Functional and organic dystonia: A psychological and kinematic study

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Abstract

Since David Marsden's studies on dystonia, it has generally been considered a disorder of the basal ganglia. His ideas steadily supplanted psychogenic models of dystonia, which held sway for much of the 20th century. Yet dystonia still sits in a borderzone between neurology and psychiatry. Patients with organic dystonia have elevated rates of psychopathology, and can be difficult to distinguish from those with functional dystonia (FD). Diagnostic criteria for FD with heavy psychological emphasis have poor inter-rater reliability, and a significant minority of patients with functional movement disorders (FMDs) have normal scores on psychological scales. The purpose of this study was to explore the psychological and kinematic character of these two subtypes of dystonia, with a view to developing better diagnostic criteria.

Thirty-three patients with organic dystonia, 13 with FD and 29 healthy controls were recruited. Self-rating questionnaires for anxiety and depression, obsessive-compulsion, fatigue, pain and depersonalisation were completed by subjects. Several finger tapping tasks—freestyle, with and without *geste*, and metronome-guided—were performed whilst subjects wore electromagnetic sensors on thumb and index finger. Separable components of movement (such as rhythm, speed and amplitude) were derived from a comparison of the coordinates of each sensor.

Patients with organic and FD could not be reliably distinguished according to any of the psychological or kinematic variables assessed. Those with FD had higher scores across all self-rated psychological scales, compared to healthy controls, whereas patients with organic dystonia displayed elevated scores for depression and pain only. A higher proportion of patients with FD (39%) than organic dystonia (10%) had 'moderate' to 'extreme' obsessive-compulsive symptoms. In organic dystonia, movements were slower and more halting. Both dystonia groups displayed reduced maximal opening deceleration.

These findings suggest there is significant overlap between functional and organic dystonia, with a commonality in both their motor and psychological characteristics.

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Author's Declaration

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Chapter One: Introduction

"*Le médecin est inséparable de l'artiste. L'un guide de l'autre; ils s'entraident mutuellement*"—Jean-Martin Charcot (1825–1893)

Compared with most other movement disorders, dystonia is a new conceptual package. The term dystonia was not introduced until 1911, when Hermann Oppenheim described the abnormal posturing of *dystonia musculorum deformans*.(1) Prior to this, its core motor manifestations—sustained or intermittent muscle contractions causing abnormal movements, postures, or both—were distributed across nosological categories such as 'spasm', 'contracture' and 'tremor'.(2) The history of medical science can be seen as an extended hermeneutic exercise, with the physicians of each era forming collective readings of the 'language' of bodily disease using the interpretative tools at their disposal, be it scalpel, microscope, electromyogram or functional MRI scanner. Such interpretations are constrained by social, political and cultural pressures, as much they are by technological limitations— the prisms that distort both doctors' and patients' perceptions of disease.

When, during the late 19th and early 20th century, a body of knowledge about dystonia was being assembled, two intellectual undercurrents were shaping the development of modern neurology. Both had a lasting effect on thinking about dystonia. With his *methode clinico-anatomique* Charcot created a separation between "organic" disorders, which could be matched to structural changes in the nervous system, from "functional" disorders (*névroses*), which could not. Within this schema spasms or contractures without a neuroanatomical substrate were classified as neuroses. These conditions remained relatively poorly defined for several decades. Dystonia was not perceptible as a distinct disease because of its variable distribution and puzzling inconsistencies. These same features meant that for many decades its signs were conflated with those of another bizarre and inexplicable condition— "the great neurosis", hysteria.

Sigmund Freud (1856–1939) was the other dominant *fin-de-siècle* influence. Within his psychodynamic framework the term neurosis took on a different meaning—denoting conditions in which unconscious conflicts or defence mechanisms were transduced into physical symptoms. For a time psychogenic

models of dystonia, based on Freud's ideas, were ascendant, but there remained a dissenting organic school of thought. Genetic and electrophysiological advances in the latter half of the twentieth century eventually provided robust evidence of organicity.

The tension between psychogenic and organic modelling of dystonia has not yet been fully resolved. Among the functional (psychogenic) movement disorders (FMDs)[1], functional dystonia (FD) poses the greatest challenge to diagnosis. There are few clinical signs that consistently distinguish FDs from their organic cousins, and to date no reliable 'laboratory supported' criteria, based on electrophysiological or neuroimaging findings, have been described. Its pathophysiology, and that of the allied condition of complex regional pain syndrome, remains a subject of debate and controversy. The high prevalence of psychopathology in both organic and FD raises interesting questions about the role of cortico-striatal neural circuitry in both movement disorders and psychiatric disease. Dualistic approaches to dystonia—shaped by gender dynamics, Cartesian concepts of brain and mind, and loose notions of real and unreal symptomatology—have failed to provide a comprehensive account of the disorder. By avoiding such ideological polarisation, it may be possible to develop more inclusive biopsychosocial models.

1.1 Dystonia: an historical perspective[2]

Nominal, cultural and epistemological discrepancies can make it difficult for the modern reader to identify diseases from historical accounts. Even disorders that must have had a conspicuous visual presence in past societies such as dystonia—"most striking and grotesque of all neurological disorders"(3)—remain invisible in written accounts until a body of knowledge is assembled around a name. The existence of dystonic entities in former civilisations must be inferred from fragmentary accounts of their various elements. The term torticollis, referring to

[1] FMDs include tremor, dystonia, myoclonus, chorea, tics and parkinsonism. Functional weakness, thought to have a similar pathophysiological basis, is usually categorised separately.
[2] A version of this history of dystonia (sections 1.1.1 to 1.1.4) was published in Newby RE, Thorpe DE, Kempster PA, Alty JE. A History of Dystonia: Ancient to Modern. Mov Disord Clin Pract. 2017;4(4):478–85.

twisting deformity of the neck, antedates the term dystonia by several centuries. But this was a catch-all descriptor for myriad disorders that could perturb the posture of head and neck, including muscular or ligamentous injury and vestibular disturbance. Hence, even with the marker of nomenclature, dissecting out references to truly dystonic manifestations can prove challenging.

1.1.1 The Ancient World

The writings of physicians of the ancient world typically begin with catalogues of symptoms, followed by lengthy discourse on potential cures. References to spasmodic cervical conditions in these texts are somewhat obscure. Hippocrates used the descriptor *traxhlos sklhros*, meaning "a stiff and painful neck", which was a fatal sign when accompanied by "contraction of the jaws, a powerful throbbing of the jugular vessels, and contraction of the tendons."(4,5) Celsus later used the term *rigor cervicis* in a similar context.(6) Both were probably referring to tetanus or meningitic neck stiffness rather than torticollis. Pliny the Elder, writing in AD 79, proposed sea-lice, beaver oil mixed with pepper and honey-wine, and boiled-down frogs as potential remedies for this malady.(7) The Moche civilisation, which occupied territory in modern-day Peru between 100 and 700 AD, produced sculptures with particular attention to physiognomic differences—ritual mutilation, cleft lip, cutaneous leishmaniasis.(8) Some authors have argued that the horizontally tensed lips and pronounced nasolabial folds of one such sculpture represents the first depiction of Meige syndrome (a form of cranial dystonia).(9)

1.1.2 Medieval and Renaissance depictions

Possible representations of some focal dystonias appear in the religious iconography and writings of the medieval period. A set of painted figures adorning the tomb of Bishop Pedro de Osma in the El Burgo de Osma cathedral in Spain appear to have cervical dystonic postures (Figure 1).(9) Though it is difficult to distinguish these from muscular torticollis arising from sternocleidomastoid injury, which may have been more common in the Middle Ages due to higher rates of obstetric complication. Convincing material evidence of dystonia affecting handwriting has been found in legal documents written by the French scribe

Bernard Blancard between 1297 and 1343.(10) These document a progressive deterioration in Blancard's script, with a multi-directional, jerky tremor and probable abnormal hand posturing. The word torticollis appears for the first time in François Rabelais' (1494–1553) *Pantegruel*, which describes the application of a poultice to the beheaded Epistemon "so as not to make him a 'wry neck'" (*afin qu'il ne fust torty colly*).(11–13)

Figure 1: Abnormal neck positions depicted on the tomb of the medieval Bishop Pedro de Osma (1040–1109), Cathedral of Burgo de Osma, Spain. These carvings were executed c.1258. Photograph by José Luis Filpo Cabana.

1.1.3 The Enlightenment

During the 17th and 18th centuries physicians gradually moved away from the authority of ancient medical writers. The neoplatonic theologic autocracy that had stunted scientific thought in the Middle Ages began to lose its power and more systematic approaches to the natural world were developed, based on meticulous observation, collection, and classification of biological and geological specimens. Thomas Sydenham (1624–1689) recognised that diseases could also be organised into groupings in this way, according to their symptoms, physical manifestations and chronology.

The medical nosological classifications of Carl Linnaeus (1707–1778), François Boissier de Sauvages (1706–1767) and William Cullen (1710–1790), mirrored the earlier botanical and zoological classification *Systema Naturae*, which had revolutionised the natural sciences when it was published by Linnaeus in 1735. These systems ordered diseases into hierarchies of Class, Order, Genus, and

Species, with a binomial genus-species nomenclature. Linneaus gave a class of MOTORII for involuntary movement. A range of spasmodic conditions appeared within the order SPASTICI, while a genus Hieranosos, for dynamic movements not otherwise specified, was assigned to the order AGITATORII. Sauvages referred to spasmodic torticollis under the class SPASMI. In his *System of Nosology*, Cullen introduced a class of NEUROSES that contained many nervous system disorders. The species obstipas spasmodica, equating to torticollis, was classified separately, under the class LOCALES.

Nicolaes Tulp (1593–1674), famous as the subject of Rembrandt's *The Anatomy Lesson*, provided one of the first cohesive descriptions of torticollis in 1672, proposing scalene muscular contraction as a likely cause.(14) Lorenz Heister (1683–1758), a German anatomist and surgeon, later distinguished *caput obstipum* (movement of the head in relation to the neck), from *collum obstipum* (isolated disruption of neck posture without separable displacement of the head).(15)

1.1.4 Nineteenth and early twentieth century: dystonia's classifications

1.1.4.1 Early onset generalised dystonia

In 1911 Oppenheim used the term *dystonia muscularum deformans* to describe a syndrome of abnormal posturing in four unrelated Jewish children.(16) The Polish neurologists Flatau and Sterling published similar observations in the same year.(17) Oppenheim's belief that the syndrome had an organic basis stood in opposition to that of Schwalbe (1883–1927), whose earlier account of a similar condition ('torsion neurosis') in three siblings strongly emphasised hysterical features.(18) The presence of 'hysterogenic zones', body areas at which pressure could elicit cramping, was central to this persuasion. Two case reports written by Destarac in 1902, largely overlooked at the time, gave a detailed account of the condition without settling on a unifying descriptive term.(19) Like Oppenheim, he believed that it had an organic basis.

1.1.4.2 Idiopathic focal dystonia

The idiopathic focal dystonias—blepharospasm; oromandibular, cervical, laryngeal, and the various occupational dystonias—were once treated as independent nosological entities. Phenomenological features such as task-specificity and relief with voluntary manoeuvres (the *geste antagoniste*, or sensory trick) were considered inconsistent with organic disease. An intimate relationship with social stress, mostly female predominance and correlation with certain personality traits further supported psychogenicity.

1.1.4.2.a Cervical dystonia

In 1888 Charcot presented a case of *spasme clonique du sterno-mastoïdien et du trapeze* in a stockbroker. The onset of the disorder correlated with catastrophic personal financial loss, establishing cervical dystonia's strong tradition of psychological attribution.(20) His student, Edouard Brissaud (1852–1909), labelled it 'torticollis mental'—opining a psychogenic cause on the basis that abnormal posturing might be extinguished by a light touch to the head.(21) He dismissed this sign as:

"a simple mannerism, or childish behaviour or pathological fake…a violent muscular contraction reversed by a minor reaction".

Brissaud's pupils, Henry Meige (1866–1940) and Louis Feindel (1862–1930) coined the term *geste antagoniste efficace* and wrote in detail about the psychological causes of this sign.(22) Towards the end of the century some alternative views were put forward. William Gowers (1845–1915) distinguished hysterical torticollis from a 'true' form that he suggested might result from overactivation of lower brain centres.(23) Joseph Babinski (1857–1932) reported two cases of coincident neck and upper limb spasm and hypothesised corticospinal pathology.(24) A 1907 monograph by René Cruchet (1875–1959)—*Traite des Torticolis Spasmodiques*—emphasised the lack of nosographical specificity.(25) The 357 reported cases were divided into different aetiological classes—neuralgic, professional, paralytic, true spasmodic, rhythmic, habit and mental torticollis. He proposed peripheral neuritis as a potential cause for the spasmodic type. Habit

torticollis was conceived as a learned response to ocular or otic deficits, and mental torticollis was implied when there was 'a preponderant psychical factor in the disease'. In his review of this work, Samuel Kinnier Wilson (1878–1937) contended that the 'mental' category had been unjustifiably enlarged, quoting another of Charcot's students, Charles Féré (1852–1907)—

"a psychical theory has the immense advantage of dispensing with every effort in search after a physical cause, but it has the disadvantage of destroying all chances of finding it."

1.1.4.2.b Blepharospasm-oromandibular dystonia

Meige, who called this syndrome *spasme facial median*, discerned a melancholic, introspective temper in many of his patients. His first accounts focused on sufferers' "lack of psychical equilibrium" and "fecund imagination," with relapses and remissions following the ebb and flow of emotional stress. But later, in a 1910 monograph, he suggested the cause might be an irritative focus in the pons or midbrain.(26) Meige's *volte face* on psychological origin stemmed from his observation of torticollis, facial spasm and writer's cramp in survivors of Von Economo's encephalitis.

1.1.4.2.c Laryngeal dystonia

The first description of dystonia affecting the vocal chords, causing "nervous hoarseness" is frequently ascribed to Ludwig Traube (1818–1876).(27) While later authors cited him as evidence that laryngeal dystonia was a psychoneurotic condition, Traube had been more neutral about causation. Several of its quirks perpetuated the categorisation as a psychogenic malady. Some patients are able to sing, and others to talk flawlessly in their sleep though their waking speech is grossly disordered. Onset may be abrupt, with symptoms that worsen with stress.

1.1.4.2.d Focal upper limb dystonia (writer's cramp)

The earliest medical report of occupational disturbance of writing, from Italian physician Beradino Ramazzini (1633–1714) in 1713, was about muscular fatigue

rather than spasm.(28) The disorder as we now recognise it was originally described by Charles Bell (1774–1842), who encountered an epidemic of writer's cramp in clerks of the British Civil Service in 1830.(29) Guillaume-Benjamin Duchenne (1806–1875) was the first to distinguish occupational spasm (*spasme fonctionnel*) from occupational muscle paralysis (*paralysie musculaire fonctionnelle*).(30) Gowers' extensive account of the disorder, in *A Manuel of Diseases of the Nervous System* in 1888, concluded that faulty penmanship resulted in derangement of the writing centre in the cortex.(31) However, he also acknowledged anxiety as a pathogenetic factor. Both Wilhelm Erb (1840–1921) and Moritz Romberg (1795–1873) supported an organic cause.(32,33) Erb proposed that it might result from nutritional damage to the CNS. These early theories lost favour, and subsequent outbreaks in telegraphists and typists were regarded as hysterical manifestations in emotionally vulnerable individuals.

1.1.4.2.e Other occupational dystonias

There are reports of occupational cramps, referred to variously as 'craft palsies', 'occupational neuroses' or 'professional impotence' throughout the 19th century. The first descriptions of musician's dystonia, from Romberg in 1853 and Bianchi in 1878, were of task-specific flexion of the digits in a pianist and a flautist.(34,35) George Poore (1843–1904) published a large series of musicians with this disability:

> *"minor only to our eye…often of maximal importance to the sufferer, who possibly sees his livelihood in jeopardy because his hand has lost its cunning".*(36)

Historical evidence from this period suggests that Robert Schumann (1810–1856) may have had this disability. In correspondence he describes pain and stiffness in the fingers while playing the piano, spreading to adjacent muscles and fluctuating with stress levels.(37,38)

1.1.5 The twentieth century onwards: dystonia and the neurology-psychiatry borderland

When neurology diverged from psychiatry after the turn of the 20th century, it

retained dystonia and hysteria amongst organically unaligned or functional conditions. Progress in pathological and biochemical research slowly reduced the size of this group. In Kinnier Wilson's posthumously published reference text Neurology (1940), the list of the motor neuroses had been distilled to a relatively small number, including focal dystonias, tics, and myoclonus.(39)

Psychoanalytical theories of human behaviour, which penetrated art, literature, and popular culture in the decades after Freud's writings, came to exert a strong influence on attitudes to these disorders. Theories about underlying oedipal conflicts and psychosexual anxiety appeared, given weight by sporadic reports of relief from dystonia after psychotherapy and the perception that many of these patients had emotionally unstable personalities. Symbolic interpretations of phenomenology were popular: the twisting of the neck in cervical dystonia was thought to represent a turning away from stressful situations, and the forced eye closure of blepharospasm to signify a desire to close one's eyes on the world.(40) Within these theories, the term neurosis took on a different meaning—denoting conditions in which unconscious conflicts or defence mechanisms were transduced into physical symptoms. The rising popularity of these psychoanalytic models and the absence of concordant neuropathology led, in 1929, to the *Reunion Neurologique Internationale Annuale* consensus that dystonia was not a disease of the nervous system.(41) Meige's revisionary argument that focal cranial dystonia should be considered a disorder of the basal ganglia received little support at the time, as it fell outside mainstream opinion.(42)

Other challenges to the prevailing psychogenic model eventually appeared. The detailed descriptions of torsion dystonia by Ernst Herz (1900–1965) saw generalised dystonia accepted once more as an organic disease in 1944.(43–45) Zeman et al. demonstrated the hereditary nature of dystonia in 1959.(46) Favourable outcomes were obtained in some patients treated with thalamotomy or pallidotomy,(47) whereas Eldridge reported on the limited efficacy of psychotherapy.(48) An animal model of dystonia after basal ganglia lesioning was described by Denny-Brown in 1965.(49)

In the 1970s David Marsden (1938–1998) lifted the focal dystonias from their indeterminate classification as neuroses.(50) His argument that these disorders had a physical rather than psychiatric basis had two main threads. He observed that identical patterns of involuntary movement occurred in the setting of unequivocally organic diseases of the basal ganglia—hereditary cases of generalised dystonia and survivors of encephalitis lethargica. Using electrophysiological techniques, he found common patterns of disturbed agonist-antagonist muscle activation in dystonia that implied extrapyramidal dysfunction.(51) He thus reclassified these disparate disorders as *formes fruste* of generalised dystonia.

For a time, the pendulum swung so far away from psychological modelling of dystonia that any psychiatric symptoms were presumed secondary to the distress created by the involuntary movements. Diagnostic unease was fuelled by an incendiary article, published by Eliot Slater in the 1965,(52) in which the diagnosis of hysteria was described as:

"a disguise for ignorance…a fertile source of clinical error…not just a delusion but also a snare".

He based this assertion on his observation that up to 60% of patients diagnosed with hysteria were subsequently discovered to have an organic condition. Slater did allow that use of the adjective 'hysterical' might in some circumstances be appropriate, but he strenuously rejected the substantival view of hysteria, which he believed represented the triumph of traditional thought over evidence-based appraisal. He later asserted that the use of this diagnostic label reflected a "disorder of the doctor-patient relationship".(53)

As more precise descriptions of the phenomenological character of hereditary dystonia emerged, however, it was easier to discern atypical forms. The first large case series of psychogenic dystonia was published in 1988, in a paper that also laid out the first set of diagnostic criteria.(54) Writing at around this time, Marsden recounted a number of cases of organic dystonia that had been misdiagnosed as hysteria, underscoring the peculiar challenges to diagnosis presented by this condition.(55)

Dystonia's classification system is now informed by neurogenetics. The DYT1 gene, responsible for the majority of early-onset generalised dystonia, was localised to chromosome nine in 1989 and sequenced in full eight years later.(56,57) Since then more than 20 genetically defined dystonia subtypes have been described and many more inherited degenerative conditions are recognised to possess dystonia as part of their broader phenotype. Following international meetings of dystonia experts—Florence in 2009 and Barcelona in 2011—consensus recommendations for the classification of dystonia were generated, with categorisation defined along two axes—aetiology and clinical presentation.(58,59) This repackaging has not obliterated old fault lines that exist where psychiatric disorders border dystonia. FD proved especially hard to classify. It was finally listed as an acquired dystonia, but some questioned whether pseudodystonia might be a more appropriate descriptor.

1.2 Hysteria and functional neurological disorders in history

The modern concept of functional neurological disorder, which includes FD, stems from a much older tradition of hysteria dating back to early medical writers. Charcot's genius was to bridge archaic and modern ideas about hysteria to establish it as a neurological disorder with classifiable phenomenology. Towards the end of his career Charcot's desire to categorise and explicate this protean disorder became nearly all-consuming. Pursuing *"the sphinx that defied anatomy"*(60) in this way led him down a rabbit hole of misadventure where parallel exchanges—between physician and patient, artist and scientist—perpetually reconfigured the condition he tried to define. Of his entire oeuvre, it was Charcot's work on hysteria that drew the harshest criticism.(61) So powerful was this discrediting influence that his writings on hysteria were submerged in ignominy for over a century. Revisiting these texts today, the faults in his ideological approach do not belie the clarity his observations, many of which retain their relevance in contemporary neurological practice.

1.2.1 A note on terminology

With many fluxes in nomenclature and ideological standing to negotiate, navigating a path through the history of functional neurological disorder is challenging. Hysteria encompassed a broad and loosely connected set of symptoms.(62) Subsequent advances in medical understanding and classification progressively narrowed the definition of the disorder, as conditions such as epilepsy and melancholia (depression) were separated out. Charcot used Cullen's classifier "neurosis" for hysteria, and spoke of the *dynamic* changes in the nervous system that might underpin it. His students, and British neurological contemporaries, used the term "functional" in a similar way, as a placeholder for anticipated physiological explication. "Psychogenic" became the descriptor of choice in the early twentieth century, when Freud's psychodynamic ideas reached a zenith of intellectual influence. For a time "functional" and "psychogenic" were used interchangeably, the original meaning having been obscured by this dominant Freudian worldview. A range of other vague terms, including "non-organic" and "medically unexplained" were also deployed.

Today opinion remains strongly divided as to whether "psychogenic" or "functional" is a more appropriate descriptor.(63–67) The term functional retains some of its original sense of an antonym to "organic" but has been criticised for being too neutral about causation and liable to misinterpretation by patients, who may hear the word as *dys*functional. "Psychogenic" is preferred in circles in which the accent on psychiatric evaluation and treatment is strong. The counterargument is that psychogenic implies that all nonorganic symptoms must have a psychological precipitant, a proposition that lacks strong evidence. The term functional has some support from patients, being the descriptor with the highest "number needed to offend" of those in current usage.(68)

1.2.2 The Ancient World

There are depictions of neurological disturbance following emotional trauma in the cuneiform tablets of Mesopotamian peoples living around 4000 years ago, and allusions to possible hysterical symptoms in Egyptian papyrus scrolls dating from

1900 BC.(69,70) But since neither culture had a conceptual understanding of mind or brain—in ancient Egypt the heart was believed to be the seat of intelligence—it is difficult to align these accounts with contemporary disease models. The origins of the term 'hysteria' are often traced to the *corpus hippocratum,* written in the 5th century BC. Hippocrates described a multitude of loosely connected symptoms, many of them gynaecological, using the term *hysterikos*.(71) This was viewed as an organic disorder. Widows were apparently particularly prone to the affliction, which was believed to produce a sense of suffocation due to the ascension of the uterus into the thoracic cavity. Galen, writing around 500 years later, observed the effects of emotion on the body—such as its influence on pulse rate—and noted an excess of hysterical symptoms in sexually abstinent women.(70) He elaborated the Greek concept of *hysterikos*, proposing that symptoms might arise through 'sympathetic' connections between the womb and other parts of the body.(62)

1.2.3 Medieval and Renaissance

In the Middle Ages, when belief in the occult was widespread, a range of neurological symptoms and signs that were formerly regarded as hysterical manifestations—convulsions, muscular contortions, sensory anaesthesia—were conflated with those of witchcraft.(71) These 'stigmati diaboli' were detailed in *Malleus maleficarum*, published in 1494. Epidemics of mass hysteria, such as St Vitus' Dance, were frequent in Europe throughout this period. Members of closely-knit communities, united by strong religious belief, would gather and dance, often to the point of exhaustion.(72) Such displays might be triggered by natural disasters, with motor symptoms spreading 'contagiously' down gradients of age and social standing.(73) These, and modern examples of similar occurrences,(74,75) serve to emphasise the powerful role of sociocultural influence in hysteria.

Towards the end of the 16th century challenges to demonological psychiatry began to appear. Johann Weyer's *De praestigiis daemonum* (1563) described various mental states under the rubric 'melancholia' which were later reinterpreted as hysteria and epilepsy.(76) He argued that weakness of will and impressionability predisposed women to demonically-induced maladies, and he called an end to the

witch trials. In 1603 Edward Jorden published a lengthy discourse on the case of Anne Gunter, a teenager who developed convulsions, blindness, aphasia and hemisensory symptoms after a neighbour spoke harshly towards her. He espoused traditional Graeco-Roman ideas about the role of the uterus, arguing that it produced effects on other body parts 'by consent', through an elaborate matrix of nerves and blood vessels.(77) His account included the first description of *arc-en-circle* posturing during a hysterical seizure.(71) He was also the first to advocate a psychological approach to treatment.(70)

1.2.4 The Enlightenment

During this era there was a paradigm shift away from gynocentric models of hysteria, and the proposition that hysterical disorders might have their seat in the brain gained traction. Opinions diverged as to the precise mechanistic details. Sydenham hinted at certain personality contributions that might produce "over-ordinate commotions of the mind". He and Thomas Willis (1621-1675) proposed an imbalance of 'animal spirits' between body and mind as a potential cause.(78,79) Cullen and Sauvages put forward a model of sexual excess, rather than abstinence.(71) Others stressed the role of traumatic events in provoking hysterical symptoms in constitutionally vulnerable individuals. Towards the end of this period, and into the early 19th century, proto-Freudian concepts of hysteria as the product of "unconscious functional activity" or inhibition of sexual passions were also circulated.(80,81)

Hysteria kept company with many motor disorders now recognised to have an organic basis within the hierarchical nosologies of this period. Linnaeus, Sauvages and Cullen classified hysteria under the orders SPASTICI, SPASMI and NEUROSES, respectively. This emphasises both the prominence of motor signs in hysteria and the difficulty in distinguishing these from other forms of muscular paralysis and contracture.

1.2.5 The *belle époch* of hysteria

1.2.5.1 The French School

Charcot drew heavily on Pierre Briquet's (1796–1881) detailed case series of 430 patients in formulating his model of hysteria.(82) Like Briquet, he downplayed the aetiological significance of sex, presenting several cases of hysterical symptoms in men and pre-pubescent children. Traditional gendered conceptualisations were not entirely abandoned in his writings though—he used the analogy of a seed flourishing in hostile ground for such cases, and suggested that antecedent physical trauma played a greater role.(83) According to Briquet's view, hysteria was a polysymptomatic disorder characterised by pain, anxiety, gastrointestinal and genitourinary disturbance, disorders of mood, sexual dysfunction, and a range of neurological symptoms. This polysymptomatic presentation, once eponymously named 'Briquet's syndrome' is now known as somatisation disorder.

Charcot proposed that hysterical symptoms arose by the action of an environmental stimulus, or *agent provocateur*, on a hereditary *tache* (weakness) or *diathesis* (predisposition).(61) Though post-mortem examinations of women who had suffered from the disorder demonstrated no structural lesions, Charcot anticipated the future discovery of a neurologic cause, postulating that symptomatic expression might be driven by dynamic physiologic changes within the nervous system.(84) He strove to systematise the study of hysteria—to extract order from the *"wilderness of paralyses, spasms and convulsions"*(85) at La Salpêtrière, the Parisian hospital where he was chief physician.

Charcot's work on 'hystero-epilepsy' in particular earned him international renown. He divided hysterical seizures into phases—a prodromal phase, an epileptoid interval, a period of 'clownism', followed by the assumption of various 'passionate attitudes', and finally a period of delirium.(86) Charcot used powerful methods of suggestion such as hypnotism and 'metallotherapy' (the application of metallic elements to which his patients demonstrated peculiar sensitivity) to provoke 'artificial' seizures.(87) Through these extravagant displays he presented his model of hysteria to large audiences at his Tuesday lectures at the Salpêtrière.

In accounts of hysterical contracture, he emphasised abruptness of onset, absence of facial paralysis, and midline-splitting anaesthesia as distinguishing features.(88) He also described the typical patterns of hysterical contractures of the limbs and some distinctive qualities of hysterical hemifacial spasm (see Figure 2).(89)

1.2.5.2 The British school

An avid reader of English fictional and dramatic literature, Charcot broke free from the Gallocentricism of his peers to establish strong ties with British neurological colleagues. Several British writers of the period had devoted attention to 'local hysterias'—disorders patterned on neurologic disease, often arising after emotional or minor physical trauma. These accounts possess greater symmetry with our current phenomenological descriptions of FD than do the more elaborate manifestations of Charcot's hysterical 'muses' at the Salpêtrière.

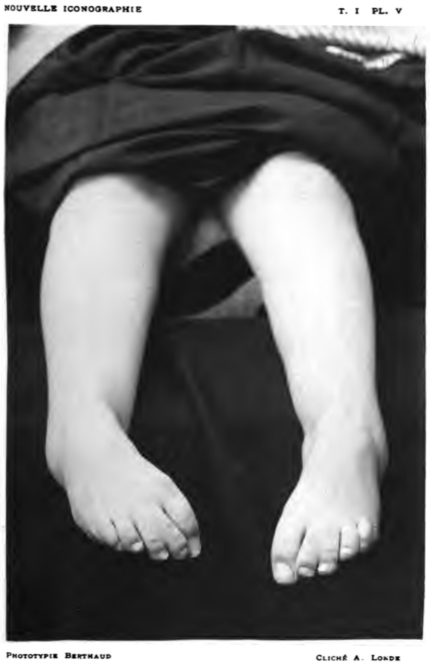
In 1837 Benjamin Brodie (1783–1862) published his 'Lectures illustrative of certain local nervous affections'.(90) He included torticollis and hemifacial spasm among these afflictions, as well as painful conditions of the limbs associated with vasomotor changes and oedema with similarities to complex regional pain syndrome (CRPS). Brodie observed the role of attention in these spasmodic conditions, which would lessen whenever the sufferer slept or was engaged in animated conversation. He suggested that symptoms might be precipitated by physical illness, minor injury or "some moral cause having a depressing influence on the constitution".

Thirty years later, Russell Reynolds (1828–1896) wrote of "disorders of motion and sensation dependent on idea".(91) He suggested that morbid rumination on an idea concerning disability produced many symptoms that mimicked organic disease of the nervous system. He included as an illustrative case that of a young boy with abrupt-onset painful flexor spasms in hands and feet following a coryzal illness. The boy's symptoms resolved fully following a rehabilitative program consisting of regular physical exercise and frequent enjoinders from medical staff

MASCARON GROTESQUE
DE L'ÉGLISE SANTA MARIA FORMOSA A VENISE

HÉMISPASME GLOSSO-LABIÉ HYSTÉRIQUE

a



CONTRACTURE HYSTÉRIQUE
RÉTRACTIONS FIBRO-TENDINEUSES

b

c

Figure 2: Images of hysterical spasm and contracture from Charcot's writings

a. L'Hémispasme Glosso-labie Hysterique (hysterical hemifacial spasm). In describing this condition, Charcot referenced a sculpture from the Santa Maria Formosa church in Venice, mentioned in John Ruskin's *The Stones of Venice*. Ruskin describes *"A head—huge, inhuman and monstrous—leering in bestial degradation"* which he presents as an example of the 'brutal mockery' and 'insolent jest' of Renaissance stonemasons. Charcot ponders whether the 16th century sculptor may have drawn inspiration from an encounter with an individual suffering from hysterical facial spasm.

b. Hysterical contracture of the foot, demonstrating the typical pattern of plantarflexion and inversion.

c. Hysterical contracture of the hand.

Images a. and b. from *La Nouvelle Iconographie de la Salpêtrière*, and image c. from Charcot's *Lectures on the Diseases of the Nervous System*.

that he "try and be a man", through which means, Reynolds asserts, the pathological idea was abolished. Importantly, Reynolds emphasised that such symptoms could arise in subjects with no prior history of mental illness, and that they could co-exist with organic disease.

James Paget (1814–1899), writing at a similar time, used the term "neuromimesis" to describe psychoneurotic replications of former disease states.(92) Minor injury as a common precipitant was noted—a gentleman who stubbed his toe subsequently developed "tetanic convulsions in the limb". The role of suggestion and social influence was also explored—the same gentleman later developed "sensations of spinal disease such as his brother died from", and it was noted that his sister had previously suffered from a severe case of hysteria. Subsequent writings on hysterical symptoms in veterans of the Franco-Prussian war ("*l'hysterique soldat*") and the victims of railway accidents (a condition known as "railway spine") expanded this body of literature.(61)

William Gowers (1845–1915) assimilated much of the work of these authors, as well as that of the American physician Silas Weir Mitchell (1829–1914), in his textbook "A Manual of Diseases of the Nervous System", published in two volumes

in 1886 and 1888. By this time the term hysteria had, in popular usage, become synonymous with simulation of disease. Gowers emphasised that general medical understanding was that it constituted a real disease, provoked by a "derangement of higher cerebral centres" and producing symptoms that varied in range, were sometimes severe, and were beyond the patient's will.(93)

Like Paget, he emphasised the importance of sociocultural influence. Gowers argued that the comparative rarity in England of the "elaborate" manifestations of hysteria common in France reflected differences in "national temperament" between the two countries. He also suggested that familial clustering of hysterical symptomatology might result from the "injudicious moral training received by the children of a hysterical mother" and the "conspicuously deficient judgement" of near relatives in perpetuating the affliction through overly solicitous behaviour. Such symptoms, he observed, could spread through "sympathetic imitation" and "moral contagion". Gowers expressed scepticism about some of Charcot's more sensationalistic approaches, including hypnotism and metallotherapy. In this he sided with the Salpêtrière's rival 'Nancy School', asserting that such therapies acted "through the mind".

Among protean expressions of hysteria, Gowers listed a number of "spasmodic affections" affecting the jaw, arm or leg, most commonly occurring after a fit or in the context of pain or local injury. He took a non-committal line with respect to pathophysiology, extolling the therapeutic benefit of "the moral influence of marriage" whilst not excluding the possibility of an underpinning "change in the finer nutrition of the nerve elements".

1.2.5.3 Les névroses traumatiques

Charcot built on these ideas to form a detailed account of post-traumatic hysteria. Many of his observations about hysterical contracture are retained in modern descriptions of FD and CRPS—the sudden onset (and offset) of symptoms, the persistence of contracture in sleep, its disappearance under chloroform anaesthesia, and the presence of pseudoclonus (then referred to as 'trepidation' of the limb), persisting long after the eliciting stimulus had been removed.(88) He

also documented autonomic disturbance and pain in a subset of patients with fixed contractures. Weir Mitchell had described similar symptoms—burning dysesthesia and dermatological changes—in gunshot casualties of the American Civil War in 1864, using the term 'causalgia'.(94)

Charcot's ideas concerning pathophysiology were prescient. He suggested that sudden strong emotion could provoke an 'obnubilation of consciousness' allowing 'involuntary and unconscious autosuggestion' to transform the sensation of injury into an *idée fixe*, a tenacious mental representation predicting disability. He noted that symptoms frequently appeared after a 'period of meditation', a lag period of months or even years, during which the unconscious motor belief was 'incubated'.(61) This functional model of traumatic neurosis was not universally accepted. Oppenheim in particular argued strenuously against it from the late 1880s until the start of World War I. Replicating older arguments that had circulated regarding "railway spine", he suggested that trauma might induce "fine organic changes" in the cerebral vasculature or glia of sufferers.(95)

Towards the end of his career Charcot's writings on the neuroses, hysteria in particular, were heavily criticised for perceived methodological and theoretical flaws. The theatricality of his hypnotic demonstrations prompted critics to cast aspersions about the validity of these displays. It was rumoured that Charcot's hysterical patients had duped him through studious simulation of his hysterical 'ideal'.(84,96) Some even suggested that the women had been coached by Charcot's coterie to enact these classical signs. An expression of the self-doubt provoked by this censure may be found in Charcot's preface to Pierre Janet's (1859–1947) PhD thesis, published in 1892, in which he adduces to support *"a thought often expressed in our lectures, namely that hysteria is largely a mental malady"*.(97) Despite this, Charcot continued to set forth a predominantly neurologic, rather than psychologic, model of the disorder, even in later lectures. At the centenary celebrations of his birth in 1925, Charcot's output in this area was branded *'une légère défaillance'* (a slight lapse) in an otherwise stellar career.(98)

1.2.5.4 Charcot's followers: divergent views

Charcot's students, Babinski and Janet, both expounded psychogenic models of hysteria. Babinski rejected his mentor's theories most vociferously, publishing 'A dismemberment of the traditional concept of hysteria' in 1919.(99) The extensor plantar reflex was among a number of signs laid out by Babinski as distinguishing features of organic neurological disease. Since these signs applied to pyramidal pathology they were of little use in distinguishing dystonia from hysterical contracture. Babinski opined that the traditional concept of hysteria was over-inclusive, encompassing some organic conditions as well as examples of deliberate feigning (malingering). He proposed a change in nomenclature to the term 'pithiatism'—from the Greek ειθω, meaning persuasion and ιατος, curable, 'curable by persuasion'—to emphasise the powerful role of suggestion in these disorders.

Janet took a more theoretic and less iconoclastic approach.(97) He ascribed hysterical symptoms to 'automatisms' produced by fixed ideas, generated within an elementary form of consciousness beneath that patient's ordinary conscious awareness. This "doubling" of self produced sensorimotor symptoms whose source was unknown to the primary personality. He proposed that a *misère psychologique*, a pathological lowering of mental energy, compromised the patient's ability to maintain unity of psychological functions, creating this *desagrégration* (dissociation).

Regarding the 'diathesis of contracture', Janet observed that paralysis and contracture were two sides of the same coin, each signifying loss of voluntary movement control and tending to oscillate within the same individual over time. He used Charcot's term 'amyosthenia' to describe loss of awareness of movement and suggested that "a transitory modification of the cells of the motor cortex" produced a sort of selective amnesia for kinaesthetic images, which precluded movement. He also drew some parallels between *la folie du doute* (obsessive-compulsive disorder) and hysteria. His conceptualisation is a prefigurement of a recently published neurobiological model of FMD, founded on a Bayesian model of the brain. Fixed abnormal beliefs are a core feature in both.

1.2.6 A parallel discourse: hysteria and other neurological disorders in nineteenth century art and literature

The late nineteenth century was a time of significant social and political upheaval. Gender dynamics were shifting—the demands of newly mechanised workplaces, implacable and unsleeping, called for a stoical, muscular, unemotional ideal of manliness. At the same time the rise of the suffragette movement threatened social order, prompting a forceful reassertion of the traditional feminine role as the 'angel of the house'.(100) This coincided with the professionalisation of medicine and increasing scientific liberalisation. As in previous historical epochs, many *fin-de-siècle* sociopolitical tensions were projected onto the 'screen' of hysteria, whose sufferers frequently reflected the images the projectionist expected to see. Physician-patient exchanges were part of a broader psychosocial correspondence. Hysteria's sensual character, and the vivid iconography that accompanied its study, captured the imagination of writers, artists and the general public alike. Hysteria was thus both a product of the Zeitgeist, and one of its architects.

1.2.6.1 The French political backdrop

In allegiance with the Catholic Church, Napoleon III's Second Empire had suppressed French medical teaching of materialistic concepts, deeming them too subversive. After nearly twenty years of imperialist rule the empire fell in 1870, when the Third Republic was established. This regime shared an ideological affinity with the medical profession, then undergoing a rapid phase of disciplinary expansion. Physicians, liberated from the Molièresque mode of doctor as a hapless buffoon, enjoyed newly elevated social standing.(96) Looking to secure their status and capitalise on more liberal governmental attitudes, they sought stable patient populations to conduct scientific research and expand their sphere of technical expertise.

At this time Charcot was in the process of transforming La Salpêtrière from a 'warehouse' for society's female outcasts into a modern teaching hospital. His work on hysteria began "quite involuntarily and by force of circumstance"(101) when the Salpêtrière building that housed epileptics and hysterics fell into disrepair and

these patients were sent to his wards. His drive to impose a rational framework on the seeming chaos of hysterical disorder stemmed from his positivist worldview and passion for clinical observation, as well as a more prosaic need to establish hysteria as a respectable subject for research in order raise the profile of his service and maintain its income stream. When Charcot's desire to define met with the hysterics' characteristic suggestibility a dynamic was established which saw the disorder reconfigured in his own image of it. Whilst elements of his descriptions seem to represent core features of functional neurological disorder—those which are still recognised today—the archetypal "grande attaque" of hystero-epilepsy appears to have been a peculiar Charcotian elaboration. Reports of such manifestations fell sharply after his death and have not been reported in other settings.(102)

1.2.6.2 Hysterical iconography

Charcot perceived a fundamental reciprocity between medicine and art:

> *"The doctor is inseparable from the artist. One is the guide of the other; they help each other".*(103)

This mutuality might not be as obvious to the contemporary neurologist, whose practice is driven by the apparent objectivity of evidence-based medicine. But art and science have never been entirely stable categories—each informs, and is informed by, their cultural milieu, and there is a continual exchange of ideas between them.

Two journals, the *Iconographie Photographique de la Salpêtrière*, published in three volumes between 1877 and 1880, and *La Nouvelle Iconographie de la Salpêtrière*, produced from 1888 until the end of the First World War, provided a visual reference for neurological and psychiatric diagnosis. Alongside clinical photographs, they contained the 'scientific artworks' of Dr Paul Richer, an anatomist and sculptor who worked closely with Charcot and shared his visual sensibilities (together they authored two art historical texts concerned with retrospective diagnosis of hysteria and neurological deformity in medieval religious portraiture).(104) The *Iconographie Photographique de la Salpêtrière*

focused mainly on female patients in various phases of hysterical seizure. The images were often highly sexualised, demonstrating a range of "attitudes passionales" (Figure 3). With exposure times in the region of 20 minutes, these were in the true sense of the word 'poses', many captured during periods of catalepsy, when patients would frequently maintain postures for several hours.(105) These voyeuristically charged photographs were widely circulated within and without medical circles, strongly influencing ideas about hysteria in popular culture.

The visual art of the early 20th century reflects the influence of these journals on artists seeking innovative ways to represent the human body and inner emotional complexity. Hysterical motifs—headless female forms in various distorted poses—began to appear in the paintings of Max Ernst, René Magritte and others (see Figure 4a). The hysterical female, with her implied intellectual liberation and free-spiritedness, was thus reinvented as a surrealist 'hero'. André Breton (1896–1966), one of the founders of the surrealist movement, became fascinated with psychiatry whilst caring for shell-shock victims as a medical student. He defined surrealism as 'pure psychic automatism', denoting a raw form of thought, stripped of any analytic, moral or aesthetic concerns.(106)

Figure 3: Plates from *Iconographie Photographique de la Salpêtrière.*
Some phases of hysterical seizure—Attitudes Passionnelles ('ecstasy' on the left and 'mockery' on the right) and Hystéro-épilepsie (contracture) in the centre.

Breton and other surrealist poets adopted the technique of automatic writing, employed by Janet to delineate subconscious fixed ideas in hysterical patients, to signify a rejection of the rational world through elementary psychic release.

For several months in 1917 Breton worked under Babinski at La Pitié hospital in Paris. Though Babinski's clinical approach to hysteria held less poetic appeal than Freud's theoretic line, Breton had an enduring admiration for the neurologist. He even included a description of Babinski's neurological examination in The First Surrealist Manifesto, published in 1924:

> *"I have seen the inventor of the cutaneous plantar reflex at work; he manipulated his subjects without respite, it was much more than an "examination" he was employing; it was obvious that he was following no set plan. Here and there he formulated a remark, distantly, without nonetheless setting down his needle, while his hammer was never still. He left to others the futile task of curing patients. He was wholly consumed by and devoted to that sacred fever."*(107)

Thus described, the neurological examination itself sounds like a form of 'mental automatism', akin to those documented in hysterical patients.(106)

Other artists, such as Egon Schiele (1890–1918), appropriated the visual tropes of hysteria as a mode of stylistic self-expression. His self-portraits display a range of abnormal postures, prompting speculation that he might have suffered from dystonia (Figure 4b), though there is little evidence from contemporary sources to support this.(108) He may have used these devices to signify madness and pain—the desirable traits of the artist. Alternatively, he may simply have been driven to paint this way for commercial reasons—in Freud's Vienna alienation was *á la mode*, making paintings incorporating these motifs highly marketable.(109)

Amedeo Modigliani (1884–1920) often evoked sensuousness in portraiture with elongation, curvature, and torsion of upper body parts that resembles dystonia. This is particularly noticeable in paintings of Jeanne Hebuterne, his common-law wife. The pose shown in Figure 5a, with two fingers lightly touching the tilted face, is typical of a sensory trick used in torticollis. There is no hard evidence that she

had cervical dystonia, although several photographs of her show head angulation and a hypertrophied right sternocleidomastoid muscle. The day after Modigliani died from tuberculous meningitis, Jeanne jumped from a fifth-floor window, killing herself and their unborn child.(2)

Constantin Brâncusi (1876–1957) was a Romanian artist who made his career in France and was a friend and neighbour of Modigliani's. He sought to achieve realism not through fidelitous visual representation but by revealing hidden meanings or essences.(110) He may also have adopted the motif of the sensory trick of dystonia to denote feminine complexity (Figure 5b).

1.2.6.3 Neurological disease in literature

Advances in medical science during the 19th century had coincided with the development of the novel as the dominant literary form. Influences extended in both directions—the use by writers of medical realism derived from new scientific knowledge, and the recognition by doctors that the narrative methods used in novels could help to organise information in clinical accounts. If correctly interpreted, Charles Dickens (1812–1870) may have been using the novelist's sharp eye for character detail to pick out examples of dystonia on the bustling streets of London, with similarities to James Parkinson's "field neurology" method for the shaking palsy 35 years earlier.(2) Dickens' David Copperfield (1850) has several possible examples of dystonia—the repeated use of the epithet "writhing" for the malevolent Uriah Heep; and the vain Mr. Sharp, who is described as "carrying his head on one side, as if it were a little too heavy for him." Mr. Creakle, young David's harsh and dictatorial headmaster, "had no voice, but spoke in a whisper," suggesting spasmodic dysphonia.(111) In line with Victorian physiognomy, these grotesque physical attributes were used to call attention to unattractive features of their inner selves.

Dickens' portrayal of *Little Dorrit's* Mrs Clennam—confined to her home by "nervous weakness" provoked by her husband's profligate, philandering lifestyle—is unforgiving and censorious. Described as "cold as stone, but raging as the fire"(112), her lurid externalisation of inner suffering is a parody of the preferred

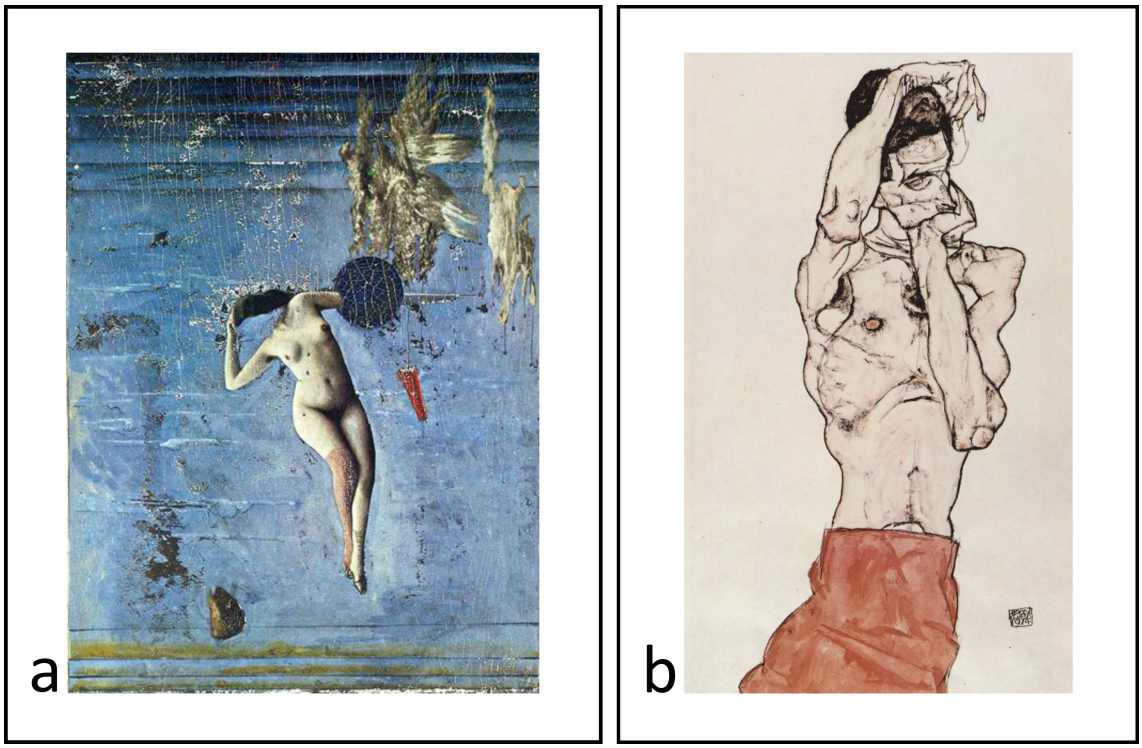


Figure 4: Motifs of hysteria and dystonia in 20th century visual art

a. Max Ernst's *Pleidades*, 1921
b. Egon Schiele's *Self portrait,* 1914

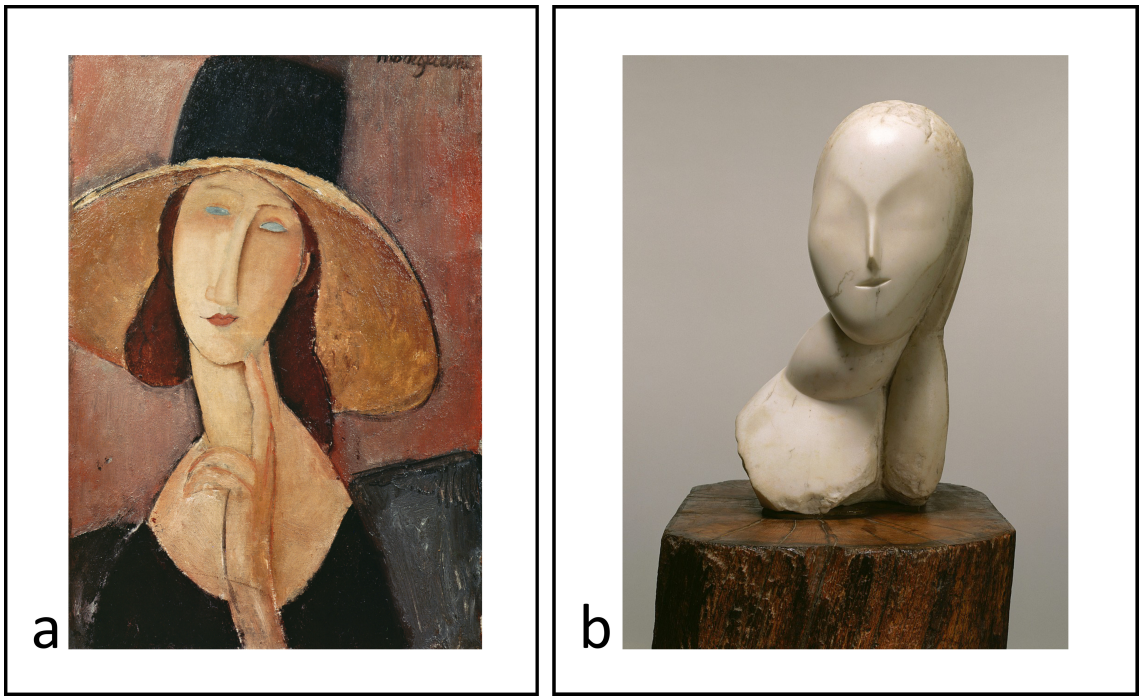


Figure 5: Representation of the *geste antagoniste* in painting and sculpture?

a. Modigliani's *Jeanne Hébuterne with Large Hat*, 1918
b. Brâncusi's *Muse*, 1912

model of Victorian womanhood, defined by quiet submission, contented domesticity and moral guardianship. Themes of sexual repression and unhealthy fixity on the past, drawn from contemporary medical texts on hysteria, are explored. Dickens toys with the question of agency, without settling on a particular stance. He may have been influenced by Robert Brudenell Carter's (1828–1918) *On the Pathology and Treatment of Hysteria*, published four years before *Little Dorrit*.(81) In this essay Carter paints an unflattering portrait of the 'tertiary' hysteric— a woman thwarted in her romantic or maternal ambitions who voluntarily initiates symptoms to achieve emotional gratification.

Émile Zola (1840–1902) established the literary school of naturalism, which sought to describe reality, in all its harshness and vulgarity, with the greatest of precision. In pursuit of medical realism he devoured medical textbooks and was known to attend Charcot's leçons du Mardi. Zola penned a cycle of 20 novels based on the hereditarian doctrine of degeneracy, exploring the proliferation of the 'taint' of mental instability within the Rougon-Marquart family.(113) These novels reflect traditional gendered notions of disease. A small number of the female characters in this cycle are portrayed as having hysteria, in all cases as the result of psychosexual pathology—either sexual frustration or excess. A separate novel, *Lourdes*, explores hysteria through the prism of faith healing. Charcot's influence may be observed in the positivistic stance of the narrator, the pronouncements of Marie's neurologist Dr Beauclair— *"elle y serait sûrement guérie, si elle était certaine de l'être"* ("she would surely be cured, if she were sure of it")—and the similarities between Marie's autohypnosis and semi-catatonic behaviour at the shrine and Charcot's accounts of his hypnotic manipulations of 'Ur' (Augustine).(114)

1.2.7 The 20th century: Freud, shell shock, and the 'decline' of hysteria

Freud moved away from Charcot's hereditarian determinism and Theodor Meynert's (1833–1892) organic psychiatry to build an entirely theoretic model of hysteria in which traumatic libidinous memories were converted into somatic symptoms.(115) This process, he conjectured, discharged the negative energy of the sufferer's "strangulated affect" and kept the offensive idea repressed. He

initially rendered his conversion theory in pseudo-neurological terms, describing the brain's "tendency to keep intracerebral excitation constant" by channelling of affective energy to regions governing motor and sensory activity.(116) Later he abandoned such terminology entirely in favour of a topographic model of the unconscious, preconscious and conscious mind. Onto this he grafted the notions of the 'it' or *id* (the native state, governed by the pleasure principle), the 'I' or *ego* (allowing socialisation and delayed gratification) and the 'I above' or *superego* (responsible for self-policing according to rules and cultural norms). Conversion could resolve conflict between these psychic levels, which was its primary gain. The concept of secondary gain—the material advantages of assuming the sick role, such as avoidance of work, or financial benefits—was also introduced.(117)

Freud's ideas, seductive in their novelistic internal cohesion and accessibility, became deeply embedded in psychiatric practice, particularly in the USA. As his work progressed, however, the theories were undermined by a substratum of symbolic interpretation, which grew ever more complex and contradictory over time. Anti-psychoanalytic sentiment gradually gathered momentum, particularly in the UK. Philosophers began to weigh in against the Freudian hagiography. Karl Popper (1902–1994) cited his falsifiability principle to demonstrate the unscientific basis of Freud's ideas.(118) Ludwig Wittgenstein (1889–1951) emphasised the impossibility of a singular veridical interpretation of Freudian symbolism.(119) On this basis Aubrey Lewis, first professor of psychiatry at the Institute of Psychiatry in London, dismissed Freud's model of hysteria as "false and absurd".(120)

Shell shock, the term used to describe myriad physical and psychological ailments of infantrymen serving in the trenches of World War I, divided opinion among neurologists and psychiatrists working at the time. The ideas and arguments in circulation bore much resemblance to those that were exchanged regarding hysteria in Charcot's era. Some, such as Frederick Mott (1853–1926), sought a microstructural basis for these symptoms.(121) Lewis Yealland (1884–1954), working at Queen Square, adopted a functional model and applied electrical therapy as a tool of suggestion, later drawing harsh criticism for these practices.(122,123) Therapies founded in Freudian principles were delivered in

several centres dedicated to the study and treatment of the war neuroses, with limited success.(124) As in the nineteenth century, social pressures played a role in shaping neurologists' practice. Some Victorian notions of hysteria—as an expression of low moral fibre or flawed character—resurfaced and were applied to this new disorder without clear cause or cure. The psychiatrist Emil Kraepelin (1856–1926) advised against

"an excessively liberal granting of compensations which might lead to a sharp rise in the number of cases and claims"(125)

and spoke derisively about the *Kriegszitterer* ('war shakers')—soldiers who received charitable donations by standing on street corners making a public show of their suffering.(126)

Shortly after the war, Henry Head (1861–1940) wrote "An Address on the Diagnosis of Hysteria", published in the British Medical Journal, a brief review that was ahead of its time in some respects.(127) He suggested that inflexible and rigidly dualistic approaches to the disorder were problematic:

"Rival theorists contend for the truth of dogmas they have elevated to the solemn position of a religious cult…the treatment of the functional neuroses has become a special branch of medical practice, carried out by men who see comparatively little of organic disease. At the same time the general physician…rarely consider(s) how large a part the mind plays even in the symptoms of gross structural disease."

He also laid out several discriminatory diagnostic signs. In cases of hysterical posturing he described active resistance to movement both away from, and in the same direction as the spasm. Head argued that all hysterical manifestations were of a positive nature—even apparently negative symptoms, such as sensory anaesthesia, arose because of an active 'refusal to accept impressions'. There was a recognition that such 'refusals' were part of the spectrum of normal experience (using the example of 'psychical blindness' of one eye during direct ophthalmoscopy), and a suggestion that this capacity might be abnormally heightened in sufferers of hysteria.

Academic interest in hysteria steadily declined after World War I.(128) As the disciplines of neurology and psychiatry became more divergent, hysteria was

consigned to a 'no-man's land' between the two. The question of feigning, strongly asserted by the war neuroses, remained unanswered. Later, Slater's work on misdiagnosis in hysteria and Marsden's reclassification of the focal dystonias introduced a bias away from considering functional diagnoses. Though there has been a resurgence of interest in this area in the last 15 years, sceptical attitudes, and an aversion to engaging with patients with functional disorders remain quite common among neurologists.(129)

1.3 The phenomenology of organic dystonia

The phenomenology of dystonia is as diverse as its aetiology, but a number of broad phenotypes are described.

1.3.1 Genetic (early-onset generalised) dystonia

Isolated dystonia with onset in childhood may be sporadic or hereditary. Several genetic mutations giving rise to this phenotype, including DYT1 and DYT6, have been described.(130) It typically begins distally, most frequently in the lower limb, and subsequently generalises. The coincident activation of agonist and antagonist muscles leads to twisting movements and abnormal postures. These are initially action-induced and may be task-specific—walking backwards or running characteristically provides relief in DYT1 dystonia.(131) Dystonic muscle activity may spread proximally, either to muscles not directly involved in the action within the same limb, or to the contralateral limb (overflow and mirror dystonia respectively).(132) It may be suppressed by willed action (the *geste antagoniste* or sensory trick).(133)

1.3.2 Adult-onset focal or segmental dystonia

When dystonia emerges after the 3rd decade it usually remains confined to one or two broad muscle groups. Most of these subtypes are idiopathic, though some cases result from genetic mutations with reduced penetrance (the mutation in TOR1A responsible for DYT1 dystonia, for example, has only 30%

penetrance).(132) The phenomenology is determined by the anatomical distribution:

1.3.2.1 Cervical dystonia

Depending on the pattern of neck and shoulder muscle involvement patients may have torti- (rotation), latero- (lateral flexion), antero- (forward flexion) or retro-collis (extension) of the neck.(134) Oscillatory activity between opposing muscles may produce dystonic head tremor, usually with a horizontal rotational no-no component.(135) A refinement of this phenomenological classification—the 'COL-CAP' concept—was recently proposed.(136) This further segregates the four main groupings according to the relative contribution of muscles acting across the atlanto-axial joint—giving rise to torti-, latero-, antero-and latero-*caput*—and those acting across the cervical vertebrae, responsible for torti-, latero-, antero- and retro-*collis*.

1.3.2.2 Blepharospasm-oromandibular dystonia, or Meige syndrome

Dystonic contraction of the periorbital muscles of facial expression causes intermittent or sustained episodes of forceful eye closure (blepharospasm), often preceded by a prodromal phase of eye irritation. This may occur in conjunction with jaw opening or closure or tongue protrusion, due to involvement of the masticatory and lingual muscles.(50,137)

1.3.2.3 Laryngeal dystonia (spasmodic dysphonia)

Two subtypes generate different symptoms. 'Abductor' dystonia, whereby the vocal cords are pulled apart, causes speech to lose volume and take on a whispering quality. 'Adductor' dystonia, in which the cords are pulled together, produces strangulated speech, characterised by sudden changes in pitch and volume. Vocal tremor can occur with both forms.(132)

1.3.2.4 Focal upper limb dystonia (writer's cramp)

The specific act of writing activates dystonic contractions in the wrist and finger flexors and extensors, generating abnormal postures, painful cramping or tremor that interferes with task execution. Over time this activity may be triggered by other activities involving fine motor manipulation, such as using tools.(50)

Involvement of contiguous muscles (segmental disease) is frequent, for instance many patients with cervical dystonia also have dystonic upper limb tremor.(138) Though familial cases of writer's cramp and cervical dystonia have been described, the majority of cases are idiopathic. Cervical and upper limb dystonia emerge with greatest frequency in the 4th and 5th decades, with cranial dystonia tending to manifest later (6th decade onwards).(139)

1.3.2.5 Occupational dystonias

These involve the specific disruption of craft skills in trained individuals, including professional musicians and sportspeople. They can present with a focal disturbance of hand function during playing or, in wind instrument players, with an orolingual dystonia, known as embouchure dystonia. Musician's dystonia develops in 1-2% of professional musicians, with a male predominance. Classical instrumentalists seem to be more susceptible than improvisational performers. In over a third of cases there is a family history of dystonia.(140)

1.3.3 Secondary dystonia

Most examples of hemidystonia result from traumatic, ischaemic, inflammatory, or infectious neurologic insults. Lesions of the basal ganglia and thalamus are the most frequent cause of such presentations.(45,141) Symptomatic craniocervical dystonia has more heterogenous pathological substratum—cases involving cerebellar, brainstem and spinal cord pathology have been reported.(142–146) Mass lesions in the posterior fossa can cause cervical dystonia that remits after excision of the tumour.(147,148) Cerebellar strokes, though a rare cause, can give rise to paroxysmal, cervical or hemidystonic phenotypes.(149–151) Brainstem

lesions in patients with dystonia involve several fibres of passage (including rubro-thalamic and meso-striatal dopamine pathways) with reduced basal ganglia activity demonstrated on positon emission tomography (PET).(152)

The phenotypic features of dystonia arising from thalamic pathology differs according to which subnuclei are involved, with those corresponding closely with the striatum producing writhing athetoid movements and those most intimately connected with cerebellar circuits resulting in more jerky, tremulous motion.(153) Parietal strokes and mass lesions have also been associated with focal hand, cranial, cervical and hemidystonia.(154–157)

Drug-induced dystonia occurs in a number of clinical settings. Patients treated with anti-dopaminergic drugs, such as metoclopramide, can acutely develop painful dystonic reactions, associated with tonic deviation of the eyes, retrocollis and orolingual dystonia, known as oculogyric crises.(158) Long-term dopaminergic blockade with neuroleptic medications such as haloperidol provokes tardive dyskinesia in a subset of patients. Usually this syndrome involves more dynamic choreic movements of orofacial and limb muscles.(159)

Tardive dystonia is much less common than tardive dyskinesia, occurring in 3-4% of individuals treated with long-term dopamine receptor antagonist agents.(160,161) A distinctive pattern of retrocollis and truncal dystonia with internal rotation of the arm, elbow extension and wrist flexion occurs in younger patients, often with shorter latency from first drug exposure than is usual in tardive dyskinesia.(162) Milder cases resemble adult onset idiopathic dystonia. Large surveys of tardive dystonia have shown that it is not restricted to schizophrenic patients and can occur with milder dopamine receptor blocking drugs such as prochlorperazine and metoclopramide.(162)

Levodopa therapy in Parkinson's disease is eventually complicated by motor fluctuations, which may be associated with the appearance of painful dystonia in the extremities or trunk as the levodopa effect wanes towards the end of each dose cycle.(163)

1.3.4 Dystonia-parkinsonism

The conjunction of dystonia with parkinsonism (tremor, bradykinesia and rigidity) is observed in a number of genetic conditions. A rapid onset, often in response to physical or emotional stress, is suggestive of DYT12, whereas an X-linked pattern of inheritance implies DYT3 mutation.(164,165) The presence of other neurological features, such as spasticity or cognitive impairment, expands the differential to encompass disorders such as Wilson's disease and NBIA (neurodegeneration with brain iron accumulation).(59)

1.3.5 Myoclonus dystonia

The conjunction of dystonia with 'lightning' jerks, or myoclonus, is observed in a number of genetic conditions. DYT11, caused by a mutation in the ε–sarcoglycan gene, is responsible for 65% of familial cases, but another unknown gene, on chromosome 18 (DYT15) can give rise to the same phenotype.(166,167) Myoclonus may also complicate DYT1 and dopa-responsive dystonia (DYT5).(168–170)

1.3.6 Paroxysmal kinesigenic, non-kinesigenic and exercise-induced dystonia

These rare genetic conditions present in childhood, or early adulthood and involve sudden onset, stereotyped, dyskinetic or dystonic movements. In the kinesigenic variant these are precipitated by sudden movements, which cause brief motor disturbance—comprising elements of dystonia, chorea and ballismus—lasting seconds to minutes. Mutations in the proline-rich transmembrane protein 2 (PRRT2) gene give rise to this phenotype (along with hemiplegic migraine and episodic ataxia in some pedigrees), which typically demonstrates a good response to carbamazepine.(171,172)

Nonkinesigenic variants may be brought on by stress, fatigue, alcohol or caffeine; attacks last a little longer and may be separated by many months.(172) In contrast to the other genetic paroxysmal dyskinesias, this form can be associated with

painful dystonia. Only one gene has been characterised—encoding the paroxysmal nonkinesigenic dyskinesia protein, myofibrillogenesis regulator 1.(173) A second locus has been identified on chromosome two in a family of European ancestry.(174) Six other pedigrees have been described, for which the pathogenic loci are unknown.

Episodes of exercise-induced dyskinesia, which can also be triggered by exposure to low temperatures, characteristically occur on a weekly basis and have the longest duration (30 to 180 minutes). The phenomenology may vary substantially between individuals, but intra-individual variability is rare.(175) Mutations in the SCLA21 gene, which codes for the glucose transporter type 1 (GLUT1) protein, have been linked with this phenotype in 14 families. Adherence to a ketogenic diet can ameliorate symptoms.(171,172)

1.4 The phenomenology of functional dystonia

FD encompasses a broad phenotypic spectrum, which overlaps with that of its organic counterpart. Distractibility, one of the core features of functional motor disorders, can be difficult to distinguish from the task-specific alterations in motor performance observed in idiopathic focal and generalised dystonia. Three broad functional phenotypes that have been outlined in the literature are detailed below, though these archetypal presentations account for only a portion of cases seen in clinical practice. Instances of FD involving more gradual onset of symptoms, or more dynamic posturing, present the greatest diagnostic challenges.

1.4.1 Fixed functional dystonia

The most striking presentation of FD is fixed posturing of a limb. This most commonly affects the foot, but spread to other regions occurs frequently. In two thirds of cases this is preceded by minor injury to the afflicted limb. Onset is typically sudden, but may take up to a year to fully manifest, and the posture may even be retained in sleep, leading to wasting and contractures.(176) In the feet plantarflexion, inversion and clawing of the toes is typical. Upper limb manifestations involve flexion at the metocarpophalangeal joints, particularly of

the fourth and fifth digits, with sparing of the thumb and index finger. Rarer cases involving the neck, shoulder and jaw have been described.(177) FD may be mobile, but overflow and mirror dystonia does not occur and the phenomenon of *geste antagoniste* is considered rare.(178)

Pain is a frequent corollary and a major feature in forty per cent of cases. The other signifiers of CRPS—sudomotor and trophic skin and hair changes—are present in a significant minority, with 20% meeting the criteria for this disorder in one case series, highlighting the substantial overlap between these two conditions.(176) The phenomenology may by complicated by other disorders of movement, including tremor, myoclonus and give-way weakness.

1.4.2 Paroxysmal functional dystonia

This may be distinguished from its organic counterpart by the unusual age of onset, atypical triggers and intra-individual phenomenological variability. Tremor may also be present, a feature not reported with any of the organic subtypes.(175) Symptoms may evolve from an exaggerated startle reaction. Response to suggestion, non-physiological manoeuvres or placebo may be demonstrated. There is some crossover with dissociative seizures (non-epileptic attacks), as responsiveness may be altered during attacks.(177)

1.4.3 Cranial functional dystonia

In contrast to Meige syndrome, functional cranial dystonia involves asynchronous contraction of upper and lower facial muscles. Spasms also tend to be more sustained and can be painful. When the lower face is affected unilateral depression of the lip with contraction of the platysma is common. Upper facial involvement may cause constant tonic eye closure or 'psychogenic pseudoptosis' (eye closure without prominent muscle activity). Variants mimicking hemifacial spasm may be distinguished by the absence of the 'other Babinski sign'—the synchronous contraction of frontalis and orbicularis oculi, giving rise to eye closure with eyebrow elevation—observed in organic hemifacial spasm.(177,179)

1.5 Psychopathology in organic dystonia

A broad range of non-motor features, including disruption of sleep, cognition and sensory processing have been described in dystonia.(180) Most germane to this research are the psychiatric features, which are reviewed here.

1.5.1 Genetic (early-onset generalised) dystonia

Some mutations responsible for generalised dystonia have non-motor effects that include psychiatric symptomatology. DYT1 (early-onset generalised dystonia) carries a relative risk of recurrent major depressive disorder that is significantly increased in both manifesting and non-manifesting carriers, suggesting this is an endophenotypic feature. Depressive symptoms begin earlier in mutation carriers but there is no correlation with motor severity.(181)

A much larger range of psychiatric morbidity has been reported with the DYT11 (myoclonus-dystonia) gene mutation. Generalised anxiety and obsessive-compulsive disorder are most strongly associated but affective or phobic disorders and alcohol dependence are also common.(182) In comparisons with 'diseased' controls (non-DYT11 hyperkinetic movement disorder or alcohol-responsive tremor), the association with anxiety and obsessive-compulsive disorders remained significant.(183,184) Unlike DYT1, manifesting and non-manifesting carriers have divergent rates of psychopathology, and psychiatric symptoms may correlate with motor disease severity.(185)

As regards other genetic dystonias, only a handful of small studies have been done. A single case-control study of patients with DYT3 (X-linked dystonia-parkinsonism) suggested anxiety spectrum symptoms were most common, though mean depression scores were also significantly greater.(186) DYT5 (dopa-responsive dystonia) comprises mutations with different psychiatric tendencies (affective and obsessive-compulsive disorders with GTP-cyclohydrolase deficiency(187–189) and anxiety or behavioural problems with sepiapterin reductase deficiency(190)). Individuals with DYT12 (rapid-onset dystonia-parkinsonism) may be predisposed to affective disorder and psychosis.(191)

Relatively newly recognised genetic dystonic disorders, such as ADCY5-related dyskinesia, have also been reported to possess a psychiatric dimension.(192)

1.5.2 Adult-onset idiopathic focal dystonia

Although early commentary on the personality traits associated with idiopathic focal dystonia (IFD) was anecdotal and somewhat judgmental, the impression that psychiatric disorders are excessively prevalent in some IFDs has been supported by case-controlled studies.

Psychiatric abnormalities may be endogenous to IFD rather than secondary to disability or disfigurement. Such symptoms frequently precede the onset of dystonia and, for the most part, do not correlate with its severity. Several authors have documented a greater burden of psychiatric disturbance in IFD patients than those with comparable regional peripheral nerve lesions. Families of patients with IFD have increased rates of mental illness, implying a common genetic substrate. Each IFD subtype has a slightly different psychological profile (Table 1).

1.5.2.1 Cervical dystonia

Cervical dystonia (spasmodic torticollis) has the strongest tradition of psychological attribution. Mid-twentieth century studies focused on its correlation with 'neurotic' personality traits such as shyness, anxiousness and obsessiveness.(193–195) These earlier observations are corroborated by a recent analysis of 86 IFD patients, most of whom had cervical dystonia.(196) Personality disorders, particularly cluster C avoidant or obsessive-compulsive ones, were more prevalent than in a population sample. There were higher neuroticism scores, especially in women. Greater agreeableness and conscientiousness but lower scores for openness suggested a conventional, conservative mind-set.

A current or lifetime psychiatric disorder is present in 92% of patients with cervical dystonia, compared with 35% in the general population.(197) The most consistent findings have been a two to four times higher rate of depressive symptoms.(197–200) Most(197,200,201) but not all(199) also report higher rates

of disorders on the anxiety spectrum, particularly social phobia. Obsessionality and compulsiveness are over-represented in mixed cohorts of focal dystonia consisting mainly of craniocervical cases.(198,202–204)

1.5.2.2 Blepharospasm-oromandibular dystonia

Data from recent studies of psychopathology in this condition is conflicting. Some have reported higher rates of depressive symptoms compared with controls,(199,202) whereas others found no significant difference.(205,206) Findings on scores for obsessive-compulsive symptoms, whilst somewhat more convincing, also lack consistency.(199,202,205–207)

1.5.2.3 Laryngeal dystonia

There are few case-controlled studies of psychiatric comorbidity. A comparison with vocal cord paralysis, based on the DSM-IV structured clinical interview, demonstrated significantly increased rates of current psychiatric disorder in laryngeal dystonia, (42% vs. 20%). This correlated with the severity of voice impairment. Significantly more laryngeal dystonia patients recalled a stressful antecedent event.(208)

1.5.2.4 Focal upper limb dystonia (writer's cramp)

The relatively small scale of published studies does not provide compelling evidence for psychopathology in focal hand dystonia. In one survey of 40 patients, rates of obsessive-compulsive and depressive disorders were elevated above population levels but there was no control group and some cases of musician's dystonia were included.(209)

Table 1: Studies of psychiatric disorders in adult onset focal dystonia

Study	Patients/ Controls	Assessments	Results (IFD vs Control)
Blepharospasm			
Bihari et al.(207) **(1992)**	**21 BSP** 19 HC	OCD rating scale	**Higher OCD scale scores**
Broocks et al.(206) **(1998)**	**13 BSP** 13 HFS	Psychiatric interview (SCI-DSM-III) SCL-90/ OCD rating scale	**Higher OCD scale scores**
Munhoz et al.(210) **(2005)**	**30 BSP** 30 HFS	Psychiatric interview (SCI-DSM-IV) OCD rating scale	No significant differences
Fabbrini et al.(199) **(2010)**	**28 BSP** 26 HFS 23 HC	Psychiatric interview (SCI-DSM-IV) Depression, anxiety and OCD rating scales	**Higher psychiatric burden** Psychiatric disorder preceded BSP in ~75%
Fontenelle et al.(205) **(2011)**	**22 BSP** 31 HFS	Psychiatric interview (SCI-DSM-IV) Depression, anxiety and OCD rating scales	No significant differences
Cervical Dystonia			
Bihari et al.(200) **(1991)**	**22 CD** 29 HC	SCL-90/ Depression and OCD rating scales	**Higher scores for depression, anxiety, OCD and somatisation**
Gundel et al.(201) **(2001)**	**119 CD** Population reference	Psychiatric interview (SCI-DSM-IV) SCL-90/ Social phobia and social anxiety rating scales Life events and general health questionnaires	**10 x more social phobia** **2.4 x more affective disorder** Life event in year prior to symptom onset in 50%
Gundel et al.(197) **(2003)**	**48 CD** 48 AA Population reference	Psychiatric interview (SCI-DSM-IV) SCL-90/ Social phobia scale	**Higher lifetime prevalence of psychiatric disease:** CD 92%, AA 60%, population 35% **Higher self-rated social phobia**
Fabbrini et al.(199) **(2010)**	**34 CD** 32 HC	Psychiatric interview (SCI-DSM-IV) Depression, anxiety and OCD rating scales	**Higher rate of mood disorder** Psychiatric disorder preceded CD in 68% of cases
Laryngeal Dystonia			
Gundel et al.(208) **(2007)**	**48 LD** 27 VCP	Psychiatric interview (SCI-DSM-IV) SCL-90/ Life events and general health questionnaires	**Higher rate of current psychiatric diagnosis:** 42% vs. 20% (depression, anxiety, adjustment disorder) Correlated with severity of voice impairment
Fabbrini et al.(199) **(2010)**	**16 LD** 12 HC	Psychiatric interview (SCI-DSM-IV) Depression, anxiety and OCD rating scales	No significant differences

Key: AA = Alopecia areata; BSP = blepharospasm; CD = cervical dystonia; DC = diseased controls (with non-dystonic neurological disease); DSM = Diagnostic and Statistical Manual; FHD = focal hand dystonia; HC = healthy control; HFS = hemifacial spasm; IFD = idiopathic focal dystonia; LD = laryngeal dystonia; OCD = obsessive compulsive disorder; OR = odds ratio; SCI = structured clinical interview; SCL-90 = Symptom Checklist-90, a screening questionnaire for a broad spectrum of psychopathology, including depression, anxiety and obsessionality; UL = upper limb; VCP = vocal cord paralysis.

Table 1: Studies of psychiatric disorders in adult onset focal dystonia

Study	Patients/ Controls	Assessments	Results (IFD vs Control)
Upper Limb Dystonia			
Kubota et al.(211) **(2001)**	**12 WC** 12 DC 12 HC	OCD rating scale	**Higher OCD scores than both control groups**
Fabbrini et al.(199) **(2010)**	**11 UL dystonia** 10 HC	Psychiatric interview (SCI-DSM-IV) Depression, anxiety and OCD rating scales	No significant differences
Voon et al.(209) **(2010)**	**39 FHD** Population reference	Psychiatric interview (SCI-DSM-IV) OCD, depression and anxiety rating scales	**Higher lifetime rates of** • **OCD** (x 6) • **Depression** (x 1.5) **Higher anxiety and OCD scores**
Mixed Focal Dystonia			
Cavallaro et al.(203) **(2002)**	**76 IFD** 129 HC	Psychiatric interview (SCI-DSM-IV) OCD rating scale	**Higher rates of OCD (20% vs. 1%)** OCD preceded motor symptoms
Lencer et al.(196) **(2009)**	**86 IFD** Population reference	Psychiatric interview (SCI-DSM-IV) Personality trait checklist	**Lifetime prevalence of psychiatric disorder 71%** • Social phobia OR 21.6 • OCD OR 8.4 • Mood disorder OR 3.0 Most predated motor symptoms
Barahona-Corrêa et al.(202) **(2011)**	**45 IFD** 46 DC 30 HC	Psychiatric interview (SCI-DSM-IV) SCL-90/ OCD rating scale	**Higher OCD scale scores** **Higher anxiety and somatisation scores** (versus HC only) No correlation with disease severity or duration
Mula et al.(204) **(2012)**	**19 IFD** 18 HFS 23 HC	Psychiatric interview (SCI-DSM-IV) SCL-90/ Anxiety and OCD rating scales	**Higher rates of OCD** (versus HC)
Lehn et al.(198) **(2014)**	**103 IFD** 78 HFS 93 HC	Depression, anxiety and OCD rating scales	**Higher OCD and anxiety scores** **Higher Depression scores** (versus HC)

Key: AA = Alopecia areata; BSP = blepharospasm; CD = cervical dystonia; DC = diseased controls (with non-dystonic neurological disease); DSM = Diagnostic and Statistical Manual; FHD = focal hand dystonia; HC = healthy control; HFS = hemifacial spasm; IFD = idiopathic focal dystonia; LD = laryngeal dystonia; OCD = obsessive compulsive disorder; OR = odds ratio; SCI = structured clinical interview; SCL-90 = Symptom Checklist-90, a screening questionnaire for a broad spectrum of psychopathology, including depression, anxiety and obsessionality; UL = upper limb; VCP = vocal cord paralysis.

1.5.2.5 Occupational dystonia

Of this heterogeneous group of task-related disorders, musician's dystonia has been the best studied. Jabusch et al.(212) compared musicians who had focal dystonia with healthy musicians and musicians with chronic pain. Though both the dystonia and pain groups had increased levels of anxiety, exaggerated

perfectionistic traits were specific to dystonia.(212) Higher levels of social or specific phobia(212) and neuroticism(213) have been noted, which either predated the onset of dystonia(212) or did not correlate with its duration.(213) A recent study administered psycho-diagnostic questionnaires to dystonic and healthy musicians.(140) Those with dystonia were six times more likely to possess anxiety and perfectionistic characteristics. Yet 50% displayed none of these features, suggesting two distinct psychological backgrounds in musician's dystonia.

1.6 Psychopathology in functional dystonia

Schrag *et al.* compared the psychological profiles of patients with fixed (presumed functional) dystonia and organic dystonia. Affective and dissociative disorders were more common in the fixed dystonia group, though only a third met the criteria for clinically definite FD. In addition, no effort was made to control for the disability and disfigurement associated with fixed dystonia and the study did not include an analysis of the temporal relationship between psychopathology and motor symptoms.(176)

A larger case-controlled analysis of 64 FMD patients (one fifth with a dystonic presentation), 38 healthy controls and 39 patients with focal hand dystonia assessed personality, environmental and psychiatric factors using self-rating scales and interviews. The frequency of categorical psychiatric diagnoses and negative life events in the year prior to symptom onset did not differ between the groups. FMD patients reported higher levels of emotional abuse and neglect in childhood, more fear associated with traumatic events, and greater depression and anxiety scores. Physiological rather than emotional symptoms of anxiety predominated.(214)

Two case-controlled studies, comprising FMD groups that included a small number of FD patients reported higher self-rated depression, anxiety and dissociation in these mixed groups.(215,216) Another report examined 50 FMD patients (30% with dystonia), who were interviewed about life events and selected psychiatric symptoms in period immediately before the evolution of motor symptoms. Eighty

per cent described a physical event, often accompanied by physical symptoms of panic, at the onset of their disorder.(217) An over-emphasis on psychological factors may obscure this historical detail, which may play a key role in pathogenesis. A summary of these case-controlled reports is included in Table 2, beneath.

Table 2: Case-controlled reports of psychopathology in functional dystonia

Author	No. FMD (% FD)	Diagnosis of FMD	No. organic controls (% dystonia)/ No. of HC	Psychological assessment	Findings in FMD vs. organic motor disorder
Schrag et al. (2004)(176)	26 (100%)	Clinical (fixed dystonia) — One third 'clinically definite' (FW)	20 (100%)/ No HC — 13 secondary — 4 'classic' CD — 3 DYT1	Psychiatric interview	**Higher rates of:** — **Dissociative disorder** (11% vs. 0%) — **Affective disorder** (50% vs. 15%) — **Somatisation** (5% vs 29%)
Defazio et al. (2017)(215)	31 (26%)	FW criteria — 18 'clinically definite' — 13 'probable'	31 (100%)/ No HC — Idiopathic focal/ segmental	Psychiatric interview Self-rated: depression, anxiety and dissociation (somatisation only)	— No difference in categorical psychiatric diagnoses — **Higher self-rated depression** — Similar levels of anxiety and overall somatisation
Kranick et al. (2011)(214)	64 (17%)	FW criteria — All 'clinically definite'	39 (100%)/ 39 — Idiopathic focal hand dystonia	Psychiatric interview Self-rated: depression, anxiety and dissociation	— No difference in categorical psychiatric diagnoses — **Higher self-rated depression and anxiety** — Scores for dissociation in both patient groups similar to HCs
Van der Hoeven et al. (2015)(216)	51 (4%)	Clinical (specialist opinion)	34 (15%)	Self-rated: general psychopathology and dissociation (somatic and psychological)	— **Higher scores for dissociation** (somatic and psychological) — Lower percentage anxiety and depression scores (not significant)
Morgante et al. (2018)(218)	12 (100%)	GL criteria — All 'clinically definite'	10 (100%) — Idiopathic CD	Self-rated: depression and anxiety	— **Higher self-rated anxiety and depression**

Key: FD = functional dystonia; FMD = functional movement disorder; FW = Fahn-Williams; GL = Gupta-Lang; HC = healthy control.

1.7 Diagnostic criteria

1.7.1 Diagnosis in organic dystonia

The diagnosis of dystonia is made on clinical grounds. There are no specific criteria, but consensus guidelines published in 2013 recommended classifying dystonic conditions along two axes.(59) The first, according to clinical criteria—age of onset and temporal pattern, anatomical distribution and associated neurological features, such as additional movement disorders, cognitive impairment, pyramidal dysfunction and psychiatric disturbance. The second axis categorises along aetiological lines—neuroanatomical changes (due to trauma, infection, inflammation, infarction or neurodegeneration etc.), genetic mutation or idiopathic.

1.7.2 Diagnosis in functional dystonia[3]

The three sets(219–221) of more specific diagnostic criteria for FD provide modest guidance.(222) Historical features such as abrupt onset, variable course and stress-related exacerbations are posited as functional markers, although all may be observed in organic disease. The presence of psychiatric features, another poor discriminator,(214) is given disproportionate weight. These criteria have poor inter-rater reliability when applied to clinically ambiguous cases. The gold standard for research is a 'documented' or 'clinically established' diagnosis according to the Fahn-Williams criteria, but these are seldom used in clinical practice.

Phenotype-specific guidelines for FD (Table 3) are more useful to clinicians.(223) Comprising objective *signs* of incongruence with organic disease patterns or of internal inconsistency, they are less reliant on the subjectivity of history and psychological evaluation. Whilst the specificity for each sign in isolation is low, criteria for 'clinically definite' FD have been proposed, based on the presence of all

[3] A version of this overview of diagnostic approaches in functional dystonia (sections 1.7.2) was published in Newby R, Alty J and Kempster P. Functional dystonia and the borderland between neurology and psychiatry: new concepts. Mov Disord 2016;31:1777-1784.

Table 3: Phenotype-specific diagnosis in functional dystonia

FD subtype	Examination findings	Other diagnostic features
Cranial	– Usually asymmetric or unilateral – More prolonged spasms than idiopathic cranial dystonia or hemifacial spasm **Functional oromandibular dystonia**: • Downward lip-pulling with platysma contraction • Tongue may deviate to the affected side • Speech and swallowing usually normal **Functional blepharospasm**: • Bilateral constant tonic spasm or pseudoptosis (eye closure without spasm) • Unilateral orbicularis oculi spasm with contralateral frontalis overactivity **Functional hemifacial spasm**: • Asynchronous contraction of upper and lower facial muscles • No synchronous ipsilateral eye closure and frontalis activation as seen in organic hemifacial spasm • Functional signs in ipsilateral arm and leg	– Unusual triggers – Pain common
Fixed	**Foot**: plantarflexed and inverted with toes flexed **Hand**: 4th and 5th fingers flexed, thumb and index finger relatively spared **Shoulder**: laterocollis with shoulder elevated ipsilaterally and depressed contralaterally **Jaw**: inferolateral deviation – Distal onset, but spreads in two thirds of cases	**Criteria for clinically definite FD** All three of: 1. sudden onset 2. fixed dystonia at rest 3. variable resistance to manipulation, and/or distractibility, or absence when unobserved.
Paroxysmal	– Precipitation of attacks during examination – Presence of tremor – Variable phenomenology of attacks	– Onset after the 2nd decade – Atypical and variable duration – Atypical precipitating factors and relieving manoeuvres – Altered responsiveness during attacks
All	– **Intra-individual variation** in phenomenology – **Admixture with other movements** (tremor, myoclonus, unclassifiable movement etc.) – **Other functional signs** (e.g. collapsing weakness, non-organic sensory loss) – **Suppression with non-physiological manoeuvres**	– **Atypical age of onset** for phenotype – **Suggestibility:** strong placebo effect, *immediate* response to botulinum toxin

Adapted from Ganos et al.(177), Kaski et al.(179) and Espay et al.(222).

three of— (1) sudden onset; (2) fixed dystonia at rest; and (3) variable resistance to manipulation, or distractibility, or absence when unobserved. A weakness of this approach is that it is more applicable to fixed FD than to its other two broad

divisions, cranial and paroxysmal. The fixed dystonia at rest criterion is met by many patients with complex regional pain syndrome, and some consider these diagnoses interchangeable. Both are typically precipitated by minor injury and usually have distal limb involvement with painful muscle spasm. While the majority of fixed dystonia is functional, it should be remembered that genetic dystonia may rarely manifest in this way, that secondary post-stroke dystonia can become fixed and that organic dystonia is sometimes painful. In the absence of reliable criteria, a FD diagnosis is often based on clinical gestalt. Misdiagnosis rates of organic as FD in older studies ranged between 25%(224) and 52%.(225) Although diagnostic accuracy for functional neurological presentations has since improved,(226) dystonic presentations remain a source of clinical error,(227) underscoring the need for laboratory supported diagnoses.

The DSM-5 criteria for functional neurological disorder, whilst not specific for dystonia, possess some advantages over other diagnostic standards. In contrast to the Fahn-Williams criteria, there is no requirement to identify an associated psychological stressor to secure the diagnosis. This feature, which has been shown to have little diagnostic or prognostic value has been down-weighted to "supportive factor". The DSM-5 criteria, designed to cover a range of functional motor and sensory disorders, also have broader clinical applicability than the specific phenotype-specific criteria for FD, with their poor registration of atypical cases.

1.8 The electrophysiology of functional and organic dystonia

If a motor command is to be successful, it must inhibit undesired muscle groups, as well as activating those necessary for the execution of a movement. Electrophysiological studies in different types of dystonia have produced mixed results, but loss of inhibition, at multiple levels of the nervous system is a reproducible finding.(228) Slower, more variable movements are the result. Few studies have been conducted in FD, because of inherent diagnostic and technical challenges. Many electrophysiological tests require subjects to be at rest, a state that may be impossible to achieve in FD, particularly in subtypes associated with fixed posturing and continuous muscular contraction.

1.8.1 Kinematic and electromyogram (EMG) studies

In generalised dystonia, as well as several idiopathic focal dystonias, an alteration of the orderly activation and inhibition of agonist, antagonist and synergist muscles has been demonstrated. The normal triphasic pattern of EMG activation of agonist-antagonist pairs in self-paced ballistic movement is disrupted(229,230) and there are abnormally long EMG bursts(231), associated with agonist-antagonist co-contraction(232). In DYT1 dystonia there is an abnormal synchronising drive with intermuscular coherence at 4-7Hz. Excessive muscle activity can spread to synergist and remote muscles, visible in overflow and mirror dystonia(233).

These motor inefficiencies culminate in movements that are slower(234,235), less precise(236) and more variable in both amplitude and frequency (237), with delayed switching (longer reaction times) in complex sequential tasks.(234) Deceleration rates, particularly during the extension phase of repetitive movements, are reduced(238,239) and the number of motor arrests is increased.(234,239,240) Unlike slowness of movement in Parkinson's disease, there is no evidence of decrement in amplitude or speed in dystonia.(234,239) Some studies report a loss of the normal bell-shaped velocity curve, indicating a reliance on postdictive (feedback) rather than predictive (feed-forward) motor control.(238) Others suggest a reduction in the ability to integrate proprioceptive input with motor plans, culminating in increased error of performance in tasks without visual feedback.(238,241) It is difficult to generalise, but findings of slowness, increased variability of movement, and difficulties with phase-switching appear to be broadly consistent across a range of patient populations (idiopathic focal, genetic generalised and secondary) and using a variety of experimental paradigms and motion analysis techniques (Table 4).

Only one previous kinematic study has assessed finger-tapping movement in detail. Currá et al. compared nine patients with idiopathic focal or segmental dystonia involving the upper limb with nine healthy controls using infra-red motion analysis software.(239) The dystonia group had fewer oppositions (lower

Table 4: Kinematic and EMG studies in organic dystonia

	Patients/Controls	Paradigm/ Motion analysis	Findings in dystonia
Van der Kamp et al. (1989)(242)	**10 UL dystonia** 9 HC	Fast elbow flexion movements. Potentiometers and EMG.	• Lower and **more variable** amplitudes and **slower** movements • Longer duration of first agonist burst on EMG • Normal bell-shaped velocity curve for ballistic movement.
Agostino et al. (1992)(234)	**7 UL dystonia**/14 IPD/ 9 HD 13 HC	Fast pentagon tracing. Potentiometers.	• **Increased movement times, longer pauses, slower phase switching** • **No decrement in velocity**
Inzelberg et al. (1995)(238)	**8 DYT1** 6 HC	Targets reaching, with and without visual feedback. Digitising table with a pen-like stylus.	• **Increased deceleration times** • Loss of normal bell-shaped velocity profile • Worse performance without visual feedback (target error increased)
Currá et al. (2000)(240)	**9 Dystonia (generalised) / 6 WC** 14 HC	Fast target reaching (self-initiated and externally triggered). Infra-red video motion analysis.	• **Slower movement with more pauses** (self-initiated). • Self-initiated faster than externally-triggered for writer's cramp and HC. • **Reaction times longer** in generalised, but not focal dystonia.
Currá et al. (2004)(239)	**9 UL dystonia** 10 HC	Finger tapping "as fast and as wide as possible" Infra-red video.	• Fewer oppositions, **slower movement and longer pauses** • **Extension phase longer than flexion phase** • **No decrement in amplitude**
Beuter et al. (2004)(236)	**7 Dystonia** 11 HC	Finger-nose movement in time with a metronome. EM sensors.	• **More variable** trajectories, jerky and less symmetrical movements • **Longer movement times**
MacKinnon et al. (2004)(243)	**9 UL dystonia** 9 HC	Fast wrist flexion/extension movement. Potentiometers and EMG	• **Movement slower** • Normal first agonist burst, followed by attenuation • No EMG evidence of overflow/ co-contraction
Nowak et al. (2005)(244)	**9 UL dystonia** 10 HC	Lifting and holding and weight-catching tasks Force and linear acceleration sensors	• Increased grip strength. Shorter latency to peak grip force • Elevated peak acceleration in WC vs. HC and MC
Prodoehl et al (2006a)(245)	**18 WC** 18 HC	Rapid on/off isometric wrist and elbow flexion and extension. Torque transducer.	• Lower force, increased latency to target torque and longer relaxation times • **Longer times to rapidly reverse force**
Prodoehl et al. (2006b)(246)	**18 WC** 18 HC	Contractions of wrist and elbow. Torque transducer and EMG	• Weaker at both joints in both flexion and extension • Peak torque reduced (reduction in agonist activation)
Zeuner et al. (2007)(237)	**21 WC** 21 HC	Sentence writing and circle drawing Digitising graphics pad.	• **Reduced frequency of movement** • **Vertical peak velocity more variable**
Pelosin et al. (2009)(247)	**10 CD** 10 HC	Fast reaching movements before and after botulinum toxin. Digitising graphics pad.	• **Peak velocity and acceleration reduced** • **Increased reversal lag and longer movement times** • Asymmetrical velocity curves (feedback control)

Key: BSP = blepharospasm; CD = cervical dystonia; DYT1 = DYT1 genetic dystonia; EM = electromagnetic; EMG = electromyogram; FHD = focal hand dystonia; HC = healthy control; HD = Huntingdon's disease; MC = musician's cramp; IPD = idiopathic Parkinson's disease; UL = upper limb; WC = writer's cramp

Table 4: Kinematic and EMG studies in organic dystonia

	Patients/Controls	Paradigm/ Motion analysis	Findings in dystonia
Marinelli et al. (2011)(241)	**10 CD** 10 HC	Ballistic arm movements (with and without visual feedback). Digitising graphics pad.	• **Reduced velocity, peak acceleration and symmetry** • **Increased movement and reaction times** • Errors without visual feedback (impaired proprioceptive processing)
Hermsdörfer et al. (2011)(248)	**27 WC** 14 HC	Writing sentence x 3. Digitising graphics pad.	• **Reduced frequency and increased movement times** • Increased pen grip force and pressure
Casellato et al. (2011)(249)	**15 Dystonia (genetic)** 9 HC	Reaching and writing tasks. Visual motion capture and EMG.	• **Reduced velocity** • More variable resting EMG and less specific muscular activation
Kawamura et al. (2012)(250)	**11 UL dystonia (secondary)** 6 HC	Hand tapping with metronome. Visual motion capture.	• More involuntary movement.
Nowak et al. (2013)(251)	**7 CD/ 7 BSP** 7 HC	Fast reach and grasp task Ultrasonic motion capture	• Slower hand transport but timing and scaling normal.
De Campos et al. (2014)(252)	**11 UL dystonia (secondary)** 9 HC	Reach and grasp task. Visual motion capture	• Increased reach and hold times • Reduced elbow/shoulder correlation (non-dominant hand)
Bradnam et al. (2015)(253)	**5 WC/ 3 MC** 8 HC	Handwriting and cyclic drawing. Digitising graphics pad.	• **Slower movement** (fewer strokes per minute)
Lunardini et al. (2015)(254)	**8 Dystonia (primary/secondary)** 8 HC	Moving spoon containing marble as fast as possible between two targets (4 spoon sizes) 3D visual motion tracking.	• **Longer movement time** and increased jerkiness • **Reduced peak velocity and peak acceleration**
Bologna et al. (2016)(255)	**13 FHD/ 13 CD** 13 HC	Reach and grasp and head rotation tasks Visual motion capture	• **Reduced peak angular amplitude and velocity** in CD
Kukke (2016)(256)	**11 UL dystonia (secondary)** 9 HC	Reach and grasp task. Visual motion capture	• **Longer movement times** and more deviant trajectories (non-dominant hand only)
Sadnicka et al. (2018)(257)	**10 DYT1** 12 HC	Target reaching with and without visuomotor transformation. Robotic manipulandum.	• Median path length increased • **Increase in motor variability**

Key: BSP = blepharospasm; CD = cervical dystonia; DYT1 = DYT1 genetic dystonia; EM = electromagnetic; EMG = electromyogram; FHD = focal hand dystonia; HC = healthy control; HD = Huntingdon's disease; MC = musician's cramp; PD = Parkinson's disease; UL = upper limb; WC = writer's cramp

frequency of tapping), longer movement duration (particularly the extension phase) and longer pauses. Impairment of motor performance was greater in a sequential finger-tapping task (ordered oppositions of each digit in turn with the thumb) than in a task involving repetitive opposition of index finger and thumb.

On EMG, FD shares some features with organic dystonia, although agonist-antagonist co-contraction(258,259) is less prominent. There is some evidence that patients with FD have faster reaction times than those with organic dystonia.(259) One very small study also demonstrated pre-movement coactivation of ipsilateral antagonist and contralateral limb muscles (similar to the coactivation noted prior to the onset of functional tremor).(260) This finding is of questionable validity, however, since it was documented in only half of a sample of four patients. Finger tapping has been demonstrated to be significantly reduced in a small sample of mixed FMD patients compared to two much larger organic movement disorder groups.(261) Similar findings have been reported in studies of CRPS with and without upper limb dystonia.(262,263)

1.8.2 Spinal cord and brainstem reflexes

A range of spinal cord and brainstem reflex settings are altered in dystonia. In both generalised dystonia and focal hand dystonia there is swifter recovery of the H reflex (reflexive muscular contraction in response to electrical stimulation of 1a afferent fibres), and loss of reciprocal inhibition of antagonist muscles in the resting state (also during movement in focal hand dystonia). These changes have been observed in the unaffected limbs of patients with focal hand dystonia and cervical dystonia.(230)

At a spinal level, similar findings have been reported in patients with FD.(264) However, the disinhibition of the R2 (delayed) component of the blink reflex recovery cycle, observed in organic blepharospasm and both generalised and focal (cervical) dystonia (without clinical evidence of blepharospasm) is not present in functional blepharospasm.

1.8.3 Motor cortical activity

Bereitschaftpotentials are slowly-rising negative EEG potentials that may be recorded over the scalp prior to self-paced voluntary movements. These comprise two components, the first (NS1) arises from bilateral activity in the motor cortices and supplementary association areas about 1.5s prior to movement initiation; NS2 is generated by lateralisation of activity to the contralateral primary motor cortex about 850ms later. (265,266) Both are slowed or reduced in amplitude in secondary dystonia,(267) with an isolated reduction of NS2 in generalised dystonia and writer's cramp (see Figure 6).(265,266) Findings are inconsistent, however, and one study demonstrated increased amplitude of the Bereitschaftpotential in both functional and organic dystonia, compared to healthy controls.(264)

Various intracortical inhibitory processes have been shown to be deficient in dystonia (See Figure 7 for schematic showing how cortical inhibition is measured). Localised primary motor cortical effects are disturbed, with reductions in short- and long-latency intracortical inhibition. In patients with mirror dystonia there is also a loss interhemispheric inhibition between the primary motor cortices.(228) Two studies have shown equivalent reduction in inhibitory transmission in both functional and organic dystonia.(264,268) When afferent impulses are used as conditioning stimuli, levels of inhibition are normal in both groups.

Quartarone et al. subsequently reported a potentially distinguishing electrophysiological finding—an increase in cortical plasticity in organic dystonia but not FD, using a paired associative stimulation paradigm.(269) Concerns have been raised generally about the reliability of such approaches over time. In addition, a recent study, using slightly different methodology, revealed no difference in levels of plasticity between functional and organic dystonia.(270)

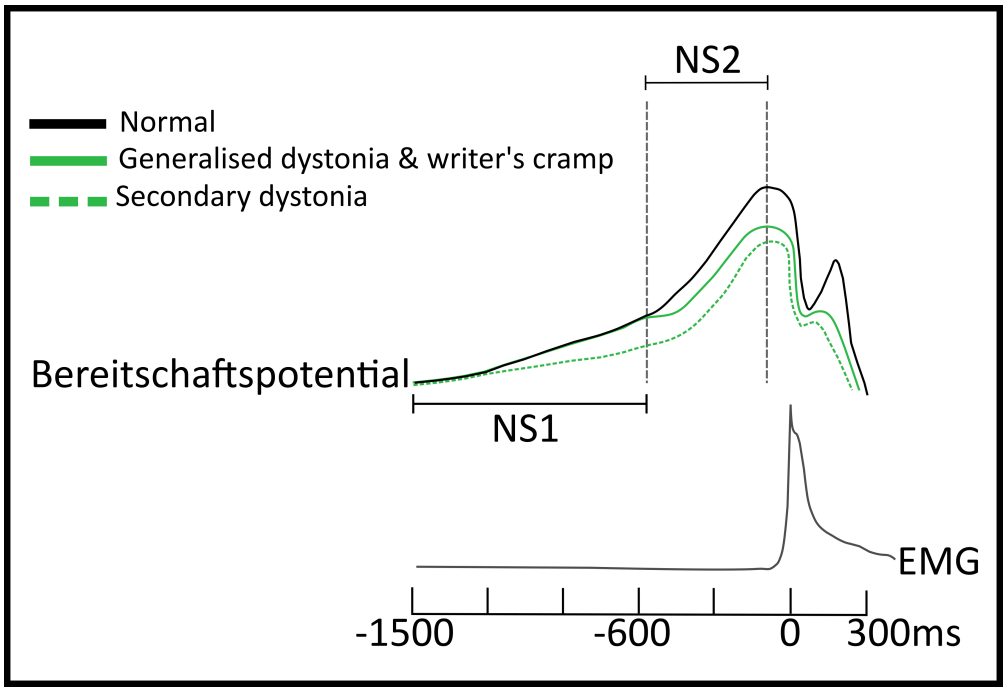
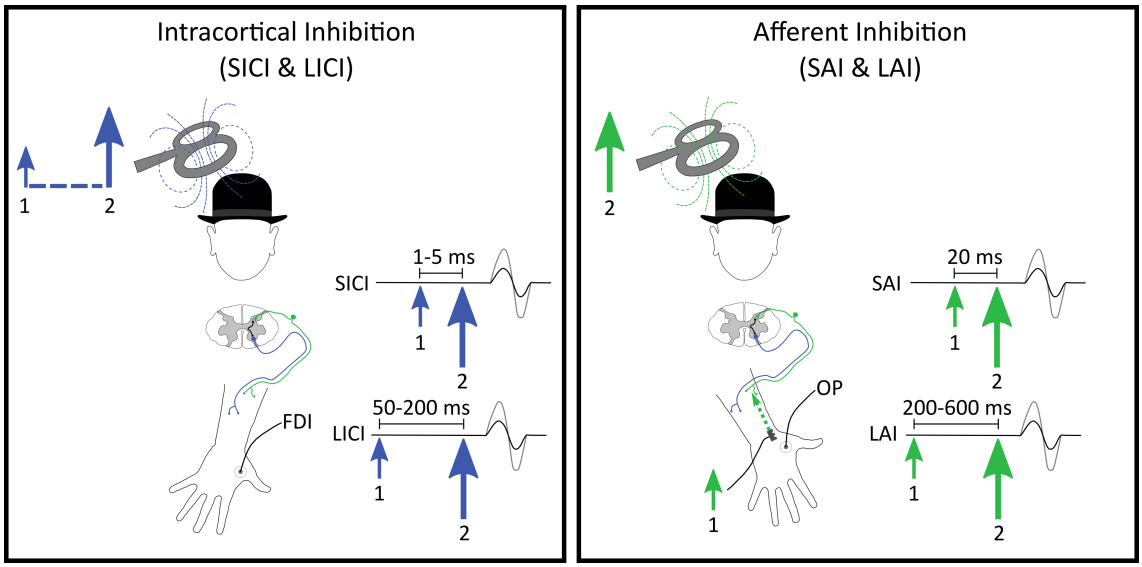


Figure 6: Schematic showing the changes reported in the pre-movement potential (Bereitschaftspotential) in dystonia

The Bereitschaftspotential has a slow-rising early (NS1) component, starting about 1500ms before movement, and a steeper late component (NS2), starting around 650ms prior to movement. Both NS1 and NS2 were found to be reduced in secondary hemi- or generalised dystonia, due to basal ganglia lesions, whereas only the NS2 component was reduced in patients with primary torsion dystonia (generalised dystonia) and writer's cramp (contralateral to the affected hand). EMG = electromyogram trace.



<u>Figure 7:</u> Diagram showing how cortical inhibition is measured using transcranial magnetic stimulation (TMS)

a. <u>Intracortical inhibition:</u> a subthreshold conditioning TMS stimulus is delivered over the motor cortex, followed by a suprathreshold TMS stimulus at either short (1-5 ms, short-latency intracortical inhibition (SICI)) or long (50-200 ms, long-latency intracortical inhibition (LICI)) latency. Motor endplate potentials (MEPs) are recorded from muscles in the contralateral hand. Grey curve = preconditioning MEP; black curve = post-conditioning MEP.

b. <u>Afferent inhibition:</u> a conditioning stimulus is delivered to a peripheral nerve (median, in this example), after which a suprathreshold TMS stimulus is applied to the contralateral motor cortex at either a short (~20ms, short-latency afferent inhibition (SAI)) or long (200-600ms, long-latency afferent inhibition (LAI) interval). Grey curve = preconditioning MEP; black curve = post-conditioning MEP.

Key: FDI = first doral interosseous; OP = opponens pollicis.

<u>1.8.4 Abnormalities of sensory processing</u>

Reduced spatial(271) and temporal(272) discrimination thresholds have been reported in both the affected and unaffected hands of patients with focal hand dystonia, as well as cervical dystonia, blepharospasm, and healthy relatives of patients with dystonia. Kinaesthesia (awareness of position and movement of body

parts) is impaired in focal hand dystonia, with an elevation of the threshold for identification of a passive finger movement and reduced perception of illusory movement provoked by vibratory tendon stimulation. Analysis of somatosensory evoked potentials (SEPs) shows abnormalities of lateral inhibition and a reduction in high frequency oscillations at around the N20 component of the SEP (thought to reflect inhibitory post-synaptic potentials) in task-specific hand and cervical dystonia.(228)

Evidence of pathological sensorimotor integration is present in the finding that muscle vibration can induce dystonic spasm in focal hand dystonia, an effect that is attenuated by local anaesthetic block.(273) The contingent negative variation, the equivalent of the Bereitschaftpotential for externally cued movement, is a negative EEG potential observed between preparatory and triggering motor cues. It is reduced when patients with IFD execute movements with the affected body part.(274,275)

Fewer analyses of sensory transmission in FD have been performed. Morgante et al measured sensory temporal discrimination threshold (TDT) in 10 patients each with functional and organic dystonia and found significantly increased TDT in both patient groups.(276) However, this finding is in conflict with the results of another similar study in 11 patients with fixed dystonia, which found no significant difference.(277) A study of SEPs at the onset of self-paced movement in patients with FMD (35% FD) demonstrated a lack of sensory attenuation, which the authors suggested might contribute to lack of agency.(278)

The documentation of many of these abnormalities in asymptomatic limbs of dystonia sufferers, non-manifesting carriers of DYT genes, and unaffected relatives of patients with dystonia, has prompted speculation that they might be endophenotypic features, or susceptibility factors for dystonia which may manifest as an organic or functional phenotype depending on other influences.(279)

The utility of these measures as diagnostic markers is limited by their lack of specificity and reliability—co-contraction is not ubiquitous in organic dystonia,(280) and intracortical inhibition and reaction times are influenced by

such factors as attention, personality and comorbid psychiatric disorder.(177) The absence of a diagnostic 'gold-standard' also provides challenges when appraising these results. The studies by Espay et al.(264), Avanzino et al.(268) and Quartarone et al.(269) (see Table 5) involve small patient numbers, with a diagnosis made according to the out-dated Fahn-Williams criteria. Espay et al. applied the highest threshold, requiring a 'clinically definite' diagnosis of FD, but the case mix included several with cervical dystonia, arguably most difficult to distinguish from organic disease. The other two studies required only a 'possible' or 'probable' diagnosis, which significantly increases the risk of inappropriate inclusion. Indeed, three patients included within the Avanzino et al. study did not meet the criteria at all (though they all had a fixed dystonia phenotype, which is generally accepted to signify functional disorder).

1.9 Imaging in functional and organic dystonia

A detailed review of the imaging findings across the full spectrum of organic dystonia is beyond the scope of this thesis. A variety of imaging paradigms have disclosed structural and functional changes in certain key areas, including the sensorimotor cortex, basal ganglia and cerebellum. Abnormal cortico-striatal and cortico-cerebellar connectivity is reported. There is also evidence of somatotopic remodelling (expansion and disorganisation of the receptive fields of the digits) of the thalamus and motor and sensory cortices in focal hand dystonia on magnetoencephalography (MEG)(283) and functional magnetic resonance imaging (fMRI).(284)

Only two studies have specifically addressed FD. PET scans demonstrated opposite patterns of brain activation in DYT1 dystonia and FD.(285) DYT1 has a 'cortical' pattern (increased blood flow in the primary motor, premotor and parietal cortices and reduced flow in the cerebellum), whereas flow was reduced in the motor cortex and increased in the basal ganglia and cerebellum in FD. Significant increases in movement-related activation of the prefrontal cortex were noted in both groups, contradicting a theory of abnormal premotor activity as a specific driver of functional neurological disorders.(286) These findings have yet to be substantiated in a larger study.

Table 5: Comparative electrophysiological studies of functional and organic dystonia

Study	Patients/Controls	Paradigm	Findings
Morgante et al. (2011)(276)	10 FD (non-fixed, limb) 10 OD (mixed IFD) 16 HC		Higher temporal discrimination threshold increased in FD and OD
Mehta et al. (2013)(260)	4 FD (fixed limb) 5 OD (DYT1) 6 HC	Surface EMG and dynamometer at rest, and with movement.	Pre-task **co-activation in ipsilateral antagonist and contralateral muscles** in FD
Van Rooijen et al. (2013)(263)	48 CRPS (31 with dystonia) 42 HC	Sensory testing: Detection thresholds (temperature & pain). SDT. Motor testing: Finger tapping. Video mapping of motion.	• Lower pressure pain threshold and higher SDT (with dystonia) • Lower amplitude and velocity • **Frequency and velocity lowest in those with dystonia**
Schilder et al. (2012)(262)	80 CRPS (29 with dystonia) 60 IPD 75 HC	Finger tapping	• **Reduced velocity and frequency with more arrests** (vs. IPD and HC) • Lowest velocity & frequency in those with dystonia
Criswell et al. (2010)(261)	13 FMD (15% FD) 32 OD 49 ET 101 IPD 130 HC	Finger tapping between 2 levers	**FMD: fewer taps than any of the other groups.**
Macerollo et al. (2015)(281)	9 Fixed FD (8 UL, 1 LL) 9 OD (secondary)	EMG (rest and with reaction time test)	**Reaction time shorter and less co-contraction in FD group**
Schwingenschuh et al. (2011)(282)	10 BSP 9 Functional BSP 9 HC	Supraorbital stimulation with EMG orbicularis occuli	Delayed phase of blink reflex recovery cycle disinhibited in BSP but not functional BSP
Espay et al. (2006)(264)	10 FD (mostly cervical) 8 OD (mixed IFD) 12 HC	Paired pulse TMS protocol for SICI, LICI, SP, CuSP and RI. Back-averaging of EEG to discern BP.	• Similar reductions in inhibition in both FD and OD • Longer CuSP in both FD and OD • BP increased in OD but not FD
Avanzino et al. (2008)(268)	12 FD (fixed limb) 10 OD (mixed IFD) 11 HC	Paired pulse TMS protocol for SICI, cSP, SAI and LAI	• SICI and CuSP reduced in both FD and OD (affected and unaffected sides)
Quartarone et al. (2009)(269)	10 FD 10 OD 10 HC	TMS over primary motor cortex with surface EMG of contralateral arm. Application of a paired associative stimulation protocol.	• Greater plasticity in OD but not FD • Intracortical inhibition reduced in both OD and FD

Key: BP = Bereitschaftspotential; BSP = blepharospasm; CRPS = complex regional pain syndrome; CuSP = cutaneous silent period, the pause in tonic EMG following stimulation of a cutaneous nerve; EEG = electroencephalogram; EMG = electromyogram; ET = essential tremor; FMD = functional movement disorder; FD = functional dystonia; HC = healthy control; IFD = idiopathic focal dystonia; IPD = idiopathic Parkinson's disease; LAI = long-latency afferent inhibition; LICI = long-latency intracortical inhibition; LL = lower limb; OD = organic dystonia; RI = reciprocal inhibition; SAI = short-latency afferent inhibition; SDT = spatial discrimination threshold; SICI = short-latency intracortical inhibition; SP = silent period, the pause in ongoing EMG activity during voluntary movement following TMS stimulation; TMS = transcranial magnetic stimulation; UL = upper limb.

Using fMRI and three tasks—one motor (finger tapping), one involving implicit recognition of emotional faces, and a third probing responses to more intense emotional imagery (designed to provoke offence or disgust)—Espay et al. compared 12 FD and 12 primary organic dystonia patients with 25 healthy controls.(287) They found a differential pattern of activation for FD that was specific to the paradigms assessing emotional responses. The authors suggest that these changes—in areas governing motor planning, spatial cognition and attentional control—may be important in the maintenance of abnormal motor behaviours through disordered striato-thalamo-cortical signalling or "functional deafferentation". However, the study was not sufficiently powered to assess whether these changes might relate to differences in levels of depression and anxiety between the two patient groups.

Functional MRI studies in mixed FMD cohorts (20-25% had FD) have used paradigms based on movement initiation and emotional cuing. Abnormalities in the strength and pattern of activation of limbic and neocortical regions may be clues about how emotional states influence motor planning in FMDs.(288,289)

Differences between willed movement and functional tremor that may be applicable to FMDs in general were found using fMRI. Activation of functional tremor produced right temporoparietal junction hypoactivity, which did not occur when the same subjects were instructed to mimic their tremor.(290) The right temporoparietal cortex, a key area for sensory integration, contributes to a sense of 'self' through the matching of actual with expected sensory data. This observation may go some way to explaining the feelings of dissociation that many patients with FMDs describe.

Though these findings are help us to improve pathophysiological understanding of FMD and to form hypotheses for future research, they have not yet yielded signifiers with sufficient specificity and reliability to form the basis of diagnostic criteria for FD.

1.10 Economical impact of functional dystonia

There is a paucity of demographic data regarding FMDs. Medically unexplained symptoms (including cardiac, rheumatological and gastroenterological presentations, in addition to neurological) are estimated to cost up to £17 billion each year in the UK.(291)

FMDs account 2-20% of referrals to movement disorders clinics(292,293). Their negative impact on quality of life matches or exceeds that of Parkinson's disease(294). Prognosis in FD is particularly poor: less than 25% of patients improved in one long-term follow-up study(295). Prompt diagnosis and early multidisciplinary input may improve outcome(176,296). However, FD can be difficult to distinguish from its organic counterpart(177,220), leading to therapeutic delays and sub-optimal management.

Several authors have highlighted the need for laboratory supported criteria,(221,222) but there have been no large-scale comparative studies of functional and organic dystonia to date.

1.11 Aims of the project

The broad aims of this study are two-fold. Firstly, to survey the psychological profile of these two patient groups to discern whether the psychological metrics, used to determine diagnosis for so many years, have any discriminatory utility. In addition to examining depression and anxiety, which have been investigated previously, this study will include measures of obsessive-compulsion and depersonalisation. Secondly, to utilise novel electrophysiological and computing techniques to explore the kinematics of functional and organic dystonia, to see if there are distinguishing motor features that might contribute towards the development of more reliable 'laboratory supported' diagnostic criteria. By exploring correlations between psychological with kinematic measures, it may also be possible explore the potential mechanistic significance of these factors.

1.11.1 Specific Aims

1. Obtain measures of depression, anxiety, obsessive-compulsion and depersonalisation in patients with FD, organic dystonia and healthy controls.
2. Compare the results across the groups to establish whether there are any distinguishing psychological features.
3. Clinically evaluate movement abnormalities using approved rating scales for organic and FD.
4. Obtain high-quality measurements of movement variables across a range of tasks in patients with FD, organic dystonia and healthy controls.
5. Analyse whether any of the findings might be used to generate a set of 'laboratory supported' diagnostic criteria for FD.
6. Frame this new information within the context of other research findings to generate new hypotheses about the pathophysiology of FD.

Chapter Two: Methodology

2.1 Participants

2.1.1 Inclusion and exclusion criteria

Thirty-three patients with organic dystonia, thirteen with FD and twenty-nine healthy control subjects were recruited. To enroll, patients with dystonia had to meet the following criteria:

Box 2.1 Inclusion criteria for patients with dystonia

Diagnosis made by a neurologist, according to accepted criteria:

i. For **organic dystonia**

   a. The preferred diagnosis of the treating neurologist
   AND
   b. Phenomenology complies with the 2013 MDS consensus update on dystonia for presence of dystonia (generalised, focal upper limb or cervical) and its syndromic diagnosis**
   AND
   c. Does not meet the DSM-5* incompatibility criterion for the diagnosis of conversion disorder (functional neurological symptom disorder)

ii. For **functional dystonia**

   a. The preferred diagnosis of the treating neurologist
   AND
   b. Meets all DSM-5 criteria for the diagnosis of conversion disorder (functional neurological symptom disorder)
   AND
   c. Dystonia present according to the 2013 MDS consensus update definition**
   WITH or WITHOUT
   d. Phenotype-specific clinical features of functional dystonia present

** DSM-5: Diagnostic and Statistical Manual of Mental Disorders*

*** 'Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.'*

For the organic dystonia group, most aetiological subtypes were included (genetic, secondary and idiopathic). However, those with dystonia following peripheral nerve trauma were excluded (see Box 2.2). There remains controversy surrounding the pathophysiological basis of this disorder, with no clear consensus

regarding its location on the organic-functional spectrum.(297) Patients who had undergone deep brain stimulation (DBS) surgery were also excluded since plastic changes in the neural circuitry of the basal ganglia, induced by stimulation, would preclude observation of the native kinematics of dystonia. Those receiving botulinum toxin injections were not excluded, but as far as possible these patients were assessed towards the end of their dosing cycle (just before their next scheduled set of injections). Since the kinematic data were to be collected exclusively from the upper limb, recruitment focused on patients with upper body dystonia. Cervical dystonia was included on the basis that it is frequently associated with brachial dystonic symptoms; and that electrophysiological markers of dystonia have been have been observed in such patients, even in the absence of clinical signs of upper limb dystonia.(241,247,251,255)

Healthy controls were capacitous adults with the physical ability to undertake the assessments. Children, adults lacking capacity to consent, and those with physical impairments that might interfere with upper limb movement, such as severe osteoartritis, were excluded.

Box 2.2 Exclusion criteria

All participants:

1. Age under 18
2. Lacking capacity to give consent
3. Unable to communicate with the researcher (non-English-speaking)
4. Physical impairments apart from dystonia, such as severe osteoarthritis, that might interfere with movement

Participants with dystonia:

1. Dystonia evolved following peripheral nerve trauma
2. Previous treatment with deep brain stimulation, pallidotomy or thalamotomy

As discussed previously, existing diagnostic criteria for FD reflect outdated conceptual frameworks for functional disorders, manifest in the disproportionate emphasis placed on psychological factors. Few neurologists rely on these criteria in clinical practice.(298) The new *DSM-5* criteria, published in 2013, place greater emphasis on objective signs and are easier to align with the phenotype-specific criteria for functional movement disorder described by Espay and Lang (2015).(222)

Box 2.3 *DSM-5* criteria for functional neurological disorder

- One or more symptoms of altered voluntary motor or sensory function
- Clinical findings that show evidence of incompatibility between the symptoms and recognised neurological or medical disorders
- Symptoms or deficit that are not better explained by another medical or mental disorder
- Symptoms or deficit cause clinically significant distress or impairment in social, occupational, or other important areas of functioning; or warrants medical evaluation

These criteria may be applied to any functional neurological disorder. Many patients with FD have a rich phenomenology, with elements of tremor, myoclonus or weakness in addition to the dystonia, so it is not possible to recruit patients with 'pure' dystonic presentations. Patients were invited to take part if dystonic features were among their most disabling motor symptoms. Phenotypic guidelines (see Table 3) were used but not slavishly adhered to, since it is likely that the full phenotypic spectrum has yet to be delineated.

2.1.2 Sample size

A sample size assessment was undertaken, assuming a power of 80% and a type I error probability of 0.01 (a lower *p* value was selected to compensate for multiple comparisons). A ratio of 3:1 (organic: FD) was chosen to reflect the higher prevalence of organic dystonia. Assuming the use of an independent student's t-test for comparison of continuous variables (components of movement e.g. speed and amplitude) between the groups, and taking into account the effect size of a similar study (38% difference between the means),(261) the following sample sizes were estimated—30 organic dystonia, 10 FD and 30 healthy controls.

2.1.3 Recruitment

Patients with dystonia were recruited through three separate streams:

1. The existing caseload of patients seen by movement disorder specialists in the Monash Medical Centre (MMC) neurology outpatient department in Melbourne, Australia;
2. Online advertisement via the Australian Dystonia Support Group;

3. The existing caseload of patients seen by movement disorder specialists at Leeds General Infirmary (LGI), Leeds, UK.

MMC and LGI are both large tertiary referrals neuroscience centres. MMC serves a population of around 1 million people in the south-eastern suburbs of Melbourne, the LGI provides care to the 780,000 residents of Leeds, as well as up to 5.4 million in surrounding areas. MMC employs five neurologists with a specialist interest in movement disorders, the LGI has four movement disorders neurologists.

All patients invited to participate were given a patient information leaflet. A week later they were contacted via telephone to establish whether they were interested in taking part and to arrange an appropriate appointment time.

Control subjects were recruited from several sources. The majority were spouses or friends of patients who attended clinics at MMC. Recruitment was also sought from members of staff. Posters advertising the study were placed in the clinic waiting area and departmental notice board, with contact details made available for interested parties. All potential control subjects received a modified information leaflet and contact was made via telephone at least one week later to garner interest and organise an appointment as appropriate.

2.1.4 Consent

Having read the information leaflet, all subjects were offered a further opportunity to ask questions on the day of their assessment, before providing written consent. All participants were made aware of their right to withdraw from the study at any time without prejudicial treatment or alteration of their clinical management. Assessments took place between September 2015 and February 2018. Ethical approval was obtained from the Monash Health Human Research Ethics Committee (HREC code: 13424B) and the Yorkshire and Humber Sheffield Research Ethics Committee (HREC code: 14/YH/0143).

2.2 Apparatus

2.2.1 Polhemus Patriot electromagnetic (EM) tracking sensor system

Assessments were performed in clinic rooms in three settings—in Monash neurology department, the translational research centre at MMC, and the outpatient department at the LGI. Participants were seated in a high-backed chair with broad arms facing the examiner. A Polhemus Patriot EM tracking sensor system (Polhemus, Inc., Vermont USA) was connected to a tablet computer and placed on a table positioned between the participant's chair and the examiner (Figure 8a).

The Patriot system includes a Systems Electronics Unit (SEU), a power supply, two sensors and one source (magnetic transmitter) (Figure 8b & 8c).

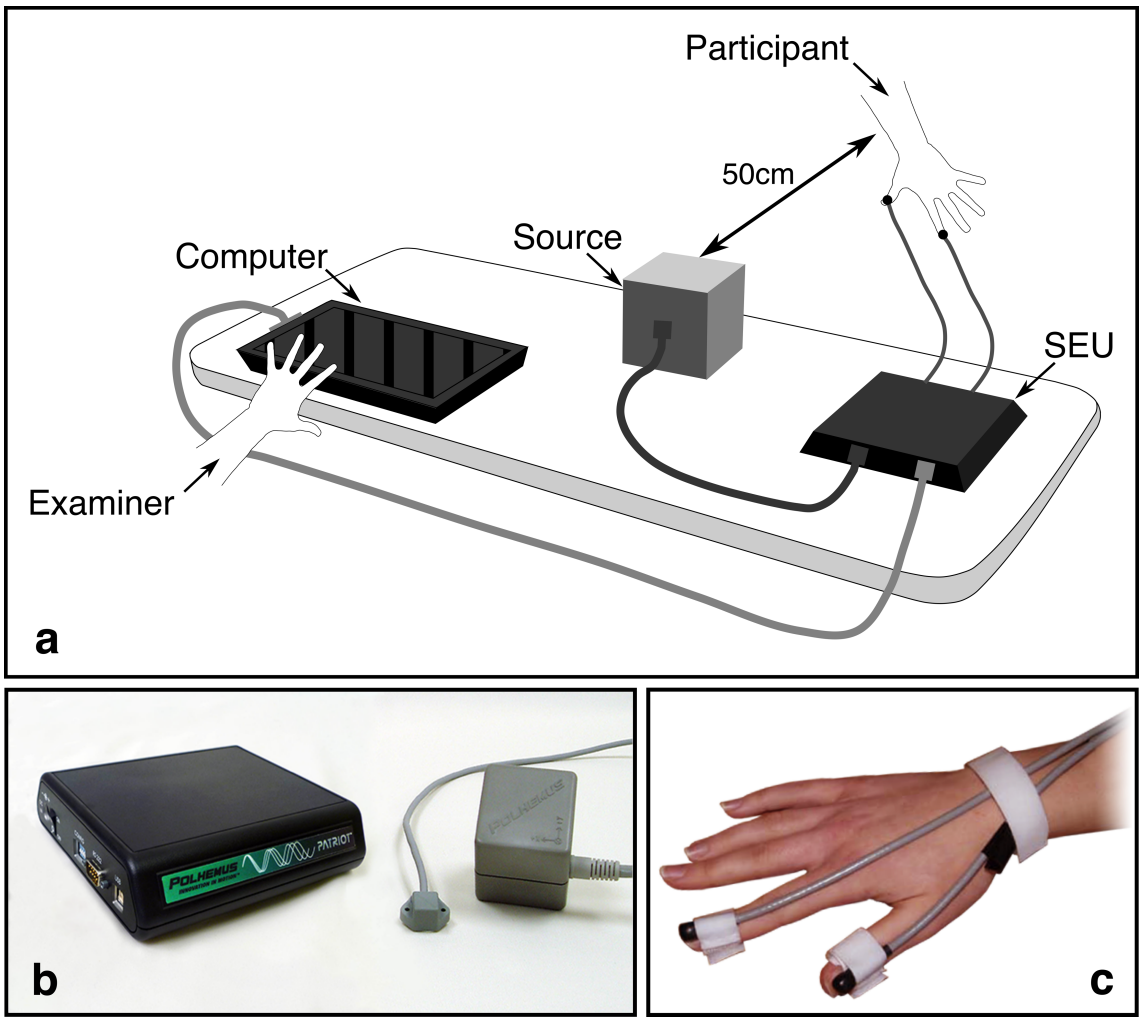


Figure 8: Experimental apparatus

a. Schematic of experimental apparatus;

b. Polhemus Patriot electromagnetic transmitter (source)—grey box—and systems electronic unit (SEU)—black box;

c. Electromagnetic sensors secured to finger and thumb with Velcro straps.

Within the source and each sensor are three orthogonally aligned EM coils. A magnetic field, generated by the passage of alternating current through the source, acts as a reference against which the movement of the sensors may be measured. The strength of the magnetic signal detected by each sensor is transmitted back to the computer through the SEU with a sampling rate of 60Hz. From this, kinematic data for each sensor, in six degrees of freedom, can be extrapolated. This data comprises three positional coordinates relative to the source's magnetic field—forward/backward (longitudinal axis, *z*), left/right (lateral axis, *x*), up/down (vertical axis, *y*) —and three coordinates denoting rotation about these axes— *roll* (longitudinal), *pitch* (lateral), and *yaw* (vertical) (Figure 9).

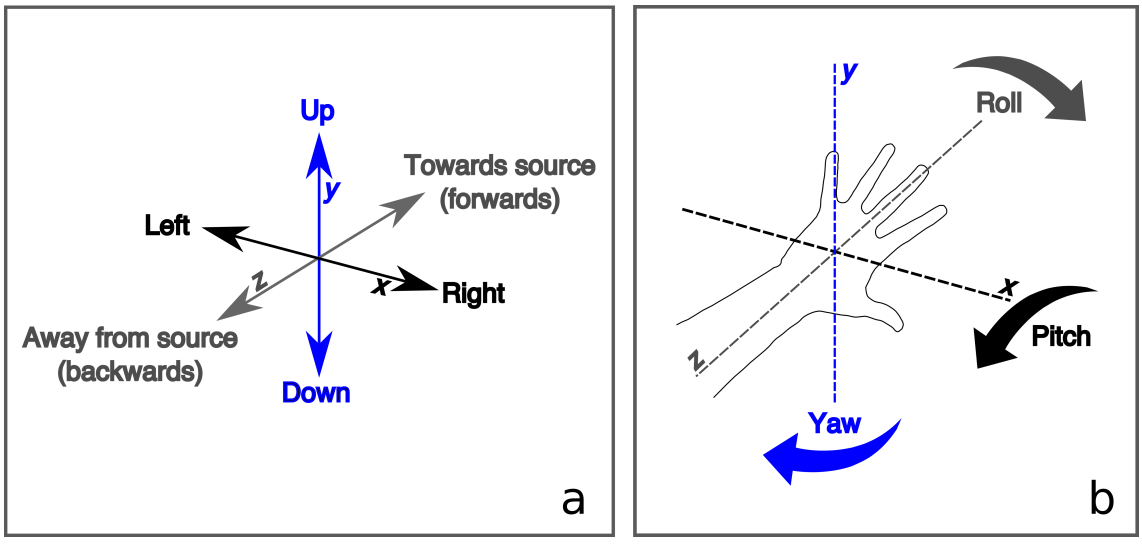


Figure 9: Positional and orientational coordinates for EM sensors

Diagram showing positional (a) and orientational (b) coordinates encoded from each sensor as it moves in relation to the magnetic field generated by the source.

The tracking sensors are compact (1cm^3) and lightweight (2g), allowing more naturalistic movement to be recorded, without the impedance associated with bulkier sensors. Readings are highly accurate, with sensitivity to very subtle

changes in position or orientation. Within a range of 30cm, their positional and orientational resolutions are 0.01mm and 0.004 degrees respectively. The high sampling rate allows movement data to be collected in real time, and transference of data from SEU to computer permits offline analysis of kinematic variables (e.g. speed and amplitude). This apparatus has previously been used in kinematic studies of Parkinson's disease and organic dystonia.(236,299,300)

Since close proximity with electronic devices and large ferrous objects can distort the transmitter's magnetic field, the manufacturer recommends that such items be placed at least 1m away from the source. For this reason participants were asked to switch off their mobile phones, and all electronic equipment apart from the tablet computer was powered-down for the duration of the assessments.

The accuracy of measurement is proportional to the distance between the sensors and the source. There is a precipitous decline in positional and orientational resolution when the distance between sensors and source exceeds 100cm. However, if the participant is positioned too close to the source there is a danger that the sensors might pass over the magnetic pole, thus corrupting the data. As a compromise, participants were seated 50cm away from the source.

The sensors were secured over the dorsal aspect of the participant's thumb and index finger (over the nail bed) using Velcro straps. A third strap was used to secure the wires at the patient's wrist, to prevent them getting tangled or obstructing movement. This arrangement was comfortable for participants and permitted free movement of the digits.

2.3 Assessment procedure

2.3.1 Collection of demographic and historical details

After consent was obtained, the following details were collected for each participant: age, gender, hand dominance, marital status, educational and employment status, country of origin and parental nationality. Handspan and finger-thumb aperture measurements were taken for each hand.

2.3.2 History taking and cognitive examination

For participants with dystonia a semi-structured questionnaire was used to explore the history of their condition. This included questions about the duration of symptoms, age of onset, speed and nature of progression, the presence of spontaneous remissions and any precipitating factors, cognition relating to symptoms (i.e. what they initially thought was causing them), associated pain or sensory disturbance, and the presence or absence of a *geste antagoniste*. They were also asked about their previous medical and psychiatric history, any prior medications used for dystonia, current medications and the date of their last botulinum toxin injections, if applicable. A family history of neurological illness, if present, was recorded.

A Montreal Cognitive Assessment (MoCA) was completed by all participants.

2.3.3 Psychological questionnaires

Each subject was provided with a booklet containing four questionnaires: the Hospital Anxiety and Depression Scale, Fatigue Severity Scale, Brief Obsessive Compulsive scale and the Cambridge Depersonalisation Scale. Details of how the forms should be completed were provided by the examiner at the start, and they remained available to answer any queries while the forms were being completed. All psychological questionnaires are reproduced in Appendix A.

2.3.3.1 Hospital Anxiety and Depression Scale (HADS)

This scale was designed by Zigmond and Snaith in 1983 as a tool for screening general medical hospital populations for emotional disorder.(301) Its strengths are that it is short (14 items, seven for depression and seven for anxiety, scored on a scale of zero to three), acceptable to patients and easy for physicians with no psychiatric training to administer. Weaknesses are the inclusion of some items (for example, “I feel as if I’m slowed down”) that could be attributable to medical disorder rather than depression, and others (“I feel as though I have butterflies in my stomach”) that do not have cross-cultural relevance.(302) Validity testing

across a range of populations and care settings has demonstrated high sensitivity and specificity (approximately 80%) for identifying depression and anxiety.(303,304) It also has good test-retest reliability.(305) It emphasises physical rather than psychological symptoms of depression and anxiety, making it a more acceptable screening tool for patients with functional disorder, many of whom might react defensively towards perceived psychological modelling of their condition. It has previously been used to evaluate anxiety and depression in a range of functional disorders.(295,306)

2.3.3.2 Fatigue Severity Scale (FSS)

This is a self-administered nine-item scale. Severity is graded for each item according to a seven-point Lickart scale and the total score is expressed as the mean of the nine individual scores. Within the movement disorders field, this scale has been most extensively applied and tested in Parkinson's disease. In this patient group it has been shown to perform well, with minimal floor and ceiling effects, significant discrimination between disease and non-diseased groups, and high levels of correlation with other fatigue scales. It is the only scale for fatigue "recommended" by the MDS as both a screening and severity-rating tool in patients with Parkinson's disease, and has been validated for use in a range of other chronic medical conditions.(307) It has been applied to patients with dystonia, and two functional disorders—chronic fatigue syndrome and fibromyalgia.(308–311) High levels of test-retest reliability have been demonstrated, and its brevity and simplicity make it acceptable to patients and easy to use in the clinic. Weaknesses include the absence of a clear definition of fatigue, and a dearth of studies examining overlap with self-rated affective symptoms. Though it has not been independently validated in functional movement disorder, based on the above findings it seemed the most appropriate choice for rating fatigue in both functional and organic dystonia. The scale is copyrighted but available free of charge.

2.3.3.3 Brief Obsessive Compulsive Scale (BOCS)

This scale, developed by Bejerot in 2002, is a short self-report tool derived from

the much longer Yale-Brown Obsessive Compulsive Scale (Y-BOCS), which is considered the gold standard for assessment of obsessive compulsive disorder (OCD).(312) Patients are first asked to complete a symptomatic screen for obsessive-compulsion, comprising a fifteen item checklist covering eleven symptom categories, including contamination/cleanliness, self-harm, sexual obsession, checking, symmetry/exactness, religious/superstistious/magical thoughts, morality and justice, hoarding/saving and somatic obsession. For each item patients must indicate whether it is 'current' (within the last week), 'past' (present previously, but not in the last week) or 'never' (never experienced). They then complete a six-item severity scale—each item rated from zero (none) to four (extremely)—indicating the functional impact of their obsessive-compulsive symptoms over the preceding seven days. Its validity in a mixed psychiatric outpatient setting has been demonstrated, with high sensitivity (85%), specificity (62%) and internal consistency (over 80%) for the symptom checklist, and also for the severity scale. It is freely available online.

At the start of the study (first 16 participants) the 'gold standard' Y-BOCS(313) was administered, but patients found this too onerous in the context of an already quite lengthy experimental protocol. The BOCS was much more acceptable. This has not been validated in non-psychiatric populations, but several studies have used Y-BOCS to evaluate obsessive-compulsive symptoms in patients with dystonia.(198,202,314) Since there is good correlation between YBOC and BOCS,(312) this seems a reasonable choice for a snapshot assesment of obsessive-compulsion in these patient groups. The methodology was therefore adapted after the study commenced, replacing the Y-BOCS with the shorter and more user-friendly BOCS.

2.3.3.4 Cambridge Depersonalisation Scale (CDS)

Within the *DSM-5*, depersonalisation is defined as 'an alteration in the perception or experience of the self so that one feels detached from, and as if one is an outside observer of, one's mental processes or body.' It is a syndrome comprising ineffable feelings of 'unreality', emotional blunting, hypervigilance, altered agency and disturbed attentional processing. Such symptoms may occur in the context of

primary psychiatric disorders (including depersonalisation disorder, depression and OCD), or with neurological disorders (such as migraine and temporal lobe epilepsy). These dissociative symptoms (and the closely aligned symptoms of derealisation—altered perceptual experience of the external world) are prevalent in functional motor disorders and are thought to play an important pathophysiological role.(315) The CDS,(316) a 29-item self-report scale, is freely available online. Scores for frequency and duration are combined to give an item score, which are then summed to provide a global severity rating. The discriminative validity and reliability of the CDS has been demonstrated in both psychiatric and non-psychiatric populations.(317–319)

2.3.3.5 Pain score (visual analogue scale)

Participants scored their pain, at the time of assessment, on a visual analogue scale from zero ("no pain") to 20 ("worst possible pain").

2.3.4 Clinical rating of dystonia

All kinematic assessments were recorded on video, along with a clinical assessment, perfomed according to the Fahn-Marsden video protocol (see Appendix A). The videos were assessed by three movement disorders specialists, blinded to the diagnosis (to obtain two independent ratings per patient). Three clinical rating scales were used.

2.3.4.1 Fahn-Marsden Dystonia Rating Scale (FMDRS)

The clinician-rated movement subscale of the FMDRS(320) was chosen as the most approriate tool for rating a patient group with a diverse phenotypic profile. The FMDRS rates dystonia severity and activity-dependence ('provoking factor') in nine body regions. Severity is rated from 0 (no dystonia) to 4 (severe dystonia). Provoking factor is rated using a similar four-point Lickart scale (0= no dystonia present at rest or with action, 4= dystonia present at rest). Scores for eyes, mouth and neck are down-weighted by a factor of 0.5, to reflect their lower contribution to overall disability. Severity and provoking factors are multiplied and then

combined to give a total score out of 120. This is the scale recommended by the MDS for use in generalised dystonia, based on evidence of good internal consistency, inter-rater reliability and sensitivity to change.(321) It has been used to evaluate DBS response in patients with cervical dystonia, along with the Toronto Western Spasmodic Torticollis Rating Scale (the most frequently used scale for cervical dystonia).(322)

2.3.4.2 Simplified Functional Movement Disorders Rating Scale (S-FMDRS)

Hinson et al. developed a scale for measuring severity of FMD in 2005.(323) This was lengthy and cumbersome to use, but a shortened version has recently been published, which has high inter-rater reliability and sensitivity to change.(324)

2.3.4.3 Finger tapping score

Neither of the scales described above contains an individual measure of finger tapping performance. The finger tapping item from the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was therefore used for this purpose.(325) This provides a score between 0 (normal) and 4 (severe bradykinesia) for the task.

2.3.5 Finger tapping assessments

The EM sensors were attached to the participant's finger and thumb. They were asked to sit up straight with their back resting against the chair and to hold their arm with the elbow flexed and unsupported, palm facing the examiner and roughly in line with the shoulder. Three finger tapping tasks were assessed. All tasks were undertaken with the dominant hand first, then repeated with the non-dominant hand. Individual tasks were repeated only if there was a technical problem (such as failure of the SEU to record, or slippage of one of the sensors).

2.3.5.1 'Freestyle' (repetitive self-paced) finger tapping

The participant was requested to "tap your index finger and thumb as big and as

fast as possible for 15 seconds, when I say begin". This task was repeated twice. The researcher provided a demonstration of the required movement—opening and closing her finger and thumb with high-amplitude, fast and rhythmic movements—but this demonstration did not overlap with recording of the participants' movements.

This task was designed to probe for variability in motor performance between trials, drawing on the approach used in a similar study of a mixed cohort of patients with various movement disorders.(261)

2.3.5.2 Finger tapping with and without metronome (1Hz, 2Hz and 3Hz)

In contrast to the 'freestyle' finger-tapping condition, in which subjects' finger-tapping was internally-driven, according to a broad instruction to tap with high speed and amplitude, the metronome tasks probed the response to pacing. For these tasks participants were instructed not to worry about the size of the movement but to focus instead on "tapping in time with the metronome (a sound emitted from the computer) for 15 seconds" (*with* metronome condition—externally paced by an auditory cue) then, when the metronome stopped, to "keep tapping at the same rate for another 15 seconds" (*without* metronome condition—internally timed tapping, in line with the remembered rhythm of the metronome). These tasks was undertaken at three different frequencies: 1Hz, 2Hz and 3Hz.

The task was designed to explore the impact of distraction (the need to maintain focus on matching rhythm with the metronome) on motor performance. Three different frequencies were chosen because a similar study in functional tremor had demonstrated a differential effect across a range of frequencies.(326)

2.3.5.3 Finger tapping with activation of geste antagoniste

For patients with dystonia who reported a *geste antagoniste*, a final finger tapping exercise, using the same instructions as those for the freestyle task, was undertaken while they activated their sensory trick.

2.3.5.4 Rationale behind choice of assessments

2.3.5.4.a Why finger tapping?

Finger tapping tasks are well established in the literature as a means of analysing different aspects of the dynamics of movement. They are simple and quick to perform and may easily be incorporated into a standard clinical assessment. These tasks have been used successfully, in conjunction with the same EM sensor technology, to study Parkinson's disease and organic dystonia.(236,299,300) Finger-tapping tasks have also been used to examine motor performance in patients with organic and functional movement disorders.(261–263)

2.3.5.4.b The duration and number of self-paced finger tapping tasks

A key feature of interest is variability in performance over time. Clinically patients with functional movement disorders display inconsistency over sequential examinations. By repeating the same task several times there is a greater opportunity to capture this inconsistency (increased variability in performance between trials) and establish whether it is more prominent in the FD group.

In the pilot phase of the study a range of durations and number of repeats were trialled. A duration of fifteen seconds with three repeats was chosen as a compromise between maximising opportunity for detecting variability (by recording for a longer period) and reducing the likelihood of physiological fatigue.

2.3.5.4.c The metronome task: the role of distraction

The modulation of motor function with attention is a central aspect of functional movement disorder. Movement fluency and speed tends to improve with distraction and worsen with directed attention towards the affected limb. This task was chosen to attempt to analyse this phenomenon. Three different frequencies were chosen. In the pilot phase of the present study, the three frequencies used Schwingenschuh et al.(326) (2Hz, 3Hz and 5Hz) were used, however, due to differences in task design (index finger-thumb tapping, rather than finger-lever

tapping), the highest frequency proved difficult for our subjects to match, so lower frequencies were selected.

2.4 Preprocessing of movement data

Before analysis, data was pre-processed to remove high-frequency noise using a low-pass (5Hz) Butterworth filter. Positional movement data was collected, with separation calculations made for every $1/60^{th}$ second time point. The x, y and z coordinates from the index finger sensor were subtracted from those for the thumb sensor to give the separation distance between the digits. The Euclidean distance, D, or overall positional separation was then calculated using the formula:

$$D = \sqrt{(x^2 + y^2 + z^2)}$$

Where x, y and z are the coordinate distances of the index finger relative to the thumb (see Figure 10).

In this manner, a sequence of digit separations over time was produced. The separation time series data were differentiated, first to give values for velocity over time (dD/t), and a second time to provide acceleration time series data (dD^2/t) (see Figure 11).

2.5 Calculation of separable movement components

2.5.1 Defining individual tap cycles

A custom-made MATLAB script was used for analysis of the separable components for the finger tapping tasks. The components for an individual tap cycle were defined first, then average values for each 15s trial were calculated by dividing the sum of the values by the number of tapping cycles per 15s period. In addition, variability and decrement of both amplitude and velocity were calculated for each trial period.

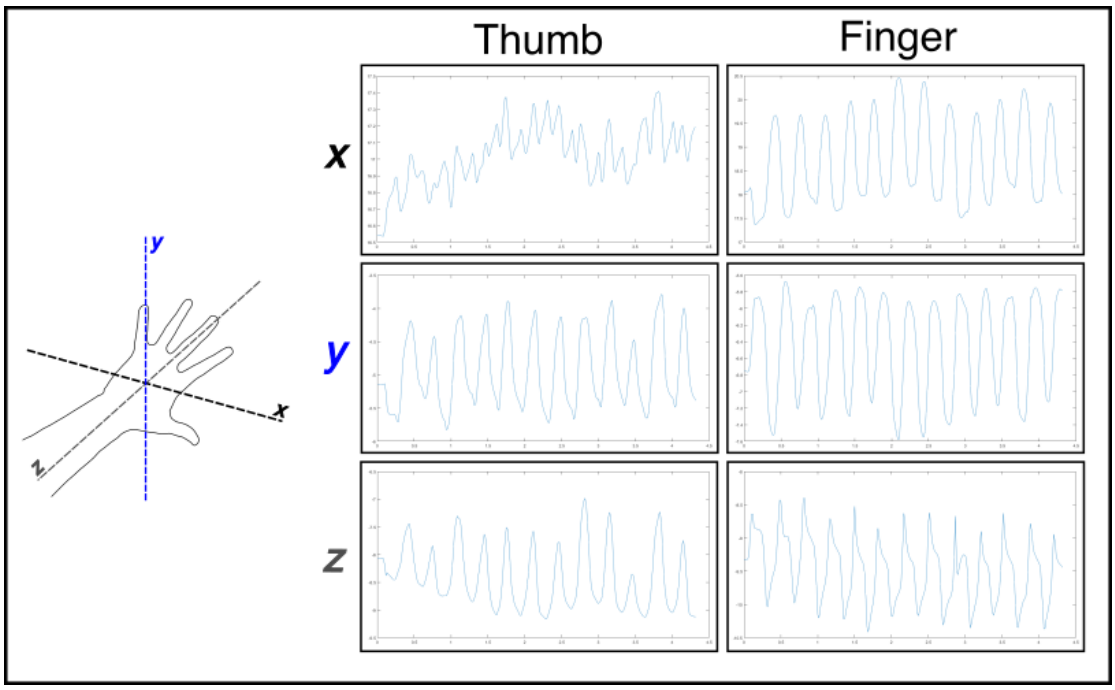
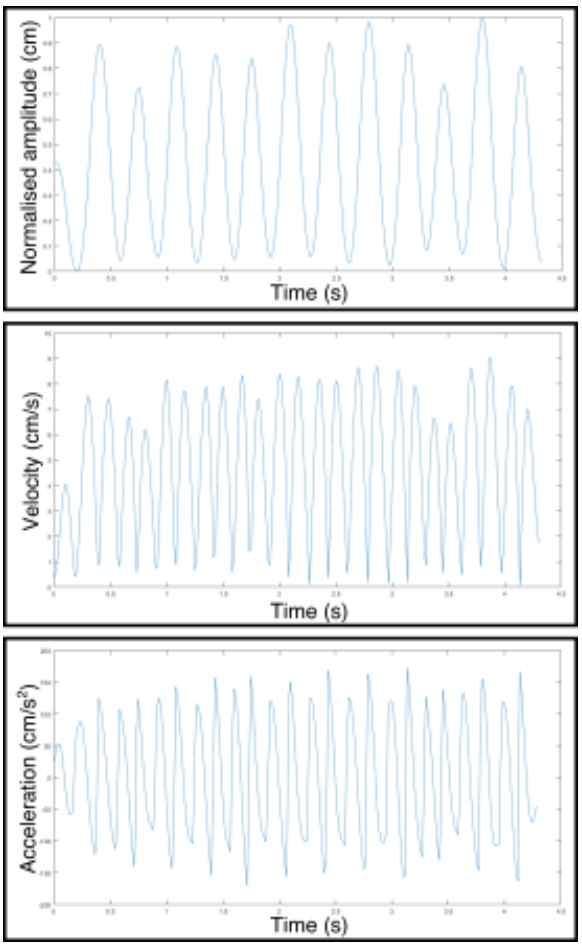


Figure 10: Raw kinematic data

Diagram showing plots of the raw data (Cartesian coordinates x, y and z in cm) over time (s) for a control subject, with the coordinates of sensor 1 (thumb) shown on the left, and those of sensor 2 (index finger) on the right. *Data series provided by Siti Muhamed.*



<u>Figure 11:</u> Kinematic data: separable components of movement

X axes show time in seconds. The first box shows normalised amplitude in cm, the second this data differentiated to give velocity over time (cm/s), and the third the second derivative of the amplitude data, showing acceleration in cm/s^2.

Data series generated by Siti Muhamed.

Each finger tapping cycle comprises an opening phase and a closing phase (Figure 12). The opening phase begins with finger and thumb in opposition and ends at the point of maximal fingertip separation; the closing phase commences at this point and ends when the digits are fully opposed again. Each 15s trial, containing multiple finger tapping movements, was divided into individual opening-closing cycles, defined as the period between two minimal separation points (i.e. two sequential oppositions).

2.5.2 Data normalisation

In order to permit comparison between measurements across subjects, it was necessary to take into account variability in hand size. Normalisation was achieved using the following formula:

$$\text{Normalised amplitude} = \frac{D - D_{min}}{D_{max} - D_{min}}$$

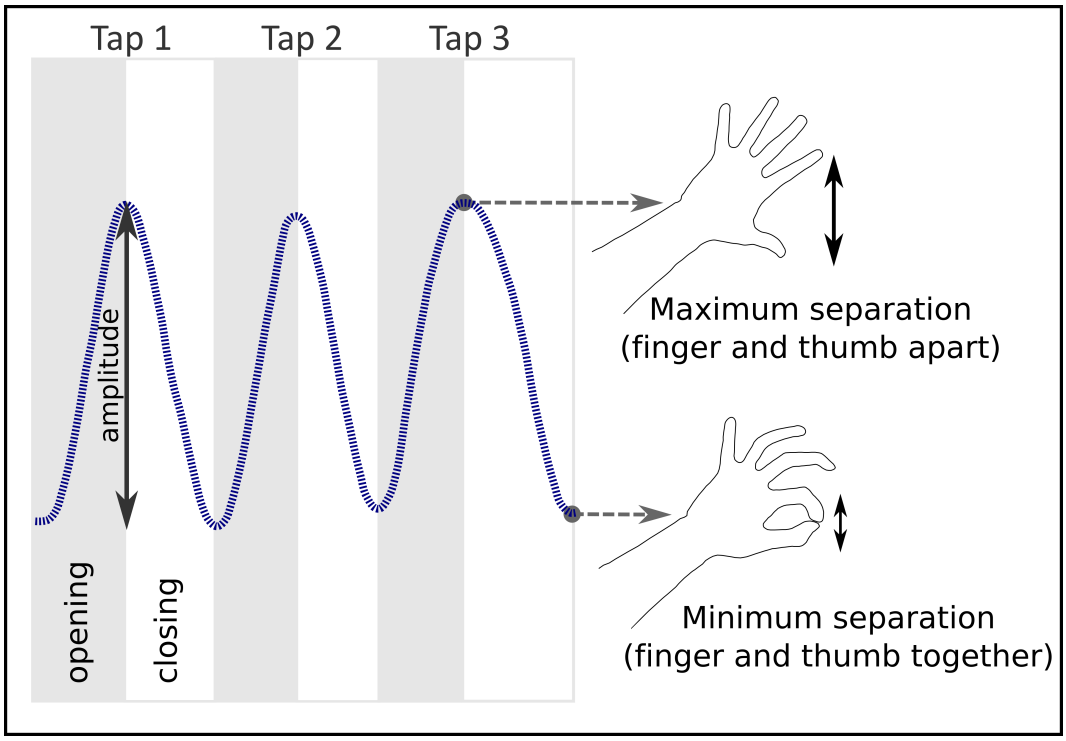


Figure 12: Representational diagram of finger tapping cycles

Diagram showing opening (grey background) and closing phases (white background) for three consecutive tap cycles.

From each calculated separation distance, D, the minimum separation D_{min} was subtracted, in order to take into account differences in the antero-posterior dimensions of the digits between subjects. The product was then divided by the maximum separation distance (D_{max} - D_{min}), to account for variation in finger-thumb aperture. Normalised amplitude values range from zero to one and represents the distance between finger and thumb, relative to the anatomical dimensions of the participants' hands.

2.5.3 Measured kinematic features

2.5.3.1 Amplitude

The maxiumum amplitude for each tapping cycle (the maximal excursion of the sensors) was calculated. These data were then averaged for each 15s finger tapping trial by summing the values and dividing by the number of tapping cycles over the 15s period.

A measure of average amplitude for each tapping cycle was also calculated by summing the separation data points for each cycle and dividing by the number of data points. A mean value for the entire 15s task was then calculated.

2.5.3.2 Frequency

This was calculated by dividing the number of tapping cycles by the time taken to complete the task.

2.5.3.3 Velocity

Values for normalised amplitude were differentiated to generate a set of velocity data points. The maximum velocity for each tapping cycle was identified, and the average calculated by summing all the maximum velocity values and dividing by the number of cycles.

Average velocity for each tapping cycle was calculated by summing all of the velocity data points in one cycle and dividing by the number of data points. From these data, a mean for each 15s task was derived. Values for maximum opening and closing velocity were also extracted, by identifying maximum values for each tapping cycle and calculating the mean of these values for the duration of the task (15s).

2.5.3.4 Acceleration

Values for velocity were differentiated to generate measures for acceleration. The maxima for opening and closing acceleration and opening and closing deceleration were identified for each tapping cycle. Averages were then calculated by summing these values and dividing by the number of cycles. Values for maximum opening and closing acceleration and deceleration were also extracted, by identifying maximum values for each tapping cycle and calculating the mean of these values for the duration of the task (15s).

2.5.3.5 Halts

A measure of haltingness was obtained by dividing the time spent at <5% maximum speed, by the time taken for the task, then multiplying by 100 to produce a percentage value.

2.5.3.6 Hesitations

A MATLAB script was written to detect and count smaller peaks in every tapping cycle. The number of hesitations for every patient is maximum value counted (in a single tap).

2.5.3.7 Coefficient of variation for amplitude

This was a measure of rhythm, calculated by dividing the standard deviation of maximum amplitude by the mean of maximum amplitude values.

2.5.3.8 Coefficient of variation for velocity

This was a measure of rhythm, calculated by dividing the standard deviation of maximum velocity by the mean of maximum velocity values.

2.5.3.9 Decrement (amplitude)

This was established by plotting the maximum amplitude values for each tapping cycle, and using a linear regression (MATLAB 'polyfit' function) to find the linear fitting line and take its slope.

2.5.3.10 Decrement (velocity)

This was derived by plotting the maximum velocity values for each tapping cycle, and using a linear regression (MATLAB 'polyfit' function) to find the linear fitting line and take its slope.

2.5.3.11 Amplitude x frequency

Better performance during the finger tapping tasks might be indicated by faster (more frequent) finger tapping cycles, or larger amplitude movements. The product of amplitude and frequency gives the excursion of the movement sensors per unit time, a measure of the average speed of movement during the 15s task. This was calculated, as per Jobbagy et al.(327) using the following formula:

$$\text{Amplitude x frequency} = \Sigma(A_i / T_i) / n$$

A_i is the amplitude for the ith tapping cycle, and T_i its time period. The sum of all amplitude-time period ratios is then divided by the number of tapping cycles, n.

2.6 Statistical analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences release 24. Data was first analysed for normality and equality of variance using a variety of methods (histogram plotting, Q-Q charts, Kolmogorov-Schimrov and Levene's testing). If data were not normally distributed, even after

transformation, non-parametric tests were used. Between groups analysis was performed using Kruskal-Wallis tests followed by *post hoc* pairwise comparisons using the Dunn-Bonferroni approach. For repeated measures analysis factorial ANOVA (analysis of variance) was applied (with adjustment for pairwise comparisons using the Games-Howell approach). When the condition of sphericity was not met, the results of multivariate analysis was quoted. For group-wise comparisons for categorical data, Fisher's exact testing with Bonferroni adjustment was used.

Chapter Three:

Results (clinical assessments)

3.1 Recruitment

A total of 75 subjects were recruited to the study—33 with organic dystonia, 13 with FD and 29 healthy controls. The sources of recruitment are displayed in Table 6.

Table 6: Sources of recruitment for the study

Subgroup	Participant Numbers		
	Monash Medical Centre	Australian Dystonia Support Group	Leeds General Infirmary
Organic dystonia	24	8	1
Functional dystonia	9	1	3
Healthy controls	29	0	0

3.2 Demographic and clinical profile of study participants

3.2.1 Demographic details

The demographic details of the three populations (minus one healthy control subject, who did not want to complete the psychological questionnaires) are summarised in Table 7.

In each of the three groups the majority were right-handed and roughly two thirds were female, with no significant group differences for gender or handedness detected on Fisher's exact testing. Since the age distribution for healthy controls was bimodal (with peaks in mid 20s and early 60s), non-parametric Kruskal-Wallis testing was used to compare the groups for age. Patients with FD were significantly younger than their organic counterparts (***p*=0.02**), but there was no difference between healthy controls and either patient group. Significantly fewer patients with organic dystonia than controls had tertiary level education (***p*=0.003**, post hoc Fisher's exact test with Bonferroni adjustment); other pair-wise comparisons for education were non-significant. MoCA scores were significantly higher in healthy controls than both functional (***p*=0.009**) and organic (***p*=0.001**) dystonia, but there was no significant difference between the patient groups. A greater proportion of patients with FD than both organic dystonia and healthy controls were unemployed (***p*=0.006** and ***p*=0.0002** respectively).

Table 7: Summary of participant demographic details (clinical assessments)

	Organic (n = 33)	Functional (n = 13)	Controls (n = 28)	P value
Age	61 (26.5)	39 (28.5)	54 (35)	**0.02**
Gender (F:M)	20:13	10:3	19:9	0.6
Handedness (R:L)	27:6	10:3	25:3	0.4
% Married/co-habiting	70	62	72	0.8
Education	25:8	7:6	9:19	**0.006**
% Unemployed	3	54	0	**<0.0005**
MoCA score	25 (4.5)	25 (3.5)	28 (4.0)	**< 0.0005**

Median values for age and MoCA score displayed with interquartile range in brackets. Ratios of patient numbers shown for gender and handedness. Ratio of secondary to tertiary education shown for education. *p* values indicate the effect across groups (pair-wise comparisons are quoted in main text).

F = female; L = left; M = male; MoCA = Montreal Cognitive Assessment; R = right.

3.2.2 Phenomenology

The phenomenological features of patients with FD are detailed in Table 8. Those for patients with organic dystonia are shown in Table 9.

Nine out of thirteen patients with FD (69%) and 23/33 patients with organic dystonia (70%) had clinical involvement of one or both upper limbs.

Of the patients recruited with organic dystonia, three (9%) had right hemidystonia (all secondary), four (12%) had generalised dystonia (one secondary, three genetic), eight (24%) had various patterns of segmental disease affecting the cranial, cervical or upper limb muscles (three genetic, the rest idiopathic). Eighteen (55%) had focal dystonia (one genetic cervical dystonia, the rest idiopathic). Of these, four had task-specific (writer's or musician's) focal upper limb dystonia, six had cervical dystonia with dystonic features in the upper limbs (subtle posturing or tremor), and eight had clinically isolated cervical dystonia.

Table 8: Phenomenological features of patients with functional dystonia

Age at onset/ time of study	Distribution	Onset type	Course	Fahn-Williams classification
22/26	Bilateral upper limb and cervical dystonia, tremor and myoclonus.	Sudden onset two weeks after witnessing the aftermath of a bomb blast.	Stable, no remissions.	Clinically established
34/35	Fixed left lower limb dystonia, with vasomotor changes and functional weakness.	Sudden onset after minor sports injury, associated with symptoms of panic and belief that had sustained spinal fracture.	Partial remission: dystonia less fixed and resolution of vasomotor changes.	Clinically established
64/68	Dystonia in left upper and lower limbs. Dynamic posturing alternating with periods of fixed posturing.	Sudden onset (few days) in context of calf pain, relapses often triggered by pain. Later spread to upper limb.	Relapsing and remitting: spells of sustained fixed posturing alternating with briefer paroxysms.	Documented
30/32	Dystonia right upper limb, neck and face. Dissociative seizures.	Sudden onset (few days) upper limb dystonia after shoulder dislocation.	Stable, subsequent development of neck and facial spasm following shoulder manipulation.	Clinically established
16/22	Truncal dystonia.	Tic disorder from age 11. Truncal movements initially conscious attempt to "turn body into a shell", gradually became unconscious and insuppressible.	Relapsing and remitting, fluctuating with stress.	Clinically established
65/66	Task-specific dystonia and intermittent tremor left upper limb, functional left hemiparesis.	Sudden onset functional hemiparesis and stuttering dysarthria following physical assault. Tremor and dystonic posturing emerged months later.	Stable. Dystonic posturing variable and somewhat task-specific.	Clinically established

Table 8: Phenomenological features of patients with functional dystonia

Age at onset/ time of study	Distribution	Onset type	Course	Fahn-Williams classification
53/59	Dynamic facial and right lower limb dystonia.	Sudden onset with no clear trigger.	Fluctuating, correlating with stress.	Clinically established
38/39	Paroxysmal craniocervical dystonia, neck and right upper limb tremor, involuntary vocalisations.	Sudden onset after road traffic accident.	Paroxysms of dystonia correlating with stress or when reminded of circumstances of RTA.	Clinically established.
24/24	Fixed left lower limb dystonia, functional weakness and tremor. Dissociative seizures.	Sudden onset weakness after episode of severe lower back pain. Dystonia emerged subsequently.	Stable.	Clinically established.
54/56	Generalised mainly upper body dystonia, tremor and weakness.	Sudden onset following chiropractic manipulation.	Paroxysms of upper limb and truncal dystonia, some episodes of fixed jaw dystonia.	Clinically established.
24/44	Mainly craniocervical. More generalized paroxysmal spasms.	Sudden onset following thunderclap headache.	Fixed hemifacial spasm. More recent painful paroxysmal spasming of both feet and hands.	Clinically established
30/34	Left upper limb and facial dystonia. Tremor in upper limbs and weakness in legs.	Sudden onset in context of stress at work.	Fluctuating. Sudden offset when discovered wife had miscarried.	Clinically established
34/43	Fixed dystonia of both hands and feet.	Sudden onset. Paroxysms of spasm evolved into continuous fixed posturing over two months.	Step-wise evolution: right hand, left hand, left foot, right foot over 12 month period.	Clinically established

Table 9: The phenomenological characteristics of patients with organic dystonia

Subtype	Number of patients	Details
Secondary	4	Neonatal hypoxic injury: lifelong right hemidystonia. Task-specific dystonia left upper limb in 6th decade.
		Left basal ganglia stroke: right hemidystonia.
		Head injury in infancy: right hemidystonia. Exacerbation following trauma to right shoulder.
		Head injury in infancy: right hemidystonia.
Genetic (unknown gene)	4	Generalised (truncal, cervical, brachial)
		Generalised (left-sided emphasis)
		Segmental (craniocervical)
		Focal (cervical)
Genetic (confirmed)	3	*DYT1*: segmental (cervical and both upper limbs)
		ADCY5: facial dyskinesia, continuous dynamic cervicobrachial dystonia, paroxysmal painful lower limb dystonia, chorea and myoclonus.
		ANO3: blepharospasm, oromandibular, cervical and upper limb dystonia
Idiopathic	22	13 Cervical dystonia: 6 with clinical upper limb involvement.
		2 Writer's cramp (both right hand)
		2 Musician's dystonia (one right hand, one both hands)
		5 Segmental (2 craniocervicobrachial, 2 writer's cramp and cervical, 1 blepharospasm and cervical)

For the functional group the distribution was slightly different but the proportions for each broad category were roughly the same: one (8%) with hemidystonia, two (15%) with truncal or generalised dystonia, three (23%) with segmental (cranio-cervico-brachial), four (31%) with multifocal (cranial with either upper or lower limb involvement), and three (23%) with fixed focal lower limb or upper limb dystonia. Two thirds of the patients had other FMDs at the time of examination (tremor, myoclonus, weakness).

In terms of historical features, 11/13 patients with FD reported a sudden onset, in the context of either pain (three patients), minor injury (twisted ankle, fall during basketball game, shoulder dislocation), or stressful incident (physical assault, road traffic accident, workplace stress, bearing witness to a bomb blast). One patient developed a severe generalised FMD following a chiropractic manipulation. Her symptoms had thereafter followed a waxing and waning course. During relapses she remarked *"my brain seems to be remembering the first injury, which comes back"*. One patient developed fixed dystonia in all four limbs, sequentially, in a step-wise fashion, over six months with no obvious trigger. Another man in his early 20s, who suffered from obsessive-compulsive symptoms and motor tics in childhood, reported assuming a flexed truncal posture in an attempt to suppress the tics or make them less noticeable, to *"turn my body into a shell that people can't see"*. Over time the truncal spasms became more prominent and were no longer under conscious control. Five of the patients recognised stress as a potential precipitating or perpetuating factor.

Interestingly, there was some overlap between the two groups in terms of these historical features. Ten patients with organic dystonia (one secondary, seven idiopathic, two genetic) reported worsening symptoms with stress or anxiety, eight (seven idiopathic, one genetic) identified stress as a trigger and five (three idiopathic, two genetic) reported a sudden-onset or precipitous decline in dystonic symptoms.

3.2.3 Disease duration

Patients with organic dystonia had a significantly longer disease duration than that of patients with FD, with a median duration of 20 years (interquartile range 26) versus four years (interquartile range 5) (**$p<0.0005$**, Mann-Whitney *U* testing), see Figure 13. This is not surprising, given the lower rate of retention of functional patients in neurology clinics.

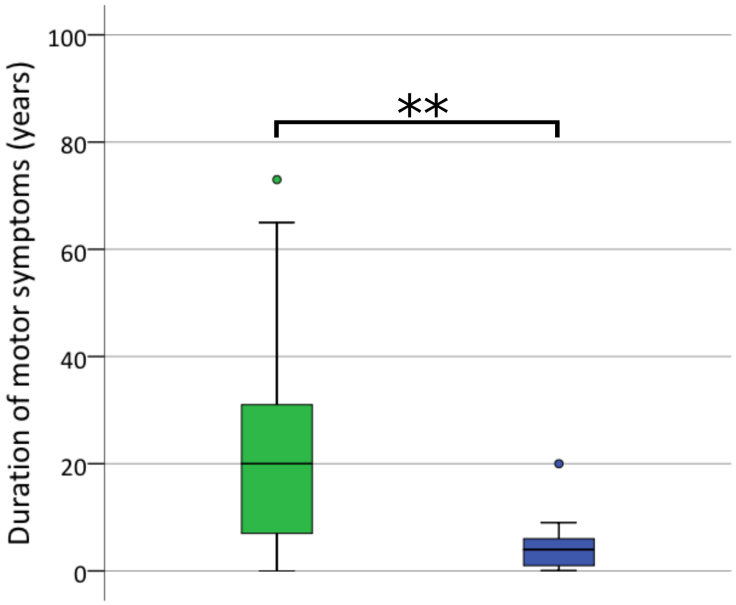


Figure 13: Duration of motor symptoms for organic and functional dystonia
Organic (green) and functional (blue) dystonia. Boxes = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Bracket with asterixes = significant difference.

3.2.4 Psychotropic medication use

Thirteen patients with organic dystonia (39%), 12 with FD (92%) and three healthy controls (11%) were taking at least one psychotropic medication (benzodiazepine, antiepileptic, opiate, antipsychotic, antidepressant or baclofen). The median number of drugs for organic dystonia was zero, compared with a median of two in the functional group. When the number of medications were compared across the groups, by Kruskal-Wallis, patients with FD were taking significantly more than either those with organic dystonia (***p* < 0.0001**) or healthy controls (***p* < 0.0001**). See Figure 14.

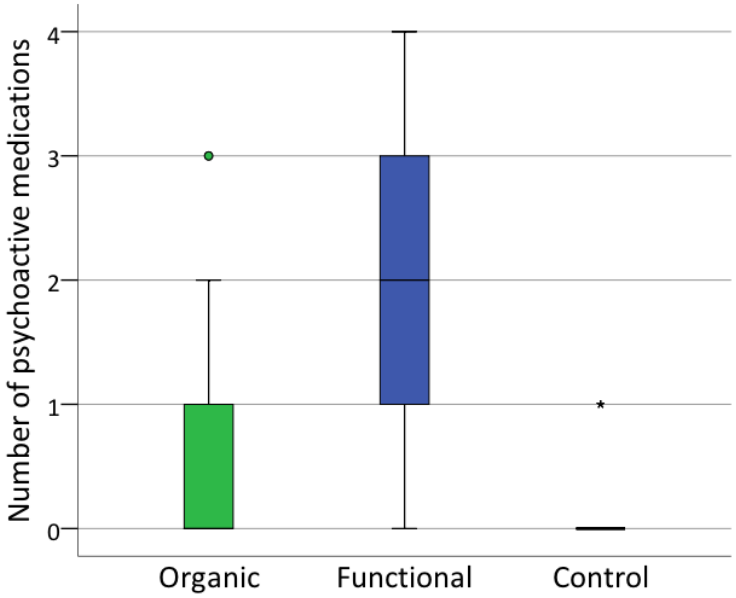


Figure 14: Psychotropic medication use

Number of medications for organic (green) and functional (blue) dystonia. Boxes = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Circles = outliers.

3.2.5 Time since last botulinum toxin injections

Attempts were made to ensure that all patients receiving botulinum toxin therapy for dystonia were assessed at least 12 weeks after their last dose, in order to reduce the influence of toxin on motor performance. Unfortunately in a minority of cases (10 organic and two functional) this was not possible, because of tight constraints on patient and clinic room availability. Of the organic patients, eight had cervical dystonia and received injections only within the cervical musculature. The other two had secondary dystonia, and had received upper limb injections nine and eleven weeks before assessment, respectively. One patient with FD had received cranial and cervical injections three days prior to assessment, the other had injections into the upper and lower limb 11 weeks prior to assessment.

3.2.6 Summary of demographic and phenomenological features

Compared to those with organic dystonia, patients with FD were younger, had a shorter disease duration and higher rates of unemployment. Both dystonia groups had lower educational status and MoCA scores, compared with healthy controls,

but they did not differ from one another in this respect. The proportion of patients with clinical involvement of the upper limbs was similar in each group. A greater proportion of patients with FD were using one or more psychotropic medication.

3.3 Clinical ratings

3.3.1 Inter-rater reliability

Two dystonia rating scales (Fahn-Marsden Dystonia Rating Scale (FMDRS) and the Simplified Functional Movement Disorders Rating Scale (S-FMDRS)) were completed by three movement disorders specialists (two for each participant), blinded to the patient's diagnosis. In addition, they gave Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores for finger tapping for both hands, with and without sensors. For all ratings the intraclass correlation (ICC) was calculated, using a one-way model, and analysing for consistency of ratings.

3.3.1.1 Fahn-Marsden Dystonia Rating Scale (FMDRS)

Comparison of ratings revealed a high degree of inter-rater reliability. Average measures ICC was 0.95, with 95% confidence intervals between 0.92 and 0.97 ($F(73,74)=19.4$, $\boldsymbol{p<0.0001}$).

3.3.1.2 Simplified FMD Rating Scale (S-FMDRS)

For this rating scale there was also a high degree of inter-rater reliability. Average measures ICC was 0.93, with 95% confidence intervals between 0.89 and 0.96 ($F(73,74)=14.5$, $\boldsymbol{p<0.0001}$).

3.3.1.3 MDS-UPDRS finger tapping scores (bradykinesia)

Comparison of ratings revealed a high degree of inter-rater reliability for MDS-UPDRS scores with and without sensors. For ratings without sensors, average measures ICC was 0.85, with 95% confidence intervals between 0.75 and 0.90

(F(72,73)=6.4, ***p*<0.0001**) for the right hand, and 0.9, with 95% confidence intervals between 0.84 and 0.94 (F(72,73)=9.9, ***p*<0.0001**), for the left hand. For ratings with sensors on, ICC was 0.84, with 95% confidence intervals between 0.74 and 0.90 (F(71,72)=6.2, ***p*<0.0001**), for the right hand, and 0.70, with 95% confidence intervals between 0.51 and 0.81 (F(71,72)=3.3, ***p*<0.0001**), for the left hand.

The mean of the two blinded raters' scores was used for further analysis. All scores were compared across groups using non-parametric Kruskal-Wallis testing.

Median scores are quoted below, with interquartile range (IQR) in brackets.

3.3.2 Group-wise comparisons for scores

3.3.2.1 Fahn-Marsden Dystonia Rating Scale (FMDRS) scores

Average rater scores for both organic (8.75 (12.75), ***p*<0.0001**) and functional (8.50 (18.75), ***p*<0.0001**) dystonia differed significantly from healthy controls, but there were no significant differences between the dystonia groups (*p*=1.0).

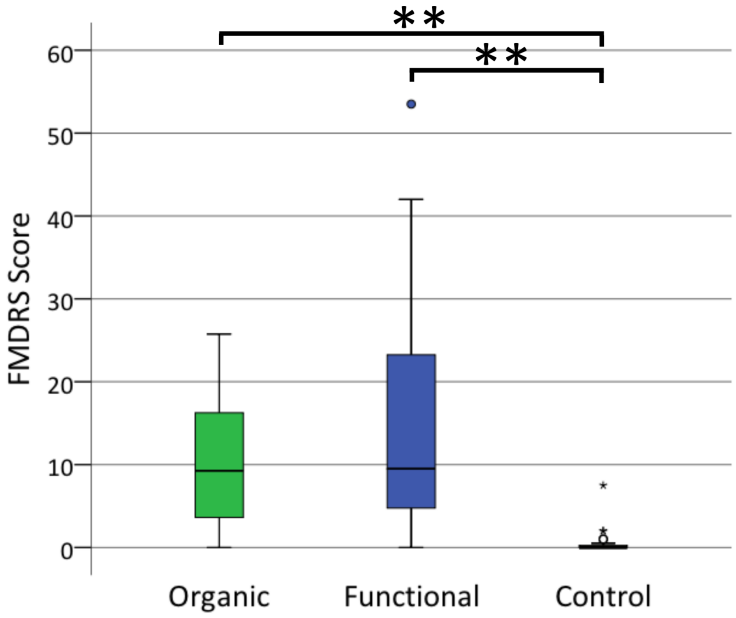


Figure 15: Organic dystonia scale (FMDRS) Scores

Boxes = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Bracket with asterixes = significant difference.

3.3.2.2 Simplified FMD Rating Scale (S-FMDRS) scores

The same pattern was observed for scores on the functional movement disorder rating scale: both organic (10.5 (11.0), ***p*<0.0001**) and functional (10.0 (19.5), ***p*<0.0001**) dystonia groups differed significantly from healthy controls, but there was not a significant difference between them (p=1.0).

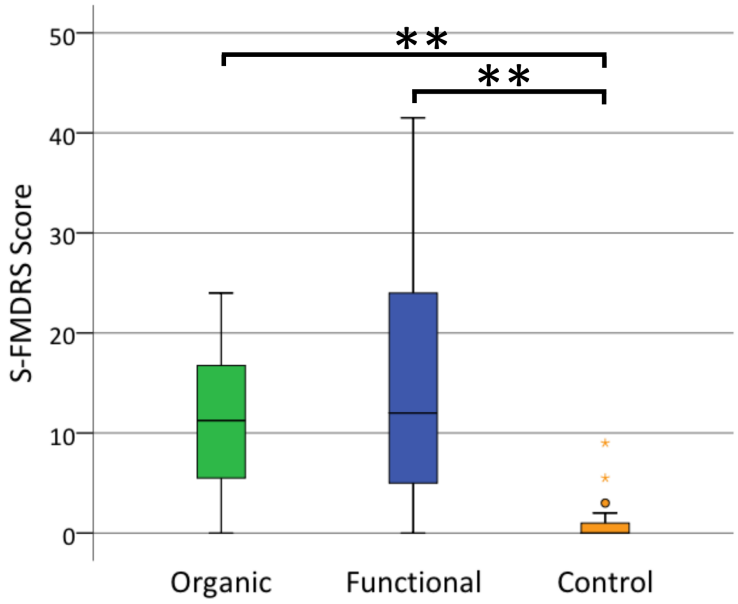


Figure 16: Functional movement disorder scale (S-FMDRS) Scores
Boxes = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Bracket with asterixes = significant difference.

3.3.2.3 MDS-UPDRS bradykinesia scores

Scores for finger tapping with and without sensors were higher in the two dystonia groups compared to healthy controls. For the organic dystonia group, significance was calculated at ***p*=0.002** for the dominant hand (median score 0 (IQR 1)) and ***p*=0.003** for the non-dominant hand (median score 0 (IQR 1.5)), without sensors. For scores 'with sensors' the values were (0.5 (1), ***p*<0.0001**, dominant) and (0.5 (1.5), ***p*=0.03**, non-dominant). For patients with FD, values were (0.5 (2), ***p*=0.001**, dominant) and (0.5 (2), ***p*=0.003**, non-dominant) without sensors; and (0.5 (2), ***p*=0.005**, dominant) and (1 (1.5), ***p*=0.006**, non-dominant) with sensors. There were no significant differences between the dystonia groups in severity of bradykinesia. Scores with and without sensors were compared using the Wilcoxon

Signed Rank test, with no significant differences found for either dominant (p=0.09) or non-dominant (p=0.63) hands.

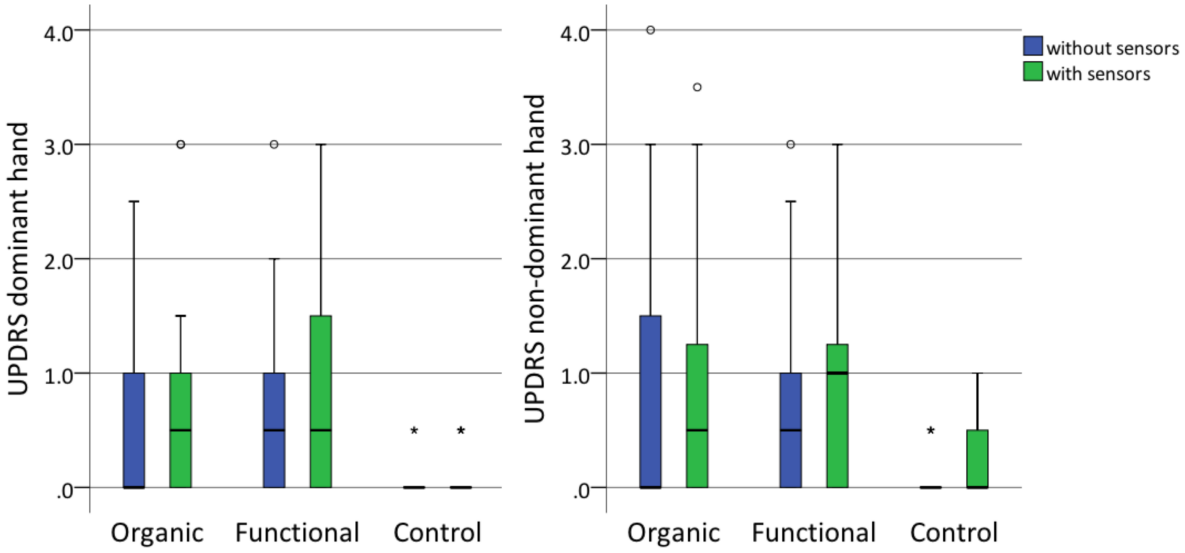


Figure 17: MDS-UPDRS finger tapping scores

Boxes = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Circles represent outliers.

3.3.3 Group comparisons for topography

The figures (18 & 19) and tables (10 & 11) below display the scores for each group, arranged according to affected body part. The topographical distribution is similar for both dystonia groups, though there is a slight excess of lower limb dystonia in the functional group, and of cervical involvement in the organic group. In a small percentage of cases normal fidgety movements or resting postures in healthy controls were misjudged by the blinded raters as dystonic.

Table 10: FMDRS (organic dystonia scale) scores by body region

(percentage of subjects scoring above zero for each region)

	Organic (% of cases)	Functional (% of cases)	Control (% of cases)
Eyes	39	42	0
Mouth	39	25	3
Speech	32	33	3
Neck	87	75	14
Right arm	71	50	14
Left arm	68	67	3
Trunk	39	33	3
Right leg	23	33	0
Left leg	13	33	0

Table 11: S-FMDRS (FMD scale) scores by body region

(percentage of subjects scoring for each region)

	Organic (% of cases)	Functional (% of cases)	Control (% of cases)
Face	55	33	3
Speech	29	42	3
Neck	87	67	14
Right arm	80	42	17
Left arm	71	67	3
Trunk	45	33	3
Right leg	23	33	0
Left leg	16	33	0
Gait	58	67	7

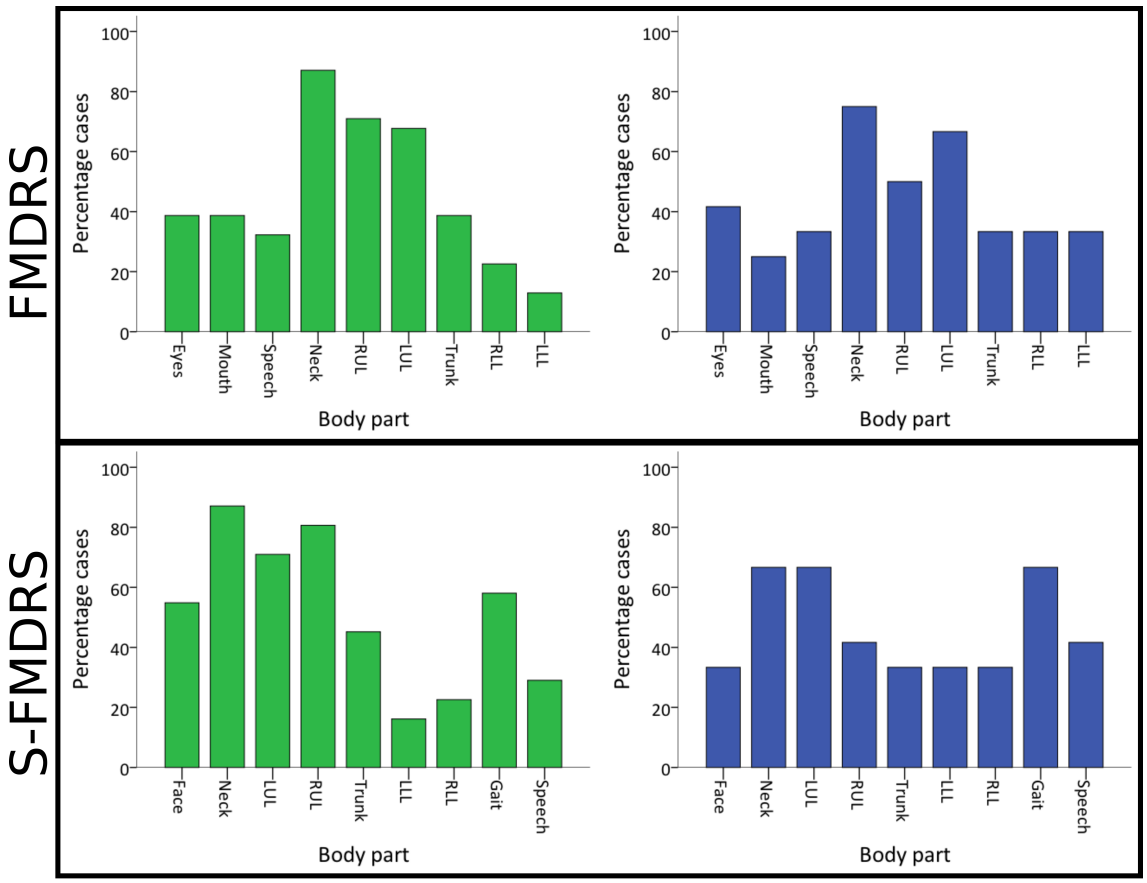


Figure 18:

Percentage of cases scoring for each body part (FMDRS and S-FMDRS)

Graphs showing the percentage of cases for each group that scored above zero for each of the body parts covered by the FMDRS and S-FMDRS. Green = organic dystonia; blue = functional dystonia. LLL = left lower limb; LUL = left upper limb; RLL = right lower limb; RUL = right upper limb.

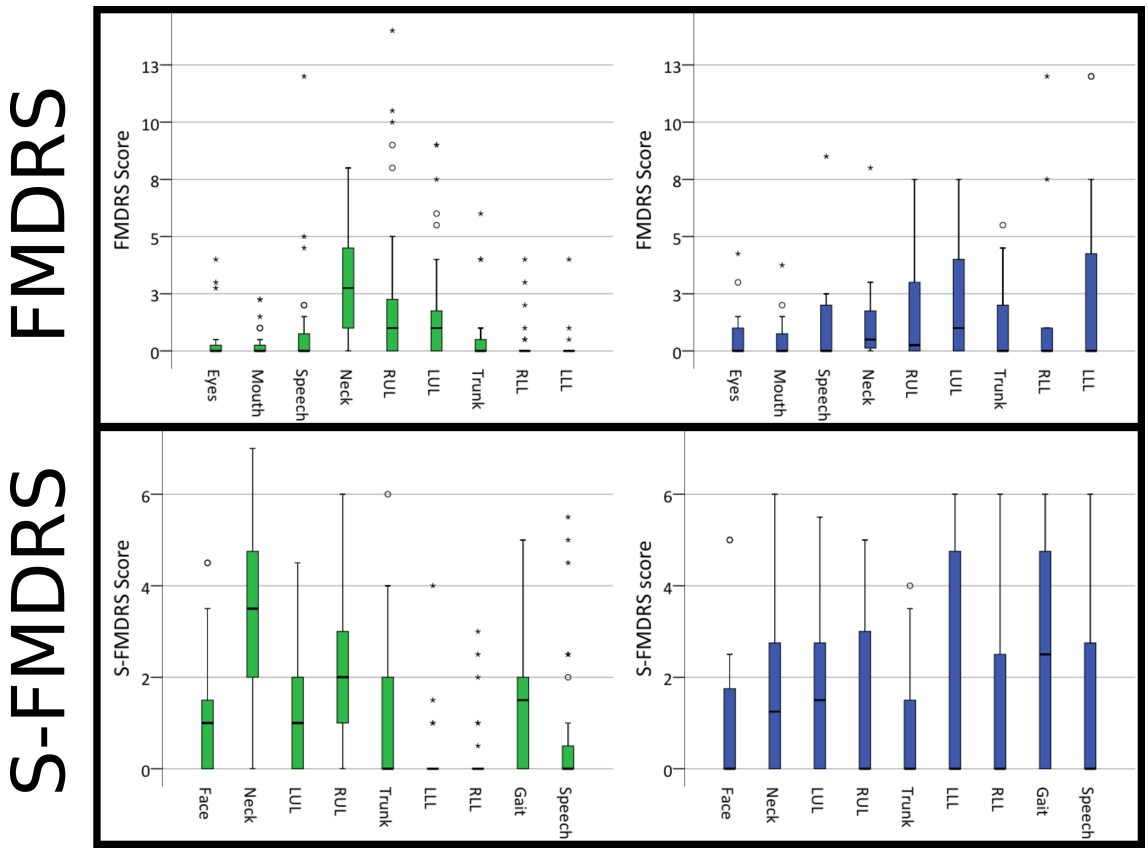


Figure 19:

Spread of scores for each body part (FMDRS and S-FMDRS)

Graphs showing the percentage of cases for each group that scored above zero for each of the body parts covered by the FMDRS and S-FMDRS. Green = organic dystonia; blue = functional dystonia. LLL = left lower limb; LUL = left upper limb; RLL = right lower limb; RUL = right upper limb.

The raters' agreement for severity scoring by body region was calculated using Kendall's coefficient of concordance, W. There was moderate to high concordance for almost every body region (see Table 12).

Table 12: Agreement of raters for motor severity ratings of different body regions (Kendall's coefficient of concordance, *W*)

Body region	FMDRS	S-FMDRS
Eyes	**0.76**	-
Mouth	**0.76**	-
Face	-	**0.79**
Speech	**0.81**	**0.78**
Neck	**0.92**	**0.90**
RUL	**0.85**	**0.75**
LUL	**0.85**	**0.84**
RLL	**0.84**	**0.83**
LLL	**0.87**	**0.89**
Trunk	**0.74**	**0.70**
Gait	-	**0.70**

LLL = left lower limb; LUL = left upper limb; RLL = right lower limb; RUL = right upper limb.

3.3.4 Inter-rater agreement for diagnosis

After completing the rating scales for each participant, blinded raters were asked to indicate which group (organic dystonia, FD, healthy control) they thought the participant belonged to. The treating clinician's diagnosis was compared with that of the blind raters using Fleiss' Kappa (κ), which gives values between -1 and +1. Fleiss' κ values can be interpreted as: 0–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial and 0.81–1 excellent agreement.

For each blinded rater's diagnosis, agreement with the treating clinician was substantial (95% confidence intervals shown in brackets):

- **Blind rating 1:**
  - κ = 0.65 (0.48-0.82) overall
  - κ = 0.62 (0.39-0.85) for 'organic'
  - κ = 0.57 (0.34-0.80) for 'functional'
  - κ = 0.74 (0.52-0.97) for 'control'

- **Blind rating 2:**
    - κ = 0.67 (0.49-0.84) overall
    - κ = 0.62 (0.39-0.85) for 'organic'
    - κ = 0.50 (0.27-0.73) for 'functional'
    - κ = 0.80 (0.57-1.0) for 'control'

Agreement between the blinded ratings (two for each participant, undertaken by three clinicians: PK, JA and JC) was higher— κ = 0.78 (0.6-0.93) overall—0.78 (0.56-1.0) for 'organic', 0.65 (0.43-0.88) for 'functional' and 0.83 (0.6-1.0) for 'control'.

Accuracy (percentage cases correctly identified) for blind rating 1 was 81% for organic dystonia and 58% for FD. For blind rating 2, 87% of patients with organic dystonia were correctly identified, compared to only 42% of those with FD.

3.4 Demographic and clinical correlations

In order to obtain a measure of the strength and direction of correlation between different clinical and demographic variables, the non-parametric Spearman correlation coefficient (r_s) was calculated. Data from each patient group was analysed separately. Correlation coefficients for patients with FD (Table 1) and those for the organic dystonia group in (Table 2) are presented in Appendix B. For healthy controls, the only significant correlations were a strong positive one between FMDRS and S-FMDRS scores (r_s=0.95, ***p*<0.0001**), and a weak negative correlation between age and MoCA (r_s=-0.47, ***p*=0.01**).

In both dystonia groups there was a strong positive correlation between scores on the organic movement disorder rating scale (FMDRS) and the functional rating scale (S-FMDRS). In patients with organic dystonia these scores both demonstrate moderate correlation with scores for bradykinesia (the worse the dystonia, the more bradykinetic their finger tapping). Similar correlations were not seen in the FD group.

3.5 Psychological profiles

Questionnaires for depression, anxiety, fatigue, obsessive-compulsion and depersonalisation were completed by all recruits, apart from one healthy control subject, who declined to answer these questions. The first twenty patients initially completed the Yale-Brown Obsessive Compulsion Scale. The shorter Brief Obsessive-Compulsive Scale (BOCS) was used from recruit number 17 onwards. The first 16 recruits were subsequently asked to complete a BOCS questionnaire via post or email. All but two (both subjects with organic dystonia) returned a completed BOCS form.

Scores for both obsessive-compulsive tests were collected for only 14 subjects (two controls and 12 patients with organic dystonia). Y-BOCS (scored out of 40) and BOCS (scored out of 24) scores were converted into percentages and compared using a Wilcoxon signed-rank test, revealing no significant difference between the scores (p = 0.09).

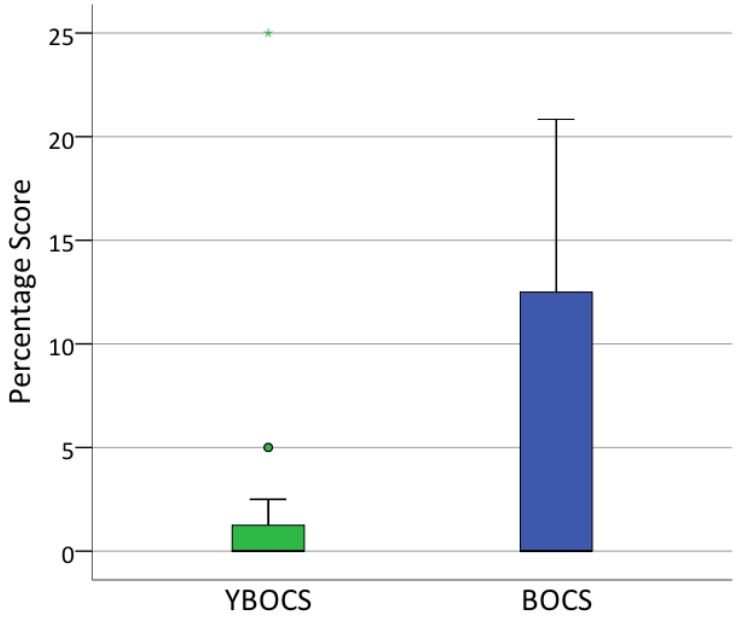


Figure 20: Comparison of BOCS and Y-BOCS scores

Percentage scores for the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) are shown in green, with percentage Brief Obsessive Compulsive Scale (BOCS) scores in blue. Boxes = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median.

As distributions of scores did not display a normal distribution, even after transformation, non-parametric testing (Kruskal-Wallis) was used to compare the median scores for each group, with *post hoc* analysis undertaken with Bonferroni adjustment. *Median scores are quoted, with interquartile range in brackets.*

3.5.1 Depression

Patients with both organic (4 (6), ***p*=0.02**) and functional (5 (7), ***p*=0.006**) dystonia differed significantly from controls (2 (3.5)) for scores on the depressive subscale of the HADS. There was no significant difference between the two patient groups.

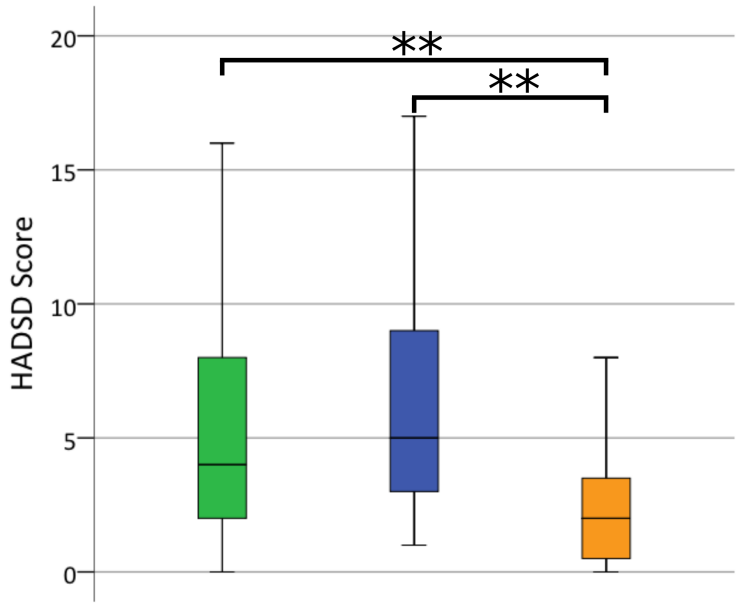


Figure 21: HADS Depression Scores

Scores for the HADS subscale for depression (HADSD, maximum score 21) were compared between organic (green) dystonia, functional (blue) dystonia and healthy controls (orange). Boxes = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Bracket with asterixes = significant difference.

3.5.2 Anxiety

Only patients with FD (8 (9), ***p*=0.02**) demonstrated significantly higher scores than healthy controls (4.5 (5)) for the anxiety subscale of the HADS, though there was a trend towards significance in the organic group (7 (7.5), p=0.055). Once again, no significant difference was demonstrated between the two patient groups.

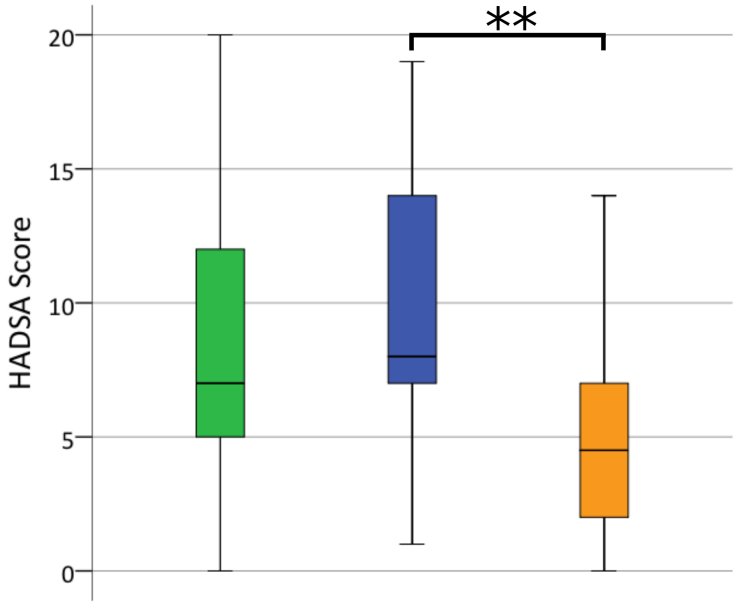


Figure 22: HADS Anxiety Scores

Scores for the HADS subscale for anxiety (HADSA, maximum score 21) were compared between organic (green) dystonia, functional (blue) dystonia and healthy controls (orange). Boxes = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Bracket with asterixes = significant difference.

3.5.3 Fatigue

As with scores for anxiety, average scores on the Fatigue Severity Scale (FSS) were significantly higher in FD (5 (2), ***p*=0.002**) but not organic dystonia (3.89 (3.22), p=0.053), compared with healthy controls (2.78 (1.78)). There was no difference between the two dystonia groups.

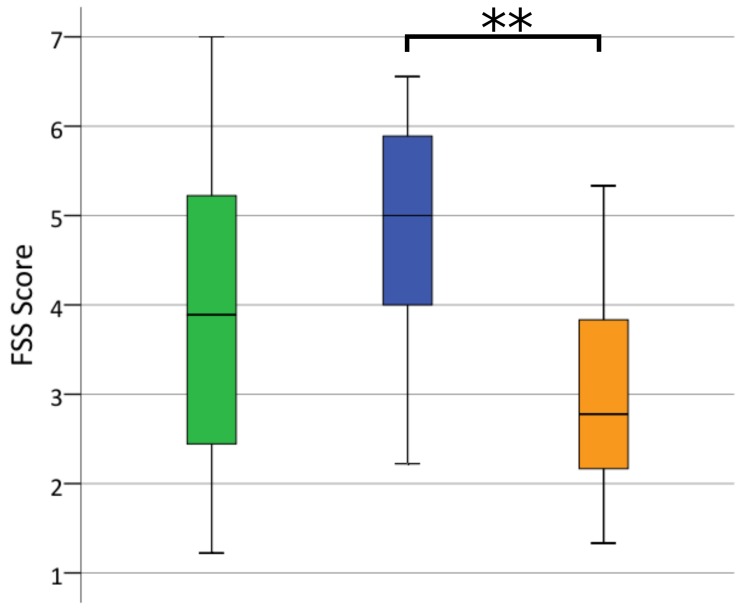


Figure 23: Fatigue Severity Scale (FSS) scores

Scores for the FSS (maximum score 7) were compared between organic (green) and functional (blue) dystonia. Boxes = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Bracket with asterixes = significant difference.

3.5.4 Obsessive-compulsion

Patients with FD (6 (14), ***p*=0.01**), but not organic dystonia (0 (4.79), p = 0.78), had significantly higher scores for obsessive-compulsion than healthy controls (0 (3)). There was not a significant group effect between organic and FD (p=0.1). Scores were subsequently divided equally into five classes of severity—subclinical (0-4), mild (5-9), moderate (10-14), severe (15-19) and extreme (19-24), in line with the manner in which the longer Y-BOCS is conventionally divided into brackets of severity. A higher proportion of patients with FD (5/13 = 38.5%) compared with organic dystonia (3/31 = 9.7%) had moderate to extreme scores for obsessive compulsion. By this classification, the difference between the dystonia groups was just below the threshold for significance (***p* = 0.046**).

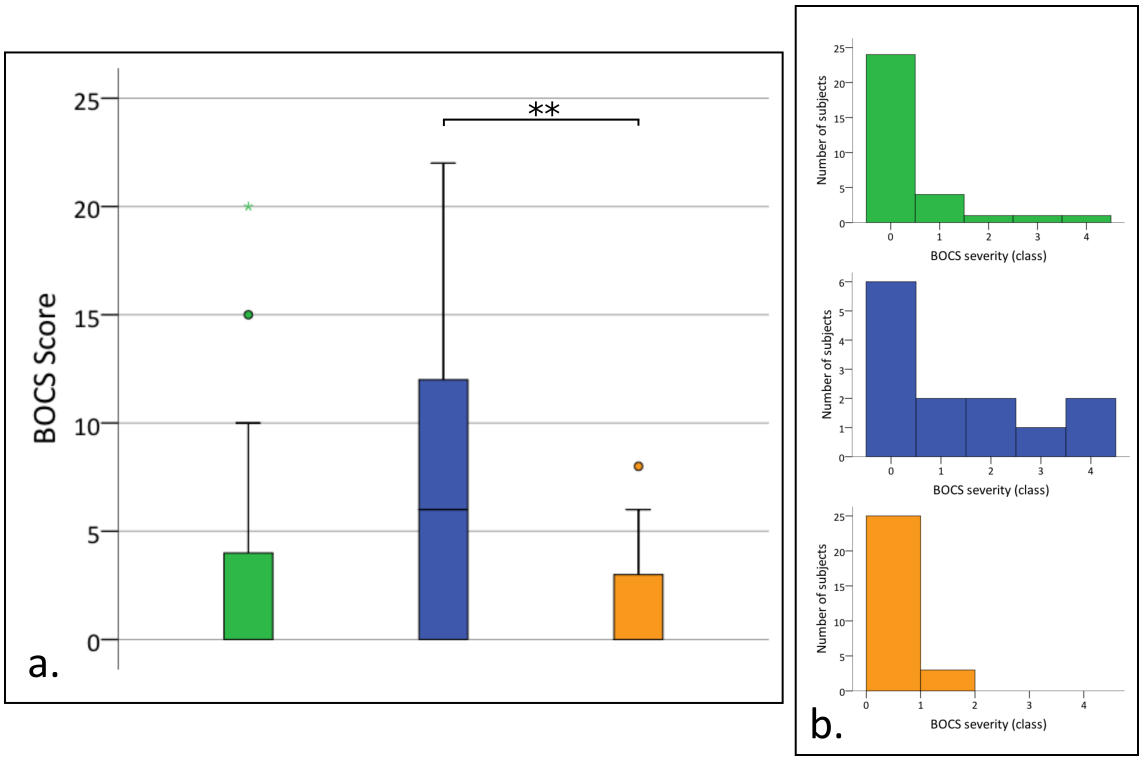


Figure 24: Obsessive-compulsive (BOCS) Scores

Boxplots showing scores for the BOCS (maximum score 24) in organic dystonia (green), functional dystonia (blue) and healthy controls (orange) are shown in **a.** Histograms showing the distribution of cases for each group by BOCS severity (0-4) are shown in **b.** Boxes = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. The asterisks represent extreme outliers, with values over three times the size of the IQR. Brackets with asterixes indicates a significant group effect.

3.5.5 Dissociation/Depersonalisation

Patients in the functional group displayed higher scores (33 (90.5), ***p*=0.006**) on the CDS than did healthy controls (5.5 (16.5), whereas the organic group did not (16 (33.75), *p*=0.06). No statistically significant difference was found between the two dystonia groups.

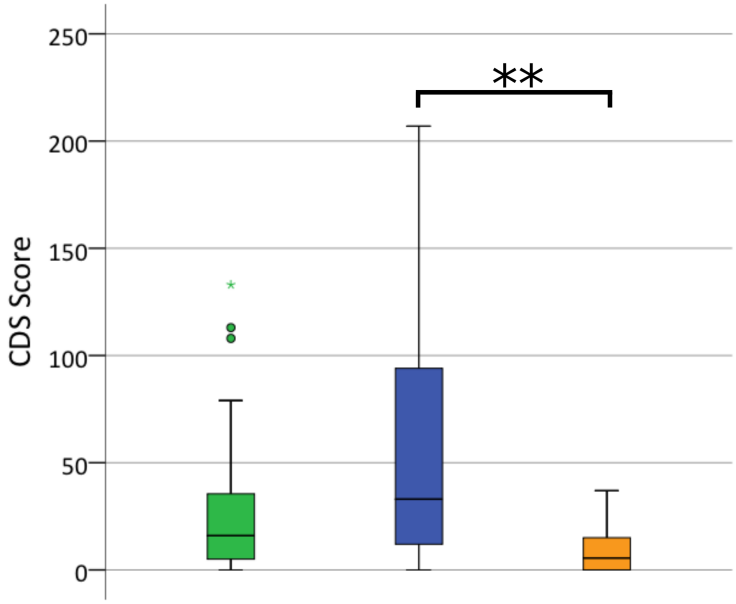


Figure 25: Cambridge Depersonalisation Scale (CDS) Scores

Scores for the CDS (maximum score 290) were compared between organic (green) dystonia, functional (blue) dystonia and healthy controls (orange). Boxes = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Circles denote outliers. Brackets with asterixes indicates a significant group effect.

3.5.6 Pain score (visual analogue scale)

Patients with both functional (6.7 (11), ***p*=0.03**) and organic (3.3 (11.8), ***p*=0.01**) dystonia scored higher on the pain scale than healthy controls (1 (3.25)), but there was no difference between the groups (p=1.0).

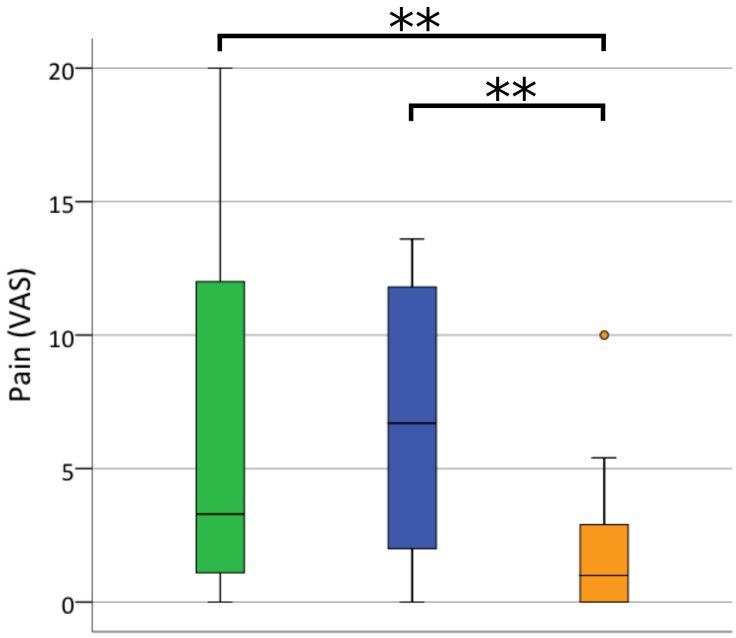


Figure 26: Pain scores

Scores for pain (visual analogue scale (VAS), maximum score 20) were compared between organic (green) dystonia, functional (blue) dystonia and healthy controls (orange). Boxes = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. The circles represent outliers. Brackets with asterixes indicates a significant group effect.

3.6 Correlations between psychological, fatigue and pain scores

For patients with FD, there were only three significant (weak) correlations—between scores for fatigue and depression, and between obsessive-compulsion and both anxiety and depressive tendencies (Table 3, Appendix B). For those with organic dystonia, however, the psychological measures correlated more strongly (Table 13, below). Firm correlations were noted between scores for anxiety, and both depression and fatigue. The strongest was between scores for depersonalisation and obsessive-compulsion, suggesting that obsessive-compulsive and dissociative tendencies may have a common foundation.

Table 13: Correlogram for organic dystonia (self-rating scales scores)

	HADSA	HADSD	Fatigue	BOCS	CDS	Pain
HADSA		0.73 ***	0.75 ***	0.62 ***	0.61 ***	0.20
HADSD	0.73 ***		0.52 **	0.59 ***	0.67 ***	0.005
Fatigue	0.75 ***	0.52 **		0.56 **	0.61 ***	0.10
BOCS	0.62 ***	0.59 ***	0.56 **		0.88 ***	0.02
CDS	0.61 ***	0.67 ***	0.61 ***	0.88 ***		0.09
Pain	0.20	0.005	0.10	0.02	0.09	

Key

>0.9 | 0.8 - 0.89 | 0.7 - 0.79 | 0.6 - 0.69 | 0.5 - 0.59

Abbreviations: BOCS = Brief Obsessive-Compulsive Scale; CDS = Cambridge Depersonalisation Scale; HADSA = Hospital Anxiety and Depression Scale (anxiety subscale); HADSD = Hospital Anxiety and Depression Scale (depression subscale).

For controls (Table 4, Appendix B), there was a weak correlation between depression and both fatigue and anxiety. Anxiety and obsessive-compulsive scores were also weakly correlated. Firm conclusions cannot be drawn from this data, in light of the small sample sizes (particularly for the functional group). However, the greater inter-connectedness of various forms of psychopathology in organic dystonia is interesting, posing questions for the future.

3.7 Correlations between self-rated scores and motor severity (FMDRS and S-FMDRS)

There was no significant correlation between any of the measures (HADSA, HADSD, BOCS, CDS, FSS or pain) and motor severity, assessed by either FMDRS or S-FMDRS.

3.8 Summary of results for self-rated psychological, fatigue and pain scores

All patients with dystonia, regardless of subtype, showed higher depressive and pain scores. Those for anxiety, fatigue, obsessive-compulsion and depersonalisation were significantly elevated only in the functional group. However, intermediate scores in the organic group were not significantly different from those of patients with FD. The BOCS measure of obsessive-compulsive tendency was the best discriminator between the patient groups, with patients with FD displaying a higher proportion of moderate to extreme scores.

To evaluate how well each of these measures discriminated between the groups, Receiver Operating Characteristic (ROC) curves were plotted. These are graphical representations of the play-off between sensitivity (proportion of true positives detected by a diagnostic test) and specificity (proportion of true negatives detected). Since there is always some overlap between groups for a given variable, a threshold value for distinguishing the groups must be chosen. Sensitivity and specificity have a reciprocal relationship across the range of thresholds. At higher threshold values, sensitivity will be reduced (higher false negative rate) but specificity will be elevated (lower false positive rate). At lower threshold values the reverse is true (sensitivity is increased as there are fewer false negatives, and specificity is reduced because of an elevated false positive rate). A measure of how well a particular characteristic discriminates between two groups can be obtained by calculating the area under the curve (AUC) on the ROC plot. Values vary between 0 (zero sensitivity and specificity) to 1 (perfectly sensitive and specific—no false positives or false negatives). An AUC of 0.5 indicates an uninformative discriminator—group assignment is no better than chance, the equivalent of a coin toss.

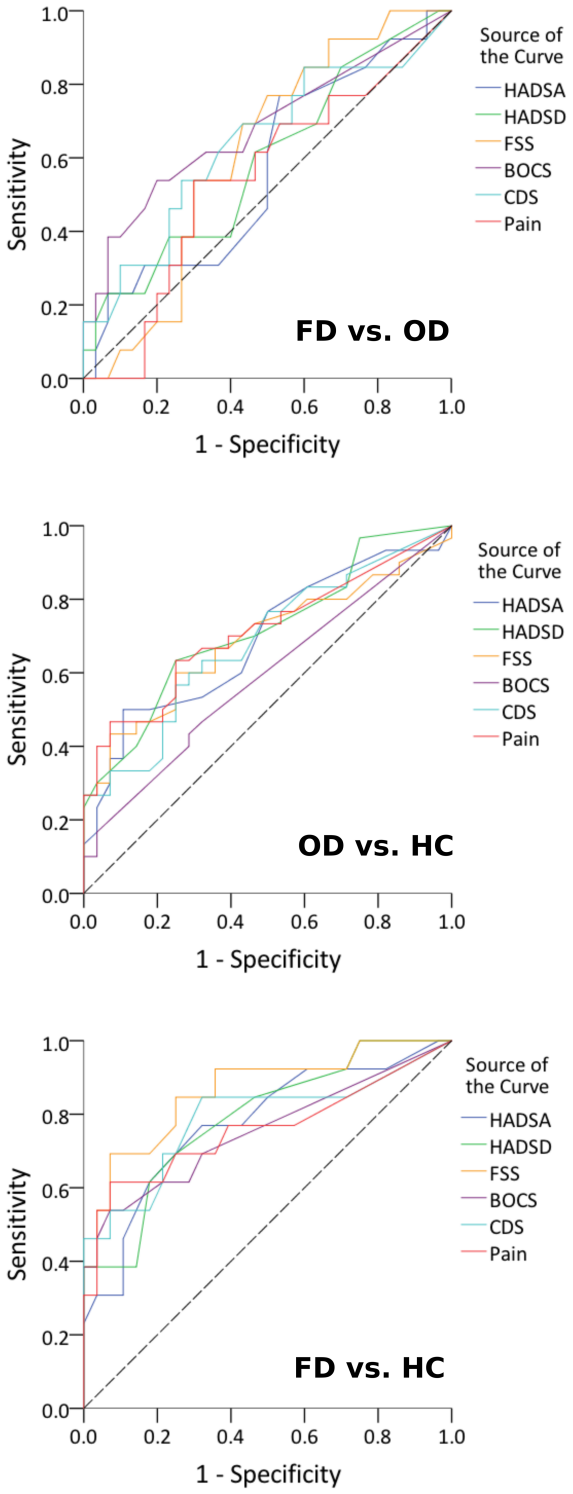
The results of this analysis are shown graphically in Figure 27, with the AUC values displayed in Table 14. None of the measures discriminated between the dystonia groups with high sensitivity and specificity (AUCs between 0.54 and 0.68) or between patients with organic dystonia and healthy controls (AUCs between 0.59 and 0.71). They were more discriminatory in comparisons between healthy controls and patients with FD. Of all the measures fatigue, with an AUC of 0.86,

appeared to distinguish best between these two groups. These results underscore the inadequacy of older clinical classifications for FD, with their heavy reliance on psychological indices.

Table 14: AUC values for psychological, fatigue and pain scores

	FD vs OD	OD vs HC	FD vs HC
HADSA	0.59	0.71	0.79
HADSD	0.57	0.69	0.78
FSS	0.61	0.69	0.86
BOCS	0.68	0.59	0.75
CDS	0.64	0.68	0.79
Pain	0.54	0.71	0.76

BOCS = Brief Obsessive Compulsive Scale; CDS = Cambridge Depersonalisation Scale; FD = functional dystonia; FSS = Fatigue Severity Scale; HADSA = Hospital Anxiety and Depression Scale (anxiety dimension); HADSD = Hospital Anxiety and Depression Scale (depression dimension); HC = healthy control; OD = organic dystonia.



<u>Figure 27:</u> ROC curves for psychological, fatigue and pain test scores

BOCS = Brief Obsessive Compulsive Scale; CDS = Cambridge Depersonalisation Scale; FD = functional dystonia; FSS = Fatigue Severity Scale; HADSA = Hospital Anxiety and Depression Scale (anxiety dimension); HADSD = Hospital Anxiety and Depression Scale (depression dimension); HC = healthy control; OD = organic dystonia.

Chapter Four:

Results (kinematic data)

4.1 Participants

Of the study recruits, three dystonia patients were not included in the kinematic analysis. One patient with FD was unable to complete the finger-tapping tasks because the severity of their FMD precluded it. One patient with organic dystonia was unable to undertake task because they had a pacemaker fitted (risk of interference from the EM source). The data set for one further patient with organic dystonia was incomplete (measurements from non-dominant hand failed to upload) and was therefore excluded from analysis. In total, 72 kinematic data sets were analysed (31 organic dystonia, 12 FD and 29 healthy controls). Demographic details for this group are shown in the Table 15. These are similar to the demographics for the participants included in the self-rating scales analysis: patients with FD were younger than those with organic dystonia (***p* = 0.02**), with higher rates of unemployment than either those with organic dystonia (***p* = 0.003**) or healthy controls (***p* = 0.0006**). Fewer patients with organic dystonia than healthy controls had tertiary level education (***p* = 0.006**), and MoCA scores were lower in both dystonia groups compared to healthy controls (***p* = 0.02 for FD, *p* = 0.02 for organic**).

Table 15: Summary of participant demographic details (kinematic assessments)

	Organic (n = 31)	Functional (n = 12)	Controls (n = 29)	P value
Age	58 (28)	37 (28)	54 (35)	**0.03**
Gender (F:M)	19:12	9:3	19:10	NS
Handedness (R:L)	25:6	9:3	26:3	NS
% Married/co-habiting	74	58	72	NS
Education	23:8	7:5	9:20	**0.003**
% Unemployed	3	50	0	**<0.0001**
MoCA score	25 (5)	25 (3)	28 (4)	**0.001**

Median values for age and MoCA score displayed with interquartile range in brackets. Ratios of patient numbers shown for gender and handedness. Ratio of secondary to tertiary education shown for education. *p* values indicate the effect across groups (results of pairwise comparisons in main text). F = female; L = left; M = male; MoCA = Montreal Cognitive Assessment; NS = not significant; R = right.

4.2 Kinematic data: trial-by-trial analysis

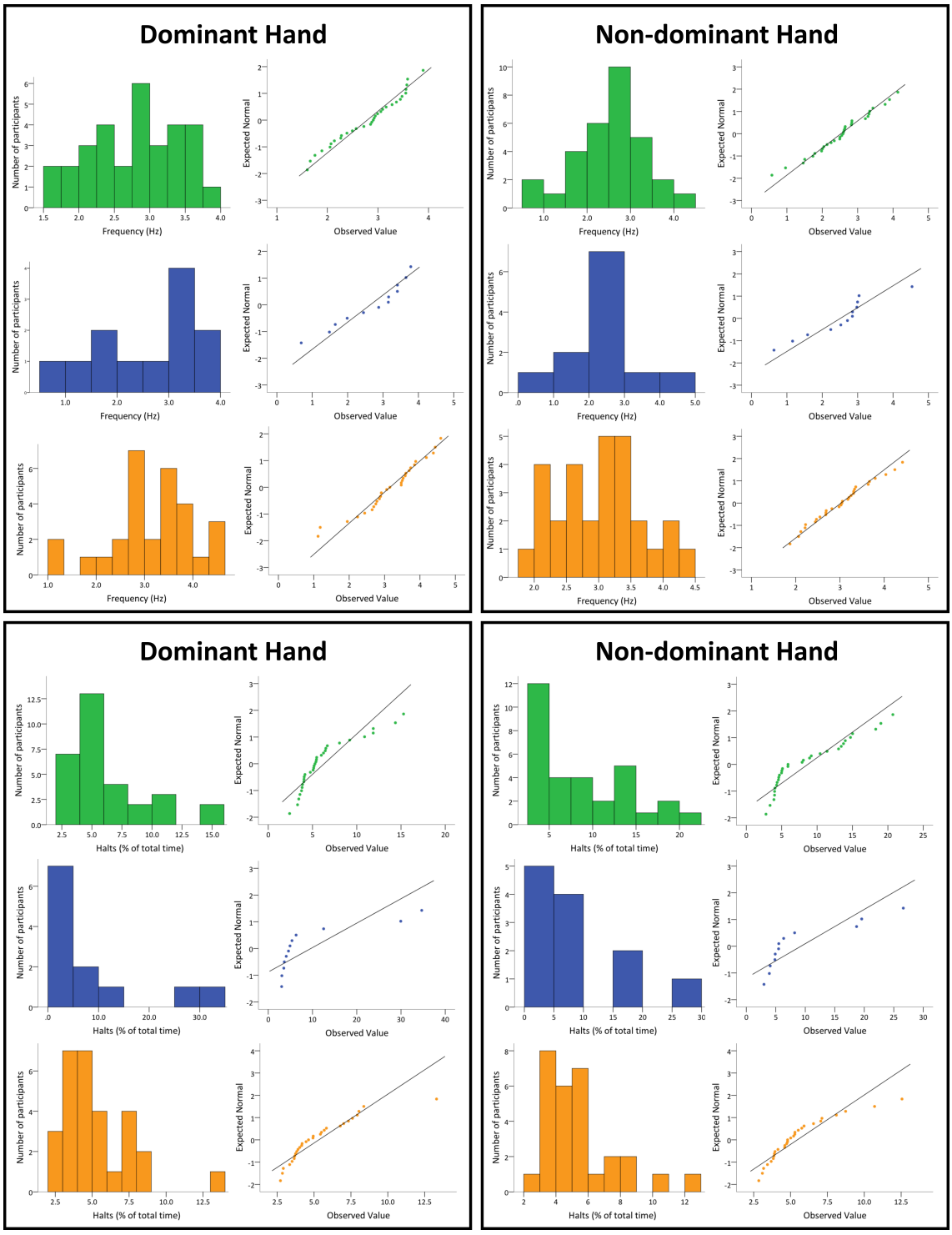
Data from each 15s trial was analysed for normality. A majority (12/19) of the separable motor components demonstrated a normal distribution across the groups (skew and kurtosis between -2 and +2 and/or Kolmogorov-Smirnov >0.05, see Figure 28 and Table 1 in Appendix C). Likewise, no significant differences in variance between the groups were demonstrated by Levene's test for the majority of components. Of the measures that were not normally distributed, six (maximum opening acceleration, coefficient of variation for amplitude and velocity, decrement in amplitude, halts and hesitations) demonstrated a positive skew, and one (closing deceleration) was negatively skewed. Logarithmic and square root transformations failed to correct this divergence (see Figure 29).

In spite of these deviations from normality, it was considered appropriate to perform a trial-by-trial analysis using a parametric approach for two reasons: 1) more sophisticated multi-level non-parametric approaches would not be supported, owing to the small sample size for the FD group; and 2) the ANOVA is a robust test, capable of withstanding some deviation from normality.

A repeated measures ANOVA was applied to the data, using HAND (dominant vs non-dominant) and TRIAL (1^{st}, 2^{nd} or 3^{rd}) as within-subjects factors, and GROUP (organic dystonia, FD and healthy control) as a between-subjects factor. *Post hoc* testing using the Games-Howell adjustment was used, since this is the most reliable test when sample sizes are unequal. No significant differences between performance across the trials, or between dominant and non-dominant hands, were demonstrated across the groups.

4.3 Freestyle finger tapping: between-groups analysis

Since there were no significant differences in performance between trials and by hand (see Figure 30), data across the three trials for both hands were collapsed prior to between-groups analysis. Taking into account the finding that some of the data was not normally distributed, non-parametric Kruskal-Wallis testing was



<u>Figure 28:</u> Frequency distributions for kinematic data

Representative histograms (left hand side of each box) and Q-Q plots (right-hand side of each box) for two motor components. The upper two boxes show plots for Frequency (Hz), showing a normal distribution across groups. The lower two boxes show Halts (% of time), showing that this measure had a positively skewed distribution in all three groups (green = organic dystonia; blue = functional dystonia; orange = healthy controls.).

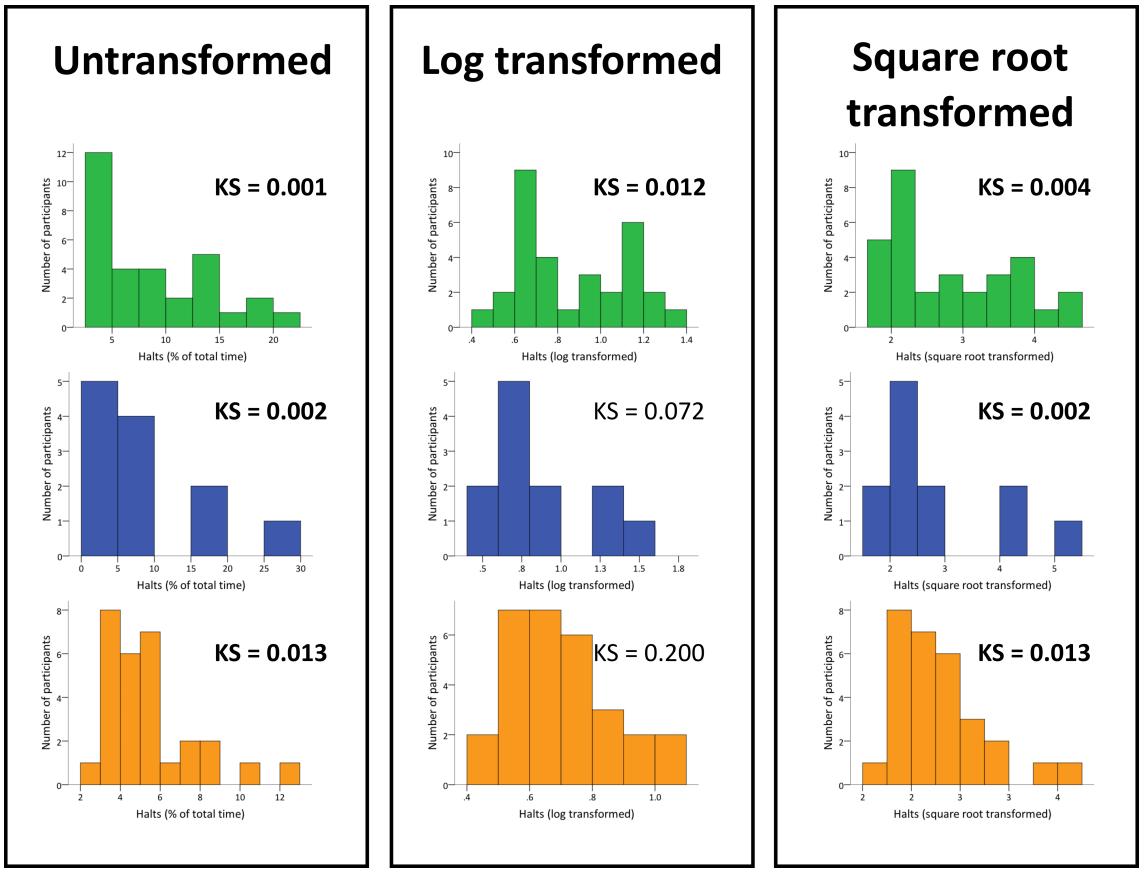
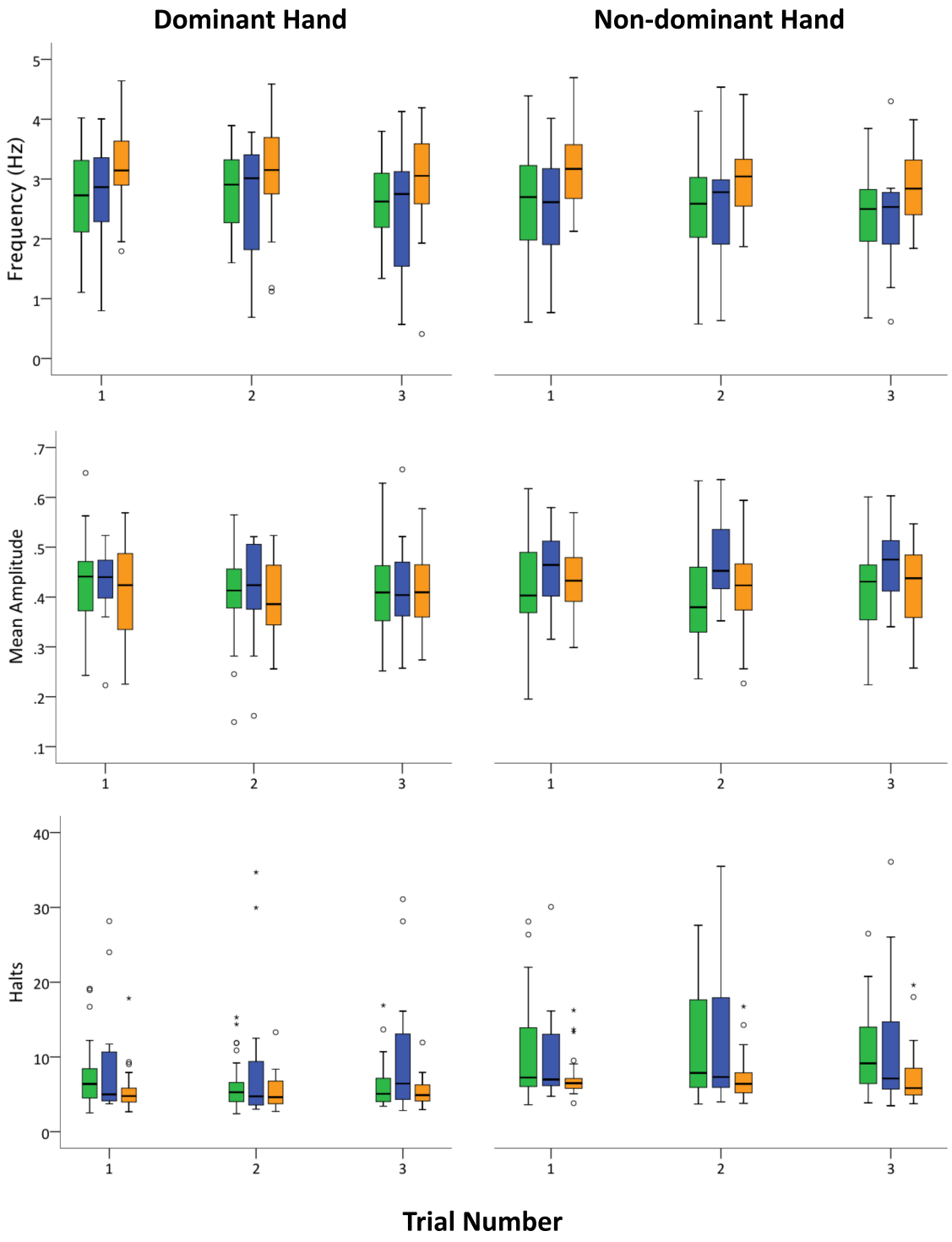


Figure 29: Kinematic data transformations

Histograms displaying data for Halts (% of total time) from the non-dominant hand for each group (green = organic dystonia; blue = functional dystonia; orange = healthy controls). Neither logarithmic nor square root transformation succeeded in correcting for positive skew across all groups. KS = Kolmogorov-Smirnov values (significant values, indicating significant deviation from normal distribution, shown in bold).



<u>Figure 30:</u> Trial-by-trial analysis for freestyle finger tapping task

Representative boxplots for three separable motor components (Frequency, Mean amplitude and Halts) across the three trials in each of the three groups.

Green = organic dystonia; blue = functional dystonia; orange = healthy controls.

Box = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Outliers are denoted by asterixes (>3 times IQR) and circles (1.5 to 3 times IQR).

chosen as a method for between-groups analysis. The Bonferroni correction was applied to correct for multiple comparisons on *post hoc* testing.

4.3.1 Frequency

A significant difference between groups for **Frequency (Hz)** was detected by Kruskal-Wallis analysis (***p* = 0.034**). *Post hoc* testing revealed a significant difference between patients with organic dystonia and healthy controls (***p* = 0.008**). There was no difference between FD and healthy controls ($p = 0.135$) or between the two dystonia groups ($p = 0.794$).

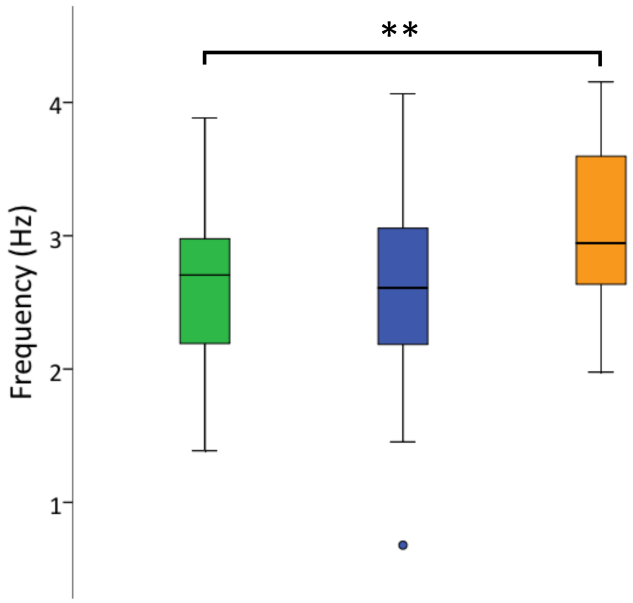


Figure 31: Boxplot for Frequency (Hz)
Green = organic dystonia; blue = functional dystonia; orange = healthy controls.
Box = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median.
Bracket with asterixes indicates a significant difference.

In their kinematic study, Criswell et al. identified a significant effect of age on finger tapping score (frequency x time, or number of taps per trial) equivalent to a reduction of 0.338 taps per year for a 30s tapping period.(261) Since there is a significant difference in age between the organic and FD groups, further analysis was required to establish whether a similar trend might be masking a significant

difference in frequency between the two dystonia groups. For this purpose, values for finger tapping score were derived by multiplying the average frequency across the trials by trial length (15s). A scatterplot of these values is shown in Figure 32.

Simple linear regression analyses of these scores by age (healthy controls alone and all three groups together) revealed no significant effect of age on finger tapping score (Pearson's correlation coefficient -0.14, $p = 0.24$), indicating that age is unlikely to have significantly skewed results for frequency in the functional group.

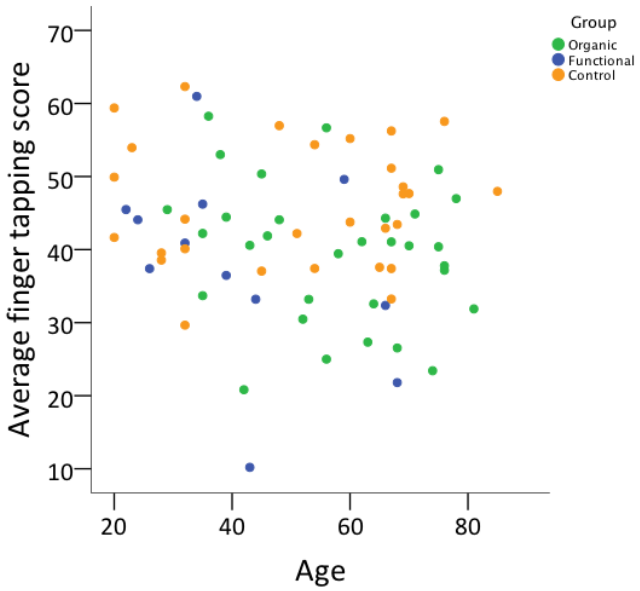


Figure 32: Scatterplot for finger tapping score vs. age
Average values for finger tapping score (frequency x time) across the three 15s trials plotted against age for the three groups, demonstrating no clear correlation.

4.3.2 Amplitude

No significant differences between the groups were established for either maximum ($p = 0.43$) or mean amplitude ($p = 0.27$).

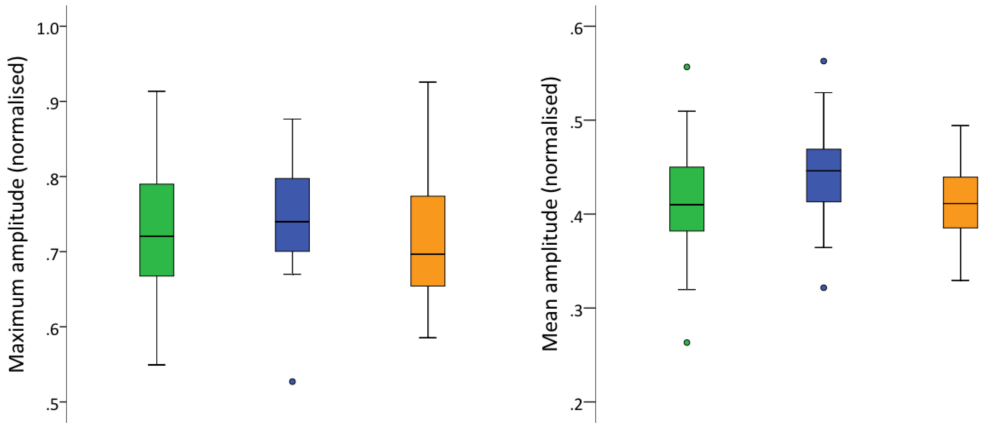


Figure 33: Boxplots for amplitude (maximum and mean)

Green = organic dystonia; blue = functional dystonia; orange = healthy controls. Box = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Outliers are denoted by asterixes (>3 times IQR) and circles (1.5 to 3 times IQR).

4.3.3 Velocity

For maximum velocity (opening, closing and overall) no significant difference was detected between the groups. A borderline significant difference for mean velocity was reported (***p* = 0.045**), with *post hoc* analyses revealing lower values in the functional group (*p* value just above the threshold for significance after Bonferroni adjustment (*p* = 0.056)).

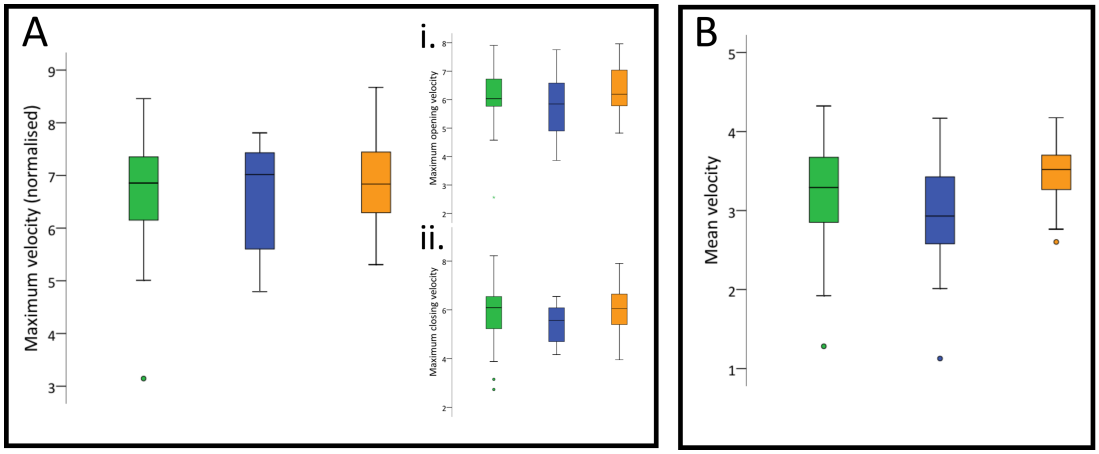


Figure 34: Boxplots for velocity (maximum and mean)

Data for maximum velocity shown in A, with maximum opening and closing velocity boxplots shown in insets i. and ii. respectively. Data for mean velocity shown in B. Bracket with asterixes indicates significant difference.

Green = organic dystonia; blue = functional dystonia; orange = healthy controls. Box = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Outliers are denoted by asterixes (>3 times IQR) and circles (1.5 to 3 times IQR).

4.3.4 Opening and closing acceleration/deceleration

Maximum opening acceleration (p = 0.23) and closing deceleration (p = 0.48) were not significantly different between the groups. However, movement initiation and cessation about the point of maximal extension in the tapping cycle was impaired in the dystonia groups (see Figure 35). Maximal opening deceleration was significantly lower in both organic (***p* = 0.01**) and functional (***p* = 0.02**) dystonia compared to healthy controls; there was no difference between the patient groups. A significant group difference for maximal closing acceleration by Kruskal-Wallis (***p* = 0.04**) was driven by lower values in the functional group compared to healthy controls, though this difference was not significant after Bonferroni adjustment (p = 0.08).

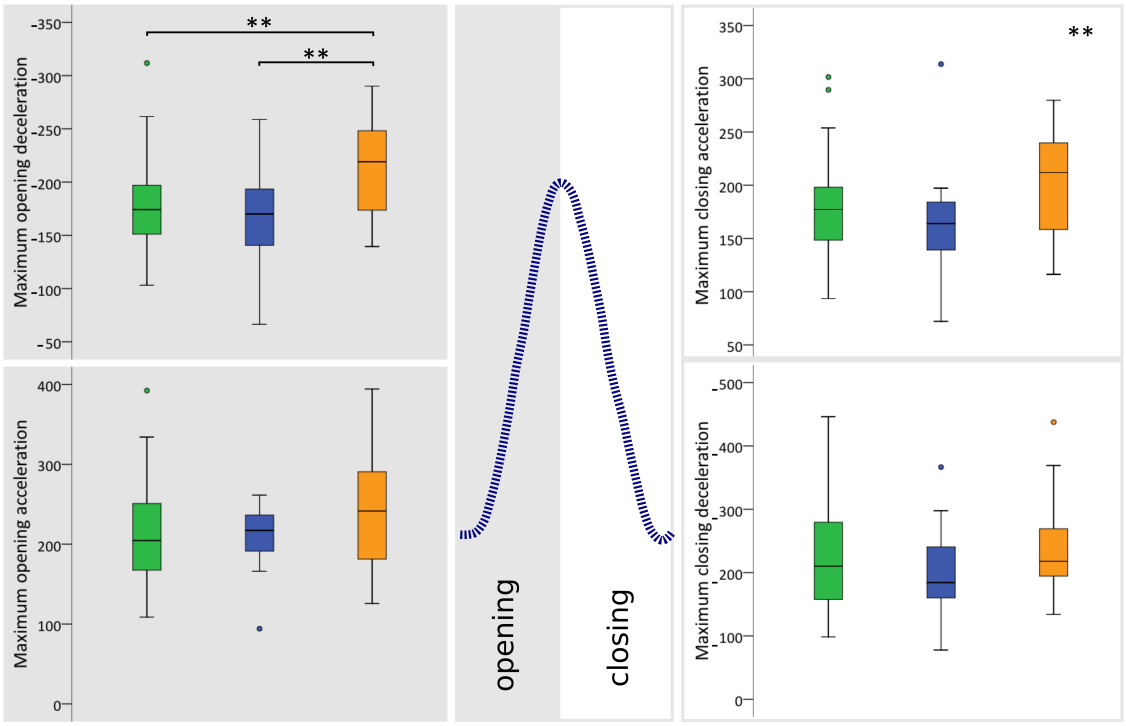


Figure 35: Boxplots for opening and closing acceleration and deceleration
Movement about the point of maximal extension (shown by the representative tap cycle in the middle panel) was impaired in dystonia (see text). Asterixes denote a

significant group effect that did not reach significance after Bonferroni adjustment. Bracket and asterixes indicates significant post hoc differences (after Bonferroni adjustment). Green = organic dystonia; blue = functional dystonia; orange = healthy controls. Box = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Outliers are denoted by asterixes (>3 times IQR) and circles (1.5 to 3 times IQR).

4.3.5 Rhythm

There was no significant group effect for coefficient of variation for amplitude (p = 0.74) or velocity (p = 0.22).

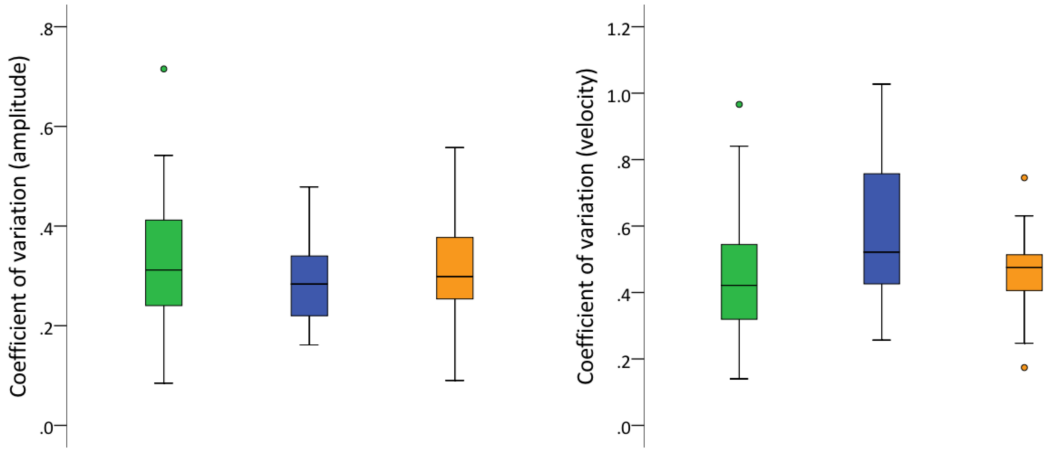


Figure 36: Boxplots for coefficient of variation (amplitude and velocity)
Rhythmicity did not vary across the three groups. Green = organic dystonia; blue = functional dystonia; orange = healthy controls. Box = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Outliers are denoted by asterixes (>3 times IQR) and circles (1.5 to 3 times IQR).

4.3.6 Halts and hesitations

Patients with organic dystonia spent a greater proportion of time at under 5% maximal velocity (more halting performance) than healthy controls (***p* = 0.02**). Those with FD did not differ significantly from healthy controls (p = 0.15) or those with organic dystonia (p = 0.54). In contrast, patients with FD showed more hesitations (***p*= 0.04**) than healthy controls,

whereas those with organic dystonia did not (p = 0.10). There was no significant difference between the patient groups (p = 0.21).

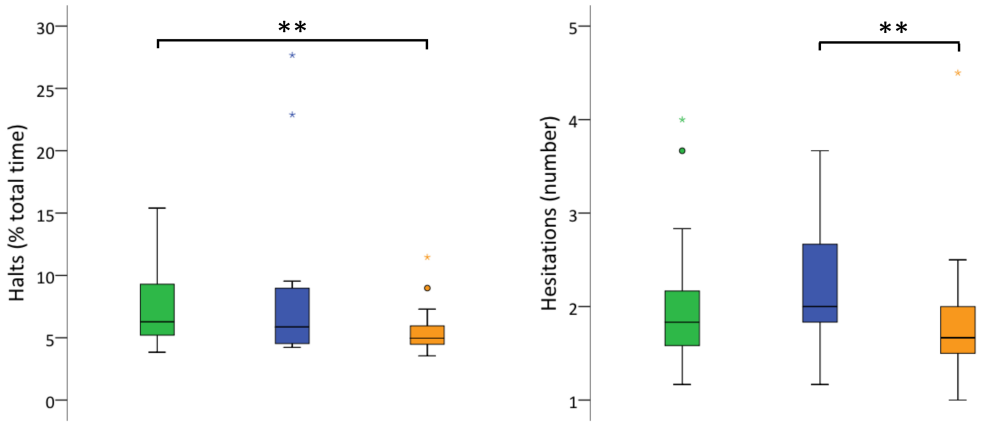


Figure 37: Boxplots for halts and hesitations

Patients with organic dystonia spent a greater proportion of time at <5% of maximal velocity, whereas those with FD showed a higher frequency of hesitations, compared with healthy controls. There were no differences between the two patient groups. Bracket and asterixes indicates significant post hoc differences (after Bonferroni adjustment). Green = organic dystonia; blue = functional dystonia; orange = healthy controls. Box = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Outliers are denoted by asterixes (>3 times IQR) and circles (1.5 to 3 times IQR).

4.3.7 Decrement (amplitude and velocity)

Neither dystonia group demonstrated decrement, and there was no significant difference across the groups for either amplitude (p = 0.06) or velocity (p = 0.20) decrement.

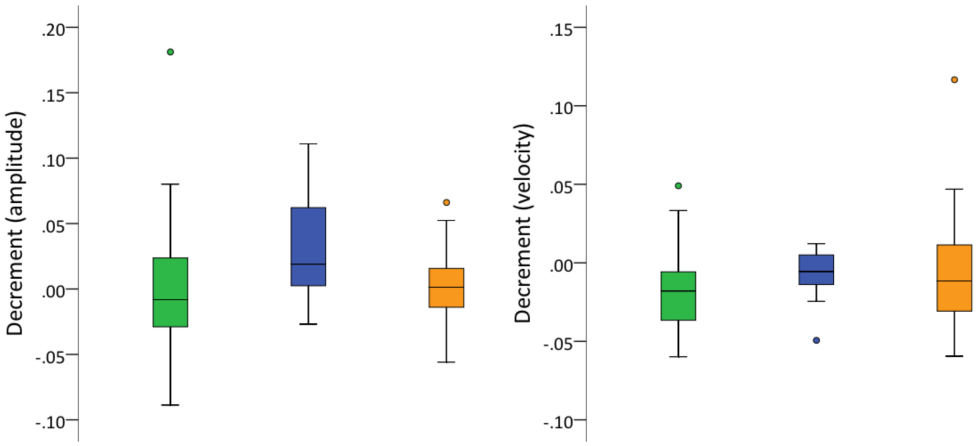


Figure 38: Boxplots for decrement (amplitude and velocity)

There were no differences between the two patient groups and healthy controls for decrement. Green = organic dystonia; blue = functional dystonia; orange = healthy controls. Box = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Outliers are denoted by asterixes (>3 times IQR) and circles (1.5 to 3 times IQR).

4.3.8 Overall speed of movement (amplitude x frequency)

Patients with organic dystonia displayed slower movement compared with healthy controls, when frequency and amplitude of movement were combined (***p* = 0.008**). The performance of those with FD was no different to that of healthy controls (p = 1.0) or patients with organic dystonia (p = 0.135).

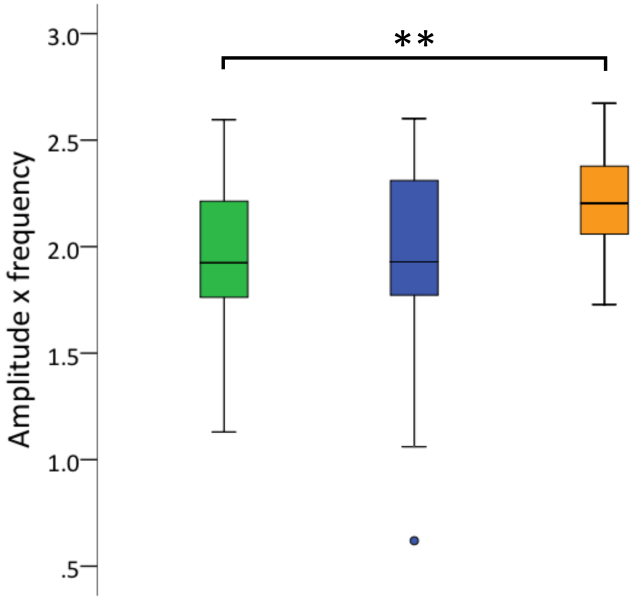


Figure 39: Boxplot for amplitude x frequency

Green = organic dystonia; blue = functional dystonia; orange = healthy controls. Bracket and asterixes indicates significant post hoc differences (after Bonferroni adjustment). Box = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median.

4.3.9 Summary of freestyle finger tapping between-groups analysis

For some separable motor components, speed and scaling of movement in dystonia appeared comparable to healthy controls—no significant differences in amplitude or velocity were observed. However, frequency of finger tapping, and the product of amplitude and frequency (overall speed of movement, or sensor excursion per unit time), were reduced in organic dystonia. Patients with both types of dystonia showed slower movement initiation and cessation about the point of maximal finger-thumb separation. The reduction in overall speed in organic dystonia was associated with a greater tendency to pause during the finger tapping cycle (more halts), whereas those with FD showed more hesitations ('false starts').

4.4 Correlations with clinical ratings

The Spearmann correlation coefficient (r_s) is a non-parametric measure of the strength of the relationship between two variables. This was calculated to determine the relationship between clinical ratings (for bradykinesia of finger tapping and severity of dystonia) and equivalent kinematic measures.

Clinical MDS-UPDRS scores (average score of two blinded raters) were weakly negatively correlated with frequency for both dominant (r_s = -0.4, ***p* = 0.001**) and non-dominant (r_s = -0.33, ***p* = 0.004**) hands. Amplitude x frequency and halts were chosen as measures of overall severity of dystonia. These correlated significantly with clinical scores for both FMDRS (r_s=-0.38, ***p* = 0.001** for amplitude x frequency and r_s = +0.33, ***p* = 0.005** for halts) and S-FMDRS (r_s=-0.38, ***p* = 0.001** for amplitude x frequency and r_s = +0.33, ***p* = 0.004** for halts).

4.5 Correlations between separable motor components

The Spearmann correlation coefficient (r_s) was calculated for each of the separable motor components that displayed significant groups differences. Results for each group are displayed in separate correlograms below.

There is a striking difference in the pattern of correlation between separable motor components across the three groups. Patients with FD display a greater number and stronger correlations. This suggests that FD involves disturbances in motor outflow that are consistent across individuals with the disorder, whereas patients with organic dystonia have more heterogenous patterns of movement. This is especially interesting in light of the phenomenological heterogeneity of both dystonia groups (see Tables 16 and 17).

Table 16: Correlogram for functional dystonia (kinematic measures)

	Freq.	Mean velocity	Max OD	Max CA	Halts	Hesit.	Amp x Freq
Freq.		0.70 *	0.84 **	0.90 ***	-0.99 ***	-0.71 *	0.92 ***
Mean velocity	0.70 *		0.57	0.60 *	-0.67 *	-0.83 **	0.78 **
Max OD	0.84 **	0.57		0.92 ***	-0.83 **	-0.34	0.78 **
Max CA	0.90 ***	0.60 *	0.92 ***		-0.90 ***	-0.46	0.79 **
Halts	-0.99 ***	-0.67 *	-0.83 **	-0.90 ***		0.69 *	-0.92 ***
Hesit.	-0.71 *	-0.83 **	-0.34	-0.46	0.69 *		-0.70 *
Amp x Freq	0.92 ***	0.78 **	0.78 **	0.79 **	-0.92 ***	-0.70 *	

Key

>0.9 | 0.8 - 0.89 | 0.7 - 0.79 | 0.6 - 0.69 | 0.5 - 0.59

Abbreviations: Amp = amplitude; CA = closing acceleration; Freq. = frequency; Hesit. = hesitations; Max = maximum; OD = opening deceleration.

The strongest correlations were between maximum closing acceleration, maximum opening deceleration, frequency, amplitude x frequency, and halts. Maximum closing acceleration and opening deceleration were strongly correlated for all three groups (r_s +0.92 FD vs. +0.9 OD vs +0.88 HC), indicating that in normal movement these two features are closely inter-related. This relationship is retained in dystonia. Frequency (and amplitude x frequency) showed a strong negative correlation with halting tendency (r_s -0.99 and -0.92 respectively) in the functional group, and a weaker correlation in the same direction for the organic group (r_s -0.66 and -0.68) and healthy controls (r_s -0.57 and -0.64). Maximum closing acceleration was also strongly positively correlated with frequency (r_s +0.9), and negatively correlated with halts (r_s -0.9). A similar relationship, albeit weaker, was noted for organic dystonia (r_s +0.79 and -0.49).

Table 17: Correlogram for organic dystonia (kinematic measures)

	Freq.	Mean velocity	Max OD	Max CA	Halts	Hesit.	Amp x Freq
Freq.		0.68 ***	0.76 ***	0.79 ***	-0.66 ***	-0.45 *	0.80 ***
Mean velocity	0.68 ***		0.50 **	0.53 **	-0.52 **	-0.69 ***	0.89 ***
Max OD	0.76 ***	0.50 **		0.90 ***	-0.50 **	-0.17	0.59 ***
Max CA	0.79 ***	0.53 **	0.90 ***		-0.49 **	-0.10	0.65 ***
Halts	-0.66 ***	-0.52 **	-0.50 **	-0.49 **		0.42 *	-0.68 ***
Hesit.	-0.45 *	-0.69 ***	-0.17	-0.10	0.42 *		-0.53 *
Amp x Freq	0.80 ***	0.89 ***	0.59 ***	0.65 ***	-0.68 ***	-0.53 *	

Key

>0.9 | 0.8 - 0.89 | 0.7 - 0.79 | 0.6 - 0.69 | 0.5 - 0.59

Abbreviations: Amp = amplitude; CA = closing acceleration; Freq. = frequency; Hesit. = hesitations; Max = maximum; OD = opening deceleration.

Patients with dystonia have lower overall speed of movement during finger tapping tasks (lower amplitude x frequency). Previous studies have shown motor performance to be particularly disturbed during the extension phase of finger tapping in patients with focal hand dystonia.(239) The strong association between frequency, halting tendency and maximum opening deceleration and closing acceleration may indicate that slowness of movement in dystonia is generated by delayed switching between extensor and flexor programmes, giving rise to more halting performance. This will be discussed further in later chapters.

4.6 Finger tapping with and without *geste antagoniste*

Twenty-three patients with organic dystonia, and three with FD had a *geste antagoniste* or sensory trick (simple movements involving or directed to the region affected by dystonia that transiently improve dystonic contraction). A summary of the character of these *gestes* is shown in Table 18.

Data for the finger tapping task with *geste* deviated significantly from a normal distribution for Halts, Hesitations, and Coefficient of Velocity in the organic dystonia group. Testing for normality in the functional group was not possible, in light of the low n number. For this reason non-parametric statistical methods were used. The two dystonia groups were separated for analysis of the effect of *geste*, and a related samples Wilcoxon signed ranks test was applied. Initial comparisons of finger tapping data from dominant and non-dominant hands with *geste* revealed no significant differences between hands, so these trials were collapsed. This data set was then compared with the average values used in the analysis of freestyle finger tapping tasks (above).

In order to compare speed and rhythmicity of movement with and without activation of the sensory trick, five measures were selected for comparison between the two dystonia groups: amplitude x frequency (overall speed), coefficients of variation for amplitude and velocity (rhythm), halts and hesitations.

Table 18: ***Gestes*** **in patients with organic and functional dystonia**

Participant Number	Dystonia type/ distribution	*Geste antagoniste*
1	Secondary (generalised dystonia)	Holding wrist
5	IFD (cervical dystonia plus hand tremor)	Touching chin
7	IFD (cervical dystonia)	Touching chin
13	Musician's dystonia (focal hand dystonia)	Wearing splint/ holding forearm
15	Genetic (generalised dystonia)	Holding wrist
19	Secondary (right hemidystonia)	Supporting arm (e.g. on pillow)
20	IFD (cranio-cervico-brachial dystonia)	Holding forearm
21	Genetic (cervical dystonia)	Holding chin
22	Genetic (cervico-brachial dystonia)	Holding forearm
23	IFD (cervical dystonia)	Holding chin
24	**Functional (cervico-brachial dystonia)**	**Holding back of head**
26	IFD (cervical dystonia	Holding back of head
27	IFD (cervical dystonia)	Touching chin
28	Secondary (right hemidystonia)	Holding wrist
29	IFD (cervical dystonia)	Touching cheek
31	IFD (writer's cramp)	Holding wrist
32	IFD (cervical dystonia plus hand tremor)	Touching cheek
33	IFD (cervical dystonia)	Touching cheek
37	Musician's dystonia (focal hand dystonia)	Massaging arm/ pressure to certain points
39	Genetic (generalised dystonia)	Sitting up very straight
47	**Functional (cranio-cervico-brachial)**	**Applying pressure to certain points on arm**
49	**Functional (truncal dystonia)**	**Deep breathing/ sitting up straight**
54	IFD (cervical dystonia plus hand tremor)	Holding neck
58	IFD (writer's cramp plus cervical dystonia)	Touching hand
64	IFD (cervical dystonia and writer's cramp)	Touching chin
78	Genetic (cranio-cervico-brachial dystonia)	Resting head in hand

Patients with FD highlighted in bold. IFD = idiopathic focal dystonia

4.6.1 Amplitude x frequency with and without *geste*

In the organic dystonia group there was a significant effect of *geste*, with improved performance (faster overall speed) noted with *geste* than without (**$p < 0.0001$**). No significant effect was noted for the FD group ($p = 0.07$); this statistical comparison was underpowered as a result of the very small sample size, but a similar trend towards improved performance was noted (see Figure 40). Performance with *geste* was comparable to the performance of healthy controls. When values for amplitude x frequency with *geste* were compared with those of healthy controls (by Kruskal-Wallis testing), no significant group effect was detected ($p = 0.13$).

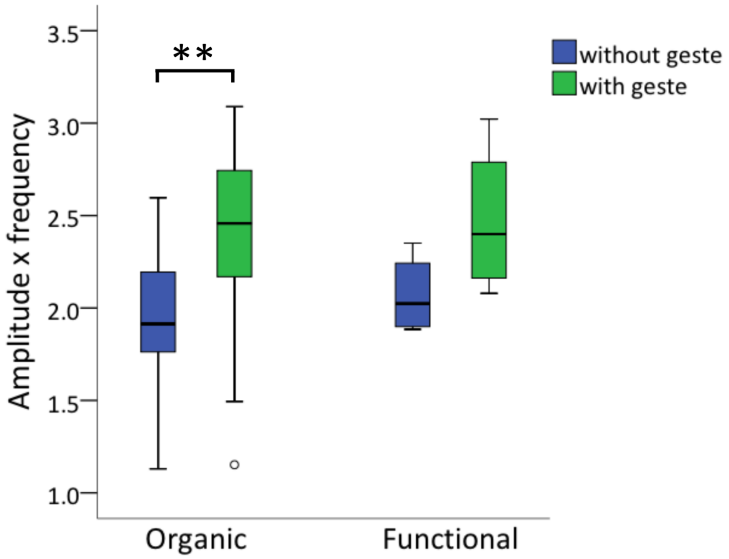


Figure 40: Boxplot for Amplitude x Frequency (with and without *geste*)
Speed of finger tapping was enhanced in patient with organic dystonia when they activated their *geste*. A similar trend was noted in the FD group, though this did not reach statistical significance. Bracket and asterixes indicates statistically significant comparison. Box = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Outliers are denoted by asterixes (>3 times IQR) and circles (1.5 to 3 times IQR).

4.6.2 Coefficient of amplitude and velocity with and without *geste*

Overall rhythmicity, as measured by coefficient of amplitude and velocity, did not differ with versus without *geste* in either dystonia group (p = 0.26 and 0.50, respectively, for the organic group; and p = 1.0 and 1.0 for the functional group).

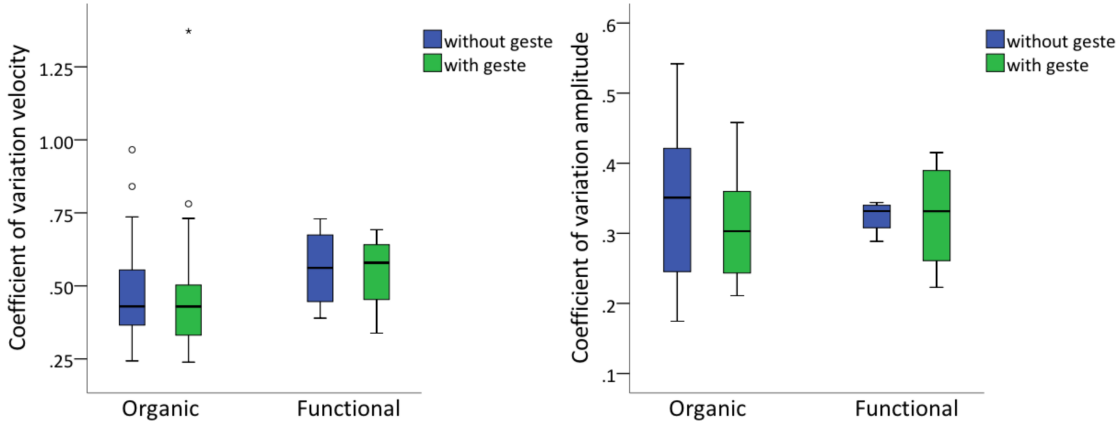


Figure 41: Boxplots for coefficient of variation for amplitude and velocity (with and without *geste*)

This measure of rhythmicity did not vary in either group depending on whether the patient activated their sensory trick or not. Bracket and asterixes indicates statistically significant comparison. Box = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Outliers are denoted by asterixes (>3 times IQR) and circles (1.5 to 3 times IQR).

4.6.3 Halts

Patients with organic dystonia displayed a less halting performance when they activated their *geste* (**p = 0.008**). No significant effect was noted for the functional group (p = 0.07), but a similar trend was observed (see Figure 42). Performance with *geste* was comparable to the performance of healthy controls. When values for halts with *geste* were compared with those of healthy controls (by Kruskal-Wallis testing), no significant group effect was detected (p = 0.31).

4.6.4 Hesitations

No significant differences in number of hesitations with and without *geste* were detected for either group (p = 0.32 for patients with organic dystonia, and p = 1.0 for patients with FD).

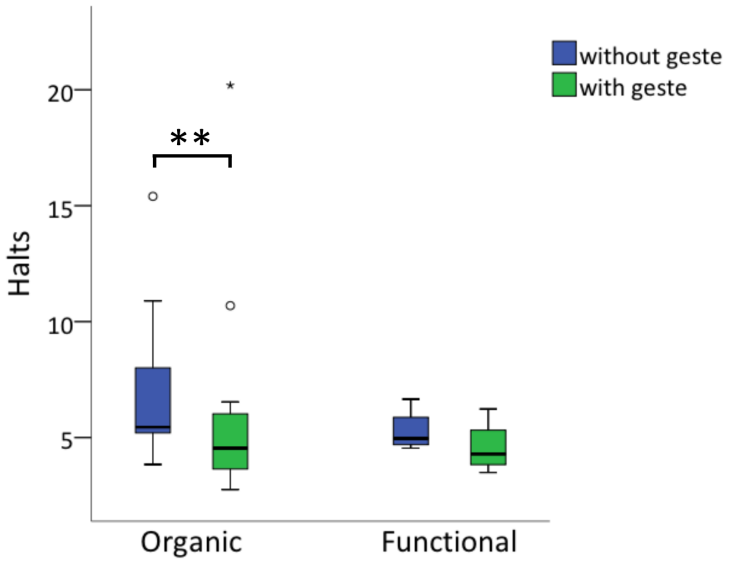


Figure 42: Boxplot for halts (with and without *geste*)

The number of halts was lower when patients activated their *geste*. A similar trend was observed in the functional group, though this did not reach statistical significance. Bracket and asterixes indicates statistically significant comparison. Box = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Outliers are denoted by asterixes (>3 times IQR) and circles (1.5 to 3 times IQR).

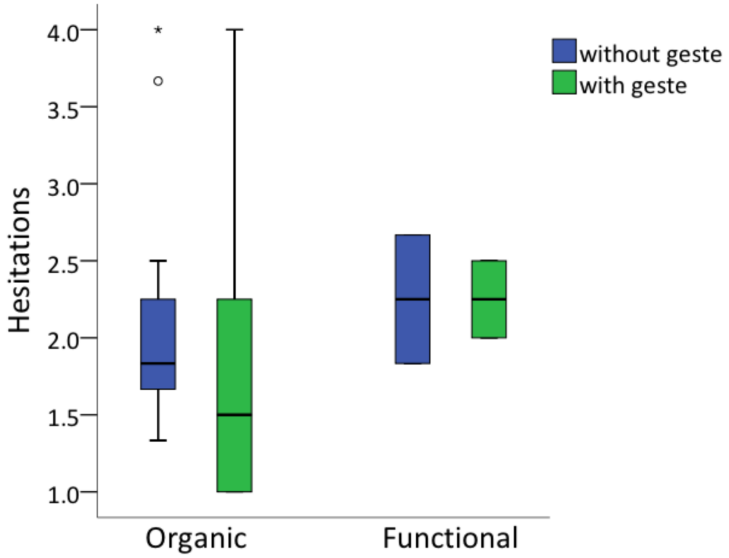


Figure 43: Boxplot for hesitations (with and without *geste*)

The frequency of hesitation did not alter with activation of *geste*. Bracket and asterixes indicates statistically significant comparison. Box = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Outliers are denoted by asterixes (>3 times IQR) and circles (1.5 to 3 times IQR).

In order to obtain an estimate as to whether there was any significant group effect for these measures, an analysis by factorial ANOVA, using factors GESTE (with and without *geste*) and HAND (dominant and non-dominant) as within subject factors and GROUP (organic and functional) as a between subjects factor was performed. A strongly significant effect of GESTE was demonstrated for (amplitude x frequency) but not for the other measures. There was no significant effect of HAND or GROUP.

4.6.5 Summary of finger tapping with and without *geste*

Finger tapping performance in patients with dystonia appears to improve with activation of their *geste antagoniste*. The proportion of halts is reduced and amplitude x frequency (overall speed of movement) increases with *geste*. These effects were significant for the organic group. A similar trend was also noted in FD, though the small size of this group meant that the difference did not reach the threshold for statistical significance.

4.7 Finger tapping with and without metronome

4.7.1 Error in frequency-matching performance

In order to establish how well each group maintained the target frequency (1, 2 or 3Hz), the measured frequency for each trial was subtracted from the target frequency. This data did not meet the criteria for parametric analysis, therefore error values were first adjusted, by taking the square root of the square of each value, to ensure that all values were positive integers. The differences between error for trials one and two, one and three, and two and three were then calculated. A non-parametric Kruskal-Wallis test of independent samples for these comparisons was performed for each condition—WITH metronome (externally paced, the first 15s of the task, when an audible metronome tone was available to guide movement) and WITHOUT metronome (internally timed, the second 15s of the task, when the metronome ceased to sound but the participant was asked to keep tapping at the same rhythm).

Raw error values, rather than percentage error rates were used, so that deviations from target frequencies at higher rates of finger tapping were not down-weighted. For the WITH metronome condition, patients with organic dystonia performed significantly more accurately at 3Hz than at 1Hz by comparison with healthy controls, but there were no other significant pair-wise comparisons. In the WITHOUT metronome condition there were no significant group effects and error rates did not vary between 1, 2 and 3Hz.

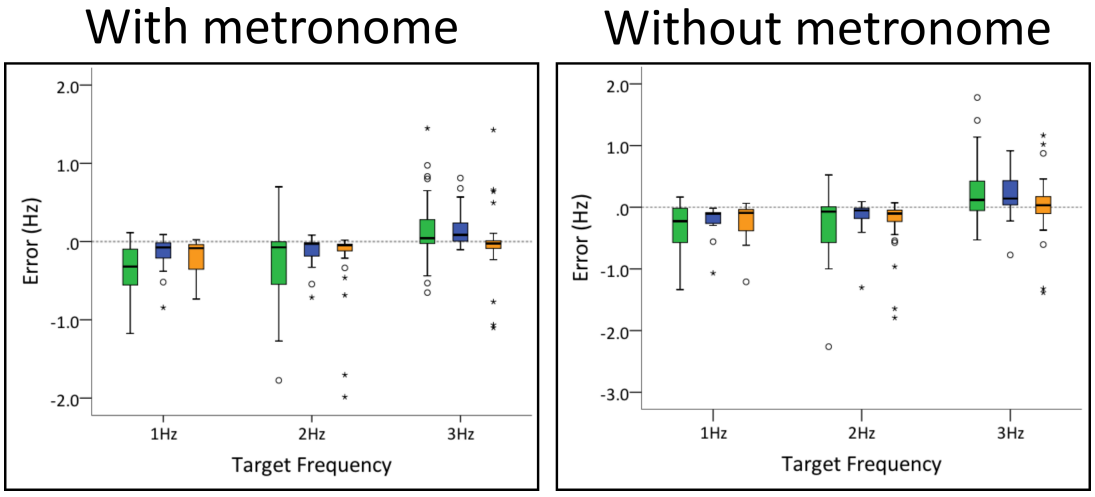


Figure 44: Boxplots for frequency-matching error *with* and *without* metronome

Error was calculated by subtracting observed from target finger tapping frequency, thus more negative values indicate performance that exceeded the target frequency and positive values indicate performance that fell short of the target frequency. The dashed line at zero on the y axis indicates perfect performance (exactly matching target frequency). Bracket and asterixes indicates statistically significant comparison. Box = interquartile range (IQR); whiskers = highest and lowest values within 1.5 x IQR; band inside box = median. Outliers are denoted by asterixes (>3 times IQR) and circles (1.5 to 3 times IQR).

This finding indicates that, broadly speaking, the accuracy of externally paced and internally timed movement is not impaired in the dystonia groups. This is particularly interesting in the case of FD, where abnormal movement-directed attention has been advanced as an important pathophysiological feature.

4.7.2 Comparison of freestyle and metronome-guided finger tapping at different tapping speeds (1Hz, 2Hz and 3Hz)

Four measures of rhythmicity were assessed across the three groups and three target frequency conditions, Coefficient of variance of amplitude (COVamp), Coefficient of variance velocity (COVvel), Halts and Hesitations. The overall speed (Amplitude x frequency) and maximum opening deceleration (MaxOD) were also examined.

Analysis of the spread of data for each motor component revealed some deviations from normality (positively skewed distribution for COVamp, COVvel and hesitations). Logarithmic transformation corrected this deviation for COVamp and COVvel, but not for hesitations. Preliminary analysis suggested that there was no significant difference in performance between dominant and non-dominant hands, therefore averaged data from both hands was used for further analysis. Comparisons were made with average values (dominant and non-dominant hands, and all three trials combined) for the freestyle finger tapping condition. A factorial repeated measures ANOVA, which is robust to deviations from normality, was applied to the data (log-transformed for COVamp and COVvel, untransformed for Halts, Hesitations, Amplitude x frequency and MaxOD), using FREQUENCY (Freestyle, 1 , 2 and 3Hz) as a within-subjects factors, and GROUP (organic, functional and healthy control) as a between-subjects factor. Since Mauchly's sphericity test was significant (indicating that the condition of sphericity was not met) for six of the data sets, the results of multivariate analysis are used. Because the sample sizes are different, the Pillau's trace statistic is quoted. *Post hoc* testing between groups was performed with the Games-Howell adjustment. The Bonferroni adjustment was applied for between-frequencies comparisons.

Performance with external pacing (WITH audible metronome) and internal timing (WITHOUT metronome—internally paced to memory of metronome cue) was then compared with maximal internally-paced finger tapping (the 'freestyle' condition, wherein subjects were simply asked to tap 'as fast and big as possible').

4.7.2.1 Tapping to target frequency WITH metronome guide versus freestyle tapping (externally paced)

For all six measures, there was a significant effect of FREQUENCY across the groups, with a similar profile across the groups and no significant differences between them. The results of multivariate analysis (overall effect of FREQUENCY) are quoted in the text, with *post hoc* pairwise comparisons for between-frequencies analysis detailed in Table 19. Differences for COVamp ($V = 0.32$, $F(3, 66) = 10.4$, $\mathbf{p<0.0001}$), COVvel ($V = 0.74$, $F(3, 66) = 62.0$, $\mathbf{p<0.0001}$) and

hesitations (V = 0.75, F(3, 66) = 66.8, $\mathbf{p<0.0001}$) were driven by discrepancy between freestyle data and values at 1Hz—higher COVamp, lower COVvel, and fewer hesitations. As expected, given the additional time waiting for the metronome tone, percentage halts (V = 0.92, F(3, 66) = 266.1, $\mathbf{p<0.0001}$) and amplitude x frequency (V = 0.91, F(3, 66) = 220.3, $\mathbf{p<0.0001}$) also differed. Halting tendency was higher at 1Hz and 2Hz, compared to freestyle data, but lower at 3Hz. Overall speed was reduced at 1Hz and 2Hz, but was statistically equivalent at 3Hz. A similar profile was noted for MaxOD (V = 0.65, F(3, 66) = 40.8, $\mathbf{p<0.0001}$), except that deceleration rates at in the 3Hz metronome task exceeded those noted in the freestyle condition (across the three groups, as a result of performance in the dystonia groups shifting towards the normal range for healthy controls). Previous studies have suggested that the 'preferred tempo' of human finger tapping is around 2Hz (tapping speed selected by subjects for greatest comfort).(328) This data suggests that it is closer to 3Hz when subjects are instructed to optimise scaling and speed of movement.

Since Box's test was significant for COVamp and Halts, indicating that the condition of equality of covariance might not be met, the variance/covariance matrix for the groups was examined to ascertain whether the group-wise statistics are reliable. This revealed that for 'Halts' the smallest (functional) group accounted for more of the covariance than the larger groups, suggesting the multivariate statistics are likely to be excessively liberal. Thus, it can be concluded with confidence that there was no significant group effect.

For COVamp, the functional group accounted for a smaller proportion of the covariance than the other groups, indicating that results might be overly conservative.

Table 19: Pairwise comparison of freestyle and metronome-guided finger tapping at 1Hz, 2Hz and 3Hz (*with* metronome—externally paced)

	COVamp	COVvel	Halts	Hesitations	Amplitude x frequency	MaxOD
Free vs. 1Hz	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Free vs. 2Hz	NS	NS	0.001	NS	<0.0001	<0.0001
Free vs. 3Hz	NS	NS	0.03	NS	NS	<0.0001
1Hz vs. 2Hz	NS	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
1Hz vs. 3Hz	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
2Hz vs. 3Hz	0.001	NS	<0.0001	0.04	<0.0001	<0.0001

COVamp = coefficient of variation for amplitude; COVvel = coefficient of variation for velocity; Free = freestyle; MaxOD = maximum opening deceleration.

4.7.2.2 Tapping to target frequency WITHOUT audible metronome guide versus freestyle tapping (internally timed)

A similar significant effect of FREQUENCY for all six measures across the groups, with no significant group effect was noted . Differences for COVamp (V = 0.41, F(3, 66) = 15.1, ***p*<0.0001**), COVvel (V = 0.55, F(3, 66) = 27.0, ***p*<0.0001**), and hesitations (V = 0.74, F(3, 66) = 63.2, ***p*<0.0001**) were once again driven by discrepancy between freestyle data and values at 1Hz—higher COVamp, lower COVvel, and fewer hesitations. Percentage halts (V = 0.87, F(3, 66) = 151.4, ***p*<0.0001**), Amplitude x frequency (V = 0.91, F(3, 66) = 218.1, ***p*<0.0001**) and MaxOD (V = 0.56, F(3, 66) = 28.4, ***p*<0.0001**) showed an identical pattern of pair-wise comparisons to the WITH metronome condition (see Table 20).

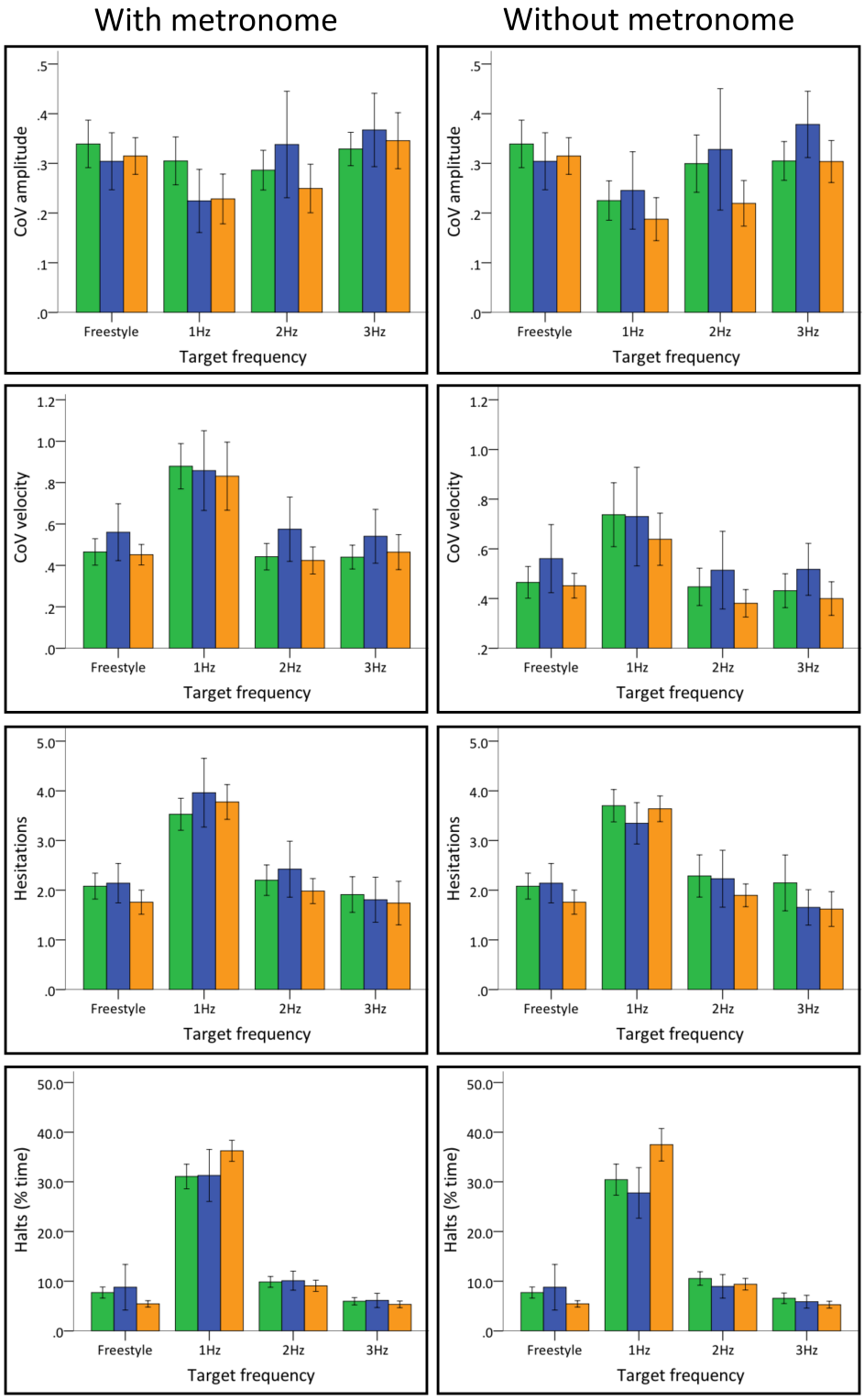


Figure 45: Bar charts for measures of rhythmicity at different finger tapping frequencies

Bars display mean values for each group. CoV = coefficient of variation. Green bars = organic dystonia; blue bars = functional dystonia; orange bars = healthy controls. Error bars indicate 95% confidence intervals. Without metronome = 15s when metronome no longer audible, but subjects tapping at the same frequency.

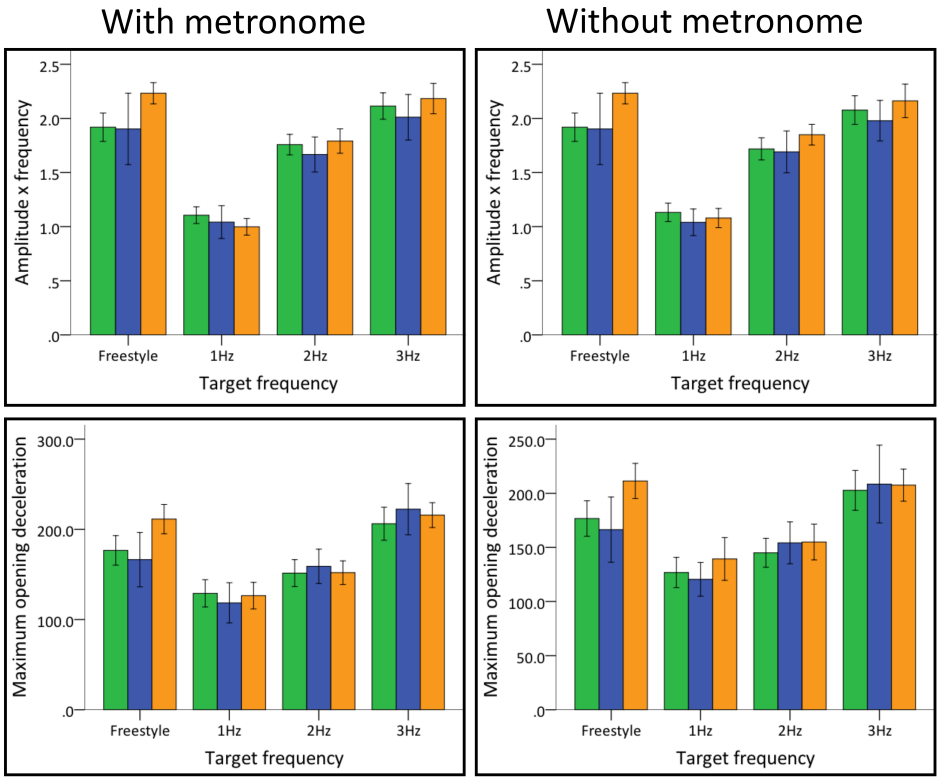


Figure 46: Bar charts for amplitude x frequency and maximum opening deceleration at different finger tapping frequencies

Bars display mean values for each group. Green bars = organic dystonia; blue bars = functional dystonia; orange bars = healthy controls. Error bars indicate 95% confidence intervals. With metronome = 15s when metronome was audible. Without metronome = 15s when metronome no longer audible, but subjects asked to continue tapping at the same frequency.

Box's test was significant for COVvel, Halts and Hesitations. In all three cases the functional group made a disproportionately high contribution to the covariance, indicating that statistics were likely to be excessively liberal. Hence it is unlikely that a significant group effect was missed.

Table 20: Pairwise comparison of freestyle and metronome-guided finger tapping at 1Hz, 2Hz and 3Hz (*without* metronome—internally timed)

	COVamp	COVvel	Halts	Hesitations	Amplitude x frequency	Max OD
Free vs. 1Hz	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Free vs. 2Hz	0.01	NS	0.009	NS	<0.0001	<0.0001
Free vs. 3Hz	NS	NS	0.05	NS	NS	0.008
1Hz vs. 2Hz	0.007	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
1Hz vs. 3Hz	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
2Hz vs. 3Hz	0.002	NS	<0.0001	0.05	<0.0001	<0.0001

COVamp = coefficient of variation for amplitude; COVvel = coefficient of variation for velocity; Free = freestyle; MaxOD = maximum opening deceleration.

4.7.3 Summary of metronome-guided finger tapping results

The findings in relation to variations in motor performance at different frequencies could be anticipated, and are likely to reflect differences in the mode of motor control used to complete the tasks. Faster performance (at higher prescribed frequencies and in the freestyle 'as fast as possible' condition) would be expected to utilise ballistic 'feed forward' motor control, resulting in more smooth overall performance with fewer pauses or false starts, compared with slower finger tapping rates, when continuous 'online' feedback control would produce more hesitant movement (representing interruptions in movement as a result of the need to make adjustments for sensory feedback).

The absence of a significant group effect for any of the components examined indicates that patients with dystonia are able to reliably produce rhythmic movements in response to externally paced and internally timed (from memory of metronome) frequency targets with accuracies similar to that of healthy controls.

4.8 Summary of kinematic results

Finger tapping in dystonia is generally slower, in terms of the overall distance covered per unit time. Patients can produce similar velocities and amplitudes of movement to healthy controls, but cyclical movement is disrupted by an increased tendency to halt or hesitate. Motor switching between extension and flexion at the point of maximal finger-thumb aperture seems to be preferentially impaired. None of the separable motor components examined distinguish reliably between functional and organic subtypes of dystonia. This is demonstrated graphically in the ROC curves shown in Figure 47 (with AUC values for these curves shown in Table 21). The most discriminant features in comparisons with healthy controls were halts (for organic dystonia, AUC = 0.71) and hesitations (for FD, AUC = 0.74). Activation of the *geste antagoniste* appears to normalise motor performance—when patients' activated their *gestes* values for amplitude x frequency and halts were statistically equivalent to control values. Accuracy of externally paced movement is preserved in both organic and FD, and patterns of performance on externally and internally paced finger tapping tasks were consistent across all three groups (more halting and less hesitant tapping at higher frequencies).

Table 21: Table showing AUC (area under the curve) for separable motor components for three group comparisons

	FD vs OD	OD vs HC	FD vs HC
Frequency	0.51	0.68	0.69
Max OD	0.54	0.72	0.77
Max CA	0.59	0.65	0.71
Halts	0.55	0.71	0.63
Hesitations	0.63	0.63	0.74
Amp*Freq	0.52	0.73	0.69

Amp = amplitude; Freq = frequency; FD = functional dystonia; HC= healthy control; Max CA = maximum closing acceleration; Max OD = maximum opening deceleration; OD = organic dystonia.

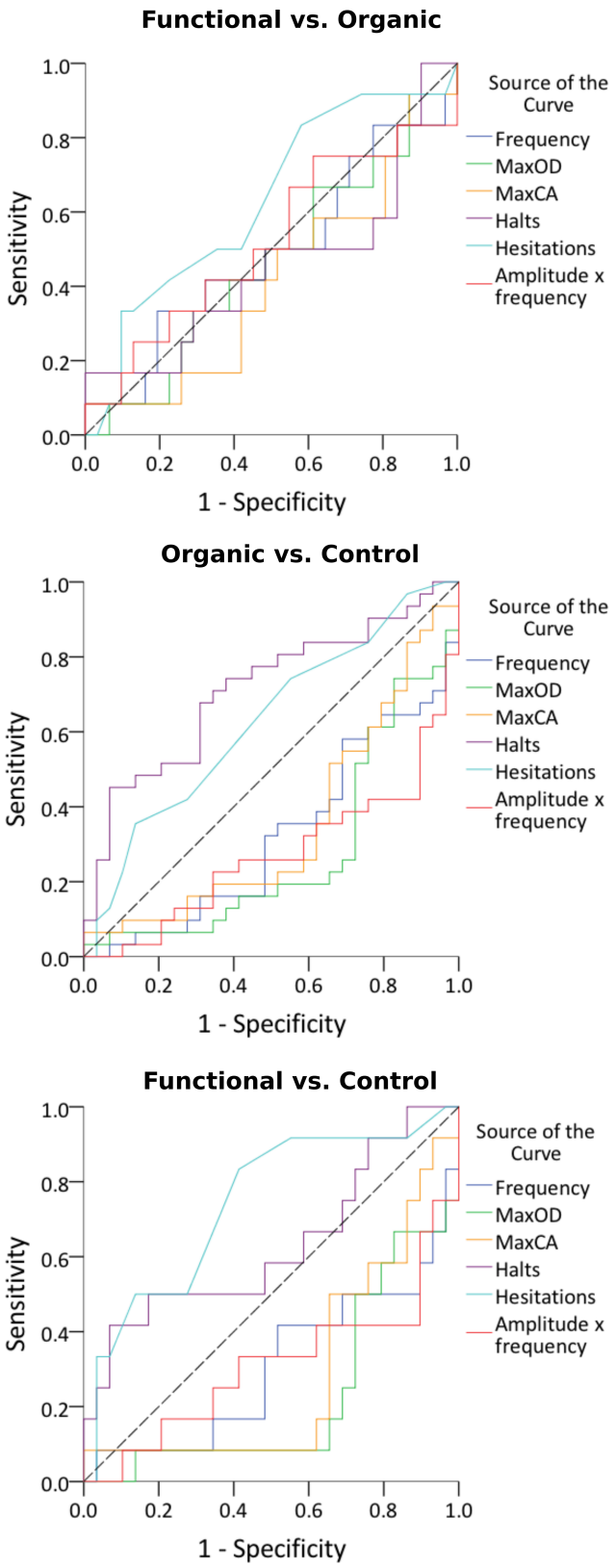


Figure 47: ROC Curves for kinematic measures

CA = closing acceleration; OD = opening deceleration.

Chapter Five: Discussion

The overall aim of this study was to perform a detailed psychological and kinematic assessment of dystonia with a view to better understanding its complex phenomenology, and the place of FD within the broader spectrum of dystonic diseases. By adopting an inclusive approach to recruitment, and applying novel kinematic approaches (externally paced finger tapping and assessments with and without *geste*), and a wide range of psychological assessments, including scales for obsessive-compulsion and depersonalisation, it was possible to examine functional and organic subtypes in greater detail than in comparative studies undertaken to date.

The main findings are as follows:

1. **There is an excess of self-rated psychopathology in both functional and organic dystonia.** Patients with organic dystonia and patients with FD both have higher scores for self-rated depression and pain, compared with healthy controls. Additionally, those with FD have elevated anxiety, obsessive-compulsive, fatigue, and depersonalisation scores. None of these measures reliably distinguished the patient groups. The most discriminative measure was obsessive-compulsive tendency, where there was small statistical excess in the functional group when scores were subdivided into classes (subclinical, mild, moderate, severe, extreme), which was not detected in group comparisons by raw score alone.
2. **Repetitive voluntary movements in dystonia are slower and show greater discontinuity.** Finger tapping performance in both functional and organic dystonia was impaired, compared with healthy controls, with deficits in overall speed and more motor interruptions (more halting performance in organic dystonia and more frequent hesitations, or false starts, in FD), as well as reduced opening deceleration, contributing to slower phase-switching.
3. **Activation of the *geste antagoniste* improves motor performance.** Kinematic performance of patients *with geste* was indistinguishable from that of healthy controls. This effect that does not seem to be confined to organic dystonia.

4. **Externally paced movement is normal.** The ability to maintain rhythmic movement at a pre-defined frequency with and without external pacing is intact in both dystonia subgroups.
5. **Organic and functional dystonia cannot be distinguished on kinematic or psychological grounds.** None of the kinematic or psychological features differentiated organic from FD with high sensitivity and specificity.

This final conclusion raises intriguing questions about the validity of existing conceptual frameworks for functional and organic movement disorders. The hegemony of mind-brain dualistic thinking over 150 years of neurological practice has left a strong imprint on attitudes to dystonia. Rigid classifications of the condition—based on the segregation along psychological lines, or invoking sharp delineations between voluntary and involuntary action—have failed to fully accommodate its complex and changeable character. Even David Marsden, who argued for greater collaboration between neurology and psychiatry, and was responsible for a major reformulation of dystonia in the 1970s, was not immune to dualistic thinking. He proposed that the function of the basal ganglia was purely motor, despite their extensive afferent input—visual, auditory, tactile and olfactory. The non-motor character of disorders of the basal ganglia are now well recognised—disturbances of sleep, psychological balance and cognitive and sensory processing have all been reported. The recognition of psychopathological dimension to undeniably organic movement disorders, such as Parkinson's or Huntington's disease, might be expected to loosen this dualistic stranglehold. Yet attitudes in contemporary neurological practice remain highly polarised. This study adds to a growing body of evidence in support of a more nuanced biopsychosocial modelling of movement disorders, both organic and functional.

5.1 Clinical phenomenology and rating scales

In this section the following points will be addressed: 1) a justification for the selection of broad inclusion criteria and choice of clinical rating scales; 2) evidence for a pervasive motor disturbance in patients with dystonia, including those with apparently focal manifestations; 3) how blinded topographic scores for both patient groups showed that a majority of individuals had involvement of one or

both upper limbs, irrespective of the main focus of dystonia; and 4) the correspondence between treating clinician and blinded raters for overall diagnostic impression (functional, organic or control).

5.1.1 Reliability and validity of rating scales

Three clinicians—PK, JA and JC (see acknowledgements)—provided blinded clinical ratings. Each study participant was independently rated by two of the three blinded assessors.

Inter-rater correlation for all three movement rating scales (FMDRS, S-FMDRS and MDS-UPDRS) was between 85% and 95%, in line with previously published values for inter-rater reliability for these scales.(329–331) Assessment of inter-rater agreement for individual body regions (by Kendall's coefficient of concordance, *W*) also revealed strong correlations, with *W* values above 0.75 (indicating 75% agreement) for almost all ratings.

Are these scales a valid means of rating motor severity and topography in the selected groups? The FMDRS is validated for use in generalised organic dystonia(320) (12% of the organic group) but it has also been applied to other types of dystonia, including secondary(332,333) and idiopathic focal (cranial and cervical) dystonia(334–337), suggesting that is considered an acceptable tool for monitoring dystonia with more localised expression. Additionally, in one of the reports on cervical dystonia, the pattern of FMDRS scores mirrored that of a validated cervical dystonia scale (the Toronto Western spasmodic torticollis rating scale).(335)

Though the FMDRS is not validated for use in FD, the strong correlation between these scores and those for the S-FMDRS indicate that the two scales are measuring dystonic motor disturbance in a similar fashion. Significant (albeit weak) correlations were noted between both the clinical ratings of motor severity (FMDRS and S-FMDRS) and kinematic measures for overall speed (negative correlation) and halting tendency (positive correlation), indicating that the clinical

scales provide a reliable indication of presence of dystonia, if not its severity (by kinematic parameters).

5.1.2 Comparison of topography and severity

There was no significant difference in motor severity between the organic and functional patient groups, judged by either scale, indicating that they were well matched in terms of the burden of motor symptomatology. Both groups had significantly higher scores than healthy controls but could not be distinguished according to their ratings on either scale. Comparison of the boxplots for these scores shows that, though the medians for the groups are very similar, the interquartile range is larger in the functional group, with a skew towards higher scores. There was a strong correlation between scores on functional (S-FMDRS) and organic (FMDRS) rating scales for both groups (r_s=0.89, $\boldsymbol{p<0.0001}$ for organic dystonia and r_s=0.98, $\boldsymbol{p<0.0001}$ for FD). Since the S-FMDRS takes into account all abnormal movements, not just dystonia, the strength of this correlation suggests that recruited patients had a dominant dystonic phenotype, and that additional motor symptoms (tremor, myoclonus, weakness) present in the functional group did not significantly contribute to overall motor severity.

Comparisons of scores by body region for each group revealed that they had very similar topographic profiles. A slight excess of lower limb dystonia in the functional group, and of cervical involvement in the organic group, was noted. Seventy-five percent of patients with FD, and 77% of those with organic disease had involvement of one or both upper limbs, according to the blinded clinical assessments. This, along with existing evidence of electrophysiological markers of dystonia in clinically asymptomatic body regions (see below) supports the methodological decision to recruit patients with focal, as well as generalised, dystonia.

5.1.3 Validity of inclusion of patients with cervical dystonia and lower limb functional dystonia

5.1.3.1 Cervical dystonia

The inclusion of 18 patients with isolated cervical dystonia might be questioned, as it could be argued that an isolated analysis of finger tapping is unlikely to capture dystonic kinematic disturbances in patients whose primary locus of dystonia is not the upper limb. However, overflow dystonia—the spread of dystonic muscular contraction to regions outside the primary locus—is common, so these patients often have mild clinical markers of dystonia in contiguous body parts (for instance, upper limb tremor frequently attends cervical dystonia).(138) Certain muscles primarily associated with cervical dystonia, such as Trapezius and Levator Scapulae, attach to the scapula and thus are engaged in movement of the arm *en bloc*. There is also evidence of electrophysiological overlap—co-contraction in upper extremity muscles and disturbed reaching movements have been recorded in patients with dystonia that is clinically confined to the cervical musculature (see more detailed discussion below).(247,251,255) In the current study, 13 out of the 18 patients with dystonia primarily affecting the cervical muscles (just over 70%) had visible dystonia in one or both upper limbs, according to blinded FMDRS scores.

The inclusion of the remaining five patients (and the two other individuals within the organic group for whom no clinical involvement of either upper limb was demonstrated) can also be defended. Dystonic disturbances of upper limb motor function have been recorded at an electrophysiological level in those without clinical evidence of upper limb dystonia. Three separate examinations of reach and grasp movements in patients with cervical or cranial dystonia (without clinical involvement of the upper limb) have all shown kinematic impairments—slower movement and reaction times, lower values for peak velocity and acceleration, and impaired switching between flexion and extension movements.(241,247,251) In addition, generalised disturbances in sensory and motor processing, thought to have pathophysiological relevance in dystonia, have been demonstrated in focal disease states. Ridding et al. reported reduced short intracortical inhibition in both

symptomatic and asymptomatic limbs of patients with focal hand dystonia;(338) and raised temporal and spatial discrimination thresholds for sensory stimuli have been recorded in the unaffected limbs of patients with both cervical and focal hand dystonia.(339,340)

5.1.3.1 Functional dystonia affecting the lower limb

Four of the 13 patients in the FD group had no clinical upper limb involvement (three with predominantly lower limb and one with primarily truncal dystonia). The proposition that FD is a manifestation of a more general motor and perceptual disturbance is broadly accepted. Patients frequently present with more than one functional motor disturbance, either simultaneously—functional weakness accompanying dystonia, for instance—or sequentially over the time-course of their illness.(177) Janet described paucity and excess of movement in hysteria (weakness and contracture) as two sides of the same coin, both denoting a fundamental disturbance in voluntary motor function.(341) According to one neurobiological theory of FMDs, these disorders are defined by abnormal sensorimotor 'beliefs' (or probabilistic expectations concerning sensory input) encoded at a subliminal level (see Section 5.6.5.2, below).(342) These give rise to autonomous movements over which patients have no sense of control (a loss of agency). In response to changes in 'top-down' (conscious) illness beliefs or 'bottom-up' sensorimotor feedback, these expectations can shift, thus producing different motor disturbances at different times.

This schema predicts a general rather than localised disturbance in sensorimotor processing that is borne out by electrophysiological studies. Two studies of finger tapping in CRPS showed impairments in patients with and without clinical evidence of dystonia.(262,263) In alignment with findings in organic dystonia, temporal discrimination thresholds were elevated above controls in both the symptomatic and non-symptomatic limbs of patients with FD.(276) Finally, a bihemispheric reduction in short intracortical inhibition has been demonstrated in patients with unilateral FD.(268)

5.1.4 Diagnostic impressions: correspondence between treating clinician and blinded raters

Comparisons of the diagnostic impressions of the blinded raters with that of the treating neurologist, revealed substantial agreement overall, with Fleiss' κ values above 0.6. Observed agreement for FD was lower than that for organic dystonia (50% agreement versus 84%), with κ values of 0.57 and 0.50 for the two blinded ratings. However, as reported previously in functional myoclonus(343) and organic movement disorder(344), video-based assessment in isolation, without supporting information, can be associated with poor inter-rater reliability (the equivalent κ value for functional myoclonus in the aforementioned study was 0.28). Thus the higher rate of disagreement between the blinded rating neurologists (whose only source material was the video) and treating neurologist for FD does not necessarily call into question the validity of the latter's diagnostic impression.

5.2 Psychological measures: previous findings and current study

The small sample size in the functional group makes it difficult to generalise from these results to the broader population with confidence; however, some potentially interesting results were revealed that, if reproducible, may assist in establishing a more complete understanding of the psychological character of dystonia. All patients, regardless of dystonia subtype, scored higher than healthy controls for depression and pain. Levels of anxiety, fatigue, obsessive-compulsion and depersonalisation above those observed in healthy controls were noted in the functional group. Patients with organic dystonia generally scored in the intermediate range and were statistically indistinguishable from those with FD for all scales. The BOCS measure of obsessive-compulsive tendency displayed the best (albeit still weak) discriminative capacity of all comparisons between the patient groups, with a higher proportion of moderate to extreme scores in the functional group.

5.2.1 Anxiety and depression

The profiles of scores in the two dystonia groups were very similar for both anxiety and depression. Though the organic group was not statistically different to the healthy control group for anxiety, both dystonia groups showed a similar trend towards higher scores, and the *p* value for the control vs. organic dystonia comparison only just failed to reach the threshold for significance ($p = 0.055$).

Higher rates of psychopathology have been reported, across a range of organic dystonias (genetic and idiopathic adult-onset focal). Affective disorders are more common in DYT1 and DYT12,(181,191) and rates of anxiety spectrum disorders are elevated in DYT3, DYT5 and DTY11.(186–190) Patients with cervical dystonia have more depressive and neurotic tendencies, with lifetime psychiatric disorder rates of up to 92%.(345) Musician's dystonia may be associated with perfectionistic traits, social phobia and elevated anxiety.(140,212,346) Patterns of psychiatric disorder in blepharospasm, writer's cramp and laryngeal dystonia are less clear, as only a handful of small studies have been performed in these conditions (see Table 1).

The absence of a significant difference between organic dystonia and healthy controls for anxiety or obsessive-compulsion in this study may reflect the heterogeneity of the clinical sample, with subtypes without a strong predisposition towards these disorders skewing the results towards the healthy range. Alternatively the relatively small sample size, by limiting statistical power, may have resulted in a type II error (failure to reject the null hypothesis in the presence of a true effect). The small sample size also precluded meaningful subgroup analysis. Rough plots of the psychological indices by subgroup indicate that the range of scores for patients with secondary dystonia (arising as a result of hypoxic or ischaemic brain injury) is closer to that of healthy controls, so it is possible that the inclusion of this group has reduced the group average for organic dystonia.

High levels of anxiety and depression in functional motor disorder have been reported in a number of studies, but only a handful have included comparative analysis with an organic movement disorder control group. Some of these applied

diagnostic criteria for FMD that were lacking in stringency, or included the presence of psychopathology, calling into question the reliability of results.

Schrag et al. compared 26 patients with fixed (presumed functional) dystonia with 20 for whom a diagnosis of "classical" organic dystonia had been made (13 secondary, 3 genetic (DYT1), 4 idiopathic cervical dystonia).(176) Higher rates of affective disorder following the onset of motor symptoms (50% vs. 15%) and higher lifetime dissociative disorder (42% vs. 0%) were reported in the functional group. Only a third of patients with fixed dystonia met the criteria for 'documented' or 'clinically established' FD under the Fahn-Williams criteria, which has poor specificity at lower levels of diagnostic certainty. Binzer et al. compared 30 patients with functional paralysis with 30 organic diseased controls and found more DSM-IV axis-I disorders (mainly depression), higher rates of personality disorder and increased self-rated pain and depression in the functional group.(347) No specific diagnostic criteria for FMD were applied, the diagnosis was one of exclusion. Defazio et al. compared a cohort with mixed FMD (31 patients, 18 'clinically definite', 13 'probable' according to Fahn-Williams criteria) with 31 who had adult-onset focal dystonia.(215) The authors found elevated levels of self-rated depression and anxiety, but similar profiles of categorical psychiatric disorder across the two groups.

More recent papers, which apply diagnostic criteria for FMD based on phenomenology rather than psychopathology, are likely to give a more accurate picture of the profile of psychological disturbance in organic and FD. These give a fairly consistent account of higher *self-rated* anxiety and depression in mixed cohorts with FMD, with no differences in categorical psychiatric diagnosis or personality disorder. Van der Hoeven et al. measured self-rated depression, anxiety, and personality disorder in a cohort with mixed FMD (mostly weakness, gait disturbance and tremor, only two of 51 patients had dystonia) compared with a roughly matched group with organic motor disorders.(216) They found that a significant minority in both groups (approximately two fifths) scored within the normal range on all tests. This implies that, as in musician's dystonia, psychological profiles may not be uniform among patients with FD. Unfortunately the functional sample in the current study is far too small to permit further subgroup analysis.

In summary, the findings of the present study align with previous reports that disclose higher levels of self-rated depression and anxiety in FD. Since a high proportion of patients with organic dystonia also show this trend, these scores are poorly discriminative between organic and functional subtypes.

5.2.2 Obsessive-compulsion

Comparison of the spread of BOCS scores between organic and FD reveals more divergent profiles, with higher scores present more frequently in the functional group. Though functional patients had a higher proportion of moderate to severe scores, the two groups could not be separated statistically.

It could be speculated that a study with higher power (with a larger functional group) may have disclosed a significant difference. Alternatively, since individual patients' responses have greater influence in small samples, it is possible that this result reflects sampling bias, rather than a true group effect (one patient from the functional group had premorbid tic disorder with obsessive-compulsive features, his BOCS scores may have had a disproportionate effect on the group average). Further examination of these features in a larger population is clearly required, but on the basis of this preliminary data it would seem unlikely that scores for obsessive-compulsion could be used as a reliable metric for group differentiation, since there is a sizeable overlap of scores.

Case-control studies have reported elevated rates of obsessive-compulsion in genetic (DYT11 and DYT5) and a range of IFDs (see Table 1). None have specifically examined obsessive-compulsive tendency in FMD, though the idea that functional motor disorders might share common pathophysiology with OCD has a longer tradition—in his PhD thesis, published in 1901, Pierre Janet drew parallels between *la folie du doute* (OCD, 'the madness of doubt') and hysteria.(348) This aligns with functional imaging data that reveals partially overlapping patterns of cortico-striatal activity in dystonia and OCD.(285,349) It is possible that an imbalance in transmission through direct and indirect pathways within the basal

ganglia may contribute to the premotor cortical hyperactivity observed in OCD, functional and organic dystonia.

The patient within the functional group who had a history of OCD tendencies prior to the onset of his movement disorder described involuntary truncal spasms developing on the foundation of a voluntary manoeuvre employed to suppress tics. Obsession-compulsion may reflect a shift cortico-striatal dynamics that favours not only the formation of not only intrusive patterns of thought, but autonomous motor programmes.

5.2.3 Fatigue and pain

Scores for fatigue and pain were elevated above healthy controls in both dystonia groups, with significant differences for both in FD, and for pain alone in organic dystonia (with a near-threshold *p* value for fatigue: 0.053).
Fatigue and pain in FMD have mainly been assessed qualitatively, by report at interview. High rates of fatigue and pain (82% and ~33%, respectively) were noted in a large case series of functional weakness.(306) In mixed FMD cohorts (comprising ~25% dystonia) fatigue is reported in 16-60% of cases, and pain in about three quarters.(350,351) Quantitative measures were made in a group of 61 FMD patients, of whom just over a third had dystonia. In this study fatigue (FSS score) and pain (VAS score) were significantly elevated compared to healthy controls (mean values 5.4 and 5.5, respectively).(352) Corresponding mean values for the present study are similar (FSS: 4.8, Pain VAS: 6.4).

Morgante et al. recently compared tactile and pain thresholds in 10 patients with FD, 12 with cervical dystonia and 16 healthy controls, finding higher pain tolerance in the functional group (an effect apparently specific to fixed FD).(218) Subjective pain scores between the two groups were not statistically different.

5.2.4 Depersonalisation

Dissociation describes a complex of disturbances in awareness, sensorimotor integration, emotion and sense of identity that gives rise to a sense of disconnectedness from one's environment (derealisation) or body (depersonalisation), accompanied by the experience of loss of control over one's actions (compartmentalisation). The current study found significantly elevated CDS (a measure of detachment) scores for FD compared to healthy controls, but not by comparison with patients with organic dystonia.

Previous studies have reported mixed findings in relation to measures of dissociation in FMD. Demartini et al. examined scores for three dissociative scales (for general dissociation (Dissociative Experience Scale, DES), detachment (CDS) and compartmentalisation (Somatoform Dissociation Questionnaire, SDQ)), in patients with mixed FMD (of whom only 15% had FD) and non-epileptic seizures.(353) For DES and CDS they found an elevation above healthy controls in the seizure group, and an isolated increase in SDQ scores in the FMD group. This aligns with Kranick et al., who found equivalent DES scores across FMD, organic dystonia and healthy controls.(214) Since the SDQ was developed to measure somatoform symptoms in FMD, a finding of higher scores in this group is unsurprising. Another report, using a different metric to examine somatisation, found similar overall levels in FMD and organic dystonia (though a higher average number of somatisations were reported in FMD).(215) Van der Hoeven found elevated scores for both psychological and somatic dissociative symptoms in FMD, compared with organic motor disorder, which correlated with the severity of psychopathology.(216)

An association between functional neurological disorder and dissociative symptoms—depersonalisation and derealisation—has long been recognised. Dissociation formed the basis of Pierre Janet's model of hysteria; he described a 'doubling' of self that allowed sensorimotor symptoms to evolve outside the sufferer's conscious awareness. Deficits in emotional (alexithymia) and interoceptive processing, both of which have been reported in FMD, may contribute to this experience of detachment.(354,355) More recent work has

drawn attention to the potential importance of these symptoms in kindling aberrant sensorimotor expectation in functional neurological disorders, particularly in functional weakness and non-epileptic seizures.(315,356)

5.2.5 Summary of psychological data

Elevated scores for depression and pain were noted in patients with dystonia, regardless of subtype. While those with FD appeared to have a broader range of psychiatric disturbance—encompassing anxiety, obsessive-compulsion and depersonalisation, as well as depression—none of these measures were discriminatory between the two dystonia groups. Future studies in larger populations will be able to clarify whether OCD tendencies are disproportionately elevated in FD. If this were the case, it would be potentially interesting from a pathophysiological standpoint—obsession-compulsion might represent the psychological manifestation of the altered cortico-striatal dynamics that give rise to abnormal posturing in FD.

5.3 Kinematics: previous findings and current results

5.3.1 Freestyle finger tapping data

This study revealed a reduction in frequency and overall speed of movement in organic dystonia, with more halting performance and reduced maximal opening deceleration (during extension phase, approaching maximal finger-thumb aperture). Similar profiles were observed in the functional group, though only the reduction in maximal opening deceleration reached significance. In contrast to participants with organic disease, finger tapping in FD was characterised by more hesitant (i.e. more false starts), rather than more halting performance.

5.3.1.1 Freestyle finger-tapping: general findings in dystonia

The findings in organic dystonia are in alignment with several previous reports. Most prior kinematic studies of organic dystonia have focused on idiopathic focal upper limb dystonia. They give a fairly consistent account of slower, more variable

and lower frequency movement, with more motor arrests and delayed phase-switching. However, because of the broad range of experimental paradigms and varied case mixes there are some inconsistencies. Loss of the normal bell-shaped velocity profile for ballistic movements (indicative of impairment of 'feed-forward' motor control) has been reported in generalised and idiopathic cervical dystonia, whereas normal velocity curves were demonstrated in focal upper limb dystonia. Most studies report reduced peak velocity and acceleration, but acceleration was increased in one study of writer's cramp. Reaction times in externally cued tasks are delayed in focal upper limb, cervical and secondary dystonia, but were normal in one group with writer's cramp (see Table 4 for more details).

The finding of reduced opening deceleration is particularly interesting. This corresponds with the observations of Curra et al.(239)—who documented slowing, longer pauses and a disproportionately increased extension phase (and pause prior to extension) for individual finger oppositions in patients with focal and segmental upper limb dystonia—and Inzelberg et al.(238)—who found reduced deceleration rate in target-directed movements recorded on a digitising graphics pad in DYT1.

Curra et al. theorised that this selective prolongation of the extension phase might be a consequence of primary motor cortical underactivity in dystonia (since greater activation is required for extensor compared to flexor muscles), with consequent deficits in focusing of voluntary muscle activation producing higher levels of co-contraction in the extension phase. EMG studies have shown that rapid movements that are mechanically stopped have a different profile of activity to those that are not, with brisker offset of antagonist activity and increased agonist activity. To investigate this further, the authors performed double end-stop experiments, using an aluminium cast, in which both flexion and extension movements were mechanically stopped. In these circumstances there was no disproportionate lengthening of the extension phase, the pause before extension was reduced, and the halt prior to flexion lengthened (presumably due to the reduction in antagonist flexor activity during the extension phase).

That patients with both functional and organic dystonia displayed this pattern suggests that they might have overlapping pathophysiology. Functional imaging has demonstrated reduced primary motor cortical activity in FD,(285) which according to the theory of Curra et al. would predispose patients to co-contraction and selective impairment of individual finger movements.

5.3.1.2 The different character of 'bradykinesia' in dystonia and Parkinson's disease

The term bradykinesia in Parkinson's disease denotes not only slowness of movement but a complex set of motor disturbances, including: impaired motor initiation, loss of rhythmicity, and decrement in speed and/or amplitude with repetitive activity.(357,358) Atypical parkinsonian disorders probably have distinctive bradykinetic profiles—progressive supranuclear palsy, for instance, seems to involve more prominent hypokinesia (reduction in amplitude) compared to idiopathic Parkinson's disease.(359) In contrast to parkinsonian bradykinesia, slowness of movement in dystonia in this study was not accompanied by hypokinesia (finger tapping amplitudes were similar to healthy controls), and there was no decrement in either amplitude or velocity during the 15 second tasks. Coefficients of variation for amplitude and velocity were similar to healthy controls, suggesting that movement in dystonia broadly retains rhythmicity, despite a greater halting tendency or more frequent hesitations. Deficits in ballistic "open loop" or predictive motor control have been noted in Parkinson's disease. Velocity profiles for patients with dystonia in this study appeared relatively normal, with a preserved bell-shaped appearance, indicating that predictive motor control is preserved.

5.3.1.3 Freestyle finger-tapping: comparing functional and organic dystonia

There is a paucity of data relating to the electrophysiology of FD. One study reported increased co-activation preceding each of three test conditions—'rest', 'posture' and 'move'—in two out of four patients with fixed dystonia of the right lower limb, compared to five with DYT1 dystonia affecting the same leg.(260) Another compared nine patients with fixed lower limb dystonia and nine with

secondary dystonia, revealing less co-contraction and lower reaction times (closer to the range seen in normal subjects) in the functional group.(281)

The kinematics of finger-thumb tapping has been examined in CRPS patients with dystonia by two research groups.(262,263) The pathophysiological basis of motor disturbance in CRPS remains controversial, but within neurological circles it is broadly accepted that dystonia in CRPS has a functional basis. Both these kinematic studies recorded reduced velocity and frequency of finger-tapping compared to healthy controls. All CRPS patients (including those without clinical dystonia) showed a greater frequency of pauses than either healthy or organic controls (including patients with Parkinson's disease).

Only one other study has directly compared finger tapping in functional and organic movement disorder. Criswell et al. used a different experimental paradigm—alternating button presses with the index finger, rather than finger-thumb oppositions—to examine finger tapping in 130 healthy controls, 182 patients with organic movement disorder (17.5% of whom had dystonia) and 13 patients with FMD (15% of whom had dystonia).(261) They found that patients with FMD tapped significantly more slowly than any of the patients with organic motor disorder.

No significant differences were found between the functional and organic groups for any of the kinematic parameters examined in the present study. This may be because the study was underpowered (see 'Limitations of the study' discussion below). However, since sample size was calculated based on the assumption of a 25% difference between patient groups, if the low sample size has resulted in type II error, it may be assumed that any missed differences between the groups would be relatively subtle.

Qualitative appraisal of the profile of performance across the separable motor components suggests that, in general, the functional group occupies an intermediate position between healthy controls and patients with organic dystonia. Previous studies have disclosed a loss of inhibition at multiple levels of the neural axis in both organic and FD. It has been proposed that this might be

indicative of a common pathophysiological basis for the two disorders, with precise phenomenology being governed by independent factors (such as affect, impulsivity and prior trauma). Data from this study is consistent with this proposition.

There are several reasons why the findings of the present study might be at odds the observations of Criswell et al., who demonstrated a clear divergence in performance in those with FMD from that of patients with other organic motor disorders. The clinical sample selected in their study was more heterogenous, comprising mainly functional tremor with only a minority of patients with dystonia included. Functional tremor can more easily be distinguished from organic tremor on clinical grounds, and the presence of functional tremor is recognised to interfere with rhythmic movements in the contralateral limb (which would make the motor profiles of these patients easier to distinguish from those of healthy and diseased controls). It is also possible that motor performance is selectively impaired in alternate button pressing tasks (where motor efficiency additionally depends on factors such as directness of path between buttons and the dynamics of force generation with each button press) compared to simple finger-thumb oppositions.

5.3.2 Finger tapping with and without *geste*

The *geste antagoniste*, or sensory trick, is a peculiarity of dystonia that is frequently observed in idiopathic focal dystonia, occurring in 70-80% of those with cranial and cervical subtypes.(360,361) It is also well recognised in genetically-based generalised dystonia.(362) Its pathophysiology remains obscure, but it has been suggested that these manoeuvres work by rebalancing abnormal muscle activity or adjusting proprioceptive feedback. To date, no studies have directly examined its influence on motor kinematics in dystonia.

Twenty-three of the 33 patients with organic dystonia enrolled in this study described a *geste*. The phenomenon was once considered exclusive to organic dystonia, but a *geste* has been reported in at least one case of functional craniocervical dystonia (relief of retrocollis and facial spasm with gum-chewing or

a light touch to the face). Three of the thirteen patients with FD in the present study reported having a *geste*. One patient, with a rich phenomenology comprising fluctuating myoclonus, tremor and dystonia (retrocollis with some dystonic posturing in the upper limbs), obtained transient relief by holding the back of his head. Another, with axial dystonia, had noticed that deep breathing exercises, or sitting up straight against a chair back, produced a reduction in truncal spasm. The third patient, who developed upper limb and facial dystonia following a shoulder injury, described amelioration of abnormal posturing with self-stimulation of certain 'pressure points' around the shoulder girdle. These accounts suggested that the phenomenon of *geste* may not be as exceptional in FD as once was thought.

The analysis of the kinematics of finger tapping with and without *geste* reported here suggests that these manoeuvres may improve motor performance, even when directed towards distant body parts (13/23 patients in the organic group had *gestes* involving the head and neck, and only one of the three *gestes* reported in the functional group involved the upper limb). Overall speed of movement increased (to within the range observed in healthy controls) when the *geste* was activated, and halting tendency decreased. Although the effects of *geste* were significant only in the organic group, a similar trend was documented in patients with FD, which did not reach statistical significance due to the low sample size.

Perhaps these sensory tricks produce a similar effect to that observed in the double end-stop experiments of Curra et al., described above—reducing co-contraction to allow more focused muscular activation and improved speed of phase-switching. Or maybe sensory feedback from these manoeuvres—associated with a high expectation of beneficial response—provides a sort of sensorimotor reference point, down-weighting sensorimotor noise in other proprioceptive channels, sharpening the signal to noise ratio, and thereby transiently reducing dystonic output. This is mere speculation; larger and more in-depth studies would be required to confirm and characterise this preliminary observation.

Since all subjects performed finger tapping without *geste* first, followed (after a number of other tasks) by finger tapping with *geste*, it is not possible to completely exclude a motor learning effect as the basis for the observed improvement in

motor performance. However, since no such effect was noted between Trial 1 and Trial 3 in the sequential freestyle finger tapping tasks. Since the task with *geste* was performed after a delay of approximately 20 minutes (when subjects performed other tasks, such as hand opening-closing and pronation-supination), it seems unlikely that motor learning could, on its own, account for this finding. The small sample size means that it is not possible to generalise from these results with confidence.

5.3.3 Finger tapping with and without metronome

For rhythm, overall speed of movement, opening deceleration, halts and hesitations, there were no significant differences between the two patient groups and healthy controls at 1, 2 and 3Hz, either *with* or *without* audible metronome guidance—during the 15s when the metronome was audible (*with*) and the subsequent 15s when it was not but subjects were asked to maintain the same rhythm (*without*). This suggests that an ability to maintain rhythmic movements with externally and internally driven pacing is preserved in dystonia.

The purpose of this task was primarily to examine how patients with FD would respond to external pacing. It was anticipated that this might operate in one of two ways, depending on how attentional resources were allocated. The demands of maintaining a pre-determined rhythm might be expected to lessen the FMD by reducing the attentional focus available for its expression. Alternatively, elevated body-directed attention might exacerbate functional dystonic contraction. Either way, it was anticipated that this effect might distinguish the functional and organic groups. This was not the case. All three groups were able to frequency-match with low error rates. As expected, performance in the 1Hz task was interrupted by more halts and hesitations, than either the freestyle or higher frequency metronome tasks. There was no preferential enhancement or deterioration with pacing in the functional group.

The significant increases in halts and hesitations in the freestyle finger tapping task (more hesitations for the functional group and more halting performance in the organic group) compared to healthy controls were not observed in the

metronome tasks. These effects were relatively weak (owing to the multiple comparisons in this study, *p* values above 0.01 should be viewed with caution, see 'Limitations of analysis' below), raising the possibility that they may be spurious results (representing a chance rejection of the null hypothesis). However, if they are accepted as true effects, it is interesting to consider why external pacing obliterates this effect. The auditory tone might act in a similar manner to the visual and auditory cues that can be used to relieve freezing of gait in Parkinson's disease,(363,364) diminishing dystonic contraction and freeing up movement by activating movement via an alternative cortico-striatal pathway. In other words, the metronome could be acting as an auditory sensory trick.

Response to external pacing has been examined in musicians with dystonia. Cheng et al. compared the performance of professional pianists with and without dystonia playing a scale in time with a metronome, with and without auditory feedback (accurate and delayed).(365) They found no differences in performance across the tasks.

The metronome task was also an opportunity to observe slow and fast movements in dystonia, providing insight into the operation of postdictive (feedback) and predictive motor control in these disorders. Writing in the nineteenth century, Woodworth described the inverse relationship between speed and accuracy of movement.(366) He contended that at speeds of 1Hz or below, the accuracy of movement was reliant on visual input, with increased motor errors arising when subjects were deprived of this feedback. At higher frequencies (2Hz and above), by contrast,

"it is no longer possible to control movements separately. Much has to be left to the automatic uniformity of the hands' movements."

These two broad subtypes of voluntary movements—"fast jumps", driven by predictions about motor outcome, and "slow groping", guided by corrective feedback control—are both normal in dystonia for simple externally-driven repetitive movements, according to the findings of the current study. Two previous kinematic reports document an increase in target error without visual feedback in idiopathic focal and DYT1 dystonia.(238,241) Both involved fast reaching

movements of the upper limb. This would suggest that Woodworth's model of visually-driven slow movements and 'automatic' fast movements may be an over-simplification.

5.4 Limitations of the study

5.4.1 Case definition and sampling bias

5.4.1.1 Diagnostic accuracy bias: absence of 'gold standard'

Cases of organic dystonia that met with the definition of dystonia laid out in the 2013 MDS consensus statement were included.(59) In a minority of cases this diagnosis was substantiated by genetic testing (three) or contralateral ischaemic lesions on neuroimaging (three out of the four cases of secondary dystonia). However, for the most part diagnoses were made clinically. As noted in Chapter Three, some patients with adult-onset focal dystonia, those with cervical dystonia in particular, had historical features which overlapped with those documented in the functional group—such as sudden-onset symptoms, and fluctuations with mood or life events. Though their treating clinician clearly considered that their condition aligned with accepted organic disease patterns (congruency in terms of age of onset, phenomenology and consistency of symptomatology), as with all clinical diagnoses, there is an element of subjectivity, which leaves open the question of misdiagnosis. Other comparative studies of organic and FD have attempted to avoid this error by restricting their examination to genetic or secondary dystonia. A more inclusive approach was taken in the present study in order to obtain a more rounded view of motor and psychological aspects of dystonia across the full range subtypes.

Misdiagnosis rates for functional neurological disorders in general coalesce at around 4% for studies undertaken after the 1970s.(226) Since FD is widely considered the most challenging FMD to diagnose, it might be expected that the rate is a bit higher for this group. However, FMDs are not uncommon, accounting for 2-20% of patients referred to specialist movement disorder clinics, so a

familiarity with their phenomenological profile is expected.(367) Diagnostic criteria that align most closely with neurologists' standard approach to diagnosing FMD were used in this study, placing emphasis on its phenomenology rather than associated psychopathology. Older studies applied the Fahn-Williams criteria, which had much heavier psychological emphasis (loose case definition allowed for a diagnosis of 'possible' FMD on the basis of psychological disturbance alone, without otherwise inconsistent or incongruent clinical findings). By using the DSM-V criteria, the inherent psychological selection bias of the Fahn-Williams criteria is avoided. Though the rate of misdiagnosis in FMD is reportedly low, patients with FMD may have coincident organic motor disorder that is masked by the more florid functional signs. It is difficult to exclude this possibility entirely.

More objective 'laboratory supported' criteria for FD are required to prevent erroneous case assignment (though these are difficult to define, see discussion below).

5.4.1.2 Case ascertainment bias

In order to maximise recruitment, the research project was advertised through posters, displayed on departmental noticeboards, and through presentation at academic meetings. However, referral was dependent on the individual movement disorders physicians' willingness and ability to discuss the study and pass on patient details appropriately. In busy clinics this is difficult to do reliably, so it is likely that some potentially eligible candidates were not approached to take part.

5.4.1.3 Heterogeneity of sample populations

Broadly inclusive criteria for dystonia were applied, encompassing a range of topographies and aetiologies. An obvious drawback of this approach is that it increases the amount of variability within each group. This increased noise might make the signal of group identity more difficult to detect statistically (i.e. it has the effect of inflating the type 2 error rate). The organic dystonia patient group comprised individuals with varying aetiological (genetic, idiopathic, secondary) and topographic (cervical, focal upper limb, generalised) profiles. The rationale

behind this approach was to obtain as broad a view of the phenomenon of dystonic motor disturbance as possible. Argument might be made that the pathophysiological underpinnings of secondary and generalised dystonia are distinct,(368) making it difficult to draw meaningful conclusions from combined analysis.(176,254) The counter-argument is that the twisting movements and postures that characterise dystonia are the final common pathway for all aetiological subtypes. Peer-reviewed articles have adopted a similar approach, suggesting that this is a valid one.

Patients in the FD group also displayed heterogenous phenotypes, both in terms of topography (craniocervical, limb, truncal, generalised) and admixture with other disorders of movement (tremor, paralysis, myoclonus). Variability and richness of phenomenology are characteristic features of FMD, which present challenges to researchers seeking to phenotype-match clinical groups. Attempts to ensure phenotypic alignment between the groups was further frustrated by difficulties with recruitment (described below).

5.4.2 Control definition and sampling bias

It was originally intended that control subjects would be recruited by approaching the spouses or partners of patient recruits. This would ensure that controls and patients had roughly the same age and sex distribution. Unfortunately, owing to the lengthy nature of the experimental protocol, this was not always possible. MMC is a tertiary referral centre with a large catchment area and many patients travelled long distances to reach appointments, so it was often not appropriate to ask partners to return on a different day for assessment. As a result, only just over half of control subjects were recruited this way (15/29), the rest were staff members at MMC (six doctors, three medical students, three neurophysiology technicians, one research nurse and one member of administrative staff).

It cannot be assumed that either the partners of patients attending neurology clinics, or healthcare professionals working in and around those clinics, are representative of the general population. The demographic differences between healthy controls and organic dystonia, in terms of MoCA score and level of

education, may have been in large part because of the inclusion of such a high proportion of professionals. Another concern would be that these participants might have a tendency to down-weight their psychological scores, because of greater concerns about the social stigma attached to mental illness. Partners of individuals with neurological disease might be expected to have proportionately higher rates of psychopathology than the general population, because of the stresses associated with caring for someone with a chronic neurological condition. A comparison of scores from the two broad control subgroups, by Mann Whitney *U* testing revealed no significant differences for any of the self-rating scales (*p* values 0.24 – 0.96). MoCA scores for the staff member group were significantly higher, but with a *p* value that only just exceeded the threshold for significance (*p* = 0.046).

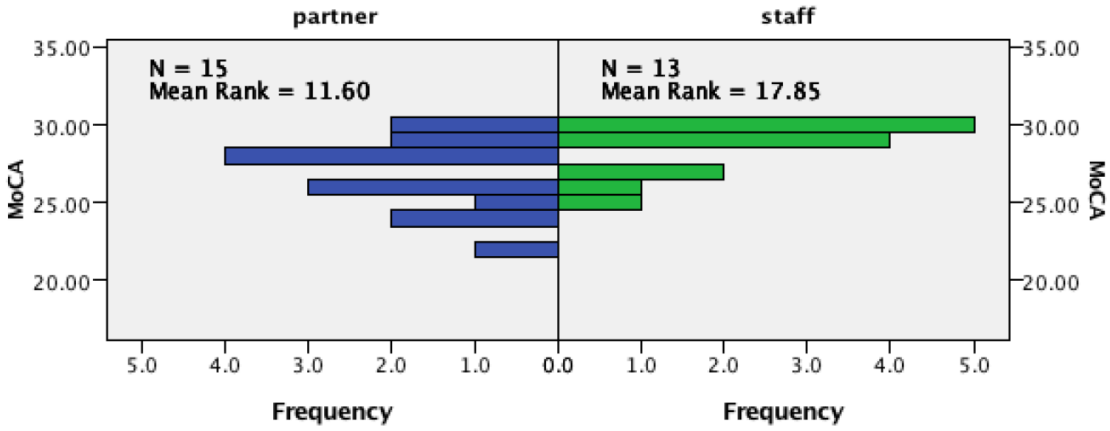


Figure 48: Comparison of MoCA scores for controls (staff vs. non-staff)
Mann-Whitney U comparison of MoCA scores between control subjects who were members of staff, and those who were not.

5.4.3 Recruitment bias

By focusing on recruitment from specialist hospital clinics (at MMC and LGI), rather than through primary care, potentially suitable participants (who for whatever reason were not referred or did not attend hospital appointments) may have been missed. However, since most primary care physicians will have a relatively small number of patients with dystonia within their caseload, and FD is not a diagnosis that could be reasonably made outside a specialist movement

disorders clinic, there was not an alternative to this approach. This means that patients from low-income backgrounds, with inflexible work timetables or burdensome carer responsibilities may not be well represented in the current sample (since they would not be able to afford the time or money to attend appointments).

In order to mediate this non-recruitment bias, the study was also advertised through a local dystonia charity. Just under a quarter of patients were recruited through the Australian Dystonia Support Group. This may have introduced its own bias, since patients who actively engage with such groups may not be representative of the population as a whole. All such patients had been assessed and managed by a neurologist with expertise in movement disorders at other hospitals in Melbourne. A third source of recruitment, through a specialist functional neurological disorders clinic at The Austin hospital in Melbourne, was explored, but owing to the low frequency of clinics, a relatively low incidence of FD among attendees, and frequent non-attendance, recruitment via this channel was not possible.

A total of fifty-nine patients with organic dystonia, and twenty-one with FD, were approached to take part in the study in Melbourne. Fifty-six percent of organic patients and 62% of functional patients approached were recruited. Of those that did not take part, 22 organic patients and five functional patients declined, citing a variety of reasons—physical illness, prior engagement with other research studies, family commitments. Seven organic patients and three functional patients initially expressed interest, but were repeatedly unable to attend, either because they were too busy or lived too far away.

A further phase of recruitment was undertaken at the LGI. Eight patients (two with organic dystonia and six with FD) were invited to take part. Four patients declined (one with organic dystonia, three with FD), the other four participated in the study. As time was short, it was not possible to extend LGI recruitment beyond this small group.

There is a risk that the recruits and non-recruits differ in some systematic way, and that this may have biased the results. This is a fundamental bias in any piece of research, which is impossible to eliminate. It is important to consider how this might have skewed the results. The variety of reasons for refusal makes this difficult, but it is likely that within this group are patients with higher levels of physical disability, carer responsibility, and comorbid psychopathology. Thus results may underestimate the severity of kinematic and psychological disturbance in the population as a whole.

5.4.4 Timing of assessment bias

5.4.4.1 Variable motor symptoms

Dystonia is characteristically a variable motor disorder, hence some patients recruited to the study did not have particularly active symptoms at the time of assessment. Within the organic group were six patients with task-specific dystonia—four writer's cramp and two musician's dystonia—who did not display any clinical signs of dystonic contraction during the simple finger tapping tasks. A portion of the functional patients (3/13) had paroxysmal symptoms, which were visible during the course of the assessment period as a whole, but not necessarily during the finger tapping tasks. Two functional patients were in partial remission at the time of assessment. It could be argued that these factors have skewed the results and might, in part, be responsible for the negative findings. Electrophysiological markers of dystonia have been documented in clinically unaffected limbs of patients with focal dystonia, and in non-manifesting carriers of DYT1.(230) If Marsden's supposition about adult-onset focal dystonia is correct—that these are *formes fruste* of genetically based genetic dystonia—then one might expect to see some changes in kinematic parameters, even in the absence of clinically obvious dystonic contraction.

5.4.4.2 Differing disease durations

The median duration of motor symptoms for patients with organic dystonia was 20 years, compared to only four years in the functional group. It is thus difficult to

exclude the possibility that observed kinematic features are the consequence not of the disease *per se*, but of not some compensatory motor adjustment to long-term motor disability. Within such timescales extensive plastic remodelling of cortico-striatal circuits might be expected. This is not a problem that can be easily addressed. The last few decades have seen huge changes in diagnostic practices and thinking about dystonia. The label 'functional dystonia' would not have been applied twenty years ago, and up until very recently it would have been the standard practice of many neurologists to refer these patients to psychiatry and discharge them. Analyses of attitudes of neurologists towards functional disorders suggest that younger consultants engage much more readily with the diagnosis and are more comfortable in dealing with it.(129) Hopefully this attitudinal shift, combined with more objective diagnostic criteria, will allow for better recognition and retention of patients with FMD in neurology clinics, which will aid future research.

5.4.4.3 Timing of antecedent botulinum toxin therapy

Attempts were made to ensure that all patients receiving botulinum toxin injections for dystonia were assessed 12 weeks or more after their last set of injections, in order to reduce the potential influence of the toxin on motor performance. Unfortunately, because of the logistical challenges of arranging assessments to fit in with patient availability, this was not possible in a minority of cases (10 patients with organic dystonia and two with FD). Since only three of this subset received botulinum toxin injections to the upper limb, it is expected that any bias introduced by this would be small.

The mechanism of action of botulinum toxin in dystonia is not completely understood. It has been suggested that, aside from its peripheral effects, this therapy induces plastic changes in the central nervous system that contribute to the amelioration of dystonic symptoms.(369) If this is the case, then including these patients in the sample might lead to an underestimation of kinematic deficits associated with dystonia. The only way to avoid this bias would be to exclude all patients with dystonia receiving botulinum toxin therapy. The exclusion of such a large group of patients would result in a sample that was not representative of the

population as a whole. It was therefore considered more appropriate to include them in the analysis.

5.4.4.4 Timing of BOCS assessments

The majority of patients completed the battery of psychological questionnaires on the same day as they underwent kinematic testing. A handful of patients, who due to time constraints were unable to do so, took the questionnaires home and returned them via post in the following week. For the twenty patients who initially completed the Y-BOCS, there was a much longer delay (several months) between their motor assessments and completion of the BOCS. This limits any conclusions we might draw about correlations between motor performance and BOCS scores, since their obsessive-compulsive symptomatology might have changed between assessments. Statistical comparison of the small number of cases for whom both scores were available (14 participants, 12 organic dystonia and 2 healthy controls) revealed no significant differences between scores, indicating that this is unlikely to have contributed significant bias.

5.4.5 Measurement bias

5.4.5.1 Kinematic measurement bias

5.4.5.1a Lack of counterbalancing: fatigue and motor learning effect

Finger tapping tasks—freestyle (without *geste*), metronome-guided (externally then internally driven), freestyle (with *geste*)—were performed sequentially in the same order in every subject, first with the dominant and then the non-dominant hand (excepting the 'with *geste*' task, which was omitted for patients without a recognisable *geste*, and for controls). This may have systematically biased the results. Either fatigue, or a motor learning effect, may have skewed the results in comparisons between finger tapping performance in first, second and third freestyle trials, with and without *geste*, and with and without metronome. Repeated measures ANOVAs comparing the freestyle tapping trials failed to demonstrate a significant deterioration or enhancement in performance, but this is not to say such an effect did not exist (due to the statistical limitations described

below, the null hypothesis for these comparisons may have been inappropriately accepted). Much larger sample sizes would be needed to facilitate a counter-balanced assessment of these factors.

5.4.5.1b Sensor-induced changes in motor performance

Dystonia has been modelled as a disorder of sensorimotor integration. As such, the presence of sensors and straps may have modulated motor performance in unforeseen ways. This 'observer effect' is common to all kinematic studies and cannot be completely avoided. Steps were taken to minimise its influence—small, lightweight sensors were used, and the wires were secured at the wrist to reduce interference with movement. Comparison between bradykinesia scores with and without sensors revealed no significant difference, suggesting that their presence did not substantially distort motor behaviour (at least for simple repetitive finger-thumb oppositions).

5.4.5.2 Psychological

5.4.5.2a Problems with self-assessment

Scales that rely on self-rating for psychological aspects of health are subject to bias for a number of reasons. Firstly, they depend on an accurate subjective appraisal of one's inner emotional state. Individuals' capacity to discern this varies within populations. Higher levels of alexithymia (an inability to accurately judge one's own emotions) have been reported in FMDs,(370) which might lead this group to misjudge their psychological state. Secondly, subjects may underscore their symptoms due to concern about the social stigma attached to mental ill health. This anti-psychological response bias applies to all three groups, but might be expected to be particularly strong in the functional group because of a determination not to have their disorder characterised as 'psychogenic', fuelled by a history of encounters with clinicians who have told them their symptoms are 'all in your head'. As part of the pre-assessment interview, participants were asked about triggering and exacerbating factors for their condition. Thirty-eight percent of those with FD and 54% of those with organic dystonia identified stress or

emotional disturbance as a relevant factor in determining either the onset or severity of their symptoms, suggesting that if a bias away from reporting psychological symptoms was present in the functional group this was not a universal, or particularly strong effect. The fact that patients with FD demonstrated statistically robust differences from healthy controls on all of the scales tested tends to suggest there was not a significant factor.

5.4.5.2b Misinterpretation of bodily symptoms registered on psychological scales

Certain items on the HADS, such as 'I feel as if I'm slowed down' or 'I feel restless, as if I have to be on the move', might be the direct result of motor disorder rather than psychological disturbance. This might lead to an overestimation of affective and anxiety disorder. Using alternative scales and cross-comparing them would be one way of addressing this potential bias. Since the protocol for this study was already lengthy, this was not felt to be a viable option as it would be too burdensome for participants.

5.4.5.2c Poor understanding of obsessive-compulsive scale

Early participants in the study, when faced with the Y-BOCS, a lengthy and detailed register of all potential obsessive-compulsive symptoms, found this difficult to understand and complete. The shorter and more compact BOCS was much more user-friendly and easier for subjects to fill out. Nevertheless, some still struggled to grasp the definitions for obsession and compulsion. They had particular difficulty in establishing where normal behaviour ended and compulsion began, for instance, what level of checking behaviour might be considered 'normal' versus that which would be broadly considered excessive (i.e. compulsive). Clearly there is inherent subjectivity in this assessment, such behaviours lie on a spectrum and the determination as to whether it is excessive or not is a personal one, according to how intrusive it is on a day-to-day basis. Very assiduous participants, however, found it difficult to configure their responses around this rather grey definition. To ameliorate the error this might introduce into responding (either through inaccurate reports or non-response), participants were encouraged to complete the questionnaires on the same day as they attended for kinematic assessment, so

that the investigator could assist with any queries they might have about the rating scales.

5.4.6 Limitations of statistical analysis

5.4.6.1 Low sample size/ inadequate power

Though targets for recruitment were met, the small size of the functional group limits the generalisability of results. There were a number of reasons why recruitment to the functional group proved difficult. Firstly, it was not the standard practice of many neurologists in the main recruitment centre, MMC, to keep patients with functional neurological disorder under follow-up. Hence only those presenting for the first time with FD could be approached for enrolment in the study. Since this is one of the less frequent functional presentations, compared to functional paralysis or tremor, even in a tertiary referral area the size of MMC, the rate of presentation with this problem is relatively low. Of those who were seen and offered follow-up, a sizeable proportion did not attend these appointments. In some cases because complexity in their social life (such as carer responsibility for a child with disability or forthcoming court attendance) precluded it, in others because of discordance with the treating neurologist. Such discordance has been reported to be more frequent in FMD sufferers than in patients with analogous organic movement disorders.(371) This may reflect a failure of some neurologists to behave 'normally' in consultations with patients with functional neurological disorders.(372,373)

Of course these potential biases and limitations must be borne in mind when interpreting the results. However, this is a preliminary study of the kinematics of different types of dystonia, designed to explore relatively uncharted territory. It compares favourably with the small number of similar case comparisons in the literature, in which sample sizes below 10 are reported.

5.4.6.2 Correction for multiple comparisons

This study includes nine statistical comparisons for psychological ratings and 27 comparisons for kinematic data across three groups. Though *post hoc* group-wise evaluations were corrected using either Bonferroni or Games-Howell adjustments, the performance of so many statistical comparisons increases the likelihood of a significant result occurring by chance (with an alpha value of 0.05 (5%) one would expect one to two of the significant kinematic results to have occurred by chance). In these circumstances, common practice is to set a more conservative alpha level, and to treat any p values above 0.01 with caution. In the setting of a study that broadly favours retention of the null hypothesis, however, it is also important to examine whether a significant effect was obscured. Where possible, *post hoc* comparisons were quoted with Games-Howell adjustment, which is most appropriate when sample size is not equal across the groups. However, within SPSS the Bonferroni adjustment is automatically applied for non-parametric analyses, which were used for the freestyle finger tapping analysis. The Bonferroni is a very conservative adjustment, meaning that we can have reasonable faith in the reliability of significant findings within the freestyle kinematic data set. Its application could potentially have obscured a significant difference between functional and organic dystonia groups, though examination of the boxplots for this data would suggest this is unlikely.

5.4.6.3 Confounders

Confounding occurs when two variables are related not only to a particular outcome (such as the development of a disease) but also to one another. Participants within this study were matched for sex, but not age, educational status or duration of motor symptoms. Patients with FD were younger, had a shorter median duration of disease, and were taking more psychotropic medications than those with organic dystonia. Both dystonia groups had lower educational status and higher self-rated depression. This means there is potential confounding bias. For instance, organic dystonia was associated with both lower finger tapping frequencies and higher self-rated depression. Since depression can cause psychomotor retardation, and reduced speed of finger tapping has been reported

in such patients,(374) the lower frequency in the organic group might be an epiphenomenon of their increased depressive tendency, rather than an inherent part of its motor phenotype. Also, since finger tapping scores decline with age, it is possible that a significant difference between the dystonia groups was not seen because it was masked by an age-dependent deterioration in performance in the organic group. The absence of a correlation between any of the psychological scores and kinematic measurements, and of any association between age and finger-tapping frequency in a regression analysis, suggest that neither of these potential confounders is likely to have introduced significant bias.

5.5 Towards 'laboratory supported' criteria for functional dystonia?

One of the aims of this project was to generate a set of kinematic criteria for FD that would improve diagnostic sensitivity and specificity. Since none of the measurements, kinematic or psychological, reliably distinguished between the dystonia groups such 'laboratory supported' criteria remain elusive. Perhaps the 'sphinx that defies anatomy' also defies electrophysiology? Before engaging further with this endeavour, it is important to reflect on a few questions posed by this study.

5.6 Functional dystonia: lessons and unanswered questions

5.6.1 To what degree is functional dystonia a distinct entity?

Authoritative conclusions about the comparative psychological profiles of functional and organic dystonia cannot be drawn from a study of this size, but the evidence presented here does align with other reports that indicate there is sizeable overlap between the groups in terms of psychopathological burden. Larger case-controlled assessments would be required to establish if FD has a distinctive profile of psychological disturbance. The existing literature on kinematic evaluations of FD is so small and highly focused that it is not possible to extrapolate these findings to larger populations, but evidence for distinguishing kinematic features so far has been weak.

It is possible, as the current study suggests, that functional and organic dystonia possess more features in common than features that divide them. The breadth and authority of Marsden's research, which supported his re-categorisation of the adult-onset focal dystonias as *formes fruste* of hereditary torsion dystonia—placing them as emphatically under the 'organic' heading—also eclipsed some earlier impressions that implied a blurring of the physical-psychological demarcation in these disorders. Of course, the middle-aged patient with sudden-onset fixed dystonia of the foot following minor injury may be easily distinguished from the child with mobile action-induced lower limb dystonia, which gradually generalises over time. But for patients that fall on the spectrum between these two extremes, the distinction between 'functional' and 'organic' causation may not be as clear-cut. The existence of similar changes in excitability at multiple levels of the neural axis in both functional and organic dystonia has prompted some authors to speculate that the two may have a common pathophysiological basis. Reports of cases of FD in DYT1 pedigrees lend some support to this hypothesis.(375)

In addition to demonstrating overlapping kinematic and psychological profiles, this study also found qualitative evidence of overlap between the groups in terms of many historical features. Sudden-onset symptoms were reported in a subset with organic dystonia, a significant minority of whom recognised a correlation between their motor symptomatology and stress levels. This underscores the weakness of diagnostic classification systems that emphasise these features.

5.6.2 Why is functional dystonia harder to evaluate?

The prevalence of FD is not known. Though it is the second most common FMD, after functional tremor, the experience of this study would suggest that (in Melbourne at least) patients with a dystonic phenotype were encountered much less frequently than those with tremulous presentations. This is probably one of the reasons why so few studies in the literature have focused specifically on FD, instead recruiting patients with a range of FMDs. Dystonia comprises a set of variable, often task-specific motor disturbances, meaning that the movements of interest may not be readily elicited in an experimental setting. The broad

phenotypic spectrum and greater intra- and inter-individual variability of dystonic movements increases the noisiness of samples, and can make group-wise comparisons difficult to interpret. Sustained posturing in functional fixed dystonia presents a particular challenge to electrophysiological assessment, as true resting state measurements may be difficult to obtain. Finally, the interconnectedness of motor and psychological disturbances makes it hard to draw definitive conclusions about the origin and significance of kinematic disturbances in dystonia.

5.6.3 What conclusions can be drawn about functional dystonia from this study?

As acknowledged above, an important weakness of this study is the small sample size for the functional group, with the attendant statistical challenges (namely, the necessity to apply less powerful non-parametric statistics in many analyses). Compared to other comparative kinematic or electromyographic studies in this area a sample size of 12 is quite respectable. Nevertheless, it is certainly possible that a significant group effect has been missed due to under-powering.

There are powerful machine learning tools—evolutionary algorithms— that can be applied to complex data sets. Such approaches were outside the scope of the study, but subsequent to its completion, a collaborative researcher used these algorithms to probe for group effects that may have been missed by conventional statistical analysis. These algorithms are a form of computational intelligence that operate according to the principles of Darwin's theory of evolution.(376) They comprise a population of potential solutions to a classification problem. By competition (against the performance of other classifiers) and the introduction of 'mutations' (randomly selected fragments from less well performing classifiers to preserve diversity) over successive iterations (or generations), a classifier with the highest level of 'fitness' (greatest capacity to accurately classify data) is evolved.

In the case of this study, the fittest classifiers are those which incorporate the most discriminatory kinematic features to form a mathematical expression for accurately predicting which clinical group an individual belongs to. To facilitate this, kinematic data is first separated into 'training' and 'testing' (or validation)

sets. The first set is presented to the software with the clinical diagnosis revealed. Once a suitable classifier has been evolved, it is then tested using the validation data (with diagnostic label removed) to determine how accurate it is in distinguishing diagnosis. By operating outside the constraints of linear statistical methods, and without *a priori* hypotheses, such approaches can establish patterns that might not be apparent using conventional methods of analysis. For this study, the best performing algorithm distinguished functional from organic dystonia with a mean accuracy (percentage of correctly classified cases) of 70%. For comparisons between organic dystonia vs. healthy control, and FD vs. healthy control the accuracies were 60% and 74% respectively (evolutionary algorithm data analysis performed by Siti Muhamed).

Whilst the performance of the classifiers exceeds that of blinded clinical raters (who correctly identified FD by video assessment only 50% of the time), the relatively poor performance of the algorithms corroborates the null findings drawn from conventional statistical analyses. It would be necessary to replicate this in a larger sample, with closer phenotype-matching, in order to improve confidence in this conclusion.

5.6.4 Lumping and splitting, does it really matter?

As we move away from slavish adherence to dualistic thought, it may be possible to adopt more flexible and inclusive approaches to movement disorders, allowing individualised treatment to focus on the particular deficits (motor and psychological) in each patient. This is already the model used in most specialist clinics for patients with functional neurological disorders, where physiotherapy and/or psychotherapy is offered in accordance with individual patient needs. The place of idiopathic focal dystonia within the neurology-psychology borderland is constantly shifting, and it is unlikely that its current position will be its final resting place. A subset of these patients may benefit from therapeutic approaches more frequently employed in FMD, including psychological treatments such as cognitive behavioural therapy.

5.6.5 Functional dystonia: new concepts and directions

If more flexible biopsychosocial frameworks are to be workable in neurology clinics, a shift in attitude, and broader acceptance of the notion that these disorders are 'neurological' in nature, will be necessary. Though there has been a resurgence of interest in these disorders in the last fifteen years, evidence from surveys suggest that some older neurologists retain out-dated models of functional neurological disorder, founded on Freudian notions of conversion of psychosocial stress, and demonstrate some reluctance to engage with patients with functional disorders in the clinic.(129)

There is a schism between patients' and clinicians' judgement of the voluntariness of FMDs—functional movements are experienced as unwilled yet, to onlookers, often seem deliberate, or consciously generated.(377) The unspoken question of feigning generates tension in many neurological consultations about FMDs, and likely contributes to higher levels of discordance between neurologists and patients in these groups. In the past, many of those with organic dystonia met with similar scepticism, when their apparently physiologically implausible motor quirks, such as the *geste antagoniste*, were dismissed as "childish behaviours".(21) By reappraising the dystonias, and what they tell us about basal ganglia function, it may be possible to better understand both functional and organic manifestations.

5.6.5.1 Dystonia and the interface between voluntary and involuntary movement

"The ganglia, situated at the base of the brain still, to a large extent, retain the characteristic of basements—viz, darkness."—Samuel Kinnier Wilson, 1925(378)

The advances in neuroimaging, neurogenetics and neurophysiology of the last century have failed to furnish us with a comprehensive understanding of the workings of the basal ganglia, and their precise contribution to perceptive, motor and cognitive processing. As new evidence has come to light, prompting re-evaluation of accepted clinical wisdom, dystonia has been conceptually repackaged a number of times, its place within the neurology-psychiatry borderland continually shifting.

The earliest signs of dystonia, regardless of aetiology, relate to a disruption of voluntary movement. A loss of the ability to focus motor outflow leads to co-contraction and inefficient activation of synergists, ultimately disrupting goal-directed movement. Such selective motor dysfunction was highlighted in early accounts:

"*If the man does not write, he has normal strength and he is able to hold up a heavy chair in the air with the hand."*(379)

This was used by some writers as evidence for a psychogenic basis for the disorder. But dystonia is not the only basal ganglia disorder that interferes with volitional movement in a selective fashion. Parkinson described the shaking palsy as a condition in which

"…the hand (fails) to answer with exactness to the dictates of the will."(380)

A selective disintegration of certain motor programmes, with preservation of others—such as an ability to run but not walk—is also recognised in Parkinson's disease.

Functional movements possess an apparent voluntariness. They frequently require attention to manifest and demonstrate distractibility—attenuation or extinction when attentional resources are directed elsewhere. In FMDs, like organic dystonia, a poverty or excess of motor output disrupts goal-directed actions, leaving more reflexive movements intact:

"She says, as all such patients do, 'I cannot'; it looks like 'I will not'; but it is 'I cannot will'"(381)

Judgements that deem FMDs 'more voluntary' than recognised organic movement disorders fail to take into account the phenomenological thinness of voluntary action, which can be readily misperceived even in health.(382)

Convergent evidence from lesioning studies in animals, and functional imaging in humans, suggests that there are three functionally distinct cortico-striatal networks, organised in a labile hierarchy.(383) The 'associative striatum', which includes the caudate, mediodorsal thalamus and pre-frontal cortex, detects contingency between actions and outcomes and is responsible for goal-directed behaviour. This is the system that is most active when subjects are asked to pay

close attention to their actions. It is strongly modulated by anticipation of reward, which is signaled through connections with the 'limbic striatum' (nucleus accumbens, mediodorsal thalamus, orbitofrontal and ventral premotor cortices). The 'sensorimotor striatum' (putamen, ventral thalamus and sensorimotor cortices), on the other hand, is engaged when actions become habitual. A particular stimulus evokes a certain response, independent of outcome. This represents a lower level of functional integration. Movements generated by activity in these circuits have greater automaticity, but are more effector-specific and inflexible. As behaviour becomes more habitual, it is also more susceptible to transfer of control. According to one computational model, the control of movement is ceded to whichever system (sensorimotor or associative) encodes the lowest level of uncertainty.(384)

Perhaps functional motor disorders represent an imbalance in motor governance between the two systems? Abnormal functional connections between limbic and sensorimotor association cortices, as well as underactivity in prefrontal regions, have been documented in FMD.(285,289) Under the influence of limbic activity, the associative network might be suppressed, allowing sensorimotor circuits to take over. This might explain why more automatic or reflexive movements remain intact in FMD, while goal-directed actions that require explicit attention are stymied. A neurobiological framework for FMD, founded on Bayesian models of brain function, which attempts to reconcile this paradox of volition is described below.(342)

5.6.5.2 Functional dystonia: the Bayesian model

The brain is constantly bombarded by complex, sometimes contradictory, information from the sensory organs. It must efficiently sift through this information, identify the most reliable and important aspects, assemble an image of the external world, and choose the most appropriate ways of interacting with this outer domain. The predictive processing account of cognitive function attempts to explain this by conceiving of the brain as a machine for generating and testing hypotheses (through perception and action).(385,386) Central to this account is Bayes' rule for the conditional probability of events, where

expectations—predictive beliefs, or *prior probabilities*—are updated in response to new evidence to yield continually rectified *posterior* probabilities.

In the brain, this inferential process is realised by a constant drive to minimise prediction error (or to reduce any discrepancy between anticipated and recorded sensory input). Bayesian predictive theory explains the control of movement by considering prediction error minimisation as a two-way process. Error messages generated by unexpected sensory inputs may be reduced by either refining higher-level predictions (perceptual inference) or adjusting sensation through action to fit with existing expectations (active inference).

A network of prior probabilities—synaptic assemblies encoding past experience—are distributed throughout the brain's hierarchy. Stable expectations about the world created by associative learning over the longest timescales sit at higher levels and guide the inferences drawn from more changeable aspects. It is like the senior physician who tempers the young doctor's diagnostic zeal with a reminder that 'common things are common'. The balance between 'top-down' priors and 'bottom-up' prediction error determines perceptual content.

Attentional processes play a key role in maintaining an optimal balance between prior beliefs and input for both perceptual and active inference. Each prediction error signal is afforded a certain precision weighting. Those with higher expected precision have greater modulatory access to prior probabilities encoded at higher levels—they can drive associative learning at a higher rate. A salient environmental signal will attract more attentional resources (it will receive greater precision up-weighting) and thus have a greater capacity to modify predictive beliefs. Attention, within the Bayesian schema, optimises expected precision, allowing the mind to selectively focus on certain items to the exclusion of others. It operates on multiple levels and has both conscious and subconscious facets (endogenous and exogenous attention). When functioning effectively, attentional processes filter sensory input so that the most reliable and relevant data has the greatest capacity to refine predictive beliefs (in perceptual inference) or elicit action (in active inference).

Predictions for the sensory experience of the moving body are arranged hierarchically—reflexive movements represented at lower levels being recruited to achieve complex goals. Motor plans thus define a particular flow of expected sensory information (a sequence of proprioceptive targets) that guides movement (Figure 49).(387) They depend on a transient suspension of attention to the unfolding action, the sensory attenuation effect. This prevents sensorimotor feedback from confounding execution by prematurely updating proprioceptive priors. Learning how best to balance perceptual and active inference is a key task. A shift in emphasis towards one or other results in impoverished representations of the world—either overly generalised or highly particularised.

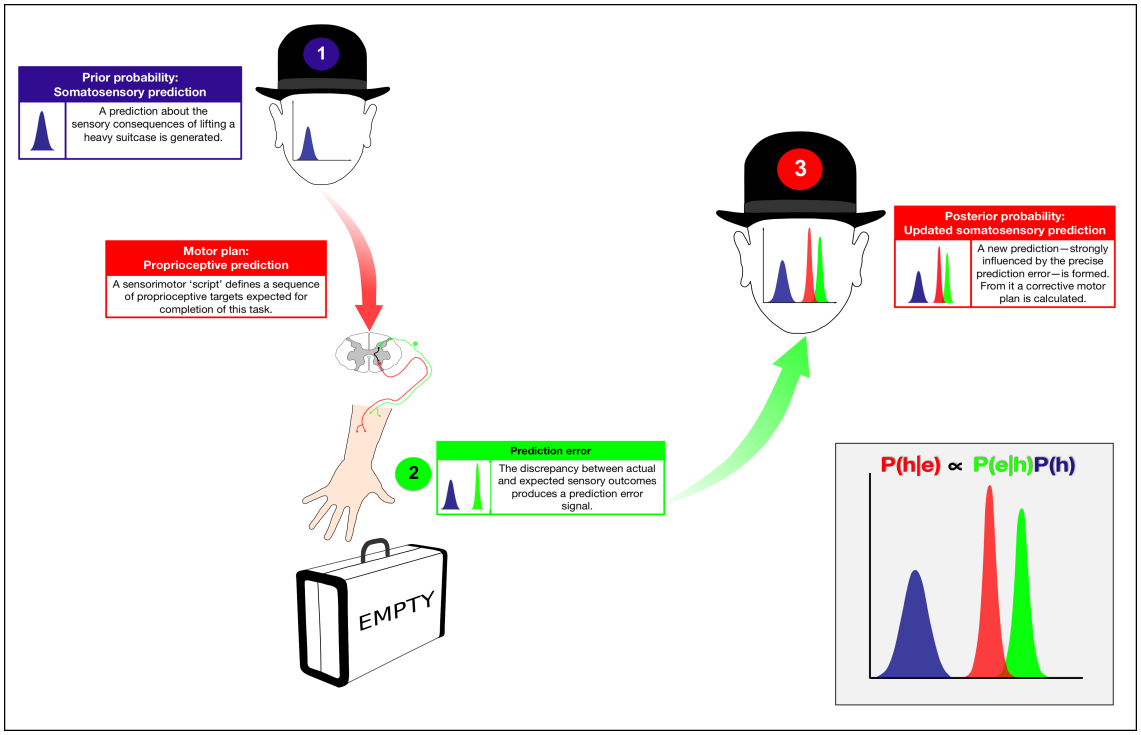


Figure 49: Movement as Bayesian active inference

A motor command contains the proprioceptive predictions for lifting a heavy suitcase. Unexpectedly, it is empty. Needlessly strong muscle action causes rapid upward acceleration, returning multisensory feedback that was not anticipated. The discrepancy is encoded as a prediction error, producing a posterior probability that reflects the true mass of the suitcase. The inset shows Bayes' rule and a statistical representation of its probability distributions (prior probability—blue; prediction error—green; posterior probability—red).

A neurobiological model of FMDs,(342) drawing on the principles of predictive processing, describes how functional symptoms can arise from disturbed attention (precision optimisation) and faulty predictive beliefs (prior probabilities), see Figure 50. In this model, aberrant belief encodes a particular 'action possibility' (tremor, dystonic contraction, weakness) at an intermediate level of the motor hierarchy. When strengthened by attentional focus, this prior cannot be extinguished by rectifying sensory signals from below. Prediction error is therefore minimised through active inference—a trans-hierarchical cascade of autonomous neural activity that culminates in the activation of spinal reflex arcs to produce the expected (functional) movements.

In fixed FD, beliefs have often been kindled by the sensory imprint of a minor injury.(217) Because motor function is inextricably tied to sensory feedback, distortions can hijack motor programs, resulting in abnormal movement. Although superior regions may participate in the attentional release of lower-strata beliefs, they do not predict their content. Hence, there is a loss of agency and a secondary, conscious inference that the movements are the product of disease.
In healthy subjects, experimental conditions can reproduce responses that typify FMDs such as illusory perception prompted by prior expectation(388,389) and motor decrement with self-directed attention.(390) The brain's predictive powers are fallible, and in individuals with a sufficient conjunction of predisposing factors—personal or cultural persuasions, altered mood, cognitive bias—processing flaws may be elaborated into symptoms.

Whilst it is important not to become too seduced by a single model, the predictive processing account offers a framework around which hypotheses about FMD can be assembled and tested. Paradigms that assess perceptual sensitivity or movement under conditions of expectational and attentional modulation have been developed and applied to FMDs, and have the potential to deepen pathophysiological understanding of these disorders.(391,392)

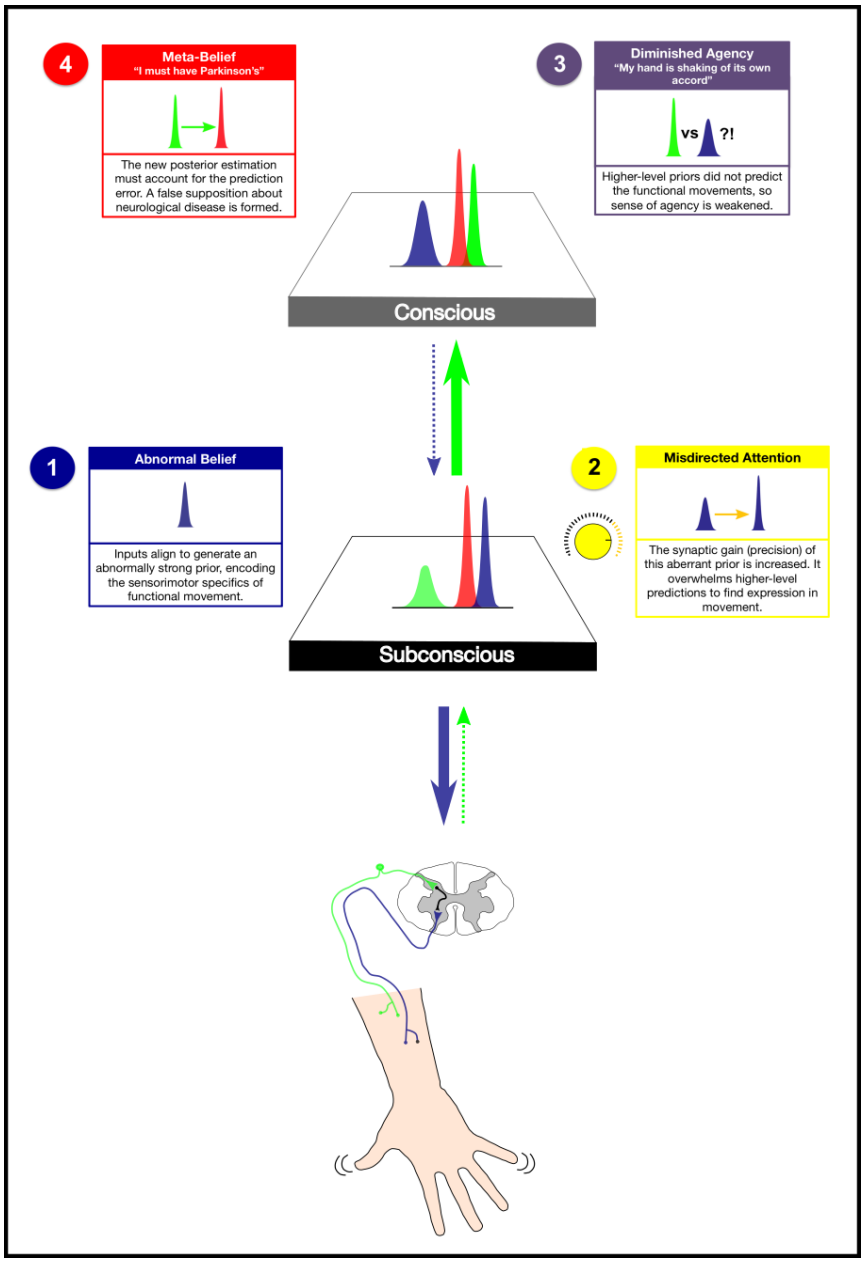


Figure 50: A Bayesian model of FMDs

This model attempts to explain how unexpected sensory input from illness or injury might generate an internal belief predicting functional movement (dystonic posturing or tremor, as in this example). Synaptic inputs from below (pain, physical symptoms of panic) and above (cognitive bias, affective state) converge on an intermediate level of the motor hierarchy. A strong prior that predicts certain sensory feedback is formed, and this drives tremulous movement. Discrepancy between actual and predicted signals at higher levels is interpreted as loss of agency.

5.7 Conclusions and future directions

Mindful of the various limitations already outlined, some concluding statements can be made about this study of dystonia, placing it in the context of previously published work.

1. Both organic and FD are disorders of voluntary movement that possess a prominent psychological dimension. Diagnostic systems that prioritise psychopathological features as a means of distinguishing these subtypes have proven unreliable.
2. Functional and organic dystonia are both associated with higher rates of self-rated depression and pain than healthy controls. Though a broader range of psychopathology (anxiety, obsessive-compulsion, and depersonalisation) was observed in FD, sizeable overlap with scores in the organic dystonia group meant that no discriminatory profile of psychological disturbance was identified.
3. The motor kinematics of FD shares some similarities with that of organic dystonia, including slower, more halting or hesitant internally driven ('freestyle') movement. A reduction in opening deceleration, common to both, has been modelled as an implicit marker of co-contraction. Its presence in FD may imply a common pathophysiological substrate for both disorders.
4. The *geste antagoniste*, even when directed to anatomically remote body parts, seems to improve motor efficiency (normalising speed and continuity of movement) in organic dystonia, with a similar trend in a small number of patients with FD. This is the first study to investigate kinematic response to the activation of the *geste antagoniste*.
5. Externally driven motor pacing with a metronome improves motor performance in functional and organic dystonia, and may be operating as an auditory 'sensory trick'.
6. This effect is retained for a period immediately after the external auditory cue is removed if subjects are instructed to maintain the same rhythm (i.e. internal pacing to a remembered auditory cue also results in improved performance).

7. Correlations between psychological and kinematic variables are different in organic and FD, with closer correlation between psychological measures for organic dystonia and between kinematic variables in FD. This implies more uniformity of psychological profile in organic dystonia and greater consistency of motor profile in FD. If reproduced in larger populations this may prove a useful diagnostic tool, and could inform future thinking about pathophysiology.
8. Laboratory-defined gold standard diagnostic criteria to differentiate functional and organic dystonia have proved difficult to establish. On the basis of the evidence presented here, it seems unlikely that distinguishing characteristics will be found at a basic sensory processing or kinematic level. Advances in functional neurological imaging and new approaches from cognitive neuroscience perhaps hold greater promise for future classification systems.

In order to build on this work in future the following avenues could be explored:

1. Repetition of key components of this analysis in a larger population to test the validity of significant findings, and allow more informative sub-group analysis.
2. Compare the kinematics of finger tapping in dystonia with that of other movement disorders for which there is a well-developed pathophysiological understanding (such as Parkinson's disease), and that of normal aging. By looking for common kinematic features between these disorders, it may be possible to advance understanding of the ways in which corticostriatal pathways are disturbed in dystonia.
3. Re-test freestyle, *geste* and metronome driven tasks using a counterbalanced design, to more firmly establish the mechanism of these effects.
4. Examine the phase of halts and hesitations to test the hypothesis that halting is more prominent around the point of maximal extension (due to increased co-contraction in the extension phase).
5. Refine machine learning techniques in order to explore associations and separations without the constraint of *a priori* hypotheses.

6. Apply these kinematic and computational techniques to the examination of some of the testable hypotheses embedded in the Bayesian model of FD.

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Appendix A:
Structured interview, psychological questionnaires and clinical rating scales

Dystonia Research Study: Investigator Booklet

Patient Number:

Date:

Investigator:

Consent:

- PICF read and signed?
- Any questions?
- Dated copy in notes?

Date PICF sent:

Time of arrival:

Time of assessment:

Time of departure:

Any complications?

	Dominant (L or R)	Non-dominant
Hand span (mm)		
Finger thumb aperture (mm)		

Diagnosis:

Genetic dystonia

Idiopathic focal dystonia

Idiopathic generalised dystonia

Secondary dystonia (details)_____

Functional dystonia (details)_____

Healthy Control

Other (details)_____

_____

Structured Clinical Interview

1. How long have you had the dystonia and how old were you when the symptoms started?

2. Where did the symptoms start and how did they spread?

3. How quickly did your symptoms start and was there any obvious trigger (give details)?

4. What (if anything) did you think might be causing your symptoms when they started?

5. Have your symptoms ever got better/ disappeared for periods since they started?

6. Are there any associated symptoms (e.g. pain, sensory symptoms)?

7. Do the affected limbs feel different in any way (please describe)? **Do you have a *geste antagoniste*?**

8. Do you have any other history of medical or psychiatric problems (give details)?

9. What medications have you tried for the dystonia, when and for how long?

10. What other medications are you on?

Date of last botox:

Fahn-Marsden Video Protocol

1. Sitting at rest, arms on legs	45 sec
a. Whole body	
b. Zoom in to different body regions (head and neck, each hand, trunk, each foot)	
2. Speak—name, date, describe speech, swallowing, and current problems	45 sec
a. Film whole body	
b. Zoom in to different body parts	
3. Arms suspended in front of body—15 sec	45 sec
Finger-to-nose 5 times	
Rapid succession movements: each hand and foot	
4. Arise and stand; turn 90° 4 times	30 sec
5. Walk	60 sec
a. Whole body	
b. Zoom in to different body regions	
6. Write with each hand	30 sec
Name, date, sentence, spiral	
Videotape whole body and zoom in	
Total	4 min, 15 sec

Fahn-Marsden Dystonia Rating Scale

Table 1. Dystonia movement scale

Region	Provoking factor		Severity factor	Weight	Product
Eyes	0-4	×	0-4	0.5	0-8
Mouth	0-4	×	0-4	0.5	0-8
Speech/ swallowing	0-4	×	0-4	1.0	0-16
Neck	0-4	×	0-4	0.5	0-8
R arm	0-4	×	0-4	1.0	0-16
L arm	0-4	×	0-4	1.0	0-16
Trunk	0-4	×	0-4	1.0	0-16
R leg	0-4	×	0-4	1.0	0-16
L leg	0-4	×	0-4	1.0	0-16
				Sum: (maximum = 120)	

I. Provoking factor

A. General

0 - No dystonia at rest or with action
1 - Dystonia on particular action
2 - Dystonia on many actions
3 - Dystonia on action of distant part of body or intermittently at rest
4 - Dystonia present at rest

B. Speech and swallowing

1 - Occasional, either or both
2 - Frequent either
3 - Frequent one and occasional other
4 - Frequent both

II. Severity factors

Eyes

0 - No dystonia present
1 - Slight. Occasional blinking
2 - Mild. Frequent blinking without prolonged spasms of eye closure
3 - Moderate. Prolonged spasms of eyelid closure, but eyes open most of the time
4 - Severe. Prolonged spasms of eyelid closure, with eyes closed at least 30% of the time

Mouth

0 - No dystonia present
1 - Slight. Occasional grimacing or other mouth movements (eg, jaw open or clenched; tongue movement)
2 - Mild. Movement present less than 50% of the time
3 - Moderate dystonic movements or contractions present most of the time
4 - Severe dystonic movements or contractions present most of the time

Speech and swallowing

0 - Normal
1 - Slightly involved; speech easily understood or occasional choking
2 - Some difficulty in understanding speech or frequent choking
3 - Marked difficulty in understanding speech or inability to swallow firm foods
4 - Complete or almost complete anarthria, or marked difficulty swallowing soft foods and liquids

Neck

0 - No dystonia present
1 - Slight. Occasional pulling
2 - Obvious torticollis, but mild
3 - Moderate pulling
4 - Extreme pulling

Arm

0 - No dystonia present
1 - Slight dystonia. Clinically insignificant
2 - Mild. Obvious dystonia, but not disabling
3 - Moderate. Able to grasp, with some manual function
4 - Severe. No useful grasp

Trunk

0 - No dystonia present
1 - Slight bending; clinically insignificant
2 - Definite bending, but not interfering with standing or walking
3 - Moderate bending; interfering with standing or walking
4 - Extreme bending of trunk preventing standing or walking

Leg

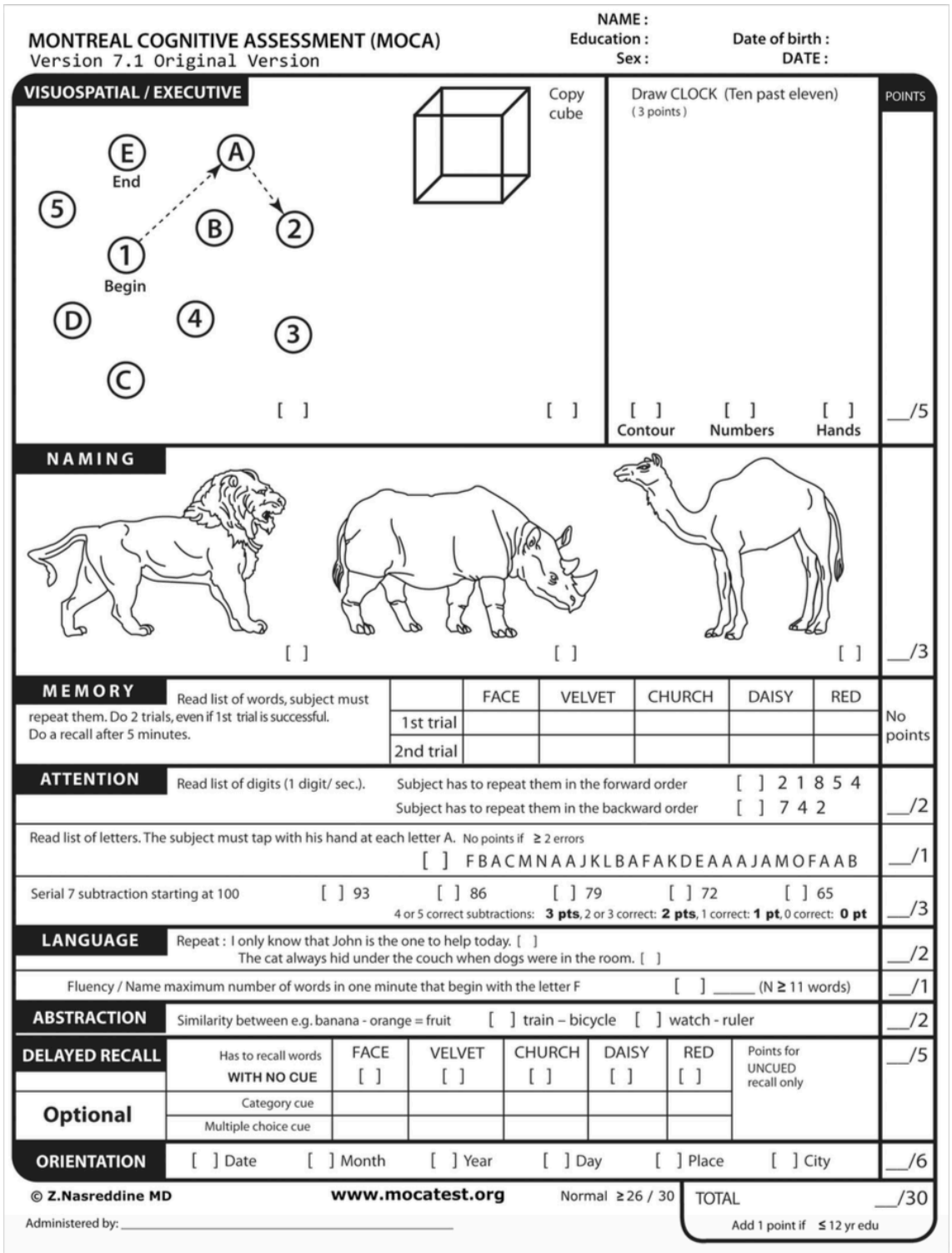
0 - No dystonia present
1 - Slight dystonia, but not causing impairment; clinically insignificant
2 - Mild dystonia. Walks briskly and unaided
3 - Moderate dystonia. Severely impairs walking or requires assistance
4 - Severe. Unable to stand or walk on involved leg

Simplified Functional Movement Disorder Rating Scale

Regions	Severity	Duration	Total
Face & tongue			
Head & neck			
Left UL & shoulder girdle			
Right UL & shoulder girdle			
Trunk & abdomen			
Left LL			
R LL			
Function			
Gait			
Speech			
		TOTAL	

Scoring		
	Severity	**Duration**
0	None	None of the time
1	Mild	Occasionally
2	Moderate	Frequent
3	Severe	Constant

MoCA



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Dystonia Research Study

Patient Questionnaire Booklet

Patient Number:

Date:

Investigator:

A few questions about yourself:

Gender (please circle):

Male Female

Age:

Education (age when left full-time education):

Employment:

Marital status (please circle):

Single Married Common-law partner Divorced

Widow/Widower

Dominant hand (please circle):

Right Left Ambidextrous

Please now complete the questionnaires overleaf.

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week. **Don't take too long over you replies: your immediate response is best.**

I feel tense or 'wound up':		**I feel as if I'm slowed down:**	
Most of the time		Nearly all the time	
A lot of the time		Very often	
From time to time, occasionally		Sometimes	
Not at all		Not at all	
I still enjoy the things I used to enjoy:		**I get a sort of frightened feeling like 'butterflies' in the stomach:**	
Definitely as much		Not at all	
Not quite so much		Occasionally	
Only a little		Quite often	
Hardly at all		Very often	
I get a sort of frightened feeling as though something awful is about to happen:		**I have lost interest in my appearance:**	
Yes definitely and quite badly		Definitely	
Yes, but not too badly		I don't take as much care as I should	
A little, but it doesn't worry me		I may not take quite as much care	
Not at all		I take just as much care as ever	
I can laugh and see the funny side of things:		**I feel restless as if I have to be on the move:**	
As much as I always could		Very much indeed	
Not quite so much now		Quite a lot	
Definitely not so much now		Not very much	
Not at all		Not at all	
Worrying thoughts go through my mind:		**I look forward with enjoyment to things:**	
A great deal of the time		As much as I ever did	
A lot of the time		Rather less than I used to	
From time to time, but not too often		Definitely less than I used to	
Only occasionally		Hardly at all	
I feel cheerful:		**I get sudden feelings of panic:**	
Not at all		Very often indeed	
Not often		Quite often	
Sometimes		Not very often	
Most of the time		Not at all	
I can sit at ease and feel relaxed:		**I can enjoy a good book or radio or TV program:**	
Definitely		Often	
Usually		Sometimes	
Not often		Not often	
Not at all		Very seldom	

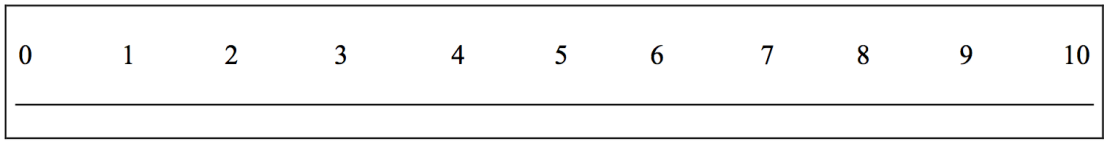
Fatigue Severity Scale

Please circle the number between 1 and 7 which you feel best fits the following statements. **This refers to your usual way of life within the last week.** 1 indicates "strongly disagree" and 7 indicates "strongly agree."

Read and circle a number.	Strongly Disagree → Strongly Agree						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

Visual Analogue Fatigue Scale (VAS)

Please mark an "X" on the number line which describes your global fatigue with 0 being worst and 10 being normal.



BOCS
Brief Obsessive Compulsive Scale

By S. Bejerot. Based on Wayne Goodman's YALE- BROWN OBSESSIVE COMPULSIVE SCALE
and CHILDREN'S YALE- BROWN OBSESSIVE COMPULSIVE SCALE

The patient (>15 years) can complete the checklist as a self-rating procedure, while the information from younger children should be obtained by interview. The questions on page 4 are to be completed by the clinician in an interview setting.

The terms "obsessions" and compulsions" may be described in the following way:

"Obsessions" are distressing **thoughts**, ideas, feelings, fantasies, images (pictures) or impulses that keep coming into your mind even though you do not want them to. Since obsessions cause distress, compulsions are readily carried out to reduce it.

"Compulsions" on the other hand, are **habits,** rituals or behaviors, you feel you have to do, although you may know that they do not make sense, or are excessive. At times you may try to stop from doing them, but this might not be possible. While most compulsions are observable behaviors, some compulsions may be hidden mental acts that go on in your head, such as silent checking, or repeating certain words to yourself each time you have disturbing thoughts.

Check the obsessions and compulsions that trouble you *right now* (during the past week) in the "current" box. If they have occurred previously but not any longer, check the box marked "Past". There are examples of each symptom to help you decide if you have an obsessive-compulsive symptom. If you never have had the obsession or compulsion, check the box marked "Never".

Contamination/Cleanness	**Current**	**Past**	**Never**
1. I am worried about dirt, germs, virus. *Ex. Fear of getting germs from touching door handles or shaking hands or sitting in certain chairs or seats or fear of getting AIDS.*	☐	☐	☐
2. I wash my hands very often or in a special way to be sure I am not dirty or contaminated. *Ex. Washing one's hands many times a day or for long periods after touching, or thinking one has touched, a contaminated object.*	☐	☐	☐

Harming obsessions	**Current**	**Past**	**Never**
3. I fear that my actions might harm others. *Ex. Fear of poisoning other's food, fear of hurting babies, fear of pushing someone in front of a train, fear of causing harm by giving bad advice.*	☐	☐	☐
4. I fear I will loose control and do something I don't want to do. *Ex. Fear of driving into a tree, fear of running over somenoe, fear of stabbing someone.*	☐	☐	☐
Sexual obsessions			
5. I have unpleasant forbidden or perverse sexual thoughts, images or impulses that frighten me. *Ex. Unwanted bad sexual thoughts about strangers, family members, children or friends.*	☐	☐	☐
Checking			
6. I must check the stove or other electrical appliances, that I have locked the door or make sure that things have not disappeared. *Ex. Repeated checking of door locks, the stove, the iron or electrical outlets before leaving home; repeated checking that one's cupboard at school is locked, or if one is properly dressed.*	☐	☐	☐
Religion/Magical thoughts/Superstition			
7. My dirty words, thoughts and curses directed towards God bothers me; I have a fear of offending God. *Ex. Worries about being punished for such sins and thoughts now, later in life or after death.*	☐	☐	☐
8. In order to prevent something terrible to happen I must have special thoughts or acts done in a special way. *Ex. Touching an object like a telephone insures that someone in the family will not get sick.*	☐	☐	☐
Morality & Justice			
9. I am occupied with morality issues, justice or what is right or wrong. *Ex. worries about always doing "the right thing", having told a lie, or having cheated someone.*	☐	☐	☐
Symmetry/Exactness/Ordering			
10. How things are placed or how they are positioned is important to me. It needs to feel "just right" (but isn't associated with magical thinking). *Ex. Worries about papers and books being neatly placed, worries about calculations or handwriting being perfect or not evening up.*	☐	☐	☐
11. I get a compelling urge to put my things in a special order. *Ex. Straightening paper and pens on a desktop or books in a bookcase, wasting hours arranging or lining up things in the house in "order" and then becoming very upset if this order is disturbed.*	☐	☐	☐

Just right/ Repeating rituals/ Counting	**Current**	**Past**	**Never**
12. I have a compelling urge to repeat certain actions until it feels just right. *Ex. Repeating activities like turning the tap or appliances on and off, combing one's hair, going in and out of a doorway.*	☐	☐	☐

Hoarding & Saving

14. I must follow strong impulses to collect and hoard things. *Ex. Saving old newspapers, notes, cans, paper towels and wrappers for fear that if one throws them away one may some day need them; picking up useless objects from the street.*	☐	☐	☐

Somatic obsessions

15. I have worries that I look peculiar; I am concerned that something is wrong with my looks. *Ex. Worries that one's face, ears, nose, eyes, or another part of the body is hideously ugly, despite reassurance to the contrary.*	☐	☐	☐

Self-damaging behaviors

16. I do things that injure my body. *Ex. Scratching and tearing the skin, cut oneself or banging one's head.*	☐	☐	☐

If you have other obsessive-compulsive problems (*obsessions/thoughts*, *compulsions/habits)* that are not included in the checklist, enter them here:

1. _____
2. _____
3. _____

Mark *the most troublesome* obsessive-compulsive problems, and enter them here:

1. _____
2. _____
3. _____

What is worse, your obsessions or your compulsions?

*Please respond to **either** question* A or B.

A. If you separate your obsessions and your compulsions, what percent are the former and what the latter?

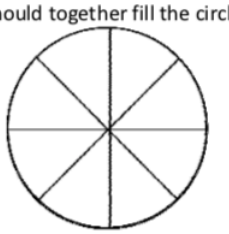
Obsessions: _____ %
Compulsions: _____ %

B. Obsessions and compulsions should together fill the circle.

Please dash the sections that correspond to your compulsions/ habits. The empty sections correspond to your obsessions/thoughts.

☐ = Obsessions/thoughts

☐ = Compulsions/habits



*Review the current **obsessive-compulsive problems** (obsessions/thoughts and compulsions/habits).*
Ask the patient to respond according to the situation during the last seven days (including today).

1. **Approximately, how much of your time is occupied by obsessive-compulsive problems?**
   0= None.
   1= Occasional symptoms or less than one hour per day.
   2= Frequent obsessive-compulsive symptoms or1-3 hours per day.
   3= Very frequent symptoms or more than 3 and up to 8 hours a day.
   4= Almost constantly or more than 8 hours a day.

2. **On the average, what is the longest amount of consecutive waking hours per day that you are completely free of obsessive-compulsive problems? ___hrs/day.**
   0= No symptoms.
   1= Long symptom-free interval, more than 8 consecutive hours/day symptom-free.
   2= Moderately long symptom-free interval, more than 3 and up to 8 consecutive hours/day symptom-free.
   3= Short symptom-free interval, from 1 to 3 consecutive hours/day symptom-free.
   4= Extremely short symptom-free interval, less than 1 consecutive hour/day symptom-free.

3. **How much do your obsessive-compulsive problems interfere with your everyday life, work or school, or social functioning?**
   0= No interference.
   1= Mild; slight interference with social or occupational/school activities, but overall performance not impaired.
   2= Moderate; definite interference with social or occupational/school performance, but still manageable.
   3= Severe interference; causes substantial impairment in social or occupational/school performance.
   4= Extreme; incapacitating interference.

4. **How much distress do your obsessive-compulsive problems cause you?**
   0= None.
   1= Mild; not too disturbing.
   2= Moderate; disturbing, but still manageable.
   3= Severe; very disturbing distress.
   4= Extreme; near constant and disabling distress.

5. **How much control do you have over your obsessive-compulsive problems? How successful are you in stopping or diverting them? If you rarely try to resist, please think about those rare occasions on which you did try.**
   (Note: Do not include here obsessions stopped by doing compulsions).
   0= Complete control.
   1= Much control; usually able to stop or divert obsessive-compulsive problems with some effort/concentration.
   2= Moderate control, sometimes able to stop or divert obsessive-compulsive problems only with difficulty.
   3= Little control, rarely successful in stopping or dismissing obsessive-compulsive problems but they can be delayed for the moment.
   4= No control, are rarely able, even momentarily, to ignore obsessions or refrain from performing compulsions; they cannot even be delayed for the moment.

6. **Have you been avoiding doing anything, going anyplace or being with anyone in order to avoid your obsessive-compulsive problems?**
   0= No deliberate avoidance.
   1= Mild, minimal avoidance.
   2= Moderate, some avoidance; clearly present.
   3= Severe, much avoidance; avoidance prominent.
   4= Extreme, very extensive avoidance; patient does almost everything he/she can to avoid triggering symptoms.

Obsessions:_____%
Compulsions:_____%
(refer to the question on page 3)

BOCS TOTAL (add items 1 - 6) ☐

CAMBRIDGE DEPERSONALIZATION SCALE

(Sierra & Berrios, 1996)

==========

PLEASE READ INSTRUCTIONS CAREFULLY:

This questionnaire describes strange and 'funny' experiences that normal people may have in their daily life. We are interested in their: (a) frequency, i.e. how often you have had these experiences ***over the last six months*** and (b) their approximate duration. For each question, please circle the answers that suit you best. If you are not sure, give your best guess.

==========

1. Out of the blue, I feel strange, as if I were not real or as if I were cut off from the world.

Frequency	**Duration**
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

2. What I see looks 'flat' or 'lifeless', as if I were looking at a picture.

Frequency	**Duration**
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

3. Parts of my body feel as if they didn't belong to me.

Frequency	**Duration**
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

4. I have found myself ***not being frightened at all*** in situations which normally I would find frightening or distressing.

Frequency	**Duration**
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

Please go to page 2 ⇒

5. My favourite activities are no longer enjoyable.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

6. Whilst doing something I have the feeling of being a "detached observer" of myself.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

7. The flavour of meals no longer gives me a feeling of pleasure or distaste.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

8. My body feels very light, as if it were floating on air.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

9. When I weep or laugh, I do not seem ***to feel*** any emotions at all.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

Please go to page 3 ⇒

10. I have the feeling of ***not having any thoughts at all***, so that when I speak it feels as if my words were being uttered by an 'automaton'.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

11. Familiar voices (including my own) sound remote and unreal.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

12. I have the feeling that my hands or my feet have become larger or smaller.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

13. My surroundings feel detached or unreal, as if there was a veil between me and the outside world.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

14. It seems as if things that I have recently done had taken place a long time ago. For example anything which I have done this morning feels as if it were done weeks ago.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

Please go to page 4 ⇒

15. Whilst fully awake I have "visions" in which I can ***see*** myself outside, as if I were looking my image in a mirror.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

16. I feel detached from memories of things that have happened to me - as if I had not been involved in them.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

17. When in a new situation, it feels as if I have been through it before.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

18. Out of the blue, I find myself not feeling any affection towards my family and close friends.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

19. Objects around me seem to look smaller or further away.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

Please go to page 5 ⇒

20. I cannot feel properly the objects that I touch with my hands for, it feels ***as if it were not me*** who were touching it.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

21. I do not seem able to picture things in my mind, for example, the face of a close friend or a familiar place.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

22. When a part of my body hurts, I feel so detached from the pain that if feels as if it were 'somebody else's pain.'

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

23. I have the feeling of being outside my body.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

24. When I move it doesn't feel as if I were in charge of the movements, so that I feel 'automatic' and mechanical as if I were a 'robot'.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

Please go to page 6 ⇒

25. The smell of things no longer gives me a feeling of pleasure or dislike.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

26. I feel so detached from my thoughts that they seem to have a 'life' of their own.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

27. I have to touch myself to make sure that I have a body or a real existence.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

28. ***I seem to have lost*** some bodily sensations (e.g. of hunger and thirst) so that when I eat or drink, it feels an automatic routine.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

29. Previously familiar places look unfamiliar, as if I had never seen them before.

Frequency	Duration
0 = *never*	**In general, it lasts**:
1 = *rarely*	1 = *few seconds*
2 = *often*	2 = *few minutes*
3 = *very often*	3 = *few hours*
4= *all the time*	4 = *about a day*
	5 = *more than a day*
	6 = *more than a week*

Thank you for answering all the questions!!

Appendix B:
Correlograms

Table 1: Correlogram for functional dystonia (demographic/clinical)

	Gender	Age	Duration	MoCA	FMDRS Score	S-FMDRS Score	MDS-UPDS (FT score)
Gender		0.59 *	-0.27	0.12	0.00	-0.05	-0.17
Age	0.59 *		0.13	-0.19	-0.38	-0.39	-0.04
Duration	-0.27	0.13		-0.26	-0.21	-0.14	0.09
MoCA	0.12	-0.19	-0.26		-0.37	-0.36	-0.64 *
FMDRS Score	0.00	-0.38	-0.21	-0.37		0.98 ***	0.34
S-FMDRS Score	-0.05	-0.39	-0.14	-0.36	0.98 ***		0.37
UPDRS (FT score)	-0.17	-0.04	0.09	-0.64 *	0.34	0.37	

Key

>0.9 | 0.8 - 0.89 | 0.7 - 0.79 | 0.6 - 0.69 | 0.5 - 0.59

Abbreviations: FMDRS = Fahn-Marsden Dystonia Rating Scale; FT = finger tapping; S-FMDRS = Simplified Functional Movement Disorder Rating Scale; MDS-UPDRS = Movement Disorders Society

Table 2: Correlogram for organic dystonia (demographic/clinical)

	Gender	Age	Duration	MoCA	FMDRS Score	S-FMDRS Score	MDS-UPDS (FT score)
Gender		-0.07	-0.03	0.04	-0.13	-0.10	0.02
Age	-0.07		0.23	0.01	0.16	0.17	0.16
Duration	-0.03	0.23		-0.12	0.45 **	0.38 *	0.52 **
MoCA	0.04	0.01	-0.12		-0.28	-0.34	-0.14
FMDRS Score	-0.13	0.16	0.45 **	-0.28		0.89 ***	0.66 ***
S-FMDRS Score	-0.10	0.17	0.38 *	-0.34	0.89 ***		0.59 ***
UPDRS (FT score)	0.02	0.16	0.52 **	-0.14	0.66 ***	0.59 ***	

Key

Abbreviations: FMDRS = Fahn-Marsden Dystonia Rating Scale; FT = finger tapping; S-FMDRS = Simplified Functional Movement Disorder Rating Scale; MDS-UPDRS = Movement Disorders Society

Table 3: Correlogram for functional dystonia (self-rating scales)

	HADSA	HADSD	Fatigue	BOCS	CDS	Pain
HADSA		0.55	0.09	0.65 *	0.30	0.19
HADSD	0.55		0.55 *	0.65 *	0.30	-0.32
Fatigue	0.09	0.55 *		0.18	0.24	-0.01
BOCS	0.65 *	0.65 *	0.18		0.53	-0.20
CDS	0.30	0.30	0.24	0.53		0.35
Pain	0.19	-0.32	-0.01	-0.20	0.35	

Key

>0.9 | 0.8 - 0.89 | 0.7 - 0.79 | 0.6 - 0.69 | 0.5 - 0.59

Abbreviations: BOCS = Brief Obsessive-Compulsive Scale; CDS = Cambridge Depersonalisation Scale; HADSA = Hospital Anxiety and Depression Scale (anxiety subscale); HADSD = Hospital Anxiety and Depression Scale (depression subscale).

Table 4: Correlogram for healthy controls (self-rating scales)

	HADSA	HADSD	Fatigue	BOCS	CDS	Pain
HADSA		0.56 **	0.42 *	0.55 **	0.41 *	0.12
HADSD	0.56 **		0.63 ***	0.43 *	0.40 *	0.04
Fatigue	0.42 *	0.63 ***		0.33	0.27	0.17
BOCS	0.55 **	0.43 *	0.33		0.28	0.32
CDS	0.41 *	0.40 *	0.27	0.28		0.04
Pain	0.12	0.04	0.17	0.32	0.04	

Key

Abbreviations: BOCS = Brief Obsessive-Compulsive Scale; CDS = Cambridge Depersonalisation Scale; HADSA = Hospital Anxiety and Depression Scale (anxiety subscale); HADSD = Hospital Anxiety and Depression Scale (depression subscale).

<u>Table 5:</u> Spearman's correlation coefficients (r) for correlations between clinical severity scores and psychological, fatigue and pain scores

Coefficients shown, with p values in brackets.

		FMDRS	S-FMDRS
		r, (p value)	r, (p value)
HADSA	FD	-0.26 (0.4)	-0.24 (0.4)
	OD	-0.02 (0.91)	-0.05 (0.78)
	HC	-0.3 (0.1)	-0.3 (0.08)
HADSD	FD	0.003 (0.99)	0.03 (0.93)
	OD	-0.1 (0.59)	-0.04 (0.82)
	HC	-0.21 (0.29)	-0.1 (0.56)
BOCS	FD	-0.31 (0.31)	-0.28 (0.35)
	OD	0.07 (0.7)	0.04 (0.84)
	HC	0.02 (0.91)	0.0 (1.0)
CDS	FD	0.07 (0.82)	0.11 (0.72)
	OD	-0.07 (0.7)	-0.09 (0.63)
	HC	0.14 (0.48)	0.16 (0.41)
FSS	FD	0.38 (0.2)	0.40 (0.18)
	OD	-0.1 (0.55)	-0.1 (0.55)
	HC	-0.3 (0.1)	-0.2 (0.28)
Pain	FD	0.26 (0.91)	0.31 (0.31)
	OD	-0.24 (0.18)	-0.3 (0.08)
	HC	-0.18 (0.34)	-0.26 (0.18)

Key: BOCS = Brief Obsessive Compulsive Scale; CDS = Cambridge Depersonalisation Scale; FSS = Fatigue Severity Scale; FMDRS = Fahn-Marsden Dystonia Rating Scale; HADSA = Hospital Anxiety and Depression Scale (anxiety subscale); HADSD = Hospital Anxiety and Depression Scale (depression subscale); S-FMDRS = Simplified Functional Movement Disorders Rating Scale.

Table 6: Correlogram for healthy controls (kinematic variables)

	Freq.	Mean velocity	Max OD	Max CA	Halts	Hesit.	Amp x Freq
Freq.		0.37 *	0.51 **	0.60 **	-0.57 **	-0.17	0.84 ***
Mean velocity	0.37 *		0.44 *	0.38 *	-0.24	-0.30	0.60 **
Max OD	0.51 **	0.44 *		0.88 ***	-0.18	-0.39 *	0.52 **
Max CA	0.60 **	0.38 *	0.88 ***		-0.08	-0.32	0.58 **
Halts	-0.57 **	-0.24	-0.18	-0.08		0.36	-0.64 ***
Hesit.	-0.17	-0.30	-0.39 *	-0.32	0.36		-0.24
Amp x Freq	0.84 ***	0.60 **	0.52 **	0.58 **	-0.64 ***	-0.24	

Key

Abbreviations: Amp = amplitude; CA = closing acceleration; Freq. = frequency; Hesit. = hesitations; Max = maximum; OD = opening deceleration.

Appendix C:

Normality and variance testing for kinematic data

Table 1: Normality and variance testing for freestyle kinematic data

		Group					
		OD = 31		FD = 12		HC = 29	
		D	ND	D	ND	D	ND
Frequency	Mean	2.79	2.53	2.64	2.51	3.15	3.02
	S.D.	0.64	0.82	0.98	1.02	0.86	0.65
	Median	2.91	2.59	3.01	2.78	3.15	3.04
	I.Q.R.	1.10	1.21	1.67	1.24	0.99	0.84
	Skewness	-0.28	-0.23	-0.75	-0.11	-0.61	0.26
	Kurtosis	-0.97	0.14	-0.51	0.90	0.45	-0.40
	Kolmogorov-Smirnov	NS	NS	NS	NS	NS	NS
	Levene's Test	NS	NS	NS	NS	NS	NS
Maximum amplitude	Mean	0.72	0.74	0.69	0.79	0.69	0.72
	S.D.	0.14	0.11	0.16	0.81	0.12	0.13
	Median	0.74	0.71	0.69	0.79	0.70	0.71
	I.Q.R.	0.16	0.20	0.20	0.12	0.22	0.19
	Skewness	-1.41	0.37	-1.55	-0.40	0.07	-0.44
	Kurtosis	**2.55**	-0.91	**3.65**	-0.52	-0.53	-0.08
	Kolmogorov-Smirnov	NS	**0.04**	NS	NS	NS	NS
	Levene's Test	NS	NS	NS	NS	NS	NS
Mean amplitude	Mean	0.41	0.40	0.42	0.47	0.40	0.42
	S.D.	0.08	0.10	0.11	0.09	0.08	0.08
	Median	0.41	0.38	0.42	0.45	0.39	0.42
	I.Q.R.	0.08	0.13	0.14	0.14	0.13	0.10
	Skewness	-0.85	0.53	-1.24	0.65	0.06	-0.24
	Kurtosis	**2.07**	-0.15	1.47	-0.32	-1.05	0.39
	Kolmogorov-Smirnov	**0.04**	NS	NS	NS	NS	NS
	Levene's Test	NS	NS	NS	NS	NS	NS
Maximum velocity	Mean	6.88	6.71	6.17	6.78	7.10	6.69
	S.D.	1.67	1.51	1.72	1.42	1.58	1.05
	Median	7.14	7.18	6.43	7.18	7.10	6.75
	I.Q.R.	1.97	2.10	3.31	2.91	2.28	1.34
	Skewness	-0.42	-1.0	-0.20	-0.68	0.15	0.20
	Kurtosis	0.27	1.47	-1.46	-1.1	-0.15	0.65
	Kolmogorov-Smirnov	**0.04**	**0.03**	NS	NS	NS	NS
	Levene's Test	NS	NS	NS	NS	NS	NS
Mean velocity	Mean	3.32	3.13	2.82	2.99	3.57	3.31
	S.D.	0.87	0.92	1.20	1.05	0.89	0.55
	Median	3.49	3.05	2.70	2.84	3.40	3.26
	I.Q.R.	1.19	1.31	2.13	1.83	1.48	0.72
	Skewness	-0.63	-0.84	0.30	0.003	-0.02	0.32
	Kurtosis	-0.50	0.79	-0.97	-0.89	-0.70	-0.03
	Kolmogorov-Smirnov	NS	NS	NS	NS	NS	NS
	Levene's Test	NS	**0.02**	NS	**0.02**	NS	**0.02**
Max OV	Mean	6.20	6.18	5.68	5.96	6.39	6.12
	S.D.	1.61	1.53	1.92	1.56	1.55	1.20
	Median	6.47	6.03	5.78	6.46	6.45	6.20
	I.Q.R.	2.16	1.94	3.92	2.95	2.20	1.61
	Skewness	-0.65	-0.69	-0.37	-0.19	-0.02	0.15
	Kurtosis	0.16	0.88	-1.16	-1.59	0.08	-0.004
	Kolmogorov-Smirnov	NS	NS	NS	NS	NS	NS
	Levene's Test	NS	NS	NS	NS	NS	NS
Max CV	Mean	6.07	5.77	5.10	5.68	6.24	5.70
	S.D.	1.72	1.57	1.55	1.73	1.59	1.04
	Median	6.26	5.72	5.01	5.48	6.36	5.61
	I.Q.R.	2.33	2.49	2.57	3.29	2.63	1.79
	Skewness	0.15	-0.39	0.30	0.10	-0.12	0.02
	Kurtosis	0.11	0.53	-0.70	-1.79	-0.59	-0.74
	Kolmogorov-Smirnov	NS	NS	NS	NS	NS	NS
	Levene's Test	NS	NS	NS	NS	NS	NS

Table 1: Normality and variance testing for freestyle kinematic data

		Group					
		OD = 31		FD = 12		HC = 29	
		D	ND	D	ND	D	ND
Max OA	Mean	227.50	202.02	220.92	184.98	259.85	231.79
	S.D.	107.54	89.96	72.89	72.40	118.53	102.58
	Median	193.73	181.67	216.08	181.77	211.66	197.47
	I.Q.R.	171.96	95.19	116.02	119.20	200.17	146.79
	Skewness	0.82	1.36	-0.09	0.32	0.95	0.93
	Kurtosis	-0.31	**3.15**	-0.83	-0.55	-0.12	-0.27
	Kolmogorov-Smirnov	**0.04**	NS	NS	NS	**0.008**	**0.003**
	Levene's Test	NS	NS	NS	NS	NS	NS
Max OD	Mean	-177.08	-191.25	-179.83	-153.99	-224.90	-203.17
	S.D.	45.16	67.45	61.90	50.82	69.22	53.16
	Median	-178.90	-184.11	-173.23	-166.54	-219.35	-196.93
	I.Q.R.	84.36	88.87	109.06	60.75	81.03	76.24
	Skewness	-0.26	-0.33	-0.14	0.78	-1.15	-0.25
	Kurtosis	-0.35	1.64	-0.80	0.69	1.91	-0.75
	Kolmogorov-Smirnov	NS	NS	NS	NS	NS	NS
	Levene's Test	NS	NS	NS	NS	NS	NS
Max CA	Mean	174.79	184.59	173.58	167.30	216.20	191.20
	S.D.	48.09	72.57	82.70	54.96	67.99	61.72
	Median	161.59	168.35	177.41	183.15	215.75	190.51
	I.Q.R.	78.07	67.02	152.40	81.89	88.29	100.66
	Skewness	0.57	1.34	0.24	-0.83	0.69	0.32
	Kurtosis	-0.56	1.92	-0.97	0.31	0.78	-0.69
	Kolmogorov-Smirnov	**0.03**	**0.03**	NS	NS	NS	NS
	Levene's Test	NS	NS	NS	NS	NS	NS
Max CD	Mean	-234.68	-218.74	-220.00	-177.08	-261.02	-222.65
	S.D.	114.98	140.11	113.26	82.45	170.21	108.19
	Median	-184.36	-178.12	-209.89	-146.50	-238.63	-193.00
	I.Q.R.	141.83	176.41	149.99	129.75	136.23	123.14
	Skewness	-1.13	-1.33	-0.82	-0.86	**-2.96**	-1.29
	Kurtosis	0.24	1.34	0.27	-0.15	**11.22**	1.03
	Kolmogorov-Smirnov	**0.002**	**<0.0001**	NS	NS	**<0.0001**	**0.002**
	Levene's Test	NS	NS	NS	NS	NS	NS
Periodicity	Mean	5.23	5.11	4.52	5.47	5.17	5.01
	S.D.	1.77	1.50	1.72	1.27	1.68	1.40
	Median	5.45	5.01	4.69	5.52	4.68	4.86
	I.Q.R.	2.07	1.88	2.65	2.23	2.97	2.06
	Skewness	-0.43	0.12	-0.23	-0.29	0.19	0.44
	Kurtosis	0.17	-0.13	-0.22	-0.62	-1.13	-0.53
	Kolmogorov-Smirnov	NS	NS	NS	NS	NS	NS
	Levene's Test	NS	NS	NS	NS	NS	NS
CoV amplitude	Mean	0.34	0.35	0.37	0.22	0.36	0.29
	S.D.	0.21	0.18	0.20	0.10	0.18	0.14
	Median	0.28	0.37	0.33	0.20	0.34	0.31
	I.Q.R.	0.23	0.24	0.26	0.15	0.21	0.21
	Skewness	**2.37**	0.42	1.33	0.40	0.77	0.49
	Kurtosis	**8.14**	0.16	**2.62**	-0.54	0.32	0.03
	Kolmogorov-Smirnov	**0.001**	NS	NS	NS	NS	NS
	Levene's Test	NS	NS	NS	NS	NS	NS
CoV velocity	Mean	0.42	0.49	0.70	0.44	0.47	0.48
	S.D.	0.29	0.27	0.39	0.14	0.23	0.21
	Median	0.38	0.45	0.66	0.41	0.43	0.43
	I.Q.R.	0.27	0.31	0.45	0.17	0.34	0.32
	Skewness	**2.08**	1.73	0.83	0.60	0.54	0.61
	Kurtosis	**5.05**	**4.84**	0.37	-0.19	-0.36	-0.003
	Kolmogorov-Smirnov	0.01	NS	NS	NS	NS	NS
	Levene's Test	NS	NS	NS	NS	NS	NS

Table 1: Normality and variance testing for freestyle kinematic data

		Group					
		OD = 31		FD = 12		HC = 29	
		D	ND	D	ND	D	ND
Decrement (amplitude)	Mean	0.03	-0.02	0.05	0.04	-0.007	0.008
	S.D.	0.14	0.12	0.18	0.10	0.04	0.05
	Median	0.008	-0.01	0.002	0.01	-0.005	0.008
	I.Q.R.	0.08	0.12	0.07	0.07	0.05	0.04
	Skewness	**3.57**	0.10	**2.46**	1.51	0.16	1.63
	Kurtosis	**15.85**	**3.06**	**6.38**	**2.72**	1.14	**6.96**
	Kolmogorov-Smirnov	**<0.0001**	**0.03**	**<0.0001**	**0.047**	NS	**0.03**
	Levene's Test	**0.03**	**0.04**	**0.03**	**0.04**	**0.03**	**0.04**
Decrement (velocity)	Mean	-0.009	-0.02	0.005	-0.02	-0.02	-0.004
	S.D.	0.04	0.07	0.06	0.06	0.07	0.06
	Median	-0.01	-0.03	-0.003	-0.03	-0.02	0.001
	I.Q.R.	0.04	0.09	0.09	0.09	0.07	0.08
	Skewness	0.77	0.74	0.30	-0.70	**-2.15**	0.11
	Kurtosis	1.79	1.46	-0.87	0.67	**8.10**	0.50
	Kolmogorov-Smirnov	NS	NS	NS	NS	NS	NS
	Levene's Test	NS	NS	NS	NS	NS	NS
Halts	Mean	6.31	8.68	9.63	9.26	5.32	5.46
	S.D.	3.31	5.23	10.94	7.79	2.28	2.25
	Median	5.28	5.89	4.74	5.49	4.62	4.80
	I.Q.R.	2.66	9.06	7.41	11.81	3.18	2.35
	Skewness	1.46	0.83	1.88	1.46	1.67	1.64
	Kurtosis	1.37	-0.49	**2.27**	0.85	**3.98**	**2.90**
	Kolmogorov-Smirnov	**<0.0001**	**0.001**	**<0.0001**	**0.002**	NS	**0.01**
	Levene's Test	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Hesitations	Mean	1.87	2.00	2.33	1.92	1.68	1.66
	S.D.	0.67	0.93	1.07	0.79	0.72	0.55
	Median	2.00	2.00	2.00	2.00	2.00	2.00
	I.Q.R.	1.00	1.00	1.75	1.75	1.00	1.00
	Skewness	0.86	0.80	0.25	0.16	1.22	0.008
	Kurtosis	**2.40**	0.04	-1.00	-1.26	**2.53**	-0.72
	Kolmogorov-Smirnov	**<0.0001**	**<0.0001**	NS	NS	**<0.0001**	**<0.0001**
	Levene's Test	**0.03**	NS	**0.03**	NS	**0.03**	NS
Amplitude x Frequency	Mean	2.02	1.87	1.87	1.97	2.27	2.16
	S.D.	0.49	0.53	0.76	0.69	0.60	0.39
	Median	2.13	1.86	1.86	2.13	2.22	2.09
	I.Q.R.	0.70	0.85	1.34	0.93	0.78	0.36
	Skewness	-0.41	-0.51	-0.03	-0.71	0.21	1.37
	Kurtosis	-0.30	0.23	-0.77	0.18	-0.18	2.00
	Kolmogorov-Smirnov	NS	NS	NS	NS	NS	0.045
	Levene's Test	NS	NS	NS	NS	NS	NS

Key: FD = functional dystonia; HC = healthy control; I.Q.R. = interquartile range; NS = not significant; OD = organic dystonia; S.D. = standard deviation.

Appendix D:

List of author's publications about dystonia and FMD

Papers related to this thesis:

1. **Newby RE**, Thorpe DE, Kempster PA, Alty JE. A History of Dystonia: Ancient to Modern. Mov Disord Clin Pract. 2017;4(4):478–85.
2. **Newby R**, Alty J and Kempster P. Functional dystonia and the borderland between neurology and psychiatry: new concepts. Mov Disord 2016;31:1777-1784
3. **Newby R,** Alty J, Jamieson S, Smith S, Kempster P. Higher self-rated obsessive-compulsion in functional compared with organic dystonia. Mov Disord 2018;33(Suppl2):S327.
4. **Newby R**, Muhamed S, Smith S, Alty J, Jamieson S, Kempster P. A kinematic analysis of finger tapping in dystonia. Mov Disord 2017;32(Suppl2):S469.
5. **Newby R,** Alty J, Jamieson S, Smith S, Kempster P. Self-assessed psychological symptoms, fatigue and depersonalisation in dystonia Mov Disord 2017;32(Suppl2):S477.

Abstracts (pending publication) related to thesis:

1. **Newby R**, Muhamed S, Alty J, Jamieson S, Smith S, Kempster P. Activation of the geste antagoniste improves speed of finger tapping in dystonia. (Presented at ABN conference 2018, pending publication in JNNP)

Papers not directly related to this thesis, focusing on dystonia and/or FMD:

1. Vijiaratnam N, **Newby R**, Kempster PA. Depression and psychosis in ADCY5-related dyskinesia—part of the phenotypic spectrum? J Clin Neurosci. 2018 Nov;57:167–8
2. Matthews J, Nagao K, Ding C, **Newby R**, Kempster P, Hohwy J. Impaired perceptual sensitivity with intact attention and metacognition in functional motor disorder. Prepr (DOI 1031234/osf.io/fz3j2). 2018

List of abbreviations

AA = alopecia areata

ADCY5 = adenylate cyclase 5

ANOVA = analysis of variance

AUC = area under the curve

BOCS = Brief Obsessive Compulsive Scale

BP = Bereitschaftspotential

BSP = blepharospasm

CD = cervical dystonia

CDS = Cambridge Depersonalisation Scale

COV = coefficient of variation

CRPS = complex regional pain syndrome

CuSP = cutaneous silent period

DBS = deep brain stimulation

DC = diseased control

DES = Dissociative Experience Scale

DSM = Diagnostic and Statistical Manual of Mental Disorders

DYT = letters used to denote genetic disorders giving rise to dystonia

EEG = electroencephalogram

EM = electromagnetic

EMG = electromyogram

ET = essential tremor

FD = functional dystonia

FDI = first dorsal interosseous

FMDRS = Fahn-Marsden Dystonia Rating Scale

fMRI = functional magnetic resonance imaging

FW = Fahn-Williams (diagnostic criteria)

FHD = focal hand dystonia

FMD = functional movement disorder

FSS = Fatigue Severity Scale

GL = Gupta-Lang (diagnostic criteria)

GLUT1 = glucose transporter type 1

GTP = guanosine-5'-triphosphate

HADS = Hospital Anxiety and Depression Scale

HC = healthy control

HD = Huntington's disease

HFS = hemifacial spasm

HREC = human research ethics committee

IFD = idiopathic focal dystonia

IPD = idiopathic Parkinson's disease

IQR = inter-quartile range

LAI = long-latency afferent inhibition

LD = laryngeal dystonia

LGI = Leeds General Infirmary

LICI = long-latency intracortical inhibition

LL = lower limb

MaxCA = maximum closing acceleration

MaxOD = maximum opening deceleration

MC = musician's cramp

MDS = Movement Disorders Society

MEP = motor-evoked potential

MMC = Monash Medical Centre

MoCA = Montreal Cognitive Assessment

MRI = magnetic resonance imaging

NBIA = neurodegeneration with brain iron accumulation

NS = not significant

OCD = obsessive compulsive disorder

OD = organic dystonia

OP = opponens pollicis

OR = odds ratio

PET = positron emission tomography

RI = reciprocal inhibition

ROC = receiver operating characteristic

SAI – short-latency afferent inhibition

SCI = structured clinical interview

SCL-90 = symptom checklist-90

SDT = spatial discrimination threshold

SDQ = Somatoform Dissociation Questionnaire

SEP = somatosensory evoked potential

SEU = systems electronics unit

S-FMDRS = Simplified Functional Movement Disorder Rating Scale

SICI = short-latency intracortical inhibition

SP = silent period

TDT = temporal discrimination threshold

TMS = transcranial magnetic stimulation

UL = upper limb

UPDRS = Unified Parkinson's Disease Rating Scale

VAS = visual analogue scale

VCP = vocal cord palsy

WC = writer's cramp

Y-BOCS = Yale-Brown Obsessive Compulsive Scale