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Sensory studies in adult-onset primary torsion dystonia

Thesis in one volume

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Submitted to the University of Dublin in fulfilment of the requirements for the Degree of Medicinae Doctor

Trinity College

2011
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Summary

Dystonia is a disorder of movement characterized by prolonged muscle contractions, causing sustained twisting movements and abnormal postures of the affected body parts. Sensory symptoms including pain are frequently reported in dystonia, and many patients use sensory tricks to alleviate the muscle contractions. Sensory changes have been found in dystonia including abnormalities of spatial discrimination thresholds, somaesthetic temporal discrimination thresholds, and sensory evoked potentials. In addition, the sensory homuncular arrangement at many levels is disorganized, and the sensory cortex shows overlapping sensory fields and enlargement in unaffected and affected sides in focal dystonia. Are these an epiphenomenon of the motor problem, or if they are primary does it suggest that dystonia is disorder of sensorimotor integration? The clinical phenotype has a low penetrance in adult-onset primary torsion dystonia (AOPTD), but would it be possible to find sensory abnormalities in unaffected family members?

The aims of the thesis were to determine spatial discrimination thresholds (SDT) in a control population, establish age thresholds for SDTs, measure affected adult-onset primary torsion dystonia patients’ SDTs, and measure their unaffected relatives in multiplex AOPTD families. The SDT can be measured using grating orientation tasks, and this type of procedure is most commonly done using using Johnson-Van Boven-Phillips (JVP) domes.

Subjects were recruited from normal healthy volunteers and multiplex families with AOPTD. Anybody with neurological illness or lesion affecting the nervous system, an abnormal sensory neurological exam or having received BoNT in the last three months was excluded.

In measuring the control SDT, a ceiling effect was identified at 45 years using the standard JVP domes. The set was expanded adding custom larger width gratings to examine older individuals as had been reported elsewhere. After assessment of the normal control data, a further ceiling effect was seen using the expanded set of JVP domes at 65 years. The controls were divided into two groups: group one (n=70), who were examined with the standard set of JVP domes, and had an upper age limit of 45 years; and group two (n=64), who were
examined using the expanded set of JVP domes, and had an upper age limit of 65 years. An abnormal SDT was defined as any measurement greater than +2.5 standard deviations above the mean. In group one, no control was above this level, but in group two, two subjects were above it.

Affected family members and unaffected relatives from the four multiplex AOPTD families (Ped 005, 006, 008, 010) were then examined according to age in group one (20-45 years) and two (45-65 years). Group one was examined using standard JVP domes, and group two using the expanded set. Fifty-eight out of 90 family members in group one were examined. In this group, five of six members with dystonia (one on regular treatment with BoNT) had abnormal SDTs, six of 13 children of affected members, none of eleven siblings, and five of 28 second-degree relatives. If this sensory abnormality represents an endophenotype, penetrance ranged from 0% (Ped 006) to 100% (Ped 010) in group one. In group two, 22 of 48 family members were examined. Only one person had an abnormal SDT who was a second-degree relative in Ped 008. In group two family members, there were four with dystonia, all receiving treatment with BoNT regularly (three monthly to six monthly). Penetration of the hypothesised endophenotype was zero in this group. Many potential candidates in families were over age 65 years and therefore could not have valid sensory testing compared to the standard normal +2.5 standard deviations using the SDT.

In conclusion, normative data for the SDT were calculated for age 20-45 years and 45-65 years. There was age related decline in the SDT in healthy controls. Sensory abnormalities measured using the SDT were suggestive of a sensory endophenotype in the younger individuals. However, SDT testing in older persons deteriorates with age. The profile of families with AOPTD is such that many members with AOPTD are older and were unable to be included in sensory testing, including many of their unaffected relatives. More group two affected patients were receiving regular treatment with BoNT also, which may have improved their SDTs for periods longer than the study’s exclusion. Further study is warranted in examining the sensory system in unaffected family members with AOPTD that may prove a useful marker for linkage studies, the understanding of the pathogenesis of the disorder, and strategies to prevent the emergence of dystonia in at-risk individuals.
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Abbreviations

AOPTD  Adult-onset primary torsion dystonia
ATP13A2  ATPase 13A2
ATP1A3  Na+/K+ATPase-alpha3
BEB  Benign essential blepharospasm
BFM  Burke-Fahn-Marsden
BoNT  Botulinum neurotoxin
CBD  Corticobasal ganglionic degeneration
CD  Cervical dystonia
CI  Confidence interval
CNS  Central nervous system
CPEO  Chronic progressive external ophthalmoplegia
DBS  Deep brain stimulation
DJ1  PARK7 associated protein of unknown function
DRD  Dopa responsive dystonia
DRD2  Dopamine receptor type 2
DRD5  Dopamine receptor type 5
DTI  Diffusion tensor imaging
DYT1  Chromosome 9q34 GAG deletion associated dystonia (ibid. TOR1A)
EOPTD  Early-onset primary torsion dystonia
FBX07  F-box protein 7
FHD  Focal hand dystonia
fMRI  Functional MRI
FTSD  Focal task specific dystonia
GCH1  Guanine triphosphate cyclohydrolase 1
GLUT1  Glucose transporter type 1
GPe  Globus pallidus external segment
GPi  Globus pallidus internal segment
HAART  Highly active antiretroviral therapy
HIV  Human immunodeficiency virus
HSP  Hereditary spastic paraplegia
IBGCl  Idiopathic basal ganglia calcification 1
ICCD  Infantile convulsions with choreoathetosis
INAD  Infantile neuroaxonal dystrophy
IPD  Idiopathic parkinson's disease
JVP  Johnson-Van Boven-Phillips
LOD  Likelihood of disease
M1  Primary motor cortex (ibid. BA4)
MELAS  Mitochondrial encephalomyopathy with lactic acidosis and stroke
MEP  Motor evoked potential
MERRF  Myoclonic epilepsy with ragged red fibres
MRI  Magnetic resonance imaging
MSA  Multiple systems atrophy
NBIA  Neuronal brain iron accumulation
NMDA  N-methyl-D-aspartate
OCD  Obsessive compulsive disorder
OMD  Orornandibular dystonia
OR  Odds ratio
PANDAS  Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection
Ped  Pedigree or family
PET  Positron emission tomography
PINK1  PTEN induced putative kinase 1
PKD  Parkoxysmal kinesigenic dyskinesia
PLA2G6  Group V1a calcium-independent phospholipase A2
PMC  Premotor cortex
PNKD  Paroxysmal nonkinesigenic dyskinesia
PRKRA  Protein kinase interferon-inducible double-stranded RNA dependent activator
PSP  Progressive supranuclear palsy
PV  Parietal ventral somatosensory area
RT-PCR  Reverse transcriptase polymerase chain reaction
S1  Primary sensory cortex (ibid. BA3)
S2  Secondary somatosensory area
SCA  Spinocerebellar ataxia
SD   Standard deviation
SDT  Spatial discrimination threshold
SGCE Epsilon sarcoglycan E
SLC2A1 The gene for GLUT1
SMA  Supplementary motor area
SNpc Substantia nigra pars compacta
SNr  Substantia nigra pars reticulata
SPECT Single photon emission computed tomography
SDT  Somaesthetic temporal discrimination threshold (cf TDT)
TAF1 TATAbox-binding protein associated factor gene
TDT  Temporal discrimination threshold
TH   Tyrosine hydroxylase
THAP1 Thanatos-associated protein 1 (DYT6)
TMS  Transcranial magnetic stimulation
TOR1A Torsin 1A gene (ibid. DYT1)
TVR  Tonic vibration reflex
TWSTRS Toronto Western Spasmodic Rating Scale
VA   Ventral anterior nucleus of the thalamus (SNpc to VA to PMC)
VBM  Voxel based morhpometry
Vc   Ventral caudal nucleus of the thalamus (somatosensory)
VDRL Venereal disease reference laboratory
VIIM Vibration induced illusion of movement
Vim  Ventrointermediate nucleus of the thalamus (motor inputs)
VL   Ventral lateral nucleus of the thalamus (cerebellar dentate to VL to M1)
Voa  Ventral oralis anterior nucleus (motor input GPi)
Vop  Ventral oralis posterior nucleus (motor input cerebellar)
VPL  Ventroposterolateral nucleus of the thalamus (lemniscal relay)
VPM  Ventroposteromedial nucleus of the thalamus (trigeminal relay)
Z-value Standardised normal value
γABA Gamma aminobutyric acid
1 Introduction

Dystonia is a disorder of movement caused by involuntary, sustained muscle contractions affecting one or more sites of the body, frequently causing twisting and repetitive movements, or abnormal postures (Fahn et al., 1998).

Voluntary movement is mediated by the cortico-spinal tracts modulated by a number of inputs including the basal ganglia and sensory afferents. Involuntary movement of skeletal muscle, including posture, relies on constant sensory feedback to provide the relevant efferent stimulation to stimulate muscle. There is accumulating evidence, which suggests that dystonia is a disorder of sensory modulation of motor outputs. In this thesis, the evidence for a sensory disorder in dystonia, in particular primary torsion dystonia, is presented and discussed.

In the clinical setting it has been noted for some time that patients with dystonia use sensory stimuli to alleviate symptoms. Up to eighty percent of dystonia sufferers report benefit from the use of “sensory tricks” or geste antagoniste (Patterson and Little, 1943). A sensory trick is a simple manoeuvre such as touching the skin on the face to help correct head posture, but may also be employed by just thinking about doing it (Edwards et al., 2008). Leis and colleagues looked at the effect of selective sensory stimulation on modulation of muscle activity in subjects with dystonia (Leis et al., 1992). Using surface electromyography, they demonstrated a reduction of root mean square voltage by 80-90% in dystonic muscles when the examiner applied a sensory stimulus (vibration or electrical stimulus applied to the skin). Sensory symptoms are also often reported by patients. In a review of presenting sensory symptoms in eleven
consecutive patients, Ghika and coworkers found that in cranial dystonia (blepharospasm, oromandibular dystonia) many patients have sensory symptoms such as dry eyes, a feeling of dirt in the eyes, burning pain around the mouth, swollen tongue, cramps and stiffness in muscles which later are affected (Ghika et al., 1993).

Many other abnormalities of the sensory system have now been described in dystonia including abnormal graphesthesia and stereognosis (Byl et al., 1996a), abnormal tonic vibration reflex (Kaji et al., 1995) and vibration-induced illusion of movement (Frima et al., 2003, Rome and Grunewald, 1999), impaired spatial and temporal discrimination thresholds (Bara-Jimenez et al., 2000a, Sanger et al., 2001, Molloy et al., 2003), disturbance of sensory evoked potentials (Reilly et al., 1992), disorganisation of the senory homunculus (Bara-Jimenez et al., 1998), overlapping fields in the primary sensory cortex (Meunier et al., 2001), and enlarged primary sensory cortex (Garraux et al., 2004). For these reasons, it has been proposed that dystonia is a disorder of sensorimotor integration (Hallett, 1995).

1.1 A brief history of dystonia

Dystonia was first described by the Dutch physician Tulpius in 1652 when he wrote in his notes regarding spasmodic torticollis (Tagliati et al., 2004). In 1713, Ramazzini described a movement disorder affecting the hand of an acquaintance, "... a notary by profession... (who) began to complain of intense fatigue in the whole arm... he began to train himself to write with the left hand, but it was not very long before it too was attacked by the same malady" (Altschuler, 2005). In 1836, a German physician Kopp wrote a treatise on "the afflictions of the hand
that writes” being the first detailed description of focal task specific dystonia (Goetz et al., 2001).

Torticollis treatment by “shampooing” (massage) was suggested in 1850 as an effective treatment combined with forcible extension of the affected area (Anonymous, 1850). Brodhurst, an orthopaedic surgeon, divided the classification of torticollis into congenital and non-congenital, later reaffirmed by Southam. He recognised that many of the causes are due to central nervous system disease including purely “spasm”. He also observed the association between torticollis and scoliosis (Brodhurst, 1864, Brodhurst, 1863, Southam, 1885). A case of torticollis in a 50 year old copper- & tin-plate worker is described by Ogle in 1873 associated with headache, peripheral sensory disturbances and peeling of the skin. It is probably toxic in origin with symptoms of arsenic or manganese toxicity (used in copper production and welding), but the author suggests spinal cord aetiology (Hewett, 1873, Aminoff, 2004). Gowers described both focal and generalised dystonia. They are represented in his section on torticollis in his pre-eminent book *A manual of diseases of the nervous system* (1888) and again described a case of *tetanoid chorea* (1893), which is a good clinical description of a generalised spasm in dystonia (Herz, 1944, Gowers, 1888). Gowers felt that all forms of spasm of the neck muscles representing torticollis should be grouped together. Although early in his text he emphasizes familial association with “a history of epilepsy or of insanity,” he mentions hereditary association with facial spasms. In his text he attributes an association of torticollis and writer’s cramp to Reynolds, and a description of post-traumatic cervical dystonia to Fournier’s thesis submitted to the University of Strasbourg.
Schwalbe is accredited with being the first to recognise dystonia as distinct from other movement disorders, such as the athetosis (αθετός, without fixed position) which had been widely recognised as organic since Hammond described it in 1871 (Parkes and Pike, 1988, Truong and Fahn, 1988, Herz, 1944). Schwalbe contributed also by making the genetic association for the disorder in describing an affected family. Although Schwalbe ultimately makes a diagnosis of hysteria, he also felt the family’s disorder closely resembled “tonic cramps” described by Meige and Feindel in one of their patients. Barraquer i Roviralta, the great Catalan neurologist, described and illustrated a case of generalised dystonia developing in a 29 year old man in 1897, although he had called it athetosis because of a close alliance with Hammond (Barraquer-Bordas and Gimenez-Roldan, 1988).

In 1910, Henry Meige eloquently described in a systematic manner the different known types of movement disorders affecting the face in the early twentieth century (Meige, 1910). In doing so, he recognised that:

en dehors des tics de la face, en dehors de l’hémispasme facial périphérique, en dehors du spasme postparalytique, du spasme facial alterné, et même en dehors du bispasme facial proprement dit, je crois qu’il existe une autre variété de convulsion facial, qui mérite d’être cliniquement distinguée des précédentes

[apart from facial tics, hemifacial spasm, postparalytic spasm, alternating facial spasm, and even apart from bilateral facial spasm, I believe that another type of facial convolution exists, which deserves to be clinically distinguished from the others]
Meige describes double convulsion palpébrale (biblépharospasme), but felt that it was rarely the sole feature, since most of his ten patients also had other facial muscle involvement. On observing the patients for a long time he noted contemporaneous bilateral spasms of frontalis, nasalis, elevator anguli oris, orbicularis oris and platysma. He felt that these patients had much in common with those that his research colleague Brissaud had described with torticolis mental. They were deeply psychosocially afflicted by their infirmity, as can be seen in the numerous distorted self-portraits by a contemporary dystonia sufferer and Secessionist/Expressionist artist Egon Schiele (1890-1918). They had all sorts of tricks to attenuate or get rid of it, similar to the antagonistic strategies of the torticollis patients. In one patient, pharyngeal muscles, orolingual muscles, and jaw muscles were also seen to contract. Meige and Brissaud who had been some of Charcot’s last interns in the Hôpital de la Pitié-Salpêtrière, were of the opinion that the disorders of movement occurred due to lesions outside the pyramidal system.

The term dystonia was first used by Oppenheim, an esteemed Berlin neurologist, in 1911 in his paper on generalised dystonia (Tagliati et al., 2004, Anonymous, 1912). He described several young boys of Jewish ethnicity affected by tonic and clonic movement, sometimes alternating, and exacerbated by voluntary movement which he thus coined as both dysbasia lordotica progressiva and dystonia musculorum deformans (Grundmann, 2005). The muscles chiefly affected are those of the thighs, pelvis and spine producing a “lordo-scoliosis”. No paralysis was found, and Oppenheim concluded that the disease must be caused by minute changes in the brain that accounts for the progression.
Kinnier-Wilson, considered by many the founding father of the modern study of movement disorders and the newly coined extrapyramidal system, published his MD thesis in 1912 entitled *progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver*. With this and later publications such as his textbook *Neurology*, he established the link between dystonia and degeneration of the basal ganglia (Parkes and Pike, 1988). Experiments in neurological surgery looking at the effect of lesions in the basal ganglia confirmed this. Denny-Brown stated in 1966 that “the pyramidal system is useless to the organism without the extrapyramidal system (Northfield, 1968).”

The emergence of fascination with mental illness, hysteria and the depiction of unusual postures in insanity prevented the recognition of many forms of dystonia in neurology and psychiatry, with many individuals treated as neurotic. Even Kinnier-Wilson listed torticollis under motor neurosis in his magnum opus *Neurology*. In primary torsion dystonia, the lack of other neurological signs, the often fluctuating unpredictable nature, and association with neurosis led many physicians to treat it as neurasthenia or psychiatric (Truong and Fahn, 1988). After a heated debate on the nosology and pathological basis of dystonia in 1929 at the Tenth International Neurological Association meeting (Paris), neurological interest dropped in dystonia, while psychiatrists brimmed with interest in ascribing a Freudian basis for it (Goetz et al., 2001).

To complicate issues, the late nineteenth century’s interest in hysterical and functional disorders had been borne out of quasi-honorable motives: the emergence of photography to document unusual clinical features, public lectures from eminent professors (e.g. Jean-Martin Charcot) and the dynamic representation of contortions of the body in art that was widely seen such as
Auguste Rodin, Henri Matisse, Egon Schiele (Goetz et al., 1995). Medicine still lacked many treatment strategies, probably enhancing public interest and demand for the emerging field of psychiatry. The treatment of dystonia, particularly torticollis, was heavily reliant on very traumatising procedures or therapies: forced extension, orthopaedic correction, galvanism, blistering, arsenic, chloroform, morphia, division of the spinal accessory nerve and tenotomy are to name but a few (Brodhurst, 1864, Hewett, 1873, Southam, 1885). To reiterate, physicians were divided and many felt patients were hysterical or malingering (Hewett, 1873).

The 1930-1950 period was fraught with the nosologic confusion arising from the clinical description, nomenclature, and localisation in extrapyramidal movement disorders. At a symposium on the basal ganglia in 1940, Alexander proposed that athetosis and dystonia were probably one and the same thing, since they so often occurred together in his clinical observation (Herz, 1944). Echoing this, but enhancing the semiological classification in his textbook *Neurology*, Kinnier-Wilson states:

“when torsion spasm appears as a symptom, it is hardly anything else than a variety of athetosis, proximal rather than distal; when it occurs in a ‘pure’ state pathology shows that at least some cases belong to lenticular disease.”

It was seven decades after Wilson’s disease was described that pure dystonia (not heredodegenerative, tardive or psychogenic) began to be widely recognised as a symptom of circuit disruption in the basal ganglia, and in turn led to rational theory on motor programs and the genesis of dystonia in the extrapyramidal system (Fahn, 1988, Marsden et al., 1985, Alexander et al., 1990, Sheehy and Marsden, 1982, Marsden, 1982). In that intervening period,
encephalitis lethargica/post-encephalitic parkinsonism, in which dystonia was seen had been correctly classified as an organic disease, and hypoxic ischaemic encephalopathy, kernicterus and carbon monoxide poisoning had been recognised pathologically in association with dystonia (Herz, 1944). Dystonia as a side-effect of the newly arrived neuroleptics such as chlorpromazine, and the anti-emetic prochlorperazine (as well as the drug-induced parkinsonian syndrome) came to light and contributed to the understanding of the neurobiology (Hare, 1958).

A serendipitous error during pyramidotomy in a patient with Idiopathic Parkinson’s Disease in 1942 led to the discovery of lesioning the thalamus to improve tremor (Benabid et al., 1996). In the late 1950’s, after successes with stereotactic surgery for dyskinesias by Cooper in Idiopathic Parkinson’s Disease, reports of stereotactic thalamotomy to the ventrolateral nucleus of the thalamus described good outcomes for several causes of hyperkinetic movement disorders (Gillingham et al., 1964). Good results were noted with childhood Oppenheim’s dystonia, or children with no motor defect other than dystonia (Hankinson, 1963).

An important landmark in the treatment of dystonia was with the advent of botulinum neurotoxin (BoNT) type A (Tsui et al., 1986). Local injection of botulinum neurotoxin type A had already been used successfully for several ophthalmological disorders and hemifacial spasm. The advantage of BoNT was its local action, no sedating properties, and the lack of other CNS side-effects seen with systemically administered drugs including anticholinergics, dopaminomimetics, and muscle relaxants. Stereotactic neurosurgery and peripheral surgical approaches had not been as successful for focal dystonia.
Eighty-eight percent of patients with spasmodic torticollis treated with BoNT injection had a significant reduction in pain and 63% had an objective improvement for movement compared to placebo.

From the late 1960’s levo-dopa treatment revolutionised Idiopathic Parkinson’s Disease treatment (Cotzias et al., 1967). Stereotactic surgery’s role now focused on complications such as hyperkinetic movement disorders and tremor (Benabid et al., 1996). Intraoperative localisation using electrodes to enhance targeting and electrical stimulation suppressed parkinsonian tremor and rest tremor (Jasper and Bertrand, 1966). Benabid and colleagues performed the first trial of chronic stimulation of the ventral intermediate nucleus of the thalamus between 1987 and 1990 with 88% overall improvement or cessation of tremor (Benabid et al., 1991). One patient with generalised dystonia was treated as a humanitarian therapeutic trial with good results, but they found that dystonia responded to different stimulation parameters compared to IPD. Going beyond the Vim in IPD to bilateral STN-DBS with success also encouraged interest in moving along with other targets in the basal ganglia for movement disorders (Limousin et al., 1995). The pallidum had become the target of choice for lesioning in dyskinesias associated with IPD, with 92% reduction in ON dyskinesias on the contralateral side, and an improvement in gait and dyskinesias during OFF periods too (Lozano et al., 1995).

Pallidotomy for generalised dystonia had good outcomes but did not always have a long-lasting effect. The advantage of DBS was that it was considered partially reversible, and success was seen in a single case of generalised dystonia using GPI-DBS (Kumar et al., 1999). Seven patients (six children, one adult) with DYT1 generalised dystonia were then successfully
treated, showing better results in children partly because of skeletal deformity in the adult (Coubes et al., 2000). Non-\textit{DYT1} generalised dystonia did not show as much of an improvement with GPi-DBS, and focal dystonia was slow to improve (Yianni et al., 2003). Improvement in severe medically refractive primary generalised dystonia has been seen with bilateral GPi-DBS in \textit{DYT1} gene-deletion-positive and -negative adult patients (Cif et al., 2003, Vidailhet et al., 2005, Vidailhet et al., 2007). However, most patients required medication post-operatively, two deteriorated and improvements were seen for physician rated motor scores with only a trend towards patient reported effect on quality of life. Further study confirmed this, demonstrating the benefit of GPi-DBS compared to sham, showing benefit in segmental dystonia, and also showing a reduction in pain scores (Kupsch et al., 2006). In focal dystonia, GPi-DBS for severe medically refractive cervical dystonia showed significant reductions in the TWSTRs overall score, and in the pain and disability subscores. Overall improvements in movement and disability scores for cervical dystonia ranged from 48 to 63\% (Kiss et al., 2007). The optimal target in dystonia is the posteroverntral GPi (Starr et al., 2006, Tisch et al., 2007).

Despite many advances in a short period of time, including the identification of 20 different genes encompassing dystonia and dystonia-plus syndromes, the aetiology of dystonia that affects most people is unknown – adult-onset primary torsion dystonia (AOPTD).
1.2 Classification, dystonia syndromes and investigations

1.2.1 Classification by aetiology

Fahn and colleagues revised the classification of dystonia to help in our understanding, clinical approach to management, and in organizing future research (Fahn et al., 1998). The classification of dystonia is according to the four major aetiological subtypes: primary, dystonia-plus, heredodegenerative and secondary. The primary dystonias are characterised by dystonia and tremor as the only clinical manifestations, in the absence of other neurological signs, and with a history and laboratory investigation that do not suggest an exogenous, inherited or degenerative cause.

1.2.2 Classification by age of onset

Under the aetiologic subtype of primary dystonia, it is possible to further classify according to age of onset. There is a bimodal distribution in the age of onset in dystonia, with early-onset and adult-onset (Bressman et al., 1989). The early-onset primary torsion dystonia (EOPTD) occurs generally before the age of 28 years, with a median age of nine years (Bressman et al., 1998). It usually presents in an extremity (arm or leg), and spread to generalised dystonia occurs in 71% (Greene et al., 1995). Adult-onset primary torsion dystonia (AOPTD) has a median onset of 45 years, and usually begins after 28 years. The cervical, cranial and arm muscles are usually involved. AOPTD spreads too, but smaller proportions (41% spread in focal hand dystonia, 37% spread in blepharospasm, 25% in cervical dystonia), and only 7.8% of all AOPTD becomes generalised (Greene et al., 1995). A third age of onset is adolescent-onset primary torsion
dystonia, which is rarely seen, but may arise in either a limb or cervical-cranial muscles (Bentivoglio et al., 1997, Holmgren et al., 1995).

1.2.3 Classification by phenotype

The primary dystonias can be further classified by age of onset and by distribution. Bressman and colleagues provide an aetiological classification in which the primary dystonias are grouped into three groups:

*Childhood and adolescent limb-onset (age <28 years)*

This early-onset primary torsion dystonia typically begins in a limb. When beginning in the leg, it is typically action dystonia, e.g. a foot that postures when running. The commonest cause of idiopathic torsion dystonia in childhood is the TOR1A/DYT1 GAG deletion in both Jews and non-Jews. Fifty to 70% of manifesting carriers of the GAG deletion will have symptoms before the age of 10 years (Bressman et al., 1989, Ozelius et al., 1989, Tarsy and Simon, 2006, Kramer et al., 1994, Bressman et al., 2000, Lebre et al., 1999).

*Mixed phenotype: onset in child/adulthood (age 12 – 28 years)*

It may begin in a limb, neck or cranial muscles.

*Adult cervical, cranial or brachial-onset (usual age of onset >28 years)*

It is autosomal dominant with a very reduced penetrance (Waddy et al., 1991). Some families have higher penetrance (Almasy et al., 1997, Leube et al., 1996, Valente et al., 2001). The phenotype usually remains localized (AOPTD) or may spread in 15- 30% (Defazio et al., 1999, Greene et al., 1995).
1.2.4 Early-onset primary torsion dystonia

This distinct genetic disorder was well described by Oppenheim in 1911 who coined the term *dystonia musculorum deformans*. The clinical phenotype based on genetic assessment by Bressman has shown that the onset is early in life, and virtually always before age 44 years (rare cases over age 24 years) (Bressman et al., 2000). One of the lower limbs is affected first in 32%, upper limb in 48%, and neck in 18%. Spread from leg onset occurs in 94% within 3.4 years on average, and 89% develop generalised dystonia in this subgroup. Spread occurred in 72% of upper limb onset and 33% of neck onset patients, and tended to be slower (6.5 years and 5.1 years respectively). Cranial structures tend to be spared, with only 8% in larger series, smaller series tending to have selection bias that artificially elevates rates (Bressman et al., 1994a, Bressman et al., 2001). Eighty-five percent of patients with onset <10 years have spread compared to 59% of those over 10 years of age. Clearly the age at onset and site of onset were therefore predictive of spread (Greene et al., 1995). Familial and sporadic EOPTD had the same proportions of ultimate spread to generalised (54%) and segmental dystonia (20%). Half of all patients with onset <10 years become generalised within three years (c.f. 34 years if onset ≥10 years). 90% of upper limb onset in EOPTD is in the dominant hand.

The inheritance pattern is autosomal dominant with reduced penetrance. Penetrence in Ashkenazi Jews is around 30%, and 40% in non-Jewish families.

A large pedigree of non-Jewish North American family of French-Canadian ancestry with early-onset primary torsion dystonia made it possible to do linkage studies (Ozelius et al., 1989). A locus was first identified at
chromosome 9q34.1. The locus, *DYT1*, was identified as a triplet deletion of GAG. The *TOR1A* gene encodes TorsinA, a heat-shock protein with a six-ring barrel-like structure, whose function is acting as a chaperone in the perinuclear cytoplasm (Ozelius et al., 1997, Ozelius et al., 1998, Bragg et al., 2004). In Ashkenazi Jews the GAG deletion accounts for ~80% of EOPTD, compared to 16-53% in a non-Jewish population (Bressman, 2004, Valente et al., 1998, Lebre et al., 1999). Limb-onset is a predictor of GAG deletion carrier status (Kamm et al., 1999).

A founder mutation in an ancestor of the affected families of Ashkenazim is presumed to be the cause, probably originating in Byelorussia or Lithuania about 350 years ago (Risch et al., 1995).

Patients with leg onset are younger (8-9 years) compared to those with initial involvement of arm muscles (12-14 years). Those with leg onset are more likely to develop generalised dystonia. The rate of progression to generalised is faster if the onset is in the leg (4.7 years) compared to arms (11.4 years). In two large non-Jewish North American families, *DYT1* was excluded, and the phenotype was of slightly later onset (28.4 ± 14.8 years in one family), and most family members affected had onset in craniocervical muscles or greater disability from craniocervical phenotypes.

The cause of the low penetrance and variable expression of the gene is unknown. Possible mechanisms include genomic imprinting, anticipation, modifying genes, and environmental factors. There is a trend though towards maternal inheritance with later age of onset, and there is some tenuous evidence of anticipation. Other investigators examined the evidence for genetic heterogeneity or the presence of modifying genes. There was a very low
correlation for age-of-onset between 23 first-degree relative pairs of generalised and segmental dystonic probands. The conclusion was that no genetic heterogeneity is present or nonallelic modifying genes (Fletcher et al., 1991a).

Though no structural abnormalities are found on MRI in DYT1 dystonia or other early-onset dystonia, white matter tract abnormalities may be found in the peri-lenticular white matter and juxtacortically in the cerebral hemispheres particularly near the motor strip (Bonilha et al., 2007, Rutledge et al., 1988). Functional imaging abnormalities are found. Brainstem perinuclear inclusion bodies are found in DYT1 with abnormalities in cholinergic neurons predominantly. This is mostly seen in periaqueductal grey matter, the pudunculopontine nucleus, cuneiform nucleus and reticular formation. Immunoreactivity is to ubiquitin, lamin A/C and TorsinA (McNaught et al., 2004).

Treatment for EOPTD is divided according to the distribution of the phenotype – focal or generalised. Focal types, if amenable to injection, are treated with botulinum neurotoxin injection. Generalised dystonia is treated initially with oral medication, typically anticholinergics, and if the response is inadequate, prominently affected regions can be injected with botulinum neurotoxin. For medically refractory generalised and segmental dystonia, the surgical gold standard is currently GPi deep brain stimulation (Geyer and Bressman, 2007). Bilateral GPi-DBS reduces overall dystonia severity by 42-53% in segmental and generalised dystonia respectively, with twelve percent suffering the commonest side-effect of dysarthria (Kupsch et al., 2006). In generalised dystonia, bilateral GPi-DBS has the same effect in DYT1 mutation
positive and negative patients, and maintains good motor improvements over at least three years (Vidailhet et al., 2007, Vidailhet et al., 2009).

1.2.5 Adult-onset primary torsion dystonia

A common aetiology for the most common primary form of dystonia, adult-onset primary torsion dystonia (AOPTD), continues to be unknown, but it is most likely a combination of different genetic loci, multiple genetic influences and environmental stimuli.

Studies of AOPTD families indicate an autosomal dominant inheritance with reduced penetrance of 12-15% (Waddy et al., 1991). Alternatively, penetrance may be higher in a subset of families with the remainder being non-genetic (Stojanovic et al., 1995, Leube et al., 1997, Defazio et al., 1993, Bressman et al., 1998). Overall, the rate of dystonia observed in first-degree relatives tends to be higher than the population prevalence.

Phenotypic heterogeneity is a feature of familial AOPTD indicating that the same genetic disorder within a family may cause widely differing clinical manifestations. In a study of twelve multiplex families with AOPTD the probands all had cervical dystonia and 22 of 126 first- and second-degree relatives were rated as affected with AOPTD; cervical dystonia was seen in 17, two had writer’s cramp, one had blepharospasm and two had spasmodic dysphonia. (O’Riordan et al., 2004b) Intra-familial phenotypic heterogeneity has also been noted in an Italian pedigree in which all known genetic loci had been excluded; of six affected members, three had cervical dystonia, two had blepharospasm and one an occupational upper limb dystonia. (Brancati et al., 2002) Other reported pedigrees have demonstrated intra-familial heterogeneity
(Uitti and Maraganore, 1993, Munchau et al., 2000, Holmgren et al., 1995,
Bressman et al., 1996). The identification of the genetic causation of AOPTD has
been difficult because informative families are rare due to the low penetrance of
the phenotype and the absence of a structural, pathological or biochemical
marker of the disease (Bonilha et al., 2007, Holton et al., 2008).

Up to 25% of patients with AOPTD may have affected relatives (Waddy
et al., 1991). Loci (DYT6, DYT7 and DYT13) have been mapped for families
which include members with AOPTD (Valente et al., 2001, Leube et al., 1996,
Almasy et al., 1997) and in several families, AOPTD has been excluded from
linkage to these known genetic loci (Uitti and Maraganore, 1993, Munchau et al.,
2000, Klein et al., 1998, Holmgren et al., 1995, Bressman et al., 1994b, Brancati
et al., 2002). The DYT6 locus has been fully characterised and is the only
autosomal dominant adult-onset form of primary torsion dystonia to have a gene,
which is positive in 25% of DYT1-negative multiplex families with the correct
phenotype—THAP1 (Fuchs et al., 2009, Bressman et al., 2009).

DYT6

The first of the adult-onset autosomal dominant primary dystonia families to be
described was a Mennonite family of German ancestry. Nine members from 120
examined were affected. It was multi-generational, with symptoms beginning
relatively early for the phenotypes (age of onset range 5-35 years). It was
predominantly cervico-brachial at onset, with spread over time to become
generalised in at least six cases, all of whom had facial involvement with
generalisation. One member had a sensory trick (Bressman et al., 1994c, Almasy
et al., 1997). A second large multiplex Menonite family with 100 contributing
family members and six definitely affected members had a similar phenotype. Onset was craniocervicobrachial, with an age of onset ranging from six to 38 years. Spread occurred in all six, and one developed generalised dystonia. Cranial muscles were affected in five cases eventually (face in four). Linkage to a candidate region on chromosome 8 was achieved. This was later confirmed by screening three Amish-Mennonite families with the identification of a gene, thanatos-associated protein 1 (THAP1) (Fuchs et al., 2009).

**DYT7**

The phenotype of this large multiplex German family was largely cervical dystonia. The pattern of inheritance was autosomal dominant and multi-generational, with one obligate carrier. Thirteen affected individuals were identified: seven definite and six possible. Eleven had cervical dystonia, one had spasmodic dysphonia and one had postural hand tremor. Two with cervical dystonia had Meige syndrome, and one had writer’s cramp. There was no spread or generalisation in any definitely affected person over time. The age of onset ranged from 28 to 70 years. Chromosome 18p was identified as the linkage site with maximum likelihood of disease (Leube et al., 1996, Leube et al., 1997).

**DYT13**

This locus was assigned to the moderately sized Italian family with highly penetrant autosomal dominant adult-onset dystonia. There were eleven affected family members with a predominant cranial-cervical onset that spread to become segmental or generalised in nine cases. Spread to the face occurred in seven. In two, spread occurred after their first pregnancy. The age of onset was five to 43
years. Jerkiness and tremor were seen in the neck and arms of six patients. A sensory trick was present in one patient. This kindred was found to have linkage to chromosome 1p36.13-36.32 (Bentivoglio et al., 2004, Valente et al., 2001).

*Multiplex autosomal-dominant AOPTD families with no loci*

Demonstration of linkage between a normal genetic trait and dystonia supports the inherited nature of dystonia, and clarifies the mode of inheritance. Linkage on single large pedigrees is optimal to reduce the masking effect of heterogeneity. Linkage analysis is most powerful through showing cosegregation of two closely associated alleles. LOD scores are calculated in any pedigree for predetermined alleles based on the odds ratio of probability of recombination versus non-recombination, where the recombination probability is calculated for a known genetic trait (e.g. ABO, Rh, etc.), or highly conserved region.

\[
\text{LOD}(\theta) = \log_{10} \left[ \frac{\text{Pr}(F; \theta)}{\text{Pr}(F;0.5)} \right], \quad F = \text{recombination information}
\]

A positive lod score favours linkage, and a value of >+3.0 is generally accepted as proof. However, genetic heterogeneity is always an issue, especially given non-paternity ranges from one to 20% in the general population (Alfred, 2002, Falk et al., 1988).

Hence there are many published multiplex families with adult-onset primary torsion dystonia and no loci. They are summarised in the table (next page).

Hereditary whispering dysphonia was assigned the *DYT4* locus. This was a large Australian pedigree, but not a primary torsion dystonia kindred. Multiple
family members had marked neuropsychiatric presentations, and two had definite
diagnoses of Wilson's disease, although later linkage to the Wilson's locus in
other members was negative (Ahmad et al., 1993, Parker, 1985).
<table>
<thead>
<tr>
<th>Publication</th>
<th>Ethnicity</th>
<th>Phenotype at Onset</th>
<th>Age of onset</th>
<th>Age at study</th>
<th>n=</th>
<th>Spread</th>
<th>Distribution</th>
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<tr>
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<td>Italian</td>
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<tr>
<td>Defazio et al, 2003 (a)</td>
<td>Italian</td>
<td>Craniocervical</td>
<td>-</td>
<td>40-71 y</td>
<td>3</td>
<td>-</td>
<td>Craniocervical</td>
</tr>
<tr>
<td>Casetta et al, 1999</td>
<td>Italian</td>
<td>Craniocervical</td>
<td>40-66 y</td>
<td>43-74 y</td>
<td>6</td>
<td>2</td>
<td>Craniocervical</td>
</tr>
<tr>
<td>Contarino et al, 2008</td>
<td>Dutch</td>
<td>Craniocervical</td>
<td>10-56 y</td>
<td>32-67 y</td>
<td>8</td>
<td>3</td>
<td>Craniocervical</td>
</tr>
<tr>
<td>Bressman et al, 1994</td>
<td>German</td>
<td>Craniocervical</td>
<td>7-50 y</td>
<td>38-75 y</td>
<td>7</td>
<td>7</td>
<td>Craniocervicobrachial</td>
</tr>
<tr>
<td>Bentivoglio et al, 1997</td>
<td>Italian</td>
<td>Craniocervical</td>
<td>5-40 y</td>
<td>32-71 y</td>
<td>8</td>
<td>6</td>
<td>Craniocervicobrachial</td>
</tr>
<tr>
<td>Klein et al, 1998</td>
<td>Italian</td>
<td>Cranialbrachial</td>
<td>4-40 y</td>
<td>41-89 y</td>
<td>6</td>
<td>6</td>
<td>Generalised</td>
</tr>
</tbody>
</table>

Table of published multiplex AOPTD families with no loci

*= non-Jewish
In summary, there are 23 published kindreds of AOPTD with no known loci. Twenty-two have onset involving the face, neck or arm. Spread of dystonic symptoms and signs occurred in eight of 13 families where it was documented. Only two families (Swedish and North Tyrol Italian) developed generalised dystonia. The sum of all familial PTD documented with spread was 30 out of 48 (63%) in this group. Spread, including \textit{DYT6}, \textit{DYT7} and \textit{DYT13} occurred in only cervical, cervicocranial and cervicobrachial types with 37 out of 68 (54%) affected by it. Where the age of onset was less than twelve years, the phenotype tended to be of leg onset in these pedigrees. Persons rated “probably affected” were not included in the table. (Bentivoglio et al., 1997, Brancati et al., 2002, Bressman et al., 1994b, Bressman et al., 1994c, Cassetta et al., 1999, Contarino et al., 2008, Defazio et al., 2003c, Defazio et al., 2003d, Defazio et al., 1993, Holmgren et al., 1995, Klein et al., 1998, Munchau et al., 2000, Uitti and Maraganore, 1993, Waddy et al., 1991)

1.2.6 Autosomal recessive dystonia and dystonia-parkinsonism

Two forms of autosomal recessive pure dystonia have been described – \textit{DYT2} and \textit{DYT17} (Chouery et al., 2008, Gimenez-Roldan et al., 1988, Khan et al., 2003). Furthermore, autosomal recessive dystonia-plus-like syndromes including the recessive form of dopa-responsive dystonia \textit{DRD5b (TH)} exist – \textit{DYT16 (PRKRA)}, adult-onset NBIA-2 (\textit{PLA2G6}), \textit{FBX07} associated parkinsonian-pyramidal syndrome, Kuför-Rakeb syndrome (\textit{PARK9/ATP13A2}), and juvenile-onset parkinsonism (Parkin, \textit{PINK1}, \textit{DJI}) (Camargos et al., 2008, Di Fonzo et al., 2007, Paisan-Ruiz et al., 2009, Schneider et al., 2009a, Williams et al., 2005).
DYT2

Six families have been reported with this disorder. The earliest dates back to 1934, but the following four relate to families of Spanish Gypsies. Nine patients were examined who had abnormal posturing of the feet and gait abnormalities followed by rapid generalisation of dystonia and stabilisation within a few years. The mean age of onset was 15 years (range 8-31). Three of the four families had consanguineous parents. One family’s dystonia phenotype was different, with prominent oromandibular dystonia and cervical dystonia, but little or no gait abnormalities. Action and rest myoclonic jerks were also seen in this kindred.

Sephardic Jews remaining in Spain after their general expulsion in the late 15th century mixed with the rest of the population to escape persecution, but Spanish Gypsies rarely mate outside their own ethnicity. Rates of dystonia are not known in Sephardic Jew descendants, but studies in Israel on the prevalence of dystonia among Jews of different backgrounds would suggest that all non-Afro-Asian Jews have much higher rates of dystonia (Korczyn et al., 1980). In any case, the commonest genetic cause of dystonia in American-European Jews is the autosomal dominant DYT1 gene.

An Iranian kindred was later found who were Sephardic Jewish, and in whom consanguineous marriage is common. The onset was between one and eight years, starting with intorsion of the foot and caudal-rostral progression over five to eleven year periods. Myoclonus was also a feature in two of the three in this sibship, and all had jerky torticollis. The dystonia was generally stable after the initial period of progression (Khan et al., 2003).
A Lebanese Shiite family with consanguineous parents had three sisters affected by dystonia in a sibship of nine. All three developed cervical dystonia in their teens, with later spread segmentally in two, and becoming generalised in one after nine years. All three had severe dysphonia and dysarthria. Neuroimaging was normal. A locus on chromosome 20 was found (20p11.22 – q13.12). No imprinting effect was suspected. They differed significantly in the phenotype to the DYT2 (leg onset), but with some overlap such as prominent craniocervical dystonia (Chouery et al., 2008).

Two Brazilian families and a single other patient, seven patients in total, with young-onset dystonia-parkinsonism were found to have mutations in the stress response protein, protein kinase interferon-inducible double-stranded RNA-dependent activator (PRKRA). There was no evidence of consanguineous marriage linking the two families. The single other patient had a brother who died aged 34 having suffered similar generalised dystonia. The age of onset was 2-12 years in six and 18 years in one. Dystonia began in the lower limbs in four, and in the hand in one. One patient developed bradykinesia in the hands as a first symptom, and another developed spasmodic dysphonia. Painful gait disturbance at onset was reported by two of the four with leg onset. Parkinsonism was present in four patients. Three had pyramidal signs, e.g. hyperreflexia. No significant improvement was seen with levo-dopa, anticholinergic or antispasticity medication. Cervico-brachial dystonia and spasmodic dysphonia were typically the most disabling features. Parkinsonism was notably
bradykinesia and freezing of gait in one. One patient reported a geste-antagoniste to alleviate his craniocervical dystonia. A single segregating homozygous variant (c.665C>T/P222L) in exon 7 or PRKRA (chromosome 2q31.3) was found in all family members and the other affected. Further testing on local dystonia patients, patients with young-onset parkinsonism and neurological controls was negative, suggesting that this is a rare mutation (Camargos et al., 2008).

The pathophysiology of PRKRA in DYT16 is unclear. It activates the latent protein kinase PKR under cellular stress circumstances, which in turn activates EIF2α, which inhibits protein synthesis. Whether the mutation causes a gain- or loss-of-function, and its significance in the pathogenesis of dystonia-parkinsonism remains to be elucidated.

Adult-onset NBIA-2
Three patients from two families have been identified as PLA2G6 (chromosome 22q12.3-13.1) mutation homozygotes, with symptoms of severe progressive dystonia, parkinsonism (including rest tremor in one), dementia, neuro-ophthalmological signs and spasticity. The age of onset was ten to 26 years. One had subacute parkinsonism and intellectual decline at onset, and two had leg onset dystonia followed by parkinsonism and dementia. Generalised dystonia occurred in all three patients within one to two years in two patients. MRI brain showed only subtle frontal white matter abnormality and no evidence of iron accumulation on T2* (gradient echo sequence). The investigators had originally included five families with the phenotype and consanguineous marriages of parents of affected patients, but two families showed no evidence of homozygosity, and a third showed no variation in PLA2G6.
PLA2G6 mutations cause Infantile Neuroaxonal Dystrophy (INAD), a disease typically that begins before age three years, and typically fatal by age seven. INAD produces iron deposition and a PKAN-like disease, hence its NBIA-2 designation. However, the “eye of the tiger” sign does not appear because although the GPi has hypointensity on T2W MRI, there is no central hyperintensity giving the eye-like appearance on axial slices. Skin biopsy typically shows neuronal spheroids in INAD, but there was no evidence of this in the adult-onset form above.

Kufor-Rakeb syndrome/PARK9
Characterised by pallidopyramidal degeneration, supranuclear gaze paresis and dementia, this syndrome first described in a Jordanian consanguineous family also has some typical dystonia with oculogyric crises, visual hallucinations and facial-facial-finger (FFF) minimyoclonus. Kufor-Rakeb is a small homestead in the northern Jordanian highlands. Disease onset was between 12 and 15 years. Oculogyric spasms were associated with the onset of profound parkinsonism in three of four patients examined. They were independent of levo-dopa. They also have an excellent but waning levo-dopa response, but suffered peak dose dyskinesias. Continuous jerky movement of the face, tongue/posterior oropharynx and fingers was noted in all four patients (FFF). Supranuclear gaze palsy was present for horizontal and vertical gaze, and slowed saccades were most evident for vertical gaze. All had markedly increased tone, hyperreflexia, and extensor plantar responses. There was also significant rigidity and bradykinesia but no tremor. None had cerebellar signs. MRI scanning in two
patients showed widespread atrophy but no focal abnormality or signal change (Williams et al., 2005).

A large non-consanguineous Chilean family with Kufor-Rakeb phenotype was analysed, and identified a loss-of-function mutation in the predominantly neuronal P-type ATPase gene, *ATP13A2* (chromosome 1p). Mutations in the same gene were found in the Jordanian family in all affected family members (Ramirez et al., 2006). *ATP13A2* is ubiquitously expressed in the body, but strongest in the brain. Using quantitative real-time PCR experiments on total RNA, it was shown that *ATP13A2* expression is almost five times higher in ventral tegmental substantia nigral dopaminergic neurons than other candidate regions (Gpi, putamen, cerebellum, neocortical areas). *ATP13A2* is upregulated in idiopathic parkinson’s disease dopaminergic neurons by as much as ten-fold. Interestingly, *ATP13A2*’s function is most important in the lysosomal degradation pathway for proteolysis (c.f. proteosomal pathway most associated with monogenic parkinson’s disease – *PARK2*).

1.2.7 Dystonia-plus syndromes

There exists a group of dystonias with other neurological features, frequently with a biochemical abnormality, but differing from the heredodegenerative group in that no uniformly occurring structural neuronal degeneration occurs. These are the dystonia-plus syndromes - dopa-responsive dystonia (*DYT5a & b/GCH1 & TH*), myoclonus dystonia (*DYT11/SGCE*), rapid-onset dystonia parkinsonism (*DYT12/ATPIA3*), myoclonic dystonia (*DYT15*), and X-linked dystonia-parkinsonism “Lubag” (*DYT3/TAF1*) (Nygaard et al., 1993, Dobyns et al., 1993, Pittock et al., 2000, Grimes et al., 2001, Kurlan et al., 1988, Quinn et al., 1988).
Dopa-responsive dystonia

This clinical syndrome of childhood-onset dystonia and a dramatic sustained levo-dopa response was first described in 1971 (Castaigne et al., 1971, Furukawa, 2004). It has three forms: one autosomal dominant guanine triphosphate cyclohydrolase 1 (GCH1 – chromosome 14q22.1-2) deficiency, and rarer autosomal recessive tyrosine hydroxylase deficiency and sepiapterin reductase deficiency (Clot et al., 2009). The onset is approximately six years of age (range 1-12 years) and the clinical features are typically of progressive lower limb dystonia, spasticity and parkinsonism. Eighty-five percent of patients with the autosomal dominant form have onset in the first decade of life (Clot et al., 2009). Segregation analysis suggests a higher penetrance in women compared to men (2:1 – 3:1), but the disease appears similar in severity for both sexes (Tagliati et al., 2004). Cognitive function is normal throughout the course of the disease. Diurnal fluctuations, an important clue in the history, occur in 77% of cases. The feet are often held in an equinovarus posture. Patients tend to fall on standing, and compensate with an exaggerated lumbar lordotic posture, and often maintain a short stature when symptoms begin in childhood (Segawa et al., 2004). Parkinsonism with fatiguability on repetitive movement and mild general increased tone is often seen. A striatal toe is also found characterised by extension of the great toe. When tremor is the presenting symptom, it is usually after the second decade (Segawa et al., 2004). Myoclonus has also been reported in DRD, causing diagnostic confusion (Leuzzi et al., 2002). Cerebellar signs have been found also in DRD with gaze evoked nystagmus and moderate gait ataxia (Chaila et al., 2006).
The syndrome arises due to striatal $GCH1$'s rate limiting effect on the production of tetrahydrobiopterin, an essential cofactor for tyrosine hydroxylase. This leads to lower levels of dopamine synthesis. Severe forms of DRD are seen in homozygotic mutations involving tyrosine hydroxylase (not the autosomal recessive variant which is a deficiency of $TH$) and 6-pyruvoyltetrahydropterin synthase. One patient with a $PARK2$ mutation was identified in a large DRD-phenotype screening series, and three of twenty-two families with levo-dopa responsive dystonia in another study (Clot et al., 2009, Tassin et al., 2000). The clinical spectrum of the DRD has expanded to include focal dystonia (cervical and oromandibular), adult-onset parkinsonism, postural tremor and myoclonus, and exercise induced dystonia (Harwood et al., 1994, Nygaard et al., 1992, Steinberger et al., 1999, Tassin et al., 2000). A family history or suspicion of parkinsonism may be a helpful clue as it is present in 14% of first-degree relatives over 40 years of age (Bandmann et al., 1998). Infantile parkinsonism is the primary presentation of tyrosine hydroxylase form (Mueller, 2003, Nardocci et al., 2003). In contrast to idiopathic Parkinson's disease patients, DRD patients do not develop late complications of levo-dopa treatment.

Myoclonus dystonia

This rare movement disorder characterised by a combination of myoclonus and dystonia was first described under many guises including hereditary essential myoclonus, paramyoclonus multiplex, and essential myoclonia, but one of the key features has been frequent family history and responsiveness to alcohol (Asmus and Gasser, 2004, Gasser, 1998). Semantics overlap considerably in this area, and it should be noted that myoclonic dystonia (cf. myoclonus dystonia)
refers to dystonia with focal/segmental myoclonus affecting the same area which has been observed in primary dystonia (Kurlan et al., 1988, Obeso et al., 1983, Quinn et al., 1988). True myoclonus dystonia accounts for 37% of all children seen by specialists in a pediatric movement disorders clinic, with the remainder including benign hereditary chorea, myoclonic dystonia, and dystonia with polyminimyoclonus (Asmus et al., 2009).

In myoclonus-dystonia, myoclonus is typically the most disabling feature, predominating in the arms (found in 88%) and axial muscles (Asmus and Gasser, 2004). Dystonia is often mild (54%), may remit, and is rarely the only manifestation when it is typically writer’s cramp or less frequently cervical dystonia (Kyllerman et al., 1993, Saunders-Pullman et al., 2002). The onset is typically in the first or second decade (mean 4 years, range 0.5–20), but can occur as late as 75 years (Foncke et al., 2006).

A mutation in the epsilon sarcoglycan gene (SGCE) has been found in only 30–50% of clinically definite myoclonus-dystonia cases (Valente et al., 2005, Tezenas du Montcel et al., 2006, Ritz et al., 2009). SGCE is a twelve exon gene, widely expressed in embryonic and adult tissues of the nervous system, localises to chromosome 7q21. It is predominantly paternally inherited with 10–15% due to maternal imprinting and a case report (Silver-Russell syndrome) of imprinting in maternal uniparental disomy (Zimprich et al., 2001, Klein et al., 2000, Guettard et al., 2008). Refined techniques to include detection of large exon deletions in clinically definite and probable myoclonus-dystonia increases SGCE mutation yield to 36% (Grunewald et al., 2008, Asmus et al., 2005). In children who have only movement related myoclonus and early gait disturbance with falls, 88% were found to have mutations in SGCE (Asmus et al., 2009). In
another study, 80% of families had mutations in \textit{SGCE} where children under the age of twelve years were all the affected members (Nardocci et al., 2008). Additional manifestations have been reported with myoclonus-dystonia, including complex partial seizures and psychiatric disturbances. Using a candidate gene approach, one group identified that a \textit{DRD2}-gene polymorphism (Val154Ile) was seen in a large kindred of Welsh-Scottish-German ancestry (Klein et al., 1999). This receptor’s importance in affect, emotion and reward behaviour links it to alcoholism and schizophrenia. In manifesting and non-manifesting carriers of \textit{SGCE} mutations, alcohol-abuse and alcohol dependence were over twice as common (40% and 25.9%) compared to non-carriers in families with myoclonus-dystonia (Saunders-Pullman et al., 2002). Obsessive-compulsive disorder (OCD) was present in 18.5% of carriers compared to none of the non-carriers ($p = 0.023$). Eighty percent of individuals with OCD were symptomatic for myoclonus-dystonia. Depression, panic attacks, and cognitive slowing have been reported by several authors. Co-existence of myoclonus-dystonia and Gille de la Tourette syndrome (OCD with motor tics is more prevalent in Tourette’s families with motor tics) has not been associated with \textit{SGCE} mutations, and there is no association with \textit{SGCE} mutations in patients with OCD and Gille de la Tourette syndrome (de Carvalho Aguiar et al., 2004a, Orth et al., 2007, Gorman, 2000). Another large Canadian family with myoclonus dystonia has been described that has alcohol responsiveness and linkage to chromosome 18p11. This new locus, \textit{DYT15}, has reduced penetrance of 85% (Grimes et al., 2001, Grimes et al., 2002).

There is no aetiological treatment, and symptomatic therapy of myoclonus-dystonia is modest. Benzodiazepines, anticholinergics, levo-dopa,
serotomimetic drugs, and antiepileptic drugs have been used. Myoclonus may benefit from levetiracetam, piracetam and zonisamide (Kinugawa et al., 2009). Benefit from alcohol has not yet been translated into a safe pharmaceutical option. Deep brain stimulation of the GPi and thalamic VIM have been reported as beneficial to both myoclonus and dystonia (Cif et al., 2004, Castelnau et al., 2005).

Rapid-onset Dystonia Parkinsonism

First described in 1993, it begins over hours or days with striking bulbar features of dysarthria (even as severe as mutism) and dysphagia, and limb dystonia and bradykinesia (Dobyns et al., 1993, Brashear et al., 1998). The extrapyramidal features are typically asymmetrical, and have a characteristic rostro-caudal gradient or face>arm>leg (Brashear et al., 2007). There is no dementia, normal eye movements, and no pyramidal or sensory signs. The severity of the phenotype varies even within families. Onset is typically in the late teens (range 4-58 years), often after a striking physiological stressor, e.g. prolonged exercise or childbirth. Progression is usually limited over a couple of weeks, usually with little or no improvement except sometime with gait (Brashear et al., 2007). Second abrupt exacerbations are reported in a several cases (Dobyns et al., 1993, de Carvalho Aguiar et al., 2004b, Pittock et al., 2000). Seizures, paroxysmal dystonia and psychiatric disturbances including depression, social anxiety and schizoid personality disorder have been observed in these patients. Neuroimaging is normal, an early suggestion that disease is a functional defect and not structural (Mueller, 2003).
Linkage to chromosome 19 (19q13) was possible in three large families, and later identification of the gene \((ATP1A3)\) as the \(\text{Na}^+/\text{K}^+\)-ATPase-\(\alpha3\) subunit (Kramer et al., 1999, de Carvalho Aguiar et al., 2004b). Subsequent analysis of the phenotypic spectrum of rapid-onset dystonia parkinsonism and the association with the genetic discovery showed that abrupt onset, rostrocaudal gradient and bulbar symptoms were the most reliable features (Brashear et al., 2007). A second locus has been proposed to explain typical presentations of familial cranial-cervical dystonia that are mutation negative, possibly also in the same pump’s \(\alpha2\) subunit (Kabakci et al., 2005). Mutations of \(ATP1A2\) gene have been linked to other disorders in the central nervous system: infantile seizures, familial hemiplegic migraine and familial common migraine (Vanmolkot et al., 2003, Todt et al., 2005).

Levo-dopa may occasionally have some modest benefit. Other treatment is aimed at seizure control, management of depression and anxiety, avoidance of stressors and relaxation therapy. Unilateral pallidotomy and GPi deep brain stimulation has been tried on two patients with no success (Pittock et al., 2000, Deutschlander et al., 2005).

**X-linked dystonia-parkinsonism “Lubag”**

This disorder is an adult-onset dystonia originating in the Phillipine islands of Luzon and Panay (Lee et al., 1991). About 1/4,000 males on the island of Panay. The name “Lubag” comes from the local Ilonggo dialect, referring to intermittent twisting movements. Fahn and Müller argue that this disorder should be included as a dystonia-plus syndrome and not heredodegenerative or secondary because neuropathological features are seen in other dystonia-predominant genetic
disorders such as *DYT1* (brainstem inclusions) and *DYT5* (mild nigral neuronal loss). It is classified as a dystonia-plus disorder in some major texts (Fahn and Ford, 2003, de Yebenes et al., 2004), but not others (Jankovic and Lang, 2004).

X-linked dystonia-parkinsonism starts focally between 30 and 45 years, and generalises after six years in most cases (Mueller, 2003). Symptom onset is in the lower extremities in 36%, axially in 29%, arms in 23% and cranially in 12%. Over 90% have a dystonic-parkinsonian gait, and 88% have generalised dystonia. The disease is so severe that virtually all patients are dependent and 13% are entirely dependent for all activities of daily living. Parkinsonism is seen in 36% of patients. Occasionally, female carriers have been described with mild dystonia and chorea (Waters et al., 1993b). Despite its severity, all dystonic and parkinsonian feature disappeared altogether during sleep in all patients.

Neuroimaging studies have shown mild atrophy on CT and MRI. Neuropathological changes have been found with neuronal loss and subtle astrocytosis in the caudate and severe gliosis in the lateral putamen (Waters et al., 1993a). These changes however are not specific and had been described in a non-Filipino man.

Disease-specific single-nucleotide changes (five) were found in the long arm of the X-chromosome in all Filipino affected men and no controls (Nolte et al., 2003). The region covers multiple transcripts in the TATA-box-binding-protein-associated factor (*TAFI*) gene, but an exon 4 base change is most likely pathogenetic in the disease. However, the exact nature of the functional change is unclear, also due to the complex interaction of overlapping genes on the antisense strand in this region. The molecular effect may result in disturbed regulation of other genes in the corpus striatum, including expression of *DRD2*.
(Makino et al., 2007). It has been estimated based the rates of natural mutations in single nucleotide polymorphisms (0.001-0.01/gamete) that the founder mutation occurred between one and two thousand years ago (Wilhelmsen et al., 1998).

Treatment is difficult, but patients may benefit from anti-cholinergics, clonazepam and zolpidem. Focal dystonia can be treated with botulinum neurotoxin injection (Muller, 2009). One 45 year old Filipino has been reported to have benefited from bilateral posterventral GPi deep-brain stimulation, who had previously had very medically refractory disabling jaw dystonia (Evidente et al., 2007).

1.3.8 Paroxysmal dyskinesias

Paroxysmal dyskinesias were often diagnosed as epilepsy in the past. They include dystonia, chorea, athetosis and ballism. They are part of a group of paroxysmal movement disorders which also encompasses hypnogenic dyskinesias, episodic ataxias and transient dyskinesias of infancy (Fahn, 2002). Mount and Reback first proposed these types of attack as paroxysmal movement disorders in 1940, and their first description was called “familial paroxysmal choreoathetosis”, now recognised as paroxysmal non-kinesigenic dyskinesia (PNKD). Despite the original nomenclature, this and the other paroxysmal dyskinesiae are symptomatically dystonic syndromes (Mark, 2004). Many secondary causes of paroxysmal dyskinesia have been reported including multiple sclerosis (25%), transient ischaemic attack (21%), trauma (13%), stroke (9%, with latency up to 6 years), hypo/hyperglycaemia (10%), CNS infection
(7%), anoxic brain injury (4%), hypocalcaemia (3%) and GLUT1-deficiency (Blakeley and Jankovic, 2002, Schneider et al., 2009b).

Six paroxysmal dyskinesia loci have been assigned: DYT8, DYT9, DYT10, DYT18, DYT19 and DYT20. However, DYT19 and DYT20 share closely overlapping regions to DYT10 and DYT8 respectively, and have similar kinesigenic and non-kinesigenic phenotypes (Muller, 2009).

Paroxysmal non-kinesigenic dyskinesia/DYT8

The attacks are characterised by sudden onset of sustained abnormal postures which can be focal affecting the hands, cranial muscles, cervical muscles and causing dysarthria or mutism. The trunk and legs can also be affected, with hyperextension, or flexion, sometimes alternating. Minor focal abnormal postures such as abduction of the little finger have been reported as an attack. Attacks may be highly stereotyped only affecting one area, e.g. the hand. Consciousness is not lost. Onset is between two months and 50 years, and it does tend to plateau or improve over a median of six years.

Attacks are typically precipitated by alcohol, caffeine, stress, resting or occur on awakening. They happen between daily and several times a year but in contrast to paroxysmal kinesigenic dyskinesia, they last on average an hour, or up to several days (Bressman et al., 1988). Fixed focal dystonia has been seen in several cases. Up to 41% of patients have premonitory symptoms before an attack, such as focal stiffening in a limb (80%) or inner feeling of anxiety (Bruno et al., 2007). Neuroimaging is typically normal. PNKD is caused by mutations in PNKD1 gene (chromosome 2), coding for myofibrillogenesis regulator 1 protein (Muller, 2009). It is a stress response protein, but its exact function and
pathogenesis in PNKD is unknown (Bruno et al., 2007). Treatment response is best with benzodiazepines, acetazolamide, haloperidol and avoidance of triggers. Anticholinergics are useful for the dystonic features in PNKD.

**Paroxysmal dystonia choreoathetosis with episodic ataxia and spasticity/DYT9**

This autosomal dominant multisystem syndrome presents with brief attacks of extrapyramidal or cerebellar symptoms lasting from minutes to days. The age of onset should be before puberty but reports range from two to 15 years. Complaints are of dystonic toe curling, choreoathetoid movements of the limbs, imbalance, dysarthria, and paraesthesia periorally and in the legs. Diplopia can occur, and headache is also reported to happen concurrently or after an attack. Attacks last ~20 minutes and happen between twice a day and twice annally. Triggers for attacks include physical exercise, emotional stress, lack of sleep, and alcohol. Almost one third of patients have evidence of spastic paraplegia on examination (increased tone, hyperreflexia and pyramidal weakness). Linkage to chromosome 1p21-p13.3 has been achieved (Auburger et al., 1996). Treatment is limited but acetazolamide and phenytoin may have a beneficial effect.

**Paroxysmal kinesigenic dyskinesia/DYT10**

Paroxysmal kinesigenic dyskinesia (PKD) is precipitated by sudden movements, but also by stress, menstruation, temperature changes, startle, excitement or hyperventilation (Jankovic and Demirkiran, 2002, Mark, 2004). Attacks begin typically in childhood and diminish with age (0.5-57 years). They last less than two minutes, but rarely up to five minutes or more. They can occur with a frequency of up to 100 per day, or as infrequently as monthly. Typical attacks are
unilateral or asymmetrical, but midline muscles may become involved. Some patients have a sensory aura such as muscle tension, paresthesia, or a formication-like sensation. It is more common in males with a ratio of up to 4:1.

Most PKD is sporadic, but familial incidence is autosomal dominant with reduced penetrance. A disease locus has been assigned to chromosome 16p11.2-q12.1. This locus overlaps with that for infantile convulsions with choreoathetosis (ICCD). PKD in families with ICCD is not always kinesigenic though. Another locus has also been mapped in this region based on a large Indian family, which does not overlap with ICCD, possibly meaning that two distinct genes could be responsible (Valente et al., 2000).

Treatment is with anti-convulsants, particularly carbamazepine or phenytoin, or even levodopa, flunarizine and tetrabenazine. However, in some cases the attacks abate in early adulthood.

Paroxysmal exercise-induced dyskinesia/DYT18

Attacks are triggered by prolonged exertion (5-15 minutes). Other precipitants are passive limb movement, talking, chewing gum, temperature changes, menses, alcohol and stress. Attacks can occur twice a day to monthly. Attack duration is intermediate between PNKD and PKD – usually five to 30 minutes. They usually only involve the legs, and rarely other body parts. Attacks can be jerky twitches in the legs or hemidystonia. Limbs can appear discoloured and cold during attacks. Premonitory symptoms are unusual in this disorder. Onset is between two and 30 years.

Paroxysmal exercise-induced dyskinesia is the PD most frequently associated with other neurological paroxysmal disorders, including childhood
epilepsy, migraine and hemiplegic migraine (Schneider et al., 2009b). Recent identification of the SLC2A1 gene (chromosome 1p35-31.1) in this disorder and its importance in the GLUT1 transporter have important therapeutic implications (Muller, 2009). PED patients with the SLC2A1 mutation more often have a history of slight developmental delay, epilepsy and slight haemolytic anaemia (Weber and Lerche, 2009). Paediatric GLUT1 deficiency syndrome is characterised by severe epilepsy, microcephaly, and developmental delay. The ketogenic diet is very satisfactory in the treatment of GLUT1 disorders. The locus for this is very close to DYT9, and the phenotype is remarkably similar (exercise induced dyskinesia, headache).

1.2.9 Heredodegenerative dystonia

Encompassing a very extensive group of inherited disorders, they are neurodegenerative diseases that often produce dystonia as a prominent feature, but are progressive and generally have many other extrapyramidal, cognitive, pyramidal, sensory, visual, auditory, bulbar, psychiatric and systemic features. Based on specialist clinic series, 23-25% of all dystonia seen is secondary excluding tardive dystonia (Ferraz and Andrade, 1992, Marsden, 1988). However, since dystonia may be the presenting feature or the most prominent symptom at presentation, these disorders must be borne in mind when seeing the patient with apparent pure dystonia. In this section, selected syndromes are outlined in a table listing the commonly recognised disorders, grouped according to the pattern of inheritance showing X-linked, autosomal dominant, autosomal recessive, mitochondrial, metabolic disorders and some miscellaneous disorders. Importantly, where dystonia is not a major feature or presenting feature of an
illness, that illness has not been included in this list (table of heredodegenerative causes of dystonia), e.g. McLeod neuroacanthocytosis (Danek et al., 2001).

**Dystonia in idiopathic parkinson's disease and parkinson's-plus disorders**

Disorders associated with Parkinsonian syndromes may have dystonia as the presenting symptom. Dystonic presenting features seen in all four major syndromes: idiopathic parkinson’s disease (parkinsonian writer’s cramp/kinesigenic foot dystonia), progressive supranuclear palsy (retrocollis/apraxia of eyelid opening), multiple system atrophy (antecollis/laryngeal dystonia/Pisa syndrome) and corticobasal ganglionic degeneration (hand dystonia) (Boesch et al., 2002, Poewe et al., 1988, Vanek and Jankovic, 2001, Tolosa and Compta, 2006, Hozumi et al., 2004).

Dystonia is reported as a presenting symptom in 2.4% and in up to 30% during the course of the illness in idiopathic parkinson’s disease (IPD) patients (Kidron and Melamed, 1987). Cervical dystonia (rotatocollis and retrocollis) has been described as the presenting feature in several patients with IPD (Papapetropoulos and Singer, 2006).

Dystonia is common in parkinson’s plus disorders. In a large multicentre German study, 68% of multiple-system atrophy (MSA) patients and 77% of progressive supranuclear palsy (PSP) developed dystonia during their illness. In MSA, truncal dystonia was present in 31%, lower limb dystonia in 29%, cervical dystonia (antecollis) in 26%, facial dystonia in 24% and upper-limb dystonia in 21%. Pisa syndrome was the first manifestation of dystonia in 9.5% of the MSA cohort.
In PSP patients, cervical dystonia was present in 56% (retrocollis/torticollis), truncal dystonia in 49%, facial dystonia in 49%, upper limb dystonia in 51%, lower limb in 44%. Upper limb or multifocal dystonia were the most common presenting types of dystonia in PSP (Schrader et al., 2005).

In a separate study on corticobasal ganglionic degeneration (CBD), dystonia was present in 59% of patients. The onset was in the upper limb in 51% and lower limb in 33%. In those CBD patients with dystonia, at least one arm was affected in 92%. Axial and craniofacial dystonia affected 31%, and laterocollis was the most frequent type of cervical dystonia (18%), but typically associated with limb dystonia (c.f. post-traumatic cervical dystonia). Pain was common (42%), particularly with hand dystonia (Vanek and Jankovic, 2001).
<table>
<thead>
<tr>
<th>Disorder and Inheritance</th>
<th>Gene</th>
<th>Type of dystonia</th>
<th>Age at onset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>X-linked recessive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelizaeus-Merzbacher disease</td>
<td>PLP</td>
<td>Segmental, Generalised</td>
<td>0-5 years</td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome</td>
<td>HPRT</td>
<td>Action dystonia, Opisthotonus</td>
<td>0.5-1 year</td>
</tr>
<tr>
<td>Partington's syndrome</td>
<td>ARX</td>
<td>Episodic hand</td>
<td>Childhood</td>
</tr>
<tr>
<td>Rett's syndrome</td>
<td>MECP2</td>
<td>Lower limb, Oculogyria</td>
<td>0.5-2 years</td>
</tr>
<tr>
<td>Mohr-Tranebjaerg syndrome</td>
<td>TIMM8A</td>
<td>Focal, Generalised</td>
<td>Adolescence</td>
</tr>
<tr>
<td><strong>Autosomal dominant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huntington's disease*</td>
<td>IT15</td>
<td>Cervical, Axial, Limbs</td>
<td>Often &lt;20 years*</td>
</tr>
<tr>
<td>Machado-Joseph disease (SCA3)*</td>
<td>ATXN3</td>
<td>Hands, Feet, Cranio cervical</td>
<td>5-30 years*</td>
</tr>
<tr>
<td>Dentato-rubro-pallido-luysian atrophy*</td>
<td>ATN1</td>
<td>Cervical, Axial, Limbs, Generalised</td>
<td>1-67 years*</td>
</tr>
<tr>
<td>SCA2*</td>
<td>ATXN2</td>
<td>Cervical, Generalised</td>
<td>6-67 years*</td>
</tr>
<tr>
<td>SCA6*</td>
<td>CACNA1A</td>
<td>Limb, Cranial</td>
<td>19-&gt;55years*</td>
</tr>
<tr>
<td>Spastic paraplegia with dystonia</td>
<td>2q24</td>
<td>Limbs, Generalised</td>
<td>Childhood</td>
</tr>
<tr>
<td>SCA12</td>
<td>PPP2R2B</td>
<td>Axial</td>
<td>8-55 years</td>
</tr>
<tr>
<td>SCA14</td>
<td>PRKCG</td>
<td>Cervical, Limbs</td>
<td>10-59 years</td>
</tr>
<tr>
<td>SCA17*</td>
<td>TBP</td>
<td>Cranial, Limb, Segmental</td>
<td>10-69 years*</td>
</tr>
<tr>
<td>Fahr's disease</td>
<td>14q</td>
<td>Cervical, Generalised</td>
<td>Adult</td>
</tr>
<tr>
<td>Huntingon's disease-like 2*</td>
<td>JPH3</td>
<td>Orafacial</td>
<td>20-45 years*</td>
</tr>
<tr>
<td>Neuroferritinopathy</td>
<td>FTL</td>
<td>Orafacial, Dysarthrophonia, Generalised</td>
<td>Adult</td>
</tr>
<tr>
<td><strong>Autosomal recessive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>ATP7B</td>
<td>Limbs, Trunk</td>
<td>6-40 years</td>
</tr>
<tr>
<td>Hallervorden-Spatz (PKAN/NBIA-1)</td>
<td>PANK2</td>
<td>Generalised, Oro mandibular</td>
<td>1-6 years</td>
</tr>
<tr>
<td>HAR syndrome</td>
<td>PANK2</td>
<td>Generalised, Orofacial</td>
<td>Childhood</td>
</tr>
<tr>
<td>Levine-Critchley (neuro acanthocytosis)</td>
<td>VPS13A</td>
<td>Orofacial, Feeding Dystonia</td>
<td>16-40 years</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>ATM</td>
<td>Generalised, Focal, Segmental, Axial</td>
<td>Childhood</td>
</tr>
<tr>
<td>Ataxia with Vitamin E deficiency</td>
<td>TTPA</td>
<td>Focal (rostral-caudal spread), Generalised</td>
<td>8-12 years</td>
</tr>
<tr>
<td>HSP with leukodystrophy and dystonia</td>
<td>FA2H</td>
<td>Trunk, Limbs, Face</td>
<td>4-6 years</td>
</tr>
<tr>
<td>Kjellin syndrome (SPG15)</td>
<td>ZFYVE26</td>
<td>Focal</td>
<td>5-23 years</td>
</tr>
<tr>
<td>Troyer syndrome (SPG20)</td>
<td>13q12.3</td>
<td>Limbs</td>
<td>Childhood</td>
</tr>
<tr>
<td>Juvenile parkinsonism (PARK2)</td>
<td>PRKN</td>
<td>Foot (5-42% @ onset)</td>
<td>7-40 years</td>
</tr>
<tr>
<td>Juvenile parkinsonism (PARK6 &amp; 7)</td>
<td>PINK1 &amp; DJ-1</td>
<td>Foot (0-17% @ onset)</td>
<td>17-52 years</td>
</tr>
<tr>
<td>Infantile bilateral striatal necrosis</td>
<td>np62</td>
<td>Generalised</td>
<td>0.5-1.5 years</td>
</tr>
<tr>
<td>Cockayne syndrome</td>
<td>CSA,B</td>
<td>Foot, Generalised</td>
<td>1-5 years</td>
</tr>
</tbody>
</table>

Outline of Heredodegenerative disorders causing dystonia

* = triplet repeat disorders showing genetic anticipation
**Other clinical findings**

- Head nodding, nystagmus, progression to death in 2nd decade
- Self-mutilation, developmental delay, gout (late)
- Mild/moderate mental retardation, contractures
- Aphasia, hand-wringing, intractable seizures
- Deafness, optic neuropathy, ataxia, dysphagia
- Chorea, rigidity, bradykinesia
- Spasticity, exophthalmos, facial fasciculations
- Chorea, ataxia, dementia, myoclonic seizures
- Slow saccades, ataxia, polyneuropathy, dysarthria
- Ataxia, nystagmus, usually slow progression
- Spasticity in legs
- Tremor, gait ataxia, dysarthria
- Gait ataxia, myoclonus, tremor
- Ataxia, dementia, extensor plantars, chorea, abnormal saccades
- Psychiatric, parkinsonism, chorea, tremor, orofacial dyskinesia
- African origin, dementia, chorea, parkinsonism, acanthocytes
- Asymmetry of signs, chorea, dementia, behavioural changes, dysphagia
- Liver disease, psychiatric, Kayser-Fleischer rings
- Chorea, parkinsonism, spasticity, seizures, retinitis pigmentosa
- As PKAN with acanthocytosis, hypobetalipoproteinemia
- Chorea, acanthocytes, behavioural changes, neuropathy, lip biting, high CPK
- Ataxia, oculomotor apraxia, lymphoproliferative disorders
- Pigmentary retinopathy, areflexia, titubation, ataxia, posterior column loss
- Spasticity in legs, ataxia
- Tetraparesis, dementia, distal amyotrophy, pigmented maculopathy
- Spastic tetraparesis, dysarthria, distal amyotrophy
- Young-onset PD, L-dopa dyskinesia, hyperreflexia, psychiatric, DRD phenotype
- Young-onset PD, L-dopa dyskinesia, sleep benefit
- Choreoathetosis, pendular nystagmus, optic atrophy, tetraparesis
- Cachectic (loss of subcutaneous fat) dwarfism, cutaneous photosensitivity

**Neuroimaging**

- CNS hypomyelination
- Mild caudate atrophy, thickened calvarium
- Normal
- Parietal cortical atrophy, frontopolar atrophy
- General brain atrophy
- Caudate atrophy
- Large 4th ventricle
- Brainstem and cerebellar atrophy
- Pontine atrophy, cerebellar atrophy
- Cerebellar atrophy
- Normal
- Cortical and cerebellar atrophy
- Cerebellar vermis atrophy
- Cerebellar vermis atrophy
- CT calcification in dentate, thalami, putamen
- Caudate & putaminal atrophy, generalised atrophy
- Low signal diffusely (T2W MRI), striatal cysts
- Putaminal lesions
- "Eye of the Tiger" sign (T2W MRI)
- Eye of the Tiger sign (T2W MRI)
- Caudate atrophy
- Cerebellar atrophy (no X-radiation)
- Cerebellar atrophy
- Demyelination
- Cerebral and brainstem atrophy
- Temporoparietal periventricular change
- Normal
- Normal
- Striatal atrophy, putaminal high signal (T2W)
- Basal ganglia calcification, white matter change
<table>
<thead>
<tr>
<th>Disorder and Inheritance</th>
<th>Gene</th>
<th>Type of dystonia</th>
<th>Age at onset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amino acid disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutaric acidemia type 1</td>
<td>GCDH</td>
<td>Generalised</td>
<td>Childhood</td>
</tr>
<tr>
<td>Methylmalonic acidemia</td>
<td>MUT, MMA</td>
<td>Generalised</td>
<td>Childhood</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>CBS, MTHFR</td>
<td>Generalised</td>
<td>Childhood</td>
</tr>
<tr>
<td>Hartnup disease</td>
<td>SLC6A19</td>
<td>Generalised, Paroxysmal</td>
<td>Childhood</td>
</tr>
<tr>
<td>Tyrosinaemia type 1</td>
<td>FAH</td>
<td>Opisthotonus</td>
<td>Childhood</td>
</tr>
<tr>
<td>Sulfite oxidase deficiency (molybdenum CF)</td>
<td>SUOX</td>
<td>Generalised, Opisthotonus</td>
<td>Infantile</td>
</tr>
<tr>
<td>Guanidinoacetate methyltransferase</td>
<td>GAMT</td>
<td>Generalised, Limb</td>
<td>Childhood</td>
</tr>
<tr>
<td><strong>Lipid disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>ARSA, PSAP</td>
<td>Generalised</td>
<td>Childho</td>
</tr>
</tbody>
</table>
### Other clinical findings

<table>
<thead>
<tr>
<th>Neuroimaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontotemporal atrophy</td>
</tr>
<tr>
<td>Acute encephalopathy</td>
</tr>
<tr>
<td>Focal deficits, mental retardation, ectopia lentis</td>
</tr>
<tr>
<td>Encephalopathic crisis, mental retardation</td>
</tr>
<tr>
<td>Mental retardation</td>
</tr>
<tr>
<td>Acute encephalopathy</td>
</tr>
<tr>
<td>Focal deficits, mental retardation, ectopia lentis</td>
</tr>
<tr>
<td>Failure to thrive, dementia, recurrent ataxia, photosensitivity</td>
</tr>
<tr>
<td>Peripheral neuropathic crises with pain, somnolence, paralysis</td>
</tr>
<tr>
<td>Axial hypotonia, intractable seizures, myoclonus, hyperekplexia, dysmorphic</td>
</tr>
<tr>
<td>Intellectual impairment, epilepsy, complex movements, ballism</td>
</tr>
<tr>
<td>Dementia, psychiatric symptoms, seizures, peripheral neuropathy</td>
</tr>
<tr>
<td>Dementia, ataxia, epilepsy</td>
</tr>
<tr>
<td>Supranuclear palsy, ataxia, dementia, dysarthria, splenomegaly</td>
</tr>
<tr>
<td>Ataxia, spasticity, parkinsonism, dementia</td>
</tr>
<tr>
<td>Ataxia, dysarthria, tremor, psychiatric disturbance, infantile fatal &lt;2y</td>
</tr>
<tr>
<td>Optic atrophy/amaurosis, progressive spastic para/tetraparesis, neuropathy</td>
</tr>
<tr>
<td>Hemolytic anaemia, leg spasticity, hypotonia, jerky intention tremor</td>
</tr>
<tr>
<td>Hyperekplexia, hypertonia, ptosis, apnoic spells, dysautonomia</td>
</tr>
<tr>
<td>Axial hypotonia, failure to thrive, microcephaly, seizures, dysmorphism</td>
</tr>
<tr>
<td>Hypotonia, ataxia, spasticity, optic atrophy, dysphagia, dysarthria</td>
</tr>
<tr>
<td>Subacute painless visual loss, postural tremor, neuropathy</td>
</tr>
<tr>
<td>Myoclonus, ataxia, deafness, seizures, neuropathy, proximal myopathy</td>
</tr>
<tr>
<td>Proximal myopathy, headaches, seizures, stroke like episodes, lactic acidosis</td>
</tr>
<tr>
<td>Ophthalmpoplegia, ataxia, neuropathy, ptosis, hypogonadism, parkinsonism</td>
</tr>
<tr>
<td>Parkinsonism, motor delay, apraxia of eye opening, dysarthria</td>
</tr>
<tr>
<td>Skin/soft tissue deposits (acneiform), hoarse, dementia, seizures, psychiatric</td>
</tr>
<tr>
<td>Parkinsonism</td>
</tr>
<tr>
<td>Middle-eastern origin, Alopecia, hypogonadism, diabetes, dementia, seizures</td>
</tr>
</tbody>
</table>
1.2.10 Secondary and symptomatic dystonia

One of the causes of a revival in the organic nature of dystonia was its recognition as a sign of focal injury in the central nervous system. Secondary dystonia has thus been useful in identifying the pathways that may be responsible for primary dystonia. In many cases, secondary dystonia is iatrogenic due to the use of dopamine blocking drugs, and may be the only feature thus mimicking pure primary dystonia (Geyer and Bressman, 2006, Fahn et al., 1998). Dystonia can be acute or late, and if late (tardive) may be associated with other clues such as tardive dyskinesia like the classic orobuccolinguomasticatory syndrome. Acute dystonic reactions can be varied from orofacial dystonia/oculogyric crisis to opisthotonus or even life-threatening laryngospasm. The Pisa syndrome, characterised by tonic retroflexion of the trunk, is recognised to be a subacute complication of dopamine blocking drugs (Sethi, 2001). Theories of how this occurs such as dopamine hypofunction/cholinergic overactivation are supported by the general good response to anticholinergic medication. Tardive dystonia is estimated to have a prevalence of 9 to 13%, and an annual incidence of 0.7% in a long-term cohort study treated with typical neuroleptics (van Harten et al., 2006).

Perinatal damage is typically from an isolated insult, usually hypoxic ischaemic encephalopathy, periventricular haemorrhage in preterm infants, or less commonly now kernicterus. The dystonia evolves in three possible time frames: at the time of the brain injury, following resolution of the cerebral disturbance masking the disorder, or in a delayed manner up to three years after birth (Calne and Lang, 1988). Dystonia after stroke usually emerges from under the cover of hemiparesis the latter regresses to a new steady-state. Movement disorders develop in 3.9% of patients after stroke (Alarcon et al., 2004). Chorea is the most
common type, occurring in 35.7%, but typically in the older patients (>66 years) and has the shortest latency to onset (4.3 days ± 3.6). Ballistic movements were all seen in combination with chorea where infarction was thalamic, but isolated hemiballismus is usually due to subthalamic nuclear infarction in stroke.

Dystonia, focal or hemidystonia, was the second most common type of movement disorder and occurred in 26.9%, with a latency to onset of 15.7 days (SD 19.9). About 30% of these will have complete resolution of the dystonia over time. Stroke subtype, infarction or haemorrhage, was the same as the general incidence (70% infarction), but deep haemorrhagic lesions carry an odd ratio of 4.8 (95% CI 0.8, 36.6) for post-stroke movement disorders. Acquired hemidystonia, is most frequently caused by stroke (48.5%), and the topography is typically the contralateral lentiform nucleus (Marsden et al., 1985, Chuang et al., 2002). The importance of the putamen in the pathway for hyperkinetic movement disorders facilitated understanding of basal ganglia thalamocortical functional loops (Burton et al., 1984, Fross et al., 1987, Alexander et al., 1990, Walker et al., 2002). Tumors, vascular malformation and demyelination among others have also caused isolated focal dystonia or hemidystonia (Marsden et al., 1985, O'Rourke et al., 2006, Jankovic, 1986). Blepharospasm has most frequently been associated with rostral brainstem lesions, bilateral infarction of the diencephalons or striatum (Brazis et al., 2001b). Infarction of the Vim and Vc nuclei of the thalamus (posterior choroidal artery territory) are associated with myoclonus and dystonia of the hand – the “thalamic hand” (Lehericy et al., 2001, Schmahmann, 2003). Dystonia of the hand has also been seen with pontine haemorrhage (Alarcon et al., 2004).
Inflammatory and autoimmune conditions can cause dystonia, typically with other features to alert the physician such as altered sensorium, encephalopathy, pyrexia, skin rash and other systemic features. Anti-basal ganglia antibodies, also seen in the controversial paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS), have been described in a series of patients with generalised dystonic syndromes (Husby et al., 1976, Edwards et al., 2004). A focal-segmental dystonic post-infectious syndrome has been reported as quite common in eastern and northern China, but no autoimmune association has been made (Tsai et al., 1983). Anti-NMDA-receptor antibodies have been found to cause a syndrome of encephalopathy marked by neuropsychiatric features, craniocervical dyskinesias, autonomic instability and hypoventilation, commonly associated with underlying ovarian teratoma (Dalmau et al., 2008).

In acquired immune deficiency syndrome patients, 5-44% had a movement disorder, mostly tremor or parkinsonism (Nath et al., 1987). Dystonia is typically seen in HIV-associated dementia patients who are treated with dopamine agonists (Tse et al., 2004). It is also a feature of complications of CNS infection, e.g. toxoplasmosis, in HIV. However, parkinsonism is a more commonly (5-50%) seen basal ganglia disorder in contemporary HAART treated patients (Tisch and Brew, 2009).

Trauma has been linked to cervical dystonia, other axial dystonia or limb dystonia (Schott, 1985). The oldest anthropological specimen of cervical dystonia, the Birmingham mummy, is believed to have suffered dystonia from an arrow to the neck (Frei et al., 2004). Sheehy and Marsden reported that nine percent of their patients blamed trauma for their cervical dystonia (Sheehy and
Marsden, 1980). Sixteen percent of patients with idiopathic torsion dystonia (generalised, axial, multifocal) felt that their dystonia was precipitated by trauma in another series (Fletcher et al., 1991b). Eleven percent of patients with cervical dystonia in unselected series in a tertiary referral centre had post-traumatic aetiology (Jankovic et al., 1991). Patients usually sustain insignificant trauma (no skeletal damage) and the dystonia begins within hours to days. Laterocollis is the most common type of cervical dystonia seen in this group (O'Riordan and Hutchinson, 2004, Frei et al., 2004). Focal dystonia has also been reported in several cases following electrical injury, distant from the site of electrocution (de Yebenes et al., 2004). Cervical cord tumors, syringomyelia and untreated- and treated cervical disc prolapse have also been linked to 24% of secondary focal dystonia of neck and upper extremities due to structural lesions (Cammarota et al., 1995, Becker et al., 2002, LeDoux and Brady, 2003). Secondary cervical radiculopathy is commonly seen (32%) in cervical dystonia patients (Jankovic et al., 1991). Cervical myelopathy has also been reported as a complication of cervical dystonia in two cases and in generalised dystonia (Spitz et al., 2006).

Pseudodystonia, which is a disorder of posture or movement mimicking dystonia, is another diagnostic issue. The disorders usually manifest with sustained postures or muscle contractions. In children, acquired non-dystonic cervical dystonia is more prevalent than dystonia after extrapyramidal drug reactions (Suchowersky and Calne, 1988). Blepharospasm in children is most often non-dystonic, but due to irritation of the eyes or tic-like disorders. A list of possible causes is given below (adapted (Fahn et al., 1998)).
### Pseudodystonia

<table>
<thead>
<tr>
<th>Causes</th>
<th>Further information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandifer syndrome</td>
<td>GORD associated torticollis</td>
</tr>
<tr>
<td>Stiff-person syndrome</td>
<td>Limb spasms, back extension</td>
</tr>
<tr>
<td>Isaac's syndrome</td>
<td>Neuromyotonia</td>
</tr>
<tr>
<td>Satoyoshi syndrome</td>
<td>Painful spasms, alopecia, diarrhoea</td>
</tr>
<tr>
<td>Rotational atlanto-axial subluxation</td>
<td>Rheumatoid, Ankylosing spondylitis</td>
</tr>
<tr>
<td>Soft tissue nuchal mass</td>
<td>Lymphoma, Scrofula</td>
</tr>
<tr>
<td>Bone disease</td>
<td>Osteoporosis, vertebral crush fracture</td>
</tr>
<tr>
<td>Ligamentous absence/laxity/damage</td>
<td>Ehler’s-Danlos</td>
</tr>
<tr>
<td>Congenital muscular torticollis</td>
<td>Neonatal onset, not reversible</td>
</tr>
<tr>
<td>Congenital postural torticollis</td>
<td>Tone imbalance in neck, reversible</td>
</tr>
<tr>
<td>Congenital Klippel-Feil syndrome</td>
<td>Fusion of any cervical vertebrae</td>
</tr>
<tr>
<td>Trochlear nerve palsy</td>
<td>Head tilt - Bielchowsky test</td>
</tr>
<tr>
<td>Vestibular torticollis</td>
<td>(Bronstein &amp; Rudge, 1986)</td>
</tr>
<tr>
<td>Focal motor seizures</td>
<td>Lesion of contralateral SMA</td>
</tr>
</tbody>
</table>

Table of causes of pseudodystonia with further information relating to diagnosis

#### 1.2.11 Psychogenic dystonia

Psychogenic dystonia accounts for about 5% of all dystonia, but for 17-50% of all psychogenic movement disorders (Shrag, 2006, Thomas et al., 2004). The clinical presentation of dystonia may look bizarre in individuals with true organic disease, and psychogenic disease may be equally indistinguishable from organic disease on clinical grounds. Diagnosis of an underlying cause, particularly in secondary dystonias that have comorbid psychiatric illness, makes it even more difficult. Psychiatric illness is seen in over 60% of patients with psychogenic dystonia (Thomas et al., 2004). Embellishment and functional overlay are often seen in true neurological illness. Co-existence of epileptic and psychogenic non-epileptic seizures occurs in 10-40% of patients with epilepsy, and pseudo-relapses are reported in relapsing-remitting multiple sclerosis (Devinsky and Paraiso, 2000, Merwick and Sweeney, 2008). Ten to twenty percent of patients with a psychogenic movement disorder, and 37% of psychogenic tremor, have an underlying organic movement disorder also (Fahn et al., 2003, Jankovic et al.,
Paroxysmal dyskinesia and paroxysmal dystonia are likely to be misdiagnosed as psychogenic, but familial occurrence of stereotyped behaviours does not rule out psychogenic aetiology.

Some features that may suggest psychogenic dystonia include: previous somatisations, onset after a minor injury, psychological stressor before onset, onset in adolescence or early adulthood, abrupt onset, rapid progression, lower limb onset, marked fluctuations in severity and exacerbations, change over time, severe pain, remission, inconsistent activation pattern, fixed postures, no geste antagoniste, distractability, suggestibility, marked persistent response to placebo/psychotherapy, history of abuse. Compensation claim and litigation proceedings may also support a psychogenic nature, but malingering is possible in this case.

Diagnostic criteria for psychogenic dystonia are outlined in the table.

<table>
<thead>
<tr>
<th>Psychogenic Dystonia</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinically definite</strong></td>
</tr>
<tr>
<td>Persistent relief by psychotherapy/suggestion/placebo</td>
</tr>
<tr>
<td><strong>AND</strong> Additional benefit from physiotherapy</td>
</tr>
<tr>
<td><strong>OR</strong> No dystonia when observed unwittingly</td>
</tr>
<tr>
<td><strong>AND</strong> Incongruent with classical dystonia</td>
</tr>
<tr>
<td><strong>OR</strong> Inconsistencies in examination</td>
</tr>
<tr>
<td><strong>AND</strong> One of</td>
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<tr>
<td>Other psychogenic signs</td>
</tr>
<tr>
<td>Multiple somatisations</td>
</tr>
<tr>
<td>Obvious psychiatric disturbance</td>
</tr>
</tbody>
</table>

| Probable                                   |
| Dystonia incongruent/inconsistent with classical dystonia |
| **OR** Psychogenic signs                   |
| **OR** Multiple somatisations              |

| Possible                                   |
| Evidence of emotional disturbance          |

**Table of Psychogenic dystonia diagnostic criteria**

Treatment of psychogenic illness involves a multi-disciplinary team. A combined neurological and neuropsychiatric approach, with hospitalisation for a
brief period allows the patient to legitimise their sick-role and see that they are taken seriously (Fahn et al., 2003). Therapeutic alliance is established in which the patient is encouraged to engage. Hospitalisation allows simultaneous diagnostic and treatment strategies to be implemented further assuring the patient that they are thoroughly investigated. Formal supportive debriefing of the patient with the neurologist and psychiatrist/neuropsychologist present in which the diagnosis is clearly compassionately explained and the treatment plan is agreed. At this juncture, formal transfer to psychiatry is usually mutually agreeable, and an effective briefing of the psychiatrist/neuropsychologist will give a clear path preventing doubt about the strategy and diagnosis by the patient (Jankovic et al., 2006). Physiotherapy input helps to encourage and rationalise return to a normal functional status. Antidepressants, anxiolytics and other psychotropic medications should be used if indicated for comorbid psychiatric illness, in consultation and agreement with the patient.

A good prognosis is seen in patients who are less than 40 years of age, have a short duration of symptoms, a change in marital status, symptom remission by the end of hospitalisation and an underlying treatable psychiatric condition. Poor outcome predictors in psychogenic dystonia include smoking (OR 44.52), complaints of unsteadiness (OR 5.11), a history of chiropractic manipulation OR 14.23), and complaints about dissatisfaction with the neurologist (OR 6.01) (Thomas et al., 2004).
1.2.12 Familial occurrence of other dystonia-syndromes with no genetic loci

*Dystonia with cerebellar atrophy (DYTCA)*

The combination of dystonia and cerebellar ataxia, with familial and sporadic occurrence, has been reported by two groups. There is considerable phenotypic homogeneity with moderate to severe cerebellar atrophy (hemispheric and vermian), a predominant craniocervical dystonia (especially spasmodic dysphonia) and an age of onset mode in the third to fourth decade (range 8-54 years). Despite the cerebellar atrophy, ataxia of gait was mild to moderate, but most patients had cerebellar eye signs. Hyperreflexia was frequently found, and extensor plantar responses in two patients (Le Ber et al., 2006, van de Warrenburg et al., 2007).

*Dystonia and scoliosis*

Scoliosis occurs secondary to EOPTD in *DYTI* and in DRD. Adolescent- and adult-onset cervical dystonia with prior scoliosis has been described in two families and sporadic cases (Defazio et al., 2003a, Duane, 1998, O'Riordan et al., 2004a). Scoliosis, defined as lateral curvature of the spine greater than 10°, occurring in two to four percent of adolescent children. Severe scoliosis, >30° lateral curvature, is ten times more common in girls but the prevalence is only 0.2% in adolescents. The main neurological causes include tethered cord, syringomyelia, spinal cord tumour, neurofibromatosis, muscular dystrophy, cerebral palsy, poliomyelitis, Friedrich’s ataxia, familial dysautonomia and Werdnig-Hoffman disease (Reamy and Slakey, 2001). In two large series of cervical dystonia, scoliosis has been seen in 16.7-39% of patients (Defazio et al.,
A history of scoliosis preceding the onset of cervical dystonia was found in 27% of patients with a family history of dystonia. Scoliosis is found in 16 - 39% of patients with sporadic cervical dystonia (Jankovic et al., 1991, Patterson and Little, 1943).

A later study of blepharospasm and scoliosis showed no evidence of higher prevalence of scoliosis. If scoliosis is associated with dystonia, it may be site specific (Martino et al., 2007).

_Dystonia-plus with cerebral calcifications ±α-synucleinopathy_

This autosomal-dominant disorder has been described in a large Canadian family. The clinical features are dystonia, dysarthria, chorea, ataxia, tremor and dementia. Some symptomatic and asymptomatic members had cerebral calcifications. The onset was typically between eight and 25 years for the eleven affected members (one outlier at 70 years). Dystonia was present in eight affected members: generalised (3), oromandibular ± writer’s cramp (4) and cervical (1). Chorea affected five, ataxia in one, postural tremor in four, and dementia in three. Cerebral calcification was present in all affected members, particularly in the basal ganglia and thalamus. The cerebellum was affected in 75% of cases. Mild to severe subcortical white matter calcification was also present in 88%. The presence of brain calcification was not found to be predictive of the extrapyramidal-dementia syndrome. Psychiatric features of Fahr syndrome were not seen in this family, although two members suffered from depression. No linkage to the IBGC1 locus was found (Wszelek et al., 2006).

A family with similar patterns of calcification, but parkinsonism, ataxia and dystonia, has also been described. One member had positive α-synuclein
immunohistochemical intraneuronal inclusions at post-mortem. Dystonia affected only one member in the upper limb. Asymptomatic members had brain calcinosis also (Lhatoo et al., 2003).

1.2.13 Diagnostic evaluation of dystonia

The diagnostic evaluation will depend primarily on the history, family history and the examination, but due to the varying clinical presentations and need to direct other treatment in non-primary dystonia, certain laboratory and neuroimaging investigations are compulsory.

There are various red flags that should alert to the possibility of secondary dystonia in the history (Edwards et al., 2008):

1) Abnormal birth/perinatal history
2) Developmental delay
3) Previous exposure to drugs (e.g. neuroleptics)
4) Continued progression of symptoms
5) Prominent bulbar involvement by dystonia
6) Unusual distribution of dystonia for age
7) Unusual nature of dystonia
8) Hemidystonia

In the history the important points to ask are age at onset, timing of onset (acute/gradual), course since, body parts affected, task-specificity, precipitating factor (brain injury/drugs/overuse), presence of geste antagoniste, other relieving and exacerbating factors (e.g. resting head against something, reading the newspaper), family history, diurnal variation and sleep benefit, other neurological symptoms (mood change, mental illness, memory/language
problem, seizures, altered vision, neuropathic symptoms, slowness, tremor, walking difficulty), and anything of note on the overview of systems (liver disease, renal disease, cardiomyopathy, splenomegaly).

All patients should have a full general systems examination to look for other clues such as described in the history, including skin findings such as telangiectasia, neurofibromas and photosensitive/other rashes. A full neurological examination is essential to document eye findings, facial and bulbar features and to search for pyramidal, cerebellar or sensory features. A dystonic toe (spontaneous or stimulus sensitive extension of the big toe) may be found, and should not be confused with a Babinski response (Marsden, 1988).

The examination of movement disorders follows a top down manner. First the patient is observed walking, looking for any change in head posture, truncal deviation, reduced arm swing, choreic movement of the hands, or posturing of the legs including the gait’s cadence, speed, stride length, presence of freezing, and any improvement with walking backwards or running. Then the patient is observed at rest for posturing, tremor, choreoathetoid movement or jerks. A series of activations is performed with ten repetitive movements of frontalis, orbicularis oculi/levator palpebrae, buccinator/orbicularis oris, pterygoids/masseter, neck rotators (splenius capitis/sternomastoid), neck flexors/extensors (sternomastoids/retrocollic muscles), shoulder elevators (trapezius/levator scapulae), hand opening/closing, finger tapping, finger-nose movement, foot tapping, foot rapid-alternating movement, arms outstretched, arms held flexed with hands in front of the chest, and finally rising from a chair. The patient will then read the “rainbow passage” (or other) out loud, while holding the page up in front of them. They should shout “Taxi”, and whisper
“one, two, three, four, five”. The patient should then demonstrate writing using a biro in both hands: normal writing (e.g. the king is in his counting house counting out his money and the queen is in the parlour eating bread and honey), continuous joined “L” across the page, and spiral drawing. It is essential that both hands are examined writing, and that the hand not writing is placed on the table at rest for observation. The written passage should be long enough to bring out abnormal posturing (Zeuner et al., 2007). The patient should be seated comfortably, orthogonally facing the desk at the correct height. For dystonia affecting only the neck, a Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) can be used as standard on each visit, or for generalised and other dystonia, the Burke-Fahn-Marsden (BFM) scale can be used.

Investigations are tailored based on the age of onset, the phenotype, and the presence of other features. Most authors advocate investigations for Wilson’s disease. Plasma copper, caeruloplasmin and slit-lamp examination are fraught with false-negatives and false-positives. Caeruloplasmin is normal in ~5% of those with neurological Wilson’s disease. It may be elevated by hepatitis, inflammatory or neoplastic disease and oestrogens. Kayser-Fleischer rings are not always present in Wilson’s disease, but may be present in primary biliary cirrhosis. If in doubt, liver biopsy is the gold standard to look for excessive copper deposition. Routine blood examination should be done including full blood count, renal/liver/bone profile, glucose, VDRL, erythrocyte sedimentation rate, anti-nuclear antibodies and extractable nuclear antigens. A blood film can be ordered to look for acanthocytes, but the specimen must be processed quickly and the lab informed to prevent artefactual changes. Serum uric acid, fasting lipid profile, lysosomal enzyme studies, very long chain fatty acids, vitamin E levels,
alpha-fetoprotein, immunoglobulins, lactate, pyruvate, serum and urine amino
acids, urine organic acids, creatine kinase, HIV testing, urine chromatography for
oligosaccharides and mucopolysaccharides, CSF pterins, CSF neurotransmitters,
CSF lactate/pyruvate ratio can all be done subsequently, depending on the age of
the patient. Bone marrow biopsy for sea-blue histiocytes and foamy macrophages
would support Niemann-Pick type C. Skin biopsy may identify neuronal
spheroids in infants. Full thickness rectal biopsy for neuronal intranuclear
inclusion disease is diagnostic. Muscle biopsy for morphology, respiratory
enzyme chain analysis and genetic testing should be done for cases of possible
mitochondrial disease (Comella, 2004). Gene testing for secondary causes can
also be considered, but bearing in mind that sporadic point mutations and even
large gene deletions may be missed with typical linkage analysis and RT-PCR of
restriction fragment polymorphisms.

Neurophysiological testing are not routinely recommended for the
diagnosis or classification of dystonia, but may serve to assist in identifying
correctly secondary causes. Conventional structural neuroimaging is normal in
primary dystonia (Rutledge et al., 1988). Structural brain imaging is necessary to
screen for secondary causes of dystonia, and MRI is preferable. More
sophisticated techniques, PET/fMRI/VBM, are not clinically useful yet
(Albanese et al., 2006). All patients with hemidystonia should be imaged, and if
vascular lesions are found, further work-up and secondary prevention instituted.

Genetic testing for primary dystonia should be performed only in
conjunction with genetic counselling beforehand, and with test results. DYT1
gene testing is recommended in patients with primary dystonia with the onset
<30 years, or ≥30 years if they have an affected relative with early-onset.
Asymptomatic individual testing is not recommended at any age unless the examination features suggest dystonia that the person is unaware of. A diagnostic levo-dopa trial is warranted in every patient with early-onset primary dystonia without an alternative diagnosis. The dose of levo-dopa used is typically 20-30 mg/kg/day, or 300 to 400 mg per day in an adult patient, either with or without dopa-decarboxylase inhibitor. Dopa-responsive dystonia can be confirmed genetically looking for mutations in the GTP-cyclohydrolase 1 gene. Individuals with myoclonus should be tested for the epsilon-sarcoglycan gene mutation (SGCE). Rapid-onset dystonia parkinsonism can be genetically tested (on a research basis) by looking for mutations on the ATP1A3 gene. X-linked “Lubag” dystonia-parkinsonism genetic testing should be considered in (Filipino) males with florid dystonia-parkinsonism and a maternal history tracing to the Panay Islands of the Philippines. GLUT1 gene testing should be considered in paroxysmal exercise induced dyskinesia with/without spasticity due to the important therapeutic implications (Albanese et al., 2006).

The likely yield of investigation in dystonia depends on the phenotype and age of onset. Overall the positive yield of investigating dystonia is 23%. Adult-onset has the lowest yield (13%) and childhood-onset the highest (41%). Focal dystonia has 12% abnormal investigations, compared to 42% in generalised and 46% in Multifocal. Segmental dystonia has similarly low rate (14%) to focal dystonia (Marsden, 1988).

In summary, patients who have an early age of onset, or progressive symptoms or abnormal other neurological findings are more likely to have secondary dystonia and should be thoroughly investigated as such. Neuroimaging will have the highest yield in these instances, but a normal scan should not
prevent further investigations. Eight of the 55 conditions listed in the heredodegenerative table have normal or near normal imaging.

**Examination shows only dystonia**

- **Onset <26 years or relative with dystonia**
  - DYT1 gene testing
  - L-dopa trial
  - Caeruloplasmin & 24hour urine copper
  - Slit lamp examination
- **Onset 26+ years**
  - Caeruloplasmin & 24hour urine copper
  - MRI brain

**Possible heredodegenerative/secondary dystonia**

- **History of neuroleptic exposure**
  - Caeruloplasmin & 24hour urine copper
- **Possible structural lesion**
  - MRI brain
  - Cerebrospinal fluid study
  - Other appropriate laboratory studies
- **Possible metabolic/inherited disease**
  - L-dopa trial
  - Caeruloplasmin & 24hour urine copper
  - MRI brain

**Tailored tests**

- Antiphospholipid antibodies
- Gene testing (Huntingtons/SCA3/Mitochondrial)
- Lysosomal enzymes
- Alpha-fetoprotein
- Blood smear for acanthocytes
- Lactate/pyruvate
- Amino acids in serum & urine
- Organic acids in urine
- Skin, muscle, nerve and bone marrow biopsy
- Cerebrospinal fluid study
- Electrodiagnostic studies

**Table of suggested investigations in dystonia**
1.3 Epidemiology and clinical features of dystonia

1.3.1 Prevalence of dystonia

The prevalence all types of AOPTD is estimated as between 11.3- 33.0/100,000 of the population (Butler et al., 2004, Claypool et al., 1995, Duffey et al., 1998, Fukuda et al., 2006, Le et al., 2003, Nakashima et al., 1995, Nutt et al., 1988, Muller et al., 2002, Warner et al., 2000). The commonest phenotype in individuals of European origin is cervical dystonia consisting of between 49% of all focal AOPTD patients, followed by blepharospasm, comprising 30% (Defazio, 1999, Warner et al., 2000, Warner et al., 1999). In Japanese studies, cranial forms of dystonia are more common, but the prevalence overall is lower with the highest report of 13.7/100,000 (Fukuda et al., 2006, Nakashima et al., 1995). Primary dystonia has been noted to have lower prevalence in non-European populations (Le et al., 2003, Marras et al., 2007).

Focal and segmental AOPTD are about ten times more prevalent than generalised PTD (Nutt et al., 1988).

Epidemiological studies have always been hampered by case ascertainment difficulties; the relative rarity of reports in the literature prior to the last two decades of the twentieth century parallels lower prevalence reports of the same era (Fukuda et al., 2006, Risch et al., 1995, Zilber et al., 1984). Prevalence rates for AOPTD and its phenotypes are illustrated in the table (table of Prevalence of AOPTD).
Task-specific dystonia

Given that writer’s cramp is the most common FTSD, and a large proportion of FHD is task-specific at onset, the prevalence of FTSD is close to the overall figure for FHD of 7-69 per million in the general population (Torres-Russotto and Perlmutter, 2008). The most accurate figures are from two studies and narrow the range to 7-14 per million (Duffey et al., 1998, Warner et al., 2000). FTSD in professional musicians occurs in 0.2-0.5%, and usually at the peak of their performing career (Frucht, 2004).

1.3.2 Incidence of dystonia

Focal, Segmental and Generalised AOPTD

The overall incidence of AOPTD is about 2.4/100,000 person-years (Nutt et al., 1988). Cervical dystonia has the highest incidence, consistent with prevalence figures, but the incidence varies in different areas of the world and is maintained in multi-ethnic population studies (Claypool et al., 1995, Marras et al., 2007). The incidence of cervical dystonia is 1.23/100,000 person-years in whites, and lower in Hispanics, Asians and Blacks (0.15/100,000 person-years). Figures for the incidence reported in the literature are given in the table (table on Incidence of AOPTD). Data on incidence are less frequently reported than prevalence, and population sizes vary considerably (Lo et al., 2009, Marras et al., 2007).
Prevalence Studies | Location | Focal AOPTD | CD | BEB
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</thead>
<tbody>
<tr>
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<td>295</td>
<td>172-479</td>
<td>87</td>
<td>29-207</td>
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<td>-</td>
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<td>Nakashima et al, 1995</td>
<td>Tottori, Japan</td>
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Prevalence of AOPTD and its phenotypes

\(^a\) = all facial dystonia
\(^b\) = generalised
<table>
<thead>
<tr>
<th>Incidence Studies</th>
<th>Location</th>
<th>Focal AOPTD /100,000/year</th>
<th>95% CI</th>
<th>CD /100,000/year</th>
<th>95% CI</th>
<th>BEB /100,000/year</th>
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<th>CD /100,000/year</th>
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^ = generalised

Incidence of AOPTD and its phenotypes
1.3.3 Clinical features of dystonia

In AOPTD, focal dystonia is frequently initially action-specific – e.g. head turning when reading, or hand cramping when writing but not using cutlery. As dystonia progresses, less specific actions of the affected area may activate dystonia. Also actions in other body parts can trigger dystonic posturing in the affected area by “overflow”, such as can be seen by examining for mirror-dystonia. Eventually, an area may have sustained posturing.

Dystonia may begin with the performance of a specific task – focal-task-specific-dystonia (FTSD). Affected professional musicians who practise instruments with repetitive highly attended-to movements are most disabled, often spending more time practising to battle with their undiagnosed problem (Frucht, 2004). Over 55 occupations & several sports have been described with FTSD including scribes, typists, tailors, cobblers, florists, fencers, tinmen, turners, auctioneers, darts players and golfers (Sheehy and Marsden, 1982, Adler et al., 2005, Scolding et al., 1995). Cervical dystonia has only been described as task specific in one case: a man with bilateral upper limb amputations who learned to write holding the pen in his mouth (Torres-Russotto and Perlmutter, 2008). Over time, dystonia may be apparent when another part of the body is engaged in voluntary activity and at rest.

Dystonic movements increase with fatigue, stress or emotional states, and as Charcot observed, they tend to be suppressed with relaxation, hypnosis and sleep (Goetz, 2006). They may have a characteristic “sensory trick” or geste antagoniste. Using this, muscle activity is diminished simply by touching the skin in a target area, usually adjacent to the dystonic muscle (Schramm et al.,
2004, Gomez-Wong et al., 1998a). This is more often reported with cervical dystonia than other types or focal dystonia (table of extra features in AOPTD).

Remission is reported in dystonia, which may be partial or complete, and temporary but rarely permanent. Pain is common also, e.g. in cervical dystonia where 68% of patients will have pain. The origin of the pain is unknown, but the posterior cervical muscles may be rich in pain fibres, excited by the contractions, and generally successfully treated by botulinum toxin injections (Greene et al., 1990). Chronic cervical dystonia also may contribute to osteoarthritic changes between facet joints and even osseous fusion in the neck contributing to pain (Weigel et al., 2007, Tagliati et al., 2004, Ishii et al., 2006).

Gait is abnormal in generalised dystonia and dystonia affecting the lower extremities and axial skeleton, and sufferer’s of cervical dystonia walk with reduced arm swing (Kagi et al., 2008). Children with generalised dystonia have a “dromedary gait”, with the neck extended while there is flexion at the hips.

Tremor, which may be an accompanying tremor resembling essential tremor, or tremor as an expression of rapid alternating rhythmic movement of dystonic muscles is seen (for example head tremor in cervical dystonia). Dystonic tremor is less regular in amplitude and periodicity than essential tremor, frequently associated with myoclonus, and tends to be postural (Jedynak et al., 1991). Prominent myoclonus and dystonia in families has been extensively described as a separate disorder, but jerky movements and myoclonic movements at the dystonic focus are seen in about one third of patients (Asmus and Gasser, 2004, Obeso et al., 1983). Patients with tremor may also have a family history of dystonia, typically AOPTD, and tremor may be found in high frequency in large families with AOPTD (Yanagisawa and Goto, 1971). Secondary causes and
heredodegenerative causes of dystonia are much more common than primary dystonia, and may present with dystonia alone (Walsh et al., 2009a).

1.3.4 Age of onset in relation to phenotype

There is a bimodal distribution of the onset of dystonia, with an early peak around 12 years of age, and a later peak around 50 years of age. The nadir is at 21 – 28 years (Elia et al., 2006, Bressman et al., 1998). Approximately 10% of all primary dystonia is early-onset (Duffey et al., 1998). The remainder is mostly adult-onset.

AOPTD phenotypes show a caudal-rostral progression for age of onset (O'Riordan et al., 2004b). Writer's cramp has the youngest mean age of onset at 37.6 years and blepharospasm/oromandibular dystonia the oldest at 55.9 years (table of Clinical characteristics in AOPTD). In this table, the age of onset of spasmodic dysphonia is younger than previous meta-analyses because of exclusion of surgical collected series that may have bias in cohort selection (Aminoff et al., 1978, Aronson and De Santo, 1983, Izdebski et al., 1984, Ludlow et al., 1988). Axial dystonia had an average age of onset of 41 years with no significant difference between men and women (Bhatia et al., 1997). Lower limb primary dystonia in adults has an average age of 48 years (McKeon et al., 2008). Familial cases may have a lower mean age of onset for all types of focal AOPTD (Elia et al., 2006).

In FTSD, the age of onset is often slightly younger for the affected area compared to a similar phenotype in AOPTD (Frucht, 2004). It spans the third to the sixth decade. Writer's cramp and spasmodic dysphonia are the most common types of FTSD (Torres-Russotto and Perlmutter, 2008).
Genetic anticipation by evidence of earlier age of onset in successive generations in families with AOPTD was suggested in one study, but has not been confirmed subsequently (Cheng et al., 1996). It is unlikely to be trinucleotide repeat disorder, which do demonstrate variable penetrance, but generally have intraneuronal inclusions and progressive multisystem neurodegeneration.

AOPTD prevalence increases with age for all focal types and segmental dystonia but declines in the seventh decade except for blepharospasm (Warner et al., 2000).

1.3.5 Gender and AOPTD

Women are affected more than men with a ratio of 2:1 overall for focal dystonia (table of Clinical Characteristics in AOPTD). Meta-analysis of the female to male ratio for each phenotype are as follows: Meige 4:3, blepharospasm 5:2, oromandibular dystonia 3:1, cervical dystonia 5:3, spasmodic dysphonia 2:1 and focal hand dystonia 2:3. Prevalence from individual studies of cervical dystonia varies, but is higher in women than men with ratios of 1.5 to 3.6:1 (Claypool et al., 1995, Defazio, 1999, Le et al., 2003, Maniak et al., 2003, Pekmezovic et al., 2003, Soland et al., 1996). Women with craniocervical dystonia tend to have later onset than men (all focal dystonia F 48.7 years, M 43.8 years; Blepharospasm F 60.2 years > M 55.5 years; Oromandibular Dystonia F 61.8 years > M 61.3 years; Cervical Dystonia F 42.9 years > M 39.2 years; Spasmodic Dysphonia F 52.3 years > M 46.3 years) (Defazio, 1999). Sex prevalence ratios have shown a female predominance in all craniocervical dystonia except FHD (Duffey et al., 1998, Nutt et al., 1988, Soland et al., 1996). This is confirmed in
neurology out-patient cohort studies (Defazio et al., 2003b, Defazio, 1999). Women have a significantly earlier age of onset of FHD than men (F 34.4 years, M 41.7 years). Axial onset has a 1:1.2 ratio, with more men affected (Bhatia et al., 1997). Primary lower limb dystonia is more common in women, with a ratio of 2.8:1 (Schneider et al., 2006b). In contrast to upper extremity dystonia, the age of onset is younger in men (41 years) compared to women (48 years).

1.3.6 Phenotypes in AOPTD

AOPTD is typically focal, affecting one and occasionally two body regions. Spread is common, usually following a topographical pattern to give rise to segmental dystonia, multifocal dystonia or more rarely generalised dystonia. The typical focal types of AOPTD are shown in the table, including age of onset, gender distribution, spread according to phenotype, percentages reported to have any remission and percentages within a series with secondary causes that could not be extracted from the data given. Cervical dystonia is the most common phenotype (49%), followed by blepharospasm (29%), focal hand dystonia (13%), spasmodic dysphonia (6%), and oromandibular dystonia (1%). The ratios of prevalence for the first four phenotypes is 8:4:2:1 to 8:5:2:1 based on large epidemiological studies (Defazio, 1999, Warner et al., 2000).
<table>
<thead>
<tr>
<th>Age of onset (years)</th>
<th>SD</th>
<th>Range</th>
<th>%</th>
<th>BEB</th>
<th>OMD</th>
<th>SD</th>
<th>CD</th>
<th>FHD</th>
<th>Truncal</th>
</tr>
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<tbody>
<tr>
<td>Females</td>
<td></td>
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</tr>
</tbody>
</table>

**Meige Syndrome**

- **Marsden, 1976**
  - Age of onset: 13 years
  - SD: 57.0
  - Range: 41-71
  - Females: 54%
  - Spread of dystonia: BEB 4, OMD 4, SD 1, CD 1, FHD 1

- **Tolosa, 1981**
  - Age of onset: 8 years
  - SD: 54.0
  - Range: 25-68
  - Females: 59%
  - Spread of dystonia: BEB 4, OMD 4, SD 31%, CD 31%, FHD 8%, Truncal 8%

**Benign Essential Blepharospasm**

- **Marsden, 1976**
  - Age of onset: 17 years
  - SD: 57.0
  - Range: 41-71
  - Females: 67%
  - Spread of dystonia: BEB 4, OMD 0, SD 0, CD 0, FHD 0

- **Grandas et al., 1988**
  - Age of onset: 264 years
  - SD: 56.0
  - Range: 20-81
  - Females: 64%
  - Spread of dystonia: BEB 188, OMD 46, SD 60, CD 26, FHD 6

- **Defazio et al., 1999**
  - Age of onset: 159 years
  - SD: 59.0
  - Range: 74
  - Females: 61%
  - Spread of dystonia: BEB 43, OMD 4, SD 15, CD 3, FHD 0

- **Mueller et al., 2005**
  - Age of onset: 66 years
  - SD: 57.0
  - Range: 12
  - Females: 74%
  - Spread of dystonia: BEB 4, OMD 0, SD 15, CD 3, FHD 1

- **Elia et al., 2006**
  - Age of onset: 230 years
  - SD: 56.0
  - Range: 10
  - Females: 74%
  - Spread of dystonia: BEB 4, OMD 0, SD 15, CD 3, FHD 1

- **Svetel et al., 2007**
  - Age of onset: 30 years
  - SD: 55.0
  - Range: 10
  - Females: 41%
  - Spread of dystonia: BEB 3, OMD 2, SD 2, CD 0, FHD 0

- **Abbruzzese et al., 2008**
  - Age of onset: 124 years
  - SD: 56.0
  - Range: 11
  - Females: 76%
  - Spread of dystonia: BEB 42, OMD 26, SD 2, CD 0, FHD 0

- **Defazio et al., 2009**
  - Age of onset: 401 years
  - SD: 54.0
  - Range: 8
  - Females: 75%
  - Spread of dystonia: BEB 82, OMD 14, SD 40, CD 11, FHD 0

- **Weiss et al., 2006**
  - Age of onset: 78 years
  - SD: 52.0
  - Range: 13
  - Females: 72%
  - Spread of dystonia: BEB 35, OMD 1, SD 24, CD 2, FHD 1

- **Greene et al., 1995**
  - Age of onset: 107 years
  - SD: 54.0
  - Range: -66
  - Females: 73%
  - Spread of dystonia: BEB 73, OMD 8, SD 19, CD 3, FHD 2

**Oromandibular Dystonia**

- **Marsden, 1976**
  - Age of onset: 7 years
  - SD: 54.0
  - Range: 37-72
  - Females: 88%
  - Spread of dystonia: BEB 0, OMD 0, SD 0, CD 0, FHD 0

- **Tan & Jankovic, 2000**
  - Age of onset: 92 years
  - SD: 51.0
  - Range: 13
  - Females: 75%
  - Spread of dystonia: BEB 52, OMD 12, SD 63, CD 16, FHD -

- **Sverfeldt et al., 2007**
  - Age of onset: 3 years
  - SD: 54.0
  - Range: 19
  - Females: 64%
  - Spread of dystonia: BEB 7, OMD 0, SD 1, CD 1, FHD 0

- **Weiss et al., 2006**
  - Age of onset: 17 years
  - SD: 51.0
  - Range: 11
  - Females: 64%
  - Spread of dystonia: BEB 7, OMD 0, SD 1, CD 1, FHD 0

**Lower Limb Dystonia**

- **McKeon et al., 2008**
  - Age of onset: 14 years
  - SD: 48.0
  - Range: 31-82
  - Females: 100%
  - Spread of dystonia: BEB 0, OMD 0, SD 0, CD 0, FHD 0

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Table of AO PTD phenotypes, 1st spread pattern, progression and remissions
<table>
<thead>
<tr>
<th>AOPTD Phenotype cont/...</th>
<th>Progression to</th>
<th>Presenting as part of segmental</th>
<th>Remission (%)</th>
<th>Secondary cases</th>
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<td>Multifocal</td>
<td>Generalised</td>
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<td><strong>0%</strong></td>
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<td>Range</td>
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<td><strong>Focal Hand Dystonia</strong></td>
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<td>17</td>
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<td>Greene et al, 1995</td>
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<td>475</td>
<td><strong>37.6</strong></td>
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<td>AOPTD Phenotype</td>
<td>Progression to</td>
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<td>Remission (%)</td>
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<td>Focal Hand Dystonia</td>
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<td>30</td>
<td>-</td>
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<tr>
<td><strong>26%</strong></td>
<td><strong>6%</strong></td>
<td></td>
<td></td>
<td><strong>2%</strong></td>
</tr>
</tbody>
</table>
**Cervical dystonia**

This is dystonia affecting the neck muscles, which may be tonic or tremulous. Head postures are commonly torticollis/rotatocollis, retrocollis, antecollis and laterocollis. Deviations may occur in any plane or combinations of planes. Rotatocollis brings the chin around the longitudinal axis of the head towards the shoulder. Antecollis and retrocollis involve turning of the head in the sagittal plane, either approximating the chin to the anterior chest/sternum, or tilting the head backwards respectively (Dauer et al., 1998). Laterocollis, or rotation of the head in the coronal plane moving the ear towards the shoulder, is unusual in primary torsion dystonia, but is common with post-traumatic dystonia (Calne and Lang, 1988, O'Riordan and Hutchinson, 2004). The muscle groups causing the postures typically have a prime mover, e.g. splenius capitis or sternocleidomastoid in rotatocollis (Tijssen et al., 2000, Patterson and Little, 1943). Constant head deviation (deviation >75% of the time) occurs in 83% of patients.

Head jerks, which are large amplitude irregular jerky movements of the head, are present in 29-35% and neck spasms, which are intermittent forceful contractions, in 37%. However, the literature is not at odds as to the division of clonic and tonic type of cervical dystonia, with some favouring a 1:2 tonic:clonic ratio (Chan et al., 1991), and others the opposite (Jahanshahi et al., 1990). Eighty-eight to 97% of patients with CD suffer with some rotatocollis, whether in isolation (18%), or combined in complex movement. (Chan et al., 1991, Patterson and Little, 1943) Retrocollis is seen in 12-32% and antecollis in 14% (Jahanshahi et al., 1990). Shoulder involvement, presumably due to levator scapulae and trapezius, is involved in 76% of CD. Shift of the longitudinal axis
of the head occurs in all directions, most commonly as a head tilt (up to 64%). About 4% of CD will have a change in the direction of head turning, most often after a remission period (Chan et al., 1991, Skogseid and Kerty, 2005). Three quarters of patients with CD complain of pain (66- 74%). Pain may be the symptom at onset in CD in 14- 17% (Patterson and Little, 1943, Jankovic et al., 1991, Pal et al., 2000). Sensory symptoms (stiffness/pain) have been described in seven of eight patients with CD, beginning up to three months before the onset of the movement (Ghika et al., 1993). Pain during the course of illness, severe in one third, with cervical dystonia is described in over 85% patients (Pal et al., 2000).

The geste antagoniste is common in CD, reported in over three quarters of patients (table of extra features in AOPTD). CD is associated with remission in 12% overall (table of phenotypes in AOPTD), and is more likely to occur in patients with a younger age of onset (Jahanshahi et al., 1990).

Blepharospasm

This is characterised by excessive blinking, eyelid closure spasm, and in severe cases functional blindness. It is the commonest form of cranial dystonia. The orbicularis oculi is the muscle affected. It may begin unilaterally or bilaterally, but typically progresses to bilateral involvement although it may remain asymmetrical (Lang, 2004). It is worse in bright light, and people affected often complain of photophobia. Sensory symptoms like grittiness in the eyes or dry eyes is also reported (Ghika et al., 1993). Local ocular symptoms are reported in 56.8% of patients which predate the onset of blepharospasm, but only 4.9% later have such symptoms (Grandas et al., 1988). Charcot’s sign, or lowering of the
eyelids during eyelid closure is said to help distinguish between organic and
psychogenic blepharospasm, where the eyebrows may be raised in the latter.

Spread in BEB is more likely to occur in women and those with a later
onset of the disease, mirroring the higher likelihood of spread with younger age
in EOPTD (Defazio et al., 1999, Defazio et al., 2009, Defazio and Livrea, 2002).
Further trans-continental work due to this observation identified a single
polymorphism rs11782 in the DYT1 gene associated with higher risk of spread in
BEB patients. Forty-six percent of BEB patients progress to have segmental
involvement (table), and only nine percent have remission either partial or
complete at any time. Some patients have tricks to have tricks to help them open
their eyes including looking down, jaw-opening, neck extension and wearing
dark glasses (Lang, 2004). Apart from functional blindness, other complications
or BEB include secondary blepharitis, excessive tearing, brow ptosis, levator
aponeurosis/lateral epicanthal tendon defects.

When occurring with another focal dystonia, most frequently
oromandibular dystonia, it is interchangeably known as Meige syndrome or

Oromandibular dystonia

This lower facial muscle dystonia phenotype may have involvement with jaw-
opening dystonia, and platysma spasm. In severe cases, patients may even
dislocate the jaw (Marsden, 1976). It is most frequently seen in combination with
blepharospasm or spasmodic dysphonia, and less so in isolation (Lang, 2004,
Jankovic and Ford, 1983). It may affect the jaw symmetrically or
asymmetrically, although the latter is rare and affects less than two percent with
OMD (Thompson et al., 1986, Tan and Jankovic, 1999). Dystonic movement is more often seen as mandibular retraction, platysma contraction, jaw opening/clenching, contractions of the lips, nasal flaring and anterior oropharynx muscle contractions. Jaw closure (63%) is the most common subtype (Tan and Jankovic, 1999, Marsden, 1976). Spasms may be prolonged, more than half a minute. The initial symptoms with OMD are often task-specific, such as talking or chewing, and may not affect other vocal registers (Marsden, 1976). Tricks such as placing a toothpick in the mouth may alleviate symptoms in some cases. When spasms are severe some patients forcibly pull open or push closed the jaw to get relief.

Pain can be severe, especially in the temporomandibular joint which may become dislocated (Lang, 2004, Marsden, 1976). Eating may be impaired by the jaw dystonia, with forceful pushing of food from the mouth. Pharyngeal dystonia may present in combination, and rarely in isolation, with dysphagia and choking. Teeth grinding may occur with oromandibular dystonia, but nocturnal bruxism without other symptoms and signs is not considered a primary dystonia (Tan and Jankovic, 1999, Jankovic, 2004).

**Writer’s Cramp (FHD)**

Writer’s cramp or focal hand dystonia (FHD) affects the forearm and finger muscles. The hand or a finger/s posture by involuntary contraction of flexors and extensors when doing simple (holding a pen) or complex (writing) movement programmes. It has been documented in many ways through the scientific literature and art. One of the earliest descriptions of writer’s cramp is from Ramazzini’s *de morbis artificum*, 2nd edition, published in 1713. In it he
describes spread of dystonia in an accountant who develops writer’s cramp in both hands, one after the other (Altschuler, 2005).

The onset of writer’s cramp is associated with an abrupt increase in time spent writing in the year prior to onset, head trauma with loss of consciousness and myopia (Defazio et al., 1998, Roze et al., 2009). In multivariate analysis, after adjustment for time spent writing, there is no association with type of writing instrument such as fountain pen. The “quill” had been suggested by Gowers as a cause of scrivener’s palsy (Pearce, 2004).

Spread to the non-dominant upper limb of writer’s cramp often occurs in patients who take up writing with the other hand (Jedynak et al., 2001, Sheehy et al., 1988).

Mirror movement is involuntary movement(s) occurring on one side of the body, which is similar in character, to a voluntary movement performed contralaterally. This takes two forms in FHD: contralateral motor overflow and mirror dystonia. Contralateral overflow affects the unaffected limb during dystonic posturing of the affected side, and mirror dystonia affects the affected limb when the unaffected limb does the task that most stimulates the FHD. Ipsilateral overflow also occurs, affecting the muscles adjacent to those normally affected. Mirror dystonia is seen in 45-67% of FHD, and contralateral overflow in only 8%, but both being twice as frequent as controls (Sitburana et al., 2009, Jedynak et al., 2001). Such a high occurrence of mirror dystonia may help in distinguishing true FHD from compensatory strategies for other reasons like carpal tunnel syndrome.
Pain is variably reported in FHD, occurring in 11-86% of patients (Sheehy et al., 1988, Jedynak et al., 2001). It is almost uniquely present with task-specificity, such as writing.

*Spasmodic dysphonia*

Spasmodic dysphonia affects the vocal cords, causing either adduction or abduction. Some patients have a combination of both (Brin et al., 1998). The adduction type, caused by thyroarytenoid muscle contraction, causes air arrest and voice production becomes hoarse or strangled with partial phonation or breaks in phonation. Abduction dysphonia, caused by posterior cricoarytenoid contraction, produces a soft breathy quality to the voice, whispering and abrupt termination or voice resulting in aphonie segments of speech. In primary SD, adductor dystonia accounts for 83% of cases, and 11% with the abductor form (Blitzer et al., 1988, Lang, 2004). Irregular voice tremor in SD is common and mostly occurs with adductor dystonia, but is very variably reported, from 23% to 100% (Blitzer et al., 1988, Aronson and De Santo, 1983, Aminoff et al., 1978).

SD may improve with shouting and is often worse on the telephone. Respiratory obstructive symptoms may be mild to severe, the latter occasionally necessitating tracheostomy.

*Focal Task Specific Dystonia (FTSD)*

FTSD presents as focal excessive muscle contraction that develops in parts of the body involved in highly skilled, over-learned tasks. In the past, the most common type of FTSD was scrivener's palsy, and as such this type of focal hand dystonia was mostly a disease affecting men (Pearce, 2004, Sheehy and Marsden, 1982).
It can vary from typing (typist’s cramp), piano-playing (pianist’s cramp), guitar playing (guitarist’s cramp) to wind-instrument playing (embouchure dystonia), but there are more than 50 occupations listed to cause a FTSD (Torres-Russotto and Perlmutter, 2008, Frucht et al., 2001). It has also been described in sports, particularly in golfers with low handicaps (the “yips”) when putting (McDaniel et al., 1989). FTSD does not spread in the manner of non-task specific dystonia. Studies with high proportions of task-specific dystonia show spread in about 15% of patients (c.f. FHD: >30% in adults, and ~70% in EOPTD) (Greene et al., 1995, Weiss et al., 2006). The aetiology behind it may be different to other forms of focal dystonia, but the nature of its focality, its relationship to typically highly rehearsed tasks, and its amenability to treatments such as constraint provide some basis for further understanding other focal dystonias (Byl and McKenzie, 2000, Candia et al., 1999, Priori et al., 2001).

*Postural Hand Tremor in AOPTD and Dystonic Limb Tremor*

Postural hand tremor is seen in almost a quarter of patients with focal dystonia (Jedynak et al., 1991). It is found in almost a third of cervical dystonia patients who do not have head tremor (Pal et al., 2000).

Hand tremor in focal hand dystonia is seen in half of the suffersers, is typically 5-7 Hz, and mostly asymmetrical affecting only the dystonic limb (Sheehy and Marsden, 1982). Primary writing tremor which is tremor produced only on writing has many neurophysiological characteristics of dystonia (short dystonic bursts independent of tremor in antagonistic muscles) and may be a form or task specific dystonic tremor, but no postural dystonic tremor is seen (Modugno et al., 2002, Sheehy et al., 1988). Dystonic limb tremor, typically of
upper extremity, has seven characteristics: 1) dystonia, which may be subtle, 2) thumb extension tremor, 3) “flurries” or task/position-specificity of tremor, 4) head tremor, 5) dystonic voice, 6) no progression to develop other features other than tremor and dystonia, and 7) no clear fatiguing or decrement with repetitive movements (Bain, 2009, Schneider et al., 2007). This classification is useful in a movement disorders clinic because application of these parameters positively selects 95% of patients with SWEDDs (Gontu et al., 2008). Patients with SWEDDs and patients with dystonic arm tremor have highest tremor amplitude during posturing or action, in contrast to idiopathic parkinson’s disease who have a combination of re-emergent tremor and highest tremor amplitude during resting conditions (Schwingenschuh et al., 2008). Rest tremor in a limb is very rare in other forms of focal dystonia, occurring in <2% of CD patients (Deuschl et al., 1997).

Head tremor in cervical dystonia

Sixty-eight percent of patients in sequential series of cervical dystonia have head tremor. It is commonly associated with hand tremor (40%) and a family history of tremor and movement disorders (Jedynak et al., 1991). Head tremor sufferers less often have a geste antagoniste, compared to cervical dystonia without head tremor (Pal et al., 2000). Men are more likely to have non-tremulous cervical dystonia. Tremor may precede cervical dystonia in 15.4% of patients, and one third of patients present with tremulous cervical dystonia. Of patients who present with head tremor, 64.3% have a family history of tremor, whereas those who developed tremor afterwards had only a 15.7% positive family history of tremor.
**Jaw tremor in AOPTD**

Jaw tremor is frequently seen in idiopathic parkinson’s disease and in severe essential tremor. But it is a feature of dystonia, both associated with jaw dystonia and distant from the dystonic site. It most commonly is an “up-down” movement, or can be complex movements (Schneider and Bhatia, 2007).

**Reduced arm swing in Cervical Dystonia**

Fifty-five percent of patients with cervical dystonia phenotype of AOPTD have asymmetrically reduced arm swing, and do not go on to develop any features of idiopathic parkinson’s disease (Kagi et al., 2008). It is more often reduced on the side the head is turned to (54.7%), but may be bilaterally reduced (16%).

**Unusual phenotypes**

Two atypical phenotypes have been identified in AOPTD: axial predominant and lower limb onset. Axial dytonia is the presenting phenotype in 28% of patients whose major disabling dystonic feature is their truncal posturing. Thirty-three percent have co-incident cervical dystonia, which is typically mild. Eleven to 33% of patients have focal cervical or segmental dystonia before the onset of their axial symptoms. Further spreading of symptoms is not known. Forward flexion spasm is the most common direction of movement (56%), followed by extensor (22%) and lateral-extensor (17%). The dystonia was typically worse with walking or standing. Treatment response to various medication combinations is generally poor. One sixth of patients described in the series were suicidal. No case was included that had prior neuroleptic exposure or a diagnosis
<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Geste antagoniste</th>
<th>FHx Dystonia</th>
<th>Dystonic Tremor</th>
<th>Postural Hand Tremor</th>
<th>Majority (&gt;90%) of spread period (y)</th>
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<tr>
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<tr>
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<tr>
<td><strong>Total</strong></td>
<td>14</td>
<td></td>
<td>7%</td>
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</table>
1.3.7 Spread of focal dystonia phenotypes

Spread of focal dystonia has been a characteristic feature of primary torsion dystonia since its early descriptions. Gowers wrote 'The sufferer who finds himself unable to write with one hand often learns to write with the other. After he has acquired the needed facility, and has written with the left hand for a time, similar symptoms develop in this hand, and they then usually progress more quickly than in the arm first affected (Gowers, 1888).’ Spread, although it occurs with many causes of dystonia, is seen more frequently than in other causes focal onset dystonia (Svetel et al., 2004). Overall 28.3% of focal onset adult-onset primary torsion dystonia spreads to at least one other location (table of Spread by Onset Phenotype in AOPTD).

Spread in familial AOPTD reports is variable. One author has reported it as more common in familial AOPTD with up to 77% showing some spread throughout the course of the disease compared to only 46% for sporadic cases in one study, but these figures included many EOPTD cases (Elia et al., 2006). Others have suggested no increased risk of spread in familial AOPTD cases compared to sporadic AOPTD (Defazio et al., 1999, Svetel et al., 2007, Weiss et al., 2006, Cheng et al., 1996).
### EOPTD

<table>
<thead>
<tr>
<th>Study</th>
<th>LE s</th>
<th>n</th>
<th>UE s</th>
<th>n</th>
<th>Head s</th>
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<td>-</td>
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<tr>
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<td>-</td>
<td>-</td>
<td>100%</td>
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<tr>
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<tr>
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<tr>
<td><strong>% spread</strong></td>
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<td>42</td>
<td>45</td>
<td>75</td>
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<td></td>
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### AOPTD

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<th>n</th>
<th>SD s</th>
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<th>CD s</th>
<th>n</th>
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<td>142</td>
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<td>-</td>
<td>-</td>
<td>19%</td>
<td>6</td>
<td>32</td>
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<td>107</td>
<td>-</td>
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<td>11</td>
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<td>-</td>
<td>-</td>
<td>18%</td>
<td>11</td>
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<td>64%</td>
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<td>28</td>
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<tr>
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<td>28%</td>
<td>112</td>
<td>401</td>
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</tr>
<tr>
<td><strong>% spread</strong></td>
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<td>1099</td>
<td>14</td>
<td>31</td>
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<td>243</td>
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<td></td>
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<td><strong>45.2</strong></td>
<td><strong>11.9</strong></td>
<td><strong>18.6</strong></td>
<td><strong>30.5</strong></td>
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</table>

Spread of focal dystonia with respect to onset phenotype (only studies primarily addressing spread included)
1.4 Motor control in dystonia and the basal ganglia

1.4.1 Anatomy of the basal ganglia

The basal ganglia are comprised of a group of grey matter nuclei located deep within the white matter of the cerebral hemispheres. The main components are the caudate nucleus, putamen, globus pallidus, subthalamic nucleus, and substantia nigra. Other nuclei such as the nucleus accumbens and ventral pallidum, which participate in limbic and basal ganglia circuits are often included. The amygdala, another closely related nucleus has a greater role in the limbic system.

The caudate and putamen are histologically and embryologically closely related and are referred to together as the striatum. The striatum receives all the inputs of the basal ganglia. The two nuclei are separated by the internal capsule, but send bridging fibres across. The caudate lies inferolateral to the lateral ventricle with its head forming the posterior wall of the frontal horn. Anterior to the putamen lies the nucleus accumbens, and where they are fused is the ventral striatum, an area important for limbic circuitry and also visual processing of structure, depth, shape, colour and detailed object visual appreciation.

Medial to the putamen lies the globus pallidus, which has an internal (GPi) and external (GPe) segment. In conjunction with the putamen, it is referred to as the lentiform nucleus. The thalamus, not strictly a part of the basal ganglia, is the most important relay station in the brain, and is located caudal to the tail of the caudate nucleus and medial to the internal capsule. Immediately inferior to the thalamus is the subthalamic nucleus (Blumenfeld, 2002).

In the striatum, there is a topographically organised motor layout of neurons. The foot lies dorsal in the putamen, the face ventromedial and the hand lies in...
between. Overlap of these territories is more prominent for face and hand (Maillard et al., 2000). The pattern differs from the linear pattern seen in the sensorimotor cortices, and may reflect the functional requirements of striatocortical activity. Motor-related activation occurs mainly in the putamen at the level of the anterior commissure, which is the site of major targets of efferents from the motor areas (M1, premotor and supplementary motor cortex) and somatosensory areas BA3, BA1, BA2 and BA5 (Gerardin et al., 2003, Alexander et al., 1990).

1.4.2 Neurophysiology of the basal ganglia

Virtually all inputs to the basal ganglia arrive via the striatum. Outputs leave via the GPi and the substantia nigra pars reticulata (SNr). The main inputs are from the cerebral cortex to the striatum, especially the putamen for motor control. Intralaminar nuclei of the thalamus send excitatory inputs to the striatum, especially from the centromedian and parafascicular nuclei. The raphe nuclei (medial to the medial lemniscus) of the brainstem also have inputs into the basal ganglia, which are serotonergic. The cerebellum has inputs to the thalamus, via the thalamic fasciculus posterior portion to the ventral lateral nucleus caudalis and medialis (VL).

GPi and SNr activity in signalling out are divided. The SNr appears to have outputs for the head and neck, and the GPi for the rest of the body, but these are not strictly true since lesioning of the GPi can help with movement disorders of the craniocervical region (Chang et al., 2002). These are inhibitory, and the main pathway out is via the VL and ventral anterior (VA) nuclei of the thalamus. Information for motor control travels predominantly to the premotor cortex (from VA), the supplementary motor area (caudalis portion of VL) and the primary motor cortex (mostly from medialis portion of VL). There are also outputs to the striatum via the
intralaminar nuclei (centromedian and parafascicular) of the thalamus, and to the mediodorsal nucleus which is involved in limbic pathways. GPi and SNr output also is directed to the pontomedullary reticular formation via the pudunculopontine raphe nucleus, influencing signalling in the descending reticulospinal tract (γABA). The SNr also projects to the superior colliculus influencing the tectospinal tract. Therefore the basal ganglia modify the lateral and medial motor systems (Blumenfeld, 2002, Alexander et al., 1990).

Within the basal ganglia, a model of their intrinsic activity has been widely accepted – the direct and indirect pathways, first described by Graybiel and Ragsdale in 1983 (Blumenfeld, 2002, Alexander et al., 1990). Much of this has been derived from knowledge of studies of motor and oculomotor circuits in primates in normal and pathologic states, using depth electrodes and anterograde/retrograde tracers. The basal ganglia exert a tonic γABA-mediated inhibitory effect on their target in the thalamus, by virtue of their high rates of continuous spontaneous discharge (70-90 Hz). The direct pathway to GPi/SNr arises from striatal neurons that contain γABA and substance P. Activation of the striatal neurons, which are normally quiescent leads to disinhibition of the thalamus. The indirect pathway to GPe, and then GPi/SNr via STN, involves γABA and enkephalin firstly, then γABA and finally glutamate. The high spontaneous discharge rate of GPe neurons tends to inhibit STN, so inhibition of GPe by γABA and enkephalin increases the excitatory drive on GPi/SNr, with the result of increased inhibition on the thalamus. Data exist that may support phasic increases and decreases in the output through these pathways that act as a gearing mechanism to control motor output from the cortex to execute complex movement. Hypokinetic states (parkinsonism) result from tonic increases in the discharge rates of GPi and STN neurons, and tonic decreases in GPe neurons. In
hyperkinetic states (dystonia), the GPi/SNr output is tonically reduced (e.g. from overactive inhibition from the putamen) resulting in thalamic overactivity in thalamocortical projections.

This simple model was revised and a dynamic model of the function of the basal ganglia was proposed (Nambu, 2004). They had found that stimulation of motor cortical neurons led to a short-latency excitation of pallidal neurons, which hypothetically could be from a hyperdirect pathway via the STN (cortico-STN-pallidum). The theory was supported by the following findings: monkey STN receives somatotopically organised inputs from M1/SMA/PMC and in turn sends outputs to the GPe and GPi/SNr; simultaneous recordings in the STN and pallidum of M1 stimuli show short-latency signals in the STN and then pallidum; STN stimulation activates the pallidum orthodromically; γABA blockade in the STN abolished short-latency and long-latency excitation in the pallidum; NMDA-receptor antagonism (glutamatergic blockade) in the STN suppressed short-latency pallidal excitation; and γABA-receptor antagonism in the STN has little effect on short-latency excitation in the pallidum. So the new model worked for the proposed mechanism of motor programme selection called “centre surround” (Mink, 2003). The model proposed that when a voluntary movement is to be initiated by the cortex, a first signal is transmitted to the GPi via the hyperdirect pathway, activating GPi neurons and resulting in inhibition of large areas of the thalamus and cerebral cortex related to the selected motor programme and other competing programmes. A corollary signal through the direct pathway is conveyed to the GPi, inhibiting a specific population of pallidal neurons in the centre area, which disinhibit their target areas in the thalamus and cortex, releasing only the selected motor programme. A third component signal is sent through the indirect pathway, the last to reach the GPi and leads to an inhibition
of the thalamus and cortex once again. Involuntary movements in the hyperkinetic state may occur if the GPi/SNr output is randomly or tonically paused.

In the cortico-subcortical loop, movement that involves a highly repetitive stereotypical task like tapping the middle finger causes activation of the putamen, the motor cortex (M1), the posterior SMA, and the cerebellum. However, when subjects learn a new sequence of movements, with additional cognitive demand, more anterior parts of the striatum are activated (caudate nucleus and putamen rostral to the anterior commissure) as well as prefrontal cortex and anterior cingulate area (Gerardin et al., 2003).

1.4.3 Neurochemistry of the basal ganglia

The corticostriatal inputs are excitatory and use glutamate as a neurotransmitter. The other important input to the striatum is nigrostriatal, using dopamine, which can be inhibitory or excitatory to the putamen. Glutamatergic inputs come from thalamic intralaminar nuclei to the striatum, and from the subthalamic nucleus to GPe and GPi/SNr. Serotonin input comes from the raphe nuclei of the brainstem. Thalamocortical outputs are predominantly inhibitory and use gamma-amino-butyric acid (γABA). Striatopallidal output is inhibitory by both γABA and substance P to the GPi/SNr and γABA and enkephalin to GPe (Nambu, 2004, Blumenfeld, 2002, Alexander et al., 1990).

1.4.4 Motor signalling abnormalities in dystonia

The dystonic state is characterised by prolonged muscle contraction, causing sustained twisting movements and abnormal postures of the body parts. Electromyography shows evidence of co-contraction of agonistic and antagonistic
muscles, and also overflow activation of extraneous muscles (Cohen and Hallett, 1988). There is a loss of the balance of the inhibitory and excitatory effects that would normally produce meaningful posture and result in abnormal movements in dystonia.

A deficit in the inhibitory component has been demonstrated in dystonia of all types. The blink reflex was found to have bilateral R1 components in blepharospasm (Gomez-Wong et al., 1998b), and there is evidence of generalised liability to a hyperexcitable state in dystonia (Cohen et al., 1989).

In dystonia, there are overactive basal ganglia, abnormal cortical activation patterns and a disinhibited motor cortex. Patients with writer’s cramp studied using activation PET showed that writing repetitively activates dorsal prefrontal cortex ipsilaterally, anterior cingulate cortex, rostral SMA, parietal cortex, contralateral lateral premotor cortex, both insulae, the thalamus, the basal ganglia and the vermis. There is significant underactivity of the caudal SMA, bilateral sensorimotor cortices, ipsilateral premotor cortex, and posterior cingulate cortex (Ceballos-Baumann et al., 1995b). In controls there was less activation of ipsilateral parietal cortex and orbitofrontal cortex, and no activation of the dorsal prefrontal areas or basal ganglia (Ceballos-Baumann and Brooks, 1998). The results are consistent with inappropriate overactivity of striatofrontal projections and impaired activity of motor executive areas. They also partially suggest that apart from doing a stereotyped activity in FHD while writing, the brain is performing as if this was an unfamiliar task (Gerardin et al., 2003).

Transcranial magnetic stimulation studies examining intracortical inhibition with double stimuli (conditioning pulse and stimulus) have shown enhanced contralateral MEPs in patients with dystonia (Ridding et al., 1995). TMS is presumed to activate intracortical inhibitory circuits using γABA, which is evident as the silent
period. There is a shortened silent period following a TMS pulse evoked MEP in
dystonic patients (Chen et al., 1997), and shorter again during involuntary dystonic
contraction (Ikoma et al., 1996). There is impairment of motor inhibition throughout
the motor cortex in patients with blepharospasm and idiopathic cervical dystonia, with
significantly shorter silent periods measured at the eye and the mouth, but not the
neck and the hand (Cakmur et al., 2004). Peripheral stimulation creates abnormally
large motor outputs in dystonia as shown in a study on focal hand dystonia subjects
who had their median nerve stimulated as conditioning prior to a TMS pulse
(Abbruzzese et al., 2001), but not in torticollis patients or controls. In addition to
these, measures of movement preparation such as the movement-related cortical
potential (Deuschl et al., 1995) and contingent-negative variation were deficient in
focal dystonia (Ikeda et al., 1996). Deficiency of these occurs in a state of loss of
inhibition (Hallett, 2004). Finally, a lack of γABA is evident in the motor cortex in
dystonia (Levy and Hallett, 2002). A reduction of γABA or blockade with bicuculline
of its receptors leads to co-contraction of agonistic and antagonistic muscles.

Neurophysiological measurements of abnormal outputs within the basal
ganglia have been examined. Vitek and colleagues examined the basal ganglia of
three patients with generalised dystonia undergoing pallidotomy using
microelectrodes (Vitek et al., 1999). Measuring the mean discharge rates from GPi
and GPe neurons compared to literature controls, they found that the discharge rate
from both is lower: 37.7 ± 28.0 Hz for GPe neurons and 50 ± 20.5 Hz for GPi neurons
\( p < 0.001 \). The discharges were erratic, coming with irregularly grouped bursts and
intermittent pauses. GPi firing rates have been found to be low in \( dt^{19} \) hamsters who
have an idiopathic paroxysmal dystonia with stress-inducible attacks (Gernert et al.,
2002). The discharge pattern was also highly irregular in those at greatest risk.
according to age. In cases of spontaneous remission, discharge patterns normalised, but rates remained slow. Substantia nigra neurons discharge rates did not differ between dystonic and non-dystonic hamsters. Benefit from pallidotomy may occur from removal of the altered discharge pattern. The effect of thalamic stimulation on the motor cortex depends on the site of stimulation, and stimulus parameters (high frequency or low frequency stimulus). Stimulation of the Vim in essential tremor led to an increased apparent excitability of the M1, as seen with enlarged MEPs (Molnar et al., 2005). However, anterior thalamic stimulation showed increased short-latency intracortical inhibition in patients with epilepsy (Molnar et al., 2006). In Parkinson’s disease, high frequency GPi DBS reduced motor cortical silent periods without altering other components (Chen et al., 2001). In generalised dystonia, high frequency stimulation of the GPi also led to a hyperexcitable motor cortex, but with clinical efficacy presumably through stimulation related “lesioning” of the cortical-basal ganglia loop (Tisch et al., 2008, Kuhn et al., 2003).

1.4.5 Imaging findings in AOPTD

Routine structural imaging studies have not identified any abnormalities in AOPTD. In both DYT1 and AOPTD dystonia, the only abnormalities on any type of structural imaging are found using diffusion tensor imaging (DTI) in subcortical white matter and deep white matter connections to the basal ganglia particularly the pallidum and putamen (Bonilha et al., 2007, Carbon et al., 2004). fMRI has shown disorganised somatotopy in the putamen in patients with FHD. Fourteen subjects examined performing finger and toe flexion/extension and lip contraction showed somatotopic disorganisation in the putamen contralateral to the affected hand. In the ipsilateral putamen, there were reduced distances between hand and lip representations without
somatotopic disorganisation (Delmaire et al., 2005). In a study on putaminal volume in idiopathic focal dystonia and blepharospasm, there was a trend towards a larger volume of putamen compared to controls (Black et al., 1998, Etgen et al., 2006). Later studies showed reduced grey matter volume bilaterally in cervical dystonia (Obermann et al., 2007). Cortical structures were also studied using voxel-based-morphometry (VBM) in 36 patients with FHD. The authors found a significant increased volume of gray matter in the primary sensory and primary motor cortex around the hand area (Garraux et al., 2004). Research following the work of this thesis examined affected and unaffected members of multiplex AOPTD families and sporadic patients and unaffected family members. Unaffected family members with abnormal sensory measurements were found to have larger corpora striata than affecteds or controls (Walsh et al., 2009b).

In DYT1 dystonia, there is significant regional hypermetabolism seen on PET, particularly of the lentiform nucleus, which is independent of activity in the thalamus. This activity dissociation suggests functional inhibition of the GPi leading to release of the thalamocortical circuit. There is then an associated increase metabolic activity in the primary motor area, the premotor area and the supplementary motor area (Eidelberg, 1998). In AOPTD, there was initially a dichotomy as to the true nature of activity in the brain, but recent studies have consistently shown hyperactivity in the basal ganglia with motor and non-motor tasks, with particular activation of the putamen in relation to movement and the thalamus with both movement and sensation (Tempel and Perlmutter, 1993, Ibanez et al., 1999, Ceballos-Baumann et al., 1995a, Peller et al., 2006). Primary cortical sensory and motor areas are bilaterally hypoactive, but there is enhanced activity in association areas and the recruitment of areas not usually associated with movement. Functional imaging using SPECT with
[\(^{123}\)I]-epidepride, a D2-receptor marker, and [\(^{123}\)I]-Beta-CIT, which binds to dopamine transporters on dopaminergic nerve endings, has shown a significantly reduced affinity bilaterally within the striata of patients with idiopathic cervical dystonia (Naumann et al., 1998).

1.4.6 Motor paradigms in non-manifesting DYT1 carriers

Eidelberg and colleagues examined metabolic substrates of brain function in manifesting and non-manifesting carriers of the DYT1 using \(^{18}\)FDG-PET. Based on previous results in two separate studies where they had examined non-manifesting carriers of the TOR1A deletion to eliminate movement artefact, they repeated the study with three groups, as above including a control group. Using two conditions, movement free (MF) and movement related (MR), they scanned all patients looking for two particular subtypes of metabolic profile that they had previously identified using factor analysis methods (scaled subprofile model). They identified a significant difference of the metabolic profiles of the DYT1 gene positive groups from the controls in the MF condition. They postulate that the clinically non-manifesting carriers metabolic profile supports the expression of the gene in the brain similar to the manifesting group (Eidelberg et al., 1998).

Edwards and colleagues examined manifesting and non-manifesting carriers of DYT1 using TMS, and assessed intracortical inhibition, intracortical facilitation, cortical silent period and spinal reciprocal inhibition. The DYT1 manifesting group showed reduced intracortical inhibition, a shortened silent period and an absent presynaptic phase of reciprocal inhibition concurring with other studies in genetically undetermined subjects with primary torsion dystonia. The non-manifesting carriers also had reduced intracortical inhibition but no change of the reciprocal inhibition
compared to controls. The results again suggest that there is the presence of a disinhibited cortex in all those with the \textit{DYTI} deletion (Edwards et al., 2003).

\textbf{1.4.5 Summary of motor control in dystonia}

The basal ganglia inputs information via the striatum primarily from the primary and associative motor and somatosensory areas of the cortex. The output is through the GPi/SNr, which is inherently inhibitory. Within the system there are two pathways that modulate GPi/SNr output to the thalamus, and hence back to the cortex: the direct and indirect pathways. The system probably operates on a model of centre-surround inhibition to select out single cortical programmes/events. In focal dystonia, the basal ganglia are hyperactive in motor and sensory tasks, but the GPi and GPe have irregular discharges that lead to thalamic disinhibition. There is also evidence that the cortex itself has widespread disinhibition but does not show increased metabolism or activation with movement or sensorimotor integration in primary areas. These hallmarks of dystonia are identifiable in non-manifesting gene carriers in genetic forms such as \textit{DYTI}. 

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1.5 Sensory involvement in primary torsion dystonia

1.5.1 Afferent central pathways: functional divisions and homunculi

The brain as a computational centre of afferent and efferent signals sources much information through various sensory inputs to modulate its motor output. For the processing of motor commands, it relies on information regarding current posture provided by memory of most recent posture, most recent action, muscle spindle afferents, Golgi organs in muscle tendons, proprioceptive signals from joints, somatosensory inputs from skin, orientation in relation to gravity through the vestibular system, and visual cues. Sensation is probably best described anatomically, with respect to its functional organisation. The human being is an autonomous organism, but depends highly on tropism (ie sensory inputs) to generate new movement.

Cutaneous receptor afferent fibres are bipolar cells: their cell bodies lie in the dorsal root ganglia, with sensory endings in the skin and terminal ends within the central nervous system. The dorsal roots have a cutaneous pattern that is derived from the embryological development of the CNS, but there is significant overlap between adjacent dermatomes. There are two main types of sensory receptors in the skin: encapsulated; and free endings. Meissner’s corpuscles, Ruffini endings, Merkel discs, Pacinian corpuscles are encapsulated, and are mostly found in glabrous skin areas such as finger pads, palms, eyelids, lips, external genitalia, and soles of feet (Carpenter, 2003). Encapsulated sensory receptors generally have A\textsubscript{\beta} nerve fibres, which are large and myelinated. Free endings usually have small A\textsubscript{\delta} or C fibres, which are unmyelinated.
All enter the central nervous system via the dorsal root, where they are organised in the dorsal horn. This is typically divided into six layers – Rexed’s laminae. Laminae I, II and V contain the small Aδ and C fibre endings, which synapse with second order neurons which relay information to the thalamus in the spinothalamic tracts. Also in laminae I and II are lateral inhibitory neurons and descending fibres which modify signal transmission. Large Aβ fibres entering the dorsal horn turn upwards and ascend in the dorsal columns to the medulla, but send branches to laminae III-V. Lamina II receives inputs from lamina IV with mechanical information from large fibres via short interneurons. The difference between the two fibres and their organisation is related to their function. Large fibres provide epicritic feedback to the central nervous system fast in order to allow efficient operation, particularly of the motor system.

The neocortex of the human brain is highly organised with six layers (I-VI). Layer IV receives the bulk of sensory afferent projection from subcortical regions like the thalamus. The large terminal trees end mostly on stellate (smooth inhibitory γABA releasing or spiny excitatory glutamatergic) neurons. The stellate cells, confined to the cortex, are arranged horizontally in the layers and also in columns about 0.5mm in diameter. Pyramidal cells are the main output from the cortex to subcortical structures. Smaller pyramidal cells though provide the connection for interaction between different columns of cortex. They have a single long apical dendrite and a group of basal dendrites, which allows the cell to interact within its column and project to other columns of cortex where it can interact further. Pyramidal cells are glutamatergic excitatory cells, although some possibly use aspartate. They principally occupy layer III, V, and VI. In the sensory cortex though, layer IV tends to be prominent with many large bushy afferent from the thalamus, ramifying into
stellate cells. In addition to these cells, other interneurons facilitate connection between layers and across layers, mostly by inhibitory signals.

Neurons from the thalamus project entirely to the cerebral cortex, and it functions not only as relay centre for all sensory input, but as an integral unit with the cortex in the processing of sensory information. Anatomically it is divided by internal medullary lamina into three main areas: anterior, medial and lateral. The somatosensory system is associated with two nuclei within the lateral division. The ventroposterolateral (VPL) nucleus receives sensory information from the trunk and limbs, and the ventroposteromedial (VPM) is concerned with sensation from the head and neck. Second order afferents ascend as the medial lemniscus after crossing via the internal arcuate fibres from the opposite side at the nucleus fasciculus cuneatus (inputs from above T6) and nucleus fasciculus gracilis (inputs from below T6) in the caudal medulla. Third order neurons then project from the VPL to the somatosensory cortex areas. The sensory homunculus, or histo-anatomical organisation of neurons in relation to their topographical origin, is preserved throughout the somatosensory pathway to the cortex. In contrast to the lemniscal pathway, the spinothalamic tract (anterior and lateral) projects to the border of the VPL (pain and light touch), central and intralaminar areas of the thalamus, and diffusely to the reticular formation of the medulla and pons (temperature). So the phylogenetically older spinothalamic sensory tracts do not project to the cortex as much at all, suggesting that it is a system more concerned with behaviour and response generation.

Apart from cutaneous sensation, the other important part of the somatosensory system relates to proprioception and joint position. The majority of sensory information from the mechanoreceptors mediating this information is afferent to the cerebellum via the posterior spinocerebellar tract, and the accessory cuneate nucleus.
Proprioceptive output from muscles is derived from specialised cells called muscle spindles and Golgi organs. Muscle spindles respond to stretch and rate of change of muscle length. Golgi organs are similar to Ruffini organs in skin. They have collagenous fibres embedded into surrounding tendon and respond to tension within the tendon.

The extrapyramidal system uses sensory information to fine tune movement. There is a constant integration of the sensory inputs and motor outputs. Apart from tracts, sensory information is relayed to discrete higher centres, where mechanisms such as surround inhibition allow for details of sensory input to be appreciated. The somatosensory cortex in most mammals involves five somatosensory areas: a primary field (S1), a second area (S2), a parietal ventral area (PV) just rostral to S2, and narrow bands of somatosensory cortex along rostral and caudal borders of S1 (Kaas and Collins, 2001).

S1 (Brodmann Area 3) organisation reflects the peripheral sensory specialisation of mammals. This can be according to area devoted to a specific peripheral sensory organ, such that in general important skin and hair areas have larger representation in the neocortex. An example is the star-nosed mole, with a nose made up of 22 appendages covered in mechanoreceptive Eimer’s organs that are used to explore the environment by touch. In S1, the eleven contralateral appendages are cytochrome-oxidase rich strips separated by areas of lighter cortex. They are heavily over-represented here. The smallest appendage, which is just over the mouth, actually has proportionately the largest area of representation, which has led to it being given the name “tactile fovea.” Similarly, the striped possum has a unique forepaw with an elongated fourth digit used for extracting insects from trees. The receptors in this digit
have an expanded representation in S1. The same findings apply to the sensory fields for the facial micovibrissae of rats, mice and other rodents.

The important tactile surfaces in primates are the glabrous hand, lips and mouth; the homunculus of Penfield shows this most eloquently (Penfield and Boldrey, 1937). The S1 regions for these areas can easily be seen on brain section with cuts parallel to the surface because they are rich in myelin and cytochrome-oxidase. There is a distinct pattern of morphological organisation for each digit and subdivisions of the hand, which has a lateromedial sequence beginning with the thumb, and each digit/hand subdivision is separated by faint septa. (For the face, there is representation for face, upper lip, lower lip, contralateral teeth, tongue, ipsilateral teeth and tongue in a rostrocaudal sequence in the cortex.) Although amputation or other deafferentation results in physiological reorganisation, anatomical integrity, as judged by the pattern of myelin staining, is not altered on the morphological map (Jain et al., 1998).

The exact function of rostral (BA3a) and caudal (BA1) somatosensory bands is largely unknown because it has been hampered by difficulty of stimulation under anaesthesia. However, the somatotopic organisation of both parallels that of BA3b.

Brodmann Area 2 (BA2) is a narrow band area along the posterior margin of BA3. It has similar topographical mapping to BA3. It has been poorly understood, but some recent work suggests that it may be unique to anthropoid primates with opposable thumbs (Eickhoff et al., 2008). It is involved in proprioception, even visual appreciation of proprioception, and thus important for movement preparation in planning expected proprioceptive afferent information as a means to tune quantity of movement, or kinaesthesia (Oouchida et al., 2004). It is thus most likely a visual association area concerned with limb movement, where visual and proprioceptive information are integrated and refined. Interestingly, the right hemisphere BA2 is
activated in right-handed individuals, irrespective of the side of the body stimulated, suggesting that it obeys the principle of bodily perception being right hemispheric (Naito et al., 2005). There is activation of the some frontal motor areas (BA4 and BA6) associated with BA2, but in contrast to BA2 right hemispheric activation, the motor areas were contralateral.

The second somatosensory area and parietal ventral area are two adjacent areas located on the upper bank and parietal operculum of the Sylvian (lateral) fissure, and have mirror reversal of each other. They are activated by any somatosensory stimulus that involves S1. As in S1, there is a somatotopic organisation too (Disbrow et al., 2000), however, it is less defined and primarily correlates with sensory stimuli in the hands. These sensory representations have very large bilateral receptive fields. The organisation of the sensation here appears to be related to dexterity and manual coordination, and may be unique to primates. The shoulder, upper limb and face represent the majority of the remaining somatic map in this area. Lesions of this area are associated with disturbance of pain and temperature, and later a thalamic type of pain (Brazis et al., 2001a). Vibratory stimuli to a single hand have been shown to cause the bilateral activation using PET and fMRI.

1.5.2 Sensory integration in movement

Proprioceptive feedback is an important part of movement planning and execution in humans. Intuitively we know that visual inputs are also important, but visually impaired subjects have much greater motor control than those with proprioceptive sensory loss and preserved vision. Given the importance of functional flexibility for motor planning and execution, Sober and Sabes examined target-directed reaching movement in normal subjects (Sober and Sabes, 2005). They confirmed that
proprioception is more accurate than visual input in guiding movement using a simple goal directed task. They measured movement vector at initiation of movement and joint angle change to correct for target location. This experiment highlights the importance of sensory inputs for accurate movement execution, and how much dependence is on sensory integration in the planning/executive part of movement. This work had been planned with a background of similar work in Macaque monkeys which demonstrated the importance of integration of proprioceptive and visual inputs in the premotor cortex (Graziano, 1999). The results showed less of an influence from proprioceptive inputs directly when measuring single neuron receptive fields in the premotor cortex. Possibly, proprioceptive information is first integrated in the medial parietal lobe after cortical representations are processed as mapped in kinaesthesia studies that have identified BA2 (Oouchida et al., 2004, Naito et al., 2005).

Movement is contingent on sensory afferent information, and therefore the somatosensory system must be involved in the preparation of movement. Murase and colleagues examined how the sensory system prepares the cortex for movement by examining sensory signals using sensory evoked potentials, and eliminating the effect of contingent negative variation (Murase et al., 2000). In their study comparing controls and focal hand dystonia, they found that normal subjects have a reduction in sensory potential amplitude in the premovement stage, but in dystonic subjects there was no reduction. They used subtraction of the contingent negative variation to eliminate the central effect on movement preparation, and their results support the theory that there is sensory dysfunction associated with movement in dystonia.

There are possible abnormalities of vestibular function that have mostly been studied in patients with cervical dystonia. This is no doubt because of the nature of the often-noticeable laterality of the movement, with rotation, lateral tilt, and
retrocollic flexion, plausibly symptomatic corrective postures. The neck has important proprioceptive inputs for the vestibular system, and focal dystonia has been frequently reported in association with cerebellar lesions (O'Rourke et al., 2006, Zadro et al., 2008, Loher and Krauss, 2009). The cerebellum projects to the prefrontal cortex (BA9, BA12 and BA46) from the dentate nucleus via the thalamus (Middleton and Strick, 2001). The dentate origins of the pathway help with planning movement, and are integrating the sensory proprioceptive inputs from descending projections from S1 allowing constant sorting and shifting for controlled motor output. Vestibular dysfunction by itself rarely produces torticollis (Munchau and Bronstein, 2001). However, disorders affecting the neck musculature may be responsible for unsteadiness or provoke dizziness (Brandt and Bronstein, 2001). Vibratory induced posture, kinetic, and gait abnormalities have been shown with neck muscles, and Bove and colleagues examined if neck proprioceptive afferents were dysfunctional in cervical dystonia (Bove et al., 2004). With various paradigms of neck muscle vibration, it was shown that subjects with cervical dystonia improved the rate of error with stepping-in-place compared to controls, and the average body rotation with lateral neck muscle vibration did not show any difference. However, stepping-in-place without vibration was significantly different from controls. This is comparable with the improvement in neck electromyography activity seen by Leis (1992) when neck muscles were vibrated. This does not answer the question about how vibration might improve cervical dystonia.

The sensory trick, or geste antagoniste, is a modulator of dystonic activity that reduces dystonic movement by providing sensory feedback from a particular area. This has been documented since the late nineteenth, and may have contributed to the later idea of dystonia being a psychosomatic problem. However, the effect of sensory
stimulation in modulating dystonic activity has been looked at by both surface electromyography (Leis et al., 1992, Schramm et al., 2004) and using H\textsubscript{2}\textsuperscript{15}O positron emission tomography (Naumann et al., 2000). Sensory stimulation can reduce dystonic muscle activity by 26% in all patients with cervical dystonia irrespective of their reported benefit from a *geste antagoniste*. In those with a sensory trick, there is a 38-49% reduction, when externally or internally applied (by an examiner or the patient). Overcorrection of head posture can further improve the reduction by up to 55%, which corresponds to patient reports of muscle pain and activity being improved when they correct their head posture. Positron emission tomography (PET) study shows decreased activation of BA3 with a Z-score of 5.58 when comparing activity with no sensory trick versus using a trick stimulus on the contralateral cortex to the side of rotation. In this experiment on cervical dystonia patients by Naumann and colleagues all seven subjects had effective tricks ipsilateral to the direction of head rotation (Naumann et al., 2000). This sensory cortical change was contemporaneous with a reduction in activity in the motor cortex contralateral to the direction of rotation (BA4). The supplementary motor area (BA6) showed bilateral reduction in activity. On the opposite hemisphere, there was enhanced activation of BA40, 2/5 and 7. This suggests that trick application also modulates motor activity at a cortical level. This study also showed bilateral activation of the occipital cortex (BA17, 18) and the ipsilateral posterior parietal lobule (BA7, 40). The posterior parietal cortex is an association area that integrates sensory information from the contralateral hemisphere yielding cognitive spatial awareness. The activation of these visuospatial areas suggests that the sensory trick gives a new egocentric frame of reference to an abnormal internal alignment in primary torsion dystonia (Anastasopoulos et al., 1997a, Anastasopoulos et al., 1997b).
1.5.3 Functional measures of sensory cerebral activity in dystonia

In primary torsion dystonia, there are no abnormalities seen on routine imaging of the brain. In individual patients, the sensory areas are grossly entirely normal. However, reports of lesions of the primary somatosensory cortex seen on MRI have been documented to be associated with dystonia/pseudoathetosis (Liepert et al., 2003). As imaging techniques have improved with higher power MRI scanners, and statistical parametric mapping software has become more refined, it has been possible to look at the structure of the primary somatosensory cortex in more detail in dystonia. Garraux and colleagues examined 36 patients with focal hand dystonia using VBM, a technique to measure brain volume (Garraux et al., 2004). They found bilateral increased volume of the hand representation area of the primary somatosensory cortex, and to a lesser extent the motor cortex. Of note there was no difference in lentiform nucleus volume, and all values were corrected for multiple comparisons and small volume measurement of a spherical mass. Z-values for BA2, 3b, and 3b/4 on the contralateral side were 3.68, 3.24 and 3.77 respectively. On the ipsilateral side (unaffected) they were 3.72, 3.81 and 3.90. Thus the presence of these bilateral changes, without differences in motor areas alone, suggests that sensory abnormalities may be primary in dystonia.

Given that there are no generally identifiable abnormalities with structural imaging of the brain, functional imaging using positron emission tomography and functional MRI was a logical progression. In an early landmark study of regional cerebral blood flow (rCBF) measured using H$_2^{15}$O PET, Tempel and Perlmutter described a reduction in rCBF at the sensorimotor cortex using vibration of the forearm muscles in eleven patients with dystonia: nine with unilateral focal hand
dystonia, and two with idiopathic torsion dystonia (Tempel and Perlmutter, 1990). They used the paradigm of vibration of muscles having observed that vibration of a dystonic muscle elicited a contraction, and believing that it would eliminate the multiple cortical changes involved with task performance. Despite poor resolution of imaging, they remarked on the bilateral reduction in rCBF, irrespective of the dystonic hand in these subjects, and concluded that sensorimotor processing must be abnormal in primary dystonia. Ceballos-Baumann and colleagues examined regional cerebral blood flow using H$_2^{15}$O PET in six patients with idiopathic torsion dystonia (Ceballos-Baumann et al., 1995b), however, five out of the six patients had early-onset primary torsion dystonia, three of the six had generalised dystonia, and three were DYT1 deletion carriers. Similar to Tempel and Perlmutter's observations, they did not find a difference in global resting regional cerebral blood flow compared to six controls. However, using their paradigm of motor task performance with a joystick, they found enhanced activation of the contralateral lateral premotor cortex (BA6), the rostral supplementary motor area (rostral mesial BA6), mesial BA8, the ipsilateral dorsolateral prefrontal cortex (BA9, 46) and the anterior cingulate cortex (BA32). Slightly less enhanced activation was seen in the ipsilateral anterior insula, the ipsilateral medial temporal gyrus (BA21), both lentiform nuclei, and bilateral lower premotor cortex (BA6) adjacent to the insula. In summary, the areas of maximal activation were ipsilateral dorsolateral prefrontal cortex, and contralateral rostral premotor cortex, rostral supplementary motor area, anterior cingulate and lentiform nucleus. These correspond with the basal-ganglia thalamo-cortical loops (Alexander et al., 1990). Areas of reduced activation were ipsilateral caudal supplementary motor area and bilateral somatosensory cortex. The increased cerebral blood flow in the prefrontal areas, and underactive cortical areas during movement
suggest the dysfunction of motor program execution and planning in dystonia, even though there was no difference in motor performance for the task between groups in this study (one sample t-test, p>0.2). The contrasting relative reduction in blood flow to cortical areas such as the somatosensory cortex could be attributed to dysfunction in the loop for motor activation. The dual activation of rostral and caudal supplementary motor areas is possibly due to their differing functional nature. The caudal supplementary motor area is very much executive, with projections to the primary motor cortex and the spinal cord. However the rostral area is primarily involved in movement selection.

Regional cerebral blood flow has also been examined in focal dystonia, but only writer's cramp, probably because it lends itself to CNS imaging while using the affected hand. The researchers examined seven patients and seven control subjects, using three paradigms: sustained contraction of finger/wrist muscles, tapping, and writing. They found that there was bilateral deficiency in somatosensory cortical rCBF during sustained contraction and writing, and contralateral reduction in rCBF here for tapping. In comparing the two groups using subtraction from the resting state, a significant difference was shown for the contralateral SI (z-score 4.96, p=0.007). They state that handwriting stimulates the greatest change in rCBF in nonprimary motor regions in normal subjects, and thus it must also in dystonic subjects. The simpler task of sustained contraction may have been better at identifying the reduced rCBF by showing greater abnormality in the primary somatosensory cortex that is important in the pathogenesis of focal dystonia.

When one examines cortical areas in DYT1 dystonia using cerebral glucose metabolism, motor areas are functionally overactive at rest, but not somatosensory areas (Eidelberg, 1998). In an earlier study on 16 patients with torticollis, no focal
area of abnormality was identified, although the general appearance suggested a bilateral pallidothalamic breakdown on correlation analysis between regions of interest selected (Stoessl et al., 1986). There was increased metabolism in the basal ganglia using $^{18}\text{F}-2$-fluoro-$2$-deoxyglucose (FDG), particularly the lentiform nucleus and thalamus that did not correlate with the head of caudate nucleus activity compared to controls. However, they did not examine primary somatosensory cortex.

Preibisch and colleagues examined twelve patients with writer’s cramp using functional magnetic resonance imaging, which would give data on neuronal activation rather than blood flow or metabolism (Preibisch et al., 2001). Their paradigm was designed to look at motor activation, but they report that activation of the sensorimotor cortex extended further caudally in subjects with writer’s cramp. They also found that activation of the thalamus was only seen in writer’s cramp (ventrolateral nucleus) suggestive of greater interneuronal activity modulating sensory input.

To examine the sensory interaction between adjacent fingers in writer’s cramp, Sanger and colleagues employed functional magnetic resonance imaging (Sanger et al., 2002). They studied five patients and seven controls with a 1.5 tesla MRI, with four stimulation conditions: at rest digit 2; at rest digit 3; simultaneous stimulation of both digits with a medium bristle brush oscillating along the axis at 2 Hz. They found that the measured area of the somatosensory cortex produced a 12% error for combined stimulation in controls versus 29% in dystonia ($F = 11.0, p = 0.008$). The response in the normal subjects was well approximated by a linear superposition of individual finger responses, which was not the case in the dystonia subjects. Cluster analysis with error and age as principal components did not yield distinct groups, hampered perhaps by very small numbers. However, the results do show that
Simultaneous somatosensory activation occurs in a non-linear fashion in writer’s cramp, consistent with the hypothesis of dedifferentiation of sensory fields in dystonia. The dedifferentiation could still occur at many levels in the medial lemniscal pathway or thalamocortical tract.

Butterworth and colleagues examined nine patients with writer’s cramp and nine controls with fMRI stimulating digits 2 and 5 with an 8-second duration 80 Hz sinusoidal electrical stimulus (Butterworth et al., 2003). Vibrotactile stimulation with this resulted in activation of BA1, 3b, 40, 5 and S2 in both groups. However, differences in the spatial activation patterns were found for three-dimensional reconstructed digit 2 and 5 between controls and dystonic subjects. Patients had less separation than controls in BA1 (4.14 mm ± 0.23 vs 9.60 mm ± 1.24, p<0.001). However, 3-D separation in BA3b, 40, S2, and 5 were not significantly different. Similar to magnetoencephalographic and sensory evoked potential findings, the order of digits was also reversed in the antero-posterior and superior-inferior directions on two-dimensional analysis. Butterworth mentions in his discussion that a previous study by his group and others have had difficulty in detecting digit separation in healthy controls using vibrotactile stimuli, even with 4-tesla fMRI in S1 (Maldjian et al., 1999), but this has been shown using electrical stimuli in BA3b with fMRI. The lack of distinct separation using vibrotactile stimuli even in normal subjects elucidates our knowledge of the difficulty using vibration to measure sensory discrimination.

Magnetoencephalography is a technique using dipole moments from evoked potentials to map out cortical structures. Meunier and colleagues used the classical sensory homunculus to map the digit representation in the primary somatosensory cortex in patients with unilateral focal hand dystonia (Meunier et al., 2001, Penfield and Boldrey, 1937). They mapped the S1 areas for digits 1, 2, 3 and 5 (D1=thumb,
D5=little finger), examining the order of the areas, and the Euclidean distance between each digit area. In control subjects, there was correct order of digits (D1, D3, D5) in 72% on the non-dominant hemisphere, but only 56% in the dominant hemisphere ($\chi^2$, p<0.01). This is theoretically due to neuroplastic dedifferentiation from overuse feedback from the dominant hand. A similar result was found with the focal hand dystonia subjects: 61% correct order in the non-dominant hemisphere versus 47% in the dominant ($\chi^2$, p<0.05). In comparing controls against subjects for bilateral organisation of finger representation, about half of controls had correct ordering, but only 25% of subjects with focal hand dystonia ($\chi^2$, p<0.02). The most common finding was superimposed and inverted digital cortical areas for successive fingers, but occasionally they also found complete inversion of digital areas, with the thumb and little finger switched. Their measurements of interdigital distances (maximum distance and distance between adjacent fingers) showed significant differences on both sides for adjacent fingers, but only in the non-dominant hemisphere for maximum distance. They calculated a measure of somatotopic organisation too, and this was significant for the non-dominant side. Further subgroup analysis found that there was linear correlation between severity of clinical dystonia (Burke-Fahn-Marsden score) and degree of somatotopic disorganisation (p=0.02, r=0.979). In less severely affected patients, the somatotopy index was normal for the dominant hemisphere, but not for those with a Burke-Fahn-Marsden score of >10, where overlapping and disorganisation in S1 were very marked. Overall, the severity of clinical dystonia correlated with the degree of sensory disorganisation in the non-dominant hemisphere. They postulate that dystonia may arise in the dominant hand as a result of use – a maladaptive neuroplastic remodelling of the sensory cortex to help with motor execution that results in motor abnormality. Similar bilateral findings
were reported by Elbert and colleagues in their study on musicians with focal hand dystonia (Elbert et al., 1998)

1.5.4 Sensory testing in AOPTD

In a study by Byl and colleagues on the effect of dystonia on sensorimotor integration, they examined 15 subjects with unilateral focal hand dystonia and compared them to control subjects and subjects with tendonitis from repetitive strain (Byl et al., 1996a). Study subjects were examined using four of seventeen tests in the standardized Sensory Integration and Praxis Test (SIPT), which is a conglomerate of tactile motor tests and tactile perceptual tests. Subjects with focal hand dystonia performed poorer than others in the tactile perceptual tests of graphaesthesia (affected hand 78.5% correct, p<0.0143; unaffected hand 71.0%, p<0.0143) and manual form perception (percent correct 80%, p<0.0141; time to complete 7-14 seconds, p<0.008). In their discussion, they mention that graphaesthesia was measured not only on the palmar surface, but also the dorsum of the hands tested. Stereognosis (form perception) requires clearly defined receptive fields and the input of information from multiple fingers as objects are manipulated. In their testing, they found that subjects with focal dystonia performed better on tests of tactile localization on their affected side than their unaffected side. They conclude that overall somatosensory disturbances exist bilaterally in focal hand dystonia, but how this relates to the pathogenesis of dystonia is unclear. In this study they had found similar disturbance of sensorimotor integration using the SIPT, and hypothesized that sensory retraining may improve or reverse tendonitis and focal hand dystonia. Following on this hypothesis, Candia and Priori respectively tried limb immobilization to induce a biofeedback reversal of dedifferentiation that putatively occurred with a focal occupational dystonia (Candia
et al., 1999, Priori et al., 2001). Candia treated eleven professional musicians (piano, guitar and wind-instrumentalists) by splinting and coordinated finger exercises done daily (Candia et al., 2002). Candia’s group had already showed alterations of the somatosensory cortex in focal hand dystonia (Elbert et al., 1998), and now attempted to show that combined splinting and practise in coordinated movement would improve dystonic symptoms. This behavioural therapy worked for the string instrumentalist and pianoforte musicians, but not the wind instrumentalists. Priori and colleagues splinted the affected hand in eight guitar players for a mean of 4½ weeks (± 0.75), and showed a marked improvement in four, moderate in three and no improvement in one at 24 weeks follow-up. The question arises whether sensory abnormalities in focal hand dystonia are akin to those seen in repetitive strain, which are likely to be secondary to overuse. Overuse, deafferentation and retraining has been shown to cause neuroplastic changes in the primary somatosensory cortex where these neurons are particularly plastic (Van Boven et al., 2000, Xerri et al., 1999, Wang et al., 1995, Zeuner et al., 2002). While these potential changes suggest functional changes in somatosensory cortical organisation, they do not support the concept of sensory changes being “hard-wired” in the central nervous system of patients with idiopathic dystonia (Moore and Schady, 2000).

On a background of expanding literature in support of sensory abnormalities in dystonia, various aspects of sensory function presented themselves for investigation. An important and quantifiable measure of somatosensory processing is the ability to analyse somesthetic stimuli delivered at different time intervals. Tinazzi and colleagues reported that there were abnormal temporal discrimination thresholds in dystonia, having examined seven subjects (five with generalised dystonia) and compared them to controls (Tinazzi et al., 1999). They measured the closest temporal
difference that electrical stimuli could be identified as separate by stimulating the index finger of both hands with a 0.2 millisecond square wave pulse, three times over the sensory threshold. They found similar results on both hands in both groups of subjects. Using factor analysis for between-subjects factors, they identified that group and procedure were significant indicators of a difference: controls = 35.48 ms, dystonics = 96.91 ms. They looked at correlation between degree of motor impairment and the somaesthetic temporal discrimination thresholds (STDT), but found no correlation. The abnormal STDT is arguably confounded by some element that contributes to cognitive executive deficits in primary dystonia (such as concomitant depression or use of anticholinergic medication), but the stronger evidence for these deficits lies with early-onset generalised dystonia (Scott et al., 2003). Of interest to Jahanshahi and colleagues was the known overactivation of the dorsolateral prefrontal cortex in patients with dystonia when performing joystick tasks (Ceballos-Baumann et al., 1995b). This area is known to play a significant role in cognitive executive function in humans. They examined ten subjects with dystonia: 7 with focal adult-onset dystonia, and 3 with early-onset primary generalised dystonia. They used well-known neuropsychological inventory tests including the Wisconsin Card Sorting Test, the Missing Digit Test, Word Fluency and the Stroop Colour Word Naming Test, which are all strongly associated with the dorsolateral prefrontal cortex in humans (Jahanshahi et al., 2003). They compared their subjects to age and intelligence-quotient matched controls, and found no difference. Although it is possible to surmise that abnormalities of the STDT seen in Tinazzi’s study were due to deficient programming of information, it is more likely true abnormalities of sensory recognition, because cortico-striatal and cortico-pallidal connections are very important and temporal differentiation may have similar pathogenesis to the impaired
movement initiation and execution that is seen in dystonia. Research following from this thesis in subjects with AOPTD showed that 86% have abnormal STDTs (Bradley et al., 2010, Bradley et al., 2009). In the same study, the STDT has been found to be independent of the phenotype in AOPTD.

A different technique using electrodes on the dominant hand index finger 1.5 cm apart was used by Sanger and colleagues to measure the temporal discrimination threshold (Sanger et al., 2001). Their stimuli were 1 millisecond constant-current pulses at 1.5 times the sensory threshold. However, unlike Tinazzi’s group, they didn’t find statistical significance for their results, which were controls 52 msec ± 50, and dystonia subjects 107 msec ± 41.

Bara-Jimenez examined the somaesthetic temporal discrimination threshold in 14 patients with focal hand dystonia, and compared them to 13 age- and sex-matched controls (Bara-Jimenez et al., 2000b). They stimulated the right index finger with two electrodes 5 mm apart, and a different stimulation protocol to Tinazzi. Stimulus intensities were twice the sensory threshold, and they calculated the average of the stimulus interval below which stimuli were always perceived as a single stimulus, and above which stimuli were always perceived as separate. They found that dystonia subjects had an average of temporal discrimination threshold of 96.7 msec (± 43.6) and the control average was 64.4 msec (± 15.5, p = 0.016). Interestingly, they found a bimodal distribution of temporal discrimination thresholds in their dystonia patients. They found correlation for the temporal discrimination threshold against the severity of dystonia score (Burke-Fahn-Marsden Score). They also measured spatial discrimination with single touch Von Frey monofilaments on the digits of the right hand. The subject had to identify which phalanx of which finger was touched. However no difference was noted compared to controls, and this may be a result of
the insensitivity of the test to small changes in spatial localisation thresholds. Bara-Jimenez and colleagues modified their spatial acuity test using target localisation to a narrow grid on the skin over the palmar aspect of the right index finger middle phalanx (Bara-Jimenez et al., 2000a). With target points 2.5mm apart in a square grid 2 x 2 cm, they demonstrated a significant difference in spatial localisation error for dystonia subjects versus controls (10.18 mm ± 2.21 v 7.68 mm ± 2.29, one-way ANOVA, p = 0.004).

Tinazzi's group repeated their first experiment on eight subjects with generalised dystonia and two with focal dystonia using a modified protocol which was modelled on that of Bara-Jimenez, applying stimuli to the same finger (Tinazzi et al., 2002b, Tinazzi et al., 2002a). They measured both hands for comparison to controls, and found similar abnormalities bilaterally, with similar results to their previous testing.

In assessing temporal discrimination, Tinazzi and colleagues examined ten patients with cervical dystonia (CD), comparing them to ten healthy controls, and a further five subjects with cervical pain from a recent whiplash-type neck injury (Tinazzi et al., 2004). They combined temporal discrimination with visual identification tests to examine the integration of ordering of different sensory stimuli (temporal order judgement). Significant abnormalities were found in both temporal discrimination (CD 111.8 msec ± 37, controls 68.2 msec ± 14.1, p<0.001) and temporal order judgement (112.8 msec ± 37.4, controls 73.5 msec ± 14.9, p=0.002). They examined the data to see if there was any correlation between severity of cervical dystonia and the temporal discrimination or temporal order judgement. There was no correlation, and they conclude that severity does not bias results on an attentional basis. There was no difference in the cervical injury group versus controls.
Tinazzi and his colleagues showed similar findings for temporal discrimination in focal hand dystonia (Fiorio et al., 2003). The absence of correlation of temporal discrimination thresholds with severity of dystonia is consistent with the hypothesis of a primary disorder of the somatosensory system in dystonia.

1.5.5 The Spatial Discrimination Threshold

The spatial discrimination threshold is measured using grating orientation tasks (ibid. section 1.7.2). The spatial discrimination threshold is defined as the narrowest distance of grating separation that would produce a 75% correct response rate (Van Boven and Johnson, 1994a). Spatial discrimination thresholds reflect the discrete functional and anatomical organisation of the sensory homunculus at a supramacroscopic level.

Bara-Jimenez and colleagues examined seventeen subjects with focal hand dystonia (FHD) with a mean age of 50.3 years ± 11.6, mean duration of symptoms 11.4 years ± 5.7, and a Burke-Fahn-Marsden dystonia severity score of 6.3 ± 3.1 (Bara-Jimenez et al., 2000a). They examined them for spatial localisation error and spatial discrimination thresholds on the right index finger. Group mean spatial discrimination thresholds were 2.41 mm ± 1.08 for the dystonia group and 1.28 mm ± 0.75 for controls (one-way ANOVA, p = 0.002). However, they also chose an arbitrary censorship level of 4 mm for those who did not reach the 75% level at or below 3mm, the latter being the largest width of grating used.

Sanger and colleagues examined nine subjects with FHD using grating orientation tasks (Sanger et al., 2001). The average age was 56.4 years ± 10.8 for the FHD subjects. Categorising by dominant hand, and using univariate ANOVA to compare groups, they found significant differences between the two groups for both
hands: FHD dominant hand 2.48 mm ± 0.72 (control subjects' mean SDT for both hands 1.49 mm ± 0.61, p = 0.005), and FHD non-dominant hand 2.13 mm ± 0.63 (p = 0.016). Although the non-dominant hand had a better mean spatial discrimination threshold, there was no difference between sides (p = 0.319). They examined the effect of age on SDT and found it to be significant (p = 0.004), but not on temporal discrimination thresholds (p = 0.215). Five of their dystonia subjects were censored at 3 mm. None of their control subjects were censored. The youngest dystonia subject to be censored was 52 years. Of note, the method of determination of the 75% threshold of spatial discrimination used by this group was different to that of Johnson and Phillips and later groups. They used a down-and-up approach, going to less than or equal to the 60% level, and then coming back up to greater than or equal to 90%, giving a total of 40 responses for each dome in the 60-90% correct response range.

The evidence for abnormalities of spatial discrimination thresholds in focal dystonia had thus far had been generated from patients with focal hand dystonia, and by examining the index fingertip. Despite supporting evidence for sensory disorganisation from physiological studies and brain imaging, it remained difficult to eliminate the likelihood that these clinically measurable sensory abnormalities were epiphenomena. However, Molloy and colleagues produced evidence from examining spatial discrimination thresholds at the fingertip in both hands in nine subjects with benign essential blepharospasm and ten subjects with cervical dystonia which made this less likely (Molloy et al., 2003). Using log rank statistics, they compared these groups to eleven normal controls aged 53 years ± 14.3. All their controls did well, none having a threshold above 2.2 mm for either hand. They assigned 3 mm as the censorship spatial discrimination threshold, and ten of 34 subjects with focal dystonia were censored at 3 mm. The control threshold for the dominant hand was 1.46 mm ±
0.40, and 1.49 mm ± 0.36 for the non-dominant hand. Patients with cervical dystonia had SDTs of 2.53 mm ± 0.55 and 2.35 mm ± 0.60 for the dominant and non-dominant hands respectively. Non-parametric statistical significance was reported for the unified focal dystonia group (blepharospasm, cervical dystonia and writer’s cramp) which were significantly greater (p < 0.001) bilaterally. There was a bilateral effect which was symmetrical except in the focal hand dystonia group (dominant v non-dominant hand = 2.61 mm ± 0.38 v 2.40 ± 0.51, Wilcoxon signed rank, p = 0.02).

1.5.6 Tonic Vibration Reflex/Vibration-Induced-Illusion-of-Movement
Every muscle outside the face provides information to central nervous system via feedback from muscle spindles to help regulate activity and tone. Intuitively, defective feedback can result in incorrect motor output. Vibration of a muscle transcutaneously between 50-120 Hz stimulates muscle spindle primary endings and cutaneous afferents, inducing contraction of the muscle belly— the tonic vibration reflex. The exact mechanism of this response is not clearly understood.

Kaji and colleagues examined the effect of a muscle afferent block on the tonic vibration reflex using lignocaine in 15 controls and patients with mixed simple and dystonic writer’s cramp (Kaji et al., 1995). The tonic vibration reflex was elicited by having the subjects hold a cylindrical vibrator with cycles of 120 Hz and displacement of 1.0 mm and 2.0 mm in their hand. Recordings were made with surface or concentric needle electromyography. A tonic vibration reflex was found in 40% of controls and 80% of writer’s cramp subjects. After muscle injection with lignocaine, the tonic vibration reflex was lost in 40% and attenuated in 33% of those with dystonia. Electromyography showed an improvement in muscles that had not been injected as well as those which had. They hypothesised that the correction of
muscle activity in muscles other than those injected reflects that afferent block must have a central effect. Four of the controls had lignocaine injection also, and they did not have abolition or attenuation of the tonic vibration reflex. However, there was an increase in the latency to onset, but this was not significant (11.0 sec ± 4.0 vs 15.7 sec ± 5.6, p = 0.08).

Grünewald and colleagues showed that in idiopathic focal dystonia, there is impairment of perception of vibration induced movement (Grünewald et al., 1997). Examining 31 subjects with focal dystonia (20 with cervical dystonia, nine with writer’s cramp, and two with blepharospasm), they compared blinded tracking movement of one arm at the elbow while the contralateral biceps tendon was vibrated with a 50 Hz physiotherapy vibrator over three 15 second intervals. In their controls (n = 16), vibration of the muscle elicited a flexion movement which was tracked closely by the contralateral arm. The mean difference in the final angle between arms in controls was 5.1° [± 27.3 (SD)] although they report their results with standard errors of the mean. The difference in the focal dystonia group at the final angle was 10.7° [± 18.9 (SD)]. Overall, univariate ANOVA comparing tracking arm movement in the three intervals between controls and subjects was significantly different (p<0.05). In subgroup analysis of focal hand dystonia and cervical dystonia, they examined for a difference using upaired t-tests, and found no difference in subjects with cervical dystonia whose torticollis was to the left (n = 9). There were differences in the group with torticollis to the right, and the focal hand dystonia group. They did not compare the blepharospasm group because it was too small (n = 2). Thus, they had shown abnormalities in focal hand dystonia, but failed to show the same consistently for the cervical dystonia group. The small numbers in subgroups and weak ANOVA result with large standard deviations in both controls and patients.
make it difficult to come to an overall conclusion of the role of muscle spindles in all focal dystonia. The subgroup analysis would be prone to type II error, and the single finding of significance in the torticollis group to the right could be type I (rejecting the null hypothesis when it is true) which has a 1 in 20 chance at this level of testing.

To further examine this effect, Frima and colleagues examined the effect of fatigue on vibration-induced-illusion-of-movement (VIIM) (Frima et al., 2003). They examined 21 patients with cervical dystonia (15 right torticollis) and compared them to 18 healthy controls. The average age of the subjects with dystonia was 56.4 years (range 29-72). They had cervical dystonia for 12.96 years. Baseline comparison of angle of elbow was no different between controls and subjects: control 37.7° (± 5.4°) versus 34.3° (± 5.3°). The tendon of biceps brachii was vibrated with an 80 Hz using a battery operated vibrator, and as in Grünwald's experiment, the tracking arm moved more in controls (28.6° ± 7.0° v 19.0° ± 8.1°, unpaired t-test, p < 0.01). All subjects were fatigued using a dynamometer and dumb-bell weight to ensure gradual fatigue. After fatigue, dystonic subjects had more illusion of movement such that there was no difference between groups: dystonia subjects moved 24.3° ± 11.1° and controls moved 26.9° ± 9.3° (unpaired t-test, p >0.05). Pre- and post-fatigue movement varied significantly in dystonic patients (paired t-test, p = 0.01). They hypothesize that exercise helps stretch muscle spindles and increase their elasticity, which improves their afferent signalling, allowing for more accurate tracking in the unvibrated arm. However, Grünwald's group had measured passive tracking without fatigue in controls and dystonia subjects, and found no difference between groups, and an equal degree of error in overestimation by the tracking arm. Muscle spindles are histologically normal in dystonia (Swash and Fox, 1976), and we can only assume that somatosensory processing with motor integration is defective when deprived of
fusimotor drive, but exercising independently improves motor performance (Robertson et al., 2003). Focal dystonia phenotypes may affect the facial muscles which have few if any muscle spindles (Hallett, 1995, Urban and Rolke, 2004). One of the difficulties of using vibration as a measure of sensory input is the lack of topographical distinction between stimulated areas in the sensory homunculus of BA3b and BA1 in normal subjects. The contribution of muscle spindles overall in focal dystonia remains to be further elucidated.

Curiously, Leis and colleagues had demonstrated a beneficial effect of selective sensory stimulation, including vibration, when they examined eleven patients with cervical dystonia (Leis et al., 1992). They measured the outcome by recording neck muscle activity with surface electrodes and calculating the percentage change in root mean square voltage. Although it is not discussed in the text, the five patients who had benefit from selective sensory stimulation may not have primary focal dystonia: one had generalised dystonia; one was treated with dopa-antagonists; two had cervical laminectomies; and two had post-traumatic torticollis. Only two patients out of eleven had benefit from vibration: one, a 38 year old woman with antero-retrocollis of six years duration treated with cervical laminectomies, myotomies, botulinum neurotoxin injection, and pharmacotherapy; and the second, a 56 year old man with left rotatocollis of three years duration with a history of essential tremor, who had been treated with cervical laminectomy and pharmacotherapy. They do mention that they were unable to exclude subjects with psychogenic dystonia, and say that the disturbance of proprioception produced by vibration may have induced a normalisation in factitious torticollis.
1.5.7 Sensory Evoked Potentials

The basal ganglia main output is via the globus pallidus internus to the thalamus (Ventral oral posterior – lateral to Vim) and from there the cortex. Reilly and colleagues examined cortical activity using sensory evoked potentials to measure if the N30 component was changed in dystonia, as it was reduced in Parkinson’s disease (Reilly et al., 1992). They studied six patients with focal dystonia, three with generalised dystonia, and one with segmental dystonia, comparing them to ten normal controls. They stimulated the median nerve bilaterally and found a significant difference compared to controls for the N30 at multiple electrode positions bilaterally. For example the amplitude for controls at the F3 position was 0.94 μV ± 0.46 and dystonia subjects was 2.25 μV ± 1.14 (p < 0.02). This result was greatly contributed to by three of the ten subjects, and was important in giving a difference on significance testing, which was also non-parametric and no correction was made for multiple testing. However the result is clearly discussed in their paper and they argue that the topography of the N30 places it over the supplementary motor area, from where it is thought to arise (Waberski et al., 1999). Reductions of the amplitude of N30 from right median nerve stimulation have been reported in a patient with a meningioma of the falx cerebri compressing the left supplementary motor area. It is unlikely to arise from the posterior wall of the central sulcus as previously suggested. More recently it has been suggested based on intracerebral recordings perioperatively in epilepsy patients that the N30 is a direct somatosensory input to the supplementary motor area or prefrontal motor area (BA6 and 8) (Balzamo et al., 2004). The same investigators found that a primary negative component peaking around 24-26 msec, exhibits a 4 msec delay when compared between S1 and M1. This is in favour of a direct input from the thalamus rather than cortico-cortical input from BA1/BA2.
(cortico-cortical connections between these areas (Cusick et al., 1985) have been described in monkeys). This evidence supports the hypothesis that motor area BA4 is activated directly by somatosensory inputs from the periphery. So in dystonia there is possibly excessive activation of the supplementary motor area. These findings concur with those of Tempel and Perlmutter who showed bilateral abnormal 25% reduction in regional cerebral blood flow in the primary somatosensory and motor areas, and the supplementary motor area in subjects with unilateral hand dystonia (Tempel and Perlmutter, 1993).

Kanovsky and colleagues examined cervical dystonia patients to determine if there was any correlation in asymmetry and direction of rotation or tilt (Kanovsky et al., 1997, Kanovsky et al., 2003). They examined 40 cervical dystonia patients who they compared to 20 healthy normal subjects with their heads in the primary position and 20 normals with their heads passively rotated 60 to the right. Their dystonic subjects all had rotatocollis: 20 with sternomastoid as the leading muscle (group I); and 20 with splenius capitis leading (group II). They measured the P22/N30 and found a difference between both control groups and group I for the amplitude on the contralateral side to the rotation, ipsilateral to the most clinically active muscle (p<0.01). This difference was also found in group II for the side contralateral to the active muscle, splenius capitis. The higher amplitudes of N30 concur with the results of Reilly and colleagues. The exact significance of this asymmetry is not fully understood, but it correlates with asymmetry of basal ganglia lesions that cause a lateralising cervical dystonia (Molho and Factor, 1993). The asymmetry of the P22/N30 may give some clue to the motor drive and the dis-coupling of sensorimotor interaction that occurs in cervical dystonia. The amplitudes peak on the side contralateral to the direction of head rotation, not seen in the controls with their heads.
turned 60°. Splenius capitis and sternocleidomastoideus have bilateral projections, but are controlled by the hemisphere contralateral to head rotation, although sternocleidomastoideus has ipsilateral hemisphere involvement too.

Frasson and colleagues reported on paired sensory evoked potentials in ten subjects with dystonia (eight generalised, age range 21-55 years) (Frasson et al., 2001). They delivered 0.2 msec square wave electrical pulses every 454 msec for single stimulation, and paired stimuli with inter-stimulus intervals of 5, 20 and 40 msec. They compared the stimulus response ratio ([S2/S1]*100) and found a significantly higher ratio in patients for spinal N13 and cortical N20, P27 and N30 potentials at interstimulus intervals of 20 and 40 msec (p<0.05). The latter three stimuli represent the excitability of the dorsal column/medial lemniscal system, which in dystonic patients is clearly hyperexcitable. They speculate that the normal suppression of the lemniscal responses is due to inhibitory post-synaptic potentials probably mediated by interneurons within the thalamus (VPL). There were no differences in the latencies of single or paired stimuli between controls and dystonic subjects, but the reduced inhibition during paired stimulation could imply impaired temporal processing of afferents from defective gating. Fast-relay non-NMDA interneurons at the thalamic level might help in separating the temporal difference between two stimuli (Block et al., 1993).

A consensus of speculation on results of these experiments emerged which proposed everything pointed towards disinhibition within the somatosensory cortex. Inoue and colleagues examined amplitudes of high-frequency oscillations (HFO) in the somatosensory cortex using somatosensory evoked potentials, and filtering their signal with a 300-900 Hz bandpass filter to identify the low-amplitude HFOs (Inoue et al., 2004). Comparing 13 subjects with cervical dystonia to ten controls, they found
significant results for the amplitude of early and late HFO (early amplitude $0.21\mu V \pm 0.12$, controls $0.37\mu V \pm 0.17$, $p<0.005$, late amplitude $0.27\mu V \pm 0.16$, controls $0.40\mu V \pm 0.26$, $p<0.05$). They confirmed the lateralisation of somatosensory potentials previously reported by Kanovsky and colleagues, and the larger amplitudes of the N20 in dystonia ($2.39\mu V \pm 0.1.16$, controls $1.69\mu V \pm 0.99$, $p<0.05$). This evidence suggests that interneurons that normally inhibit pyramidal cells in BA3b are weaker in cervical dystonia. It may represent activity of gamma-amino-butyric acid inhibitory interneurons in layer IV of the primary somatosensory cortex which receive a highly convergent input from a large proportion of thalamic afferent fibres. Patients with dystonia have lower levels of brain $\gamma$ABA than normal subjects (Levy and Hallett, 2002).

1.5.8 Sensory homunculus organisation in dystonia

The sensory system maintains a topographic and quantitative organisation from the periphery, through spinal cord, nuclei, ascending tracts to the somatosensory cortex and other cortical zones. According to Penfield and Boldrey, it was Harvey Cushing, the great American neurosurgeon, who was the first to stimulate the human cortex in extirpation procedures producing sensation without movement (Penfield and Boldrey, 1937). In the same paper, Penfield and Boldrey published their recordings of cortical stimulation peri-operatively on 126 patients. They gave a detailed description of sensorimotor findings in the peri-rolandic cortex. The majority of adverive head turning movement were recorded at the lower Rolandic cortex. In approximately 10-20% of areas of stimulation to the post-central gyrus, patients reported sensation of movement, and in the pre-central gyrus, sensory symptoms were also reported mixed with motor areas. As the first complete description of the sensory homunculus, one
can appreciate that hand and craniocervical areas occupy almost the lower two-thirds of the peri-rolandic cortex.

Recognising that somatosensory cortex was known to be remodelled in highly attended motor tasks with excessive sensory inputs, Byl and colleagues studied movement degradation and plasticity in the somatosensory cortex of two adult owl-monkeys engaged in such behavioural training (Byl et al., 1996b). These animals developed dystonic-like movement difficulty. The criteria used to study this were those for occupational hand cramps, such as the ability to perform the training task with 80-90% accuracy, difficulty opening or closing the hand on a handpiece, decreased rate performance, and relative decline in performance compared to a parallel motor task paradigm. They mapped cortical BA3b using microelectrodes and measuring single field potentials of individual neurons after 4 weeks of behavioural training. The electrodes were inserted to a depth of 700-800 microns where they were in layer III. They compared their findings to previously documented normal maps. In normal owl-monkeys, digital receptive fields range from 1 to 15 mm², with 90% between 2 and 9 mm². Their results were 78.0 mm² ± 22.5 and 150.4 mm² ± 237.5 (both reported p<0.0001). They showed that the digital representation had degraded too; finding 25-51% of neurons sampled in BA 3b had multiple-component receptive fields. This was in an area where normally oxidase-rich ovals for digits one to five of the hand are divided anatomically and separated by myelin laminae (Jain et al., 1998).

In conclusion they showed an associated dystonic-like movement disorder with degradation of areas of hand representation. However this animal study provoked a motor disorder and associated sensory changes in otherwise healthy subjects. Are there similar changes to be found in primary dystonia?
Bara-Jimenez and colleagues examined the homuncular organisation of the hand in six patients with dystonia using somatosensory evoked potentials mapped onto three-dimensional magnetic resonance images of the cortex (Bara-Jimenez et al., 1998). For definitive mapping to the somatosensory cortex, they measured the N20 peak using 122 tin surface electrodes mounted in a cap, and compared this to six controls. Three subjects had task-specific writer’s cramp, two had dystonic writer’s cramp and one had segmental dystonia with writer’s cramp and cranio-cervical dystonia. The finger homunculus was normal in controls, but as in magnetoencephalographic studies (Elbert et al., 1998, Meunier et al., 2001), patients’ digital representations were overlapped and with inverted topography. The mean distance between the thumb and little finger in controls was 12.7 mm ± 5.7 and in the patients 6.5 mm ± 3.0 (p = 0.0163). They also correlated the degree of topographical disarray with severity of dystonia, which had a correlation co-efficient of 0.972 (p = 0.0011), but do not comment on the possibility this type of linear relationship in different subtypes of the writer’s cramp phenotype. Another possible confounding error of correlation in this study is the range of dystonia severity of their patients (2-12) on the Burke-Fahn-Marsden scale when the maximum score is 120. Delmaire and colleagues studied putaminal somatotopic organisation using a motor paradigm and functional magnetic resonance imaging (Delmaire et al., 2005). Although looking at motor changes, what they identified in this comparison of 14 subjects with mild unilateral focal hand dystonia was that a significant difference of signal topography was abnormal only on the contralateral putamen. It may be difficult to study the putamen using fMRI and comment on somatotopy in relation to the sensory system, because although putaminal activation reflects sensorimotor corticostriatal projections, motor inputs are much stronger than sensory ones (Maillard et al., 2000).
The results of these findings raise the question: Is it possible that this represents maladaptive neuroplasticity of the motor system, manifesting as dystonia, in subjects who have bilateral "hard-wired" somatosensory defects?

1.5.9 Thalamic sensory homuncular arrangement in dystonia

The thalamus is the main relay centre for sensory afferents to the somatosensory cortex (and motor projections to all motor cortical areas), a cerebellar relay nucleus (Vim, or Vpl/Vlo in monkeys) and a pallidal relay centre (Vop). Many measurements previously discussed implicated the thalamus as being different in dystonia. Lenz and colleagues aimed to test the hypothesis with their first study that the thalamus is involved in dystonic movement (Lenz et al., 1999). They examined ten patients who were undergoing thalamotomy for dystonia. Four of the ten had primary torsion dystonia, and one had adult-onset primary torsion dystonia predominantly affecting the upper limbs and craniocervical structures (but all had lower extremity involvement). The results of examining all ten patients showed that the number of deep sensory cells which responded to movement of more than one joint was higher in dystonia than controls (28% v 8%, p<0.05). They found no difference in the percentage of deep sensory cells in the Vop (11% v controls 4*%, $\chi^2$ p=0.16, *cell count < 5), but did in the Vim (28% v 11%, $\chi^2$ p=0.009). Subgroup analysis on the small numbers of patients with primary and secondary dystonia was not helpful in determining if one group accounted for a greater percentage of the deep sensory cells, but the primary dystonia group (n = 4) had 0/6/11/48% of sensory cells in Vim and Vop, versus 0/13/61/67% in the secondary dystonia group (n = 4). The percentage of sensory cells in these areas did not correlate with duration of dystonia either (r = 0.46, p>0.05).
Lenz and Byl, in a separate paper, then examined the representation of cutaneous structures in the core of the principal somatosensory nucleus of the thalamus (Vc) in patients with dystonia (Lenz and Byl, 1999). In this study twenty-six patients were studied during the physiological exploration that precedes stereotactic thalamotomy for dystonia (n = 11, 4/11 primary torsion dystonia, all with lower extremity involvement) and essential tremor. They measured spontaneous firing pattern and neuronal activity during somatosensory stimulation which included touch or pressure applied to the skin (cutaneous sensory cells) and joint movement/squeezing muscle (deep sensory cells). By this they could determine the receptive field for each neuron. They also measured the projected field: neurons were stimulated, and the patient asked to comment on where they felt sensation, and the quality of it. The differences they found between dystonia subjects and essential tremor for both receptive fields and projected fields were significant. 71% of dystonia subjects had multiple-part projected fields (essential tremor 47%, \( \chi^2 \) p<0.0002) and 29% had multiple-part receptive fields (essential tremor 11%, \( \chi^2 \) p<0.0001). They also measured the distance between each field in both groups and found longer distances for projected fields in dystonic subjects than controls (essential tremor). Receptive field was plotted against projected field using the somatotopic response, which showed that the number of matching sites was higher for controls (36/62 or 58%) than patients with dystonia (33/103 or 32%, \( \chi^2 \) p<0.002). They looked at the effect of duration and age of dystonia onset on organisation within the cutaneous core of Vc. Longer duration of dystonia (>5 years, n = 9 v <5 years, n = 2) and younger age of onset (<10 years, n = 8 v >10 years, n = 3) were significant (p<0.001), with both having a greater percentage of cells with multiple-part receptive fields (35.7% v 7.4%, and 29.7% v 6.7% respectively). The findings suggest that there is somatotopic
difference in dystonia, but unfortunately the population studied was too heterogeneous to make any conclusion about the organisation of Vc in primary torsion dystonia. The study was done on relatively few subjects and is methodologically difficult since there was no way to determine the precise location of the recording electrode. They cite animal studies looking at Vplc (equivalent to human Vc) after deafferentation, which demonstrate plasticity in the thalamus for sensory receptive fields and projected fields that result in similar findings to their study. They hypothesize that dystonia can lead to reorganisation of the sensory core of the thalamus in a similar manner. Anatomo-clinical study of unilateral symptomatic dystonia shows that thalamic lesions can cause dystonia. It is particularly the Vc and Vim that are affected, whereas the Vop and Voa nuclei are largely spared (Lehericy et al., 1996). Curiously, it is thalamotomy of the Vop and Vim that are used to treat dystonia.

The understanding of primary dystonia from a neurophysiological viewpoint was elucidated more clearly in a later study by Zhuang and colleagues (Zhuang et al., 2004). They examined neuronal activity in the thalamus (Vop/Vim), globus pallidus internus and subthalamic nucleus of twenty patients with medically intractable dystonia (primary: n = 11, secondary: n = 9). They found no difference in the numbers of cells showing sensory bursts (1-10 Hz) in the Vop/Vim when comparing primary and secondary dystonia (50% v 47%). Receptive field firing patterns were similar in primary and secondary dystonia. Despite having no control group, this study is valuable in showing that sensory measurements in the Vop/Vim do not differ in patients with primary or secondary dystonia. Therefore thalamic somatosensory changes may be an epiphenomenon of dystonia.
1.5.10 Sensory abnormalities seen according to subtype of dystonia in AOPTD

The majority of study on phenotypes of focal dystonia has been done on FHD. Measurable sensory phenomena in focal dystonia without interference with sensory pathways have contributed to the growing body of evidence that dystonia is a sensory disorder.

Focal Hand Dystonia

Abnormal central processing of normal peripheral inputs was first hypothesised in studies on muscle spindle afferent in FHD (Kaji et al., 1995, Grunewald et al., 1997, Hallett, 1995). Kaji and colleagues examined 15 patients with FHD and showed dystonic posturing was decreased by intramuscular injection with lignocaine or ethanol to the affected muscles. Grunewald and colleagues examined nine patients with FHD using the matching of passive forearm movement and the Tonic Vibration Reflex (TVR). Subjects overestimated the matching angle, and it was concluded that central and peripheral sensory factors were contributory.

Using the fingers as the area of examination, sensory discrimination studies have shown reduced sensory discrimination ability in the hands of those who suffer from FHD, both on the affected side and the unaffected side (Molloy et al., 2003, Bara-Jimenez et al., 2000b, Bara-Jimenez et al., 2000a, Sanger et al., 2001). Sensory training was used to examine the contribution of the abnormal overlapping and non-linear sensory representations in FHD, which was shown to be beneficial and also improved spatial discrimination (Zeuner et al., 2005, Sanger et al., 2002, Elbert et al., 1998).
Patients with FHD employ excessive force to grasp despite poor function in completing a task, displaying impaired sensorimotor integration (Odergren et al., 1996). In another experiment, Serrien and colleagues showed that interference with sensory input (by vibration of forearm muscles) particularly in the affected hand, resulted in excessive grip-load force ratio in subjects with FHD (Serrien et al., 2000). They measured grip force by having the subjects slowly release grip on a drawer handle held in a pincer grip by two fingers until the drawer was pulled away by the brushless torque motor behind it. There was no difference in load force between FHD patients and controls.

Functional neuroimaging techniques have demonstrated areas of deficient activation in the sensorimotor cortex with passive sensory stimulation by tonic vibration (Tempel and Perlmutter, 1990, Tempel and Perlmutter, 1993). In contrast, during active writing, the contralateral primary and secondary sensory cortices are overactive (Ceballos-Baumann et al., 1997). Grating orientation tasks performed during fMRI imaging showed hyperactivity in the basal ganglia (Peller et al., 2006). This enhanced response may contribute to the impaired centre-surround inhibition within the basal ganglia, leading to excessive activation of somatosensory and motor cortical areas during skilled movements, as described by Ceballos-Baumann and colleagues. There is a reduction in anatomical separation of digits in FHD patients in the primary somatosensory cortex, absence of representation in the secondary somatosensory cortex (BA40), and disorganised order in secondary sensory areas on the cortex (Butterworth et al., 2003). Electrophysiologic and quantitative neuroimaging studies have shown that the hand representations on the primary somatosensory cortex of the sensory homunculus are abnormal in those with FHD (Meunier et al., 2001, Garraux et al., 2004, Bara-Jimenez et al., 1998).
Focal task specific dystonia

Focal task specific dystonia (FTSD) is a focal dystonia that occurs with only one motor paradigm, such as playing an instrument (Frucht, 2004). The model for studying this has been limb overuse especially in monkeys, who show overlapping and dedifferentiated primary sensory cortical areas for the hand (Byl et al., 1996b, Byl et al., 1997). Indeed, musicians with FTSD have smaller intra-digit cortical representations than unaffected musicians or controls (Elbert et al., 1998). Sanger and colleagues proposed a computational model for sensory disorganisation in FTSD (Sanger and Merzenich, 2000). They proposed that the dystonia is a biomechanical manifestation of an unstable sensorimotor control loop and motor abnormalities could arise from sensory de-differentiation if sensory changes led to increased loop gain. Only certain mechanical modes of the sensorimotor loop may be unstable, and as a result only FTSD may occur. A substrate for sensory disorder may exist given the finding of bilaterally abnormal sensory representations of digits in musicians with only one hand affected by FTSD (Charness and Schlaug, 2004). Sensorimotor retuning, or a method of aiming to restructure abnormal sensory maps have proved successful in treating FTSD (Candia et al., 2003, Candia et al., 2002, Priori et al., 2001).

Sensory inputs into movement generation have been studied using TMS in patients with FTSD. Muscle vibration showed facilitation of motor output (MEP) in agonistic muscles and a decrease in antagonistic muscles in controls and those affected with musician’s cramp (a form of FTSD). However, in FTSD there was less inhibition of the antagonistic muscle group leading to a disproportionate balance of muscle activation (Rosenkranz et al., 2000). This sensory input abnormality was not
shown in patients with simple FHD (Rosenkranz et al., 2005). Functional MRI imaging of guitarists playing their instrument shows contralateral primary sensorimotor cortex hyperactivity, also in contrast to what is seen in FHD (Pujol et al., 2000). The fine activation of neural networks that characterise a concert-level musician seen on functional imaging is lost in musicians with FTSD, representing a regression of sensorimotor training (Charness and Schlaug, 2004).

*Cervical dystonia*

Pain, as a sensory complaint, is often mentioned (in 68%) by those who suffer from cervical dystonia (Jankovic et al., 1991). Sensory abnormalities in cervical dystonia have shown that there is abnormality of the VIIM, spatial discrimination thresholds and increased amplitude of somatosensory evoked potential P22/N30 (Molloy et al., 2003, Kanovsky et al., 1997, Kanovsky et al., 2003, Grunewald et al., 1997, Rome and Grunewald, 1999). Spatial discrimination thresholds measured at a site distant from the affected area were also abnormal. There were bilateral increased amplitudes of the median nerve P22/N30 with the tremulous form of cervical dystonia, and unilaterally increased, localising to the contralateral side, with the tonic form (Kanovsky et al., 1999). This SEP finding may have been an epiphenomenon related to abnormal activity associated with the supplementary motor area. Siggelkow and colleagues looked at the effect of vibration of muscle (which should reproduce dystonic movement) on short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI) in cervical dystonia patients using paired-pulse TMS (Siggelkow et al., 2002). There was a lack of inhibition of the MEP with the SICI at rest compared to controls and increased facilitation with the LICI. With vibration of the muscles being measured, there was similar reduction of MEP area with SICI but
much greater reduction of facilitation with LICI. They concluded that this is some more evidence of impaired sensorimotor integration in cervical dystonia.

_Blepharospasm_

Orbicularis oculi and other facial muscles do not have muscle spindles, but patients who develop this form of focal dystonia often complain of dry gritty eyes before the onset of the BEB (Jankovic and Patten, 1987, Stojanovic et al., 1995, Jankovic and Ford, 1983). They may also benefit from a sensory trick to transiently alleviated spasms. In BEB, there is prolonged duration of the R2 component of the blink reflex elicited by corneal stimulation and bilateral R1 responses in up to 40% (Berardelli et al., 1985). Prepulse inhibition of R2 was similar to controls in patients who did use a sensory trick (Gomez-Wong et al., 1998b). In patients who use a sensory trick and in controls there was a reduction in the amplitude of R2 (Gomez-Wong et al., 1998a). They proposed that this is higher centre gating of the trigemino-facial reflex pathway. Despite these results, blepharospasm has been frequently reported with focal lesions of the brainstem, basal ganglia and thalamus (O'Rourke et al., 2006, Jankovic and Patel, 1983, Jankovic, 1986, Hutchinson et al., 2000, Singer et al., 1998). The basal ganglia and striatum have been predominantly implicated in the pathogenesis of dystonia above the tentorium cerebelli based on neuroimaging and functional imaging of the brain (Hutchinson et al., 2000, Schmidt et al., 2003). However, there may be some contribution to BEB from cortical regions since the cortical innervation of the extraorbital muscles is small and other cranio-cervical forms of dystonia are seen in 35% within five years of the onset of BEB (Defazio et al., 1999, Morecraft et al., 2001).
Oromandibular dystonia & orofacial dystonia syndrome (Meige Syndrome)

Characterised by a combination of BEB and spasms of jaw-opening or jaw-closure, occasional patients have benefit from sensory tricks, e.g. pinching the posterior neck, chewing on a toothpick (Jankovic and Ford, 1983). It is infrequently seen alone (except in tardive cases), but usually in association with other cranio-cervical forms of dystonia (Tolosa, 1981, Tan and Jankovic, 2000). In Meige syndrome, there is bilateral overactivation of the primary sensory cortex with complex motor tasks, i.e. whistling, consistent with the theory that there is a sensory abnormality in focal dystonia (Dresel et al., 2006).

1.5.11 Sensory abnormalities in DYT1 dystonia

Sensory abnormalities have been examined using grating orientation tasks in patients with DYT1 dystonia, and there is no impairment of the spatial discrimination threshold compared to controls (Molloy et al., 2003). However measurable abnormalities have been shown in temporal discrimination thresholds and temporal order judgement in both manifesting and non-manifesting carriers of the 3-base-pair GAG deletion in the TOR1A gene (Fiorio et al., 2007), mirroring the concept of the endophenotype in this disorder (Eidelberg et al., 1998, Asanuma et al., 2005, Edwards et al., 2003).

1.5.12 Neuroplasticity in S1 and subcortical nuclei

In 1894 Ramón y Cajal first proposed that the central nervous system could learn by adapting neuronal connections at an anatomical level. This hypothesis was largely disregarded until microelectrode development in the 1940s allowed work on neuronal
connections, and Penfield’s mapping of the cerebral cortex reignited interest in the mechanisms of conditioning and learning.

Neuronal representations are believed to be shaped by prior experience through physiological processes commonly referred to as neuroplasticity (Classen, 2003). Although the anatomical structure of the brain is grossly fixed from early childhood, the functional organisation of the cerebral cortex and subcortical nuclei is plastic, with changes occurring throughout life in response to normal and abnormal experience (Rioult-Pedotti and Donoghue, 2003). Change is measured in relation to highly structured and organised maps. These include areas with the somatotopic primary sensory cortex and motor cortex, the retinotopic visual cortex, and the tonotopic auditory cortex.

The central nervous system dynamically organises itself during development by several plastic mechanisms including persistence of neurogenesis in certain parts of the brain, deletion of neurons through apoptosis, and modification of synapses by sprouting and trimming (Johnston, 2004). Developmental plasticity and experience/activity-dependent refinement of synaptic connections occur synchronously and in parallel throughout life, but each mechanism occurs in different ratios with advancing age. Both are adaptive and may be normal, impaired or excessive (Quartarone et al., 2003).

The phenomenon of cortical representational change in learning occurs largely due to Hebbian (synonyms include associative, input-dependent, and homosynaptic) synaptic change mechanisms (Hebb, 1949). These are coincident input-dependent changes where inputs that nearly simultaneously engage cortical neurons are integrated in cortical neuronal responses. A presynaptic neuron stimulates the postsynaptic neuron, and when the correlation of the timing of firing is high between
the two, synaptic strength is increased. The hypothesis that long-term potentiation (LTP) occurs which is proposed to enhance learning was shown by Bliss and Lømo when they demonstrated increased synaptic strength after repetitively stimulating the perforant path linking the hippocampus and dentate gyrus (Bliss and Lømo, 1973). The importance of this contentious mechanism was challenged since it decays within hours to weeks of induction. Despite paralleling memory gain in studies on the hippocampus, it also parallels memory loss. However, homosynaptic plasticity forms the basis of conditioning, as well as the understanding of heterosynaptic plasticity. The heterosynaptic mechanism is essentially activity-dependent synaptic plasticity, where a third neuron can act to facilitate or inhibit the strength of the presynaptic signal, modulating the degree of association (Bailey et al., 2000).

The mechanism for Hebbian plasticity has been studied in detail in Schaffer collateral pathways between areas CA3 and CA1 in the hippocampus. Late long-term potentiation (L-LTP), which provides long lasting stability of a synaptic pathway, is associated with protein and messenger RNA synthesis. The induction of this L-LTP requires cyclic-AMP (cAMP), protein kinase A (PKA), and mitogen-activated protein kinase (MAPK). In the Schaffer pathway, glutamate acting on AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and NMDA (N-methyl-D-aspartate) receptors depolarises post-synaptic cells by binding to AMPA-R first, which allows removal of magnesium from the NMDA receptor channels. The activation of the NMDA receptor is the critical trigger for LTP: it allows calcium influx in the post-synaptic cell and activates protein kinases including calcium/calmodulin-dependent protein kinase II (CaMKII). Further requirement for L-LTP is that very strong or repeated cycles of this event are needed (>100Hz tetanus, multiple). Therefore, as well as CaMKII activation, tetanic cycles must increase intracellular cAMP and
recruit PKA and MAPK. PKA and MAPK translocate to the nucleus and activate cAMP response-element binding protein (CREB). In vitro studies on CREB show it activates a cascade of genes that leads to the growth of new synaptic contacts between neurons (sensory and motor), and to facilitation of synaptic strength that persists for days. In vivo studies using knockout and transgenic mice shows that CREB and this pathway are associated with weeks of memory, and when absent learning is critically impaired. A caveat though is that hippocampal LTP may not have exactly the same mechanism as spatial learning.

L-LTP can be influenced by D1/D5 dopamine receptor activation (DRD1/DRD5). Antagonism of these receptors can lead to inhibition of L-LTP, since they are positively coupled to adenylyl cyclase. Activation of DRD1/DRD5 increases cAMP levels and enhances L-LTP. There has been speculation in relation to DRD5 with adult-onset primary torsion dystonia and several authors have looked at the frequency of different single nucleotide polymorphisms of DRD5 in benign essential blepharospasm and cervical dystonia (Brancati et al., 2003, Misbahuddin et al., 2002, Placzek et al., 2001). Some SNPs (#2 and #6, of 12 studied) appear to be significantly associated with higher frequency, although the extremely low population frequency of these may result in statistical error. However, this is one of several possible candidate gene association studies in focal dystonia (Matsumoto et al., 2003). L-LTP is also enhanced by beta-adrenergic agonists in the mossy fibre pathway and the cortico-amygdala pathway. However, the homosynaptic mechanism may not be sufficient to produce long-lasting changes in pathways.

Heterosynaptic mechanisms may account for learning that outlives hebbian synaptic induction (Kandel and Tauc, 1965b, Kandel and Tauc, 1965a). Huang and colleagues looked at associative learning in mice using paired heterosynaptic
methods. They found that what is a weak hebbian mechanism (low frequency stimulation) paired with a brief conditioning stimulus in an independent afferent pathway will induce long-lasting synaptic potentiation (Huang et al., 2004). They also managed to show that this also requires PKA and protein synthesis, and that in transgenic mice without CREB heterosynaptic facilitation was impaired. The heterosynaptic facilitation enhances calcium influx in the post-synaptic cell to extend facilitation of that synapse for ~20 times longer than L-LTP by hebbian mechanisms alone. This facilitation is synapse specific, such that neurons with several dendrites will only be facilitated at the precise synapse where heterosynaptic activity occurred. In summary, heterosynaptic mechanisms enhance the duration of plastic change in a manner synergistic to hebbian changes, and sharpen synapse specificity by restricting long-term plasticity to a small set of synaptic connections. Many questions about LTP related plasticity remain, including:

1) Is there any presynaptic modification with retrograde messengers?
2) What are the intracellular cascades exactly that trigger LTP beyond CREB?
3) What are the structural changes that occur at LTP induced synapses?
4) What other mechanistic forms of receptor aside from NMDA-dependent LTP exist and how may they relate to plasticity outside the hippocampus?

1.5.13 Sensory plasticity in CNS injury

The plastic potential of the CNS in early-life injury is well documented and studied. Children with unilateral hemispheric brain lesions regain motor function due to the ipsilateral recruitment of corticospinal neurons (Benecke et al., 1991, Carr et al., 1993, Thickbroom et al., 2001, Maegaki et al., 1995) that would have otherwise
undergone developmental apoptotic reorganisation at a later stage (Oudega et al., 1994). Sensory areas in CNS injury show the same degree of fickleness. In fact, sensory maps switch to ipsilateral hemispheres viewed on functional MRI (Graveline et al., 1998), and other authors have shown ipsilateral cortical and subcortical activation using SEPs (Mauguiere and Desmedt, 1989, Villanueva and Castilla, 1988). Holloway and colleagues showed that ipsilateral sensorimotor responses can be found in children with both congenital and acquired disease for which they had hemispherectomy at different ages, suggesting that age at injury and aetiology are not absolutely predictive in regain of function (Holloway et al., 2000). Children with different extents of congenital brain injury have selective incorporation of ipsilateral pathways (Staudt et al., 2002). There is a scaled increase of recruitment of ipsilateral innervation, with relatively more premotor than primary motor cortex recruited for less severe lesions. They also found that in severely affected hemispheres, cortical activation of sensorimotor areas can be seen with passive movement of paretic hands, suggesting that sensory inputs may still be activating motor areas in the cortex, and possibly providing sensory input to the opposite hemisphere for ipsilateral premotor and primary motor cortices. Sensorimotor plasticity in early development tells us a lot about the potential for reorganisation and functional outcomes. Using MEG, Mogilner and colleagues reported the pre- and post-surgical somatosensory maps of the hand in two patients who had surgical separation of webbed fingers (amniotic band syndrome, 32 years old; Apert’s syndrome, 26 years old). After establishing control sensory homuncular arrangement, they showed that the sensory homunculus divided itself into appropriated digital areas post-operatively as early as one week (Mogilner et al., 1993).
Experimental investigation of sensorimotor plasticity in PTD

We know from transcranial magnetic stimulation (TMS) studies in dystonia that the cortex is hyperexcitable with shortening of the silent period, lack of inhibition with short interval paired stimuli (conditioning and suprathreshold) and over-facilitation with long interval paired stimuli (Ridding et al., 1995, Rona et al., 1998, Ikoma et al., 1996, Chen et al., 1997). Other models of experimentally induced methods have been used to examine plasticity too. Further rationale on the importance of plasticity in a mix of animal models, normal humans and dystonic subjects is presented below.

Sensory cortical effects of deafferentation by digit amputation in adult owl monkeys (*Aotus nancymai*) was first examined using microelectrode investigation by Merzenich and colleagues (Merzenich et al., 1984). They demonstrated that in BA3b the adjacent digits expanded their topography to the former domains of the amputated digits. The skin areas in the representation correspondingly seemed to adjust their receptive fields, but boundaries in the deprived cortical zone were indistinct. Major changes were involved less than 0.7 mm of cortex in adjacent zones though. However, there is no change in the histological representation in these areas (Jain et al., 1998), supporting the hypothesis that this rearrangement is synaptic remodelling.

The effect of acquiring a new tactile motor skill was also examined by Merzenich’s group (Xerri et al., 1999). They measured the development of cortical receptive fields in *Aotus nancymai* and *Saimiri sciureus* who acquired the skill of pellet retrieval using their hands. The digits that became the most used enlarged their receptive fields, and had less overlap than others in microelectrode mapping. Somatosensory-driven plasticity induction with γABA antagonism (bicuculine) produces cortical motor reorganisation for rat forelimb topography (Jacobs and...
Donoghue, 1991). Stimulation of the vibrissae motor cortex resulted in forelimb movement demonstrating that the field was extended to adjacent areas.

Deafferentation in humans can produce a unique opportunity for cortical structures to reorganise/remodel. Levy and colleagues examined experimentally deafferented healthy adults using J-resolved magnetic resonance spectroscopy that allowed them to examine multiple metabolites in the brain at once (Levy et al., 2002). They hypothesised that in the context of acute deafferentation, brain inhibitory neurotransmitters would change allowing plastic changes to occur. Gamma-amino butyric acid (γABA) levels in the human sensorimotor cortex were found to be quickly reduced, within minutes of deafferentation by ischemic nerve block of the forearm. Therefore rapid cortical plasticity may arise from the release of latent corticocortical projections from tonic inhibition through decreased γABA availability. Reduction of brain γABA may play a pivotal role in regulating the extent of rapid cortical reorganization after lesions or changes in sensory input. Werhahn and colleagues examined spatial discrimination tasks in 24 normal controls between the ages of 18 and 48 years using grating orientation tasks on the hand immediately after cutaneous anaesthesia of the contralateral hand. Comparing pre- and post-deafferentation SDTs, they found an $18 \pm 3.7\%$ improvement in the SDT, which was not attributable to practice (within session practice change $p = 0.2$, across session practice change $p = 0.3$). They also measured SSEPs during anaesthesia which demonstrated no change in subcortical measures (lemniscal P15), consistent with the improvement being cortical in origin. The gain in tactile spatial acuity on the non-deafferented side shows how rapid plastic change of somatosensory cortex does occur with peripheral sensory alteration. Drugs such as levetiracetam which are very
useful for disorders of cortical origin have shown efficacy in dystonia, which may indicate how intracortical modulation can improve symptoms (Zesiewicz et al., 2004).

Repetitive movements are theoretically those associated with the development of at least some forms of focal dystonia, such as writer’s cramp as described by Solly (1805-1871) in his lectures to fellow physicians on “scrivener’s palsy”, describes it as a condition disabling the person in their occupation, in an era when clerks had to write everything. A similar problem occurred in telegraphists during the early 20th century in the United Kingdom, when up to 18% were affected by “telegraphist’s cramp” (Pearce, 2004). Wang and colleagues showed that it is not only the repetitive nature of a sensory stimulus which produces a remodelling of area 3b, but also the timing of the stimuli. Synchronous stimulation of adjacent areas gave rise to integration into one receptive field with time. This appears to be strictly a cortical rearrangement, since there was no rearrangement of thalamic receptive fields in the VPL (Wang et al., 1995). Byl and colleagues used this concept as a model for development of an animal model of focal hand dystonia, Aotus nancymae (New World owl monkey) and examined the somatosensory cortex hand homunculus. They showed de-differentiation resulting in receptive fields ten- to twenty-times larger than normal, the emergence of receptive fields representing many digits, a breakdown of normally sharp segregated area 3b hand areas, and widely dispersed single digit receptive fields (Byl et al., 1996b).

Not only do repetitive tasks produce de-differentiation of the somatosensory cortex, but also induce focal hand dystonia in Aotus nancymae. Four animals were trained to do repetitive palmar hand grasp tasks (placing the hand in a mould with two metal contacts, pulling together two vibrating rods) up to 2,000 times per day, with about one trial per three seconds. One animal had a dense-array cortical implant over

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S1 to map receptive fields of the hand with time as de-differentiation occurred. By the time the animal developed focal hand dystonia, the cortex showed a considerable associated plastic rearrangement because the receptive field of the hand included some of the face. Two other monkeys also developed focal hand dystonia with equivalent S1 findings on microelectrode recordings by craniotomy under areflexic anaesthetic. The fourth, even one year later, did not have any abnormality (Blake et al., 2002). Topp and Byl did similar work with four monkeys inspecting them for work-induced tendonitis, after five weeks of repetitive movements. The one with a tendon restriction developed movement abnormalities (Topp and Byl, 1999).

1.5.15 Enhancing sensory perception by sensory training

In a study by Xerri and colleagues two different types of monkeys (*Aotus nancymai* and *Saimiri sciureus*) were trained to retrieve pellets from different size wells on a Kluver board. The digital representations on surface microelectrode mapping of BA1 and BA3b showed double-size receptive fields of digits involved in pellet-retrieval behaviour and less overlap for receptive fields of trained digits after an eight to fourteen week training period (Xerri et al., 1999). Blind people have been shown to have higher spatial discrimination sensitivity than normal controls (Van Boven et al., 2000). In a study comparing the two (Zeuner et al., 2002), blind subjects had a spatial discrimination threshold of 0.8 mm in the Braille reading finger, and 1.12 mm in the non-reading-finger, compared to controls whose average SDT was 1.46 mm (p = 0.03). Subjects with FHD and controls who were taught to read Braille also improved spatial discrimination thresholds with eight weeks training. There was a corresponding improvement in dystonia (writing) and a correlation on the Fahn Dystonia Scale with the improvement of the spatial acuity. However, blind subjects
also use the occipital cortex for Braille reading whereas sighted individuals do not (Cohen et al., 1997, Buchel et al., 1998, Zangaladze et al., 1999), making the comparison in spatial acuity less robust.

Constraint-induced movement therapy was first developed for use in stroke patients to improve upper extremity movement. In a paper discussing the use of this in FTSD (musician’s dystonia), Candia and colleagues describe the beneficial effect of this on five professional musicians (Candia et al., 1999). Immobilisation by splinting the unaffected fingers and performance of repetitive exercise paradigms for 1.5 to 2.5 hours daily over eight consecutive days resulted in two patients feeling normal at one month, and the remainder feeling moderately improved. Two musicians resumed concert performances after nine months. They did a further study on this with a one-year therapy period on eleven professional musicians with FTSD, including three wind instrument players who acted as adventitious placebo controls (Candia et al., 2002). All eleven had dystonia affecting the fingers during performance. The “Sensory Motor Retuning” worked in all guitarists and pianists (except one non-compliant), but not in the wind-instrument players. They also showed that the digital representation in S1/BA3b normalised to become symmetrical with unaffected side in these musicians (Candia et al., 2005). Priori and colleagues did a study using limb-immobilisation with a splint over four to five weeks on a mix of patients with FTSD including one with non-occupational FHD. There was improvement that was long-lasting in seven of the eight patients, including in FHD (Priori et al., 1995). Those who respond to limb-immobilisation therapy have: more severe dystonia at onset and a larger number of joints involved; a shorter disease duration (<5 years); a transient improvement after a fatiguing contraction of the hand; younger age (<37 years); an
onset related to overuse; and no previous treatment with botulinum neurotoxin (Pesenti et al., 2004).

1.5.16 Sensorimotor plasticity and transcranial magnetic stimulation in PTD

Transcranial magnetic stimulation (TMS) can be used to stimulate corticospinal pathways and sensorimotor pathways to examine plasticity in each by using hebbian and heterosynaptic mechanisms in vivo. Repetitive stimulation (rTMS) to induce long-lasting synaptic change may be a therapeutic option given the correct formula for reorganising neural circuits. Repetitive stimulation is one of several paradigms used in TMS and can produce excitability patterns outlasting the period of stimulation. High frequency stimulation (>5 Hz) produces a hyperexcitable cortex, and low frequency stimulation (≤1 Hz) can create a depressed cortex that mimics the long-term depression (LTD) seen in synaptic connectivity experiments looking at conditioning (Filipovic et al., 2004). This type of silencing of synapses is considered the antithesis of LTP but synergistic to useful pathways learned in associative conditioning.

Tamburin and colleagues showed that the interaction between the sensory and motor systems can be validly explored using TMS in dystonia (Tamburin et al., 2002). Their aim was in fact to show that sensorimotor somatotopy was abnormal in dystonia, and they examined eight patients with FHD, four with CD, six patients with Parkinson’s disease and ten healthy controls. They gave conditioning electrical stimuli to the second or fifth digit on one hand, followed by a cortical motor TMS pulse, with different inter-stimulus intervals (10 to 100 msec). However, the sensory stimulus was delivered at three times the sensory threshold, with duration of 0.1
milliseconds. They recorded motor evoked potentials (MEP) over the first dorsal interosseous or abductor digiti minimi on the same hand. The MEP inhibition recorded showed a somatotopic distribution in the 26 muscles studied for controls. Stimulation of control contiguous fingers (e.g. D2 conditioned with sensory stimulus, and FDI stimulated by TMS) showed inhibition (range 32-60% of unconditioned MEP amplitude, ISI 20-50 msec, ANOVA p<0.05). Non-contiguous fingers (e.g. D2 conditioned, and ADM recorded given TMS) did not though (range 80-93%). In the patients with focal hand dystonia and cervical dystonia, they found inhibition for ISIs of 30-50 msec (conditioned MEP 48-70% of unconditioned amplitude) in contiguous fingers and 30-70 msec in non-contiguous fingers (45-69% of unconditioned MEP amplitude). Data were similar for affected and unaffected sides in the focal hand dystonia subgroup. In the Parkinson’s group, facilitation was found in contiguous finger stimulation only (ISI 20-50 msec, ANOVA MEP amplitudes, p<0.05). Post hoc analyses showed significant differences for the non-contiguous finger measurements in the dystonia group only. This study demonstrated three important things in focal dystonia:

1) Cutaneous afferents topographically distant from the affected areas (e.g. CD) show somatotopic disorganisation
2) Somatotopic integration between sensory and motor systems is abnormal
3) Cutaneous afferents have a mainly inhibitory effect on the cortex

The disorganised somatotopy in focal dystonia supports the work of others (Elbert et al., 1998, Meunier et al., 2003).

If cutaneous inputs can inhibit motor output at the cortex, then it should be possible to compare cortical inhibition by motor output using two paradigms: cortical inhibition by peripheral stimulation, and paired-pulse TMS. Sailer and colleagues
examined this to determine if they were comparable, and they found that there was some correlation between long- interval intracortical inhibition and median nerve stimulation, but not short- interval intracortical inhibition (Sailer et al., 2002). It is likely that long- interval intracortical inhibition (100-200 msec) is mediated by the same neurons as those involved in sensory inputs. Major sensory inputs to the motor cortex terminate in superficial cortical layers (layers II and III), where late inhibitory post-synaptic potentials (IPSP) are generated in animal studies (150-200 msec). These late IPSPs are mediated by $\gamma$ABA$_B$ receptor-rich inhibitory interneurons, which are dense in layer II. They inhibit pyramidal cell discharge in the corticospinal tract, resulting in a lower MEP.

Urban and Rolke examined ten subject subjects with idiopathic rotational torticollis using TMS (Urban and Rolke, 2004). They were all treated with botulinum neurotoxin also, and TMS was performed to examine if the same degrees of facilitation existed as before treatment. They found that there was an increased facilitation of sternocleidomastoid compared to controls when combined with vibration, which was depressed by botulinum neurotoxin injection, and recovery was seen after 12 weeks. The effects of botulinum neurotoxin are not assumed to be central but mediated by peripheral changes. Others have noted transient reductions in reciprocal inhibition (Priori et al., 1995) and intracortical inhibition in focal hand dystonia following botulinum neurotoxin injection (Gilio et al., 2000). There may be transient sensory reorganisation, but despite these effects, studies humans and on healthy feline central nervous systems treated with peripheral botulinum neurotoxin suggest that central motor reorganisation does not occur (Moreno-Lopez et al., 1997).

Transcranial magnetic stimulation produces different effects on the cortex depending on the paradigm used. Repetitive stimulation at high or low frequency may
produce facilitation or inhibition. Functional imaging correlates depend on metabolism and regional cerebral blood flow, and these are not necessarily positively correlated, sensitive or specific. Low frequency (1 Hz) repetitive may have transcallosal or cortico-subcortico-cortical effects on the contralateral motor areas (Okabe et al., 2003). Repetitive TMS at 1 Hz has been shown to reduce the amplitude of MEP in relaxed hand muscles (thus modulating the corticospinal tract) and also reduces the amplitude of long-latency stretch reflexes and decreases facilitation within intraneuronal connections in the sensorimotor cortex (Stinear and Byblow, 2004a, Stinear and Byblow, 2004b). Lee and colleagues postulated that the increase in regional cerebral blood flow seen in the sensorimotor cortex with rTMS of the motor cortex may be due to compensatory excitatory presynaptic and intracortical activity to stimulate the pyramidal cells whose trans-synaptic functionality has been inhibited by the repetitive stimulation (Lee et al., 2003). They also showed that sensorimotor cortical areas can flexibly reassign themselves to sensorimotor tasks near the areas that are inhibited to allow task function. This intraneuronal horizontal connection facility is thought to be the primary substrate for rapid plasticity in the cortex. The cortical area where remapping occurs correlates with the length of horizontal connections in layer II/III (Huntley, 1997). Rat studies have shown that 2 Hz rTMS can induce LTD in these neurones, preventing such rapid remapping. Using the same motor task (tapping with the right index finger), Rounis and colleagues showed that high frequency rTMS of the motor cortex (5 Hz) causes increased regional cerebral blood flow bilaterally in the rostral dorsal premotor cortex, dorsolateral prefrontal cortex and medial prefrontal cortex compared to 1 Hz rTMS. However, just as in low frequency stimulation, 5 Hz stimulation also causes increased blood flow at the site of stimulation (dominant motor cortex). Widespread increased blood flow is also seen
throughout M1, the ipsilateral ventral premotor area, bilaterally in the somatosensory cortices, anterior cingulate, intraparietal and superior parietal cortices. Others have found this paradoxical increase at the site of stimulation with both excitatory and inhibitory TMS protocols, which may reflect that regional cerebral blood flow is a measure of activity in all circuits (excitatory and inhibitory). The bilateral frequency specific differences seen are for the cerebellum and rostral premotor areas, but it is impossible to comment on why these exist: different subpopulations of neurons with differential frequency responses, contributions from intracortical areas, cortico-subcortical interactions. In summary, functional imaging using regional cerebral blood flow does not provide good correlates to the known physiological changes that occur with different rates of TMS stimulation.

Siebner and colleagues studied rTMS (1 Hz) of the dorsal premotor cortex and measured regional cerebral blood flow ($H_2^{15}O$ PET) (Siebner et al., 2003). Using their simple motor task paradigm (pressing a button), before rTMS, they demonstrated that there was increased blood flow in the ipsilateral primary sensory cortex, supplementary motor area, primary motor cortex, and insula. On the contralateral hemisphere, there was increased blood flow in the SII, and the frontal opercular cortex. Bilateral increases were seen in the cerebellum and inferior parietal lobule. They used cluster analysis to determine if there were groups post rTMS. However, most of their clusters contain only one variable (a single brain region), making it difficult to draw definite conclusions, especially in view of the large number of variables in cluster one (they probably used a hierarchical clustering, when maybe a K-means might have been more sensitive, because so many of the variables are correlated in normals).
Neural circuit plasticity does not fit purely with the eloquently simple model of hebbian plasticity. These circuits mould by experiential learning, embracing peripheral lesions, peripheral sensory stimulation, perceptual inputs and repetition. It is not yet possible to know what weight is given to different inputs in the thalamocortical driven network within the S1/BA3b for somatosensory experiential plasticity. However, there is a good understanding of the multifaceted aspects of rat whisker sensory physiology (Feldman and Brecht, 2005).

Receptive fields in S1 receive inputs in two pathways: classic thalamocortical and the second afferent pathway. Both send projections from the VPM to layer IV, but the classic pathway is more focused on specific peripheral sensory zones and sends secondary projections to layer II/III neurons in the same column. This results in barrels extending to the neocortex from the specific inputs and septal projections from the thalamus send broad inputs simultaneously. Barrel formation early in life is governed by peripheral input involving multiple activity-dependent processes (Van der Loos and Woolsey, 1973).

Rapid plasticity in adult-rat S1 occurs in layer II/III and V, within the cortex itself, but rarely in the anatomically patterned thalamocortical barrels of IV. S1/BA3b has a very appreciable capability for hebbian plasticity, i.e. areas of underuse will be taken over by areas of overuse, and vice versa (Pons et al., 1991, Garraghty et al., 1994, Merzenich et al., 1983, Moore and Schady, 2000). In this context, the other component of hebbian plasticity is that the neural input into deprived areas is proportionally reduced also, possibly giving rise to dominance in another area where Bienenstock-Munro dynamics are not obeyed (Bienenstock et al., 1982). A cellular basis for this process is weakening of the layer IV input to layer II/III. The twinned process is to enhance the input to the spared area, and second afferent pathway
projections from spared areas will have greater influence in columns receiving weakened barrel inputs, giving rise to the effect of spread of the S1 representation (Bruno and Sakmann, 2006). Short-term over-stimulation of a larger area creates enhancement of several adjacent columns, which manifests as overlapping and disorganised representations on S1.

Abrupt early termination of layer II/III input leads to these neurons adopting broad unfocused receptive fields, while the layer IV map remains normal. The degraded topography extends across columns and disrupts the normal thalamocortical input segregation of the barrel and septal projections. Layer II/III neurons then receive abnormally strong layer IV septal inputs.

Longer duration over-stimulation of an area leads to weakening of inputs, and gradual shrinkage of the receptive field, a homeostatic response probably related to increased numbers of γABAergic synapses onto the spines of layer IV neurons.

Layer II/III receptive fields are known to shrink and become more acute in environments of novelty, arousal and exploration (Castro-Alamancos, 2004). Novel environment exposure in the case of partial deafferentation obeys Bienenstock-Cooper-Munro synaptic dynamics (to maintain the status-quo of the receptive field).

In classical hebbian plasticity, slow adaptation is explained by the above anatomical models, but fast adaptation is a physiological response – long-term-potentiation (LTP) and long-term-depression (LTD). Non-hebbian mechanisms are still poorly understood. S1/BA3b synapses are commonly NMDA receptor-dependent LTP and LTD. LTP strengthens synapse activity, and LTD weakens it. Each layer has differing capacity for more LTP or LTD, depending on its functional connections (Finnerty and Connors, 2000). LTP connections are driven by calcium/calmodulin protein kinase-2 (α-CaMKII) and cAMP response element binding protein (CREB).
LTP may occur at synapses between columns of spared projections to neighbouring columns (layer II/III). LTD is the major substrate for hebbian shrinkage of unused areas, affecting only layer II/III synapses and sparing IV (Allen et al., 2003). Therefore in S1/BA3b, plasticity is bidirectional (enhanced by layer IV to layer II/III positive feed, and weakened by lack of layer II/III cross stimulation).

Experiential plasticity is based on the pre- and post-synaptic activity, LTP/LTD, rate of firing and spike-timing. Layer IV-layer II/III synapses exhibit both rate-dependent and spike-timing dependent plasticity (STDP). In S1/BA3b, STDP occurs when an layer IV neuron fires briefly before an layer II/III neuron and induces LTP. LTD is induced if layer II/III fires first. STDP based on LTD behaves in a theoretically more useful way for cortical synaptic dynamics than with LTP. Simple inputs such as peripheral stimulation in a non-patterned manner is enough to induce LTD. Rate-dependent firing does not have as much importance in producing LTD, and a weaker hebbian response with LTP. The important neurochemical driver of receptive field plasticity in S1/BA3b is Acetylcholine, released in the cortex by basal forebrain inputs.

Changes in dendritic branch dynamics in adults are primarily in relation to lesions peripherally, and so the release of neurotrophic factors to change the structure does not necessarily influence the experiential learning within S1/BA3b. However, spines on dendrites do contribute to plasticity in a rapid manner, even over a period of hours. Spines are heterogenous in size and turnover rate, and turnover decreases with age. Spine synapse formation in S1/BA3b has been shown to be balanced by equal rates of dendritic retraction.

Questions remain on intracortical dynamics of plasticity: the weighting of different cell inputs, the seemingly illogical wiring specificity between neighbouring
columns, and the relationship between structural plasticity and functional changes in synaptic efficacy.

1.5.17 Homeostatic plasticity in PTD

Tactile stimulation synchronously applied to different areas repetitively can lead to representational remodelling in the somatosensory cortex, without concurrent reorganisation in the ventro-posterior thalamic nucleus (Wang et al., 1995), suggesting that most, if not all, plastic change occurs at the cortex with somatosensory input. The deficient inhibition of the somatosensory areas in dystonia has been reported by Lim and colleagues in relation to musicians/pianists with musician’s cramp, a task-specific focal dystonia (Lim et al., 2004). They found that contingent negative variation (CNV), which is the EEG potential that appears between a warning (S1) and a go (S2) stimulus in a reaction-time task, was increased in late amplitudes (after S2) of these affected musicians compared to controls (tactile S1) (Hallett, 2004). The CNV theoretically represents the dynamic process of sensorimotor integration. They further established that only the reaction times in their controls correlated with the amplitude of the late CNV. However, Ikeda and colleagues studied the CNV (auditory S1) in focal hand dystonia and found that the CNV is slightly decreased in central leads (Cz, Fz) compared to controls (Ikeda et al., 1996). However, most authors agree that the CNV is context specific and very variable. The type of condition stimulus (tactile or auditory) may therefore affect the subsequent negativity amplitude differently. It does suggest though that in focal dystonia, there is a loss of inhibition in cortical processing, and that this is important in the somatosensory cortex where it may result in excessive disorganised motor output.
So can the somatosensory cortex learn to improve itself if it is plastic? Godde and colleagues examined twelve healthy subjects using magnetoencephalography to see if sensory thresholds improved by tactile co-activation for two-point discrimination could be mapped (Godde et al., 2003). Two-point discrimination was assessed on three consecutive days with no significant improvement in performance (median day 1: 1.76 mm; day 2: 1.53 mm; day 3: 1.54 mm, significance not given). Then temporally random (8 to 1761 msec) tactile co-activation was done on the index finger-tip for three hours using a solenoid (mean stimulation 1.7 Hz), which allowed simultaneous stimulation to different locations of the finger-tip area being examined. After this, retesting of the two-point discrimination threshold improved to a median of 1.23 mm. The difference was significant, with the results reported using Chi-square statistics ($p = 0.03$) and a post-hoc t-test ($p<0.05$). The right index finger showed a shift in the dipole moment on MEG assessment (compared with the little finger), which did not occur in the left hand. Unfortunately, there was no correlation between the threshold reduction and the dipole movement in the nine of twelve subjects whose two-point discrimination threshold improved. Pleger and colleagues showed that this method of hebbian induced improvement in spatial discrimination performance deteriorates within 24 hours, returning to normal (Pleger et al., 2001). Interestingly though, they were able to also show that there was a correlation between change in dipole moment (using somatosensory evoked potential N25) and the improvement in two-point discrimination threshold. In another study looking at the effect of timing with synchronous (which leads to overlapping of tactile fields) and asynchronous stimulation, Pilz and colleagues showed that digit representations of D1, D3 and D5 became more distinct with asynchronous stimulation, whereas synchronous stimulation improved cortical organisation seen on functional magnetic resonance
imaging (Pilz et al., 2004). There was a similar post-test difference between the two groups two-point discrimination thresholds (p < 0.005), which returned to baseline in the recovery test performed one week later. These results correlate with our knowledge of spatial acuity patterns in blind Braille readers. Early blind Braille readers have an expanded finger representation in the somatosensory cortex, but those who report using a single dominant finger for reading have significantly better spatial discrimination thresholds than those who use two or more (Van Boven et al., 2000).

Zeuner and colleagues followed ten patients with dystonia over eight weeks during which they had 30-60 minutes daily of Braille training (Zeuner et al., 2002). They measured pre- and post-testing spatial discrimination thresholds and Fahn dystonia severity scale rating. Thresholds improved in both groups (patients: week 1 = 2.38 mm ± 1.09; week 8 = 1.75 mm ± 0.69, p = 0.03), and patients had some correlation with improvement also seen in their dystonia severity (r = 0.27). One year later, three patients had continued their Braille reading and had still some improvement in their dystonia (Zeuner and Hallett, 2003).

Since the sensorimotor cortex seems abnormal in dystonia, and this is the area of greatest plastic potential, Quartarone and colleagues examined associative plasticity of the motor cortex in focal hand dystonia (Quartarone et al., 2003). The horizontal fibres have been implicated in rapid adapting plasticity, and strengthening of horizontal connections in layers II and III in the motor cortex has been demonstrated with the acquisition of new skills (Rioult-Pedotti et al., 1998), which Rioult-Pedotti hypothesised is not unique to this area. This type of associative conditioning uses LTP, which is supported by evidence that it can be inhibited by blocking NMDA receptors using dextromethorphan (Stefan et al., 2002). Quartarone and colleagues gave a single electrical stimulus of 300% suprathreshold to the right
median nerve, followed by a single pulse suprathreshold TMS to the motor area
maximally associated with the right abductor pollicis brevis muscle (APB). There was
a significant increase in the MEP with both subjects and controls induced by the
associative sensory stimulus at an interstimulus interval of 25 msec (the time
estimated needed for stimulus to reach cortex and travel through layer II/III to
associated motor cortex). They used a factor analysis and created three new variables
which showed that *time* (before or after stimulus) was the strongest predictor ($F_{1,18} =
47.2; p < 0.001$). This is obviously due to the fact that all the measured variables are
known to change with stimulation. They examined the other correlated factors and
found that the *time x group* interaction was significant ($F_{1,18} = 12.4; p = 0.003$),
indicating that there are significant differences between groups, pre- and post-
stimulation. There was also a significant *time x muscle* interaction ($F_{1,18} = 7.2; p =
0.017$), which was answerable mostly to the effect of facilitation in the APB and the
first dorsal interosseous (FDI). The next effect that they looked at was within subject
factors such as time (before or after stimulus). For the patient group, there was a
significant effect for *time* ($F_{1,9} = 31.5; p < 0.001$), but not for *time x muscle* ($F_{1,9} = 1.9;
p = 0.20$). With controls, there was a significant effect for *time* ($F_{1,9} = 19.5; p = 0.002$)
and *time x muscle* ($F_{1,9} = 7.4; p = 0.026$). Essentially, this suggests that there is loss of
somatotopic interaction and representation, and therefore abnormal associative
plasticity in the sensorimotor interaction in writer’s cramp. These results can be
compared satisfactorily with those of Tamburin and colleagues who showed the loss
of digit specific inhibition of MEP by digital sensory stimulation (Tamburin et al.,
2002). In relation to the shortened cortical silent period, in dystonia the intracortical
horizontal fibre $\gamma$ABA$_B$ receptors are deficient, and there is little evidence to suggest it
is excessive glutamatergic stimulation (NMDA). This studies shortened silent period
confirms the attenuation of the inhibitory system in dystonia in the absence of supportive evidence of hyperexcitability. Thus, patients with focal hand dystonia may also be more likely to strengthen disorganised synaptic connections.

However, we know from all the experiments on LTP and LTD that they are controversial as true learning mechanisms, despite their importance in our understanding of plasticity. If associative learning were allowed to exist in an unchecked manner, stable cortical circuitry would be disturbed by new homosynaptic and heterosynaptic stimulation, leading to constant disorganisation. In theory a mechanism must exist that does not allow for disruption of healthy experiential circuits. This has been termed homeostatic plasticity (Turrigiano and Nelson, 2004). Experimental evidence is accruing that individual neurons can sense how active they are and adjust themselves to maintain activity levels around a certain fixed point. It is likely to be regulated by post-synaptic activity: post-synaptic cells whose activity is reduced e.g. quantal amplitude, have positive feedback to the pre-synaptic cell which increases the number of pre-synaptic transmitters released. This has also been shown in muscle: hyperpolarisation of muscle by selective expression of inwardly rectifying potassium channels leads to a transient increase in pre-synaptic transmitter release. The data comes from experiments in mice, where a reduction in post-synaptic clustering of acetylcholine receptors (from downregulation of neuregulin) led to a pre-synaptic increase in acetylcholine release. When change occurs in homeostatic circuits, the slow change that occurs requires many hours on input at a steady low level (from in vitro models). In the motor system, to combat the effects of multiple inputs all the time, it is likely that cells such as pyramidal neurons have set background-firing rates (in vitro data). How cells can know what their average excitation rate is at the synapse is as yet unknown, but calcium is known to be
instrumental in determining intrinsic excitability, and may thus have a role in homeostatic plasticity? A calcium/calmodulin antagonist (KN93, a calcium-dependent kinase inhibitor) blocks changes in the amplitude/frequency of miniature excitatory post-synaptic currents in hippocampal neurons that are normally a feature of homeostatic plasticity.

To examine if homeostatic mechanisms are abnormal in dystonia, Quartarone and colleagues examined eight patients with simple writer’s cramp (Quartarone et al., 2005). They used cathodal (inhibitory), anodal (excitatory), or sham pre-conditioning of the motor cortex using ten minutes of trans cranial direct current stimulation (TDCS) and 1 Hz rTMS for 15 minutes at 85% of the motor threshold. They measured motor thresholds by single pulse resting and active motor thresholds (to produce 50 mV and 200 mV peak-to-peak MEP in five of ten stimuli), and intracortical facilitation with paired-pulse stimulation (to elicit 0.8-1 mV using a 80% of active motor threshold conditioning stimulus). For short intervals, interstimulus intervals of 2 and 4 msec were used, and for long intervals, times between integer values of 9 and 12 msec were used (inclusive). Again, they did a factor analysis and repeated measures ANOVA. Both forms of conditioning influenced the amplitude of MEPs: anodal TDCS increased cortico-spinal excitability in both groups, but cathodal TDCS only decreased control MEP amplitudes. They found differences for the interaction between the factors type of priming x time of measurement (F₁₁₄ = 3.3; p = 0.02), type of priming x time of measurement x group (F₃₄₂ = 6.9; p < 0.001). Therefore, the type of conditioning influenced the measurement in the groups in different ways. Repetitive stimulation TMS reversed the changes of TDCS in controls, but did not affect the subjects with dystonia. Sham TDCS showed no effect in any group or protocol. On intracortical measurements,
there was no effect other than what is expected to be seen – loss of inhibition at short interval intracortical stimulation in the dystonia group ($F_{1,14} = 7.7; p = 0.01$). They conclude that in normal subjects, LTD-like effects were enhanced by 1 Hz rTMS (with excitatory pre-conditioning) and LTP-like effects were enhanced with rTMS after inhibitory pre-conditioning. However, neither was seen in dystonia subjects. The reversal of the mechanism in normal subjects shows an alteration of normal homeostasis as suggested by the Bienenstock-Cooper-Munro model of homeostatic plasticity (Bienenstock et al., 1982). In contrast, the dystonic cortex in focal dystonia shows little inclination to change long-term and enhance correction of the altered egocentric frame of reference. This concurs with the measurements of lack of inhibition (and by extension, excitability), lending itself to motor facilitation in dystonia. The results of this study though are highly important in understanding plasticity in dystonia: there is reduced efficacy of the mechanisms that might alter homeostatic plasticity in dystonia, as well as enhanced ability to learn new pathways. However, to better understand adult-onset primary torsion dystonia, the experiment needs to be reproduced in focal dystonia that is not task-related or musician’s dystonia.

1.5.18 Dynamic remodelling of S1 in focal task-specific dystonia

It can be seen from descriptions of the literature that many measurements in dystonia are abnormal. However, we have also seen that the organisation of sensory and motor areas differ between rest and when movement is performed. We have also seen the rapid re-assignment of motor areas in the cortex that occurs after deafferentation. So what activity can be seen in the sensory cortex when a motor task is in train? Braun and colleagues looked at the sensory cortex using magnetoencephalography in seven
subjects with simple focal hand dystonia and controls, both at rest and during motor
tasks, which included brushing and writing (Braun et al., 2003). Measurements were
taken from BA3b using a helmet mounted 151 lead MEG whole head system. Initially
at rest, the distances between DI and D5 were different between patients and controls
($F_{1,12} = 5.52, p = 0.037$). Then for tasks, in the patient group, during writing the polar
angle ($\Delta \theta$, the distance between the central sulcus and the measured area) changed by
only $5.86 \pm 0.62^\circ$ (controls $= 10.33 \pm 1.51^\circ$), and during brushing it changed by $6.51$
$\pm 0.98^\circ$ (controls $= 10.13 \pm 1.44^\circ$). ANOVA results are reported, but the data that is
being compared is not clear, i.e. combined patients and controls for different
conditions, or patients only, etc. However they also report on dipole strength in the
two groups, and showed that there is a significant group effect ($F_{1,12} = 8.39; p =$
$0.013$) and task effect ($F_{2,24} = 9.52; p = 0.0009$). There was less dipole moment
strength in the patient group than the controls, and paired comparisons of tasks versus
rest was significantly different in both groups. What this experiment importantly
shows is that as well as abnormal organisation of the sensory cortex at rest in
dystonia, and that there is less dynamic reorganisation for movement tasks (compared
to controls), which may be the functional abnormality. This experiment in the light of
others creates many questions. Is there a qualitative or quantitative difference
structural organisation in the cortex in AOPTD$^1$, attempting to adapt with enhanced
excitability and mal-adaptive plasticity (Tang et al., 2001, DeFelipe et al., 1999)? Are
the sensory deficits seen in dystonia hard-wired and could they be seen in pre-
symptomatic individuals, or asymptomatic carriers of an AOPTD gene?

$^1$ Volume of grey matter is associated with synaptic density
1.5S Summary of sensory abnormalities in AOPTD

In AOPTD, patients have been shown to have abnormal spatial and temporal discrimination thresholds, abnormalities of the tonic vibration reflex, decreased activation of the somatosensory cortex, enhanced activation of the thalamus and basal ganglia structures, overlapping enlarged receptive fields, over-excitable cortex and abnormal plasticity of the sensorimotor cortex. Sensorimotor integration is impaired, but sensory retraining to improve function has been successful in those who have been compliant. The range of sensory disturbances in AOPTD indicate a central sensory disorder, which has its localisation pointing towards the thalamocortical-basal ganglia loop involved in sensorimotor integration. The lack of structural abnormality (except enlargement of S1 on VBM) on neuroimaging and post-mortem studies support the electrophysiological and functional imaging studies that suggest a disorder of function in the cerebral hemispheres. The ability to change the phenotype severity with appropriate sensory codes and inputs in conjunction with all the other data, make it likely to be a hard-wired sensorimotor integration disorder with mal-adaptive plasticity.
1.6 Genetics in AOPTD

1.6.1 Epidemiological evidence for inheritance in AOPTD

With a prevalence as high as 330 per million of the population, primary torsion dystonia is common enough for familial cases to be recognised (Nutt et al., 1988, Waddy et al., 1991, Zeman et al., 1959). Truong and Fahn translated an early twentieth century thesis by Schwalbe describing a Jewish Lithuanian family with three siblings affected by severe involuntary movements (Truong and Fahn, 1988). Rare families with large numbers of affected individuals were frequently given alternative diagnoses such as Huntington’s disease or Wilson’s disease (Parker, 1985). Occasional reports within the literature strongly support a genetic basis for focal forms of dystonia, such as that occurring in monozygotic twins (Factor, 2002).

Due to the heterogeneity, age-related onset and low penetrance, a family history may not be revealing in AOPTD. Examination of first-degree relatives of patients with all phenotypes of AOPTD finds that up to 25% of other seemingly sporadic cases will have family members with clinical evidence of dystonia (Waddy et al., 1991). Of the 40 probands in this study, six families only (nine other clinically affected cases) were identified by examination (15%). Of the nine identified on examination, four had postural tremor of the upper limbs with dystonic posturing of the hands, three had asymptomatic blepharospasm, and two had asymptomatic cervical dystonia. A further four were identified by history of deceased relatives, with three having writer’s cramp. An Italian group looked at first-degree relatives of patients with blepharospasm and cervical dystonia. Identifying 29 probands, they found six affected relatives (five siblings and one parent) by examination in six families (21%) (Defazio et al., 1993). A further three cases in two families could be
elicited by history. No secondary case was found among children of index cases. This may have been hampered by the young age (median 39y, range 7 – 48y). In former Yugoslavia, 43 AOPTD proband’s families were examined. Ten relatives were identified in ten families (23%) (Stojanovic et al., 1995). Half of the examined relatives had postural tremor of the upper limbs with or without some dystonic posturing of the hands.

In these three studies, only two index cases with writer’s cramp were found to have affected family members, both of whom also had writer’s cramp. This would suggest that intrafamilial heterogeneity of craniocervical dystonia including its asymptomatic hand tremor phenotype may be genetically distinct from writer’s cramp. Primary blepharospasm has been reported as an autosomal dominant trait in two Italian families, and craniocervical dystonia predominates as for intrafamilial heterogeneity including hand tremor, but without typical writer’s cramp (Defazio et al., 2003d, Brancati et al., 2002).

In neuropsychiatric disease, the reliability of family history when given by a proband has been studied in Parkinson’s Disease (IPD), Depression and Dementia (Marder et al., 2003). In IPD, there is a very good inter-reporter reliability for recognition of disease when it is clearly present (κ = 0.8 – 0.92), but over-reporting tended to occur when liberal weighting was given to reports, and poorer intrafamilial agreement was seen (κ = 0.41 – 0.72). This has been reported as even poorer where the phenotype may not be as clear, such as depression.

When interviewed, only 9.5-13% of adults with AOPTD craniocervical dystonia give a positive family history (Greene et al., 1995, Grandas et al., 1988). In multivariate analysis, family history of dystonia and postural tremor are found to be associated with increased risk of having AOPTD (Defazio et al., 1998).
1.6.2 Sensory testing in family members of AOPTD

An abnormal threshold for Vibration-Induced-Illusion of Movement (VIIM) was found in a significantly larger proportion of first-degree relatives of 30 patients with dystonia compared to controls. Parents, siblings and children were found to have about a three to four times higher likelihood of abnormal VIIM compared to controls (Frima et al., 2008). Fatiguing the vibrated arm, tends to exacerbate VIIM in dystonic patients, but this effect was not seen in the first-degree relatives. A limitation of this study is that 21% of normal subjects also have abnormal VIIM measurements.

Sensory abnormalities in families with apparently sporadic AOPTD have been assessed using SDTs. We examined 25 such families using the Johnson-Van Boven-Phillips domes and found abnormal SDTs in 14 families (56%). In eight of these at least two first-degree relatives with abnormal thresholds were identified (32%) (Walsh et al., 2007).

1.6.3 Penetrance in AOPTD and other examples

Penetrance “reflects the fraction of individuals with a genotype who have signs or symptoms of the disease.” (Saunders-Pullman et al., 2004) Penetrance has also been defined as “the frequency, under given environmental conditions, with which a specific genotype is expressed by those individuals that possess it, usually given as a percentage.” (Wikipedia, 2007) The National Institutes for Health on-line resource defines penetrance as “the probability of a gene or genetic trait being expressed. Complete penetrance means the gene or genes for a trait are expressed in all the population who have the genes. Incomplete penetrance means the genetic trait is
expressed in only part of the population. The percent penetrance also may change with the age range of the population.” (NIH, 2007)

Penetrance which is complete will result in the expression of the genotype of a disease as a phenotype in each gene carrier, irrespective of the heterogeneity of the phenotype. Depending on the gene’s primary effect, the phenotype may or may not be clinically detectable. Penetrance, which is less than complete may be a result of complex genetics, where other genes can influence the phenotypic expression, and environmental influences. In AOPTD, low penetrance and the caudal-rostral phenotype in relation to age of onset probably reflects these interactions. (O’Riordan et al., 2004b) However, the very low penetrance in AOPTD of 12-15% suggests a protective effect of these influences, which may disappear with increasing age. (Waddy et al., 1991) Alternatively, they may have a deleterious effect which appears with increasing age.

In AOPTD, the combination of low penetrance with a variable phenotype and older age of onset, reduces the possibility of finding large multiplex families. Single gene disorders with high penetrance or clinical importance are rarely seen. Genes with high penetrance must confer a very elevated risk to carriers. Genetic polymorphisms may result in a less severe phenotype, or code for processes that indirectly lead to the phenotype. The latter possibility is more frequently associated with lower penetrance, with greater susceptibility in an carrier to environmental influences (Vineis et al., 2001, Ottman, 1995).

However, penetrance is not an entirely intrinsic characteristic to a gene. Some genetic disorders are highly penetrant (eg. Huntington’s disease) but do not reach 100%. There are six factors which determine penetrance:

(1) the functional importance of the gene product
(2) the mutation/deletion/duplication effect

(3) knock-on effect on other gene transcription

(4) any new somatic mutations

(5) environment interactions

(6) the burden of the gene defect and alternative pathways

AOPTD is a very challenging disorder to understand genetically, made even more difficult by lack of diagnosis or misdiagnosis in many individuals. A sensitive easy-to-administer method to detect a gene carrier, bypassing all the above determinants might assist in identification of new genetic loci in large families with AOPTD.

Non-manifesting carriers of the *DYTI* gene were studied with [18F]FDG-PET using a two by two matrix of paradigms consisting of awake/sleep and movement free/movement related measurements of regional cerebral metabolic rates. The non-manifesting gene carriers had similar patterns of increased cerebral metabolism to manifesting carriers, different to controls (Eidelberg et al., 1998). Furthermore, non-manifesting carriers were found to have a similar pattern of cortical excitability studied using Transcranial Magnetic Stimulation. There was a significant reduction of intracortical inhibition and the silent period, but normal spinal reciprocal inhibition (Edwards et al., 2003). However, in both of these studies, non-manifesting carriers did not have the full complement of traits seen in clinically affected patients.

Temporal discrimination thresholds have been examined in non-manifesting *DYTI* carriers also, with the results showing abnormalities that may represent an
endophenotype. In this study, manifesting and non-manifesting carriers were compared to non-carrier relatives and external controls. Both gene carrying groups had similar results, with abnormally high thresholds (Fiorio et al., 2007).

1.6.4 Multiplex families in AOPTD

Despite 16 different dystonia genetic syndromes with loci [DYT1-13 and 15-17](Wider et al., 2008), only six have a phenotype of pure dystonia, with the remainder being referred to as Dystonia-Plus syndromes (Gimenez-Roldan et al., 1988, Almasy et al., 1997, Leube et al., 1996, Valente et al., 2001, Chouery et al., 2008, Parker, 1985). Of these, three are adult-onset primary torsion dystonias, and all three are autosomal dominant with reduced penetrance. They are DYT6, DYT7, and DYT13.

*DYT6* was locus mapped to chromosome 8, and more recently the gene has been identified as *THAP1*, which is a transcription factor regulating the downstream expression of other genes (Fuchs et al., 2009). In the original two Amish-Mennonite families and two others, a founder mutation exists. In a family of German origin with the same phenotype, a SNP in the same gene resulting in abnormal *THAP1* was also found. *DYT6*’s phenotype is a cranial-cervical dystonia that is focal/segmental, and has a relatively higher penetrance of the order of 60% (Almasy et al., 1997).

*DYT7* was described in a German family with seven definitely affected individuals (6 cervical dystonia, 1 spasmodic dysphonia), six possibly affected (5 cervical dystonia, 1 writer’s cramp) and postural hand tremor was seen in six others (3 definite, 3 possible). Linkage analysis on 206 satellites was done, and 118 were informative. One marker had a likelihood-of-disease (lod) score >2.0, (D18S62),

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\(^2\) DYT14 was reclassified as DYT5
which localised to chromosome 18p (Leube et al., 1996). A further family of mother and son affected was later described with an unbalanced translocation at the 18p site. The mother suffered from dystonia early in childhood, a tic disorder and a relatively progressive course. Her son suffered congenital cardiac problems and has remained severely developmentally delayed, with oromandibular dystonia (Nasir et al., 2006).

DYT13 linkage was found in an Italian AOPTD kindred characterised by craniocervical or upper limb dystonia, and marked jerky tremor in these locations. Initial examination of the family counted eight definitely affected and six probably affected members. Re-examination six years later showed eleven definitely affected members. The three newly affected kin were previously "probably affected". The remaining three members were not included in linkage analysis. A candidate region on the short arm of chromosome 1 generated a lod score of 3.44, and the locus was refined to 1p36 (Valente et al., 2001).

1.6.5 Endophenotypes

An endophenotype is a subclinical trait associated with the expression of an illness and representing the genetic liability to the disorder in non-affected subjects. The concept of an endophenotype began to emerge over 40 years ago in psychiatric literature, looking for ways to differentiate schizophrenia from other psychotic disorders (Gottesman and Gould, 2003). Endophenotypes have gained widespread use in the last decade both in psychiatry and medicine. Endophenotypes may be biologically measured, appraised as a clinical trait, or exist as a vulnerability marker. For example, the presence of polyspike and wave on an EEG in Juvenile Myoclonic Epilepsy (JME), or serum ferritin in Haemochromatosis.
In the study of genetic disease, the ideal endophenotype would have monogenic origins. There are other characteristics of an endophenotype that are desirable for it to be effective:

1) it is associated with illness in the population
2) it is heritable
3) it is state-independent (it always manifests in carriers)
4) within families, endophenotype and illness co-segregate
5) endophenotypes found in unaffected family members are present to a much greater extent that in the general population

The five desirable features of an endophenotype as outlined above make their study interesting. Assuming that an endophenotype obeys all the five rules, its penetrance should be close to 100%. Penetrance of the endophenotype is often age related, for example in Fragile-X Tremor Ataxia Syndrome (Jacquemont et al., 2004). The endophenotype is the \textit{FMR1} premutation, and premutation carriers are generally asymptomatic until after the late 50’s. Penetrance for the age groups 50-59y, 60-69y, 70-79y, and \( \geq 80y \) is 17%, 38%, 47% and 75% respectively. The endophenotype is easily measured in all age groups.

Endophenotypes may remain silent forever. Family members in large JME kindreds with abnormal EEGs may never have seizures. Combining the EEG signature with family members allowed linkage to chromosome 6p21.2-p11 in eight families (Liu et al., 1995). Penetrance was assumed to be close to 100% in this study.

Research in dystonia has produced many postulated endophenotypes: VIIM thresholds, temporal discrimination thresholds, cerebral metabolism on PET, and hyperexcitable cortex and interhemispheric connections. Despite a harlequin-like
array of possibilities, in AOPTD no endophenotype has been identified in unaffected members of large multiplex families.

1.6S Summary of genetics of AOPTD

Family studies of AOPTD suggest an autosomal dominant inheritance pattern with low penetrance. Very few gene loci have been identified, limited to DYT6, DYT7 and DYT13. In these families penetrance was higher than that usually observed. Endophenotypes, or traits that may represent carrier status, have been used in other diseases to allow linkage analysis and improve understanding of diseases such as hemochromatosis and juvenile myoclonic epilepsy. Using sensation as an endophenotype in sporadic AOPTD, a small proportion of abnormal individuals are found compared to controls. DYT1 dystonia non-manifesting gene carriers do show signatures of their carrier status on studies using PET, transcranial magnetic stimulation and temporal discrimination thresholds. DYT1 patients are also found to have higher spatial discrimination thresholds. Multiplex families with AOPTD have not been studied using sensation as an endophenotype.
1.7 Sensory receptors and assessment of peripheral sensory organs

1.7.1 Anatomical arrangement of sensory receptors

Sensory stimuli on the skin and other parts of the body are first sensed by dedicated and different types of receptor (Mowzoom and Flemming, 2007):

<table>
<thead>
<tr>
<th>Receptor type</th>
<th>Sensory detection</th>
<th>Fiber group</th>
<th>Fiber name</th>
<th>CV, m/s</th>
<th>Fiber size, μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociception mechanical</td>
<td>Sharp/prickle</td>
<td>Aδ</td>
<td>III</td>
<td>25</td>
<td>1-6</td>
</tr>
<tr>
<td>Thermal mechanical</td>
<td>Burning</td>
<td>Aδ</td>
<td>III</td>
<td>4-36</td>
<td>1-6</td>
</tr>
<tr>
<td>Thermal mechanical</td>
<td>Freezing</td>
<td>C</td>
<td>IV</td>
<td>0.4-2</td>
<td>0.2-1.5</td>
</tr>
<tr>
<td>Polymode nociceptor</td>
<td>Burning</td>
<td>C</td>
<td>IV</td>
<td>0.4-2</td>
<td>0.2-1.5</td>
</tr>
<tr>
<td>Thermal receptor</td>
<td>Cool</td>
<td>Aδ</td>
<td>III</td>
<td>4-36</td>
<td>1-6</td>
</tr>
<tr>
<td></td>
<td>Warm</td>
<td>C</td>
<td>IV</td>
<td>0.4-2</td>
<td>1-6</td>
</tr>
<tr>
<td>Meissner Corpuscle</td>
<td>Touch</td>
<td>Aα, Aβ</td>
<td>Rapid adapt</td>
<td>72-120</td>
<td>12-20</td>
</tr>
<tr>
<td>Merkel Disc</td>
<td>Pressure/textures</td>
<td>Aα, Aβ</td>
<td>Slow adapt</td>
<td>72-120</td>
<td>12-20</td>
</tr>
<tr>
<td>Pacinian Corpuscle</td>
<td>Vibration</td>
<td>Aα, Aβ</td>
<td>Rapid adapt</td>
<td>72-120</td>
<td>12-20</td>
</tr>
<tr>
<td>Ruffini Ending</td>
<td>Skin stretch</td>
<td>Aα, Aβ</td>
<td>Slow adapt</td>
<td>72-120</td>
<td>12-20</td>
</tr>
<tr>
<td>Golgi tendon organ</td>
<td>Muscle contraction</td>
<td>Aα</td>
<td>lb</td>
<td>72-120</td>
<td>12-20</td>
</tr>
<tr>
<td>Muscle spindle Receptor</td>
<td>Muscle length/speed</td>
<td>Aα</td>
<td>la</td>
<td>72-120</td>
<td>12-20</td>
</tr>
<tr>
<td>Joint capsule Receptor</td>
<td>Joint angle</td>
<td>Aβ</td>
<td>II</td>
<td>36-72</td>
<td>6-12</td>
</tr>
</tbody>
</table>

Each receptor has its own type of function, and this leads to differential expression of receptors throughout the body.

Sensory receptors on the skin are organised to give maximum advantage for certain types of sensory detection. The palm of the hand and the lips have the greatest concentration of specialised sensory receptors. In the hand, the pulps of the fingertips have further clustering again to allow fine touch differentiation of texture, pressure zones, and two point discrimination at its finest. Specialised receptors that are almost exclusively found in the fingertips called Merkel discs are most adept to fine touch sensation (Appendix 5 & 6).
Merkel discs are slow adapting superficial sensation mechanoreceptors in volar skin and some mucous membranes. Friedrich Sigmund Merkel first described them in 1875, noting their presence in glabrous skin, and assuming their function by naming them Tastzellen (Halata et al., 2003, Boot et al., 1992, Harmse et al., 1999). Characteristics of Merkel discs are their oval shape about 10-15 μm in diameter, close individual contact with nerve terminals, and clustering in the base of epidermis. They have long thin cytoplasmic protrusions that interdigitate with surrounding keratinocytes. The cell (Merkel disc) membrane is apposed to a nerve terminal with specialised arrangement of discoid free endings of small myelinated fibres 3-5 μm in diameter. Clusters are composed of an average 28 discs in glabrous skin with a density here of 756 ± 386/mm² compared to less than 50/mm² outside the fingertip, which correlates well with reported numbers of myelinated nerve endings per square millimeter (59.0 ± 29.3) in glabrous skin (Reinisch and Tschachler, 2005, Nolano et al., 2003). They are located near the penetration of sweat gland ducts at the base of epidermal ridges. The long axis of the oval Merkel disc is orientated parallel to the surface of the skin, and the disc nerve terminal opposes the membrane of the disc underneath it at the basal lamina. Each cluster is supplied by one axon.

Merkel disc function is difficult to study using microelectrodes due to their position. They may function by synaptic transmission through mechanically triggered neurotransmitter release, and this would be suggested by the irregular bursts of action potentials and their slow adapting response. However, they rapidly respond to sinusoidal stimuli suggesting they direct mechanical stimuli to the nerve terminal. From neurochemical studies, it would appear that glutamate is the main neurotransmitter for Merkel discs (Fagan and Cahusac, 2001).
Merkel discs are found in the skin, innervated in high numbers from birth. In neonates, up to 95% of them have axons in skin grafts sampled. Their survival in adult life is independent of nerve function. They appear to have paracrine function in the skin as a separate role due to the large numbers of granules and exocytosis can be seen, possibly suggesting why some are not innervated.

In hereditary sensory neuropathy patients, despite loss of innervation, Merkel disc remain in normal numbers, suggesting they do not rely on trophic input from nerves (Narisawa and Kohda, 1995). Merkel discs are also seen in normal or increased numbers in scleroderma (Tachibana and Nawa, 2002). In patients with vitiligo, Merkel discs are absent in affected skin areas possibly due to their keratin (Bose, 1994).

Merkel disc generation and survival is dependent on Neurotrophin-3 (NT3). NT3-knockout mice have been shown to have no Merkel discs. Treatment with NT3 induces Merkel disc generation, since they are likely to derive from neural crest cells and later ectoderm. Some diseases associated with the suppression of NT3, such as chronic obstructive pulmonary disease, which may affect Merkel disc survival (Groneberg et al., 2005). Age related decreases in target neurotrophin expression also leads to decline in numbers of Merkel discs as they become destroyed by wear and tear (Bergman et al., 2000). Neurodegenerative conditions such as Alzheimer’s Disease, Parkinson’s Disease, amyotrophic lateral sclerosis, peripheral neuropathy and schizophrenia have been shown to have lower levels of NT3 compared to controls (Kunugi et al., 1998, Connor and Dragunow, 1998).
1.7.2 Measuring fine sensation

Two-point discrimination is constrained by the mechanical limitations of skin. Subjects with nerve injury in longitudinal follow-up can discriminate two points but not large grating orientations, suggesting that two-point acuity uses non-spatial cues (Van Boven and Johnson, 1994b). Gap detection using Von Frey monofilaments has been tried in Focal Hand Dystonia, and was found to be abnormal (Bara-Jimenez et al., 2000a). However, patients performed worse with grating orientation tasks. Van Boven commented that two point discrimination tasks and spatial discrimination are mediated by different pathways and measure different things. In performing a spatial acuity/two point discrimination examination, one measures individual mechanoreceptor groups edges only (Van Boven, 2001).

Grating orientation tasks using Johnson-Van Boven-Phillips domes can be placed on to skin and held stationary, eliminating temporal and movement cues. This method preferentially engages slowly adapting afferent fibres and a maximum resolution of 0.5 mm in humans using this method has been reported by Johnson and Phillips (Johnson and Phillips, 1981). It is the preferred method of measuring spatial acuity because the pathways are well understood, it affords an almost parametric measure of human performance, there is no subject movement involved and it is passively applied (Van Boven et al., 2005).

Rigid spatially complex stimuli applied to the skin produce force profiles with high values near edges and low values under broad flat areas. When using gratings with bars, it is imperative to bear in mind skin mechanics. Using a continuum mechanics model which assumes that skin has elastic properties that obey Hooke’s law, Phillips and Johnson predicted that approximately a 1000 µm indentation under a bar will change load dynamics for an area of 6 mm around the point of pressure.
(Phillips and Johnson, 1981). Forces near an isolate edge are high, since they are sustained and deflect skin up to 3 mm distant. In the case of a gap, two edges approximate and share deformation burden. So edge forces are reduced quite dramatically. Application of a grating results in compressive deformation and tensile/shear deformation, but only in two planes (e.g. x and y). No strain occurs in the z-plane, which provides differential input into a composite of sensory interpretation. For slowly adapting fibres, responses are related qualitatively to maximum compressive strain, and the static discharge rate is a linear function of the strain. Slowly adapting fibres reach static discharge about 600-950 msec after the onset of the stimulus. The examiner using spatial discrimination thresholds needs to be aware of these mechanical and physiological properties to correctly use the technique of grating orientation tasks.

Sinclair and colleagues used single neuronal firing rates to examine the effect of gratings widths (range 500-2900 μm) and bar patterns on anaesthetised macaque monkeys (Sinclair et al., 1996). They found that in the digit areas of the primary somatosensory cortex, the responses of neurons in BA3b and BA1/BA2 were different. This study used temporal/movement cueing as well as spatial information, and they examined four digits. The neurons of BA3b were predominantly slowly adapting (SA), and had greater firing rates for increasing sizes of groove width, and more recordable measurements for narrower gratings. Small receptive fields and low thresholds were typical of BA3b neurons. Using the index finger, they showed linear increase in firing for grating widths up to 2900 μm, but non-index distal digital fat pad glabrous skin areas showed a inverse U-shaped curve for firing with increasing groove width. The rapidly adapting cells (RA) provided a more linear representation of velocity of movement over the skin than SA neurons, which gave a better
representation of force. However, both SA and RA neurons contributed to roughness discrimination (groove width), which when tested in a psychophysical experiment in humans and animals is undoubtedly going to have elements of spatial and temporal cues combined. This experiment helps in understanding that peripheral mechanoreceptors respond to skin deformation proportional to the amount of skin falling between each ridge on a grating.

It should also be noted that the grating orientation task measures not only the individual spatial response properties, but also nerve density, and the spatial integration of multiple sensory inputs of a group of SA neurons (Van Boven, 2001).

The central recognition of grating orientation localises to the left intraparietal sulcus, consistent with other measures of stereognosis (Van Boven et al., 2005, Zhang et al., 2005). Van Boven and colleagues showed that regional BOLD fMRI levels were increased here by comparing two paradigms in patients tested. They had to detect either grating orientation or grating location. The latter localised to the right temporoparietal junction. Selective activation of bilateral BA3b was also seen.

The first measurement of spatial discrimination thresholds using gratings was done on three subjects by Johnson and Phillips (Johnson and Phillips, 1981). They measured spatial discrimination at the fingertip and found it to be 0.84 mm. In repeating this test later, Van Boven and Johnson determined it to be 0.94 mm in 15 normal healthy subjects, aged 23 to 25 years (Van Boven and Johnson, 1994a). Their study also looked at the repeatability of the test, but due to the continuous variable (spatial discrimination threshold) they did not report kappa. Simple linear regression by session (over six sessions) was done to examine for a learning effect, which was not significant for the finger, but with a small negative slope of -0.007 mm per session. Combined data from spatial discrimination thresholds measured at the lip,
tongue and fingertip showed a 2% improvement per session, which compared favourably to a 4% per session improvement in letter identification performance reported by other authors.

Van Boven and Johnson draw a correlation between afferent fibre innervation density and the spatial discrimination threshold they measured. These fibres which have a centre-to-centre spacing of 1.0 mm in the fingertip are subject to surround inhibition in the somatosensory cortex giving them enhanced spatial resolution though.

Sathian and Zangaladze assessed spatial acuity using grating orientation tasks at the lip and each fingertip of both hands (Sathian and Zangaladze, 1996). They examined seven healthy controls, all right handed who had a mean SDT on the right index finger of 0.96 mm (± 0.16), on the left of 0.83 mm (± 0.24), and a mean SDT of 0.89 mm (± 0.19). The SDT results for both hands are tabulated below:

<table>
<thead>
<tr>
<th></th>
<th>Right SDT (mm)</th>
<th>Left SDT (mm)</th>
<th>Mean SDT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thumb</td>
<td>0.99</td>
<td>1.01</td>
<td>1.00</td>
</tr>
<tr>
<td>Index</td>
<td>0.96</td>
<td>0.83</td>
<td>0.89</td>
</tr>
<tr>
<td>Middle</td>
<td>0.96</td>
<td>0.90</td>
<td>0.93</td>
</tr>
<tr>
<td>Ring</td>
<td>1.13</td>
<td>0.99</td>
<td>1.06</td>
</tr>
<tr>
<td>Little</td>
<td>1.44</td>
<td>1.44</td>
<td>1.44</td>
</tr>
<tr>
<td>Lip</td>
<td>0.46</td>
<td>0.51</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Analysis of their results showed no difference between sides, and no difference from digits 1 to 4, but a higher threshold on the little finger (D5). The lip SDT was also significantly different from digital thresholds, with evidence of far greater sensitivity.
1.7.3 Reliability of sensory measurement

Repetitive sensory stimulation may alter sensory receptive fields and improve spatial acuity and spatial discrimination thresholds. Sensory training effects though take weeks of daily training, and improving one type may affect the other (Byl et al., 2003, Candia et al., 2002, Van Boven et al., 2000). For measurement of current spatial discrimination thresholds in individuals not undergoing any sensory training, repeated measure of SDTs does not show a training effect over five trials in twelve subjects (Bleyenheuft and Thonnard, 2007). The use of grating orientation tasks is not influenced by the force of application. Merkel discs respond to changes in skin conformation, and make no change in their response after forces of 0.4N (10 grams). Also, the duration of application did not affect the results.

In normal subjects, haptic perception of spatial orientation is worst for oblique presentations. Subjects presented with rods placed on the hand will make more errors with oblique presentations than with vertical and horizontal presentations. Similar errors are made using visual orientation tasks. Haptic frame of reference is not purely gravitational or visual, since orientation tasks are performed equally well by blindfolded subjects tilted in space. Blindfolded subject presented with rods of different orientations in space show anisotropy favouring vertical orientations. However as with rods placed in the hand and in grating orientation tasks, other authors have reported no evidence of anisotropy (Bleyenheuft and Thonnard, 2007, Gentaz et al., 2008).

1.7.4 Spatial discrimination thresholds, age and occupation

Younger age may show a poorer SDT, which improves as one reaches the mid teens (Bleyenheuft et al., 2006). Both spatial acuity and spatial discrimination thresholds
deteriorate with age and standard JVP domes used are unsuitable (Tremblay et al., 2000, Stevens, 1992). SDTs measured in frequent computer users (>2h/day) showed a 40% higher threshold compared to infrequent users. The results correlated with measures of manual dexterity using a 9-hole peg board test (Tremblay et al., 2002).

1.7 S Summary of sensory measurement

Fine touch sensation at the fingertip for spatial discrimination tasks starts with Merkel discs, conducted by slowly adapting mostly Aβ type I fibres. Cortical processing of complex spatial sensory information is processed in secondary somatosensory cortex and the spatial association area of the left intraparietal sulcus. Many disease states, even non-neurological, may interfere with the most distal component of this pathway. Grating orientation tasks would appear to be useful only within a restricted age range possibly due to early lack of brain maturation and late-life decline in sensory function. Despite this, in healthy subjects the reliability and validity of SDT testing appears very good. Grating orientation tasks are superior to two-point discrimination, allow parametric interpretation, and are not subject to the confounding of subject determined illusion of movement.
1.8 Aims and Objectives

The aims of this thesis were as follows:

1) To determine the SDT in a normal healthy population, examining its distribution over different age groups and to establish normative data for comparison in further study

2) To measure SDTs in an older population by modification of the standard set of JVP domes and establish normative data

3) To determine the SDT in patients from multiplex AOPTD families, affected by dystonia and compare them to the standard normal determined

4) To examine the SDT of relatives of affected persons in multiplex AOPTD families, and to examine the family structure of abnormal SDTs in those unaffected relatives in relation to affected individuals, with a calculation on penetrance if appropriate

5) To examine the sensitivity of SDT assessment in younger and older patients as compared to the normative data
2 Materials and Methods

2.1 Method of measuring the spatial discrimination threshold

The spatial discrimination threshold was measured using the method of applying gratings of different widths (Johnson-Van Boven-Phillips domes) to the palmar surface of the index finger-tips of both hands.

2.2 Subjects

Controls were healthy normal volunteers recruited from hospital staff, friends of hospital staff, people accompanying patients to the neurology clinic (unrelated), and friends of the examiner. Over one hundred controls were to be recruited to establish normative data. Identification of a ceiling effect in the control group led to division of all individuals tested into two groups according to age: 20-45 years and 45-65 years. Due to a ceiling effect with the second protocol, individuals over the age of 65 were not included.

Four multiplex families were examined in the same age ranges as before (Ped 005, Ped 006, Ped 008, Ped 010). The probands of the families attended the neurology botulinum toxin injection clinic at St. Vincent’s University Hospital where a record of the severity of their dystonia prior to each injection was made using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) if appropriate. In a previous study on the genetics of dystonia, these families had been ascertained by family history taking at the clinic, identification of potential multiplex families, and blinded videotape assessment of first-degree and second-degree relatives by two movement
disorders specialists (Tim Lynch and Michael Hutchinson) to diagnose asymptomatic family members (O'Riordan et al., 2004b).

The probands were asked to volunteer for SDT measurement and to help recruit all family members between 20 and 65 years of age for examination of the SDT by simple grating-orientation tasks. Only affected members between 20 and 65 years of age were included. The examiner was blinded to the videotape rating of the unaffected members of the pedigrees.

2.2.1 Description of multiplex AOPTD families: members aged 20-45 years

Pedigree 005
This was a family from the east coast of Ireland with four affected members. There were no affected members between 20 and 45 years. There were nineteen members in the age range that could be recruited. There were no affected members within the age limits. The family tree is shown in Appendix 12.4.1.1. Nineteen members (IV:1, III:15, III:16, III:23, III:24, III:29, III:30, III:32-III:43) were in the 20 to 45 year age range, which were seven first-degree relatives and twelve second-degree relatives.

Pedigree 006
This was a family from the east coast of Ireland with three affected members, two of whom were in the age range. The family had 24 members between 20 and 45 years. III:8 was rated affected on videotape examination with rotatocollis and tremor. III:22 was the other affected member with clinically diagnosed spasmodic dysphonia prior to enrolment in the study. The family tree is shown in Appendix 12.4.2.1. Twenty-
four members are in the 20 to 45 years range (III:3-III:26). Nine were first-degree relatives and 13 were second-degree relatives.

**Pedigree 008**

This was a family from the north-west of Ireland with six affected members. The family had 35 members between 20 and 45 years of age.

There were three other affected members in the age range (IV:16, IV:23, IV:24). IV:16 and IV:23 both attended a neurologist for treatment of cervical dystonia using botulinum neurotoxin. IV:24 had simple writer’s cramp and upper limb tremor diagnosed on videotape examination. The family tree is shown in Appendix 12.4.3.1. Thirty-five members are in the 20 to 45 year age range (IV:11, IV:16-IV:29, V:1-V:11, V:14-V:17, V:19, V:20, V:22, V:23, V:26). Eleven were first-degree relatives and 24 were second-degree relatives.

**Pedigree 010**

This family from the east coast of Ireland had three members affected by dystonia. There were twelve members in the age range required for the study. There was one affected member (IV:13) in the necessary age range who had cervical dystonia with cervical dystonia and simple writer’s cramp. The family tree is shown in Appendix 12.4.4.1. Eleven other members were in the 20-45 year age range (IV:6-IV:10, IV:12-IV:18). Seven were first-degree relatives, and three were second-degree relatives.
2.2.2 Description of multiplex AOPTD families: members aged 45-65 years

Pedigree 005

There were two affected members between 45 and 65 years. There were 24 members in the age range that could be recruited. The proband (III:1) was a 55 year-old man with cervical dystonia. He had a right rotatocollis with hypertrophy of right splenius capitis and left sternocleidomastoidus. He reported between moderate and complete benefit from a sensory trick (1-2/2 on TWSTRS score), which was to touch the side of his neck with either hand. His overall TWSTRS score was 25/85, with 11/35 on the Torticollis Severity Scale subscore.

There was one other affected member in the family within the 45 to 65 years range (III:1). This member also suffered from cervical dystonia with a right rotatocollis. The pedigree is illustrated in Appendix 12.5.1.1. Twenty-four family members were in the 45 to 65 years age range (II:9, III:1, III:2, III:4-III:13, III:16-III:21, III:24-III:27, III:30). They consisted of eleven first-degree relatives and eleven second-degree relatives.

Pedigree 006

Only one affected individual, the proband, is within the 45 to 65 years age range. Four other family members are within the age range. The proband (II:6) suffered from cervical dystonia. He had a tremulous left rotatocollis with some benefit from a sensory trick (1/2 on TWSTRS score) which was to touch the side of his face on the affected side. The muscles mainly involved were the left splenius capitis and right sternocleidomastoid. His overall TWSTRS score was 59/85 with a Torticollis Severity Scale subscore of 21/35.
None of the other affected members of the family were in the necessary age range. The pedigree is illustrated in Appendix 12.5.2.1. Six members are indicated within the age range (II:4-II:6, III:1, III:2). Two unaffected members are first-degree relatives and two are second-degree relatives.

**Pedigree 008**

There are 12 family members aged between 45 and 65 years. The proband was a 58 year old woman (IV:1) with cervical dystonia characterised by left rotatocollis and left saggital shift who reported some benefit from a sensory trick (1/2 on TWSTRS score) which was to touch her chin on either side. The muscles mainly involved clinically were the left splenius capitis and right sternocleidomastoid. Her overall TWSTR score was 40/85 with a Torticollis Severity Scale subscore of 15-22/35.

There were no other affected members in the age range for this experiment. The pedigree drawing is shown in Appendix 12.5.3.1. There are twelve members in the age range (IV:1-IV:10, IV:14, IV:15). Five are siblings of affected members and six are second-degree relatives.

**Pedigree 010**

There were seven members in the age range for the study. The index case was a 62 year-old man with cervical dystonia characterised by a left rotatocollis and retrocollis. He had moderate to complete relief with a sensory trick of touching the back of his head with his hand (1-2/2 on TWSTRS score). The muscles mostly affected on clinical examination were the retrocollics bilaterally, splenius capitis bilaterally, left levator scapulae and right sternocleidomastoid. His overall TWSTRS score ranged
from 33-62/85 (median 54) and a Torticollis Severity Scale subscore of 17-26/35 (median 20).

There were no other affected phenotypes in the age range for the study. The family tree is illustrated in Appendix 12.5.4.1. Six other members were in the required age range (III:1-III:6, III:11). Five were second-degree relatives and one was a sibling and child of affected members.

2.3 Measurements and Exclusion

Individuals were identified by a sequential numbering system with a database of this information kept separately. Details were gathered on gender, date of birth, handedness, medical history, neurological symptoms and injury, occupation, exposure to alcohol and cigarettes, and family history of movement disorders (Appendix 2) Handedness was determined by the examiner using the Abbreviated Edinburgh Handedness Inventory. The dominant hand was decided upon using the criteria in this inventory (Oldfield, 1971). All volunteers were included after completing the examiner-based questionnaire, a brief neurological physical assessment and signing the consent form.

When a possible neurological problem was identified in the history, there was no further participation in the testing. Family history of specific common movement disorders, or a description consistent with any movement disorder sign resulted in exclusion. Subjects who were unable to appreciate the testing protocol or understand the different orientations of the Johnson-Van Boven-Phillips (JVP) domes were excluded. Nobody with a dementing illness was allowed to participate. A brief focused neurological examination for sensory abnormalities, movement phenomena, digit amputations and skin integrity on the hands was done. Failure to pass was at
the discretion of the examiner, but was determined by congruous disturbance of sensation modalities in an anatomical distribution, the presence of tremor, any weakness, deformity or heavy callouses on the hands/fingers. Subjects were excluded if botulinum neurotoxin had been used at any anatomical site in the previous three months. Subjects who operated vibrating tools/machines for more than 15 minutes daily were excluded because of the possible presymptomatic Hand-Arm Vibration Syndrome/Vibration-White-Finger (Gemne, 1997).

2.4 Experimental protocol, ethics approval and consent

Ethics approval for examination of healthy volunteers to measure SDT using the JVP domes was given by the Ethics Committee of St. Vincent’s University Hospital. Subjects were explained the need to collect information that would remain confidential and database locked. They were explained the procedure for the examination and that consent could be withdrawn at any time. All informed subjects signed consent forms (Appendix 1).

The SDT was tested using JVP domes (Stoelting Co., Illinois). The set consists of eight hemispheric acrylic domes with parallel grooves and ridges of uniform width 0.35 mm, 0.50 mm, 0.75 mm, 1.0 mm, 1.2 mm, 1.5 mm, 2.0 mm and 3.0 mm (Appendix 4). An opaque screen of dark material separated the subject and the examiner. It was one metre high and one and a half metres wide. No part of the examiner, the JVP domes box, the protocol sheets or other test related procedure could be seen by the subject. The examiner could not see the subject being tested except for the hand being examined. Subjects were seated erect comfortably opposite the examiner at a flat open desk, facing the screen, both arms on the table. The arm of the side being examined was held in a comfortable supine position with the dorsum of
the hand against the table. The index finger was held in a comfortable extended position with the nail opposed against the table. The skin over the index fingertip’s distal fat pad was used bilaterally. Each candidate was shown visually the meaning of “down” and “across” by outlining the long axis of the finger and stating that anything parallel to this meant “down”. The other possible direction of application was “across” and this was also indicated visually. When the examiner was satisfied that the directions were understood, three standard applications were made with the largest dome width and the direction was called out to the subject each time. The examiner checked with the subject if they had felt them and if necessary repeated this once.

The domes were consistently applied to the skin for one to two seconds with enough pressure to indent approximately one millimetre. Applications were in an orthogonal direction relative to the long axis of the finger, either parallel (“down”) or perpendicular (“across”). There were 20 applications of each dome in random order determined by a binary outcome random number assignment (Appendix 3). Beginning with the largest width dome and proceeding through gradually narrower ones, the blinded subject was required to identify the orientation immediately (while the dome was in contact with the skin) and received no feedback, answering with a forced choice paradigm. The candidate was instructed to guess if they did not know. The examiner used his non-dominant hand to mark the score sheet with a “√” for correct answers only, and the score was calculated after each dome was completed. The testing was done on both index fingers. Each alternate subject was started on either the right or left hand. Subjects progressed to successively narrower grating widths on the same side being tested until less than 60% were correctly answered (less than 12 of 20). Both hands were tested in the same manner. In the case of a subject losing concentration or not having responded within the allowed time-frame, the examiner...
instructed that there would be one repeat application and an answer was required immediately.

2.5 Custom JVP domes for examination of subjects over 45 years

In the original set of JVP domes, the largest change of groove/ridge width was from the 2.0 mm to the 3.0 mm dome. This had resulted in poor averaging of SDTs compared to other dome pairs. The next narrowest dome in the original set was 1.5 mm. Therefore, an intermediate dome width was added, and three more greater than 3.0 mm. Based on work by Tremblay and colleagues in which SDT in older people was measured, domes of 3.5 mm, 4.0 mm and 4.5 mm were also added. These were identical acrylic domes with the grooves and ridges of these widths cut by the manufacturer of the standard set (Tremblay et al., 2003). The widths of JVP domes in this experiment was 0.35 mm, 0.5 mm, 0.75 mm, 1.0 mm, 1.2 mm, 1.5 mm, 2.0 mm, 2.5 mm, 3.0 mm, 3.5 mm, 4.0 mm and 4.5 mm. The protocol for testing was identical to that for the original set, but proceeding in the reverse order from the 4.5 mm groove width.

2.6 Statistical Analysis

Statistical analysis was performed using Microsoft Excel 11.3 (Microsoft Corporation, 2004), GraphPad Prism 4.0 (GraphPad Software Inc., 2004) and Minitab 14.0 (Minitab Inc., 2004). The number of subjects recruited, included, excluded were calculated. Handedness, occupation, medical history and medications used at the time were also presented.
The calculation of the SDT was done using the value of the dome width at which the subject scored less than 60% correct (\(w_2\)) and the dome width immediately preceding it (\(w_1\)) (Johnson and Phillips, 1981, Van Boven and Johnson, 1994a). The fraction of correct answers for each was also used (\(x_1, x_2\)). The spatial discrimination threshold was then calculated by linear interpolation of the width that would represent a 75% correct response rate:

\[
SDT = 0.75 - \left[ \frac{(x_1 - w_1 m)}{m} \right], \quad m = (x_1 - x_2)/(w_1 - w_2)
\]

A scatter plot for the SDTs of each hand was done to look at the distribution of the data and the relationship between the right and left hand SDT were examined using linear regression.

The overall mean SDT (SDT_{\text{X}}) was calculated by averaging all right (SDT_{\text{right}}) and left hand SDTs (SDT_{\text{left}}). The mean SDT for each subject (SDT_{\text{mean}}) was calculated by averaging the SDT_{\text{right}} and SDT_{\text{left}}. The mean of all right hand SDTs (SDT_{\text{RIGHT}}) and all left hand SDTs (SDT_{\text{LEFT}}) was also calculated and compared using paired t-tests and 95% confidence intervals. The SDT_{\text{right}} and SDT_{\text{left}} were plotted against age to examine the relationship with age, and to identify the onset of a ceiling effect.

**Comparison of groups according to relationship to an affected member**

Pooled family data was divided into four groups for comparison of the SDTs: affected (AOPTD), unaffected children, unaffected siblings, unaffected second-degree relatives. Where an individual was both the child of an affected member and a sibling of an affected member, their relationship as a sibling took precedence. Non-parametric one-tailed ANOVA was used to compare the SDTs of these groups (Kruskal-Wallis). Post-hoc comparison of individual groups using Dunn’s multiple
comparisons test with correction was also done. A p-value of <0.001 was considered significant in the latter. Chi-square analysis of the proportions in the groups was not performed because of the small numbers of affected members, children of affected members and siblings of affected members.

*Combined results of family members aged 20-65 years*

Individual family member mean SDTs ($SDT_{\text{mean}}$) were converted to standard normal (Z) values using the equation:

$$Z = \frac{SDT_{\text{mean}} - \mu}{\sigma/\sqrt{n}},$$

where $\mu$ was the mean SDT of the control sample, $\sigma$ was the standard deviation, and $n$ was the number of observations.

The data was then examined by pedigree and by relationship to an affected member.
3 Results

3.1 The spatial discrimination threshold in persons over 20 years

3.1.1 Number of subjects

One hundred and twenty-one subjects were recruited who agreed to be interviewed and examined. One hundred and twelve subjects were eligible for inclusion. A total of nine were excluded for the following reasons:

1) two subjects had symptoms of myelopathy with a history of neck injury
2) two subjects had numbness in fingers
3) two subjects with bilateral impaired vibration sensation (2/8 on both hands)
4) severe anaemia, with impaired sensation in both hands, and in feet
5) atrial fibrillation, rate controlled
6) left wrist fracture, severe back pain and on opiate medication

3.1.2 Demographics of the normal control population

There were 31 men and 81 women. The average age was 38.4 years (standard deviation ± 13.9 years). The median was 33.4 years (range 20 to 78 years).

One hundred and four were right-hand dominant and eight were left-hand dominant. There were 47 healthcare professionals, 15 students, 37 administration employees, three labourers, five in other employment and five had retired. There was a past medical history in 26 subjects: asthma (6), diabetes mellitus (1), epilepsy (1), ischaemic heart disease (2), hypertension (8), thyroid disorders (4), gastro-oesophageal reflux disease/peptic ulcer disease (5), hypercholesterolaemia (1), depression (1) and urinary incontinence (1). Thirty-six subjects were on regular
medication as follows: oestrogen ± progestogen therapy (13), inhalers (6), proton-pump inhibitors (6), angiotensin-related drugs (3), beta-blockers (3), thiazide diuretics (3), alpha-blocker (2), calcium-channel blockers (1), statins (2), acetylsalicylic acid (2), l-thyroxine (3), antidepressants (3), anti-epileptic medication (1) and anti-cholinergic medication (1). Ninety-six subjects consumed alcohol regularly, and 22 were smokers.

3.1.3 Spatial discrimination thresholds for each hand

The mean dominant hand SDT was 1.51 mm ± 0.74, and the mean non-dominant hand SDT was 1.53 mm ± 0.73. The $\text{SDT}_{\text{RIGHT}}$ was 1.51 mm ± 0.72 (95% CI: 1.38, 1.65), and the $\text{SDT}_{\text{LEFT}}$ was 1.53 mm ± 0.74 (95% CI: 1.39, 1.66). The mean of the right/left difference on paired t-testing was -0.01 mm (95% CI: -0.14, 0.11). Further statistical testing was not performed because of the inclusion of data censored at 3 mm, as can be seen in the figure (Figure 1).

![Figure 1. SDT (mm) of both hands, 20-78 years](image-url)
3.1.4 Mean spatial discrimination threshold (SDT$_{\text{X}}$)

The SDT$_{\text{X}}$ was 1.52 mm ± 0.73 (95% CI: 1.42, 1.61) (Figure 2). The median was 1.27 mm. The censored subjects at 3 mm are seen as a row across the top of the scatterplot. There is a suggestion of a bimodal distribution of data points with a subgroup having higher SDT$_{\text{mean}}$, almost distributed around the upper error bar.

![Mean SDT](image)

**Figure 2.** Mean spatial discrimination threshold, error bars ±1SD, 20-78 years

3.1.5 Variation of spatial discrimination threshold with age

SDT$_{\text{right}}$ and SDT$_{\text{left}}$ were plotted against age in scatter plots. A ceiling effect is noted early at 45 years in the SDT$_{\text{right}}$ (Figure 3), and at 48 years in the SDT$_{\text{left}}$ (Figure 4). Regression lines were not fitted because of the ceiling effect and also the appearance of a J-shaped distribution with age.
Figure 3. SDT right (mm) versus Age (years)

Figure 4. SDT left (mm) versus Age (years)
Identification of a ceiling effect with standard JVP domes

Using the standard JVP domes, 11 of 112 subjects had an SDT that was at least 3 mm on the right hand, and 10 of 112 on the left hand. Since the ceiling effect onset was with subjects as young as 45 years, the data was split. The younger half was called "group one" and was those persons between 20 and 44.9 years. Group one consisted of 56 women and 18 men (n = 74). Seventy were right-hand dominant. The average age was 29.8 years ± 6.4, and the median age was 29.1 years. The mean SDT in group one was 1.20 mm ± 0.36 (95% CI: 1.11, 1.28) and the median SDT was 1.10 mm (range 0.46 to 1.94).

Analysis of group one data

A regression analysis of the SDT\textsubscript{left} against the SDT\textsubscript{right} was performed, which showed four data-points with large residuals. Due to the large hand-to-hand discrepancy in SDT in these four individuals, they (35, 48, 69, 70) were removed and the statistics were calculated (Table 1). This gave an SDT\textsubscript{mean} of 1.16 mm ± 0.33 (95% CI: 1.08, 1.23; range 0.46 to 1.92), an SDT\textsubscript{right} of 1.14 mm ± 0.36 (95% CI: 1.05, 1.22; range 0.50 to 2.10), and an SDT\textsubscript{left} of 1.18 mm ± 0.44 (95% CI: 1.07, 1.28; range 0.40 to 2.17) (Figure 5).
Table 1. Regression and ANOVA of 20-45 year Controls

The regression equation is
Left SDT (mm) = 0.744 + 0.380 Right SDT (mm)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coef</th>
<th>SE Coef</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.747</td>
<td>0.1665</td>
<td>4.47</td>
<td>0.000</td>
</tr>
<tr>
<td>Right SDT (mm)</td>
<td>0.380</td>
<td>0.1396</td>
<td>2.72</td>
<td>0.008</td>
</tr>
</tbody>
</table>

S = 0.420907 R-Sq = 9.8% R-Sq(adj) = 8.5%

Analysis of Variance

<table>
<thead>
<tr>
<th>Source</th>
<th>DF</th>
<th>SS</th>
<th>MS</th>
<th>F</th>
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<tbody>
<tr>
<td>Regression</td>
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<td>1.3142</td>
<td>1.3142</td>
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<td>Residual Error</td>
<td>68</td>
<td>12.047</td>
<td>0.1772</td>
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</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>13.3612</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 5. Group One - SDT mean, SDT right, SDT left with 1SD bar
3.1.6 Defining an abnormal SDT in the 20-45 year group

From a visual examination of the SDT scatter plots, it is clear that there is a skew in the distribution of the values towards higher values. An acceptable outer limit for normal data was decided upon to be 2.5 standard deviations, which represented an upper limit spread of 49.4% of a standard normal population. This gave an upper limit for normal $SDT_{mean}$ of 1.98 mm. No subject in the control group lay above this point.
3.2 The spatial discrimination threshold in persons over 45 years

3.2.1 Number of subjects

Ninety-three subjects over 45 years were recruited, interviewed and examined. Seventy-two subjects were eligible for inclusion. Twenty-one members of the recruited sample were excluded by interview and examination for the following reasons:

1) Seven had an abnormal sensory exam
2) Two had a history of serious cervical spine injury
3) One had unilateral deformity of the fingers (absent finger-tips)
4) Four had disorder of the skin integrity on the finger-tips
5) Two suffered from serious neuropathic pain in the arms
6) Two had significant occupational exposure to vibrating tools
7) One had disabling essential tremor
8) Two were unable to understand the test protocol

3.2.2 Demographics of the sample population

There were 13 men and 59 women. The average age was 56.1 years (standard deviation ± 7.6 years). The median was 54.5 years (range 45 to 79 years). Sixty-nine were right hand dominant and three were left hand dominant.

There were 32 administration employees, 28 healthcare workers, three labourers, four retired and five in other employment. Seventeen subjects had a medical history: hypertension (10), asthma (4), hypercholesterolaemia (3), hypothyroidism (2), diabetes mellitus (2), gastro-oesophageal reflux disease/peptic ulcer disease (1), ischaemic heart disease (1) and depression (1). Sixteen subjects were on regular medication: angiotensin-related drugs (5), inhalers (5), statins (5),
beta blockers (4), calcium-channel blockers (2), alpha blockers (2), l-thyroxine (2),
proton-pump inhibitors (1), oral hypoglycaemics (1), antidepressants (1), and non-
steroidals (1). Fifty-five subjects admitted to regular alcohol consumption with an
average of 14.5 units per week (mode <10 units per week). There were 17 smokers
with an average history of 24.9 pack years (missing data on eleven subjects in relation
to smoking only).

3.2.3 Spatial discrimination thresholds for each hand

The mean dominant hand SDT was 2.01 mm ± 0.92 (95% CI: 1.79, 2.22), and the
mean non-dominant hand SDT was 1.84 mm ± 0.92 (95% CI: 1.63, 2.06). The
SDT_{right} was 2.00 mm ± 0.88 (95% CI: 1.79, 2.21), and the SDT_{left} was 1.85 mm ±
0.95 (95% CI: 1.63, 2.07) (Figure 6). The mean of the right/left difference on paired t-
testing was 0.16 mm (95% CI: -0.03, 0.33). The y-axis upper limit in the figure is set
at the maximum grating width on the custom JVP dome set.

![Figure 6. SDT (mm) of both hands, error bars ±1SD, over 45 years](image_url)
3.2.4 Mean spatial discrimination threshold (SDTᵋ₅ₐₓ)

The SDTᵋ₅ₐₓ in the over 45 year group was 1.92 mm ± 0.81 (95% CI: 1.73, 2.11) (Figure 7). However, as can be seen from the figure this mean was limited by a ceiling effect, as in the first experiment. There is a large skew in the tail of the data towards a higher SDTₘₑᵃⁿ.

![Figure 7. Mean SDT (mm) of subjects over 45 years, error bars ±1SD](image)

3.2.5 Variation of spatial discrimination threshold with age

A scatterplot of all right and left SDTs measured shows a ceiling effect reached at 65 years (Figure 8 & Figure 9). No linear regression was done on the data because of the observed ceiling as this would give rise to erroneous interpretation of the relationship between the SDTₘₑᵃⁿ and age.
Figure 8. SDT right (mm) versus age (45-79 years)

Figure 9. SDT left (mm) versus age (45-79 years)
Identification of a ceiling effect with custom JVP domes

Using the custom JVP domes, two of 72 subjects had an SDT\textsubscript{right} that was greater than or equal to the largest grating width, and three SDT\textsubscript{left} were similar. This ceiling effect was first noted in the right hand of a subject aged 65.8 years. Therefore, as in experiment one, the data was split. Those subjects between 45 and 65 years were called “group two”. This was composed of 54 women and 10 men (n = 64). Sixty-one were right hand dominant. The average age was 54.3 years ± 5.6, with a median age of 53.8 years. Other demographic features changed insignificantly. The mean SDT of group two was 1.79 mm ± 0.62 (95% CI: 1.63, 1.94; range 0.66 to 3.40) and the median was 1.79 mm.

Analysis of group two data

Linear regression of group two data using the right hand SDTs as predictors and left hand SDTs as observed to examine hand to hand correlation showed a larger discrepancy overall between both sides (Figure 10). However, on the normal probability plot those subjects that have the largest standardised residuals (18, 38 and 39) all fall within the range of 1-99% (Figure 11). No further changes to the data for group two were done. The mean SDT, right hand SDT and left hand SDT are presented in the scatterplot (Figure 12).
Figure 10. Standardised residuals versus fitted, group two

Figure 11. Normal probability plot of standardised residuals in group two
3.2.6 Defining an abnormal SDT in 45-65 year group

Inspection of the data in group two shows a similar distribution of the $SDT_{mean}$ compared to group one. Two and a half standard deviations above the mean of the mean SDT in group two was decided on as the upper limit of normal for comparison in future experiments, which was 3.33 mm. Two controls had a $SDT_{mean}$ greater than this.
3.3 Spatial discrimination thresholds of affected and unaffected members of multiplex families with AOPTD aged 20-45 years

3.3.1 Pedigree sizes

There were 90 family members aged between 20 and 45 years, of whom 60 were willing or available to participate in the study. In ped 005, most who did not participate were concerned about a genetics study. In ped 006, the family did not have contact with those who did not participate as they lived abroad. In ped 008 many of the young generation who were eligible travelled and had education and work responsibilities that precluded them from having time to spare. In ped 010, it was a combination of no contact with some family members, and others who did not wish to participate that reduced recruitment numbers.

Pedigree 005

In this pedigree, there were six of 19 subjects in the age range required willing to be examined (IV:1, III:14, III:23, III:28, III:32, III:36). Three were unaffected first-degree relatives, and three were unaffected second-degree relatives.

Pedigree 006

Of the 24 members eligible to be included in this experiment, 17 agreed to be examined (III:7-III:15, III:17-III:20, III:22, III:24-III:26). There were two affected members, five first-degree relatives, and ten second-degree relatives.
Pedigree 008

Twenty-nine of the 35 individuals in the age range of 20-45 years participated in the study and were all included (IV:11, IV:16-IV:24, IV:27-IV:29, V:1-V:11, V:14, V:16, V:17, V:20, V:26). There were three affected, nine first-degree relatives and 17 second-degree relatives.

Pedigree 010

In this family, there were eight examined out of the twelve in the age range.

Fifty-eight out of a possible 90 were included who were in the age range. There were two exclusions.

In Ped 005, III:32 was excluded due to severe head injury from a road traffic accident. In Ped 006, III:17 had suffered serious cervical spine injury with neurological sequelae in a motorbike accident.
3.3.2 Spatial discrimination thresholds in each family

Pedigree 005

There were two abnormal SDTs in this family out of five tested. Subjects examined and the two with the abnormal SDTs are shown in the figure in Appendix 12.4.1.2. Individual SDTs are shown in the table (Table 2). The results are graphically presented in the grouped variable scatterplot (Figure 13).

Table 2. SDTs of subjects examined in Ped 005 aged 20 to 45 years

<table>
<thead>
<tr>
<th>Generation ID</th>
<th>Gender</th>
<th>Age</th>
<th>Dominance</th>
<th>SDT R (mm)</th>
<th>SDT L (mm)</th>
<th>Mean SDT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III 14</td>
<td>F</td>
<td>37.2</td>
<td>Right</td>
<td>1.200</td>
<td>1.200</td>
<td>1.200</td>
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<td>III 23</td>
<td>F</td>
<td>39.0</td>
<td>Right</td>
<td>1.500</td>
<td>1.500</td>
<td>1.500</td>
</tr>
<tr>
<td>III 28</td>
<td>F</td>
<td>39.5</td>
<td>Left</td>
<td>2.571</td>
<td>1.917</td>
<td>2.244</td>
</tr>
<tr>
<td>III 32</td>
<td>M</td>
<td>37.8</td>
<td>Right</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>III 36</td>
<td>F</td>
<td>42.1</td>
<td>Right</td>
<td>1.833</td>
<td>2.167</td>
<td>2.000</td>
</tr>
<tr>
<td>IV 1</td>
<td>F</td>
<td>21.5</td>
<td>Right</td>
<td>1.800</td>
<td>1.160</td>
<td>1.480</td>
</tr>
</tbody>
</table>

Figure 13. SDTs of all ped 005 members tested versus controls
Pedigree 006

Three members of this family had elevated SDTs. They are indicated in the figure in Appendix 12.4.2.2. The results are tabulated below (Error! Reference source not found.). The data are plotted in the grouped variable scatterplot (Figure 14).

Pedigree 006, 20 to 45 years SDT

<table>
<thead>
<tr>
<th>Generation ID</th>
<th>Gender</th>
<th>Age</th>
<th>Dominance</th>
<th>SDT R (mm)</th>
<th>SDT L (mm)</th>
<th>Mean SDT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III 7</td>
<td>M</td>
<td>38.0</td>
<td>Right</td>
<td>1.300</td>
<td>2.167</td>
<td>1.733</td>
</tr>
<tr>
<td>III 8</td>
<td>F</td>
<td>35.6</td>
<td>Right</td>
<td>2.833</td>
<td>1.500</td>
<td>2.167</td>
</tr>
<tr>
<td>III 9</td>
<td>F</td>
<td>23.3</td>
<td>Right</td>
<td>1.300</td>
<td>1.650</td>
<td>1.475</td>
</tr>
<tr>
<td>III 10</td>
<td>F</td>
<td>40.2</td>
<td>Right</td>
<td>1.250</td>
<td>1.100</td>
<td>1.175</td>
</tr>
<tr>
<td>III 11</td>
<td>F</td>
<td>36.0</td>
<td>Right</td>
<td>1.500</td>
<td>1.600</td>
<td>1.550</td>
</tr>
<tr>
<td>III 12</td>
<td>F</td>
<td>34.6</td>
<td>Right</td>
<td>0.525</td>
<td>1.000</td>
<td>0.763</td>
</tr>
<tr>
<td>III 13</td>
<td>M</td>
<td>31.9</td>
<td>Left</td>
<td>1.575</td>
<td>0.750</td>
<td>1.163</td>
</tr>
<tr>
<td>III 14</td>
<td>F</td>
<td>26.2</td>
<td>Right</td>
<td>0.875</td>
<td>0.875</td>
<td>0.875</td>
</tr>
<tr>
<td>III 15</td>
<td>F</td>
<td>37.7</td>
<td>Right</td>
<td>0.650</td>
<td>1.150</td>
<td>0.900</td>
</tr>
<tr>
<td>III 17</td>
<td>M</td>
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<td>Right</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>III 18</td>
<td>M</td>
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<td>Right</td>
<td>0.875</td>
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<tr>
<td>III 19</td>
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<td>Right</td>
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<td>III 20</td>
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<tr>
<td>III 22</td>
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<td>Right</td>
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<td>2.167</td>
<td>2.083</td>
</tr>
<tr>
<td>III 24</td>
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<td>Right</td>
<td>1.600</td>
<td>1.083</td>
<td>1.350</td>
</tr>
<tr>
<td>III 25</td>
<td>M</td>
<td>24.4</td>
<td>Right</td>
<td>1.800</td>
<td>1.083</td>
<td>1.442</td>
</tr>
<tr>
<td>III 26</td>
<td>F</td>
<td>22.7</td>
<td>Right</td>
<td>1.620</td>
<td>1.500</td>
<td>1.560</td>
</tr>
</tbody>
</table>

Figure 14. SDTs of all Ped 006 members tested versus controls
Pedigree 008

Six family members had an elevated SDT which can be seen in the pedigree drawing in Appendix 12.4.3.2. The full tabulated form of the results can be seen in the table (Table 3). Two affected members of the family had abnormal SDTs, but one did not (IV:16). One first-degree relative of an affected person had elevated sensory thresholds (IV:28). The other three were second-degree relatives (IV:11, V:7, V:9).

The scatterplot of the results is presented below (Figure 15).

Table 3. SDTs of subjects examined in Ped 008 aged 20 to 45 years

<table>
<thead>
<tr>
<th>Generation</th>
<th>ID</th>
<th>Gender</th>
<th>Age</th>
<th>Dominance</th>
<th>SDT R (mm)</th>
<th>SDT L (mm)</th>
<th>Mean SDT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>11</td>
<td>M</td>
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<td>3.000</td>
<td>3.000</td>
</tr>
<tr>
<td>IV</td>
<td>16</td>
<td>F</td>
<td>43.8</td>
<td>Right</td>
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<td>1.857</td>
<td>1.604</td>
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<tr>
<td>IV</td>
<td>17</td>
<td>M</td>
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<td>1.440</td>
<td>1.440</td>
<td>1.440</td>
</tr>
<tr>
<td>IV</td>
<td>18</td>
<td>M</td>
<td>41.5</td>
<td>Right</td>
<td>1.267</td>
<td>1.800</td>
<td>1.533</td>
</tr>
<tr>
<td>IV</td>
<td>19</td>
<td>M</td>
<td>39.7</td>
<td>Right</td>
<td>1.280</td>
<td>2.500</td>
<td>1.890</td>
</tr>
<tr>
<td>IV</td>
<td>20</td>
<td>F</td>
<td>38.7</td>
<td>Right</td>
<td>1.120</td>
<td>1.440</td>
<td>1.260</td>
</tr>
<tr>
<td>IV</td>
<td>21</td>
<td>F</td>
<td>36.7</td>
<td>Left</td>
<td>1.200</td>
<td>1.250</td>
<td>1.275</td>
</tr>
<tr>
<td>IV</td>
<td>22</td>
<td>M</td>
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<td>Left</td>
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<td>2.600</td>
<td>2.350</td>
</tr>
<tr>
<td>IV</td>
<td>24</td>
<td>M</td>
<td>44.6</td>
<td>Right</td>
<td>2.000</td>
<td>2.583</td>
<td>2.292</td>
</tr>
<tr>
<td>IV</td>
<td>27</td>
<td>F</td>
<td>37.3</td>
<td>Right</td>
<td>1.600</td>
<td>2.100</td>
<td>1.850</td>
</tr>
<tr>
<td>IV</td>
<td>28</td>
<td>F</td>
<td>34.6</td>
<td>Right</td>
<td>3.000</td>
<td>2.100</td>
<td>2.550</td>
</tr>
<tr>
<td>IV</td>
<td>29</td>
<td>F</td>
<td>28.9</td>
<td>Right</td>
<td>1.200</td>
<td>1.900</td>
<td>1.550</td>
</tr>
<tr>
<td>V</td>
<td>1</td>
<td>M</td>
<td>26.9</td>
<td>Right</td>
<td>1.380</td>
<td>0.792</td>
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</tr>
<tr>
<td>V</td>
<td>2</td>
<td>M</td>
<td>25.3</td>
<td>Right</td>
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<td>0.650</td>
<td>0.800</td>
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<td>F</td>
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<td>1.167</td>
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<td>1.250</td>
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<tr>
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<td>0.750</td>
<td>1.200</td>
</tr>
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<td>V</td>
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<td>M</td>
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<td>2.571</td>
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<td>M</td>
<td>29.5</td>
<td>Right</td>
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<td>2.125</td>
<td>2.413</td>
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<td>0.750</td>
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<tr>
<td>V</td>
<td>11</td>
<td>M</td>
<td>26.9</td>
<td>Right</td>
<td>1.200</td>
<td>0.750</td>
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<td>1.140</td>
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<td>23.5</td>
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<td>Right</td>
<td>2.167</td>
<td>1.800</td>
<td>1.983</td>
</tr>
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</table>
**Pedigree 008**

3.00-

2.75-

2.50-

2.25-

2.00-

1.75-

1.50-

1.25-

1.00-

0.75-

0.50-

0.25-

0.00-

Figure 15. SDTs of all Ped 008 members tested versus controls

**Pedigree 010**

Eight family members were examined and five had abnormal SDTs as shown in the figure in Appendix 12.4.4.2. The only affected subject had an abnormal SDT, as did four others who were all first-degree relatives of other affected members. The SDT numerical results are tabulated below (Table 4). They can be seen plotted against the control group in the figure below (Figure 16).

**Table 4. SDTs of subjects examined in Ped 010 aged 20 to 45 years**

<table>
<thead>
<tr>
<th>Generation ID</th>
<th>Gender</th>
<th>Age</th>
<th>Dominance</th>
<th>SDT R (mm)</th>
<th>SDT L (mm)</th>
<th>Mean SDT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV 6</td>
<td>M</td>
<td>41.4</td>
<td>Right</td>
<td>3.000</td>
<td>2.500</td>
<td>2.750</td>
</tr>
<tr>
<td>IV 7</td>
<td>M</td>
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<td>2.375</td>
<td>1.200</td>
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<td>Right</td>
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<td>2.800</td>
<td>2.900</td>
</tr>
<tr>
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<td>F</td>
<td>37.1</td>
<td>Right</td>
<td>2.333</td>
<td>3.000</td>
<td>2.667</td>
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<td>Right</td>
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<td>1.704</td>
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</table>
3.3.3 Mean spatial discrimination threshold

The mean SDT of each family member was plotted on a scatterplot grouped into a relationship to the closest affected member of their pedigree (affected, children, siblings, second-degree relatives). In Ped 008 two family members were censored at 3.0 mm for the SDT on the right hand (IV:23, IV:28). One member in the same family was censored bilaterally at 3.0 mm (IV:11). In Ped 010 four members were censored on the right hand at 3.0 mm (IV:6, IV:13, IV:15, IV:16) and one on the left hand (IV:14). The SDT mean was calculated using 3.0 mm as the relevant SDT in these cases. There are five of six affecteds with abnormal SDTs, six of thirteen children of affecteds with abnormal SDTs, one of eleven siblings of affecteds with abnormal SDTs, and six of 28 second-degree relatives of affecteds with abnormal SDTs (Figure 17). The median threshold for each group is as follows: affecteds 2.23 mm, children
of affecteds 1.85 mm, siblings of affecteds 1.48 mm, and second-degree relatives 1.19 mm (control median SDT 1.08 mm). A null-hypothesis test of non-parametric data looking at several groups (Kruskal-Wallis test) was significant with p<0.0001 (Kruskal-Wallis statistic 43.59). Post-hoc testing using Dunn’s Multiple Comparison Test gave significant values for Controls v Affecteds (p<0.001) and Controls v Children of affecteds (p<0.001). There was no significant value difference for other comparisons although numbers were small.

Figure 17. SDTs grouped by relationship to affecteds (all families)

The data broken down by family into each group is summarised in the table (Table 5). It can be seen from the table and the grouped variable scatter plot of all the families together that the sum of the visual effect of adding “siblings” and “affecteds” together gives a semblance of the data for “children”. The distribution of the data for the “second-degree relatives” below the 2.5 standard deviation limit is similar to that of the control group.
Table 5. Proportions of abnormal SDTs in all families, 20 to 45 years

<table>
<thead>
<tr>
<th>Pedigrees examined</th>
<th>005</th>
<th>006</th>
<th>008</th>
<th>010</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number in family aged 20-45 yrs (number examined)</td>
<td>19 (5)</td>
<td>24 (16)</td>
<td>35 (29)</td>
<td>12 (8)</td>
<td>90 (58)</td>
</tr>
<tr>
<td>SDT &gt; 2.5SD (affected by AOPTD)</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>SDT &gt; 2.5SD (children)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>4 (7)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>SDT &gt; 2.5SD (siblings)</td>
<td>0 (0)</td>
<td>0 (5)</td>
<td>0 (6)</td>
<td>0 (0)</td>
<td>0 (11)</td>
</tr>
<tr>
<td>SDT &gt; 2.5SD (2nd degree relatives)</td>
<td>1 (2)</td>
<td>1 (9)</td>
<td>3 (17)</td>
<td>0 (0)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Total abnormal SDTs (examined)</td>
<td>2 (5)</td>
<td>2 (16)</td>
<td>6 (29)</td>
<td>5 (8)</td>
<td>16 (58)</td>
</tr>
</tbody>
</table>

3.3.4 Unaffected members with abnormal spatial discrimination thresholds

A total of eleven family members between 20 and 45 years of age had abnormal SDTs (Table 5). In the group of unaffected children, six out of 13 (46%) had abnormal thresholds, compared to five of 17 in the combined group of affecteds and their siblings (29%). These came predominantly from Ped 010, but one out of three came from both Ped 005 and Ped 008. Although there were no unaffected children from Ped 006, one of the children (sibship of five, three unaffected siblings examined) of the proband had clinically symptomatic AOPTD.
3.3.5 Numbers of affected members and those with abnormal SDTs in sibships

*Pedigree 005*

In this family, due to the absence of clinically affected members in the age group, and lack of participation of unaffected first- and second-degree relatives, results on sibships are not reported.

*Pedigree 006*

In this family there are two sibships with an affected member. In the first sibship (III:4-III:9), only three members out of six were examined although all six were in the age range. The affected member (III:8) had an abnormal SDT, but neither of the two unaffected members examined had an abnormal SDT. The other sibship (III:22-III:26) had three unaffected members examined. The affected member (III:22) had an abnormal SDT, but none of the unaffected siblings had abnormal SDTs.

*Pedigree 008*

There are two sibships in this family with affected members in the age range (IV:14-IV:23 and IV:24-IV:26). The first sibship had eight in the age range (III:16-III:23) including the two affected members. None of the unaffected members had abnormal SDTs. Only one of the two affected members had an abnormal SDT (IV:23).

*Pedigree 010*

There was one sibship in this family with an affected member (III:13) but the other sibling in the age range did not with to participate. This affected member had an abnormal SDT. There are two other sibships which were completely examined (III:6-
III:7, III:14-III:18). In the first, one of the two brothers had an abnormal SDT. In the second, three of the five had abnormal SDTs.
3.4 Spatial discrimination thresholds in subjects 45-65 years in multiplex families with AOPTD

3.4.1 Pedigree sizes

There were a total of 48 family members aged between 45 and 65 years. Twenty-eight were willing to participate. Half of all these subjects were from ped 005, but due to an intervening suicide in the family, very few were willing to volunteer for the study. Ped 006 and 010 had a distinct lack of members in the age range.

*Pedigree 005*

In this family there were 14 out of 24 members willing to have their SDT measured (II:9, III:1, III:2, III:4, III:5, III:7-9, III:11, III:17, III:18, III:20, III:24, III:25). Including the two affected members, there were seven unaffected first-degree relatives, and five second-degree relatives.

*Pedigree 006*

One member, the affected proband, was willing to participate in the study (II:6).

*Pedigree 008*

All twelve members within the age range were willing to participate. There was one affected member, five first-degree relatives, and six second-degree relatives.

*Pedigree 010*

Only the affected member (II:6) was willing to be examined.
Twenty-one subjects were included out of 28 volunteers between 45 and 65 years. In Ped 005, III:9 was employed in cleaning and suffered from bilateral hand pain and weakness with bilateral reduced vibration sensation (2/8 on Riedel-Seiffer tuning fork). III:17 suffered from Dementia Pugilistica. III:24 had Non-Hodgkins Lymphoma and Breast Cancer for which she had received chemotherapy. In Ped 006, there was no exclusion. In Ped 008, III:1 (proband) also suffered from Ectodermal Dysplasia, and had several missing digits. III:3 had bilateral hand weakness and pins and needles with a diagnosis of Carpal Tunnel Syndrome. III:10 had severe neck injury and symptoms of paraesthesia and weakness in her hands intermittently, with neck pain on straining. In Ped 010, there was no exclusion of subjects.
3.4.2 Spatial discrimination thresholds in each family

Pedigree 005

There were no abnormal SDTs in this family, including the two affected individuals. A total of eleven subjects were included. The subjects who were examined and those excluded can be seen in the pedigree drawing in Appendix 12.5.1.2. Individual SDT mean, handedness, age and gender are presented in table format (Table 6). A scatterplot of the data compared with controls shows the distribution of the SDTs (Figure 18).

Table 6. SDTs of subjects examined in Ped 005 aged 45 to 65 years

<table>
<thead>
<tr>
<th>Pedigree 005, 45 to 65 years SDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generation ID</td>
</tr>
<tr>
<td>II 1</td>
</tr>
<tr>
<td>II 2</td>
</tr>
<tr>
<td>II 3</td>
</tr>
<tr>
<td>II 4</td>
</tr>
<tr>
<td>II 5</td>
</tr>
<tr>
<td>II 6</td>
</tr>
<tr>
<td>II 7</td>
</tr>
<tr>
<td>II 8</td>
</tr>
<tr>
<td>II 9</td>
</tr>
<tr>
<td>II 10</td>
</tr>
</tbody>
</table>
Figure 18. SDTs of Ped 005 members aged 45-65 years
Pedigree 006

In this family only one person was examined in the age range, and his SDT was normal. He was right-hand dominant with a SDT\textsubscript{mean} of 1.76 mm (Table 7). The pedigree drawing is shown in Appendix 12.5.2.2 and the result is shown in the scatterplot (Figure 19).

Table 7. SDTs of subjects examined in Ped 006 aged 45 to 65 years

<table>
<thead>
<tr>
<th>Pedigree 006, 45 to 65 years SDT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generation</strong></td>
</tr>
<tr>
<td>II</td>
</tr>
</tbody>
</table>

Figure 19. SDTs of Ped 006 members aged 45-65 years
Pedigree 008

Nine family members examined showed no abnormal SDTs. The pedigree drawing with these subjects shown and those excluded can be seen in Appendix 21.5.3.2. The results are tabulated with details of age, gender, handedness and individual SDT mean in the table (Table 8). A grouped scatterplot of the SDT data is also presented (Figure 20).

Table 8. SDTs of subjects examined in Ped 008 aged 45 to 65 years

<table>
<thead>
<tr>
<th>Generation ID</th>
<th>Gender</th>
<th>Age</th>
<th>Dominance</th>
<th>SDT R (mm)</th>
<th>SDT L (mm)</th>
<th>Mean SDT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV 2</td>
<td>M</td>
<td>57.1</td>
<td>Right</td>
<td>3.000</td>
<td>2.000</td>
<td>2.500</td>
</tr>
<tr>
<td>IV 4</td>
<td>M</td>
<td>54.3</td>
<td>Right</td>
<td>1.300</td>
<td>2.833</td>
<td>2.067</td>
</tr>
<tr>
<td>IV 5</td>
<td>F</td>
<td>57.1</td>
<td>Right</td>
<td>3.000</td>
<td>2.100</td>
<td>2.550</td>
</tr>
<tr>
<td>IV 6</td>
<td>F</td>
<td>56.6</td>
<td>Right</td>
<td>3.000</td>
<td>2.750</td>
<td>2.875</td>
</tr>
<tr>
<td>IV 7</td>
<td>M</td>
<td>54.3</td>
<td>Right</td>
<td>1.560</td>
<td>1.900</td>
<td>1.730</td>
</tr>
<tr>
<td>IV 8</td>
<td>F</td>
<td>52.8</td>
<td>Right</td>
<td>4.083</td>
<td>3.773</td>
<td>3.928</td>
</tr>
<tr>
<td>IV 9</td>
<td>M</td>
<td>51.1</td>
<td>Right</td>
<td>1.414</td>
<td>1.171</td>
<td>1.293</td>
</tr>
<tr>
<td>IV 14</td>
<td>F</td>
<td>46.7</td>
<td>Left</td>
<td>1.000</td>
<td>2.000</td>
<td>1.500</td>
</tr>
<tr>
<td>IV 15</td>
<td>M</td>
<td>45.4</td>
<td>Left</td>
<td>1.875</td>
<td>1.250</td>
<td>1.563</td>
</tr>
</tbody>
</table>

Figure 20. SDTs of Ped 008 members aged 45-65 years
Pedigree 010

The proband is the only person examined in this family. He was a 62-year old right-handed man with a SDT\textsubscript{mean} of 2.75 mm (Table 9). The data is presented in the pedigree drawing (Appendix 12.5.4.2) and in the scatterplot (Figure 21).

Table 9. SDTs of subjects examined in Ped 010 aged 45 to 65 years

Pedigree 010, 45 to 65 years SDT

<table>
<thead>
<tr>
<th>Generation ID</th>
<th>Gender</th>
<th>Age</th>
<th>Dominance</th>
<th>SDT R (mm)</th>
<th>SDT L (mm)</th>
<th>Mean SDT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III 6</td>
<td>M</td>
<td>62.7</td>
<td>Right</td>
<td>3.000</td>
<td>2.500</td>
<td>2.750</td>
</tr>
</tbody>
</table>

Figure 21. SDTs of Ped 010 members aged 45-65 years
3.4.3 Mean SDT of all subjects by relationship

The data was also examined according to the grouped variables “affected by dystonia” (affected), “children of affected” (children), “siblings of affected” (siblings) and “second-degree relatives” (2nd degree relatives). No subject was censored on either hand for the right and left SDT. None of the four affected individuals in this group had abnormal SDTmean. None of the siblings (four examined) or children (three examined) of an affected had an abnormal SDTmean. One second-degree relative (IV:8) had an abnormal SDTmean (Figure 22). The median SDT for each group was as follows: affecteds 2.04 mm, children 2.02 mm, siblings 2.07 mm, and second-degree relatives 2.18 mm (control median SDT 1.79 mm). Using a one-way ANOVA test for comparing non-parametric data (Kruskal-Wallis), there was no significant difference between groups (p = 0.42).

Figure 22. SDTs grouped by relationship to affecteds (all families)
The data is summarised in the table according to the group relationships (Table 10). From the scatterplot, it can be seen that most of the points lie within one standard deviation of the control values. Only one value is above the 2.5 SD line which was a second-degree relative (Ped 008, IV:8). Five values lie between one and two standard deviations of the control mean. One is an affected member, and two are from both the sibling group and the second-degree relative group. Otherwise, the groups’ overall distribution reflects that of the control group.

Table 10. Proportions of abnormal SDTs in all families, 45 to 65 years

<table>
<thead>
<tr>
<th>Pedigrees examined</th>
<th>005</th>
<th>006</th>
<th>008</th>
<th>010</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number in family aged 45-65 yrs (number examined)</td>
<td>24 (11)</td>
<td>5 (1)</td>
<td>12 (9)</td>
<td>7 (1)</td>
<td>48 (22)</td>
</tr>
<tr>
<td>SDT &gt; 2.5SD (affected by AOPTD)</td>
<td>0 (2)</td>
<td>0 (1)</td>
<td>0 (0)</td>
<td>0 (1)</td>
<td>0 (4)</td>
</tr>
<tr>
<td>SDT &gt; 2.5SD (children)</td>
<td>0 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (3)</td>
</tr>
<tr>
<td>SDT &gt; 2.5SD (siblings)</td>
<td>0 (3)</td>
<td>0 (0)</td>
<td>0 (4)</td>
<td>0 (0)</td>
<td>0 (7)</td>
</tr>
<tr>
<td>SDT &gt; 2.5SD (2nd degree relatives)</td>
<td>0 (3)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Total abnormal SDTs (examined)</td>
<td>0 (11)</td>
<td>0 (1)</td>
<td>1 (9)</td>
<td>0 (1)</td>
<td>1 (22)</td>
</tr>
</tbody>
</table>

3.4.4 Unaffected members with abnormal spatial discrimination thresholds

In this study of family members aged 45 to 65 years, only one subject had an abnormal SDT. She was a second-degree relative in Ped 008 (IV:8) with a SDT$_{\text{mean}}$ of 3.93 mm (SDT$_{\text{right}}$ 4.08 mm, SDT$_{\text{left}}$ 3.78 mm) (Table 8). Eight second-degree relatives had been examined giving a 12.5% group prevalence of elevated sensory thresholds.
3.4.5 Numbers of affected members and those with abnormal SDTs in sibships

*Pedigree 005*

This family had significantly more members in the age range for the study than others, and twelve of the eligible 19 were willing to participate. This was cut to nine (47.4%) by three exclusions. Two were affected members who had normal SDTs, three were siblings of affected members who also had normal SDTs.

*Pedigree 006*

There is one sibship with an affected member in this family, but only the affected member (II:6) was within the age range, and his SDT was normal.

*Pedigree 008*

There are two sibships in this family with an affected member (IV:1-IV:4, IV:14-IV:23). All of the first sibship members were within the age range, but only the two eldest in the second. There was two exclusions from the first sibship (IV:1, IV:3). None of the other siblings had abnormal SDTs.

*Pedigree 010*

There was one sibship again in this family with affected members, but only one of three was within the age range who was also an affected individual (II:6). His SDT$_{\text{mean}}$ was normal.
3.4.6 Combined results of family members 20-65 years using standard normal

In this section, the results of section 3.3 and 3.4 are combined. A tabulated summary of family numbers between 20 and 65 years is given below (Table 11). Given that they are two different studies using two different sets of tools, and have two different control groups, the results are transformed to a standard normal and presented in the following paragraphs. The standard normal (Z) can be used to combine the results because the random variable (SDT_{mean}) should be present in the normal distribution of the control SDTs.

Table 11. Summary statistics of families seen, affected members and abnormal SDTs

<table>
<thead>
<tr>
<th>Pedigree</th>
<th>005</th>
<th>006</th>
<th>008</th>
<th>010</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number in family aged 20-65 yrs</td>
<td>43</td>
<td>29</td>
<td>47</td>
<td>19</td>
<td>138</td>
</tr>
<tr>
<td>Number of volunteers</td>
<td>20</td>
<td>18</td>
<td>41</td>
<td>9</td>
<td>88</td>
</tr>
<tr>
<td>Exclusions</td>
<td>(4)</td>
<td>(1)</td>
<td>(3)</td>
<td>(0)</td>
<td>(8)</td>
</tr>
<tr>
<td>Affected with AOPTD</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Number of unaffecteds with abnormal SDTs</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Combined number of affected and abnormal SDTs</td>
<td>6</td>
<td>4</td>
<td>11</td>
<td>8</td>
<td>29</td>
</tr>
</tbody>
</table>
Pedigree 005

There are two abnormal SDTs in unaffected members of this family (III:28, III:36) and four members were affected with AOPTD (II:3, II:8, III:1, III:4). Of the 14 members examined there were two affected and two with abnormal SDTs (Table 11).

Pedigree 006

Seventeen family members were examined in total (Table 11). There was one unaffected family member with an abnormal SDT (III:20) and three affected with AOPTD (II:6, III:8, III:22).

Pedigree 008

There were five unaffected family members (IV:8, IV:11, IV:28, V:7, V:9) with abnormal SDTs out of the 32 unaffected members examined (Table 11). Six family members had AOPTD (III:1, III:6, IV:1, IV:16, IV:23, IV:24).

Pedigree 010

Nine family members were examined in this family (Table 11), and there were four affected members (II:3, II:5, II:6, III:13). Four unaffected family members were found to have abnormal SDTs (III:7, III:14, III:15, III:16).

SDTs by relationship to an affected member

All the SDTs were converted to standard normal values according to the control group they were compared to (Group 1 or Group 2). For the purposes of viewing the data, all Z-scores representing higher SDTs are positive values. The data is presented in the graph, and a +2.5 standard deviation line is marked on the x-axis (Figure 23). There
are five out of the ten family members affected with AOPTD who have Z-scores over the +2.5 standard deviation limit. Six out of 16 children, one out of 18 siblings, and seven out of 36 second-degree relatives also had Z-scores greater than +2.5. The numerical data is also presented in the table below (Table 12).

Table 12. Standard normal scores on all subjects aged 20-65 years

Z-scores of all subjects in Ped 005, 006, 008 and 010

<table>
<thead>
<tr>
<th>Affecteds</th>
<th>Children</th>
<th>Siblings</th>
<th>Second-degree Relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.31</td>
<td>5.31</td>
<td>2.52</td>
<td>5.62</td>
</tr>
<tr>
<td>3.64</td>
<td>4.86</td>
<td>2.23</td>
<td>3.83</td>
</tr>
<tr>
<td>3.46</td>
<td>4.60</td>
<td>1.76</td>
<td>3.70</td>
</tr>
<tr>
<td>3.08</td>
<td>4.25</td>
<td>1.69</td>
<td>3.47</td>
</tr>
<tr>
<td>2.82</td>
<td>3.79</td>
<td>1.23</td>
<td>3.31</td>
</tr>
<tr>
<td>1.56</td>
<td>2.57</td>
<td>1.16</td>
<td>3.06</td>
</tr>
<tr>
<td>1.36</td>
<td>2.11</td>
<td>1.15</td>
<td>2.52</td>
</tr>
<tr>
<td>0.85</td>
<td>1.92</td>
<td>0.97</td>
<td>1.76</td>
</tr>
<tr>
<td>-0.05</td>
<td>1.67</td>
<td>0.87</td>
<td>1.58</td>
</tr>
<tr>
<td>-0.28</td>
<td>1.33</td>
<td>0.86</td>
<td>1.24</td>
</tr>
<tr>
<td>-</td>
<td>1.20</td>
<td>0.65</td>
<td>1.20</td>
</tr>
<tr>
<td>-</td>
<td>0.98</td>
<td>0.59</td>
<td>1.05</td>
</tr>
<tr>
<td>-</td>
<td>0.81</td>
<td>0.46</td>
<td>0.99</td>
</tr>
<tr>
<td>-</td>
<td>0.38</td>
<td>0.38</td>
<td>0.89</td>
</tr>
<tr>
<td>-</td>
<td>0.13</td>
<td>0.36</td>
<td>0.85</td>
</tr>
<tr>
<td>-</td>
<td>-0.28</td>
<td>-0.36</td>
<td>0.65</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-0.46</td>
<td>0.64</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-0.79</td>
<td>0.32</td>
</tr>
</tbody>
</table>
Figure 23. Standard normal values of all subjects by relationship to an affected member.
4 Discussion and Conclusion

4.1 Sensory abnormalities in unaffected family members

Despite the difficulty in finding large multiplex families with AOPTD, 58 out of a possible 90 family members in four families were available and eligible for examination in the 20-45 year age group (64%). Of the unaffected members examined, six of 13 children of affected members had abnormal SDTs (46.2%). None of the eleven siblings of affected members in this group had abnormal SDTs. A further five out of 28 second-degree relatives had abnormal SDTs. These figures could be in keeping with an autosomal dominant disorder with reduced penetrance, and sensory abnormalities as an endophenotype. In the second study on family members aged 45-65 years, 22 of 48 members were examined (46%). No first-degree relatives were identified with abnormal SDTs. One second-degree relative had an abnormal SDT. Recruitment from larger families was hampered by the members’ wariness of genetic studies or living abroad.

Previous studies looking at VIIM identified 45–63.6% of unaffected first-degree relatives with abnormal thresholds (Frima et al., 2008). However, 21% of controls also had abnormal responses in this study. In sporadic cases of AOPTD, family members are less frequently found to have abnormal sensory responses (Walsh et al., 2007).

4.2 Sensory abnormalities in affected family members

Abnormal SDTs at the fingertip are found in approximately half of all sporadic patients with focal adult-onset primary torsion dystonia irrespective of the affected
site (O'Dwyer and Hutchinson, 2004b, Molloy et al., 2003, Van Boven, 2001). We identified six affected family members in the 20-45 year age group, and five had abnormal SDTs. If sensory abnormalities are truly an endophenotype, we should expect to find abnormal SDTs in all affected members in this age group. The only different aspect of this person's treatment was that they were one of only two in this age group being treated with botulinum neurotoxin for several years (Walsh and Hutchinson, 2007). The other four were BoNT naïve. There was no occupational reason for improved sensory thresholds.

Botulinum neurotoxin temporarily alters central excitability in dystonic patients (Gilio et al., 2000). This effect is thought to be related to plasticity in the cortex. BoNT has been identified travelling rostrally in animals injected in the gastrocnemius, as well as influencing central neurotransmitter release (Berardelli et al., 2002). The SDT in dystonia patients improves after botulinum toxin injection (Walsh and Hutchinson, 2007). It is possible that untreated dystonia is the manifestation of cortical sensory reorganization, since the cortex of patients with dystonia is hyperexcitable and displays greater degrees of plasticity than normal subjects (Quartarone et al., 2003). This effect may not be seen in the primary somatosensory cortex, and it is more likely to be truly found in secondary sensory areas that modulate sensorimotor integration such as the secondary somatosensory cortex or the basal ganglia (Braun et al., 2003, Peller et al., 2006, Etgen et al., 2006, Delmaire et al., 2005, Black et al., 1998). However, primary somatosensory cortical maps are known to be abnormal in focal dystonias, even in areas of cortical representation not clinically affected (Meunier et al., 2001, Garraux et al., 2004, Tamura et al., 2009, Elbert et al., 1998). Interestingly, during movement, S1 functionally reorganizes briefly for focal areas not affected by the dystonia (Braun et
al., 2003). It has been suggested that is the manifestation of aberrant cortical reorganization in an abnormally plastic cortex that has an underlying primary abnormality, which may be a sensory disorder (Hallett, 1995, Tamura et al., 2009, Defazio et al., 2007).

In the older age group 45-65 years, not one of four affecteds had an abnormal SDT. There are two possibilities to be considered, including that they do not have a sensory abnormality or that SDT measurement is too insensitive in older individuals. A case-control study matching all participants for age, sex, cigarette use, alcohol use and medical comorbidities might improve the sensitivity, but establishment of normative data was thought to be more reliable and feasible with moderate sized multiplex families.

4.3 Limitations of JVP domes

One hundred and eleven healthy controls were originally examined with the standard set of JVP domes. However, it was found that a ceiling effect occurred at the age of 45 years. Similar problems had been encountered elsewhere, and had been overcome through the introduction of intermediate and larger width grating JVP domes (Tremblay et al., 2000). Hand to hand differences were found in a minority of individuals and there was no significant difference in the mean SDT between hands. Simple linear regression showed the non-dominant hand tended to have a slightly higher threshold which may reflect less use.

Using an expanded set of domes, a healthy control population was examined, showing a ceiling effect this time at the age of 65 years. Although Merkel cells do not degenerate normally with age, and glabrous skin and other areas show stability of the numbers of small nerve fibres in the epidermis with advancing age, small myelinated
fibre axons are known to be significantly lost in peripheral nerve with age (McArthur et al., 1998, Ridley, 1969). This would contribute to deafferentation and overlapping sensory fields in the aging brain which is known to have less synaptic connectivity (Masliah et al., 1993, Merzenich et al., 1983).

4.4 Penetrance of the endophenotype

Penetrance reflects the fraction of individuals with a genotype who have signs or symptoms of disease (Saunders-Pullman et al., 2004). We hypothesized that sensory abnormalities may be an endophenotype that could be identified in unaffected members of large multiplex AOPTD families. Penetrance may be calculated in a single pedigree. Ideally, the endophenotype should be found in individuals who have the full phenotype (Gottesman and Gould, 2003). The families were examined in two groups, divided by age. The penetrance of the endophenotype in the 20-45 year age group was: 67% in Ped005, 0% in Ped006, 11% in Ped008 and 100% in Ped010. However, results for all pedigrees in the older age groups for the endophenotype were 0% (Appendix 7).

From the pedigree charts, it would appear that Ped010 is the strongest candidate family for an autosomal dominant condition with endophenotype and phenotype results combined. Ped008 also is highly informative in this regard. However, Ped005 and Ped006 are less so. Sensory abnormalities may not underlie all forms of AOPTD, and in some cases may be an epiphenomenon.

4.5 Possible role of sensory abnormalities in AOPTD

So are sensory abnormalities a true primary disorder in dystonia? Patients with dystonia may have sensory symptoms such as pain, simple sensory injury may trigger
dystonia, patients may get relief from sensory tricks, they have abnormalities of muscle spindle function, spatial and temporal discrimination are abnormal, there are metabolic abnormalities in sensory areas, including representations the primary somatosensory cortex, the secondary somatosensory cortex and the left intraparietal sulcus, and there are many functional and structural abnormalities in a variety of types of primary dystonia.

However, dystonia is a disorder with excessive plastic potential in the central nervous system. There are also many motor features, although they do not convincingly appear primary, and it is generally accepted that motor function is endpoint of sensory processing and sensorimotor integration. In other words all motor function is similar to tropism in lower order species. Plasticity might lead to aberrant sensory receptive fields to compensate for abnormal motor function, but dynamic reorganization of primary somatosensory field during movement remains a cloak over the hard-wired abnormalities of secondary sensory areas, basal ganglia nuclei with large sensory components, and sensory association cortex. It is a complex mesh of sensory abnormalities. To borrow from the colloquial: “where there is smoke, there is fire.”

4.6 Genetic modifiers that may affect penetrance

Age of onset has been examined in AOPTD because of the nature of its predisposition for increasing age and certain phenotypes. Dystonia and basal ganglia disorders are known to be associated with dopamine and the higher rate of dystonic choreoathetoid movement seen in patients treated with dopamine receptor (DRD) antagonists stimulated groups to look at single nucleotide polymorphisms particularly of DRD5 and its influence on the age of onset (Brancati et al., 2003, Misbahuddin et
The results showed significance in an Italian and British sample population for lowering the age of onset in BEB and CD, but numbers were very small, and similar distributions of polymorphisms were not detected in both nationalities. A study powered to truly examine SNPs of DRD5 would require over a thousand patients with a single phenotype, and differences in SNP distributions between ethnic backgrounds make multicentre study difficult. For this reason the present study did not examine DRD5 SNPs and their relationship to sensory abnormalities.

Apolipoprotein E ε4/ε4 allelic status has been implicated in Alzheimer’s Disease as a modifier of risk, leading to earlier onset and greater likelihood of disease. However, apoEε4 is not pathologically involved, since Alzheimer’s Disease is a tauopathy. Matsumoto and colleagues examined the effect of apoE genotype on the age of onset in a mixed group of 300 patients with AOPTD (Matsumoto et al., 2003). On average, apoEε4 carriage (heterzygous or homozygous) led to an earlier onset of dystonia by ten years.

More women suffer from craniocervical dystonia than men, but men have a higher incidence of writer’s cramp (Soland et al., 1996). Sex has been hypothesized as a genetic risk factor. The Epidemiologic Study of Dystonia in Europe group examined age of onset in primary dystonia from several countries (Defazio, 1999). They found that men had an earlier average age of onset than women for all focal dystonia except FHD. In a similar study on Irish patients with CD, no significant difference in the age of onset was found (O'Dwyer and Hutchinson, 2004a).
4.7 Using the sensory system to treat dystonia

Another promising aspect of sensory research in dystonia has been the advantages of sensory retraining in certain forms of dystonia, particularly FHD (Candia et al., 1999, Candia et al., 2003, Zeuner and Hallett, 2003, Zeuner et al., 2002). The results of such work have shown reorganization in the somatosensory cortex after retraining, and continued benefit when therapy is done regularly. Sensory tricks have been shown to reduce dystonic neck muscle activity in CD (Leis et al., 1992). The result is that many patients benefit from physiotherapy combined with botulinum neurotoxin treatment (Warner and Bressman, 2007).

4.8 Conclusion

"At whatever period of life a peculiarity first appears, it tends to appear in the offspring at a corresponding age (Darwin, 1859)." Genetics has progressed a lot since then, but the concept of the phenotype manifesting at a certain age with reduced penetrance is important in looking for an endophenotype in human disease.

Sensory abnormalities measured by SDT analysis were found in many unaffected relatives in multiplex AOPTD families, raising the possibility that this is a true endophenotype. Similar changes were found in most affected individuals. Study of older individuals was hampered by either insensitivity of this test in older persons, absence of sensory abnormalities in older individuals affected by AOPTD, or lack of a true endophenotype. The effect of botulinum neurotoxin in treated subjects may have improved SDTs for significantly greater than three months or had long term plastic effects. Naïve affected subjects in the younger age group were the majority and not affected by this phenomenon related to botulinum neurotoxin (Walsh and Hutchinson, 2007).
Further work on the endophenotype using alternative methods has not be affected so much by age such as temporal discrimination thresholds and structural brain imaging studies yielding support for and being stronger measures of an endophenotype (Bradley et al., 2009, Walsh et al., 2009a). Sensorimotor integration is a dynamic process that responds to many genetic and external influences during life. Paired associative plasticity studies of somatosensory cortex in relatives “at risk” in these multiplex studies using TMS is another possible future direction. Drugs that modulate plasticity including NMDA-receptor antagonists and γABA-receptor agonists could be tried in conjunction with sensory-training related therapies.

The findings of this research enhance our understanding of the potential inherited sensory pathogenesis of AOPTD. They stress the importance of expanding on the endophenotype of sensory abnormality that is combined with maladaptive plasticity in this type of dystonia.
CONSENT FORM:

GENETICS OF MOVEMENT DISORDERS/DYSTONIA

I give my full informed consent to participate in this study. I understand that I will have a clinical history taken, an examination including specialised sensory examination, a videotaped segment and a blood sample taken.

Signed: 
Name: 
Date: 
Witnessed by: 
Name: 
Date:
Appendix 2

SPATIAL DISCRIMINATION STUDY

SUBJECT DETAILS

Name

Date of Birth ___/___/_____

Gender

Male □ Female □

Address

Telephone/Contact Work_____________________

Home_____________________

Control

Yes □ No □

Dystonia Group Ped No__________ Yes □ No □

Phenotype CD □ BEB □ SD □ WC □ OMD □

Onset age__________ TWSTR__________ BFM__________

Dominant Hand (Abbrev Edinburgh) Right □ Left □

1) writing □
2) drawing □
3) throwing □
4) scissors □
5) toothbrush □
6) knife (without fork) □
7) spoon (eg soup) □
8) broom/vacuum cleaner (upper hand) □
9) striking a match (match) □
10) opening a jar/box (lid) □
   i. which foot do you prefer to kick with? □
   ii. which leg do you throw over a bicycle? □

PMHx

A □ DM □ ΔTSH □ TB □ RhF □ HBP □

IHD □ CVA □ MI □ CRF □ MycLep □ Other □
C Spine disease/injury  

Shoulder injury  

Upper limb injury  

CTS  

Neuropathic symptoms  

Tremor in limbs  

Spasms  

Duration  

Head Injury (LOC+)  

Medication  

1)  

2)  

3)  

4)  

5)  

6)  

BOTOX  

NEUROBLOC  

Duration of Treatment  

Last Injection  

Occupation  

Vibrating tools (>3h/day)  

Alcohol  

Units  

<10/wk  

<21/wk  

Cigarettes (pack years)  

21-40/wk  

>40/wk  

Family History  

Parkinsons  

Dystonia  

Tremor  

Chorea  

Myoclonus  

Tics  

Other  

Yes ☐  No ☐
Sensorimotor examination of upper limbs

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Impaired</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pin prick</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light touch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint position</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vibration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor ( R / L Postural / Kinetic )</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Power (5/5)</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Other movement</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Deformity</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Skin integrity on finger tips</td>
<td>Normal</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Calloused</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Heavy callouses</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Other (specify)</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Cognition</td>
<td>Normal</td>
<td></td>
<td>Impaired</td>
</tr>
<tr>
<td>Understands “across” and “down”</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

Signed:

Date:
Appendix 3

Spatial discrimination threshold test score sheet example

Each box with “down” or “across” is generated by random number assignment in Microsoft Excel with the rule that numbers lower than 500 be “down” and numbers greater than or equal to 500 be “across”.

<table>
<thead>
<tr>
<th>Name</th>
<th>Hand</th>
<th>Right / Left</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>4.50</th>
<th>4.00</th>
<th>3.50</th>
<th>3.00</th>
<th>2.50</th>
<th>2.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>down</td>
<td>across</td>
<td>across</td>
<td>across</td>
<td>across</td>
<td>across</td>
</tr>
<tr>
<td>down</td>
<td>down</td>
<td>across</td>
<td>across</td>
<td>across</td>
<td>across</td>
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<tr>
<td>down</td>
<td>across</td>
<td>down</td>
<td>across</td>
<td>across</td>
<td>across</td>
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<tr>
<td>down</td>
<td>across</td>
<td>across</td>
<td>down</td>
<td>across</td>
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<td>down</td>
<td>across</td>
<td>across</td>
<td>across</td>
<td>across</td>
<td>across</td>
</tr>
<tr>
<td>down</td>
<td>across</td>
<td>across</td>
<td>across</td>
<td>across</td>
<td>across</td>
</tr>
<tr>
<td>1.50</td>
<td>1.20</td>
<td>1.00</td>
<td>0.75</td>
<td>0.50</td>
<td>0.35</td>
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</tr>
<tr>
<td>down</td>
<td>down</td>
<td>down</td>
<td>down</td>
<td>down</td>
<td>across</td>
</tr>
<tr>
<td>down</td>
<td>down</td>
<td>down</td>
<td>down</td>
<td>down</td>
<td>down</td>
</tr>
<tr>
<td>across</td>
<td>down</td>
<td>across</td>
<td>down</td>
<td>across</td>
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<td>across</td>
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<td>across</td>
<td>across</td>
<td>across</td>
</tr>
</tbody>
</table>

267
Appendix 4

A selection of Johnson-Van Boven-Phillips domes (scale approx magnified x2), showing the acrylic dome shaped heads with grooves and ridges of equal width.
Electron micrograph transverse section of a skin Merkel disc (MC) with a nerve ending beside it containing neurotransmitter (NT)

Source (Reinisch and Tschachler, 2005)
Figure of Merkel discs (red) and nerve endings (green) stained with fluorescent immunohistochemical agents. The Merkel discs are distributed in a tree like manner branching off nerve endings in the skin

Source: idem
Appendix 7

Penetrance of Endophenotype

Calculation of Endophenotype penetrance in the 20-45 year age group:

<table>
<thead>
<tr>
<th>Pedigrees examined, 20-45 years</th>
<th>005</th>
<th>006</th>
<th>008</th>
<th>010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number ‘at risk’</td>
<td>7</td>
<td>9</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Number of ‘at risk’ examined</td>
<td>3</td>
<td>5</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Number ‘at risk’ with abnormal SDT</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Possible penetrance at age 20-45 years</td>
<td>67%</td>
<td>0%</td>
<td>11%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Calculation of Endophenotype penetrance in the 45-65 year age group:

<table>
<thead>
<tr>
<th>Pedigrees examined, 45-65 years</th>
<th>005</th>
<th>006</th>
<th>008</th>
<th>010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number ‘at risk’</td>
<td>11</td>
<td>2</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Number of ‘at risk’ examined</td>
<td>6</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Number ‘at risk’ with abnormal SDT</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Possible penetrance at age 45-65 years</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Appendix 8

Abstracts associated with this research


O'Dwyer JP, Hutchinson M. The age of onset in cervical dystonia is independent of the level of education. Movement Disorders, 2004; 19: S115

O'Dwyer JP, Hutchinson M. Evidence for symmetrically reduced spatial discrimination threshold at the fingertip in cervical dystonia with rotation to dominant and non-dominant sides. Neurology, 2004; 62(S5): P06.146
Appendix 9

Publications arising from this research


Appendix 10

Standardised Video Protocol for Dystonia

<table>
<thead>
<tr>
<th>Region</th>
<th>Recording position</th>
<th>Conditions</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>front</td>
<td>1) look straight at camera, normal light</td>
<td>60s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) look straight, count backwards</td>
<td>45s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3) look straight, forced repetitive fist closures</td>
<td>30s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4) 10 forced voluntary eye closures looking at bright light</td>
<td>30s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5) read small print</td>
<td>30s</td>
</tr>
<tr>
<td>Neck</td>
<td>front</td>
<td>1) spontaneous head position during unsupported sitting</td>
<td>60s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) 5 smooth voluntary maximal head rotations to R and L</td>
<td>30s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3) spontaneous head position unsupported, count backwards</td>
<td>45s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4) spontaneous head position unsup/seatad, rep.fist closures</td>
<td>30s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5) spontaneous head position walking on spot</td>
<td>30s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6) forced walk over 30m</td>
<td>90s</td>
</tr>
<tr>
<td></td>
<td>right, then</td>
<td>1) spontaneous head position during unsupported sitting</td>
<td>60s</td>
</tr>
<tr>
<td></td>
<td>left, &amp; back</td>
<td>2) 5 smooth voluntary maximal head rotations to R and L</td>
<td>30s</td>
</tr>
<tr>
<td>Trunk</td>
<td>front</td>
<td>1) spontaneous trunk position during unsupported sitting</td>
<td>60s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) forced walk over 30m</td>
<td>60s</td>
</tr>
<tr>
<td></td>
<td>front, one side, back</td>
<td>1) spontaneous trunk position during walking on the spot</td>
<td>90s</td>
</tr>
<tr>
<td>Arms</td>
<td>front</td>
<td>1) resting arms in lap</td>
<td>60s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) holding arms in front of chest in wing position</td>
<td>30s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3) tapping all fingers consecutively on thumb</td>
<td>30s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4) writing standard sentence in normal handwriting</td>
<td>30s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5) write standard sentence in print</td>
<td>45s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6) copy objects – serial ‘LLLLL…’</td>
<td>45s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7) draw spiral from centre out, with arm resting on elbow</td>
<td>30s</td>
</tr>
</tbody>
</table>
8) 10 forced repetitive fist closures, fingers spreading open   30s

Legs  front  1) spontaneous sitting   60s
2) walking on the spot   30s
3) forced walk over 30m   60s

Voice 1) read standard passage with normal volume

2) cough
3) breathe in
4) breathe out (sigh)
5) whisper count from one to five
6) humm “mmmmmmmmmm”
7) say “Aaaaaaaah” in low pitch
8) say “Aaaaaaaah” in high pitch
9) glide up on a scale of “La”
10) glide down on a scale of “La”
11) pitch “Aaaah” low then high
12) pitch “Aaaaaah” high then low
13) count from one to ten in alternating pitch
14) shout “Taxi”
15) read standard passage with loud volume
16) conversation

Standard Passage

THE NORTH WIND AND THE SUN
The north wind and the sun were arguing one day about which of them was the stronger, when a traveller came along, wrapped in a warm coat. They agreed that the one who could make the traveller take off his coat would be considered stronger than the other one. Then the north wind blew as hard as he could, but the harder he blew the tighter the traveller wrapped his coat around him. And at last the north wind gave up trying. Then the sun began to shine warmly, and right away the traveller took off his coat. And so the north wind had to admit that the sun was stronger than he was.
Appendix 11

Glossary of terms

\(^{18}\text{FDG-PET}\)

Radioligand associated PET to show metabolism

Bienenstock-Cooper-Munro model

Neurons will respond to excitatory and inhibitory stimuli in a hebbian manner, but will aim to maintain an overall status quo of synaptic activity in temporal and spatial measures, contingent on patterned inputs and background noise

Brodman areas

A region of the cortex defined based on its cytoarchitecture

\(\text{dl}^{32}\text{ hamsters}\)

An animal model of primary paroxysmal non-kinesiogenic dystonic choreoathetosis

\(\text{H}_2^{15}\text{O PET}\)

Heavy water PET to demonstrate blood flow
= affected with AOPTD (all ages)
Bar above symbol denotes age 20-45 years

Appendix 12.4.1.1 Ped 005
= abnormal SDT (age 20-45y)
= affected with AOPTD (all ages)
= dystonia phenotype and abnormal SDT (age 20-45y)

Cross above symbol denotes that SDT was measured
Cross in symbol denotes excluded subject

Appendix 12.4.1.2 Ped 005
= affected with AOPTD (all ages)
Bar above symbol denotes age 20-45 years

Appendix 12.4.2.1 Ped 006
[ ] = abnormal SDT (age 20-45y)
[ ] = affected with AOPTD (all ages)
■ = dystonia phenotype and abnormal SDT (age 20-45y)
Cross above symbol denotes that SDT was measured
Cross in symbol denotes excluded subject

Appendix 12.4.2.2 Ped 006
= affected with AOPTD (all ages)

Appendix 12.4.3.1 Ped 008
• = abnormal SDT (age 20-45y)
■ = affected with AOPTD (all ages)
■ ■ = dystonia phenotype and abnormal SDT (age 20-45y)
Cross above symbol denotes that SDT was measured

Appendix 12.4.3.2 Ped 008
= affected with AOPTD (all ages)
Bar above symbol denotes age 20-45 years

Appendix 12.4.4.1 Ped 0010
\[\text{\(\Box\)}\text{ = abnormal SDT (age 20-45y)}\]
\[\text{\(\square\)}\text{ = affected with AOPTD (all ages)}\]
\[\text{\(\blacksquare\)}\text{ = dystonia phenotype and abnormal SDT (age 20-45y)}\]

Cross above symbol denotes that SDT was measured

\textbf{Appendix 12.4.4.2 Ped 010}
= affected with AOPTD (all ages)
Bar above symbol denotes age 45-65 years

Appendix 12.5.1.1 Ped 005
= abnormal SDT (age 45-65y)
= affected with AOPTD (all ages)
= dystonia phenotype and abnormal SDT (age 45-65y)
Cross above symbol denotes that SDT was measured
Cross in symbol denotes individual excluded

Appendix 12.5.1.2 Ped 005
= affected with AOPTD (all ages)
Bar above symbol denotes age 45-65 years

Appendix 12.5.2.1 Ped 006
= abnormal SDT (age 45-65y)
= affected with AOPTD (all ages)
= dystonia phenotype and abnormal SDT (age 45-65y)

Cross above symbol denotes that SDT was measured

Appendix 12.5.2.2 Ped 006
□ = affected with AOPTD (all ages)
Bar above symbol denotes age 45-65 years

Appendix 12.5.3.1 Ped 008
= abnormal SDT (age 45-65y)

= affected with AOPTD (all ages)

= dystonia phenotype and abnormal SDT (age 45-65y)

Cross above symbol denotes that SDT was measured

Cross in symbol denotes individual excluded

Appendix 12.5.3.2 Ped 008
= affected with AOPTD (all ages)
Bar above symbol denotes age 45-65 years

Appendix 12.5.4.1 Ped 0010
<table>
<thead>
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<th>Symbol</th>
<th>Description</th>
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<tr>
<td>■</td>
<td>abnormal SDT (age 45-65y)</td>
</tr>
<tr>
<td>■</td>
<td>affected with AOPTD (all ages)</td>
</tr>
<tr>
<td>■</td>
<td>dystonia phenotype and abnormal SDT (age 45-65 y)</td>
</tr>
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</table>

Cross above symbol denotes that SDT was measured.

Appendix 12.5.4.2 Ped 010
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