapped at the level of single subjects. In 7 of the 9 control participants and in D.F., the two areas did not overlap at all (Figure 5 a-c) with the VWFA always being located in more anterior and dorsal parts of the fusiform gyrus than FFA. To quantify this difference we ran separate t-tests on the x, y, and z values of the Talairach coordinates in control participants. The results showed that the VWFA lies significantly anteriorly [y values: $t(8) = -2.86$, $p = 0.021$] and dorsally [z values: $t(8) = 3.04$, $p = 0.016$] with respect to the left FFA, though the two areas did not differ in the x dimension [x values: $t(8) = -0.138$, $p = 0.89$]. Importantly, when we compared D.F.'s Talairach coordinates for the left FFA and the VWFA we found no significant difference from controls (VWFA, for all three coordinates, $p > 0.22$; left FFA, $p > 0.22$).

To investigate further the independence of the two areas, we checked the pattern of activity for the easy lexical task in the left FFA. If left FFA and VWFA are separate, then we would expect different patterns of activation. As noted above, the pattern of response to the easy task in the VWFA had a distinct linear trend with brain activity being proportional to the likelihood of the stimulus being considered a word ($W > AC > PW > LS$). Peak averaged %BSC values for the easy task (Figure 5d, lower panel, empty bars) were extracted from control participants' left FFA and submitted to a univariate ANOVA using stimuli (W, AC, PW, and LS) as a within-subject factor. The main effect failed to reach significance [$F(3,24) = 1.15$, $p = 0.35$], showing that area FFA does not distinguish between the different categories of alphabetic stimuli. Importantly, the linear within-subject contrast also failed to reach significance [$F(1,8) = 1.94$, $p = 0.20$] indicating that left FFA carries different information from the left VWFA. We then performed two different analyses on the %BSC (for the easy task) from D.F.'s left FFA (Figure 5d, lower panel, filled bars). First we compared D.F. versus control participants using Crawford's modified t-test for each condition, and found no significant difference (for all conditions $p > 0.07$). Second, we computed D.F.'s linear R^2 and compared this to those of the control participants (Crawford et al., 2003). The results showed no significant difference between D.F. and controls [$t(8) = -0.039$, $p = 0.485$]. Taken together, these results clearly indicate that left VWFA and left FFA each represent functionally distinct clusters of activity in both D.F. and control participants.

Please insert Figure 5 and Table 3 here

3.2.4. LO in D.F. and controls

Our thinking concerning the functioning of the VWFA in D.F. is premised on previous structural and functional evidence that she has lost area LO bilaterally (James et al., 2003; Cavina-Pratesi et al., 2010a; Bridge et al., 2013). To look for an additional internal confirmation of those earlier findings, we examined some relevant data within the current dataset, specifically within the Face localizer data. Within that task, we had used pictures of tools (objects) as well as other categories of stimuli (body parts and places). We therefore made specific comparisons of tools versus these other stimuli, to check whether we could activate LO, both in D.F. and in the controls. As expected, the comparison of tools versus bodies, faces, hands, or places did show clear activations in right LO (Talairach coordinates:

x= 43; y= -61; z= -10) and in early visual cortices (Talairach coordinates: x= 0.4; y= -82; z= 8) in our control participants. The same comparison in patient D.F., however, showed activations in early visual cortices (Talairach coordinates: x= 0.4; y= -85; z= -8), and bilaterally in the posterior parietal cortex left: Talairach coordinates: x= 24; y= -75; z= 35; right: Talairach coordinates: x= 27; y= -81; z= 35), but not in area LO. This evidence provides further confirmation of D.F.'s functional loss of area LO, and is in full agreement with expectations from our earlier work.

Discussion

4.1. Re-test of D.F.'s word recognition after 20 years

Detailed series of tests of D.F.'s word recognition had been carried out in 1990, chiefly by our colleague Dr RS Johnston, only 2 years following the anoxic episode that precipitated D.F.'s visual form agnosia. The results were briefly reported by Milner et al (1991). We now report that when retested on the same standard reading tests – the British Ability Scales Word Reading Test (BAS) and National Adult Reading Test (NART) – in 2010, D.F. had not improved her performance, even showing a drop in the latter test. Nevertheless, her level of performance on the BAS on both occasions, equivalent to a reading age of 11, illustrates that she was clearly processing the visual information contained in words with a remarkable degree of success, given her profound visual form agnosia. Despite this ability, however, D.F. was quite unable (on both testing occasions) to report or discriminate single letters successfully (except through touch), nor was she able to recognize single digits, despite being relatively well able to read them when presented as words. She continued also to be quite unable to read words presented vertically – presumably these did not constitute “words” as represented in the brain structures mediating her ability to read conventionally presented (i.e. horizontal) words (cf. Vinckier et al., 2006). Finally, when presented with jumbled versions of words, D.F. performed significantly less well than with their correctly-spelt equivalents. When the words were embedded in meaningful sentences, however, her performance on jumbled words improved, becoming as good as the correctly spelt words.

These behavioural results may provide clues as to how D.F. achieves her word recognition success. Evidently a word has to be presented as a conventional gestalt, since neither single letters nor vertically presented words evidently engaged the system she is using. (Indeed when a word is rotated to the vertical – i.e. with the letters themselves oriented at right-angles to their normal orientation – she finds it near-impossible even to *guess* what it might be.) Semantic context influences her performance, as demonstrated by the jumbled-words results and also by the nature of her erroneous responses to correctly spelt words. Yet the system mediating her performance does not yield conscious word recognition: D.F. reports that she is guessing. It seems that her brain is operating at a primitive level whereby the visual features of letters are pieced together to constitute a “word form”, but without those visual features themselves reaching an explicit level of representation as letters *per se*, and indeed without the “word form” itself attaining a fully conscious percept *qua* word. Our starting hypothesis, based on D.F.'s behaviour, was that perhaps she had retained an intact “visual word form area” (VWFA) which can still be activated visually, albeit – due to her extensive lateral-occipital damage – only partially, due to the primitive nature of the surviving visual inputs. This might allow D.F. to guess word identity at above-chance levels, but without her ever

achieving genuine word recognition, for which the VWFA would require a fully processed visual input.

4.2. Localization of VWFA in D.F.

One of the major aims of this study was to establish whether or not patient D.F. might indeed have retained a functionally responsive WVFA, despite having lost her lateral occipital area (LO) both structurally and functionally (James et al., 2003). We did this by presenting high-frequency English words as opposed to digit strings, letter strings, Hebrew words, and line drawings, following the procedures of previous studies (Baker et al., 2007; Reinke, Fernandes, Schwindt, O'Craven, & Grady, 2008). We found that D.F., like our healthy control group, showed a clear focus of net activation in the left fusiform gyrus when words were contrasted with digit strings. This focus appears to correspond well to the VWFA as defined by others (Bolger, Perfetti, & Schneider, 2005; Jobard, Crivello, & Tzourio-Mazoyer, 2003; McCandliss, Cohen, & Dehaene, 2003; Price, 2000). Neural activation in this area in our controls was also significantly greater for real words than for strings of letters or Hebrew characters, although it did not differ significantly from activation elicited by line drawings of familiar objects. Patient D.F. showed a qualitatively comparable, and not significantly different, profile of activity to the controls. The activation in the VWFA to line drawings in both D.F. and the controls is a puzzling, but not a novel, finding (Price & Devlin, 2003; Starrfelt & Gerlach, 2007). Dehaene and colleagues have explained such findings in terms of their "recycling" hypothesis, according to which line drawings, which contain numerous line junctions, would be particularly effective at activating the VWFA (Dehaene & Cohen, 2011). As Dehaene et al point out, when drawings and written words are matched in visual complexity, the words give a significantly stronger response in the left VWFA (Ben-Shachar et al., 2007; Szwed et al., 2011). However the left hemisphere is known to play a role in recognizing drawings of familiar objects (Vitkovitch & Underwood, 1992), so it would not be entirely surprising if the areas involved in that processing overlapped with word-recognition mechanisms. Accordingly there may be a subset of voxels within the "VWFA" as localized that are not specialized only for words, but respond also to readily verbalizable drawings (Price & Devlin, 2004). In the present study we found evidence that in several of our controls and in D.F. herself, the localized area contained definite clusters of voxels that responded to words only, and not to drawings.

We were also able to differentiate clearly between the VWFA and the left "fusiform face area" (FFA) in all of our participants. We localized the FFA bilaterally by contrasting pictures of faces with pictures of houses, and found that in 8 out of our 10 participants, including D.F., there was no overlap between VWFA and the left FFA. In the remaining two controls, there was minimal overlap only. This separation was confirmed statistically by analysing the y and z Talairach coordinates for each participant. Furthermore, we found no evidence that activation of FFA was differentially affected by word stimulus class during the experimental runs, either in the control subjects or in D.F.

4.3. The functioning of D.F.'s VWFA

The present data do not allow of any firm conclusions as to the modus operandi of the intact VWFA in D.F. It is apparent, however, that the degree of activity in this area parallels the extent to which D.F. construes a letter string to be a normal printed word. Thus in our lexical decision task, the greatest activation was elicited by real words correctly identified as such, followed by real words in alternating case, then pseudo-words, and then random letter strings;

and the least of all by real words wrongly identified as non-words. It may be that in the absence of a strong visual signal reaching D.F.'s VWFA (after all, her behavioural performance in the experimental fMRI task did not exceed chance), the activation of the area is driven largely by top-down influences based on context and expectations. It is notable that a similar pattern is seen in our controls, suggesting that similar top-down modulations affect the normal VWFA as well. In support of that idea, there are a number of neuroimaging studies demonstrating that activation in the VWFA is modulated by top-down processes involving symbolic meaning (Song, Tian, & Liu, 2012), task demands (Twomey, Kawabata Duncan, Price, & Devlin, 2011) and nonvisual stimulus attributes (Twomey et al., 2013; Yoncheva, Zevin, Maurer, & McCandliss, 2009). Yet in the original word localizer task, there was clearly higher activation in D.F.'s VWFA to real English words than to Hebrew words or random strings of letters or digits, indicating that bottom-up visual information too was having a significant role in activating the area. Presumably therefore D.F.'s word recognition in the behavioural tasks must depend partially on a bottom-up activation of her VWFA. Our experimental fMRI study showed that this visual activation was greater when a real word was presented, even when it was in alternating format, compared to 'word-like' pseudo-words and random letter strings; thus our "hypothesis 1" fits her data better than our "hypothesis 2", which was based on the idea that frequently encountered letter pairs might be a major factor. Our results would be consistent with Price and Devlin's (2011) proposal that the functionality of VWFA depends on interactions between bottom up sensory inputs and top-down predictions mediated by feedback connections from other brain regions.

If these speculations are correct, what visual basis might DF's word recognition have? Our preferred suggestion is that basic visual features (orientation, relative position, length, line-intersections) are processed successfully in D.F.'s early retinotopic visual areas, but that the outputs of this processing can gain only limited access to higher brain systems due to her occipital damage. The accessed areas might include the word-form system, while excluding systems for conscious letter identification and simple shape recognition (through deafferentation and/or destruction). We know already that similar basic featural information is passed successfully to dorsal-stream areas to guide prehension movements (James et al., 2003), such that D.F. can, for example, demonstrate an implicit appreciation of stimulus orientation and location through her overt behaviour (reaching fluently with the correct hand orientation to oriented targets (Goodale et al., 1991; Milner et al., 1991).) Orientation information can also prime the McCollough colour after-effect in D.F. (Humphrey, Gurnsey, & Fekete, 1991), most probably at the level of area V1. We propose that the word identification system receives direct input from such early visual specification of retinal positions, element sizes, orientations and intersections, but does so in the absence of the usual more structured perceptual information conveyed by areas such as LOC. In support of this contention Szwed et al (2011) showed greater activation to written words compared to line drawings in early visual areas (V1/V2 and V3/V4) for normal readers. Also a recent study by Yeatman, Rauschecker and Wandell (2013), which used diffusion tensor imaging (DTI) to map out the circuitry associated with VWFA, provides evidence of the possible connections between VWFA, retinotopic regions in the occipital lobes and other regions involved in the reading network. Yeatman et al. (2013) mapped three white matter fasciculi lying in close proximity to VWFA, respectively connecting this region to the inferior frontal lobe and retinotopic regions (inferior fronto-occipital fasciculus), to the lateral occipital region and the inferior parietal lobe (vertical occipital fasciculus), and to the anterior and medial temporal lobe and retinotopic regions (inferior longitudinal fasciculus). Clearly, given the location of D.F.'s lesions, the connections between VWFA and LO no longer function normally. However, VWFA lies close to both the VO and TO visual field maps in the occipito-temporal

cortex (Rauschecker et al., 2011; Yeatman et al., 2013), and it is possible that D.F.'s VWFA still receives input from VO (but not TO or LO1 and LO2 given the location of her lesions), as well as from other visual regions in occipital cortex.

A direct route from V1 to the ventral occipital cortex might support input from standard typefaces and across a range of font sizes. The responses of VO visual field maps, for example, show sensitivity to the statistical regularities associated with more complex stimuli such as objects and words (Arcaro, McMains, Singer, & Kastner, 2009; Brewer, Liu, Wade, & Wandell, 2005; Rauschecker et al., 2011). This would obviate the need to specify word shape cues, and it would also account for the relatively small and inconsistent effects of alternating case, and words printed in uppercase, on normal word reading. It is possible moreover that the route is a quick one, providing sufficient visual information for speed reading in healthy subjects without the necessary intervention of consciously registered word identities (Dehaene et al., 2001; Szwed et al., 2011). If the neural pathway to the VWFA from earlier cortical areas could only transmit rudimentary information, D.F.'s reading would be expected to be vulnerable to manipulations of whole word shape. The crudeness of the visual information reaching the VWFA would cause least problems for word reading in regular print, since experience would have established maximal neuronal sensitivity to word features in familiar fonts and orientation (see Perrett & Oram, 1998).

Our proposed involvement of the VWFA in D.F.'s reading would account for the partial double dissociation that her performance provides with the converse pattern seen in typical cases of letter-by-letter readers (so-called pure alexia patients), who show impairment in reading whole words despite relatively preserved letter identification (Leff et al., 2001). This mirror image of D.F.'s reading is thought to reflect the loss of fast and parallel mechanisms for integrating letter information from multiple retinal locations, either through loss or deafferentation of the VWFA (Cohen & Dehaene, 2004; Cohen, Jobert, Le Bihan, & Dehaene, 2004; Dehaene & Cohen, 2011). We presume that an activated VWFA would trigger the retrieval of the most probable word from the person's lexicon on the basis of such top-down influences as semantic context. Such top-down links from higher semantic processing areas to the VWFA are probably largely preserved in D.F., allowing her to respond with words from her lexicon whenever the VWFA is activated by a real word or a non-word letter string. Indeed, when we contrasted correctly identified words against letters strings in the lexical decision task we found activation in the left IFG and left pMTG (posterior middle temporal gyrus) in D.F. and in controls. Left IFG and pMTG are both associated with semantic processing (Devlin, Matthews, & Rushworth, 2003; Gold, Balota, Kirchoff, & Buckner, 2005; McDermott, Petersen, Watson, & Ojemann, 2003; Newman & Joanisse, 2011; Simos et al., 2002). It should be noted, however, that unlike controls, D.F. did not show activation in pMTG or the anterior temporal cortex in the localizer task. This may be due to differences in word processing whilst performing the n-back task which does not explicitly require participants to read. Control participants may automatically read the words, whereas D.F. might resort to a pattern matching strategy, given her difficulties with reading.

4.4. Responses to alternating-case words

Previous research tells us that neurons in the VWFA are sensitive to knowledge of orthographic regularity derived from perceptual experience (Binder et al., 2006; Vinckier et al., 2007). It is rare, of course, to see words depicted in an alternating-case format outside the laboratory. Indeed, many behavioural studies have shown performance decrements for alternating-case compared to single-case words (Besner & McCann, 1987; Mayall,

Humphreys, & Olson, 1997). We have argued that it was possible in our experiment that the pseudo-words would elicit increased activation relative to the alternating-case condition on the grounds that high frequency bigrams were more visually familiar than alternating-case letter pairs. Research by Binder et al. (2006) provided evidence that neurons in VWFA are tuned to the familiarity (i.e. frequency) of letter pairs. However, this hypothesis was not supported in our data. Instead, we observed greater activation for meaningful words (single-case and alternating-case) compared with pseudo-words and letter strings. According to Price & Devlin's interactive account (2011) the relative differences in activation between our real word and non-word stimuli in the VWFA could arise because of feedback from higher-order regions involved in phonological and conceptual processing. The interactive account is consistent with the anatomical connections between the VWFA and other brain regions associated with language processing (Yeatman et al., 2013). And perhaps the mirrored pattern of activity we find in left IFG and VWFA is a result of feedforward and feedback processes involved in the lexical decision task.

There are, however, alternative explanations to consider. One possibility is that neurons in the VWFA are case-invariant. Research by Dehaene et al. (2004) found repetition priming between upper and lower case words suggesting that VWFA is invariant to case when the case is consistent within a word, but they did not test alternating cases. Neuroimaging studies comparing alternating-case with single-case words provide mixed results. Xu et al (2001) and Kronbichler et al., (2009) found increased activation to alternating case compared with lower case words in the posterior occipito-temporal region bilaterally. Their results suggest that neural coding in this region is not case-invariant when the case is mixed within a word. In contrast, Mayall et al. (2001) found increased activation to alternating case compared to lower case words in the right superior parietal lobe, though not in occipito-temporal cortex. Furthermore, in a series of patient and TMS studies, Braet and Humphreys (2006a, 2006b, 2007, see also Vinckier et al. (2006) for an interesting discussion on the role of the parietal lobe in alternative reading strategies) found a consistent link between the parietal lobe and performance on tasks involving alternating-case words. In light of these results, we analysed activations elicited by the alternating-case condition to see whether the parietal lobe was involved in our lexical decision task. We found that a contrast of alternating-case versus same-font words produced activations in the left medial and posterior intra parietal sulcus (medial and posterior IPS), as well as in premotor cortex (left and right PMd), right lateral occipital (LO) cortex, and area V3a bilaterally (see Table 2). These activations are consistent with Braet and Humphreys' argument that mixed-case stimuli increase the demands on spatial attention for letter identification. Certainly in our behavioural data participants were less accurate in the alternating-case condition than in any other condition, consistent with the alternating-case condition being more attentionally demanding. However this accuracy difference did not manifest itself in the activations we recorded in VWFA and IFG, where we found no reliable difference between alternating-case and same-font words.

4. Conclusions

Our data show that D.F. has retained over a 20-year period a level of visual word identification that is higher than would be expected given her profound problem in shape discrimination. Furthermore, we have found that visually-presented words activate an area in her left occipito-temporal cortex that appears to correspond to that observed in healthy subjects, commonly (if controversially) referred to as the "visual word-form area" (VWFA). Our fMRI data also show that the visual and semantic properties of this activated area in D.F.

correspond quite closely with those of the healthy VWFA. We tentatively conclude that this spared area plays an important role in D.F.'s residual word-identification ability.

As well as helping us to understand D.F.'s residual word recognition, our study provides data which may bear on the current debate as to exactly how the VWFA operates in the healthy brain. First, it is clear that the area can be activated without the need for processing in area LO (which is absent/non-functional in D.F.), strongly suggesting that a parallel pathway exists that presumably provides input to VWFA in the intact brain – in addition to a primary one that depends on letter-by-letter processing (for which the LO seems to be required.) Second, the fact that we found greater VWFA responses in both D.F. and our control subjects to alternating-case real words than to pseudowords (which contain familiar same-case bigrams) supports the idea that top-down lexical-semantic influences play a major role in VWFA function, even when the cortical visual pathway via area LO is intact.

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Table 1: Areas localized by comparing Word>Digits in the Word Localizer task for D.F. and Controls.

<i>Brain Areas</i>	<i>Talairach Coordinates</i>			<i>#</i>
	<i>x</i>	<i>y</i>	<i>z</i>	<i>Voxels</i>
<i>D.F.</i>				
Left Fusiform Gyrus	-40	-48	-24	918
Left Inferior Frontal Gyrus	-52	-3	18	1996
Left Early visual areas	-15	-89	-33	1091
Left Motor/Somatosensory Cortex	-53	-23	45	1707
<i>Controls</i>				
Left Fusiform Gyrus	-42	-34	-12	951
Left Inferior Frontal Gyrus	-48	10	7	2137
Left Posterior Middle Temporal Gyrus	-58	-44	1	929
Left Anterior Temporal Cortex	-38	-9	-29	1425

Table 2: Areas localized by comparing $W+ > LS+$; $W > PW+$, and $AC+ > W+$, in the lexical decision task for controls and D.F.

<i>Brain areas</i>	<i>Talairach coordinates</i>			<i>#</i>
	<i>x</i>	<i>y</i>	<i>z</i>	<i>Voxels</i>
<i>D.F.</i>				
<i>W+ > LS+</i>				
Left IFG	44	19	4	811
SMA	-9	18	47	729
Left pMTG	-56	-61	-9	4403
Left VWFA	-46	-54	-25	872
<i>W+ > PW+</i>				
Left pMTG	-57	-61	-11	1518
<i>AC+>W+</i>				
None				
<i>Controls</i>				
<i>W+ > LS+</i>				
Left IFG	-47	20	14	961
SMA	-3	10	46	1077
Left Insula	-39	19	2.4	9449
Right Insula	32	19	1	875
Left pMTG	-51	-45	-1	1068
Left VWFA	-48	-42	-19	950
<i>W+ > PW+</i>				
Left SPL	-15	-55	52	947
<i>AC+>W+</i>				
Left PMd	-49	2	29	952
Right PMd	41	0	29	1440
Right IPS (medial)	37	-44	42	2431
Right IPS (posterior)	27	-66	46	1800
Right LOC	50	-57	6	4622
Right Area V3a	32	-83	3	1957
Left Area V3a	-30	-83	7	2385

Table 3 Areas localized in the fusiform gyrus by comparing Words>Digits and Faces>Houses at the level of single subjects; s8 and s9 are age matched controls.

<i>Brain Areas</i>	<i>Talairach Coordinates</i>			<i># Voxels</i>
	<i>x</i>	<i>y</i>	<i>z</i>	
<i>Word>Digits</i>				
s1 Left Fusiform Gyrus	-44.2	-29.7	-18.4	885
s2 Left Fusiform Gyrus	-42.4	-39.5	-12.7	888
s3 Left Fusiform Gyrus	-44.3	-40.5	-14.9	799
s4 Left Fusiform Gyrus	-42.5	-12.3	-17.3	903
s5 Left Fusiform Gyrus	-44.3	-31.7	-12.6	943
s6 Left Fusiform Gyrus	-35.7	-13.0	-14.7	846
s7 Left Fusiform Gyrus	-35.0	-36.4	-19.9	829
s8 Left Fusiform Gyrus	-38.3	-37.2	-16.3	791
s9 Left Fusiform Gyrus	-44.3	-42.2	-14.4	716
D.F. Left Fusiform Gyrus	-46.3	-48.0	-17.6	918
<i>Face>House</i>				
<i>Left hemisphere</i>				
s1 Left Fusiform Gyrus	-43.4	-40.6	-24.7	955
s2 Left Fusiform Gyrus	-42.6	-53.2	-25.2	632
s3 Left Fusiform Gyrus	-43.3	-47.3	-23.3	805
s4 Left Fusiform Gyrus	-38.6	-48.2	-16.1	889
s5 Left Fusiform Gyrus	-40.8	-40.9	-22.6	858
s6 Left Fusiform Gyrus	-41.3	-47.2	-16.4	698
s7 Left Fusiform Gyrus	-37.6	-49.6	-20.6	868
s8 Left Fusiform Gyrus	-42.3	-45.4	-17.5	968
s9 Left Fusiform Gyrus	-39.6	-33.2	-22.4	689
D.F. Left Fusiform Gyrus	-42.0	-57.0	-25.0	367
<i>Right hemisphere</i>				
s1 Right Fusiform Gyrus	42.8	-42.9	-14.8	766
s2 Right Fusiform Gyrus	39.7	-44.7	-22.4	926
s3 Right Fusiform Gyrus	31.8	-44.6	-24.7	866
s4 Right Fusiform Gyrus	29.8	-56.5	-15.2	637
s5 Right Fusiform Gyrus	38.5	-49.5	-21.5	989
s6 Right Fusiform Gyrus	33.2	-43.4	-18.4	693
s7 Right Fusiform Gyrus	36.6	-30.6	-16.7	829
s8 Right Fusiform Gyrus	32.2	-46.1	-19.5	942
s9 Right Fusiform Gyrus	38.6	-36.5	-22.8	920
D.F. Right Fusiform Gyrus	45.0	-51.0	-26.0	272

Figure Captions

Figure 1.

Brain areas activated in the comparison of Words versus Digits in the word localizer task for patient D.F. (a) and control participants (d). Percent BSC was extracted from the common activated areas: left VWFA and left IFG in D.F. (b, c) and controls (e,f). For the VWFA, solid colour bars show the profile of activation found when the cluster of voxels and the time-course were obtained using the same data set and striped colour bars show the same profile when the cluster of voxels and the time-course were obtained using independent data sets. VWFA: “Visual word form area”; pMTG: posterior middle temporal gyrus; IFG: inferior frontal gyrus. Errors bars depict standard errors. Asterisks highlight significant differences with respect to baseline (zero).

Figure 2.

Lexical decision accuracy in (a) the “Difficult” and (b) the “Easy” condition. (a) Data for the whole control group are depicted in grey, and for the age matched controls alone in white. (b) Data for D.F. are depicted in black and for the control group in grey. Control participants were at ceiling for all conditions in the Easy task. W: words; AC: alternating case; PW: pseudo-words; LS: letter strings.

Figure 3.

Percent BSC during the lexical decision tasks, extracted from the left VWFA (upper panels) and the left IFG (lower panels) for both Hypothesis 1 (upper figure) and Hypothesis 2 (lower figure) in both patient D.F. (a,d,g,j) and in controls (b,c,e,f,h,i,k,l). D.F. and control participants were asked to perform a lexical decision task upon the presentation of words (W, depicted in blue), words in alternating case (AC, depicted in green), pseudo-words (PW, depicted in yellow) and random letter strings (LS, depicted in red). D.F. performed the easy task only (a,b,g,j), while the controls performed under both the Easy (b,e,h,k) and Difficult (c,f,i,l) lexical decision conditions. Trials for the easy task in D.F. (a,d,g,j) and for the difficult task in controls (c,f,i,l) have been split into correct (white panels) and incorrect (grey panels) trials. While D.F. committed errors on non-word trials (depicted as dotted bars in panels a,d,g,j), the control participants did not. For all tasks, quadratic correlation coefficients (plain lines, Qu/R^2) and/or linear correlation coefficients (dotted lines, Li/R^2) are reported to highlight the main trends in the data with respect to both Hypothesis 1 and Hypothesis 2. + **sign** indicates correct trials; - **sign** indicates error trials. Errors bars depict standard errors.

Figure 4.

Overlay activations for W+ versus LS+ (lexical decision task, difficult condition – in green) and Words versus Digits (word localizer task – in blue) are shown for both D.F. (a) and controls (b). VWFA: “Visual word form area”; pMTG: posterior middle temporal gyrus; IFG: inferior frontal gyrus; SMA: supplementary motor area, M1: primary motor cortex, S1: primary somatosensory cortex.

Figure 5.

Brain areas FFA and VWFA in the left hemisphere are shown for (a) D.F., (b) averaged controls, and (c) the two age matched controls. While FFA was localized by comparing Face stimuli versus Place stimuli in the Face Localizer task, VWFA was localized by comparing Words versus Digits using the Word localizer task. The histograms in (d) show left FFA responses (%BSC) in the face localizer task (upper panels) and in the easy lexical decision

task (lower panels) for both D.F. (left panels) and all controls (right panels). W: words, AC: words in alternating case, PW: pseudo-words, LS: letter strings.

Figure 1

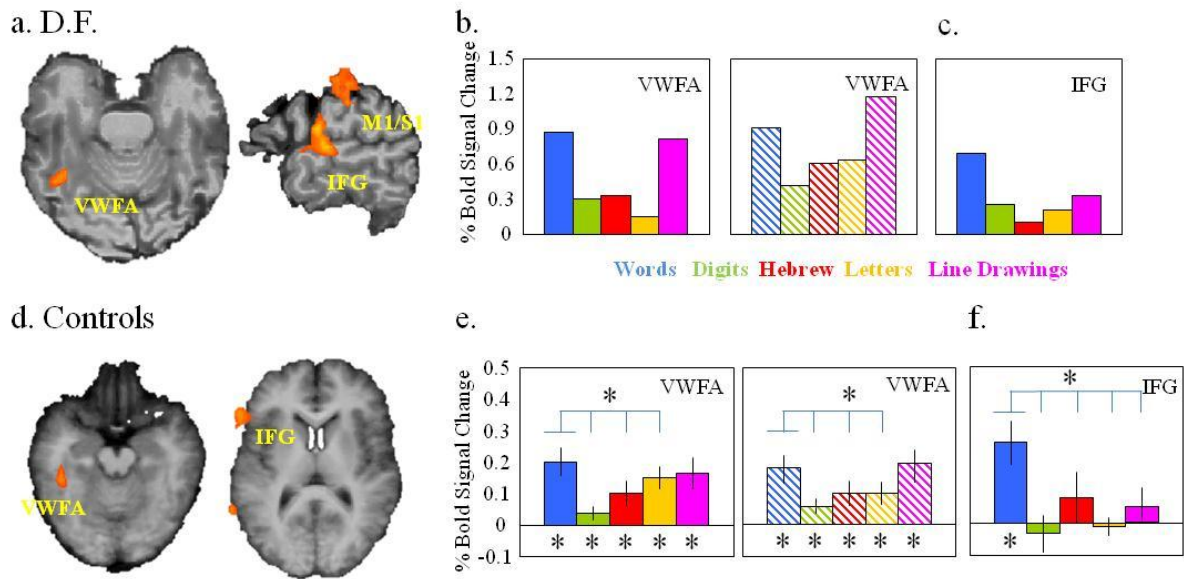


Figure 2

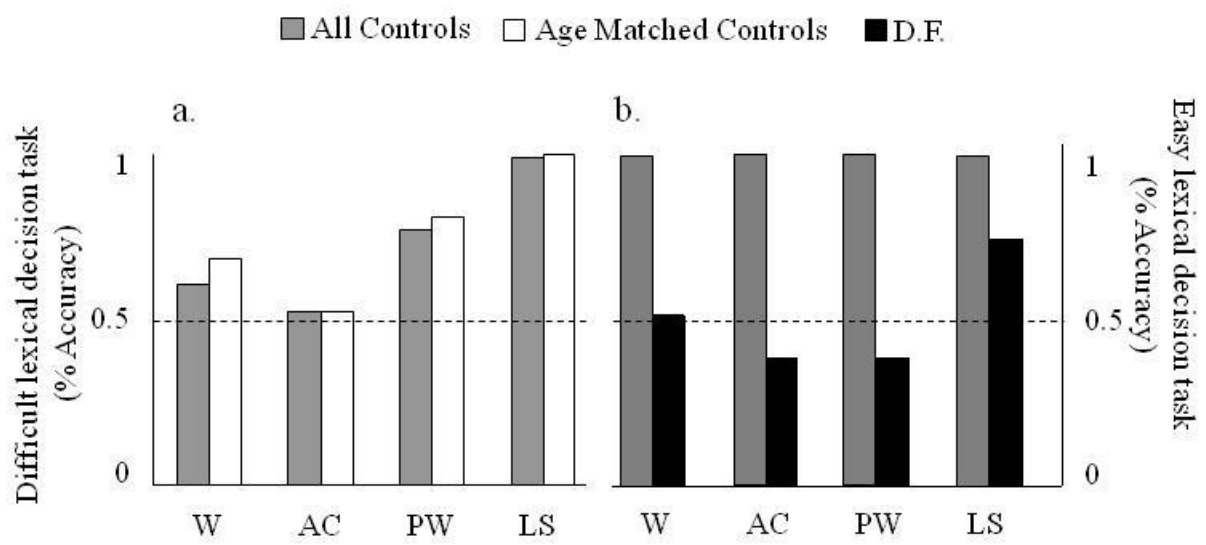


Figure 3

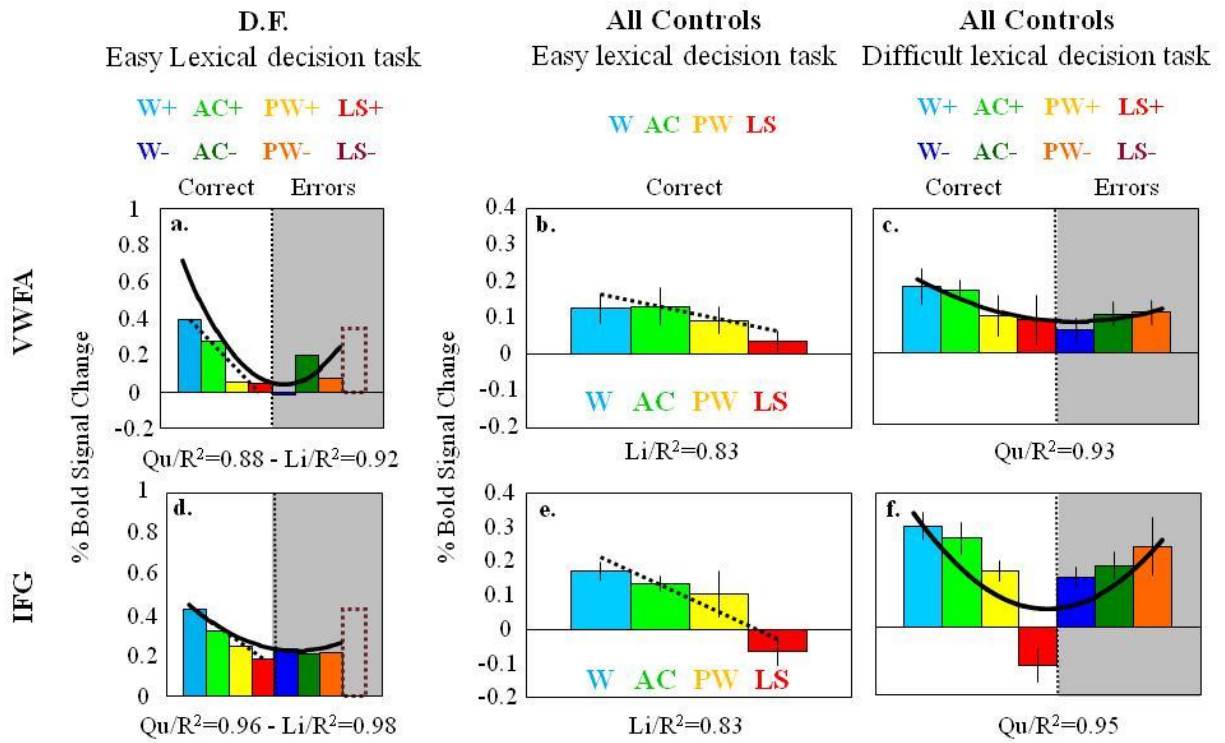


Figure 4

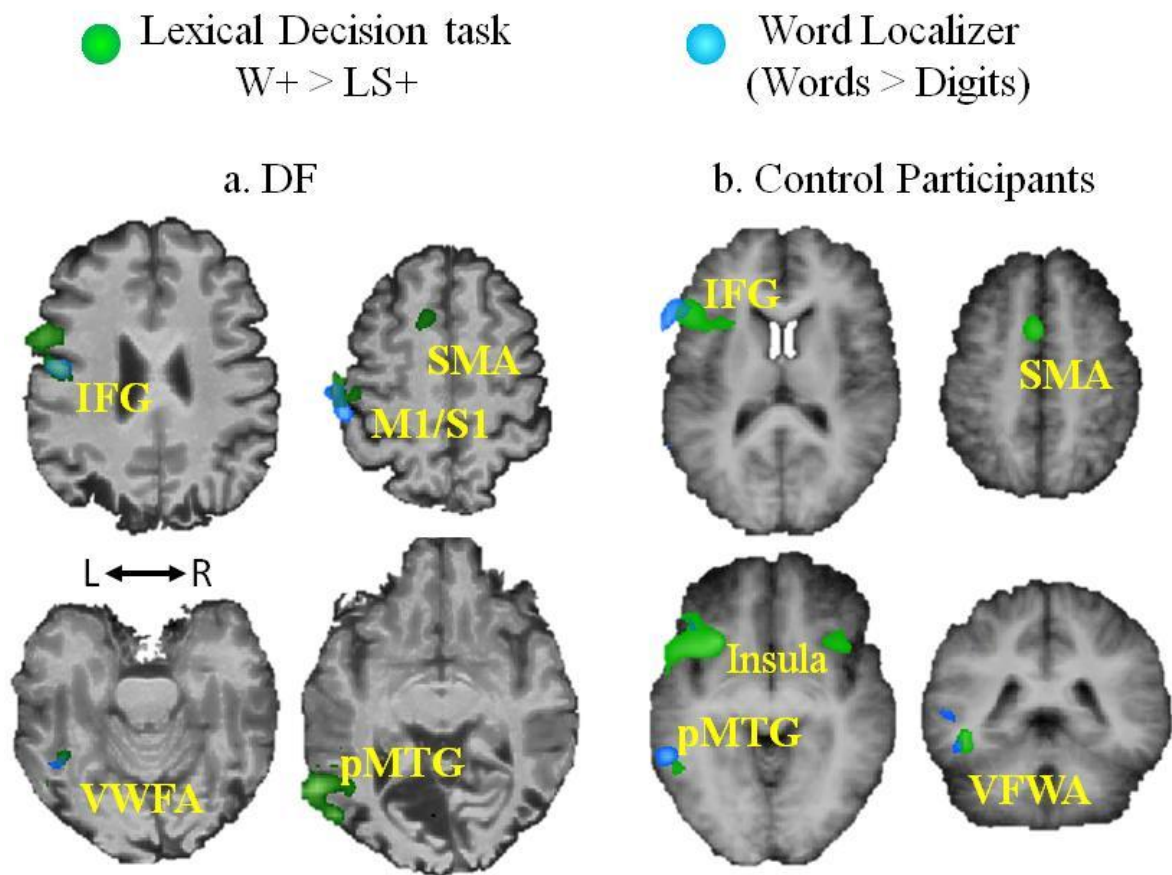


Figure 5

