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Neuroplasticity following pallidal stimulation for dystonia

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Abstract

Dystonia is a disabling condition characterised by involuntary muscle spasms and abnormal postures. Its pathophysiology is incompletely understood but most lines of evidence point to an underlying defect of basal ganglia function leading to abnormal corticomotor output. Various abnormalities have been shown, including abnormal neuronal activity in basal ganglia output nuclei, defective neural inhibition at the spinal, brainstem, cortical level and sensorimotor misprocessing. More recently, increased neural plasticity has been found in dystonia patients in response to transcranial magnetic stimulation (TMS) protocols which induce motor cortex plasticity. Excessive plasticity might contribute to dystonia by promoting or reinforcing abnormal patterns of connectivity. The most significant advance in the treatment of generalised dystonia has been the development of globus pallidus internus (GPi) deep brain stimulation (DBS). Interestingly its beneficial effects are progressive over weeks to months rather than immediate. A plasticity effect has been implicated but physiological evidence has been lacking. Furthermore it is unknown what impact GPi DBS has on the underlying pathophysiology such as defective inhibition or excessive plasticity. The aim of the present work was to examine the impact of GPi DBS on underlying pathophysiological features such as disinhibition and abnormal motor cortical plasticity. In this thesis, studies in a consecutive series of dystonia patients, mainly those with primary generalised dystonia, who underwent bilateral GPi DBS, are presented. Patients were studied in a prospective, longitudinal manner with both clinical assessment of dystonia using a validated rating scale and electrophysiological studies including blink reflex excitability and forearm H-reflex reciprocal inhibition. In addition, once stable improvement had been achieved, the impact of GPi DBS on motor cortex plasticity was studied using TMS paired associative stimulation (PAS). The clinical study of these

patients confirmed the therapeutic efficacy of GPi DBS and provided direct evidence of the superiority of the posteroventral globus pallidus as the optimal target. The longitudinal studies of blink and H-reflex, showed progressive normalisation of brainstem and spinal excitability, which correlated with the time-course of clinical improvement. These data provide the first evidence of reversal of underlying dystonia pathophysiology by GPi DBS and are compatible with progressive long-term neural reorganisation (plasticity) playing a role in the mechanism of action of GPi DBS. Furthermore, the result of TMS PAS experiments demonstrated that GPi DBS reduces the short-term plasticity of the motor cortex, the magnitude of this effect also correlated with therapeutic effect. This result is compatible with the concept that excessive plasticity promotes dystonia and reversal of these abnormalities may be another mechanism by which GPi DBS acts. In conclusion, work presented in this thesis provides the first electrophysiological correlates of clinical improvement in dystonia after GPi DBS, which collectively supports the notion that both long and short-term plasticity within the central nervous system are involved in the mechanism of GPi DBS action.

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Abbreviations

AL	Ansa lenticularis
APB	Abductor pollicis brevis
BFM	Burke-Fahn-Marsden (dystonia rating scale)
CM-Pf	Centromedian-parafasicular nucleus of the thalamus
CT	Computer tomography
DBS	Deep brain stimulation
EEG	Electroencephalography
EMG	Electromyography
GPi	Globus pallidus internus
GPe	Globus pallidus externus
IPG	Implanted pulse generator
LF	Lenticular fasiculus
LML	Lateral medullary lamina
LTD	Long-term depression
LTP	Long-term potentiation
MEP	Motor evoked potential
MML	Medial medullary lamina
MRI	Magnetic resonance imaging
PAS	Paired associative stimulation
PET	Positron emission tomography
PGD	Primary generalised dystonia
PKAN	Pantothenate kinase associated neurodegeneration
RI	Reciprocal inhibition
SNr	Substantia nigra pars reticulata
SNc	Substantia nigra pars compacta
SRC	Stimulus response curve
STN	Subthalamic nucleus
TMS	Transcranial magnetic stimulation
VA	Ventral anterior nucleus
VL	Ventral lateral nucleus
Vim	Ventralis intermedius
Voa	Ventralis oralis anterior
Vop	Ventralis oralis posterior
VTA	Ventral tegmental area

Publications

The publications marked * are derived from work presented in this thesis. The remaining publications describe other collaborative work undertaken during the period of PhD study.

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Chapter 1. Introduction

1.1 Basal ganglia

The basal ganglia comprise the striatum (caudate nucleus and putamen), the globus pallidus (internus, GPi and externus, GPe), the subthalamic nucleus (STN) and the substantia nigra (reticulata, SNr and compacta, SNc). The striatum is the main input structure and receives afferents from the cortex, thalamus and also SNc. GPi and SNr are the main output structures and project mainly to the thalamus and the brainstem. The basic scheme of basal ganglia organisation is one of topographically maintained projections from cortex through the basal ganglia nuclei, thalamus and back to the cortex as parallel circuits, with additional output nodes to the brainstem.

1.1.1 Basic anatomy and neurotransmitters

1.1.1.1 Striatum

The striatum receives glutamatergic afferents from most areas of the cerebral cortex. These corticostriatal neurons synapse mainly with medium spiny neurons which are the main striatal efferent neurons. Within the striatum a sensorimotor, associative and limbic territory can be identified according to the cortical origin of the afferents (Alexander et al 1986, Alexander and Crutcher 1990, Parent & Hazard 1995a, Middleton & Strick 2000). The sensorimotor territory in the dorsolateral putamen and caudate receives projections from the primary motor cortex, the somatosensory cortex, premotor cortex and supplementary motor area. Primate recordings indicate that neurons in the sensorimotor territory respond to movement and electrical stimulation in these areas can cause movements (Alexander & DeLong 1985). Within the sensorimotor striatum (putamen) there is a somatotopic arrangement which respects the

body map of the cortical afferents, such that the leg is more dorsal and the trunk, arm and head more ventral (Crutcher & DeLong 1984, Flaherty & Graybiel 1991, Miyachi et al 2006). Recent work suggests that the sensorimotor striatum receives not only direct cortical afferents which terminate in the putamen but also collaterals of cortical afferents destined for brainstem targets (Parent & Parent 2006). The associative territory receives inputs from frontal areas, temporal, inferior parietal, preoccipital and parahippocampal cortex and comprises mostly the caudate nucleus and the rostral part of the putamen (Alexander et al 1986). The limbic territory receives projections from the limbic cortex, paralimbic cortex, amygdala and hippocampus and is located in the ventral part of the caudate and putamen, the nucleus accumbens and portions of the olfactory tubercle. The striatum receives dopaminergic afferents from the SNc and the VTA which play a critical neuromodulatory role in striatal function, as evidenced by the consequence of their loss in Parkinson's disease. The striatum receives glutamatergic afferents from the thalamus mainly the centromedian/parafascicular (CM-Pf) complex (Sadikot et al 1992). The portion of the CM-Pf that receives afferents mainly from the motor cortex and GPi, projects mainly to the putamen. The striatum also receives serotoninergic projections from the midline Raphe nuclei and noradrenergic projections from the locus ceruleus.

The majority of efferent neurons from the striatum are GABAergic medium spiny neurons (Smith et al 1987), which project mainly to GPe, GPi or SNr where they inhibit the neurons within these target structures (Chavalier & Deniau 1990). Efferents to the pallidum are mainly from the putamen and sensorimotor and those to the SNr are mainly from the caudate and associative (Parent & Hazrati 1995a).

1.1.1.2 Globus pallidus

The globus pallidus lies medial to the putamen and lateral to the internal capsule. It is divided into a smaller internal segment globus pallidus internus (GPi) and an external segment globus pallidus externus (GPe), the two segments separated by the medial medullary lamina (MML). The lateral medullary lamina (LML) separates GPe from the putamen. The GPi is further divided into lateral (GPi-l) and medial (GPi-m) portions by the accessory medullary lamina. The globus pallidus is also organised in parallel functional domains. The sensorimotor area of the pallidum receives mainly projections from the putamen. It is located in the ventrolateral two-thirds and posterior portion of the pallidum (Nauta & Mehler 1966, Parent et al 1984, Smith & Parent 1986, Hedreen & DeLong 1991). In the sensorimotor area, the same somatotopy as in the striatum is found with the leg being dorsal, the head ventral and the upper limb in-between (DeLong et al 1985, Hamada et al 1990; Hedreen & DeLong 1991). The associative territory receives afferents from the caudate nucleus, within GPe it is located at the level of the anterior commissure and dorsomedially within GPi (Nauta et al 1966, Parent et al 1984). The limbic area is in the ventral pallidum in the ventromedial part of GPi and GPe (Parent 1990). Most of pallidal afferents come from the striatum and are GABAergic and inhibitory. The entire globus pallidus receives glutamatergic excitatory input from the STN. There are GABAergic reciprocal connections between GPi and GPe (Hazrati et al 1990). In GPi, afferents from GPe and STN project to the same cells. The pallidum also receives dopaminergic afferents from SNc and serotoninergic afferents from the anterior VTA (Parent & Smith 1987). Both GPe and GPi receive afferent input from the thalamus, mainly CM-Pf nucleus and the pedunculopontine nucleus. Pallidal efferents are GABAergic and inhibitory upon their target structures. Efferents from GPe are mainly to STN and GPi/SNr (Hazrati et al 1990, Carpenter et al

1981a, Nauta & Mehler 1966). GPe efferents to STN complete the indirect pathway from the striatum to the pallidum. Efferents from GPi project to the thalamus, VA (pars principalis), VL (pars medialis) and CM-Pf (Hazrati & Parent 1991; Kim et al 1976). The efferents to VA, VL from GPi maintain the division of motor, associative and limbic information, project to the thalamus and from there to motor cortex, premotor cortex and SMA (Hoover & Strick 1993). The projection from GPi to CM-Pf and thence striatum provides a subcortical feedback loop between basal ganglia output and input structures. GPi also projects to pedunculopontine and lateral habenular nuclei. The major outflow tracts of efferent fibres from GPi are the lenticular fasiculus (LF) and the ansa lenticularis (AL) (Nauta & Mehler 1966). The LF and AL sweep medially to merge in Forel's field en route to the thalamus. The LF and AL were originally thought to derive from the GPi-m and GPi-l respectively (Kuo & Carpenter 1973, Kim et al 1976), however it is now clear that neurons from throughout GPi may contribute axons to the LF and AL (Parent & Parent 2004).

1.1.1.3 Substantia nigra reticulata

SNr is one of the major output structures of the basal ganglia. The main afferents to SNr come from the striatum, GPe and STN. SNr efferents are GABAergic and inhibitory and project to the VA and VL thalamic nuclei, (Kilpatrick et al. 1980; Ilinsky et al 1985; Carpenter et al 1976), mesopontine tegmentum, SNc, superior colliculus and pedunculopontine nucleus.

1.1.1.4 Subthalamic nucleus

The STN receives glutamatergic afferents from primary motor cortex, the somatosensory cortex, premotor cortex, prefrontal cortex and cingulum (Carpenter et al

1981b, Kunzle 1978, Kitai & Deniau 1981) as well as GABAergic afferents from GPe. There is also some glutamatergic afferents from the CM-Pf thalamic nuclei. The dorsolateral portion of the STN is the sensorimotor part (Wichmann & DeLong 1993) and constitutes 80% of the STN (Parent & Hazrati 1995b) and projects mainly to GPi. STN efferents are glutamatergic excitatory and project mainly to GPi, GPe and SNr (Carpenter et al 1981a,b, Nauta & Cole 1978).

1.1.1.5 Direct and indirect pathway

As noted above, the striatum receives massive cortical input, which is then processed and projected through the other basal ganglia structures. The arrangement of the striatal output is classically divided into the direct and indirect pathway (Albin et al 1989, DeLong 1990) Figure 1.1. The direct pathway projects from the striatum to the output nuclei of the basal ganglia, that is GPi and the SNr. The indirect pathway projects to GPi/SNr via the GPe and STN. The direct and indirect pathways are considered to produce opposing effects on the thalamic targets of basal ganglia outflow to respectively facilitate or suppress cortically initiated activity. Activation of the direct pathway between the putamen and GPi/SNr results in disinhibition of thalamic nuclei, which, in turn facilitate cortically initiated activity. In contrast, the net effect of activity in the indirect pathway from the subthalamic nucleus to the GPi/SNr via the external segment of the globus pallidus (GPe) is increased inhibition of thalamic targets and consequently reduced thalamic input to cortical areas. The direct and indirect pathway model has become widely accepted and provides a framework for understanding basal ganglia diseases such as Parkinson's disease, chorea and dystonia. According to this model in Parkinson's disease, loss of striatal dopamine leads to underactivity of the direct and overactivity of the indirect pathways resulting in overactivity of STN and

GPi, which results in excessive thalamic inhibition and defacilitation of cortical motor areas. In hyperkinetic movement disorders such as chorea and dystonia, converse abnormalities of direct and indirect pathway activity result in underactivity of GPi/SNr and excessive facilitation of motor cortical areas. The direct/indirect pathway model, while providing a conceptual framework, has major limitations, perhaps best illustrated by the paradox that GPi lesions are beneficial for both Parkinson's disease and dystonia (Marsden & Obeso 1994). This led Marsden and Obeso to propose a major refinement of the model, namely that the pattern rather than the rate of activity within basal ganglia structures carries the information signal for both normal function and characterisation of disease states. This concept has found accumulating support from experimental data as will be reviewed in the next section.

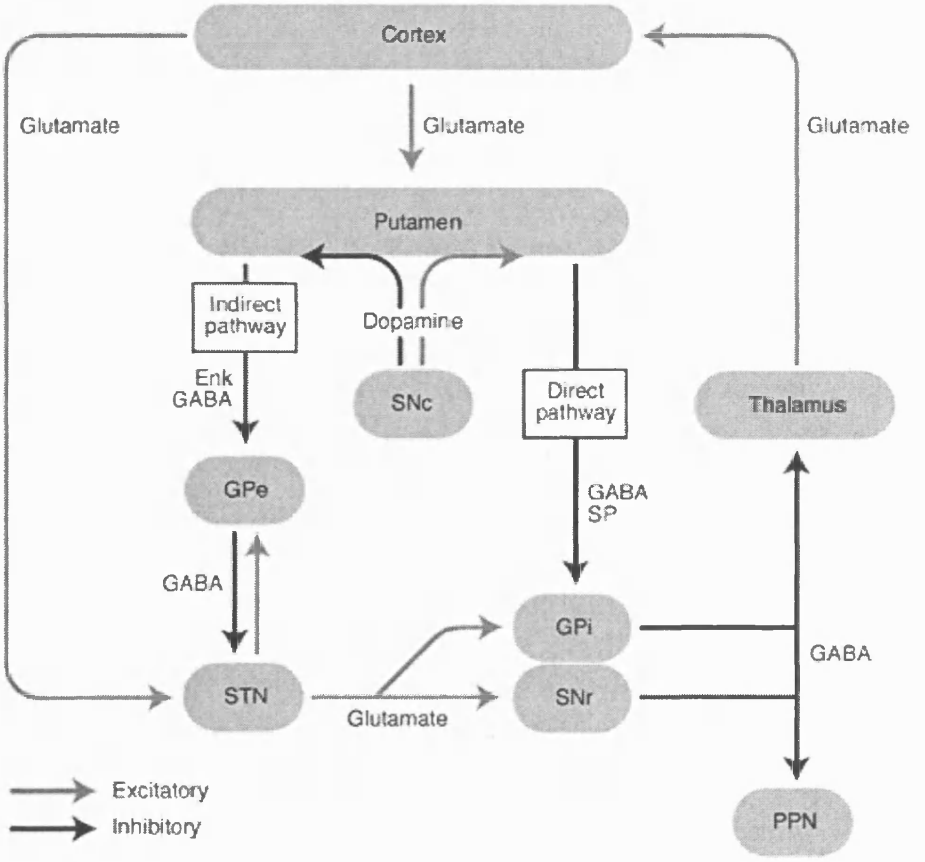


Figure 1.1 Schematic diagram of direct and indirect pathways within the basal ganglia. (Adapted from Lewis et al 2003)

1.1.2 Physiology

The basic role of the basal ganglia in the control of normal movement can be summarised as a secondary processing network which takes cortical information of various types, integrates some of it, and then delivers temporally and topographically encoded output to assist cortical motor areas in controlling the movement within the prevailing sensory, experiential and motivational context. This view of basal ganglia function is derived from the known anatomical connections and experimental observations of basal ganglia activity and effects of basal ganglia lesions in awake performing monkeys and human subjects undergoing stereotactic interventions on the basal ganglia. This section will focus on these data and attempt to bridge them with putative derangements of basal ganglia function underlying dystonia.

1.1.2.1 Effects of basal ganglia lesions

Unilateral lesions of the sensorimotor GPi/GPe result in slowing of contralateral limb movement without altering the reaction time or sequence of specific muscles activated (Hore & Vilis 1980, Horak & Anderson 1984, Mink & Thach 1991a). Cocontraction of agonists and antagonist muscles, tonic postural changes across a joint, often with a flexor predominance, and degradation of the quality of movement also occur (Mink & Thach 1991a, Kato & Kimura 1992, Inase et al 1995). Inase et al (1995) showed that postural drifts at joints following GPi lesions are active and related to overactivity of the agonist muscle, which the animal could correct for when visually reminded of the target. Furthermore, the postural perturbations were associated with corresponding increases in VA/VL thalamic neuronal activity, suggesting their origin to be disinhibition of thalamocortical activity as consequence of the GPi lesion. Collectively, these data suggest that basal ganglia output is involved in scaling the magnitude of

motor drive for an intended movement without necessarily dictating the overall pattern of muscles employed or the initial command to move. Furthermore, they suggest that the globus pallidus is involved in postural stability of limb movements. The fact that even after pallidal lesions, movements can be executed correctly, albeit more slowly, particularly if visual cues are provided, illustrates the relative redundancy of the basal ganglia and the ability of other motor areas to compensate. It is tempting to extrapolate from these animal studies to dystonia where cocontraction, abnormal postures and slowness of movement are often found. Not surprisingly, pallidal lesions in humans may result in contralateral hemidystonia after a variable latency (Bhatia & Marsden 1994). Overall, these observations support the view that dystonia is a basal ganglia disorder, in which abnormal basal ganglia output plays an important role.

1.1.2.2 Basal ganglia activity during movement

Recordings of neuronal activity from GPe/GPi in awake monkeys have shown topographically restricted zones of neurons, which display changes in firing rate corresponding to passive movements and active movements of a joint. (Delong 1971, Georgopoulos et al 1983, Anderson & Horak 1985, Hamada et al 1990, Mink & Thach 1991b, Turner & Anderson 1997). Typically, these changes represent an increase in firing rate above the background level of high frequency tonic activity, or in some circumstances, a decrease. The modulation of pallidal neuronal activity depends on the direction, amplitude or velocity of limb movements (Iansek & Porter 1980, Georgopoulos et al 1983, Mitchell et al 1987, Hamada et al 1990, Mink & Thach 1991b, Turner & Anderson 1997). Studies using limb loading to dissociate the effects of direction and pattern of muscle use have identified subpopulations of putamenal and pallidal neurons responding to movement direction or pattern of muscle use but usually

not both (Crutcher and Alexander 1990, Mitchell et al 1987), suggesting the existence of subchannels within the motor circuit, processing different aspects of the movement (Alexander & Crutcher 1990). Individual pallidal neurons respond to a variety of types of movement (Mink & Thach 1991b) which suggests that the basal ganglia operate flexibly using a similar process under a wide range of movement parameters. The neuronal activity in basal ganglia nuclei depends not only on the kinematic properties of the movement but also on the level of familiarity with the task, whether it is spontaneous or cued and the level of reward, in other words, its behavioural context (Brotchie et al 1991a, Gdowski et al 2001, Samejima et al 2005, Turner & Anderson 2005). Temporally, changes in pallidal neuronal activity tend to occur after the onset of EMG activity in the agonist muscle (Anderson & Horak 1985, Mink & Thach 1991c, Brotchie et al 1991b, Turner & Anderson 1997), which indicates that the basal ganglia are not responsible for movement initiation. Instead, they appear to be involved in scaling the amplitude of corticomotor output during movement (Anderson & Horak 1985, Turner & Anderson 1997). This temporal sequence is in agreement with recordings from primary and supplementary motor cortex and striatum during visually cued movements, which show that cortical neuronal discharge usually occurs before that in the putamen, suggesting motor initiation begins in the cortex (Alexander & Crutcher 1990). While there does appear to be some evidence that the basal ganglia are involved in on-line modulation of movement, particularly with respect to scaling of amplitude, this may not be their main function. The timing of movement-related changes in GPi neuronal activity and the fact that they are usually an increase in firing rate (which should inhibit ongoing thalamocortical activity) have led to alternative views that the basal ganglia are more concerned with termination of movements (Brotchie et al 1991b) or the selective inhibition of unwanted competing motor activity

(Mink 1996). This latter concept of surround inhibition is an attractive model for conceptualising the possible derangement of basal ganglia function in dystonia where motor overflow and cocontraction might result from inefficient selective inhibition of competing motorneuronal pools.

Control of saccadic eye movement fits better with the basal ganglia model based on disinhibition of output targets. Saccadic eye movements are associated with a transient reduction in SNr output to the superior colliculus, which is disinhibited, allowing a saccade to be generated (Hikosaka & Wurtz 1983). A refinement to the disinhibition model in the motor circuit, which helps explain why the pallidum tends to become more active with movement, has been put forward, based on the cortico-subthalamo-pallidal pathway which provides a rapid route of GPi excitation (Nambu et al 2000, Nambu et al 2002). Under this model, cortically generated motor commands are initially sent via STN to GPi, resulting in thalamocortical inhibition of the desired and competing motor programs, the same signal arrives later via the putameno-pallidal route releasing the desired motor program, Figure 1.2. Action selection by these mechanisms is behaviourally contextualised by the basal ganglia so that movement achieves environmentally dictated objectives. There is accumulating evidence that the basal ganglia play an important role in motor learning which is dependent on dopamine (Kermadi & Joseph 2005, Matsumoto et al 1999). Basal ganglia activity appears to encode the probability of reward associated with a particular action, weighting action selection at the cortical level in accordance with experience (learning) and expectation (Doya et al 2000, Samejima et al 2007). There is evidence that in the primate premotor cortex, several motor programs for alternative actions are prepared in parallel, then biasing occurs to facilitate the desired action (Cisek et al 2005). This arrangement, although computationally wasteful, has the advantage of speed, but relies on intact

basal ganglia instruction to selectively suppress and facilitate the competing motor programs. At the neuronal level, these processes are thought to involve corticostriatal synaptic plasticity, which is critically modulated by dopamine (Calabresi et al 2007, Costa 2007).

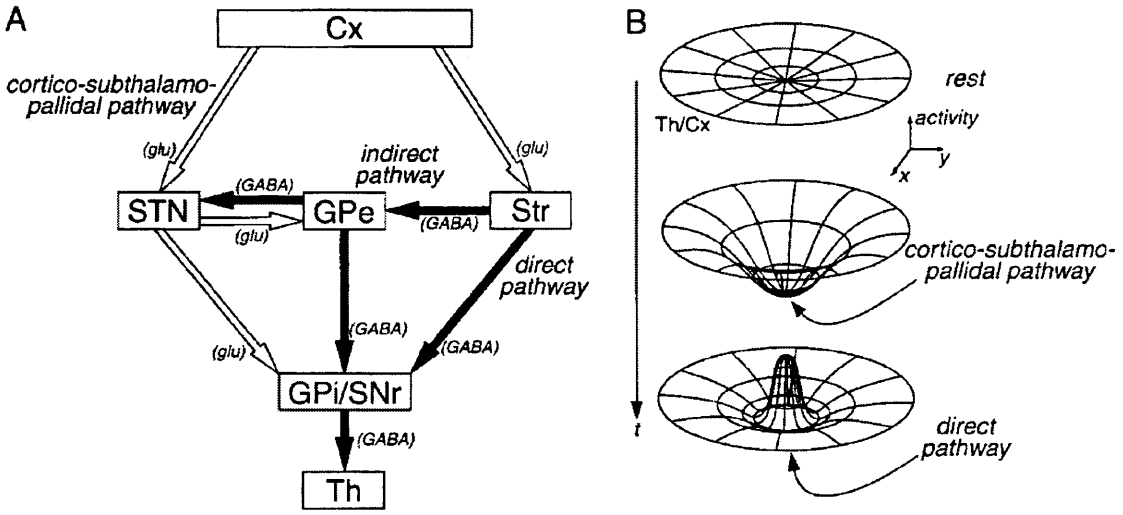


Figure 1.2 Modified schema for basal ganglia circuitry incorporating the corticosubthalamopallidal pathway, which primes voluntary movement by effecting surround inhibition, then followed by centre activation of intended movements via the direct corticostriatopallidal route (From Nambu et al 2002).

1.1.2.3 Oscillatory activity as an information signal in the basal ganglia

There is accumulating evidence that oscillatory activity within cortical-basal ganglia networks serves to bind functionally connected ensembles of neurons to coordinate their activity both temporally and spatially. These models have obvious advantages over simple wiring models of basal ganglia connectivity where interactions are either

positive or negative, since they can incorporate not only the rate but patterns of neuronal firing as an information signal.

In the resting state, most studies have shown basal ganglia neurons fire in an independent and predominantly non-oscillatory manner (Bergman et al 1998, Raz et al 2000). Correlation studies using dual microelectrodes have found very little correlation between pallidal neurons in the normal monkey at rest (Bergman et al 1998). More recently, studies using local field potential recording from multiple sites in the putamen of awake, performing monkeys have demonstrated that significant synchronous oscillations in the beta band occur across wide regions of the putamen (Courtemanche et al 2003). As in previous studies very few putamenal neurons fired rhythmically, however, for many their firing was phased-locked to the LFP. Furthermore these synchronous oscillations were focally attenuated during saccades raising the possibility that such desynchronisations represent a mechanism for selective recruitment of task-related neuronal subpopulations.

Brown et al (2002) identified that amplitude of beta oscillations recorded from the GPi in patients with Parkinson's disease or dystonia during a hand movement task correlated with the eventual movement duration suggesting the strength of oscillations may carry some information signal, particularly with respect to the timing of movements (Brown et al 2002). Similarly LFPs recorded from human STN during a go/no-go movement task show pre-movement beta desynchronisation, the latency of which correlates strongly with reaction time and which is attenuated in the no-go trials (Kuhn et al 2004). This suggests the level of oscillatory activity within basal ganglia nuclei might encode some parameters of movement preparation and execution. LFP oscillations in the gamma band are absent in the untreated Parkinsonian state, but coupling of LFPs at these frequencies exists between GPi and STN, and these structures and cortex,

especially SMA after Parkinsonian subjects are treated with levodopa. These changes occur before and during movement, suggesting that in the presence of a normal dopaminergic drive elements within the pallidum, STN and cortex form a dynamic functional network resonating in the high gamma band (Brown 2003). Phase relationships indicate activity in GPi and STN leads the cortex in this frequency band suggesting that the normal basal ganglia may play a specific role in desynchronising low frequency idling cortical rhythms, thereby allowing temporal binding of distributed cortical elements into a functional ensemble in the gamma band.

The probable role of oscillations as an information signal in normal basal ganglia is underscored by the fact that diseases such as Parkinson's disease and dystonia are associated with characteristic patterns of abnormal, often excessively synchronised, oscillatory activity (Brown 2003, Gatev et al 2006). The role of abnormal oscillatory activity in the pathogenesis of dystonia is further discussed in the Pathophysiology section 1.2.4.3.

1.2 Dystonia

1.2.1 Classification and clinical features

1.2.1.1 Clinical features

Dystonia is an involuntary movement disorder, characterised by muscle contractions resulting in spasms, twisting repetitive movements and abnormal postures (Fahn et al 1998). Its clinical expression is diverse, ranging from static hypertonia with fixed postures to phasic spasms, tremor or myoclonic jerks, but some component of sustained contraction is a consistent feature. The contractions are not random, rather they usually exhibit directional preponderance leading to a particular posture. A characteristic feature is cocontraction of muscles with opposing actions across a joint. Sustained

hypertonic postures may eventually lead to joint contractures and orthopaedic deformity. Another important general feature of dystonia is its modulation of expression by action; dystonia is usually made worse by voluntary movement and some forms of focal dystonia only occur during specific tasks, such as writing. Particular actions may temporarily alleviate dystonia, so called geste antagoniste or sensory tricks, examples include touching the chin or back of the head to lessen spasmodic torticollis or walking backwards with improvement of gait in generalised dystonia. The fact that dystonia may be so intimately linked to specific actions reflects its status as a higher order movement disorder, which may selectively involve execution of specific motor programs.

1.2.1.2 Classification by distribution of involvement

Dystonia may involve part or all of the body, allowing a system of classification by affected body region (Fahn et al 1998, Geyer & Bressman 2006). In focal dystonia, one discrete body region is affected (e.g. blepharospasm, writers cramp). In segmental dystonia, two or more adjacent body regions are affected (e.g. cervical and upper limb dystonia). Multifocal involves two or more non-contiguous body segments (e.g. blepharospasm and upper limb). Generalised dystonia must involve one or both legs, the trunk and at least one other body part. Hemidystonia involves just one side of the body and is frequently associated with a focal structural lesion in the contralateral basal ganglia or thalamus.

1.2.1.3 Classification by age of onset

Dystonia may also be classified on the basis of age of onset: childhood onset (0-12 years), adolescent onset (12-20 years) and adult onset (>20 years). Alternative

classifications have proposed division into early (<26 years) or late onset (>26 years) (Bressman 2004). The important distinction in this classification is that childhood or adolescent onset imparts a much higher risk that the dystonia will spread to other body regions and become generalised. Conversely adult onset dystonia is usually focal and while it may progress to segmental distribution, rarely spreads to become generalised (Marsden et al 1976, Greene et al 1995).

1.2.1.4 Classification by aetiology

Classification by aetiology has the advantage of conferring diagnostic and prognostic specificity, but because dystonia may present variably even within aetiological categories, additional classification by distribution and age of onset remains important. The main division in the aetiological classification is between primary and secondary dystonia (Fahn et al 1998). In primary dystonia, also referred to as idiopathic torsion dystonia, the clinical features must be purely dystonia, which may include tremor, and the brain must be structurally normal. Secondary dystonia results from acquired structural lesions of the brain or as a consequence of drugs (e.g. tardive dystonia). Further subgroups include dystonia-plus syndromes, in which features other than pure dystonia are present, but in other respects the picture is similar to primary dystonia in that the brain is structurally normal (eg. myoclonic dystonia and dopa-responsive dystonia). Heredodegenerative dystonia comprises disorders which result in brain degeneration, often with clinical features additional to dystonia such as spasticity, parkinsonism, oculomotor abnormalities and include conditions such as pantothenate kinase associated neurodegeneration (PKAN) and Wilson's disease. Developments in molecular genetics have greatly advanced the aetiological classification of dystonia and

the genes responsible for various forms of primary, dystonia-plus and heredodegenerative dystonia have now been identified (Nemeth 2002).

1.2.2 Aetiology and epidemiology

1.2.2.1 Primary dystonia

Early onset primary dystonia typically begins in middle to late childhood starting in the arm or leg and usually progresses to become generalised within 5 years. When familial, the usual pattern of inheritance is autosomal dominant with incomplete penetrance. The most common genetic abnormality identified in young onset primary generalised dystonia is the DYT1 mutation, a GAG deletion of the Torsin A gene on chromosome 9 (Ozelius et al 1997, Bressman et al 2000). The clinical spectrum of DYT1 dystonia is broad and ranges from profound disability in childhood to mildly affected adults and about 70% of individuals with the DYT1 mutation are asymptomatic. Rarely, DYT1 may present as late onset dystonia (Edwards et al 2003a). The prevalence estimates of primary generalised dystonia range from 0.3/100,000 to 5/100,000 (Duffey et al 1998, Castelon-Konkiewitz et al 2002, Defazio et al 2004, Asgeirsson et al 2006). In late onset primary dystonia, the DYT 7 locus has been identified in one family with mainly cervical dystonia. Other loci include DYT6 (Almasy et al 1997) and DYT13 (Bentivoglio et al 1997), which both display mixed early or late onset, with mainly craniocervical and sometimes generalised dystonia. These latter entities describe only a few families, the causative genes are unknown and other phenotypically similar families have been found to lack these loci (Jarman et al 1999), suggesting genetic heterogeneity.

1.2.2.2 Secondary dystonia

Secondary dystonia can be defined as dystonia arising from an environmental insult to the brain such as trauma, infections, vascular lesions or drugs. Focal structural lesions of the basal ganglia, particularly the globus pallidus and putamen, or thalamus may result in contralateral focal or hemidystonia (Marsden et al 1985, Bhatia & Marsden 1994, Chuang et al 2002). Among the secondary generalised dystonias, those due to perinatal hypoxic ischaemic cerebral injury form a large group and may be associated with multifocal cerebral lesions or more selective bilateral involvement of the basal ganglia that with MRI imaging may appear as increased signal in the putamen or pallidum. Typically the onset of dystonia is delayed by a variable period up to many years after the occurrence of the structural brain lesion with longer delay if the lesion occurs in early childhood (Pettigrew et al 1985, Scott & Jankovic 1996, Chuang et al 2002). Secondary dystonia differs from primary dystonia in its clinical appearance in that it is more often present at rest, tends to be tonic or athetoid rather than jerky and is rarely accompanied by a sensory trick (Svetel et al 2004). Tardive dystonia occurs secondary to exposure to centrally acting dopamine receptor antagonists, typically neuroleptic drugs used to treat psychiatric disorder (Burke et al 1982). It may follow relatively short exposure to dopamine antagonists, the distribution is often axial with cervical involvement, and retrocollis and truncal hyperextension are frequently present. In some patients classical orobuccal tardive dyskinesias coexist with dystonia (Kang et al 1988).

The heredodegenerative dystonias, although not strictly secondary, since many are now recognised to be on a genetic basis, can be considered together since they often display distinctive neurodegenerative basal ganglia lesions, and have significant clinical overlap with the secondary dystonias. Of these disorders, pantothenate kinase

associated neurodegeneration (PKAN) is of relevance to the present work. PKAN, formerly known as Hallervorden-Spatz syndrome, is a rare autosomal recessive condition, which usually presents in childhood with progressive generalised dystonia, often affecting orobulbar regions and subsequent cognitive impairment. Later onset milder forms of the disease are recognised (Thomas et al 2004, Hayflick et al 2003). The gene responsible is PANK2 on chromosome 20 and encodes pantothenate kinase (Taylor et al 1996, Zhou et al 2001), and multiple different causative mutations of this gene have been identified (Hayflick et al 2003). The characteristic histopathological feature is deposition of iron in the globus pallidus and substantia nigra (Halliday 1995). T2 weighted MRI appears as bilateral pallidal hyperintensity with surrounding hypointensity, the so called "eye of the tiger", present in most patients with PANK2 mutations (Hayflick et al 2003, Hartig et al 2006).

1.2.2.3 Dystonia-plus syndromes

This group of disorders includes dopa-responsive dystonia (DYT 5), the paroxysmal dystonias (DYT 8, 9, 10) and rapid onset dystonia-Parkinsonism (DYT12). Myoclonus dystonia (DYT 11) usually presents in early childhood with myoclonic jerks and dystonia involving predominantly the upper body, the symptoms may be alcohol responsive (Quinn et al 1996). This condition is often familial with an autosomal dominant pattern of inheritance with incomplete penetrance. Mutations of the epsilon sarcoglycan gene on chromosome 7 have been identified as the cause in most of the affected families (Zimprich et al 2001, Asmus et al 2002).

1.2.3 Therapy

1.2.3.1 Medical therapy

The medical treatment of dystonia can be divided into the following general categories: systemic medications, botulinum toxin injection therapy, intrathecal baclofen and physical therapies. In this section the pharmacological therapies will be reviewed with an emphasis on the treatment of generalised dystonia.

Anticholinergic medications are the most effective class of drug for primary dystonia, including generalised and segmental (Fahn 1983, Burke et al 1986). Secondary dystonia responds less well (Lang 1986). In some patients, an initially favourable response is not sustained. The most widely used drug is Trihexphenidyl, and large doses, up to 100 mg per day, may be required, which is usually well tolerated in younger patients although cognitive side-effects are common (Taylor et al 1991). Baclofen is beneficial in some patients with generalised and segmental dystonia (Greene and Fahn 1992). Intrathecal baclofen is useful in severe generalised dystonia, particularly where there is associated spasticity (Ford et al 1996, Albright et al 2001). Dopamine replacement therapies, principally Levodopa, have a crucial role in the diagnosis and treatment of dopa-responsive dystonia (DYT 5) and is effective in low doses (Segawa et al 1976). Levodopa is also sometimes beneficial in primary generalised or segmental dystonia, although there is no trial data to support this. Paradoxically dopamine antagonists or depleting agents are sometimes beneficial (Lang 1988). Tetrabenazine is the most effective, particularly for tardive dystonia, and has the advantage that it does not induce tardive dyskinesia/dystonia although it may cause Parkinsonism or depression (Jankovic 1982, Jankovic 1997). Benzodiazepines are modestly beneficial in some patients for both focal and generalised dystonias, although there are no studies to support their use.

Botulinum toxin injections are the most effective treatment for locoregional dystonic syndromes, particularly cervical, cranial, laryngeal and limb dystonia (Jankovic et al 2004). The majority of patients achieve long term improvement by repeated injections (Hsiung et al 2002). EMG guidance of injection can improve the efficacy of treatment in some circumstances. Neutralising antibodies have been described to both BTX-A and B, and may cause secondary therapy failure (Jankovic et al 1995, Berman et al 2005). For generalised dystonia, BTX is often a useful adjuvant treatment for particular regions such as the neck or larynx.

1.2.3.2 Functional neurosurgery

1.2.3.2.1 Ablative procedures

The advent of human stereotactic surgery with Spiegel and Wycis in 1947 paved the way for the development of functional neurosurgery for dystonia. The initial attempts to treat dystonia with functional neurosurgical intervention involved ablative lesions in the pallidum (Cooper 1956, Guiot & Brion 1952, Hassler 1960) and thalamus. Cooper achieved good results with unilateral and staged bilateral thalamotomy for generalised dystonia in about a quarter of his large series, some with dramatic sustained improvement (Cooper 1976). This experience popularised thalamotomy and it became the most widely performed operation for dystonia. Andrew et al (1983) reported results of thalamotomy in a series of 55 patients with dystonia; the benefit in generalised dystonia was less than that reported by Cooper, and more than half the patients developed dysarthria when thalamotomy was performed bilaterally. Secondary hemidystonia responded well to unilateral thalamotomy, with a low risk of speech complications leading Andrew to consider it a good indication. Renewed interest in pallidotomy for dystonia occurred after the reintroduction of Leksell's posteroventral

pallidotomy for Parkinson's disease by Laitinen (Laitinen et al 1992). The observation of marked improvement of Levodopa-induced dyskinesias and dystonia in Parkinson's disease patients following pallidotomy (Laitinen 1992, Lozano 1995) led to some reports of bilateral posteroventral pallidotomy for generalised dystonia (Iacono et al 1996, Lozano et al 1997, Ondo et al 1998, Lin et al 1999). In these case reports and small series, favourable results were achieved in the majority of patients, particularly those with primary dystonia, with lesser improvement in patients with secondary dystonia (Lin et al 1999). Combining the larger studies of Ondo and Lin, of the 23 patients with generalised dystonia (19 secondary) who underwent simultaneous bilateral pallidotomy, none was reported to have dysarthria as a consequence of surgery. In fact, an overall improvement in speech was reported in these patients. From these studies bilateral posteroventral pallidotomy appears to be an effective and relatively safe treatment for generalised dystonia particularly when primary in aetiology. However, pallidotomy is now rarely performed for dystonia, and has been largely superseded by GPi DBS which is considered safer and more reversible than a permanent lesion. Thalamotomy when performed bilaterally is associated with excessive complications, particularly dysarthia, however unilateral thalamotomy may retain a role, including the successful treatment of focal musician's dystonia (Taira et al 2003).

1.2.3.2.2 Thalamic DBS

Since the 1950's, it had been observed that high frequency stimulation (>50Hz) of brain targets such as the motor thalamus could lead to suppression of tremor, similar to that achieved by a thermal lesion, but in a reversible fashion (Walker 1982, Speelman 1991). Thus high frequency stimulation became an important tool to test the

effectiveness of brain targets prior to making a permanent lesion. These observations led to the use of chronic high frequency DBS for movement disorders and pain. Cooper et al (1982), reported results of DBS for various movement disorders including 8 patients with dystonia treated with DBS targeting the ventrolateral thalamus unilaterally or bilaterally; the best response was in the patients with cervical dystonia but the benefit was modest. Benabid and colleagues in Grenoble pioneered the practical use of chronic deep brain stimulation initially in the motor thalamus for tremor (Benabid et al 1987, 1991), but also dystonia (Vercueil et al 2001). They reported 8 secondary and 4 primary dystonia patients, all but one generalised who underwent either unilateral or bilateral DBS targeting the Vim nucleus of the thalamus. In these patients, tremor, when present, improved and in about half, the patients' global functioning scores improved, and in the 7 patients in whom motor dystonia scores were recorded, 4 benefited by about 25%, the others showed no improvement. In one of these patients with primary generalised dystonia who failed to respond to bilateral thalamic DBS, subsequent bilateral GPi DBS led to 67% improvement in motor scores. Similarly, Trottenberg et al (2001) reported a patient with tardive dystonia who failed to improve with bilateral Vim thalamic DBS but improved by 73% on BFM score with bilateral GPi DBS. This contrasts with the report of Ghika et al (2002), who reported very good improvement in severe secondary generalised dystonia following bilateral Voa DBS despite previous failed GPi DBS. There is limited experience with thalamic DBS for dystonia, but from the available studies it can be concluded that it might offer some therapeutic possibilities, but its precise role remains undefined.

1.2.3.2.3 STN DBS

STN DBS has been tried in a few patients with dystonia. The Grenoble group reported 4 patients with generalised dystonia, 3 with PKAN, and 1 late onset primary who underwent bilateral STN DBS (Detante et al 2004a). There was no improvement in dystonia with STN DBS either with chronic stimulation or by comparison of the ON and OFF stimulation condition. The authors concluded that STN DBS is not useful for dystonia, in sharp contrast to its marked benefits for OFF period dystonia in Parkinson's disease (Krack et al 1999).

1.2.3.2.4 GPi DBS

The growing acceptance of the pallidal target in dystonia and acceptance of DBS as an alternative to ablative lesions led Coubes in 1996 to first use GPi DBS in a young girl with life-threatening DYT1 negative primary generalised dystonia, with marked improvement (Coubes et al 1999). Subsequently, several groups reported favourable results with bilateral pallidal DBS for generalised dystonia in children and adults (Coubes et al 2000, Tronnier & Fogel 2000, Vercueil et al 2001, Bereznai et al 2002, Cif et al 2003, Katayama et al 2003, Yianni et al 2003, Krauss et al 2004, Krause et al 2004, Coubes et al 2004, Starr et al 2004). More recently, two larger prospective blinded studies have confirmed the beneficial effects found in small series for primary generalised and segmental dystonia (Vidailhet et al 2005, Kupsch et al 2006). A consistent feature among these studies is that improvement in dystonia after GPi DBS is not immediate but progressive over weeks to months which has led some authors to speculate that brain plasticity may underly the therapeutic effect (Bereznai et al 2002, Yianni et al 2003, Vidailhet et al 2005). To date, however, physiological evidence for neural plasticity has been lacking. It should be noted that progressive improvement in

dystonia was also noted after pallidotomy (Lozano et al 1997), suggesting that it may be more a property of dystonia than GPi DBS per se.

1.2.4 Pathophysiology of dystonia

The pathophysiology of dystonia is characterised by a range of abnormalities involving both motor and sensory systems. These abnormalities have been identified largely through electrophysiological and imaging studies in dystonia patients. Owing to the technical challenges posed by performing these types of studies in patients with severe dystonia, much of the available information in this area has been gleaned from patients with focal dystonia who are easier to study. Some studies, however, are available in generalised dystonia, which show a similar range of abnormalities. An important theme which emerges in dystonia pathophysiology is that abnormalities may be found in parts of the nervous system subserving body regions unaffected by dystonia, or even in non-manifesting carriers of the DYT1 mutation (Edwards et al 2003b). The recognition that the physiological hallmarks of dystonia may be present without overt clinical dystonia has led to the concept of endophenotypic abnormalities (Meunier et al 2001). In other words, patients with dystonia express a pathophysiological substrate, which may be genetic, and under appropriate environmental influence may lead to the development of clinical dystonia. This general model can be further adapted to incorporate newer information concerning the role of plasticity.

1.2.4.1 The role of defective inhibition

The pathophysiology of dystonia is characterised by abnormally reduced excitability of inhibitory connections within the brain and spinal cord. The finding of reduced inhibition within brainstem blink reflex (Berardelli et al 1985) and spinal H-reflex

circuits (Nakashima et al 1989) were the first to be identified and provided some of the early evidence of organic dysfunction in dystonia, which helped establish it as an organic rather than psychological condition. Like other abnormalities, defective inhibition may be dissociated from clinical symptoms (Chen R et al 1995, Deuschl et al 1992), and can be considered part of the dystonia endophenotype.

1.2.4.1.1 Motor cortex

In patients with focal dystonia, transcranial magnetic stimulation (TMS) studies have shown abnormally reduced short latency intracortical inhibition in the motor cortex (Ridding et al 1995). Similar reductions in intracortical inhibition have been demonstrated in patients with segmental and generalised forms of dystonia due to DYT1 (Edwards et al 2003b). In addition to reductions of intracortical inhibition at rest, patients with focal hand dystonia have abnormally reduced motor cortex inhibition preceding (Gilio et al 2003) and during voluntary movement (Chen R et al 1997a), particularly during tasks requiring selective finger movement (Stinear & Byblow 2004, Bütefisch et al 2005). Another related abnormality found in patients with focal hand dystonia is abnormally increased recruitment of cortical motorneurons with action (Ikoma et al 1996). Defective inhibition, at the level of the motor cortex, could contribute to dystonia by interfering with normal motor selection and suppression of unwanted movements (Mink et al 1996, Hallet 2004).

1.2.4.1.2 Blink reflex disinhibition and involved circuits

The blink reflex excitability is abnormally increased in patients with cranial (Berardelli et al 1985), cervical (Tolosa et al 1988), segmental and generalised dystonia (Nakashima et al 1990). Therefore disinhibition of brainstem blink reflex circuits is a

general feature of dystonia, often in patients without blepharospasm (Nakashima et al 1990). The blink reflex of orbicularis oculi in response to electrical stimulation of the supraorbital nerve has two components. The early R1 response is seen unilateral to stimulation and is mediated by an oligosynaptic pathway involving first division trigeminal afferents relaying via interneurons near the trigeminal sensory nucleus and then motorneurons of the facial nucleus. The later R2 response is bilateral, of longer duration and is mediated via a polysynaptic pathway involving the descending trigeminal spinal tract, caudal spinal nucleus and medullary reticular formation to project bilaterally to facial motorneurons (Aramideh et al 2002). The human blink reflex R2 component displays the property of paired pulse inhibition. Excitability of these circuits is usually measured by delivering paired stimuli and examining the degree of inhibition of the second R2 response with respect to the first (Kimura & Harada 1976). Paired pulse R2 inhibition is mediated by local inhibitory interneurons and reduced in animals treated with systemic GABA antagonists, suggesting the inhibition is mainly GABAergic (Pellegrini & Evinger 1995). The local interneuronal networks in turn receive descending modulation from basal ganglia and cortex (Esteban 1999). Basal ganglia influence on the blink reflex may involve GPi, thalamus and cortex, in turn projecting to the brainstem (Berardelli et al 1983). More recently, animal studies have shown that 6-hydroxydopamine lesions of the SNc result in blink reflex R2 disinhibition through a nigro-collicular projection via the nucleus raphe magnus (Basso et al 1996, Schicatano et al 1997). The anatomical connections permit basal ganglia influence on brainstem blink reflex circuits via both major basal ganglia output channels, the GPi or SNr. Therefore, blink reflex excitability provides a subcortical measure of changes in basal ganglia output of relevance to the study of dystonia and effects of GPi DBS.

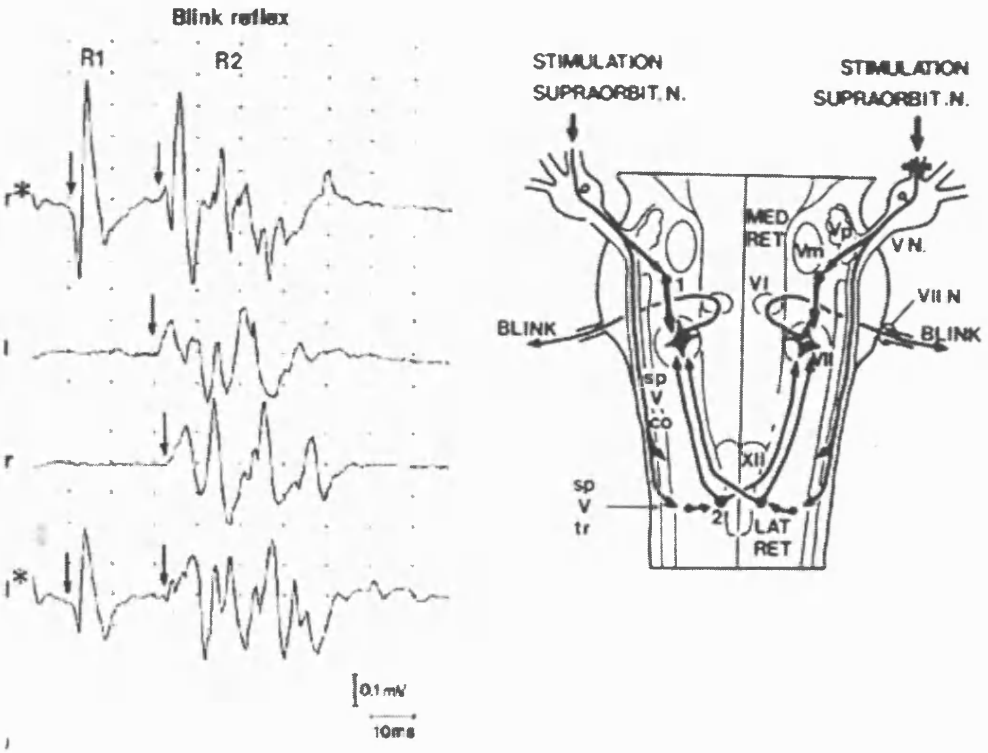


Figure 1.3. (a) The normal human blink reflex showing R1 and R2 components. Note the R1 response is unilateral to the stimulated side (*) whereas the R2 response is bilateral. (b) Shows the brainstem circuits mediating the R1 and R2 component. (From Aramideh et al 2002)

1.2.4.1.3 Abnormalities of spinal reciprocal inhibition and involved circuits

At the spinal cord level, reduced reciprocal inhibition (RI) between forearm flexor and extensor muscles has been demonstrated in patients with focal and generalised dystonia (Nakashima et al 1989, Panizza et al 1989, 1990). It is unclear whether these abnormalities contribute to dystonia because abnormally reduced RI has been found in the asymptomatic contralateral arm in writer's cramp patients (Chen R et al 1995) and in patients with spasmodic torticollis without limb dystonia (Deuschl et al 1992). Botulinum toxin therapy has been shown to reverse reductions in reciprocal inhibition in patients with dystonia involving the arm (Priori et al 1995); however, this effect is unlikely to be due to relief of dystonia, rather an effect on intrafusal fibres and Ia

afferent feedback. Spinal reciprocal inhibition is usually measured by recording H-reflex in the flexor carpi radialis with low intensity preceding stimuli delivered to the radial nerve. Three phases of reciprocal inhibition are identified. The first is maximal for ISI=0ms and is mediated by Ia afferents of the antagonist muscle spindles, which inhibit alpha motor neurons of the agonist via Ia inhibitory interneurons in a disynaptic pathway (Day et al 1984). The second phase which is maximal with ISI 10-20 ms is mediated by presynaptic inhibition of agonist Ia afferents by type I afferents of antagonist muscles (Berardelli et al 1987). The third phase is observed with ISIs of 75 to 500 milliseconds and is physiologically less well understood, but may represent continued presynaptic inhibition (Berardelii et al 1987). The Ia inhibitory interneurons, which are located in the intermediate spinal grey matter are central to the control of reciprocal inhibition and their excitability is influenced by a variety of inputs. This arrangement confers on spinal reciprocal inhibition circuits a degree of local autonomy but their behaviour is under constant descending influence of projections from the cortex and basal ganglia. These projections include the reticulospinal, rubrospinal, vestibulospinal and corticospinal tracts, which modulate excitability of both Ia inhibitory interneurons (Hultborn 1976) and interneurons involved in presynaptic Ia inhibition (Baldisera et al 1981). Reduced reciprocal inhibition in dystonia is therefore likely to be a downstream effect of abnormal descending influence on spinal circuitry as a result of disordered basal ganglia output (Nakashima et al 1989).

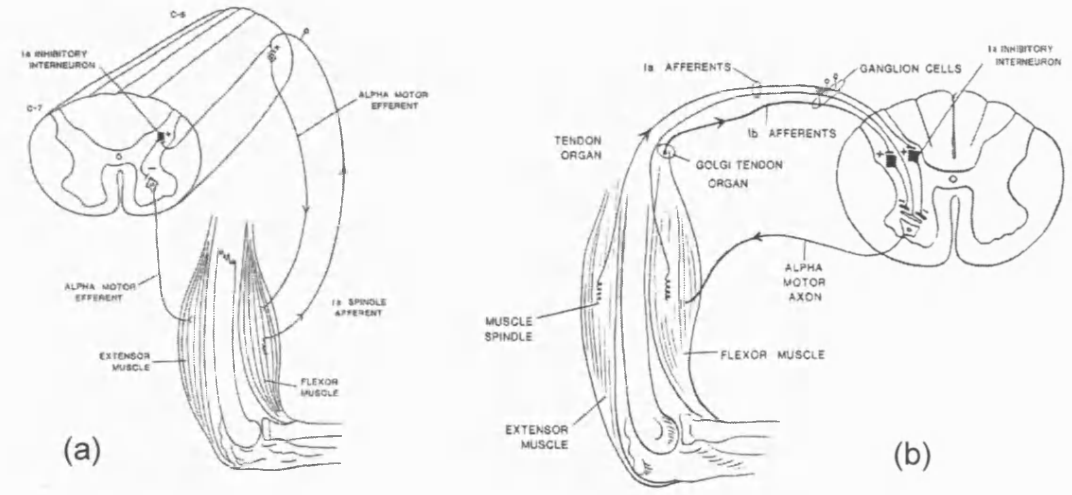


Figure 1.4. (a) Shows the pathway for disynaptic reciprocal inhibition with Ia afferents of the agonist (in this case the flexor) project to the alpha motorneurons of the antagonist via the Ia inhibitory interneuron. (b) Shows the pathway for presynaptic inhibition of the antagonist Ia inhibitory interneurons by Ia spindle afferents of the agonist (in this case the extensor).

1.2.4.2 Sensory system abnormalities

Tactile spatial discrimination is reduced in patients with focal hand dystonia (Bara-Jimenez et al 2000a). These patients also exhibit abnormal temporal discrimination of tactile and visuo-tactile stimuli, which correlate with the severity of focal hand dystonia (Bara-Jimenez 2000b, Fiorio et al 2003). Again, the mechanistic role of these abnormalities is unclear, since they may be detected in clinically unaffected body parts (Molloy et al 2003). The explanation for this may be that the physiological abnormalities are more widespread than the clinical symptoms; disorganisation of the somatosensory cortical hand representation contralateral to the clinically unaffected side has been demonstrated in patients with focal hand dystonia, suggesting that endophenotypic abnormalities exist and provide the substrate, in which, under appropriate environmental influence, dystonia may develop (Meunier et al 2001). Interestingly, tactile spatial sensory discrimination is normal in patients with primary

generalised dystonia (Molloy et al 2003). However, other sensory abnormalities have been demonstrated in patients with primary generalised dystonia including abnormal summation of cortical sensory evoked potentials in response to peripheral nerve stimulation (Tinazzi et al 2000) and dedifferentiation of sensory receptive fields within the thalamus determined from microelectrode recording of patients undergoing surgery (Lenz et al 1999).

1.2.4.3 Basal ganglia neuronal and oscillatory activity

Studies of pallidal neuronal activity in dystonia patients undergoing microelectrode exploration during functional neurosurgery have demonstrated reduced firing rates and irregular firing patterns when compared with pallidal neurons of patients with Parkinson's disease (Lozano et al 1997, Lenz et al 1998, Vitek et al 1999, Sanghera et al 2003, Starr et al 2005), although conflicting results have also been reported (Hutchison et al 2003). Neuronal firing in the GPi and motor thalamus correlates with EMG activity recorded from dystonic limbs (Zhuang & Hallett 2004). Similarly, local field potential recordings from GPi in dystonia patients have demonstrated low frequency (4-10Hz) oscillatory activity (Silberstein et al 2003, Starr et al 2005), the amplitude of which correlates with dystonic contractions in the EMG (Chen C et al 2006a) and which is synchronous with firing of local GPi neurons (Chen C et al 2006b). In cervical dystonia, application of a sensory trick with alleviation of dystonia, results in a corresponding reduction in low frequency oscillatory activity in the globus pallidus and cortex (Tang et al 2007). Taken together, these observations suggest abnormal neuronal firing patterns and excessive low frequency oscillations in GPi play an important role in the genesis of dystonia and may even be the driving signal for the expression of phasic dystonic contractions. The neuronal and oscillatory abnormalities

are consistent with a model of dystonia in which abnormal basal ganglia output adversely affects cortical motor function.

1.2.4.4 Abnormalities of regional cerebral blood flow

Further evidence of cortical dysfunction in dystonia has come from PET studies which have shown overactivity of prefrontal and underactivity of primary sensorimotor cortices during voluntary movement in patients with primary generalised dystonia (Ceballos-Baumann et al 1995a), whereas in secondary hemidystonia there is overactivation of both prefrontal and primary sensorimotor cortices during movement (Ceballos-Baumann et al 1995b). These findings may be reconciled with TMS studies showing increased excitability of the motor cortex, as the mutual result of decreased thalamocortical inhibition. PET studies have also demonstrated abnormal patterns of regional cerebral glucose uptake in manifesting and non-manifesting carriers of the DYT 1 mutation, with bilateral covarying increases in the putamen, pallidum, supplementary motor area and cerebellar hemispheres (Eidelberg et al 1998), suggesting that endophenotypic abnormalities extend to regional cerebral metabolism. A recent fMRI study in patients with writer's cramp showed bilateral increase in activation in the striatum, internal globus pallidus and lateral thalamus during a tactile discrimination task (Peller et al 2006). These changes are interpreted as consistent with defective centre surround inhibition of sensorimotor cortical areas during a tactile task, as a result of defective basal ganglia function.

1.2.4.5 Abnormalities of neural plasticity

There are several lines of evidence to suggest that abnormal brain plasticity may play a role in the pathophysiology of dystonia. Abnormal reorganisation of somatotopic

domains in the sensorimotor cortex of monkeys has been observed following excessive hand training resulting in dystonia-like involuntary movements (Byl et al 1996). Similarly task specific focal dystonia may develop with over-learned tasks such as writing or playing musical instruments, and abnormal patterns of cortical reorganisation have been shown in these patients (Meunier et al 2001, Rosenkranz et al 2005). More direct evidence for abnormal plasticity in dystonia has come from TMS studies using paired associative stimulation (PAS) repetitive TMS protocols to probe motor cortex plasticity. Patients with writer's cramp show greater potentiation of motor evoked potential amplitude (MEP) following PAS than healthy subjects (Quartarone et al 2003). Similarly, patients with focal arm dystonia show more profound changes in regional cerebral blood flow (reflecting synaptic metabolic activity) following 1 Hz repetitive TMS to the premotor cortex (Siebner et al 2003). Patients with sporadic cervical dystonia and DYT1 dystonia show more intense and longer-lasting inhibition of MEP amplitude following theta-burst repetitive TMS than healthy subjects or non-manifesting carriers of the DYT1 gene (Edwards et al 2006). Increased plasticity in subcortical circuits has also been demonstrated in dystonia patients. Quartarone et al (2006a), using methodology devised by Mao and Evinger (2001) to induce LTP-like plasticity in the blink reflex, demonstrated that patients with blepharospasm have increased responsiveness to this intervention compared with healthy subjects. Collectively, these results suggest short-term synaptic plasticity is increased in dystonia patients and could contribute to the development of dystonia by promoting maladaptive reorganisation within cortical and subcortical motor circuits (Quartarone et al 2006b).

1.2.4.6 Integrative model of dystonia pathophysiology

A successful model for dystonia must take into account the varied physiological abnormalities which have been identified. Similarly, potential interaction between these abnormalities must also be considered, which might be synergistic. For example, loss of inhibition might promote excessive neural plasticity by failing to gate the strength of synaptic inputs, thereby encouraging disorganisation of sensorimotor representations. Abnormal oscillatory activity and excessive neuronal synchrony could enhance aberrant synaptic plasticity within the basal ganglia and cortex. Such an interaction seems likely, given that neuronal oscillations may facilitate cortical plasticity (Buzsaki & Draguhn 2004). Excessive synchrony of neuronal firing within the basal ganglia thalamus and cortex could also interfere with correct spatiotemporal processing of sensory input and motor output required for normal voluntary movement. Taking the varied abnormalities into account, the model which emerges is one in which there is an underlying defect of basal ganglia function, abnormal excitability of motor circuits, misprocessing of sensory feedback and increased cortical synaptic plasticity, resulting in abnormal neural reorganisation and ultimately clinical dystonia. The proposed sequence of changes are compatible with the typical clinical course of primary dystonia with onset in one body part and subsequent gradual spread to other body regions, a time-course in keeping with progressive aberrant plasticity. Furthermore the model can accommodate the observation of subclinical physiological abnormalities, since these would represent partial evolution of the pathophysiological cascade but insufficient to manifest clinical dystonia. An important question is whether such a model can be applied to all forms of dystonia. Most of the pathophysiological studies have been in patients with primary dystonia, particularly focal hand dystonia but also segmental and generalised dystonia, with few studies in secondary dystonia. Although these categories

of dystonia differ in their clinical expression, there is significant overlap in the range of physiological abnormalities that have been identified. Therefore the proposed model mainly aims to describe primary dystonia, but may also be of relevance to secondary dystonia.

1.3 Objectives of the thesis

The development of GPi DBS has heralded an exciting development for the treatment of severe dystonia. The progressive improvement noted in dystonia after GPi DBS suggests brain plasticity is involved. Furthermore, physiological data suggests dystonia is a disorder in which abnormal synaptic plasticity and the emergence of dysfunctional reorganisation of the sensorimotor system plays an important role. From these observations, the hypothesis emerges that GPi DBS leads to brain reorganisation into a more normal physiological pattern, in this way reversing the underlying abnormal plasticity characterising the dystonic state. This hypothesis leads to the following predictions. Firstly, that physiological measures should change progressively after GPi DBS, reflecting brain reorganisation and secondly, that GPi DBS should have some effect on mechanisms of brain plasticity such as LTP. To this end, the longitudinal effects of GPi DBS on blink reflex excitability and forearm H-reflex reciprocal inhibition were studied and the impact of GPi DBS on motor cortex plasticity was assessed. These physiological measures were compared with the therapeutic response of dystonic symptoms. To probe the connections between GPi and the extent to which DBS activates these pathways, cortical evoked potentials were recorded in response to GPi stimulation. A secondary aim of this study was to assess the therapeutic efficacy of GPi DBS for dystonia with special attention to the time-course and factors influencing the magnitude of clinical improvement, in particular the effect of location

of stimulation within the pallidum. The ultimate goal of this work was to find evidence of neural plasticity underlying the mechanism of action of GPi DBS for dystonia.

Chapter 2. General Methods

2.1 Subjects

The work presented is this thesis is derived from a consecutive series of 29 dystonia patients who were all studied clinically before and after deep brain stimulation surgery, a subgroup of which underwent physiological studies. The series included 27 patients with generalised dystonia, the aetiology of which was as follows: 20 primary (10 DYT1, 10 non-DYT1), 4 secondary, 2 PKAN, 1 tardive. Two patients with secondary hemidystonia were also studied. All patients were included in clinical evaluation studies. The primary generalised dystonia patients, both DYT1 and non-DYT1, were recruited for the electrophysiological experimental studies. A group of 18 healthy volunteers, recruited mainly from within the Sobell Department, were also studied as control subjects in the electrophysiological experiments.

The description of subjects included in each study is outlined in the methods section for each chapter. All subjects gave written informed consent to participate in the experiments described in this thesis, and the studies were approved by the Joint Research Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology.

2.2 Surgical technique

The surgical technique described here was used in all the operated dystonia patients included in this thesis. The stereotactic electrode implantation is MRI guided and relies on direct targeting without the use of microelectrode recording (Hirabayashi et al 2002). The surgery is carried out under general anaesthesia. The hair is shaved completely and the Leksell G frame (Elekta Instruments, Sweden) is attached to the

skull. The frame is attached parallel to the line joining the tragus of the ear with lateral canthus, and care is taken to eliminate antero-posterior or lateral tilting and rotation. Following transfer of the patient to the MRI table, the MRI adapter and fiducial box are fitted to the frame and checks are made, using a biaxial spirit level, that the frame is completely level, Figure 2.1.

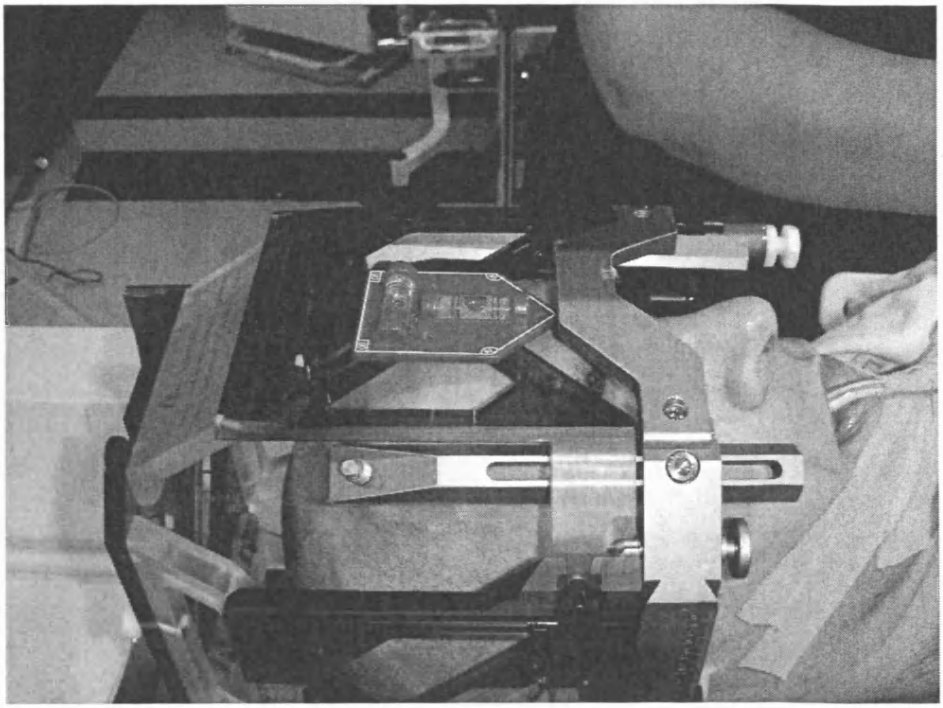


Figure 2.1 Leksell G frame in position in dystonic patient with fiducial box attached just prior to MRI scanning. Note the biaxial spirit level to check the frame is completely level in both planes.

After fitting of transmit-receive head coil, the level of the frame/fiducial box are rechecked before the patient enters the MRI. Stereotactic MRI is then obtained using 1.5 Tesla MRI (General Electric, USA) with 2 mm contiguous axial and coronal images with proton density sequences, which provide excellent visualisation of the pallidum allowing resolution of boundaries of GPe, GPi, medial medullary lamina, lateral

medullary lamina and pallido-capsular border (Hirabayashi et al 2002), Figure 2.2. Using these images, direct targeting of the posteroventral GPi is carried out using both manual and computer aided techniques (Stealth workstation, Framelink TM, Medtronic, Minneapolis USA). The patient is then transferred from the MRI suite to the operating theatre. The burr-holes are made bilaterally 2-2.5 cm lateral to the mideline at the level of the coronal suture using a pneumatic craniotome and 14 mm perforator. The dura is opened using bipolar diathermy. The ring angle (anteroposterior angle) was between 70-80 degrees, the arc angle 85-95 degrees. A rigid 1.5 mm diameter radio-frequency electrode with an uninsulated tip 2 mm in length (Elekta Instruments, Sweden) is slowly inserted to the target to create the tract for the therapeutic electrode. During insertion of the radio-frequency electrode, tissue impedance is measured and displayed continuously numerically in Ohms and as an auditory analogue tone allowing differentiation of grey and white matter (Limonadi et al 1999). Typically a drop in impedance is encountered as the electrode passes from white matter into the dorsal putamen or GPe, usually about 10 mm before the target point. The quadripolar DBS electrode model 3389 (Medtronic Neurological Division, Minneapolis USA), with four platinum-iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm in length and 2 mm centre-to-centre separation) is then implanted and fixed to the skull using the plastic cap or Navigus electrode fixation system (Medtronic Neurological Division, Minneapolis USA). In four patients operated early in the series, model 3387 electrodes were used (Medtronic Neurological Division, Minneapolis USA) with 3 mm centre-to-centre contact separation.

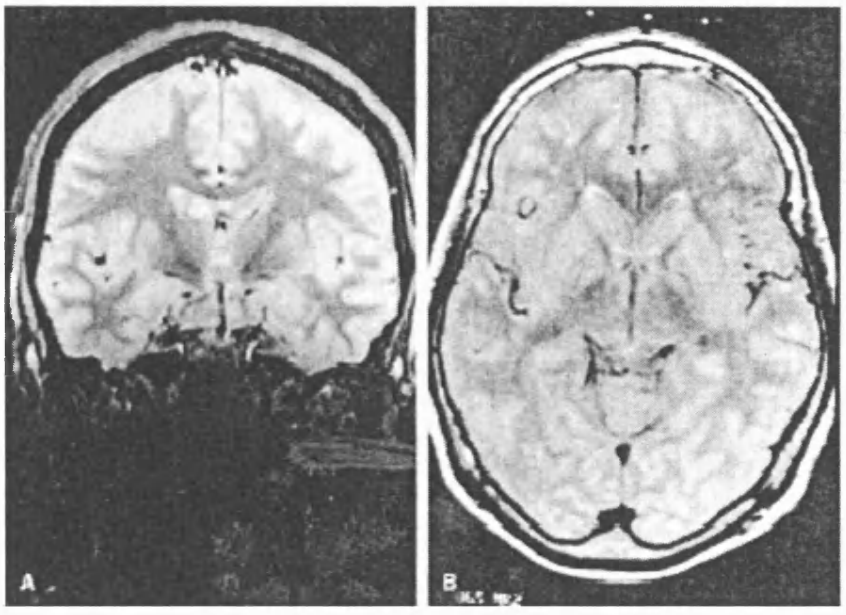


Figure 2.2 From Hirabayashi et al 2002. Proton density sequence MRI coronal (a) and axial (b) views, showing clear visualisation of pallidal boundary: laterally the putamen, medially the internal capsule and inferiorly on the coronal image the optic tract (dark) is visible. Note the medial medullary lamina separating GPi and GPe is clearly visible.

2.2.1 Post-implantation imaging and confirmation of electrode position

Immediately after bilateral electrode implantation and fixation, the stereotactic MRI is performed. The number of image slices in the immediate post-implantation MRI is limited to ensure the specific absorption rate (SAR) is kept below 0.4 W/Kg to minimise the risks of electrode or tissue heating (Rezai et al 2004). Once correct electrode placement has been confirmed, the patient is returned to the operating theatre and the pulse generator implanted (Kinetra model 7428, Medtronic Neurological Division, Minneapolis USA), usually into a left infraclavicular subcutaneous pocket and connected to the implanted electrodes. In some patients, for cosmetic reasons, the implanted pulse generator was implanted in the abdomen. By convention, the electrode

for the right hemibody is connected to Channel 1 (contacts 0, 1, 2, 3) and the left hemibody to Channel 2 (contacts 4, 5, 6, 7).

In one patient, MRI could not be performed due the presence of a metal fragment in the thalamus related to previous thalamotomy. In this patient CT was used with 2 mm contiguous slices and manual calculation of target coordinates were used. In addition intraoperative high frequency stimulation, with patient anaesthetised but non-muscle relaxed, to observe thresholds for capsular response was performed, and finally post-implantation stereotactic CT to confirm electrode placement.

2.3 Clinical Evaluation

2.3.1 Study design: prospective longitudinal assessment

In all patients clinical evaluations were performed before, and serially after surgery. Evaluations were undertaken at the following time-points; pre-operatively, 2 weeks, 1 month, 3 months, 6 months, 1 year and annually thereafter, the longest follow up being 4 years. The clinical scoring was carried out by a single neurologist rater (ST).

2.3.2 Burke-Fahn-Marsden dystonia rating scale

The Burke-Fahn-Marsden dystonia rating scale (BFM) was used throughout this work (Burke et al 1985). The BFM is divided into two parts, the movement score and disability subscales. The BFM movement score ranges from 0 to 120 and is the sum of body region items for the eyes, face/mouth, speech/swallow, neck, arms, trunk and legs. The arms and legs are scored separately for right and left sides, the other regions carry a single score. For each body region, the score is derived from the product of a provoking factor (0-4) and severity factor (0-4) multiplied by a weighting factor where zero represents no dystonia. The provoking factor ranges from dystonia present with

specific action=1 to present at rest=4, while the severity factor ranges from slight=1 to severe=4. A severity factor of 4 corresponds to no useful grip of the hand or inability to walk. The weighting factor for eye, mouth and neck regions is 0.5 reflecting their lesser impact on disability, and 1.0 for remaining regions.

The total disability score ranges from 0 to 30 and is the sum of scores for seven functional items: speech, handwriting, feeding, swallowing, hygiene, dressing and walking. All disability score items are rated (0-4) except walking which is (0-6). All patients were videotaped at the time of scoring according to a standardised protocol described by Burke et al. However, all BFM data quoted in this work pertains to scoring made by live, direct examination of patients at the stated time-point.

The BFM has been validated and shown to have good inter-rater and retest reliability (Burke et al 1985). The BFM has been compared to the more detailed Unified Dystonia Rating Scale and the relatively simple Global Dystonia Rating Scale and was found to be equivalent in terms of intra and inter-rater reliability, with an ease of use in between the two other scales (Comella et al 2003). The BFM is the most widely used dystonia scale in studies of GPi DBS for dystonia (Cif et al 2003, Yianni et al 2003, Coubes et al 2004, Vidailhet et al 2005, Kupsch et al 2006).

2.3.3 Selection and adjustment of stimulation parameters

The implanted pulse generator was switched on usually on the first postoperative day. The electrode contacts were assessed individually with monopolar stimulation, pulse width 60 μs, 130 Hz increasing progressively to 4 V to assess for any side effects or acute therapeutic effects. Stimulation was commenced using the most ventral contacts without side effects, starting with 1 V, 60 μs, 130 Hz with further increase by 0.5-1V per day until a clinical benefit was noted or an arbitrary level, usually 3.5 V, was

reached. If little or no improvement was achieved with the initial choice of contacts, then alternative contacts were tried, usually the adjacent ventral contact singly or in combination. Different contacts were compared usually over a 24-hour period to assess their impact, most of this adjustment occurring with the patient in hospital in the early post-operative period. Further adjustment of stimulation parameters was made where necessary at each subsequent follow-up visit. In most instances, this adjustment was an increase in voltage or pulse width or sometimes the addition of a second active adjacent contact or change of single contact. Clinical scores were made before change of stimulation parameters at each visit. All patients received continuous GPi DBS. Patients were provided with a personal therapy controller, allowing some adjustment of voltage within set limits.

2.4 Neurophysiological recordings

As described in the Introduction, abnormalities of inhibition at brainstem and spinal level are well documented in generalised dystonia. Furthermore, these abnormalities are measured by blink reflex R2 inhibition and forearm H-reflex reciprocal inhibition using surface EMG and are practicable to perform in patients with generalised dystonia, as evidenced by existing studies in this patient group (Nakashima et al 1990, Panizza et al 1990). In addition, abnormalities of brainstem blink and spinal H-reflex reciprocal inhibition in dystonia are thought to reflect abnormal descending modulation from cortex and basal ganglia, and therefore provide an indirect means of examining changes in activity in these regions. For these reasons, blink reflex R2 inhibition and forearm H-reflex reciprocal inhibition were selected for longitudinal study in patients with generalised dystonia after GPi DBS.

2.4.1 Surface EMG recordings

All EMG recordings were made using 1 cm Ag/Ag chloride disc electrodes and conductive gel after preparation of the skin with isopropyl alcohol. The active electrode was placed over the muscle belly and the reference at a distal nearby site. To further reduce the impedance, particularly for the blink reflex recordings, a sterile 21-gauge hypodermic needle was introduced through the disc electrode to touch, without breaking, the skin.

2.4.1.1 Amplification and filtering

The EMG signals were amplified and analogue band pass filtered using Digitimer D360 amplifiers (Digitimer Ltd, Welwyn Garden City, Herts. UK) analogue to digital converted using a 1401 AD converter (Cambridge Electronic Design Ltd Cambridge, UK) sample rate of 5 KHz and recorded on computer using Signal software (Cambridge Electronic Design Ltd Cambridge, UK). For blink reflex recordings band pass filtering was 53 Hz to 3 kHz, whilst for all other experiments 3 Hz to 2-3 kHz was used.

2.4.1.2 Artifact elimination

EMG artifact, mainly in the form of 50 Hz mains interference was minimised by adequate skin preparation to reduce impedance and positioning of amplifier box and recording wires. The 50 Hz notch filter was rarely used. To minimise the presence of involuntary dystonic EMG activity in the resting recordings, the least affected arm was studied. Unrelaxed trials with any ongoing EMG activity were rejected on-line. GPi DBS produced 130 Hz artifact in the blink reflex recordings but not the H-reflex, owing to the greater distance from the source and lower amplification gain. To eliminate DBS

induced artefacts during blink reflex recordings, stimulation parameters were changed at the beginning of the experimental session from monopolar to bipolar stimulation at 30% higher voltage.

2.4.2 Blink reflex

Surface EMG recordings were made bilaterally from the orbicularis oculi muscles. Electrical stimulation was applied to the supraorbital nerve in the supraorbital notch with a bipolar stimulating electrode and constant current generator (Digitimer Ltd, Welwyn Garden City, Herts. UK). All stimuli were 0.2 ms duration with intensity 3-4 times sensory threshold (8-14 mA). The blink reflex in response to paired stimulation was assessed at interstimulus intervals of 500 ms and 1000 ms. The 500 ms was included because a previous study found it to be the interval which most discriminated between dystonia patients and control subjects (Nakashima et al 1990), and 1000 ms to provide a comparator interval with a lesser degree of inhibition. The interval between trials was varied randomly between 10 and 20 seconds to minimise habituation of the blink response. Thirty trials at each ISI were performed in a randomised order in three blocks for both right and left sided supraorbital nerve stimulation.

2.4.3 Forearm H-reflex reciprocal inhibition

EMG recordings were made from flexor carpi radialis and extensor digitorum communis. Electrical stimulation was applied to the median nerve in the antecubital fossa and radial nerve above the elbow, using two constant current generators (Digitimer Ltd, Welwyn Garden City, Herts. UK). Stimuli to median nerve were 500 ms. Longer stimulus duration 500-1000 ms preferentially excites afferent Ia spindle fibres which assists in elicitation of the H-reflex. The intensity was adjusted to produce

the maximum H-reflex, without an M wave. Radial nerve stimuli were also 500 ms duration at an intensity to produce an EMG response of 0.1-0.5 mV. The H-reflex in response to preceding radial nerve conditioning stimuli was assessed at 8 interstimulus intervals (ISI) of –1, 0, 1, 10, 20, 30, 100 and 200 ms. Stimuli were delivered every 5 seconds. Sixty trials at each ISI and 120 unconditioned trials were performed in a randomised order in three blocks of 100 stimuli.

2.4.4. EEG for evoked potential (EP)

2.4.4.1 Origin of EEG signal and EP

The EEG signal recorded at the scalp is the electrical activity corresponding to the postsynaptic dendritic potentials of populations of neurons near the cortical surface. The postsynaptic potentials time-vary between excitatory and inhibitory, the synchronised activity of many neurons contribute to the oscillatory activity recorded as scalp EEG. In general EPs represent time-locked synchronised activity of a group of cortical neurons in response to a stimulus. The EP following a single stimulus is often invisible, embedded within the background EEG. By averaging in the time domain the EEG following many stimuli, the EP, which is relatively constant in position and waveform is reinforced while the backgound EEG cancels out. The main quantification of the resulting EP is by its latency, amplitude and cortical topography.

2.4.4.2 Montage, amplification and filtering

The EEG was recorded using the Neuroscan EEG system (Compumedics Ltd, El Paso, Texas USA). A modified 10-20 montage was used with 60 Ag/AgCl electrodes fitted with an elastic cap and chin-strap. The scalp surface was prepared with isopropyl alcohol, gentle abrasion and conductive gel to reduce electrode impedance to <1 kOhm.

Recordings were referenced to linked ears. EEG signals were amplified, band pass filtered 0.05-200 Hz and analogue to digital converted at a sample rate of 2500 Hz.

2.4.4.3 Triggering and elimination of DBS artifacts

EEG during therapeutic monopolar GPi DBS is affected by extreme artifact which precludes any meaningful recording. Therefore GPi DBS was changed to bipolar for all recordings and the frequency reduced to10 Hz, amplitude 3.5-4 V and pulse width 60-90 μs. For triggering, surface electrodes were attached to the forehead and nuchal region and the signal amplified using a Digitimer 360 amplifier (Digitimer Ltd, Welwyn Garden City, Herts. UK) and the output fed into a Schmidt trigger and displayed on an oscilloscope. This setup allowed the 10 Hz DBS artifact to be continuously displayed, the Schmidt trigger was adjusted during the experiment to ensure a consistent 10 Hz triggering signal which was fed into the Neuroscan and recorded as a triggering channel in the EEG. Recordings lasting 90-120 seconds were made during stimulation at each bipolar pair of the quadripolar electrode on both sides consecutively, with the other electrode set to zero amplitude.

2.4.5 Transcranial magnetic stimulation (TMS)

2.4.5.1 Mechanisms and principles of TMS

TMS exploits the property of a time-varying magnetic field to induce current in a conductor to excite the cortex. It was first demonstrated by Barker (Barker et al 1985) and has become a widely used tool for non-invasive cortical stimulation in awake human subjects. It replaced electrical cortical stimulation, having the major advantage that it is not painful. The basic principle involves the capacitative discharge of a large transient current into a wound hand-held coil, which results in a powerful time-varying

magnetic field. The field strength is of the order 1-3 Tesla and is oriented perpendicular to the coil. Coils exist in single and double configurations, the latter, so called figure-of-eight coils are the most widely used because the magnetic flux is delivered more focally beneath the intersection of the coils (Cohen & Cuffin 1991). The TMS pulse induces currents in the cortex which flow parallel to the surface of the brain and excites cortical neurons. The relative focality of TMS allows fairly selective stimulation of homotopic motor cortical areas for individual muscles; usually intrinsic hand muscles are tested. The basic arrangement for TMS is shown in Figure 2.3

2.4.5.2 Origin of the motor evoked potential (MEP)

A single TMS pulse applied to the motor cortex excites a pool of pyramidal cells, resulting in a descending volley of action potentials and an MEP recordable with EMG in the corresponding muscle. TMS applied to the motor cortex may activate pyramidal neurons transsynaptically producing indirect I-waves, or at higher intensities can excite the pyramidal cell axons directly producing D-waves. Because of the intervening synapses, I-waves are of longer latency than the D-waves and depending on the number of synapses I1, I2 or I3 waves may be observed at progressively longer latencies (Terao & Ugawa 2002). Coil orientation in the anteroposterior axis favours elicitation of I1 waves over D waves. For the TMS experiment described in this thesis the MEPs measured were for the most part elicited by I1 waves.

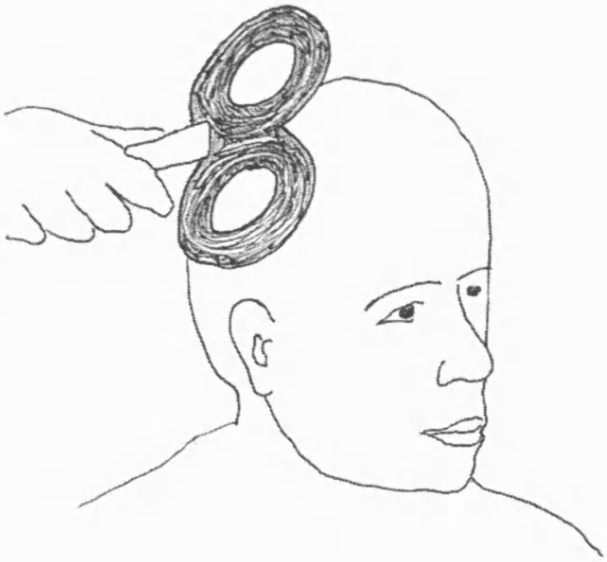


Figure 2.3 General set-up for TMS of the motor cortex using a figure-of-eight coil.

2.4.5.3 Methods of experimentally inducing plasticity using TMS

Plasticity refers to the capacity for dynamic adaptation of the nervous system and is thought to be largely mediated by alterations in synaptic efficiency. Studies using brain slice preparations have shown that particular types of conditioning stimulation can give rise to sustained increases or decreases in synaptic efficiency. Long term potentiation (LTP) describes a sustained increase in the amplitude of excitatory postsynaptic potentials (for a given presynaptic input stimulus) and is usually produced experimentally by high frequency stimulation of presynaptic neurons. This process involves calcium influx into the cell, activation and increased expression of AMPA glutamate receptors and a resulting decrease in the cell resting potential membrane potential, making it more excitable. In synapses that exhibit NMDA receptor-dependent LTP, sufficient depolarization unblocks NMDA receptors, which permits calcium influx into the cell, when bound by glutamate. NMDA receptors, at resting membrane potentials are blocked by a magnesium ion that prevents the entry of

calcium into the postsynaptic cell, however after depolarization by summation of EPSPs, the magnesium blockade is reversed, allowing calcium influx which facilitates and maintains LTP. Conversely, long-term depression (LTD) refers to sustained decreases in synaptic efficiency and is usually produced by low frequency stimulation of the presynaptic neurons, and is associated with an increased resting membrane potential. LTD may also be dependent on activity of NMDA and metabotrophic glutamate receptors. The formation of LTP or LTD is influenced not only by presynaptic inputs but also activity in the postsynaptic cell, particularly its timing in relation to these inputs, so called associative plasticity. In general when presynaptic input is coincident or just before firing of the postsynaptic cell, LTP is favoured, whereas reversal of this temporal order favours LTD.

TMS methods modelled on the observations made in slice preparations have been developed to experimentally induce plasticity in humans. A variety of protocols using repetitive TMS (rTMS), which simulate the repetitive input stimuli used in vitro, have been developed. Motor cortex conditioning with low frequency rTMS around 1 Hz results in sustained decreases in motor cortex excitability lasting 15-30 minutes (Chen R et al 1997b, Touge et al 2001). Motor cortex conditioning at higher frequency rTMS, around 5-25 Hz, results in sustained increases in motor cortex excitability (Peinemann et al 2004, Khedr et al 2007). Recently some new methods for inducing plasticity with TMS have been developed. Thickbroom and colleagues (Thickbroom et al 2005) found that conditioning with low frequency (0.2 Hz) paired suprathreshold stimulation with an interstimulus interval equal to the inter-I wave latency, resulted in marked sustained increase in motor cortex excitability. Pulsatile 50 Hz rTMS, so-called theta burst is a highly efficient means of inducing sustained decreases and increases in motor cortex excitability (Huang et al 2005).

2.4.5.3.1 Paired associative stimulation (PAS)

Stefan and colleagues (Stefan et al 2000) first demonstrated motor cortex plasticity using PAS with TMS. The technique uses paired stimulation of motor cortex and median nerve with the median nerve stimulus preceding the TMS pulse by 25 ms. This order allows time for the median afferent volley to reach the sensorimotor cortex and arrive synchronously with the motor cortex stimulus. Stefan used 90 pairs of stimuli delivered at 0.05 Hz, with the median nerve intensity of 300 % of perceptual threshold and the TMS intensity adjusted to produce a 1 mV resting MEP in abductor pollicis brevis (APB). In healthy subjects this conditioning resulted in sustained increases in motor cortex excitability, as evidenced by the size of the resting MEP, lasting up to 1 hour. The plasticity effect was topographically restricted to APB and not accompanied by changes in spinal excitability, suggesting its origin to be the motor cortex. Stefan subsequently showed the facilitatory effect of PAS 25 is blocked by NMDA antagonist, suggesting that it may be mediated by LTP-like mechanisms (Stefan et al 2002). Further evidence supporting this notion has come from experiments in which the temporal order of inputs was reversed. Conditioning with the median pulse 10 ms before the motor cortex TMS pulse, so that its arrives after pyramidal neurons have fired, results in a sustained decrease in motor cortex excitability, which can also be blocked pharmacologically (Wolters et al 2003). These observations suggest PAS can produce both LTP and LTD like effects, depending on the temporal order of stimulation, analogous to effects seen in slice preparations. It has also been shown that higher frequencies of paired stimulation including 0.25 Hz (Ziemann et al 2004) and 5 Hz (Quartarone et al 2006c) are also effective in producing sustained facilitation of motor cortex excitability, and have the practical advantage of taking less time. In the TMS experiment described in this thesis, a method of PAS identical to that of Stefan et

al (2000) was used, with the exception that 200 paired stimuli were delivered at a rate of 0.25 Hz.

2.5 Analysis

2.5.1 Clinical scores and percentage improvement

The BFM Movement and Disability subscales were analysed separately throughout. For correlation of clinical effects with physiological changes, only the Movement subscale was used. Percentage improvement in both Movement and Disability subscales was calculated as follows:

(pre-operative score – post-operative score) X 100 / pre-operative score.

This method of deriving percentage improvement has been widely used in clinical studies using rating scales, including studies of GPi DBS for dystonia (Coubes et al 2004, Vidailhet et al 2005).

2.5.2 Quantification of EMG signals

EMG data were analysed off-line using custom-written software (Nucursor 2001, Sobell Department, ION, London UK). For blink reflex data, the raw blink recordings were DC corrected, rectified and averaged. The onset latency and duration of R1 and R2 responses were determined by manual cursor marking of the beginning and end of responses. The area ratio of the conditioned R2 component to the unconditioned response was calculated. The area of the conditioned R2 was calculated over the same duration as the unconditioned response. For the H-reflex the onset and termination of the response was marked manually with cursors and the peak-to peak amplitude of each H-reflex was measured using an automated function (Nucursor 2001, Sobell Department, ION, London UK). Reciprocal inhibition at each ISI was calculated as the

ratio of the conditioned to the unconditioned response. The same method was used to measure the peak-to-peak amplitude of TMS evoked MEPs.

2.5.3 EEG analysis and derivation of evoked potentials

EEG data was analysed using Neuroscan software (Compumedics Ltd, El Paso, Texas USA). The continuous EEG recordings for each contact pair and side were epoched from –10 ms to 100 ms in relation to the 10 Hz triggering marker of DBS artifact. The epoched files were then averaged and the average trace baseline corrected for the prestimulus interval. The EP was derived from the average of 1000-1200 sweeps. The EP was analysed initially qualitatively by examining all the averaged EEGs to identify waveforms following the DBS stimulus. Waveforms identified qualitatively were then analysed quantitatively by manual marking of the onset and peak latency and the amplitude calculated and these data were used for the numerical statistical analysis. The EP was compared from contact pairs located in GPi or GPe. The identification of position of contact in relation to pallidal anatomy was made using Stealth workstation (Framelink TM, Medtronic, Minneapolis USA). Grand averages were also derived for contact pairs in GPi or GPe.

2.5.4 Statistics

All statistics were performed using SPSS for Windows version 11.5 (SPSS Inc., Chicago, Illinois USA). Data are expressed as means and standard error of the mean unless otherwise stated. For analysis of clinical and physiological time-course data, SPSS curve estimation function was used which allows the data to be modelled against several functions (linear, exponential, logarithmic etc) and computes the non-linear regression coefficients in that function, which describe the line of best fit. Repeated

measures analysis of variance (ANOVA) was used to identify significant changes in clinical or physiological data before and after surgery at one or more time point. One-way ANOVA was used where appropriate to compare data from healthy control subjects and patients. The nature of significant effects identified using ANOVA was explored using two-tailed paired or unpaired t-tests, depending on the comparison. For analysis of electrode contact location data, K-means cluster was used to identify statistically significantly segregated groups within continuous distributed data. Chi-square tests were used to identify differences in the frequency of superior clinical outcomes between different spatial clusters of electrode contacts. Correlations were performed using the Pearson correlation coefficient or the Spearman Rho coefficient where appropriate. For all statistics a probability (p) value <0.05 was considered significant. The precise factors and terms used within these statistical tests are given in detail in the Methods section for each Chapter.

Chapter 3. Therapeutic effects of GPi DBS in dystonia *

3.1 Summary

In this Chapter the therapeutic response of dystonia to deep brain stimulation in 29 patients who underwent bilateral (n=27) or unilateral GPi DBS (n=2) is presented. The series included 27 patients with generalised dystonia, the aetiology of which was as follows: 20 primary (10 DYT1, 10 non-DYT1), 4 secondary, 2 PKAN, 1 tardive. Two patients with secondary hemidystonia were also studied. Patients were studied using the BFM score with a prospective single rater design, with assessments made before and at intervals of 0.5, 1, 3, 6, 12, 24 and 36 months after surgery. In twenty patients with primary generalised dystonia (10 DYT1 positive, 14 female, mean age 41 years ± 16, mean duration of symptoms 24 years ± 14) at 6 months follow up, BFM movement score improved by an average of 68% ± 18 and disability score by 55% ± 23 ($p<0.00001$). Longer follow-up confirmed these improvements in BFM movement score to be stable: at 12 months 68% ± 20 (n=16), 2 years 71 % ± 21 (n=16), 3 years 65% ± 25 (n=10). Improvement in dystonia was progressive. In the 20 patients with primary generalised dystonia BFM movement score improved by 47% ± 21 at 2 weeks, and 55% ± 19 at 1 month. Regression analysis confirmed a progressive time course independent of changes in DBS electrical parameters. The time course of improvement in BFM movement score was closely modelled by a logarithmic function. Univariate analysis of variance identified the presence of the DYT1 mutation and orthopaedic deformity to be significant positive and negative predictors of outcome, but age and symptom duration were not predictive. The four patients with secondary generalised dystonia were more severely affected at baseline and improved significantly less, at 1 year movement score 21% ± 6.8, disability score 10% ± 6%, but still benefited in terms

of comfort and ease of management. In comparison, the patient with secondary tardive dystonia improved by 48% and the two patients with PKAN dystonia by 48% and 12% at 1 year. Two patients with secondary hemidystonia due to contralateral basal ganglia lesions both failed to improve with unilateral GPi DBS. No major complications occurred. Failure of the DBS system, due to breakage or device failure, occurred in three patients. Reversible, stimulation related side effects included dysarthria, akinesia and tremor. The present results confirm bilateral GPi DBS to be a safe and effective treatment for various forms of dystonia, particularly primary generalised. The presence of the DYT1 mutation is a favourable marker for response to DBS. The poorer response in those with orthopaedic deformity argues for earlier surgery before such deformities occur. The progressive time course of improvement in primary generalised dystonia although the result of GPi DBS, is not a by-product of serial adjustments in stimulation parameters. Instead it is likely to reflect neural plasticity underlying the therapeutic response.

* *Preliminary results of this work were presented in poster form at the Movement Disorders Society Meeting, New Orleans, USA March 2005*

3.2 Introduction

The most significant advance in the functional neurosurgical approaches to the treatment of severe, medically refractory dystonia has been the development of GPi DBS (Coubes et al 1999, Coubes et al 2000, Tronnier et al 2000, Vercueil et al 2001, Bereznai et al 2002, Cif et al 2003, Katayama et al 2003, Yianni et al 2003, Krause et al 2004, Coubes et al 2004, Starr et al 2004, 2005). More recently, two prospective blinded studies have confirmed the efficacy of GPi DBS for adult primary generalised and segmental dystonia (Vidailhet et al 2005, Kupsch et al 2006). Despite this progress, little is known about factors which might predict better outcome in primary generalised dystonia. The DYT1 mutation has been considered a favourable prognostic marker, but statistical evidence for this has been lacking. An important feature of GPi DBS effect in dystonia is that improvement is not immediate but progressive over weeks to months, which has been attributed to neuroplasticity mechanisms (Bereznai et al 2002, Yianni et al 2003, Vidailhet et al 2005). The present study sought to carefully assess the clinical consequences of GPi DBS in dystonia patients, with special emphasis on the timecourse of improvement, in an effort to better understand this phenomenon and critically examine the possible role of neuroplasticity. In addition the study sought to identify factors predictive for improvement after GPi DBS in primary generalised dystonia, and compare with the efficacy in secondary forms of dystonia.

3.3 Methods

3.3.1 Patients and surgery

A consecutive series of 29 dystonia patients undergoing GPi DBS were studied prospectively. The patients comprised 20 with primary generalised dystonia (10 DYT1

positive, 14 female, mean age 41 years ± 16, mean duration of symptoms 24 years ± 14), 4 with secondary generalised dystonia (mean age 26 years ± 6, disease duration 21 ± 5 years), 2 patients with PKAN dystonia, 1 patient with tardive dystonia and 2 patients with secondary hemidystonia. Two patients with primary generalised dystonia had undergone previous unilateral thalamotomy more than 20 years earlier. All patients underwent bilateral GPi DBS except the two patients with hemidystonia who were implanted unilaterally. Surgery was carried out in all cases under general anaesthesia using the Leksell G frame, with direct targeting of the posteroventral GPi as seen on contiguous 2 mm thick stereotactic proton density MRI images. GPi DBS was delivered with monopolar stimulation of one or two adjacent contacts on each electrode with a constant frequency of 130 Hz, with amplitude (Volts) and pulse width (μsec) adjusted to maximise clinical benefit. Further details of surgical technique and adjustment of stimulation parameters are provided in the General Methods.

3.3.2 Clinical evaluation

Clinical evaluation was performed using the BFM scale. Scoring was performed by a single rater (ST) before and at intervals of 0.5, 1, 3, 6, 12, 24, 36 months after surgery. Scoring was carried out at the beginning of each follow-up visit before interrogation or adjustment of stimulation parameters. Medications for dystonia were kept constant after surgery for a minimum of 6 months and in most patients for the first year, in order to eliminate any confounding effects on the therapeutic time course. Details of the BFM score are provided in the General Methods

3.3.3 Statistical analysis

Repeated measures ANOVA was used to identify significant effects of TIME on serial measures such as BFM scores and electrical stimulation parameters. Paired two-tailed t tests were then used to identify significant differences in measures at different time points. One-way ANOVA or unpaired two-tailed t tests were used to compare means between groups. The time course of changes in BFM was modelled using non-linear regression curve estimation to determine the best fitting function. To examine the effect of TIME on BFM scores and take into account the possible effects of serial adjustments in stimulation, a random-effects maximum likelihood regression was used, which unlike GLM repeated measures ANOVA, is able to accommodate time-varying covariates (stimulation parameter). Univariate ANOVA was used to identify independent predictive factors of improvement. All statistics were performed using SPSS 11.5, except the random-effects maximum likelihood regression, where STATA 10.0 was used.

3.4 Results

3.4.1 Primary generalised dystonia

3.4.1.1 Time-course of improvement

The time-course of improvement in BFM movement score after GPi DBS was progressive with the majority of the improvement occurring in the first 2-4 weeks and a further, more gradual improvement thereafter (Fig 3.1). The grand average time-course was best described by a logarithmic function: BMF score = 19.1 + (-2.91) x log [TIME (months)], p=0.0001. The time-course in each patient was also significantly logarithmic

(Table 3.1). The BFM score decreased significantly between consecutive time points up to 3 months, the improvement then plateauing around 6 months (Table 3.2).

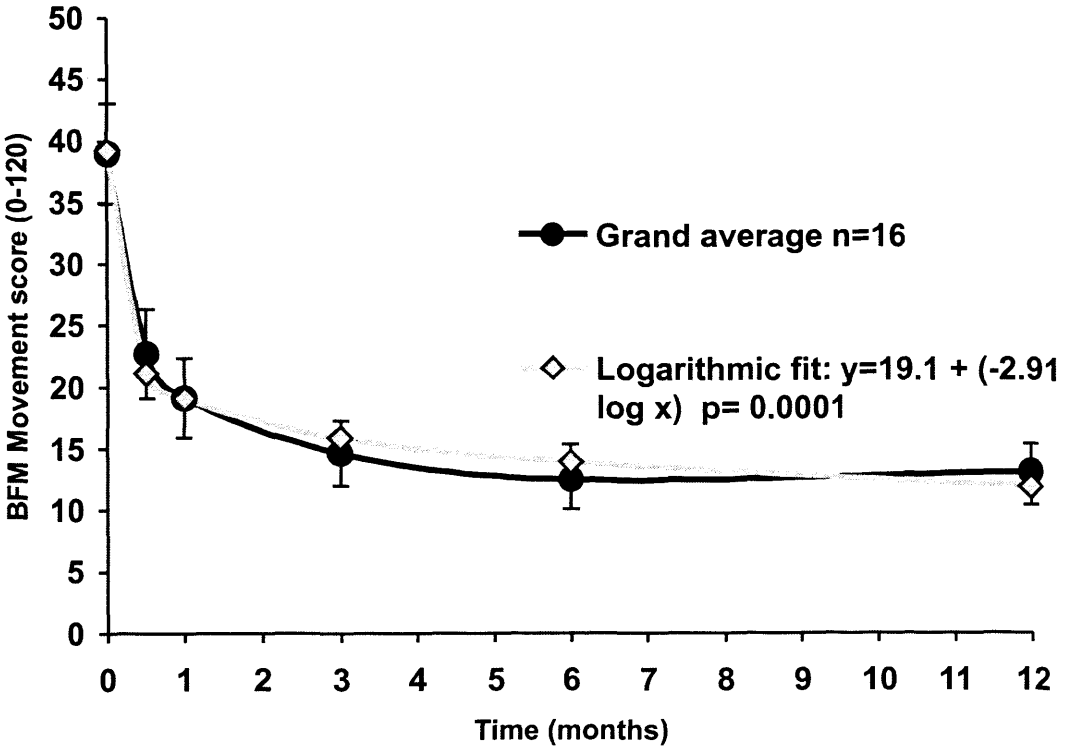


Figure 3.1 Time course of BFM movement score following GPi DBS in 16 patients with 1 year follow up. Error bars show ± 1 SEM.

Patient	*Constant*	*B*	*P value*
1	4.2 ± 0.8	-2.2 ± 0.2	0.001
2	32.3 ± 2.4	-3.2 ± 0.8	0.015
3	12.4 ± 1.1	-2.4 ± 0.4	0.002
4	4.8 ± 1.2	-2.0 ± 0.4	0.007
5	9.0 ± 1.4	-5.4 ± 0.5	0.00001
6	24.8 ± 1.3	-2.1 ± 0.4	0.006
7	23.8 ± 3.4	-4.5 ± 1.1	0.014
8	10.0 ± 0.7	-2.3 ± 0.2	0.001
9	6.7 ± 0.8	-2.4 ± 2.7	0.001
10	37.2 ± 0.6	-2.2 ± 0.2	0.00001
11	11.6 ± 1.5	-1.5 ± 0.5	0.033
12	30.6 ± 1.2	-6.2 ± 0.4	0.00001
13	18.2 ± 0.7	-1.5 ± 0.2	0.003
14	27.2 ± 3.2	-3.3 ± 1.0	0.032
15	38.9 ± 3.0	-3.6 ± 1.0	0.02
16	13.7 ± 0.8	-1.7 ± 0.3	0.003

*Table 3.1 Logarithmic regression coefficients ± SEM for time course of improvement in 16 patients over time points 0, 0.5, 1, 3, 6 and 12 months. Patients 1-8 are DYT 1+. Changes in BFM score are described by the equation: BFM movement score = Constant + (B)*log [TIME], where TIME is in months. Note that for all patients logarithmic regression of the time course was significant.*

Interval	*n*	*Change in BFM (Mean ± SEM)*	*% improvement at end of interval from baseline (Mean ± SEM)*	*P value*
pre - 0.5 month	20	17.4 ± 2.0	46.8 ± 4.8	p < 0.00001
0.5 - 1 month	20	3.3 ± 1.1	55.5 ± 4.3	p = 0.007
1 - 3 months	20	4.3 ± 1.2	64.8 ± 4.3	p = 0.002
3 - 6 months	20	1.6 ± 1.0	68.3 ± 4.0	p = 0.113
6 - 12 months	16	-0.66 ± 0.76	68.6 ± 4.9	p = 0.401
12 - 24 months	16	0.28 ± 0.61	70.5 ± 5.3	p = 0.653
24 - 36 months	10	-1.15 ± 0.50	65.5 ± 8.0	p = 0.037

Table 3.2 Changes in BFM movement score in primary generalised dystonia after GPi DBS. Note changes are the difference (pre-post) over the stated interval, positive numbers represent a decrease in score. P values are for paired two-tailed t tests of the change in mean BFM scores.

Repeated measures ANOVA of the BFM movement scores with a main factor of TIME (5 levels: pre, 0.5, 1, 3, 6 months) showed a significant effect of TIME [$F(4,76)= 67.4$, $p<0.00001$]. Since serial adjustments of stimulation were made at each time point the significance of these changes was examined. Repeated measures analysis with main factor TIME (4 levels: 0.5, 1, 3, 6 months) was then performed on the serial stimulation parameters of amplitude (mean for both sides units volts) pulse width (mean of both sides, units microseconds) and their numerical product (amplitude x pulse width). The product term was included because it describes the area of each delivered pulse and a better approximation of delivered current than either term alone. This analysis revealed a significant effect of TIME for amplitude [$F(3,57)= 12.8$, $p<0.0001$], pulse width [$F(3,57)= 7.2$, $p<0.0001$] and amplitude x pulse width [$F(3,57)= 17.1$, $p<0.0001$]. Post hoc t-tests comparing data at 0.5 months with later time points showed a significant progressive increase in amplitude (3.1 V ± 0.15 to 3.69 V ± 0.10, $p < 0.0001$), pulse width (60.8 μs ± 0.8 to 74.3 μs ± 3.8, $p = 0.003$) and their product (189.3 Vμs ± 9.3 to 275.8 Vμs ± 17.8, $p < 0.0001$), {0.5 vs 6 months, mean values ± SEM}. The recognition of concurrent significant progressive increases in stimulation intensity over the time course of interest raised the possibility that increases in stimulation parameters might account for progressive improvement observed in BFM scores. To address this question, random-effects maximum likelihood regression of BFM score with main factor of TIME (4 levels: 0.5, 1, 3 and 6 months) was performed with covariates of

amplitude, pulse width and amplitude x pulse width in separate analyses. There was an effect of TIME (z= -4.98, p < 0.0001) independent of amplitude (z= -0.12, p=0.905) or pulse width (z= 1.13, p=0.260). There was also an independent effect of TIME (z= -5.06, p <0.0001) controlling for amplitude x pulse width (z= 0.81, p=0.417).

3.4.1.2 Distribution of improvement by body region

The regional improvement in dystonia was evaluated by analysis of BFM movement scale subscores for each body region (Figure 3.3). For this analysis, 6 month follow up data in 20 patients was used. The 6 month time point was chosen since this maximised the number of subjects and time-course analysis showed stabilisation of BFM scores by 6 months.

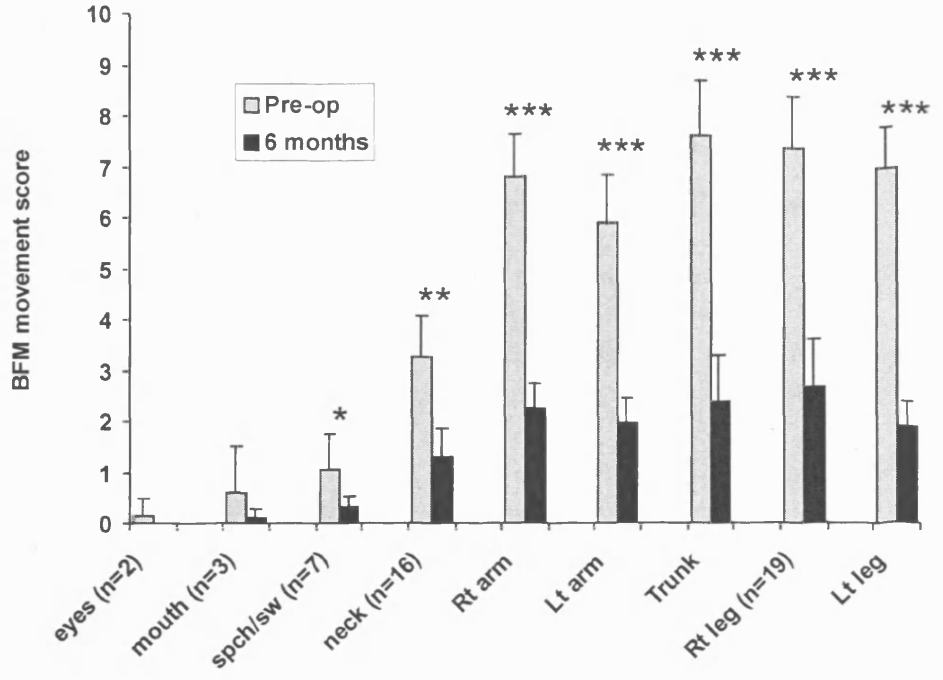


Figure 3.2. Mean BFM movement scale subscores before and 6 months after GPi in 20 patients, n= number of patients with dystonia involving the particular body region. Note eyes,

*mouth and neck are scored out of 8, the remaining items are out of 16. Error bars show ± 1 SEM, * $p<0.05$, ** $p< 0.001$, *** $p<0.0001$.*

The percentage improvement in each body region was compared using univariate ANOVA, the presence of the DYT1 mutation and orthopaedic deformity were included as between subjects factors. There was no main effect of body region [$F(8,116)=1.19$, $p=0.31$], but significant main effects of DYT1 [$F(1,116)=9.2$, $p=0.003$] and orthopaedic deformity [$F(1,116)=7.0$, $p=0.009$]. A characteristic pattern of dystonia was observed in four patients (all female, 3 DYT1, mean age 33 years) with mobile axial flexor spasms of the trunk and hips triggered by walking. These features resolved rapidly (within 2 weeks) after GPi DBS, the average overall improvement in BFM movement score in these patients at 6 months was 94% (range 87-98%).

3.4.1.3 Changes in functional status

Patients experienced significant improvement in BFM disability score following surgery. The mean disability scores at 6 months improved by 55% ± 23 ($p<0.00001$). After 6 months significant improvement occurred in all functional domains except speech ($p=0.08$).

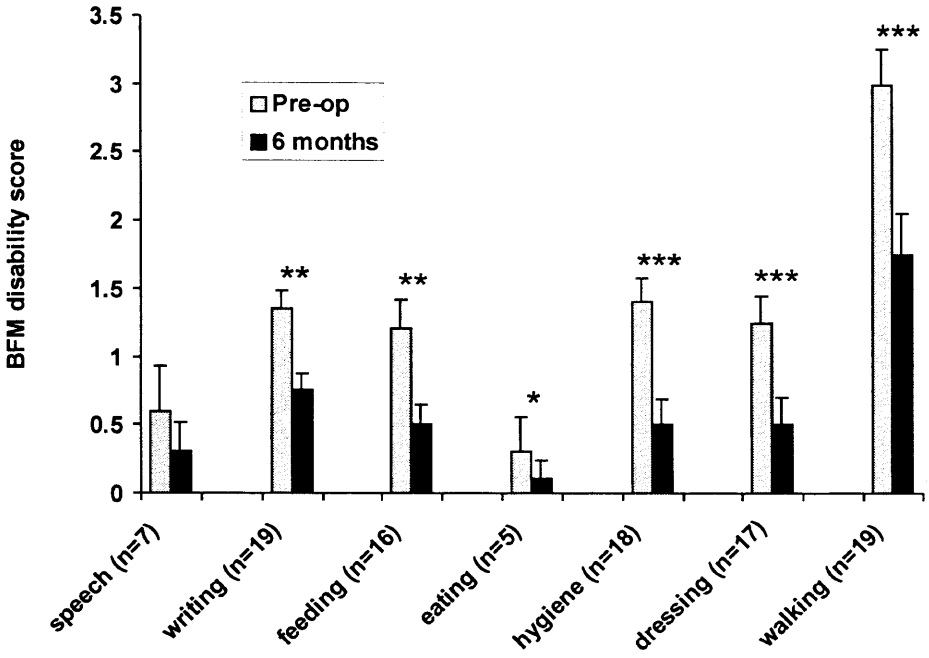
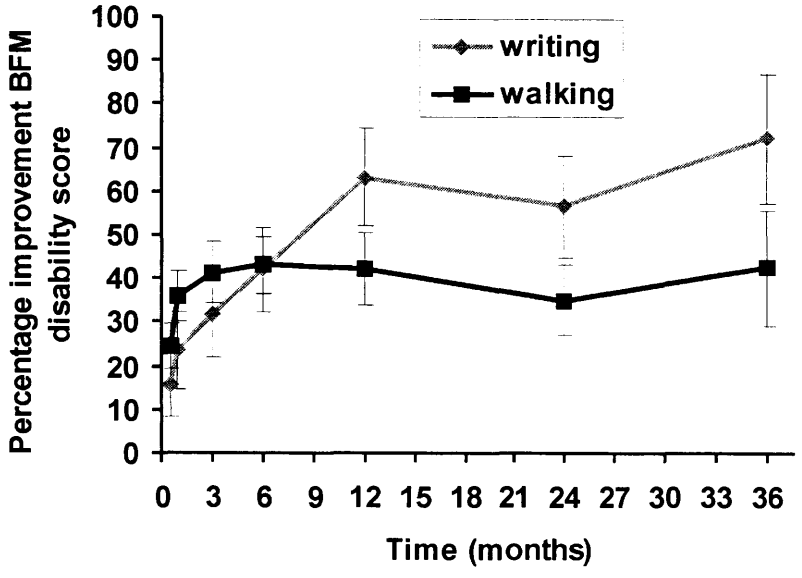


*Figure 3.3. Mean BFM disability scale subscores before and 6 months after GPi DBS in 20 patients, n= number of patients with dystonia involving the particular activity. Note walking is scored out of 6, the remaining items are scored out of 4. Error bars show ± 1 SEM, * $p<0.05$, ** $p< 0.001$, *** $p<0.0001$.*

The time-course of improvement of functional scores was progressive. An observation made during follow-up of these patients was that improvement in handwriting usually occurred after several months, whereas walking tended to improve soon after surgery (Figure 3.4a). To further analyse these differences, the time-course of handwriting and walking was compared in 14 patients with follow up of 24 months, all of whom had involvement of both handwriting and walking on the disability subscales (Figure 3.4b). The walking subscale data were normalised to a maximum score of 4 (instead of 6) to match the writing subscore. Repeated measures ANOVA with main factors of TIME (6 levels: pre-op, 1, 3, 6, 12, 24 months) and FUNCTION (2 levels: writing, walking) revealed main effects of TIME [$F(5,65)=13.1$, $p<0.0001$], FUNCTION [$F(1,13)=5.4$,

p=0.037] and TIME*FUNCTION interaction [F(5,65)=9.6, p<0.0001]. Paired t tests showed that significant decreases in disability score occurred for writing between 1 month and 12 months (p=0.008) and 1 month and 24 months (0.019) but not for walking (p=0.435 and p=0.98 respectively).

(a)



(b)

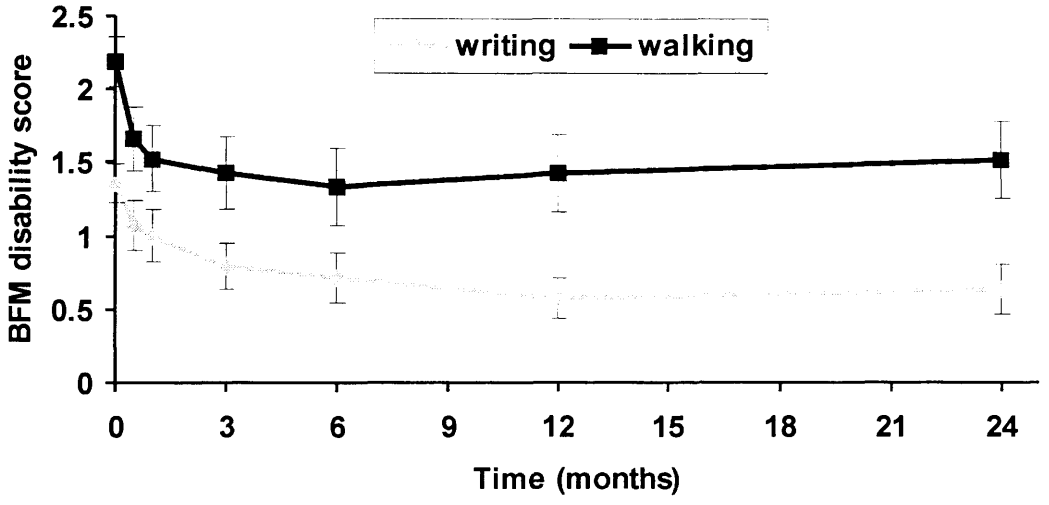


Figure 3.4 (a) Time-course of mean percentage improvement in disability subscales for writing and walking in the entire cohort at all time points (n=20 up to 6 months, n=16 up to 24 months

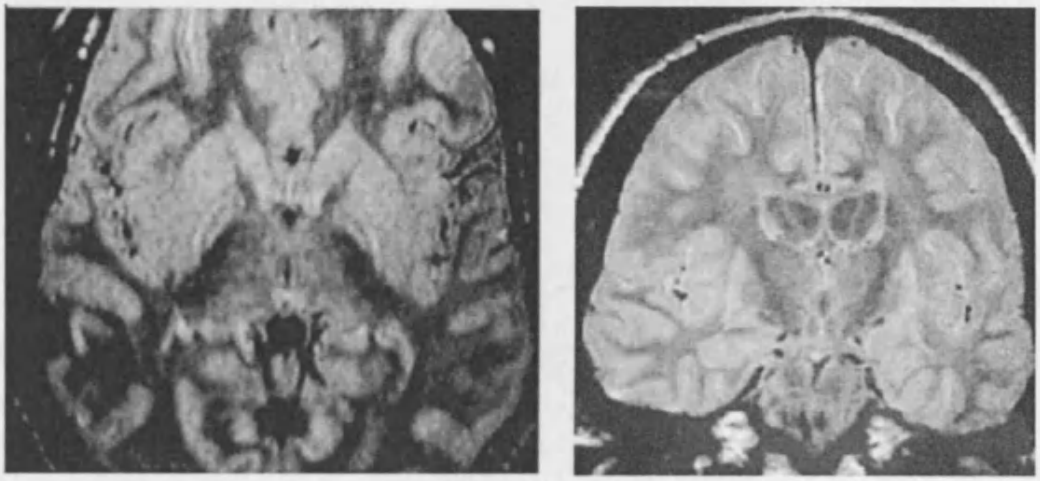
and n=10 at 36 months). Note that walking improves more steeply initially than writing whereas writing reaches its maximum improvement later. (b) Time course of mean normalised BFM disability subscores for writing and walking in 14 patients at all time points. Note writing decreases significantly beyond 1 month whereas for walking no further significant change occurs. Error bars show ± 1 SEM.

3.4.1.4 Predictive factors for improvement

To evaluate the effects of certain factors on outcome in primary generalised dystonia, the percentage improvement of BFM movement score at 6 months was analysed in 20 patients. Univariate ANOVA was used with between subjects factors of DYT1 positive and orthopaedic deformity and covariates of age, symptom duration and baseline severity (preoperative BFM movement score). This revealed independent effects of DYT1 positive [$F(1,13)=7.7$, $p=0.016$] and orthopaedic deformity [$F(1,19)=8.8$, $p=0.011$]. There was a trend to an effect of symptom duration [$F(1,19)=3.1$, $p=0.102$], while age ($p=0.63$) and baseline severity ($p=0.94$) were clearly non-significant. Six patients had orthopaedic deformity, 3 were DYT1 positive. The deformities involved spine (usually scoliosis) in 5 patients, and limb joint deformity (equinovarus foot) in 2 patients. Post-hoc comparison of groups, using one-way ANOVA, confirmed significantly better outcome in DYT1 positive patients compared to those lacking the DYT1 mutation: 77.0% ± 16.6 (Mean ± SD) vs 59.8% ±15.1 [$F(1,19)=5.9$, $p=0.026$]. Similarly those with orthopaedic deformity had significantly worse outcome compared to those without: 53.6% ± 13.6 vs 74.7 ± 15.7 [$F(1,19)=8.14$, $p=0.011$].

3.4.2 Secondary generalised dystonia

Four patients with secondary generalised dystonia were studied before and after bilateral GPi DBS (mean ± SD: age 25.5 years ± 6.1, disease duration 21.3 ± 4.8 years). These patients had one or more of the following features supporting the diagnosis of secondary dystonia: structural brain lesions or atrophy, history of perinatal cerebral insult, motor developmental delay, prominent/early orobulbar involvement, additional neurological features (cognitive impairment, pyramidal, cerebellar signs, hemiatrophy/dysmorphism, or previous epilepsy). In one patient there was a clear history of perinatal septic-anoxic encephalopathy with secondary pallidal atrophy on MRI (Fig 3.5a). Another patient had mild developmental delay and childhood onset of a progressive dystonic syndrome with cerebellar features and associated striatal and cerebellar atrophy (Fig 3.5b). In all 4 patients, investigations had excluded alternative aetiologies including DYT1, Wilson's disease, acanthocytosis, PKAN, white cell enzyme and mitochondrial disorders. All four patients were clinically quite similar at the time of surgery; all had severe generalised dystonia with marked orobulbar involvement and were non-ambulant. All were almost anarthric with eating, chewing and swallowing difficulty and required soft food, two had PEG feeding tubes. Episodes of severe generalised spasms causing pain occurred in 3 patients, and all had orthopaedic deformities in the trunk and/or limbs.



(a) (b)

Figure 3.5 Proton density MRI showing (a) pallidal atrophy in a patient with severe secondary generalised dystonia due to perinatal septic-anoxic encephalopathy. (b) Striatal atrophy particularly affecting caudate in another patient with severe secondary generalised dystonia.

The mean BFM movement score pre-operatively was 93.5 ± 13.9, and disability score 27.3 ± 1.5 out of a possible 120 and 30 respectively. Six months after surgery the BFM movement score had decreased to 76.8 ± 13.9 an 18.1% ± 6.8 improvement and by twelve months to 73.4 ± 7.7, a 21.0% ± 6.8 improvement ($p=0.02$, paired two tailed t test). This effect remained stable at 2 years post-op average improvement was 22.9 % ± 6.9 ($n=3$). Improvement in secondary dystonia was also progressive but less dramatically than in primary dystonia, since absolute improvements were smaller (Fig 3.7). To compare the relative efficacy of GPi DBS in primary versus secondary generalised dystonia, taking into account differences in baseline severity, a univariate ANOVA was performed of percentage improvement in BFM movement score at 6 months, with between subjects factors of aetiology (primary vs secondary) and presence of orthopaedic deformity, and covariates of age, disease duration, and baseline severity (Pre-op BFM movement score). This showed independent effects of aetiology

[F(1,23)=7.3, p=0.015] and orthopaedic deformity [F(1,23)=5.5, p=0.031] and no effect of baseline severity (p=0.55). One way ANOVA confirmed significantly lower percentage improvement at 6 months in secondary compared with primary generalised dystonia (18.1% vs 68.6%, [F(1,23)=30.0, p<0.00001].

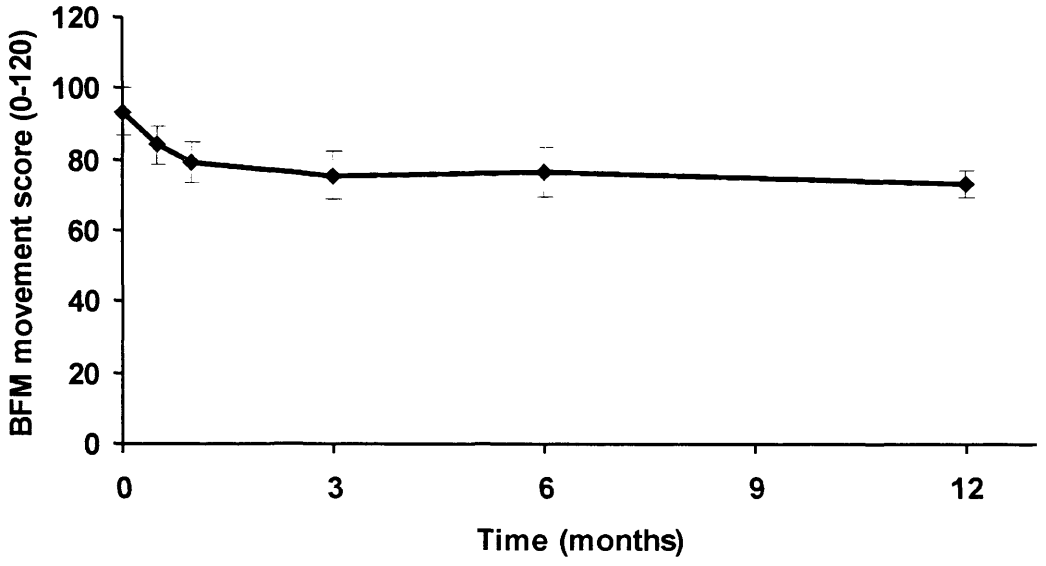


Figure 3.6 Time-course of changes in BFM movement score in 4 patients with secondary generalised dystonia. Data points show means, error bars ± 1 SEM.

The disability scores improved modestly after surgery; at 12 months 24.3 ± 2.5 an 8.9% ± 6 improvement. This translated into modest gains in writing, feeding, eating and hygiene, but speech and ambulation were in general not improved. In one patient dystonic tongue protrusion improved significantly. More importantly, and not captured in the BFM scale, patients and their carers reported improvements in posture, ease of handling for assisted care, pain and episodes of severe exacerbation of dystonic spasms. These improvements translated into noticeable benefits for patients in terms of comfort and ease of management.

3.4.3 Secondary hemidystonia

The efficacy of unilateral GPi DBS was studied in two patients with secondary hemidystonia were studied. The first patient was a 36 year old female with infantile onset right hemidystonia, which worsened in adulthood, affecting the arm more than the leg. Brain MRI demonstrated a lesion in the left posterior putamen and GPe, the likely aetiology being placental haemorrhage in late pregnancy. Pre-operatively this patient was maintained on high doses of Trihexphenidyl and Baclofen with modest benefit. The second patient was a 21 year old male, with infantile onset dystonia affecting the left leg, with flexion at the hip and knee and equinovarus posture of the foot, hemiatrophy of the left leg and chronic secondary dislocation of the hip. The dystonia was refractory to Trihexphenidyl, Levodopa and Tetrabenazine, and modestly improved with Clonazepam and botulinum toxin injections. The brain MRI showed a very small lesion in the posterior-most tip of the left GPi. In neither patient did the lesion directly encroach on the target area in the ipsilateral posteroventral GPi. Both patients showed some modest improvement in dystonic posture in the first few months after the surgery, however these improvements were not sustained. The pre-operative BFM movement scores were 18 and 16, and these were unchanged 12 months after surgery. The BFM disability scores (8 and 3 respectively) were also unchanged at 12 months. Neither patient has been able to reduce medications nor discontinue botulinum toxin injections.

3.4.4 Pantothenate kinase associated neurodegeneration (PKAN)

Two patients with PKAN generalised dystonia underwent bilateral GPi DBS (Table 3.2). Patient 1 had a relatively mild presentation of PKAN with generalised dystonia

worse in the upper limbs and oromandibular regions, amimia, dysarthric pallilalia and drooling, gait freezing and normal intellect. Patient 2 was more severely affected, with severe generalised dystonia, inability to walk, marked opisthotonic spasms, anarthria, tongue protrusion, dysphagia requiring PEG feeding and laryngeal dystonia requiring a tracheostomy.

Patient	*age gender*	*age of onset (yr)*	*PANK2 mutation*	*MRI "eye of the tiger"*	*Medications (mg/day)*	*BFM Movement pre / 12m*	*%Δ*	*BFM disability pre / 12m*	*%Δ*
1	35 / M	12	yes	yes	Baclofen 60	42 / 22	48	14 / 12	14
2	35 / M	11	yes	yes	Baclofen 100 Trihexyphenidyl 15 Levodopa 500 Diazepam 15	88 / 77.5	12	29 / 29	0

Table 3.2 Clinical data and outcome after GPi DBS in two PKAN generalised dystonia patients.

Both patients improved after surgery. In patient one, the oromandibular and upper limb dystonia improved such that he could dispense with the stick he chewed against constantly, and feed himself without difficulty. The gait freezing did not improve, and could be made worse with higher stimulation current. Patient 2 improved modestly in terms of the BFM movement score, a 12% improvement at 12 months, without any corresponding change in disability score. The most improved aspects were curvature of the trunk at rest, tongue protrusion and reduction in severe spasms. A few months after surgery it was possible to remove the tracheostomy.

3.4.5 Tardive dystonia

The patient with tardive dystonia operated was a 39 year old male with severe mobile retrocollis and truncal hyperextension, with moderate orofacial and limb dystonia of 2 years duration on the background of learning disability, anxiety disorder and prior neuroleptic exposure. The patient was known to have a chromosomal abnormality with 18p deletion, brain MRI was normal. Although the 18p deletion is associated with dystonia (Awaad et al 1999) the aetiology was deemed more likely to be tardive, because of the relatively short history, and characteristic axial extensor spasms. The patient had failed to respond to Tetrabenazine or high dose Trihexphenidyl and was under treatment with Trihexphenidyl 6 mg/day and Diazepam 30 mg/day. Following bilateral GPi DBS, there was an early dramatic improvement in the dystonia. The BFM movement score decreased from 87 preoperatively to 25 at 0.5 months, a 71% improvement, which was maintained up to 3 months. Thereafter some recurrence of dystonia occurred particularly in the neck and upper limbs, and at 12 months the BFM score was 45 (48% improvement). The disability score at 12 months had improved from 19 to 15, a 21% improvement.

3.4.6 Changes in medical therapy after GPi DBS

Reduction in oral medications after GPi DBS was effected in the most of the primary generalised dystonia patients and the patient with tardive dystonia, but not in the other patients, owing to the lesser degree of improvement after GPi DBS. Medications were deliberately not reduced for the first 6-12 months, and thereafter slowly reduced. Four of 6 patients were able to reduce Trihexphenidyl from a mean of 36 mg to 11 mg per day after 30 months. In one of these patients, Sulpiride 600 mg per day was stopped

after 18 months. The doses of Levodopa, Baclofen and Diazepam were approximately halved within 2 years in 3 patients. Of the 7 patients receiving botulinum toxin injections before surgery, 3 were able to discontinue injections completely, and three were able to stop injections for limb or trunk. The four patients who continued botulinum toxin, all received injections for residual cervical dystonia.

3.4.7 Stimulation related side effects in primary generalised dystonia

3.4.7.1 Dysarthria

Dysarthria occurred in 4 patients with primary generalised dystonia, 2 with DYT1. In each case it developed gradually after adjustment and was reported in follow-up, and in 3 was associated with a feeling of stiffness or tension in the upper lip. The dysarthia was subtle on direct examination, but in all patients brief cessation of stimulation resulted in noticeable immediate improvement in speech quality and relief of oral tension. The symptoms were permanently relieved by adjustment of stimulation parameters: in one a reduction of voltage and the other three, deactivation of a ventral contact and use of the adjacent dorsal contacts singly on both (n=2) or one (n=1) side.

3.4.7.2 Orofacial dyskinesia

In one patient with DYT1 primary generalised dystonia, orofacial-oromandibular involuntary movement developed de-novo a few weeks after change of electrode contacts from the most ventral contacts (0, 4 both located in GPi) to the adjacent dorsal contacts (1, 5 both located in GPi/MML). This change was mandated because of loss of effect on the ventral contacts (following a fall) that was later identified to be due to partial cable fracture. The movements subsided acutely with reinstatement of the

previous settings at the expense of worsening of lower limb dystonia, and were permanently relieved when the cable was repaired, allowing the ventral-most contacts to be reinstated for chronic stimulation. A second patient with non-DYT1 primary generalised dystonia experienced worsening of pre-existing orofacial dystonia, from intermittent pursing of the lips to forceful grimacing of the whole face under acute stimulation with contact 3 (located in left GPe) alone and contact 5 alone (located in GPi/MML) at 4.5 V, 60 μsec, 130 Hz. After two weeks of stimulation with contacts 2 and 6, 3.5 V, 60 μsec, 130 Hz, improvement in orofacial dystonia occurred (BFM mouth item score decreased from pre-op 3 to 1). However, the movements temporarily worsened after contacts 1 and 5 were additionally activated (BFM mouth item score 4.5). Therefore GPi DBS in this patient resulted in both temporary exacerbation and eventual improvement of orofacial dystonia/dyskinesia, that appeared to depend of the level of stimulation applied.

3.4.7.3 Akinesia

In 2 patients, one DYT 1, progressive akinetic symptoms developed 1 and 2 months after starting stimulation. Both patients complained of difficulty arising from sitting and turning in bed, slowness of gait, smaller steps, gait ignition difficulties and stiffness in the legs. There was also some slowing of foot taps, however, arm swing was preserved and there was no rigidity, amimia or dysarthria. In both patients, these features occurred with stimulation of the most ventral contacts, which were providing effective relief of dystonia. The symptoms were reversible by changing to more dorsal contacts, with improvement noted within hours of adjustment.

3.4.7.4 Tremor

In six patients upper extremity tremor was noted following GPi DBS (Table 3.3). In three of these patients some tremor was present before, but to a lesser degree. The character of the tremor was dystonic, present during posture and action. The tremor appeared within days of commencing stimulation, and in some patients was sufficient to make eating and drinking more difficult than before surgery. The tremor was a transient phenomenon and in all patients resolved within 1-3 months.

Patient	*DYT1*	*Onset (d)*	*Site*	*Pre-existing tremor*	*Type*	*Severity*	*Duration (wk)*
1	+	3	Right UE	+	postural and action	Moderate	8
2	-	6	UE, R>>L	+	postural and action	Moderate	8
3	+	4	UE, R>L	-	postural and action	Mild	12
4	-	2	Left UE	-	postural and action	Very mild	0.5
5	+	13	Left UE	-	postural and action	Moderate	4
6	-	4	UE, R=L	+	postural and action	Moderate	3

Table 3.3 Tremor in six patients following GPi DBS.

3.4.8 Stimulation parameters and DBS battery life

The average stimulation parameters for the primary generalised dystonia patients at 6, 12, 24 and 36 months are shown in Table 3.4. There was no significant difference at 6 months in the mean voltage or pulse width for DYT1 vs non-DYT1 (3.6 ± 0.4 V vs 3.8 ± 0.5 V $p = 0.47$, 68 ± 13 μsec vs 81 ± 19 μsec, $p= 0.08$) In the entire cohort, five patients required replacement of Kinetra after an average duration of 33 ± 8 months. The depletion of the Kinetra was linear with respect to time (Figure 3.8).

Time after surgery	*6 months*	*12 months*	*24 months*	*36 months*
n (patients)	20	16	16	10
Amplitude (V)	3.7 ± 0.5	3.4 ± 0.9	3.6 ± 0.6	3.7 ± 0.9
Pulse width (μsec)	74 ± 17	116 ± 100	89 ± 48	73 ± 17
Single monopolar (n, sides)	27	20	22	14
Double monopolar (n, sides)	13	12	10	6
contacts 0,1 and 4,5 in use (n, sides)	35	28	29	19

Table 3.4 Stimulation parameters in 20 patients with primary generalised dystonia at six months and later time points. Values are means ± SD. Note increase of pulse width and SD at 12 months, with corresponding decrease in voltage. This was the result of 3 sides being stimulated with pulse width of 450 μsec, in an effort to improve residual dystonia. This strategy did not produce added benefit and parameters were later reverted to shorter pulse width, higher voltage. Note also that almost all patients were stimulated on either the most or second most ventral contact singly or in combination.

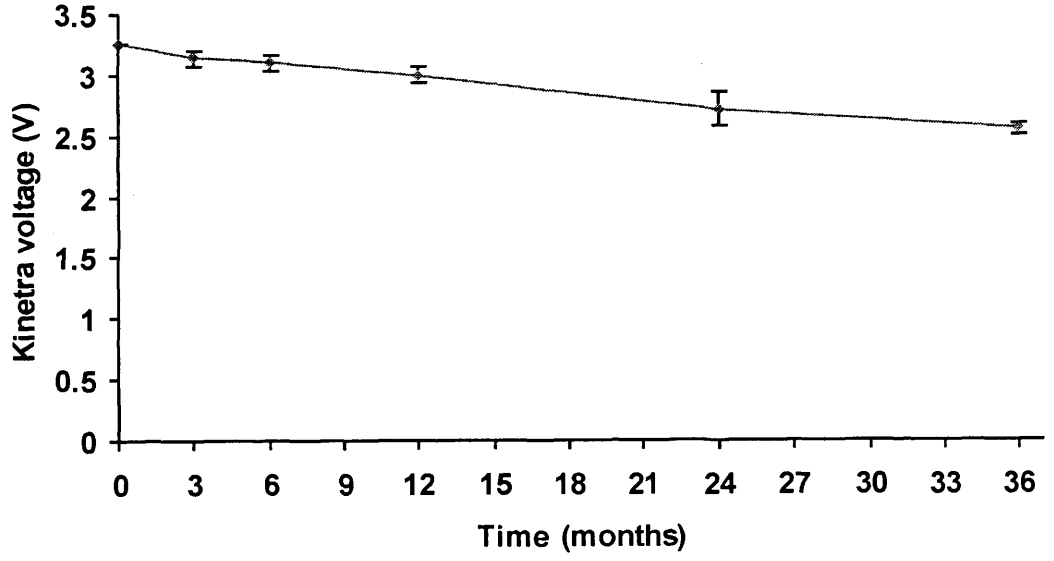


Figure 3.7 Kinetra implanted pulse generator voltage over time in patients with primary generalised dystonia. Points show means, error bars ± 1 SD. Sample size for means as follows, 3 m; n=3, 6 m; n=10, 12 m; n=12, 24 m; n=15, 36 m; n=9.

3.4.8 Complications and adverse events

There were no serious adverse events, in particular no intracranial haematoma or infection of the implanted system. There were three hardware-related complications. In one patient, the connecting cable partially fractured near the attachment to IPG due to a fall. This resulted in dystonia recurrence which was remediable, in the short term by changing to more dorsal contacts until the cable was replaced. In one patient the IPG failed abruptly resulting in recurrence of dystonia, 38 months post-implant but well before depletion of the IPG. The IPG was one of a faulty batch with a manufacturing defect of the bond wire linking battery with neurostimulator assembly inside the IPG, and was replaced with a new unit. Another patient experienced gradual worsening of dystonia following IPG replacement with unusually high electrode impedances. Test stimulation at high currents (4V, 90 μsec, contacts 0 and 4) evoked no side effect, suggesting a broken circuit, however when the left arm was elevated, sudden capsular side effects (right facial muscle contractions) occurred, suggesting an intermittent connection. Fluoroscopy of the implanted system revealed no cable fracture. At surgery, loosening of the screws fixing the cable to the IPG was found resulting in a loose connection, which was corrected.

3.5 Discussion

3.5.1 Time-course of improvement and neural plasticity

The present results show that the time-course of improvement is progressive, as has been observed previously (Yianni et al 2003, Krauss et al 2004, Vidailhet et al 2005). A novel aspect of the present findings is that the time course follows a logarithmic distribution. This was true not only of the group average but also of individual patients,

each with their own log function coefficients. A previous study looking at time course of improvement in dystonia after DBS suggested a linear distribution with patient-specific slopes (Yianni et al 2003). Examination of individual patient data from this study reveals a similar pattern to the present study, with most of the improvement achieved within the first 3 months, and then some further progressive benefit. Unlike the present study, the earliest time point was 3 months, which omits the early time course, and may explain the differing interpretation of a linear effect. The logarithmic time-course demonstrated in the present study suggests that neuroplasticity underlies GPi DBS effect. A logarithmic time-course has also been observed in recovery of upper limb motor strength following stroke, a setting in which adaptive neuroplasticity is believed to play an important role (Goodwin et al 2003, Koyama et al 2005).

An interesting feature of functional improvement after GPi DBS (as reflected in BFM disability subscales) was that different time courses occurred for handwriting and walking. Improvement in handwriting was slower, but eventually exceeded that of walking. This result is also compatible with the notion of plasticity underlying DBS effect. Walking is a semi-automated motor activity whereas writing is highly learned and more demanding of the sensorimotor cortex. Therefore functional reorganisation of representations for hierarchically more complex tasks might be expected to take longer than for more automated activity such as walking.

It has been previously reported that mobile dystonia tends to improve more quickly than tonic postures after GPi DBS (Vercueil et al 2002, Krauss et al 2002). Moreover, it has been suggested that patients with mainly mobile dystonia may respond better overall (Vidailhet et al 2005). Limitations of the BFM scale in delineating mobile and tonic aspects of dystonia precludes any firm quantitative judgement on this important point in the present series. However, based on clinical observation the same basic

pattern of response occurred, well illustrated by rapid and excellent improvement in axial flexor spasms during walking in four patients.

3.5.2 Efficacy of GPi DBS depends on aetiology of dystonia

In the present study, among patients with generalised dystonia, secondary aetiology was a strong predictor of poorer response, even after adjustment for baseline severity of dystonia. This suggests that secondary generalised dystonia is inherently less responsive to GPi DBS and that the poorer response is not an indirect consequence of it being more severe. These results agree with previous reports of poorer response to GPi DBS in secondary than primary generalised dystonia (Cif et al 2003, Starr et al 2004, Eltahawy et al 2004). Although improvement in secondary generalised dystonia was modest, the changes were both clinically relevant and statistically significant, in terms of comfort and ease of management of these severely disabled patients. The level of improvement in PKAN was intermediate between secondary and primary and the response in these two patients was poorer than that reported previously (Umemura et al 2004, Castelnau et al 2005). PKAN patients also display basal ganglia lesions, suggesting that structural lesions of the basal ganglia may negate the effectiveness of GPi DBS. This certainly appears to be true in patients with secondary hemidystonia related to unilateral structural basal ganglia lesions in whom no improvement occurred with GPi DBS. The converse also appears true, in that tardive dystonia, which lacks basal ganglia lesions responded more favourably than other forms of secondary dystonia, a result in agreement with previous reports (Trottenberg et al 2001, Starr et al 2004). Because primary generalised dystonia enjoys a superior response to GPi DBS than secondary, patients considered for GPi DBS, particularly those lacking the DYT1 mutation, should be fully investigated for secondary causes of dystonia, with particular

attention to brain MRI. For symptom palliation in secondary generalised dystonia bilateral GPi DBS appears a reasonable therapeutic option, however the present results do not support its use for secondary hemidystonia due to focal basal ganglia lesions.

3.5.3 Predictive factors for improvement in primary generalised dystonia and implications for patient selection

The striking difference between the response of primary and secondary dystonia stands as a major distinction in therapeutic effectiveness of GPi DBS for different types of dystonia. Within primary dystonia, some factors were also identified which influenced outcome. The presence of the DYT1 mutation was an independent positive predictor of outcome after GPi DBS. Several studies have noted that patients with DYT1 tend to respond well (Coubes et al 2000, Krause et al 2004, Starr et al 2004) although recent larger series have shown no significant outcome difference (Vidailhet et al 2005, Kupsch et al 2006). There are several possible reasons why DYT1 dystonia might respond more efficiently to GPi DBS. The first possibility is that DYT1 dystonia differs pathophysiologically, allowing GPi DBS to work more efficiently. Against this view, the range of physiological abnormalities in DYT1 patients is very similar to those lacking DYT1, including defective inhibition at cortical and brainstem levels and the tendency to excessive motor cortical plasticity (Edwards et al 2003b, 2006, Huang et al 2006). An alternative explanation relates to the fact that the identification of the DYT1 mutation confirms the diagnosis of primary dystonia with certainty. In patients lacking the DYT1 mutation, even those fulfilling clinical criteria for primary generalised dystonia, there remains the possibility of an unrecognised secondary aetiology, which will confer a poorer response to GPi DBS. Therefore it may not be that the DYT1 mutation has any special biological significance for GPi DBS effect, but rather it

guarantees a homogenous study population of primary dystonia. The present results indicate that the DYT1 mutation is a favourable prognostic indicator and emphasise the need for genetic testing in all young onset primary generalised dystonia patients, particularly those considered for GPi DBS.

In the present study, orthopaedic deformity predicted a poorer response to GPi DBS. Joint or spine deformity itself does not attract a score in the BFM movement scale unless accompanied by active muscle contractions or involuntary movements, which are assessed by observation and palpation of muscles. So the mere presence of the deformity does not explain the poorer scores. Instead a more complex physiological relationship between orthopaedic deformity and dystonia may exist where peripheral injury to joints alters function in skeletomuscular afferents perpetuating a pathophysiological component of the dystonia. Whatever the mechanism, orthopaedic deformity appears to confer a poorer response to GPi DBS. A related result was a trend for longer duration of symptoms to predict a poorer outcome ($p=0.102$ in the univariate analysis). Taken together, these results suggest that patients with primary generalised dystonia should be operated early, once medication refractory disability has occurred, but well before the development of fixed orthopaedic deformity.

3.5.4 Stimulation related side effects: reversibility and mechanisms

The dysarthria observed in the present series following GPi DBS may relate to spread of current to adjacent capsule and activation of corticobulbar fibres. In support of this, the symptoms were rapidly reversible with switching stimulation off and in some patients tension or stiffness was described around the mouth, suggestive of corticobulbar activation. The delayed onset of dysarthria following adjustment of DBS

parameters argues somewhat against direct capsular effects which tend to be immediate once the threshold is reached. A possible explanation is that tissue impedance falls over time, so that the delivered current increases, even with constant electrical parameters. The origin of the akinesia observed in two patients, so named because of the slowness of movement, is uncertain. However, the two main possibilities are extrapyramidal due to modification of basal ganglia output, or corticospinal due to spread of current to the adjacent internal capsule. There has been another report of reversible Parkinsonism with bradykinesia, rigidity and gait freezing, in a dystonic patient following bilateral GPi DBS also associated with stimulation of ventral contacts and relived by switching to more dorsal contacts (Watson et al 2006). In the present patients and the previous report, akinesia occurred with stimulation of ventral contacts and was relieved by changing to more dorsal contacts. These observations agree with those made during pallidal for stimulation Parkinson's disease where akinesia could be elicited with ventral GPi stimulation and dyskinesia with dorsal GPe stimulation (Bejjani et al 1997, Krack et al 1998) and support an underlying extrapyramidal mechanism. Similarly, chorea induced by GPe stimulation in a dystonic patient has been reported (Mouton et al 2006) which parallels the present observation of orofacial dyskinesia when more dorsal contacts were activated which were in the GPi/MML boundary and closer to GPe. In the present series, temporary upper extremity tremor occurred soon after commencement of stimulation in some patients. This may relate to a shift in the balance of dystonic symptoms affecting the limb. Improvement of tonic dystonia by relaxing the limbs may have allowed phasic dystonia during action to be more obvious, resulting in occurrence or worsening of tremor.

3.5.5 DBS parameter selection: are high currents necessary in dystonia?

A number of studies have found that dystonia patients with GPi DBS require high stimulation currents (Coubes at al 2000, 2004, Starr et al 2004, Krauss et al 2004). The present results challenge this notion in that the average parameters in the primary dystonics were lower than many of those published in other series. There are a few possible explanations for this discrepancy. Firstly, the present series comprised 10 DYT1 patients who respond well to GPi DBS and showed a trend for requiring lower electrical stimulation parameters (pulse width, p=0.08), therefore escalation of current to combat residual symptoms might be less needed in this group. However, other series have also included DYT1 patients so this is unlikely to be the sole explanation. The approach to adjustment of stimulation parameters may also be important. Several groups use longer pulse widths and higher amplitudes, ranging from 150-450 μsec and 1.5-10V (Kumar et al 1999b, Yianni et al 2003, Coubes et al 2004, Starr et al 2004) whereas in the present series shorter pulse widths have been used. In the study of Vidailhet et al (2005) in a comparable sample of 22 primary generalised dystonia patients with bilateral GPi DBS, the average parameters at 12 months were pulse width 139 ± 130 μsec, amplitude 3.7 ± 1.0 V and frequency 134 ± 18 Hz, the main difference being the longer pulse width. The present results would suggest that lower electrical stimulation parameters, particularly pulse width, may be equally efficacious, with the added advantage of energy conservation and prolongation of IPG life. Another issue in the adjustment of stimulation parameters in dystonia relates to the time course of improvement. Because the therapeutic response in dystonia is delayed, there may be a temptation to increase the stimulation current rather than wait for improvement to develop at a given setting. In the present study a relatively low initial current was used, and increased incrementally at later follow-ups, particularly in patients in whom

improvement appeared to have plateaued. It is of relevance that serial increases in stimulation current made during follow up did not dictate the time course of improvement, which brings into question the need for increasing the current during follow up. This also tends to imply that the bulk of GPi DBS effect is achieved with the initial current and provision of sufficient time for the dystonia to respond.

3.5.6 Study limitations

A limitation of the present study is that the same single rater (ST) performing the BFM scoring was also responsible for the adjustment of stimulation parameters, and therefore unblinded. This could have potentially introduced bias in the scoring of patients. There are a few reasons which argue against this point playing a major role in the present results. Firstly, adjustments of stimulation parameters do not lead to immediate improvement in dystonia, therefore the clinical effect corresponds to adjustment made weeks or months before. Therefore it would be difficult for a rater to mentally associate an adjustment with a corresponding clinical effect. Also patients were scored before any adjustment was made or interrogation of stimulation parameters. Secondly there were no a priori groups in this study, such as a "real" vs. "sham" stimulation, where explicit knowledge grouping might influence the rater's judgement as to what to expect.

Another limitation of the present study relates to the BFM scale. Although this scale has good intra and inter-rater reliability for the overall burden of dystonia, it has limitations with regard to dystonia evaluation in the setting of GPi DBS therapy. Firstly it does not readily distinguish between mobile and tonic forms of dystonia. Such a distinction would be potentially very useful since mobile aspects of dystonia tend to

respond more quickly and fully to GPi DBS than tonic elements; however this observation, although born out in the present study remains unsubstantiated in terms of quantitative measurement. Another limitation of the BFM scale is that it is relatively insensitive to small improvements in the motor score and unable to capture certain functional improvement in the functional score, perhaps giving a falsely low impression of improvement. This is particularly true in severely affected patients with near maximal scores, where the scale may be "saturated" and subject to ceiling effects. It should be pointed out that these limitations do not pose a direct threat to the validity of the present results, but rather highlight the need for the development of additional rating tools or forms of quantitative assessment to tackle some of these outstanding questions. Future studies using longitudinal quantitative kinematic analysis would be helpful to resolve this question.

3.6 Conclusions

GPi DBS is a safe and effective treatment for several types of dystonia, particularly primary generalised, and confers significant and sustained therapeutic benefit. Although all primary generalised patients may respond well, those with the DYT1 mutation enjoy a greater benefit. Conversely, the presence of fixed orthopaedic deformities reduces the effectiveness of GPi DBS. This makes a strong case to undertake surgery earlier, before orthopaedic deformity has occurred. The time course of improvement in dystonia after GPi DBS is progressive and logarithmic and points to neural plasticity underlying GPi DBS effect.

Chapter 4. The effect of electrode contact location on clinical efficacy of GPi DBS in primary generalised dystonia

4.1 Summary

This study sought to determine the effect of electrode contact location on efficacy of bilateral globus pallidus internus (GPi) deep brain stimulation (DBS) for primary generalised dystonia (PGD). A consecutive series of 15 patients with PGD (10 female, mean age 42 years, 7 DYT1) who underwent bilateral GPi DBS, were assessed using the BFM dystonia scale before, and 6 months after surgery. The position of the stimulated electrode contact(s) was determined from the post-operative stereotactic MRI. Contralateral limb and total axial BFM sub-scores were compared with the location of the stimulated contact(s) within GPi. The mean total BFM score decreased from 38.9 preoperatively to 11.9 at 6 months, a 69.5% improvement ($p<0.00001$). Cluster analysis of the stimulated contact coordinates identified two groups, distributed along an anterodorsal to posteroventral axis. Clinical improvement was greater for posteroventral than anterodorsal stimulation for the arm (86% vs 52% $p<0.05$) and trunk (96% vs 65%, $p<0.05$) and inversely correlated with the y coordinate. For the leg, posteroventral and anterodorsal stimulation were of equivalent efficacy. Overall clinical improvement was maximal with posteroventral stimulation (89% vs 67%, $p<0.05$) and inversely correlated with y (A-P) coordinate ($r=-0.62$, $p<0.05$). GPi DBS is effective for PGD but the outcome is dependent on contact location. Posteroventral GPi stimulation provided the best overall effect and was superior for the arm and trunk. These results may be explained by the functional anatomy of GPi and its outflow tracts.

4.2 Introduction

Primary generalised dystonia (PGD) is a movement disorder characterised by involuntary muscle contractions, causing abnormal postures and spasms (Fahn 1998). The failure of medical treatment has led to renewed interest in functional neurosurgical approaches to its treatment. Earlier positive reports of ablative pallidal surgery in dystonia (Cooper 1956) and the subsequent observations of improvement of dystonia in Parkinson's disease with posteroventral pallidotomy and DBS led to the first attempts to treat dystonia using globus pallidus internus (GPi) deep brain stimulation (DBS) by Coubes in 1996 (Coubes et al 1999). Since then GPi DBS has emerged as an effective treatment for PGD (Coubes at al 2004, Vidailhet et al 2005). Despite this progress and the more widespread acceptance of the technique there is still debate about the optimal target within the GPi to achieve the best effect in dystonia. Most surgeons target the posteroventral portion of the GPi, the classical target for pallidotomy developed by Leksell and Laitinen (Laitinen et al 1992). However to date, there has been little data to support the superiority of this target in dystonia, or to indicte whether within this region there may be an optimal zone to achieve the best effect.

The aim of the present study was to explore the relationship between the precise location of the therapeutically stimulated electrode contact and the magnitude of clinical benefit in a consecutive series of patients with PGD who all underwent bilateral GPi DBS. The aim of this analysis was to determine if within GPi there is any regional stratification of the efficacy of stimulation for dystonia.

4.3 Methods

4.3.1 Subjects

We studied a consecutive series of 15 patients with PGD. The clinical characteristics of the patients are summarised in Table 4.1. Patient 8 had a previous thalamotomy 23 years before. The study was approved by the Joint Research Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology.

Patient	*Gender*	*Age (years)*	*Disease duration (years)*	*DYT 1 gene status*	*Site of onset*	*Worst affected areas*	*BFM score pre-op/ 6 months (0-120)*	*Medications*	*DBS parameters*
1	F	18	9	+	R hand	Trunk R limbs	48/1	Trihexphenidyl	R: 4,5-, 3.9v, 60μsec, 130 Hz L: 0,1-, 3.9v, 60μsec, 130 Hz
2	M	24	16	-	R hand	Neck, trunk R limbs	73/15	Clonazepam	R: 4,5-, 3.9 v, 90μsec, 130 Hz L: 0,1-, 3.8 v, 90μsec, 130 Hz
3	M	47	37	+	L leg	Neck, trunk L side	52/22	Diazepam Tetrabenazine	R: 4-, 3.5v, 90μsec, 130 Hz L: 0,1-, 3.3v, 60μsec, 130 Hz
4	F	23	12	-	R leg	Trunk R leg	53/32	None	R: 5-, 4.0v, 60μsec, 130 Hz L: 1-, 4.2v, 60μsec, 130 Hz
5	F	52	36	+	L arm	L limbs	29/7	None	R: 4-, 3.0v, 60μsec, 130 Hz L: 0-, 3.0v, 60μsec, 130 Hz
6	F	16	7	+	R leg	R limbs Trunk	20/1	L-dopa Trihexphenidyl	R: 4-, 2.9v, 60μsec, 130 Hz L: 0-, 2.9v, 60μsec, 130 Hz
7	F	63	4	-	Trunk	Trunk Both legs	23/3	L-dopa Trihexphenidyl	R: 6-, 4.6v, 90μsec, 130 Hz L: 2-, 4.6v, 90μsec, 130 Hz
8	F	54	43	-	R hand	L limbs	24/9	None	R: 4-, 3.7v, 60μsec, 130 Hz L: 1-, 3.7v, 60μsec, 130 Hz
9	F	36	25	+	L foot	Trunk L limbs	21/1	Trihexphenidyl	R: 4-, 4.6v, 90μsec, 130 Hz L: 0-, 4.2v, 90μsec, 130 Hz
10	M	62	43	-	Neck	Neck, trunk L arm	28/15	Trihexphenidyl Baclofen Clonazepam	R: 6 -, 3.7v, 90μsec, 130 Hz L: 1-, 3.7v, 90μsec, 130 Hz
11	F	22	15	+	L foot	Trunk Both legs	51/11	Trihexphenidyl Baclofen	R: 4-, 3.6v, 60μsec, 130 Hz L: 0-, 3.6v, 60μsec, 130 Hz
12	F	64	50	-	R hand	Trunk R limbs	46/13	None	R: 5,6-, 3.5v, 60μsec, 130 Hz L: 1,2-, 3.5v, 60μsec, 130 Hz
13	M	62	7	-	L leg	Neck, L leg R arm	64/30	None	R: 4,5-, 3.5v, 60μsec, 130 Hz L: 1,2-, 3.5v, 60μsec, 130 Hz
14	M	47	26	-	Neck	Neck R arm	25/12	None	R: 4,5-, 3.5v, 90μsec, 130 Hz L: 0,1-, 3.5v, 90μsec, 130 Hz
15	F	42	30	+	R foot	R arm, leg	27/6	None	R: 5-, 3.5v, 60μsec, 130 Hz L: 1-, 3.5v, 60μsec, 130 Hz

Table 4.1 Clinical patient data.

4.3.2. Surgical procedures and stimulation parameters

All patients underwent bilateral implantation of electrodes into GPi and chronic stimulation using surgical technique outlined in the General Methods. The quadripolar DBS electrode model 3389, with four platinum-iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm in length and 2 mm centre-to-centre separation) and Kinetra model 7428 implanted pulse generator (Medtronic Neurological Division, Minneapolis USA) were used in all except four patients where model 3387 (3 mm centre-to-centre separation) electrodes were used. Confirmation of electrode placement in GPi was obtained in all patients with immediate post-implantation stereotactic MRI. All patients received monopolar stimulation with one or two adjacent active contacts. Stimulation parameters were individualised in each patient and chosen for the best clinical effect and the least side effects. Eight patients were stimulated at ventral contacts; in 7 patients (12 sides) the most ventral contacts (0 and 4) were not used for chronic stimulation. The reasons for not using the most ventral contacts were capsular (corticospinal) response, with tension in the contralateral face or arm or dysarthria (patients 8,10,15), dizziness (patient 4), better clinical effect of more dorsal contacts (patient 7), and not tried for chronic stimulation from the outset (patients 12 and 13). The stimulation parameters in each patient at 6 months are shown in Table 4.1.

4.3.3 Clinical evaluation

Clinical assessment was performed using the Burke-Fahn-Marsden scale (BFM). Patients were assessed pre-operatively and 6 months after surgery. Right and left hemibody scores were derived from the BFM Movement scores for the arm and leg. The BFM Movement scores for axial items (eyes, mouth, speech, neck, trunk), which

are unpaired data, were analysed separately on a whole patient basis rather than by sides.

4.3.4 MRI analysis and determination of electrode contact position

MRI images were analysed using the Stealth workstation (Framelink TM, Medtronic, Minneapolis USA). The investigator determining contact location was blinded to the clinical scores of the patients. Electrode contacts were identified on the post-operative stereotactic MRI. The centre of the electrode contact was determined as the centre of its artifact visible on the MRI image. Electrode contact position with respect to mid-commissural point, atlas-defined target and the visible anatomical target was determined. The visible target was spatially normalised to atlas target of x = 21 mm, y = 2 mm, z = - 5 mm in relation to mid-commissural point. The Cartesian coordinates of the active contact after this transposition were then derived. This transposition normalised for anatomical variation between and within patients. Where two adjacent contacts were stimulated, (11 sides), the geometric mean of the two stimulated contacts was used. In addition to quantitative localisation of the stimulated electrode contacts, their position in relation to anatomical boundaries of the GPi visible on MRI images was determined. Using the same MRI analysis methods, the targeting error for each electrode was determined as the distance between the intended target and the electrode position.

4.3.5 Statistical analysis

Clinical and contact location data were cross tabulated so that total hemibody, arm and leg scores were paired with the coordinates of the contralateral active electrode contact (30 sides). Total scores and axial sub scores were paired with the mean x, y, z

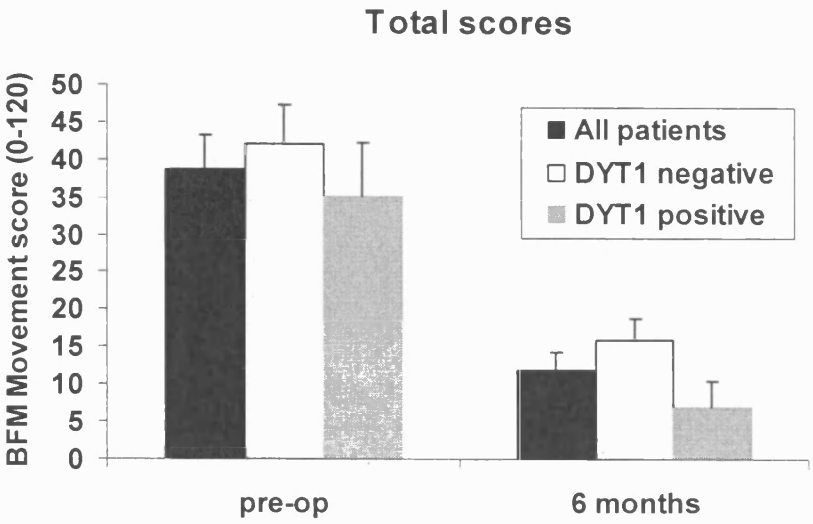
coordinates of active contacts of both electrodes (15 patients), to enable the data to be treated on a whole patient basis rather than by sides. Cluster analysis (K-means cluster) was used to identify subgroups of electrode contacts within geographically distinct domains. Differences between groups were determined using Chi square and two-tailed unpaired t-tests. Repeated measures ANOVA was used to explore the effects of coordinate and DYT1 status on clinical outcome. Correlations were performed using the Pearson correlation coefficient. A p value less than 0.05 was considered significant. All statistics were performed using SSPS for Windows version 11.5.

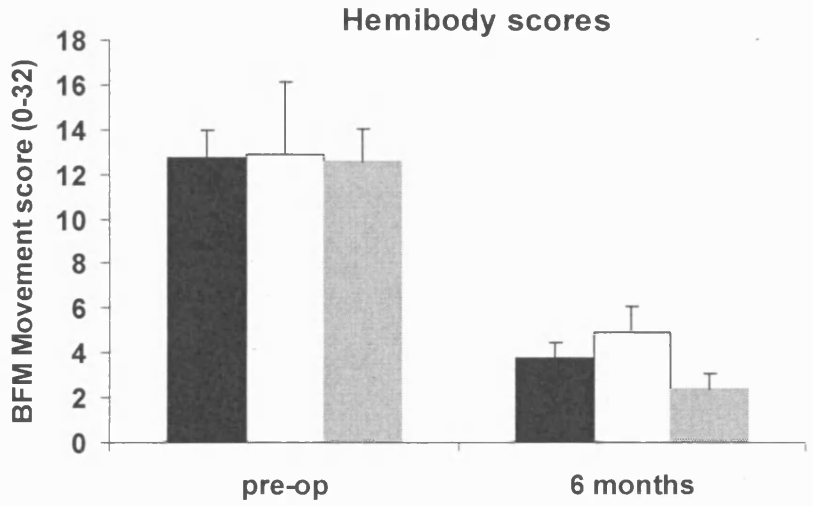
4.4 Results

4.4.1 Clinical Outcome

Dystonia improved in all patients after surgery. The mean BFM Movement score decreased from 38.9 preoperatively to 11.9 at 6 months, a 69.5% improvement ($p<0.00001$). The BFM disability score improved from 9.0 to 4.1, a 58% improvement ($p<0.00001$). The mean percentage improvement in hemibody scores was 67.8% ($p<0.0001$). There was no significant difference in outcome between arm and leg (63.8% vs 72.9% p=NS) or right and left body sides (67.5% vs 68.0% p=NS). Patients with DYT1 showed significantly greater improvement in total movement score (82.5% vs 61.5% $p<0.05$), hemibody score (81.8% vs 55.4 %, $p<0.01$) but not axial (89.4% vs 63.9% p=NS) or disability score (69.5% vs 50.9%, p=NS). Improvement in hemibody score was non-significantly greater for 3387 than 3389 electrodes (79.0% vs 63.6% p=NS). The clinical outcome results are summarised in Figure 4.1. Of note, there were 2 patients (patients 5 and 8), who developed delayed onset akinesia with gait slowing, and difficulty arising from sitting and turning in bed. In both patients, these akinetic

features occurred with stimulation of ventral contacts and improved by changing to more dorsal contacts.





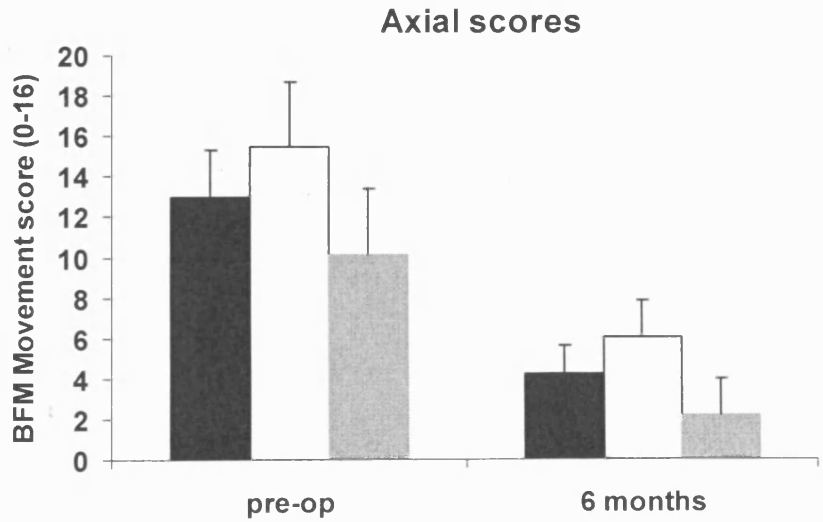


Figure 4.1. Mean BFM movement scores for whole body, hemibody (arm, leg) and axial (eyes, mouth, speech/swallow, neck and trunk) before and 6 months after bilateral GPi DBS. Error bars ±1 SEM. All decreases in BFM significant at $p<0.05$ level.

4.4.2 Electrode contact location

Table 4.2 shows the electrode contact position in relation to pallidal anatomy, for each patient side.

Patient	*Left side*				*Right side*			
	Contact 0	Contact 1	Contact 2	Contact 3	Contact 4	Contact 5	Contact 6	Contact 7
1	GPi*	GPi / MML*	GPe	GPe / LML	GPi *	GPi/MML*	GPe	GPe/LML
2	GPi *	GPi *	GPe	GPe / LML	GPi *	GPi / MML *	GPe	LML/ PT
3	GPi *	GPi *	GPi / MML	Gpe	GPi *	GPi / MML	GPe	GPe
4	GPi	GPi/MML*	MML/GPe	GPe/LML	GPi	GPi/MML*	GPe	GPe
5	GPi *	GPi / MML	GPe	Gpe	GPi *	GPi / MML	GPe	GPe / LML
6	GPi*	Gpi	GPi	Gpi	GPi*	GPi/MML	MML/GPi	GPe
7	GPi	Gpi	GPi *	GPi / MML	GPi	GPi	GPi *	GPi / MML
8	GPi	GPi *	GPi / MML	Gpe	GPi *	GPi / MML	GPe	LML / PT
9	GPi *	Gpi	GPi	GPi/ MML	GPi *	MML/ GPe	GPe	GPe/ LML
10	GPi	GPi / MML *	MML/ GPe	Gpe	IC / GPi	GPi	GPi / MML *	MML
11	GPi *	GPi / MML	MML	Gpe	GPi *	GPi /MML	MML	MML / GPe
12	GPi	GPi/MML*	GPe*	Gpe	GPi	GPi*	GPi/MML*	GPe
13	GPi	GPi*	GPi/MML*	LML/PT	GPi*	GPi/MML*	MML/GPe	GPe
14	GPi*	GPi/MML*	MML	MML/GPe	GPi*	GPe*	GPe/LML	LML/PT
15	GPi	GPi*	GPi/MML	Gpe	GPi	GPi/MML*	GPe/LML	GPe

*Table 4.2. Legend: Abbreviations; GPi=globus pallidus internus, GPe=globus pallidus externus, MML= medial medullary lamina (separates GPi and GPe), LML=lateral medullary lamina (separates GPe and putamen), PT=putamen, IC=internal capsule. * denotes stimulated contact.*

The MRI of patient 1 is shown in Figure 2. For the entire cohort, the mean coordinates of the stimulated contact were x = 20.8 mm (18.3-22.4) y = 3.2 mm (1.2-5.1) and z = -0.76 mm (–5.3-2.2). Electrode contacts on the left brain side were more medial than on the right (20.2 mm vs 21.4 mm $p<0.001$), but for Y and Z coordinates there was no significant difference between right and left sides. The mean Euclidean targeting error for all the electrodes was 0.9 mm ± SD 0.5, and not significantly different between right and left sides. Since the targeting error was acceptably small and equal on both sides, the likely explanation of the left electrode being more medial is that the GPi is anatomically more medial on the left than the right, as has been shown in a previous study (Hirabayashi et al 2002).

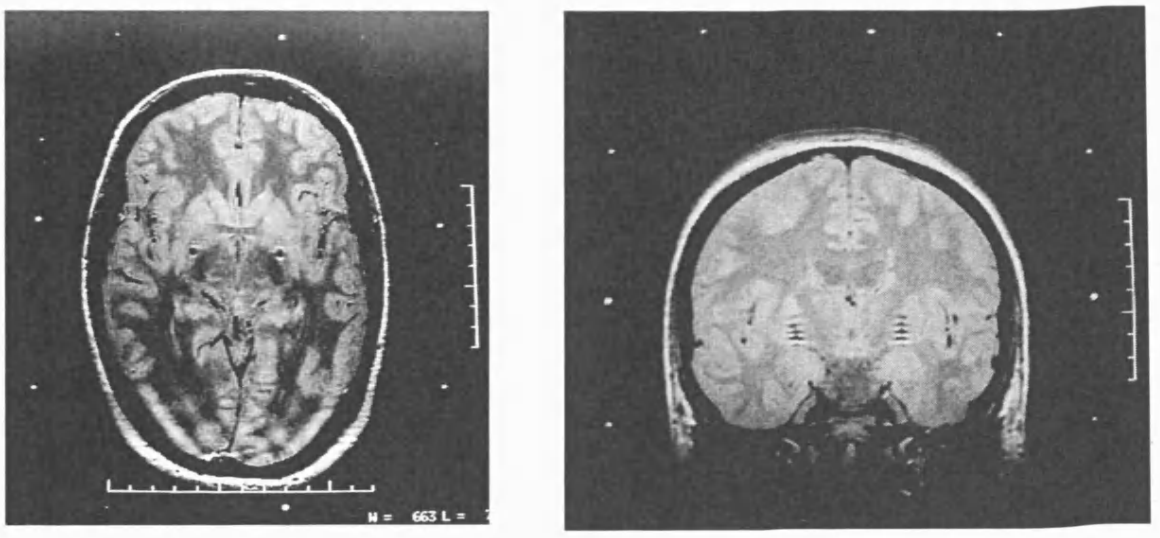


Figure 4.2. Immediate post-implantation axial and coronal MRI images of patient 1 showing quadripolar 3387 electrodes located bilaterally in the GPi.

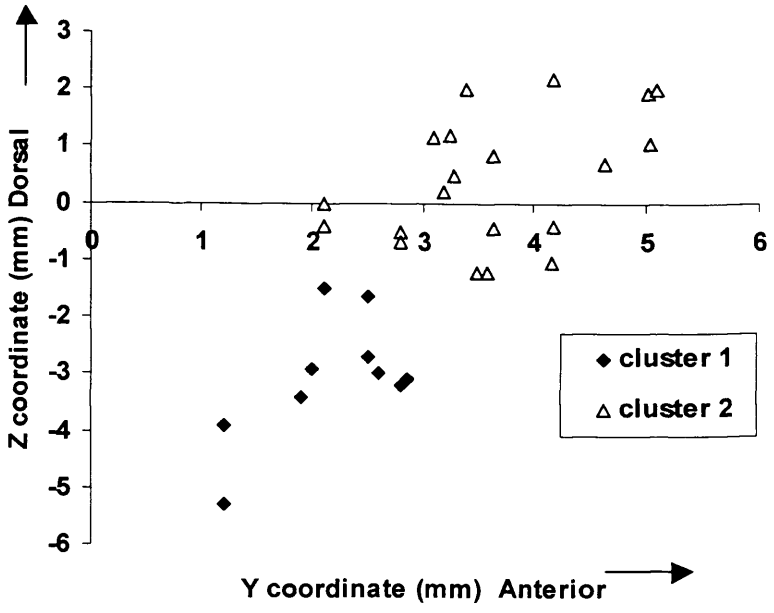
Cluster analysis of the stimulated contact coordinates identified two spatially distinct groups with the following geometric centres; cluster one (10 sides) x = 20.8 mm, y = 2.2 mm, z = -3.1 mm, and cluster two (20 sides) x = 20.8 mm, y = 3.6 mm, z = 0.4 mm. Clustering was influenced by the y ($F=22.4$, $p<0.0001$) and z ($F= 64.8$, $p<0.0001$)

coordinates but not x ($F=0.02$, $p=0.89$), reflecting less variation in x. Cluster 1 is the most posteroventral, cluster 2 is more anterodorsal. When plotted in the Y-Z plane the electrode contacts lie along a line reflecting the electrode trajectory and are significantly correlated ($r=0.748$, $p<0.001$), Figure 4.3a.

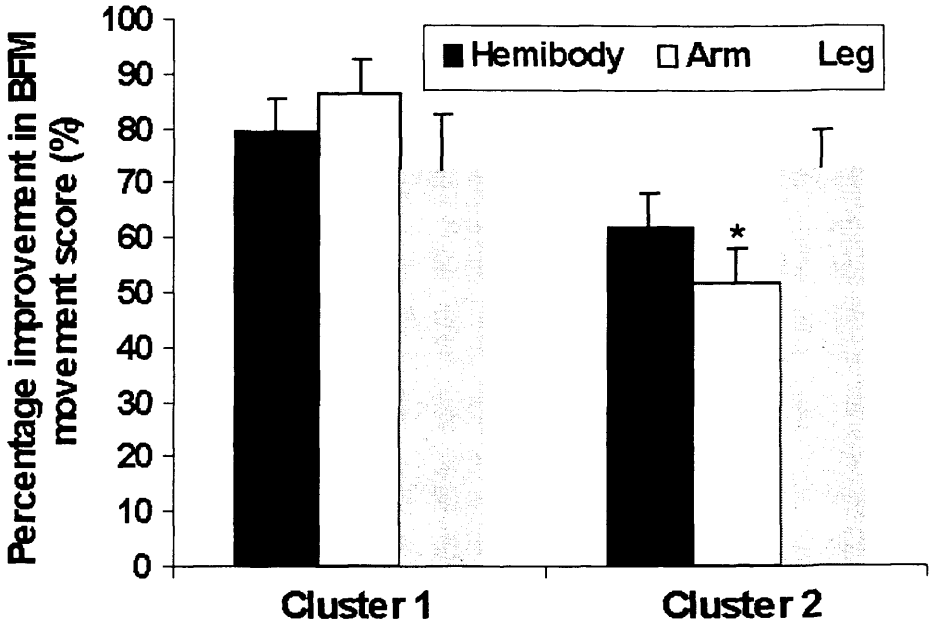
4.4.3 Effect of electrode contact location on clinical outcome

The mean percentage improvement in BFM movement scores for the contralateral hemibody, arm and leg for clusters 1 and 2 are shown in Figure 4.3b. The improvement in hemibody score was greater in cluster 1 than in cluster 2 (79.5% vs 61.9%), but this did not reach significance ($p=0.071$). Analysis of arm and leg sub-scores revealed significantly greater improvement in cluster 1 than cluster 2 for the arm (86.3% vs 51.9%, $p=0.008$) but not the leg (72.6% vs 73% p=NS). The number of sides with superior outcome defined as >80% improvement in hemibody BFM score was also determined for each cluster. The >80% level of improvement was chosen because it had been used as the cutoff in a previous study of GPi DBS for dystonia using the BFM scale (Vayssiere et al 2004). Overall, there were 16 (of 30) sides with superior outcome, which occurred more frequently in cluster 1 (8/10) than cluster 2 (8/20), (Chi-square= 4.29, $p<0.05$). The number of DYT1 sides did not differ significantly between clusters 1 (6/10) and 2 (8/20) (Chi-square=1.07, p=NS). To further investigate if DYT1 status could account for the observed superior outcome for the arm in cluster 1, repeated measures ANOVA on the arm sub-scores was performed, with main factor of TIME (before and after surgery), between subjects factor of DYT1 and covariates of y and z coordinate. The x coordinate was omitted from the ANOVA because x did not contribute to electrode contact clustering. There was a significant main effect of TIME

[F(1,26)= 11.3, p<0.005], TIME*Y interaction [F(1,26)=4.6, p<0.05], but no TIME*DYT1 interaction [F(1,26)=0.29, p=0.596].



(a)



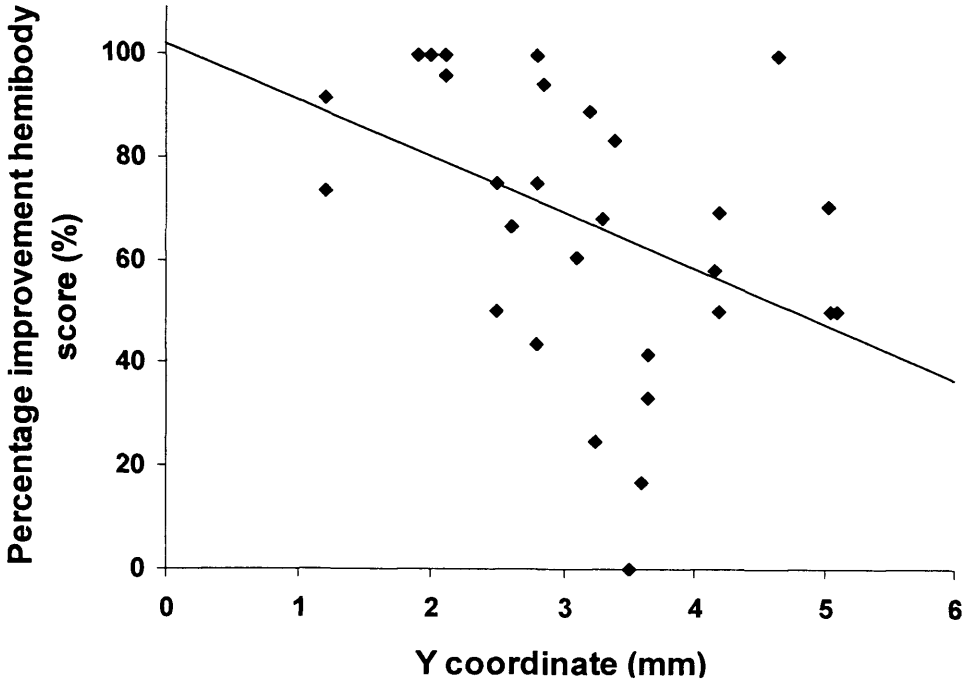
(b)

Figure 4.3. (a) Plot of Y and Z coordinate of the stimulated contact for 30 sides showing a linear distribution and the membership of spatial clusters. The origin of the plot is the mid-point of the AC-PC line. Note cluster 1 is posteroventral and cluster 2 anterodorsal. (b) Mean

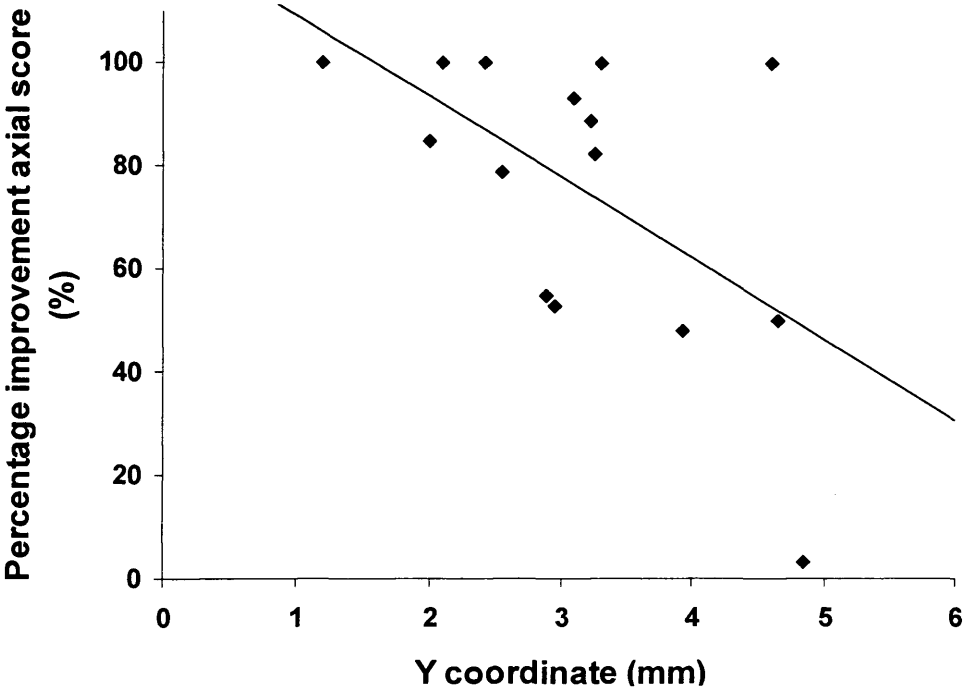
*percentage improvement in BFM movement score for hemibody, arm and leg in clusters 1 and 2. For arm scores, improvement was significantly greater in cluster 1 than 2 (*p=0.008). Error bars ±1 SEM.*

There was a significant inverse correlation between y coordinate and percentage improvement in hemibody BFM score (r= -0.42, p=0.022), arm (r=-0.43, p=0.019), but not leg (r=-0.14, p=NS). The same inverse correlation with y coordinate was observed for total axial scores(r=-0.57, p=0.025), Figure 4.4.

Cluster analysis was applied to the averaged x, y, z coordinates in each patient. This identified two spatially distinct groups, a posteroventral cluster (4 patients; centre x=20.7 mm, y=2.05 mm, z=-3.23 mm) and more anterodorsal cluster (11 patients; centre x=20.86 mm, y=3.55 mm, z=0.14 mm). The percentage improvement in axial BFM movement score was greater in the posteroventral than the anterodorsal cluster (91% vs 70.3%) and for the trunk sub score this difference was significant (96% vs 65%, $p<0.05$). Similarly, for the whole body BFM movement score, the percentage improvement was greater in the posteroventral than the anterodorsal cluster (88.7% vs 67.2%, p=0.02) and correlated with y coordinate (r=-0.62, p=0.013).



(a)



(b)

Figure 4.4. (a) Correlation between percentage change in hemibody BFM score, and the Y coordinate of the stimulated contact in 30 sides (r= -0.42, p=0.022) (b) Correlation between percentage change in axial BFM score, and the average Y coordinate right and left sides in 15 patients (r=-0.57, p=0.025).

4.5 Discussion

In the present study the main finding is that superior improvement of dystonia is associated with chronic high frequency stimulation in the most posteroventral part of GPi. The y (A-P) axis position of the electrode contact significantly influenced the efficacy of GPi DBS; the more posterior electrode contacts were therapeutically more effective.

4.5.1 Elimination of confounding effects due to DYT1

The degree of improvement in patients with primary generalised dystonia following bilateral GPi DBS was similar to that previously reported (Coubes et al 2004, Vidailhet et al 2005). In contrast to these studies, we did observe a significantly better outcome in patients with DYT1. The superior outcome in DYT1 could act as a confounding factor however this is unlikely for the following reasons. Firstly, DYT1 sides were not over-represented in the posteroventral electrode contact cluster and secondly, ANOVA showed no effect of DYT1 status and a clear effect of y coordinate on outcome.

4.5.2 Anatomical reasons for superiority of posteroventral stimulation

The initial cluster analysis identified an anterodorsal-posteroventral gradient of electrode contact effectiveness, with better outcomes occurring more frequently in the posteroventral location. The subsequent finding of an exclusive correlation between the y coordinate and contralateral clinical outcome suggests y to be the more important predictor than z of electrode contact effectiveness.

The explanation for the present findings may relate to pallidal anatomy. Anatomical and physiological studies in primates have shown the sensorimotor territory of the GPi is ventral and posterior (Iansek et al 1980, Parent et al 1995), the somatotopic

arrangement such that the face and arm are posterior and ventral and the leg central and more dorsal (Delong et al 1985). The pallidal anatomy supports the finding of superior efficacy of posteroventral stimulation since this is the sensorimotor area and modification of these circuits might be expected to alter the expression of dystonia.

Another relevant anatomical consideration is that the major routes of pallidal outflow, the ansa lenticularis and lenticular fasciculus overlap in the posteroventral GPi (Patil et al 1998), making both routes of pallidal outflow accessible to intervention in this region. It should be mentioned that although the findings have concentrated on GPi which was the targeted and stimulated structure, a contributory role of GPe, which lies in intimate relation to GPi, cannot be excluded. Congruent with the present targeting results, groups using microelectrode recording during pallidal DBS for dystonia identify an optimal target area in the posteroventrolateral GPi close to the border with GPe (Starr et al 2005). At the very least, the present data confirm the superiority of the posteroventral pallidal target, which includes GPi but may also additionally include a contribution of effect from adjacent GPe.

4.5.3 Evidence for pallidal somatotopy

In the present study it was found that posteroventral stimulation was best for the arm and overall, while for the leg anterodorsal stimulation was of equivalent efficacy. These findings agree with the somatotopic arrangement of GPi derived from primate studies, in that the arm is more posteroventral, and the leg area extends more dorsally and centrally (DeLong et al 1985). Furthermore, the present results agree with another study of GPi DBS contact location in PGD in which superior improvement for the leg was associated with electrode contact placement more centrally within GPi, whereas posterior contact location was more efficient for the arm (Vayssiere et al 2004).

4.5.4 Clinical observation of pallidal interventions and relevance

Clinical observations also provide support for the importance of the posteroventral pallidum as an area for modification of motor symptoms. Leksell observed that the beneficial effects of pallidotomy improved as the lesions were made in a more posterior location (Svenlinson et al 1960), which led to the successful re-introduction of posteroventral pallidotomy for PD (Laitinen et al 1992). In patients with PD, stimulation in the posteroventral GPi alleviates rigidity and abolishes dyskinesia, but may worsen akinesia, while stimulation of dorsal contacts improves akinesia (Bejjani et al 1997, Krack et al 1998), suggesting functional segregation of effects. The volume of lesions in the posteroventral but not anterodorsal part of GPi correlates with the relief of dyskinesias in patients with Parkinson's disease (Kishore et al 2000). In addition, two patients in the present study developed akinesia with posteroventral stimulation, which resolved when more dorsal contacts were used. Taken together these observations suggest that intervention in the posteroventral GPi is more "antikinetic" than in anterodorsal areas, and is consistent with the present finding of optimal suppression of involuntary dystonic movements with stimulation in this region.

4.5.5 Study limitations

A limitation of the present study was that it was not randomised or fully blinded which may have allowed bias to be introduced. Another potential limitation was our relatively small sample size of 15 patients; however, this was offset by evaluating each electrode and body side separately which doubled the number of observations.

Another important question is why the most ventral contacts were not used in all patients. In most patients the most ventral contacts were used, in some patients side effects limited their use, and in one patient (patient 7) more dorsal contacts were

clinically superior to initial trials of more ventral contacts. However, in patient 7, the stimulated contacts were 0.7mm and 0.45 mm below AC-PC, therefore the good outcome in this patient was still associated with relatively more posteroventral rather than anterodorsal stimulation.

4.6 Conclusions

The present results confirm the superiority of the posteroventral GPi target for effective relief of dystonia with DBS. The accepted atlas target coordinates correspond well with the most effective contact location in this series. The present data would suggest that particular attention should be paid to targeting in the antero-posterior axis to ensure sufficiently posterior placement of the electrode. Based on the present findings, it would seem reasonable that in patients with GPi DBS for dystonia, the lowermost contacts of the quadripolar electrode, without side effects, be tried for chronic stimulation first, since these, with conventional orientation of electrode trajectory, will be the most posteroventral. The identification of an anterodorsal to posteroventral gradient of contact efficacy may be explained by the functional organisation and anatomy of GPi and its outflow tracts.

Chapter 5. Changes in forearm reciprocal inhibition following GPi DBS for dystonia

5.1 Summary

Dystonia is characterised by involuntary muscle contractions, and a consistent pathophysiological feature is reduced inhibition at various levels of the nervous system, which may be detected in clinically unaffected body parts. Chronic deep brain stimulation (DBS) of the globus pallidus internus (GPi) has emerged as an effective treatment for primary generalised dystonia (PGD), although its mechanism of action and impact on inhibitory abnormalities in dystonia are unknown. The present study examined spinal excitability in patients with PGD before and after GPi DBS to explore the relationship between spinal disinhibition and dystonic symptoms and to probe the physiological basis for progressive improvement observed in dystonia after GPi DBS. Forearm H-reflex reciprocal inhibition (RI) was recorded and clinical evaluation performed using the Burke-Fahn-Marsden dystonia rating scale in 8 patients with PGD before and at intervals of 1, 3 and 6 months after bilateral GPi DBS. Following GPi DBS, there was a significant progressive increase in the first and second phases of RI, which correlated with the clinical improvement in dystonia. The time course of both clinical improvement and increases in RI followed a logarithmic distribution. These results demonstrate that GPi DBS progressively restores spinal inhibition in PGD closely paralleling improvement in dystonic symptoms. The present results support the conclusion that GPi DBS for primary generalised dystonia results in functional reorganisation of the nervous system, which includes a long-term increase in spinal inhibition.

5.2 Introduction

The pathophysiology of dystonia is characterised by an abnormal reduction of inhibition within the brain and spinal cord. Defective inhibition may contribute to dystonia by interfering with normal motor selection and suppression of unwanted movements. In patients with focal dystonia, transcranial magnetic stimulation (TMS) studies have shown abnormally reduced short latency intracortical inhibition in the motor cortex (Ridding et al 1995) and increased excitability of the motor cortex during voluntary muscle contraction (Ikoma et al 1996). The blink reflex is abnormally disinhibited in patients with cranial dystonia (Berardelli et al 1985) and segmental and generalised dystonia (Nakashima et al 1990). At the spinal cord level, reduced reciprocal inhibition (RI) of forearm H-reflexes has been demonstrated in patients with focal and generalised dystonia (Nakashima et al 1989, Panizza et al 1989, 1990). It is unclear whether these abnormalities directly contribute to dystonic cocontraction of limb muscles since abnormally reduced RI has been found in the asymptomatic, contralateral arm in writer's cramp patients (Chen R et al 1995) and in patients with spasmodic torticollis without limb dystonia (Deuschl et al 1992). Chronic deep brain stimulation (DBS) of the globus pallidus internus (GPi) has emerged as an effective treatment for PGD (Coubes et al 2004, Vidailhet 2005), however the physiological mechanisms of improvement remain unclear. In contrast to Parkinson's disease, the improvement following DBS is not immediate but progressive over weeks to months, and brain plasticity mechanisms have been implicated, although physiological evidence has been lacking (Bereznai et al 2002, Yianni et al 2003, Vidailhet et al 2005). It is unknown whether RI changes after GPi DBS for PGD. Previous work has identified that physiological abnormalities in dystonia are frequently present in clinically unaffected body parts and may be considered an endophenotype, which under certain

conditions manifests in dystonia (Meunier et al 2001). The aim of the present study was to determine if spinal disinhibition in dystonia patients would change after GPi DBS, or whether abnormalities might persist even after clinical improvement had occurred, in the same way that decreased RI can be observed in clinically unaffected limbs in writer's cramp (Chen R et al 1995). To this end we studied forearm H-reflex RI in patients with PGD before and at intervals after GPi DBS.

5.3 Methods

5.3.1 Subjects

Eight patients with PGD (5 female, mean age 50 years range 24-64, three DYT1+) were enrolled in the study. The patient characteristics are shown in Table 5.1. Patients 3 and 5 underwent unilateral thalamotomy 29 and 23 years ago. Medications for dystonia were not altered during the period of the study. All patients gave written informed consent. The study was approved by the Joint Research Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology.

Patient	*Gender*	*Age (years)*	*Disease duration (years)*	*DYT 1 gene status*	*BFM score pre-op (0-120)*	*Medications*	*DBS parameters*
1	M	47	37	+	52	Diazepam Tetrabenazine	Rt: 4-, 3.5v, 90μsec, 130 Hz Lt: 0,1-, 3.3v, 60μsec, 130 Hz
2	M	24	16	-	73	Clonazepam	Rt: 4,5-, 3.9v, 90μsec, 130 Hz Lt: 0,1-, 3.8v, 90μsec, 130 Hz
3	F	53	43	+	40.5	Diazepam	Rt: 5-, 2.9v, 90μsec, 130 Hz Lt: 1-, 3.7v, 90μsec, 130 Hz
4	F	63	4	-	23	L-dopa Trihexphenidyl	Rt: 6-, 4.6v, 90μsec, 130 Hz Lt: 2-, 4.6v, 90μsec, 130 Hz
5	F	54	43	-	24	None	Rt: 4-, 3.7v, 60μsec, 130 Hz Lt: 1-, 3.7v, 60μsec, 130 Hz
6	F	36	25	+	20.5	Trihexphenidyl	Rt: 4-, 4.6v, 90μsec, 130 Hz Lt: 0-, 4.2v, 90μsec, 130 Hz
7	F	64	50	-	46	None	Rt: 6-, 3.5v, 60μsec, 130 Hz Lt: 2-, 3.5v, 60μsec, 130 Hz
8	M	62	7	-	64	None	Rt: 4,5-, 3.5v, 60μsec, 130 Hz Lt: 1,2-, 3.5v, 60μsec, 130 Hz

Table 5.1 Clinical patient data.

5.3.2 Surgical procedures, stimulation parameters and clinical assessment

All patients underwent bilateral implantation of electrodes into GPi and chronic stimulation. The surgery and adjustment of stimulation parameters was performed a described in the General methods. The macroelectrode model 3389 and Kinetra model 7428 implanted pulse generator (Medtronic Neurological Division, Minneapolis USA) were used in all patients except in one where model 3387 electrodes were used. In patient 3, MRI could not be performed due to the presence of a metal fragment deposited in the target area during the previous thalamotomy. In this patient, targeting was performed using stereotactic computerised tomography (CT), atlas coordinates and

intraoperative stimulation to evaluate proximity to capsular fibres. Confirmation of electrode placement in GPi was obtained in all patients with immediate post implantation stereotactic MRI, except in one patient in whom immediate stereotactic CT was performed. Clinical assessment was performed using the Burke-Fahn-Mardsen scale (BFM).

5.3.3 Forearm H-reflex reciprocal inhibition recordings

EMG recordings were made from flexor carpi radialis and extensor digitorum communis using Ag-Ag surface electrodes. The EMG signals were amplified, using D360 amplifiers (Digitimer, Welwyn UK), band pass filtered 3-2000 Hz, analogue to digital converted using a 1401 AD converter (CED, Cambridge) at a sample rate of 5000Hz and collected on computer. Electrical stimulation was applied to the median nerve in the antecubital fossa and radial nerve above the elbow using two constant current generators (Digitimer, Welwyn UK). All stimuli were 500 ms with an intensity at the median nerve to produce the maximum H-reflex without an M wave, and at the radial nerve to produce an EMG response of 0.1-0.5 mV. The H-reflex in response to radial nerve conditioning stimuli was assessed at 8 interstimulus intervals (ISI) of –1, 0, 1, 10, 20, 30, 100 and 200 ms. Stimuli were delivered every 5 seconds. Sixty trials at each ISI and 120 unconditioned trials were performed in a randomised order in three blocks of 100 stimuli. RI was recorded in the clinically least dystonic arm to minimise EMG activity at rest. Trials with excessive EMG artefact were rejected on line. GPi DBS was not altered during the experimental session. Data were analysed off-line using custom-written software (Nucursor 2001). RI was calculated as the ratio of the mean peak-to-peak H-reflex amplitude at each ISI to the unconditioned response.

5.3.4 Statistical analysis

The average RI at each ISI was calculated for each patient. Repeated measures ANOVA was used to assess changes in RI over time with main factors of TIME (pre-op, 1, 3 and 6 months) and INTERVAL (-1, 0, 1, 10, 20, 30 ms). The third phase of RI (ISI 100 and 200 ms) was excluded from the ANOVA, because the first (ISI=0 ms) and second (ISI=10-20 ms) phases of RI are physiologically better understood and have been shown previously to be abnormal in dystonia. Post-hoc t tests were used to explore the nature of significant interactions found in the ANOVA. Correlation between RI and BFM score were calculated by pairing the BFM score with the corresponding value of RI at each time point (pre-op, 1, 3 and 6 months) and applying the Pearson correlation. The time-course of RI and BFM were explored using non-linear regression curve estimation function. For clinical correlations, ISI=0 ms for the first and ISI=10 ms for the second phase of RI were used. All statistics were performed using SPSS for Windows version 11.5. A P value <0.05 was considered significant.

5.4 Results

5.4.1 Longitudinal effects of GPi DBS on reciprocal inhibition

The RI curves at each ISI at baseline, 1, 3 and 6 months are shown in Figure 5.1. Repeated measures ANOVA with main factors of TIME (1-4) and INTERVAL (1-6) showed a significant effect of TIME [$F(3,21)=6.14$, $p<0.05$], INTERVAL [$F(5,35)=30.03$, $p<0.005$] and TIME-INTERVAL interaction [$F(15,105)=7.45$, $p<0.05$]. Post hoc paired t tests revealed a significant decrease in H-reflex ratio for ISI= 0 ms from 0.81 to 0.63 at 1 month ($p<0.001$) and progressive decrease by 6 months to 0.58. For ISI =10 and 20 ms there was a significant decrease in H-reflex ratio at 3 and 6 months ($p<0.05$). There was no significant change in the amplitude of the

unconditioned H-reflex after GPi DBS, at one month (2.64 mV vs 2.19 mV, p=0.412) or later time points.

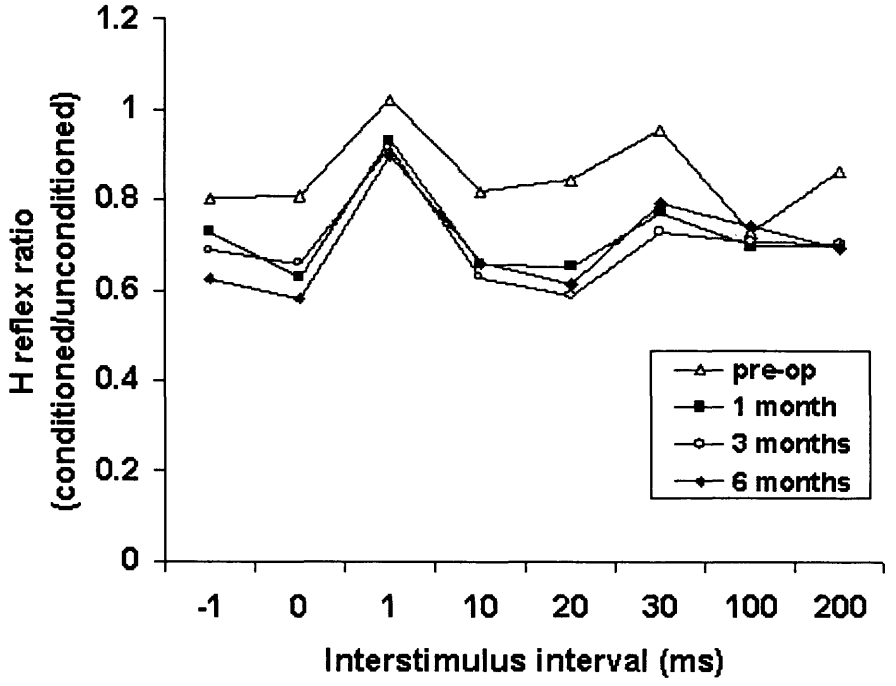
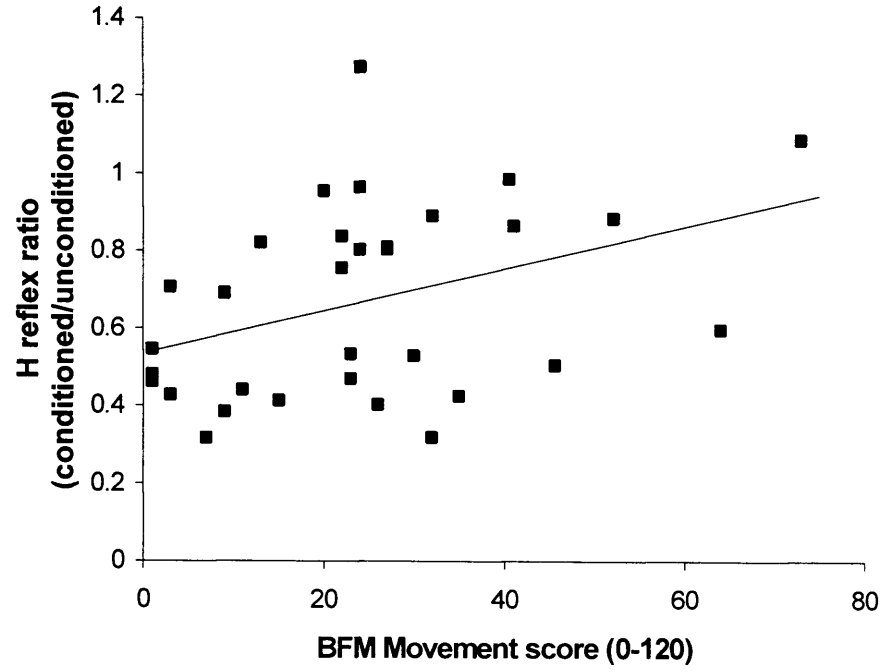


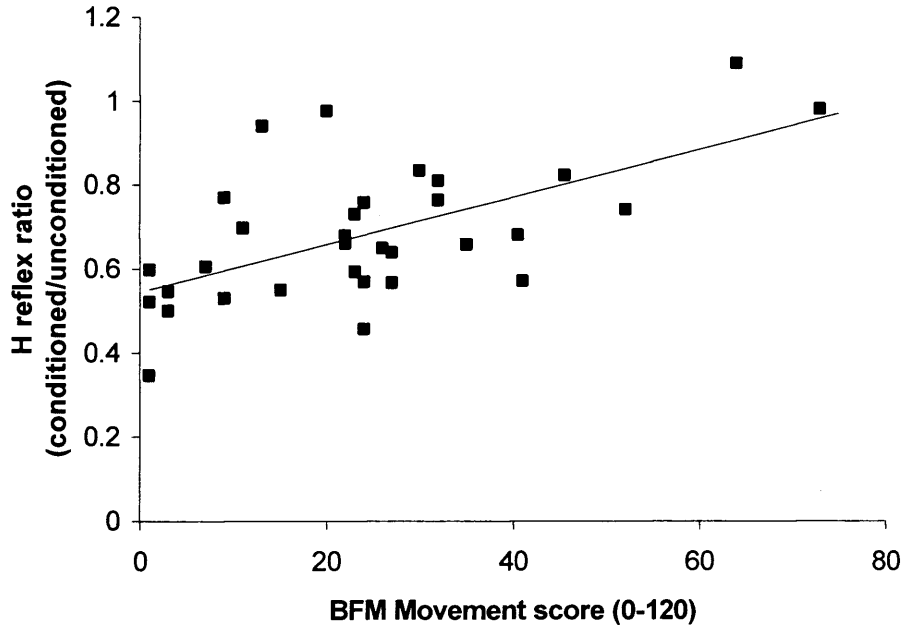
Figure 5.1. Grand average of H-reflex ratio before and after GPi DBS.

5.4.2 Correlation of physiological changes and clinical improvement

There was a significant correlation between the BFM score and the H-reflex ratio for the first ($r=0.39$, $p<0.05$) and second ($r=0.59$ $p<0.0001$) phases of RI (Figure 5.2).



(a)



(b)

Figure 5.2. Correlation between BFM movement score and RI (a) first (ISI 0 ms, r = 0.39 p<0.05, (b) second phase (ISI 10 ms), r = 0.59, p<0.0001.

5.4.3 Time-course modelling of changes in RI and clinical state

To investigate the time-course of changes in RI and clinical score, a curve estimation analysis was carried out in SPSS, which determined the function which best described the data. This revealed that changes in the second phase of RI (ISI=10 and 20 ms) and improvement in BFM score both followed a logarithmic distribution (Figure 5.3).

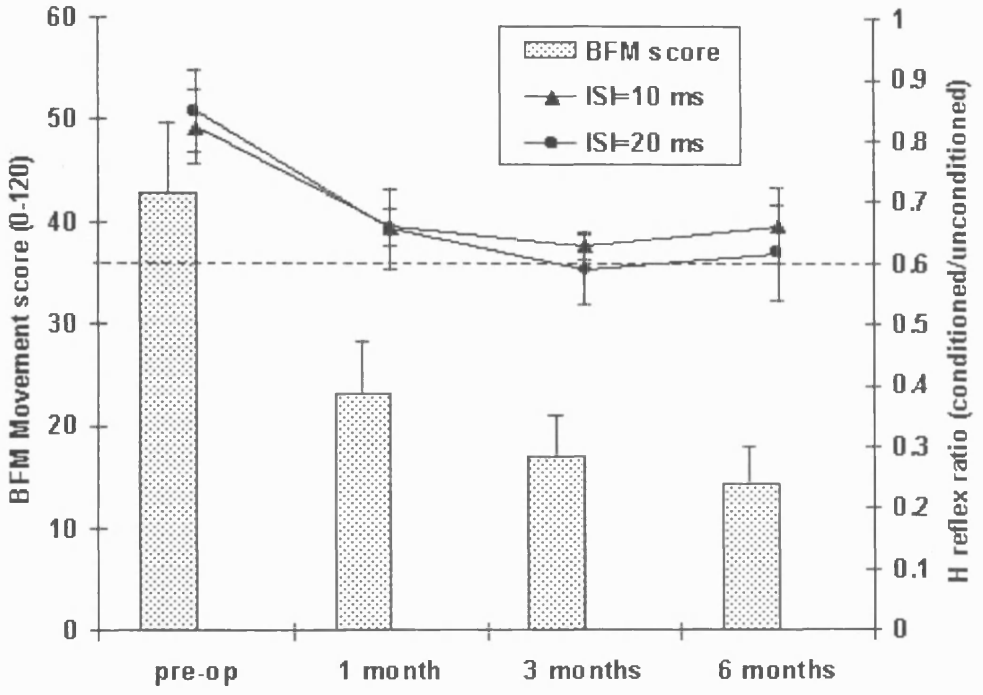


*Figure 5.3. Time course of change in the second phase of RI (ISI 10 and 20 ms) and clinical improvement. Data points show means and errors bars of ± 1 SEM. All curves follow a logarithmic distribution; BFM =20.5 - 2.47 * logTIME, p=0.01; RI[ISI 10 ms]=0.67 - 0.017 * logTIME, p=0.02; RI[ISI 20 ms]=0.64 - 0.22 * logTIME, p=0.01. A line is superimposed at 0.6, which represents a normal level of RI for the second phase in our laboratory (Huang et al 2004).*

5.5 Discussion

The main finding in the present study was a progressive increase in RI in the first and second phases following GPi DBS, which correlated with clinical improvement in dystonia. Furthermore, changes in both the first and second phases of RI and the clinical symptoms followed a logarithmic time-course. Here it will be argued that GPi DBS reverses physiological abnormality in dystonia in a manner suggestive of long-term neural reorganisation.

5.5.1 Mechanisms for alteration of spinal excitability by GPi DBS

The first phase of RI, which is maximal with ISI=0 ms is mediated by Ia afferents of the antagonist muscle spindles which inhibit alpha motor neurons of the agonist via Ia inhibitory interneurons in a disynaptic pathway (Day et al 1984). The second phase which is maximal with ISI 10-20 ms is mediated by presynaptic inhibition of agonist Ia afferents by type I afferents of antagonist muscles (Berardelli et al 1987). In the present study we observed abnormally decreased RI in both the first and second phase. Other studies in patients with focal dystonia have shown reductions both the first and second (Panizza et al 1989, Chen et al 1995), or just the second phase of RI (Nakashima et al 1989, Deuschl et al 1992). Our finding of additional impairment in the first phase of RI may be because the patients we studied with generalised dystonia are more severely affected than those with focal dystonia. This view is supported by the only previous study of RI in patients with generalised dystonia, which also found reductions in both the first and second phases of RI (Panizza et al 1990). Since dystonia is primarily a disorder of basal ganglia rather than spinal cord function, the observed reductions in RI are likely due to an abnormality of descending control of spinal interneurons as a result of basal ganglia dysfunction (Nakashima et al 1989). The basal ganglia have extensive

connections with pathways which project to the spinal cord, including the reticulospinal, rubrospinal, vestibulospinal and corticospinal tracts, which may modulate Ia inhibitory interneurons (Hultborn 1976) and interneurons involved in presynaptic Ia inhibition (Baldiserra et al 1981). The GPi is one of the main output nodes of the basal ganglia with extensive inhibitory projections to the thalamus (and thence cortex), superior colliculus and pedunculopontine nucleus. These output structures might be expected to undergo major modifications of activity after GPi DBS which would in turn modify descending output to the spinal cord. Relatively few studies to date have examined the physiological consequences of pallidal stimulation in dystonia. A recent PET study in patients with PGD found that during voluntary movement, GPi DBS reverses abnormal overactivity in premotor cortex and thalamus (Detante et al 2004b). The excitability of the motor cortex to transcranial magnetic stimulation is decreased after cessation of GPi DBS in dystonic patients, these changes were reversible within minutes of switching the stimulator back ON (Kuhn et al 2003). Taken together these observations indicate that GPi DBS induces physiological alterations in brain regions distant from the site of stimulation, in areas known to show physiological abnormalities in dystonia, and which are known to contribute to the descending tracts responsible for control of RI. A recent study found increases in the first and third phases of forearm RI to normal levels when tested immediately after application of 1 Hz repetitive TMS to the premotor area in DYT1 dystonia patients (Huang et al 2004). This confirms that intervention which alters activity in the cortex, such as GPi DBS, may modulate descending control of spinal RI in dystonia patients. The present observation that basal ganglia DBS can alter spinal reflex activity is not unprecedented. A recent study found that autogenic inhibition, which is mainly mediated by Ib afferents from Golgi tendon organs of the agonist, was increased to

normal levels in patients with Parkinson's disease during STN stimulation (Potter et al 2004). These observations support the notion that DBS within the basal ganglia can influence spinal inhibitory circuits, as we have found in dystonia.

5.5.2 Normalisation of spinal excitability after GPi DBS and relevance to clinical effect of GPi DBS

In the present study progressive reductions in RI occurred following GPi DBS to reach levels equal to those seen in healthy subjects previously recorded in our laboratory. This result confirms that the first and second phases of RI are abnormally reduced in primary generalised dystonia as described previously (Panizza et al 1990). Furthermore, normalisation of these abnormalities suggests GPi DBS reverses the pathophysiology of dystonia with respect to spinal disinhibition. Since the observed changes in RI correlated well with clinical effects, it is tempting to attribute clinical improvement in dystonia after GPi DBS to normalisation of RI. However, there are major caveats to such an interpretation. Firstly, RI may be dissociated from clinical symptoms and secondly, spinal disinhibition is one of many factors implicated in the pathophysiology of dystonia, and as such its reversal is unlikely to be the sole determinant of improvement in dystonia. The more likely explanation for the present results is that changes in RI occurred as part of more widespread changes within the nervous system at supraspinal levels after GPi DBS. These changes could account for both clinical improvement and changes in RI, by modification of descending influence on the spinal cord, and would explain the close correlation between the two variables. This interpretation does not preclude a contributory mechanistic role for reversal of spinal disinhibition in GPi DBS effect, but argues against this being the main determinant.

5.5.3 Time-course of effects and evidence for neural plasticity

In the present study, progressive improvement in dystonia after GPi DBS was observed, as has been found previously (Yianni et al 2003, Vidailhet et al 2005). Furthermore, the time-course of both clinical improvement and increases in the second phase of RI were logarithmic. Because GPi DBS does not directly stimulate the spinal cord, the effect of GPi DBS on RI must be accounted for by changes in descending drive to Ia spinal inhibitory interneurons. These changes in descending drive would in turn equate to progressive modification in the basal ganglia and cortical output to the brainstem and spinal cord. Furthermore, the observed progressive time course of changes in RI suggests that GPi DBS induces a gradual plastic modification within the brain. The site of reorganisation after GPi DBS could include both cortical and subcortical levels. Involvement of the cortex in such reorganisation seems likely, since the cortex is recognised to form abnormal sensorimotor representations in dystonia which may be modified in a plastic fashion (Byl et al 1996, Meunier et al 2001, Rozenkranz et al 2005). There are parallels between the observations in the present study and the time-course of improvement after stroke, a setting in which adaptive neuroplasticity is believed to play an important role. Recovery of upper extremity muscle strength after stroke also follows a logarithmic time course (Goodwin et al 2003), allowing logarithmic modelling to be used to predict stroke recovery (Koyama et al 2005).

5.5.4 Experimental limitations

An alternative explanation of our results might be that the reductions in RI are simply the result of decreased dystonic contractions in the limb being tested. This explanation is unlikely because decreased RI may be observed in clinically unaffected limbs (Chen R et al 1995), so that improvement in dystonia would not guarantee normalisation of

RI. In addition, trials with EMG artefact were rejected, and there was no significant change in unconditioned H-reflex amplitude after GPi DBS, suggesting that potentiation of the H-reflex by muscle contraction did not play a major role in the results. A potential limitation in the present study was that a healthy control group were not specifically studied. The rationale for this was that changes from baseline in the dystonia group were the primary point of interest and could be studied accurately without a healthy control group because of the longitudinal study design. However, comparison of the present study group with data from healthy subjects previously recorded in our laboratory using the same methodology was possible, and showed normalisation of RI following GPi DBS.

5.5 Conclusions

The finding that RI also changes progressively in parallel with clinical improvement of dystonia suggests that changes at the spinal level reflect plastic adaptation occurring at higher levels. Restoration of RI is unlikely to be the major mechanism of action of GPi DBS, since impaired RI alone is insufficient to result in dystonic symptoms, but rather a marker for collective changes at supraspinal levels. The results support the conclusion that GPi DBS for dystonia results in functional reorganisation of the nervous system, which includes a long term increase in spinal inhibition.

Chapter 6. Changes in blink reflex excitability after GPi DBS for dystonia

6.1 Summary

A pathophysiological feature of dystonia is reduced inhibition at various levels of the nervous system, which may be detected in clinically unaffected body parts. Chronic deep brain stimulation (DBS) of the globus pallidus internus (GPi) has emerged as an effective treatment for primary generalised dystonia (PGD), although its mechanism of action and impact on inhibitory abnormalities in dystonia are unknown. The present study sought to determine the effect of GPi DBS on brainstem excitability in patients with primary generalised dystonia. The blink reflex from orbicularis oculi in response to paired electrical stimulation of the supraorbital nerve was measured at interstimulus intervals of 500 ms and 1000 ms in 10 patients with primary generalised dystonia before and at intervals of 1, 3 and 6 months after bilateral GPi DBS, and in 10 healthy subjects. Patients were clinically evaluated using the BFM dystonia rating scale. Pre-operatively, the degree of R2 inhibition was significantly decreased in patients compared with control subjects and progressively increased after GPi DBS. Changes in R2 inhibition correlated with changes in BFM score. The results indicate that GPi DBS partially restores a normal pattern of brainstem blink reflex inhibition in parallel with its beneficial effects on dystonic symptoms. These effects are interpreted as the result of progressive modification of basal ganglia and cortical function by GPi DBS, reflected at the brainstem level. The results suggest that GPi DBS for primary generalised dystonia results in functional reorganisation of the nervous system, which includes a long-term increase in brainstem inhibition.

6.2 Introduction

Dystonia is characterised by involuntary muscle contractions, which result in spasms and abnormal postures (Fahn 1998). Chronic deep brain stimulation of the globus pallidus internus (GPi) has emerged as an effective treatment for primary generalised dystonia (PGD) (Coubes et al 2004, Vidailhet et al 2005) but the physiological mechanisms of improvement remain unclear. The improvement in dystonia after GPi DBS is progressive over months (Yianni et al 2003, Vidailhet et al 2005), which suggests that DBS may act by inducing gradual plastic changes within the brain. The pathophysiology of dystonia is characterised by abnormally reduced inhibition at cortical, brainstem and spinal levels. Transcranial magnetic stimulation (TMS) studies in patients with focal hand dystonia have shown abnormally reduced short latency intracortical inhibition of the motor cortex (Ridding et al 1995, Edwards et al 2003b). At the spinal cord level, reduced reciprocal inhibition of forearm H-reflexes has been demonstrated in patients with focal and generalised dystonia (Nakashima et al 1990, Panizza et al 1989, Panizza et al 1990). Similarly, the blink reflex is abnormally disinhibited in patients with cranial, (Berardelli et al 1985, Tolosa et al 1988), segmental and generalised dystonia (Nakashima et al 1990). Disinhibition may physiologically contribute to dystonia by reducing the extent to which unwanted movements can be suppressed. Nevertheless, disinhibition in dystonia may be detected in clinically unaffected body parts, for example impaired RI in the unaffected arm in patients with focal hand dystonia (Chen et al 1995), and blink reflex disinhibition is present in dystonia patients without blepharospasm (Nakashima et al 1990).

The blink reflex of orbicularis oculi in response to electrical stimulation of the supraorbital nerve has two components. The early R1 response is seen unilateral to stimulation and is mediated by an oligosynaptic pathway involving first division

trigeminal afferents, relaying via interneurons near the trigeminal sensory nucleus and then motorneurons of the facial nucleus. The later R2 response is bilateral, of longer duration and is mediated via a polysynaptic pathway involving the descending trigeminal spinal tract, caudal spinal nucleus and medullary reticular formation to project bilaterally to facial motorneurons (Arimedeh et al 2002). Blink reflex excitability is under local control of inhibitory interneurons, which in turn receive descending modulation from basal ganglia and cortex (Esteban et al 1999). With paired supraorbital nerve stimulation, the second R2 response is normally inhibited compared to the first, the degree of inhibition being more intense with shorter ISIs and recovering with longer ISIs (Kimura et al 1976). The recovery cycle of the ratio of the second to the first R2 response thus provides a measure of inhibition within brainstem interneuronal networks and also their inputs from basal ganglia and cortex. Since disinhibition may be an important physiological mechanism in dystonia and dissociated from clinical involvement, the aim of the present study was to determine if inhibitory abnormalities would improve or persist after treatment with GPi DBS. Moreover the present study sought to identify the relationship bewteen changes in blink reflex excitability and clinical state to determine if they might represent a marker for neural reorganisation which has been postulated to underly the progressive effects of GPi DBS. To this end the blink reflex in patients with PGD before and at intervals after GPi DBS was studied.

6.3 Methods

6.3.1 Subjects

Ten patients with generalised PGD (6 female, mean age 52 years range 24-64, four DYT1+) and 10 healthy control subjects (5 female, mean age 40 years range, 29-60

years) were studied. The patient characteristics are shown in Table 1. One patient (patient 2) had mild blepharospasm as part of the generalised dystonia. Patients 3 and 5 had undergone unilateral thalamotomy 29 and 23 years previously. Medications for dystonia were not altered during the period of the study. All patients gave written informed consent. The study was approved by the Joint Research Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology

6.3.2 Surgical procedures, stimulation parameters and clinical assessment

All patients underwent bilateral implantation of electrodes into GPi and chronic stimulation. The surgery and adjustment of stimulation parameters was performed as described in the General Methods. Clinical assessment was performed using the Burke-Fahn-Mardsen scale (BFM).

6.3.3 Blink reflex recordings

Surface EMG recordings were made bilaterally from the orbicularis oculi muscles using Ag-Ag surface electrodes. The EMG signals were amplified using D360 amplifiers (Digitimer, Welwyn UK), band pass filtered (53-3000 Hz), analogue to digital converted using a 1401 AD converter (CED, Cambridge) at a sample rate of 5000Hz, and collected on computer.

Patient	*Gender*	*Age (years)*	*Disease duration (years)*	*DYT 1 gene status*	*BFM score (0-120) pre-op/6 months*	*Medications*	*DBS parameters at 6 months*
1	M	47	37	+	52 / 22	Diazepam Tetrabenazine	Rt: 4-, 3.5v, 90μsec, 130 Hz Lt: 0,1-, 3.3v, 60μsec, 130 Hz
2	M	24	16	-	73 / 15	Clonazepam	Rt: 4,5-, 3.9v, 90μsec, 130 Hz Lt: 0,1-, 3.8v, 90μsec, 130 Hz
3	F	53	43	+	41 / 22	Diazepam	Rt: 5-, 2.9v, 90μsec, 130 Hz Lt: 1-, 3.7v, 90μsec, 130 Hz
4	F	63	4	-	23 / 3	L-dopa Trihexphenidyl	Rt: 6-, 4.6v, 90μsec, 130 Hz Lt: 2-, 4.6v, 90μsec, 130 Hz
5	F	54	43	-	24 / 9	none	Rt: 4-, 3.7v, 60μsec, 130 Hz Lt: 1-, 3.7v, 60μsec, 130 Hz
6	F	36	25	+	21 / 1	Trihexphenidyl	Rt: 4-, 4.6v, 90μsec, 130 Hz Lt: 0-, 4.2v, 90μsec, 130 Hz
7	F	64	50	-	46 / 13	none	Rt: 6-, 3.5v, 60μsec, 130 Hz Lt: 2-, 3.5v, 60μsec, 130 Hz
8	M	62	7	-	64 / 30	none	Rt: 4,5-, 3.5v, 60μsec, 130 Hz Lt: 1,2-, 3.5v, 60μsec, 130 Hz
9	F	52	36	+	29 / 7	none	Rt: 4-, 3.0v, 60μsec, 130 Hz Lt: 0-, 3.0v, 60μsec, 130 Hz
10	M	62	43	-	28 / 15	Trihexphenidyl Baclofen Clonazepam	Rt: 6-, 3.7v, 90μsec, 130 Hz Lt: 1-, 3.7v, 90μsec, 130 Hz

Table 6.1 Clinical patient data

Electrical stimulation was applied to the supraorbital nerve in the supraorbital notch with a bipolar stimulating electrode and constant current generator (Digitimer, Welwyn UK). All stimuli were 0.2 ms duration with intensity 3-4 times sensory threshold (8-14 mA). The blink reflex in response to paired stimulation was assessed at interstimulus intervals of 500 and 1000 ms. The interval between stimulations was varied randomly between 10 and 20 seconds to minimise habituation. Thirty trials at each ISI were performed in a randomised order in three blocks for both right and left sided

supraorbital nerve stimulation. Trials with excessive EMG artefact were rejected on line. GPi DBS was changed from monopolar to bipolar stimulation at 30% higher voltage at the beginning of the experimental session in order to eliminate DBS-induced artefacts. Data were analysed off-line, using custom-written software (Nucursor 2001). The raw blink recordings were DC corrected, rectified and averaged. The onset latency and duration of R1 and R2 responses were determined by manual cursor marking of the beginning and end of responses. The area ratio of the conditioned R2 component to the unconditioned response was calculated. The area of the conditioned R2 was calculated over the same duration as the unconditioned response.

6.3.4 Statistical analysis

The ipsilateral R2 ratio for ISI 500 and1000 ms was calculated for right and left sides in each subject. The sides were treated separately in the statistical analysis. Data from patients and control subjects were compared using one-way ANOVA. To assess for significant changes in R2 ratio over time in patients, repeated measures ANOVA was performed with main factors of TIME (pre-op, 1, 3 and 6 months) and INTERVAL (500 and 1000 ms). Post-hoc t tests were used to explore the nature of significant interactions found in the ANOVA. Correlation coefficients were calculated using the Pearson correlation or the Spearman correlation for clinical outcome data. All statistics were performed using SPSS for Windows version 11.5. A P value <0.05 was considered significant.

6.4 Results

There was a significant improvement in dystonia in all patients following surgery. The mean BFM Movement score decreased from 40 (+/- 5.8 SEM) pre-operatively to 14

(+/- 2.9 SEM) at 6 months, a 66% improvement, (paired t-test, $p<0.001$, data shown in Table 1).

6.4.1 Longitudinal effects of GPi DBS on blink reflex R2 inhibition

The average R2 ratio for 500 and 1000 ms at baseline in patients and controls and 1, 3 and 6 months in patients is shown in Figure 6.1. One-way ANOVA showed a significant difference between patients and controls at baseline and for ISI 500 ms ($F=15.8$ $p<0.0001$) and 1000 ms ($F=16.3$, $p<0.0001$). This difference between controls and patients remained significant at 1, 3 and 6 months, but the statistical strength of the difference became weaker. Repeated measures ANOVA in the patient group with main factors of TIME (1-4) and INTERVAL (1-2) showed a significant effect of TIME [$F(3,57)= 7.16$, $p=0.015$] and INTERVAL [$F(1,19)=63.0$ $p<0.0001$], but no significant TIME-INTERVAL interaction [$F(3,57)=2.49$, $p>0.05$]. Post-hoc paired t tests revealed a significant decrease in R2 ratio for ISI=500 ms from 0.63 pre-op to 0.50 at 6 months ($p=0.043$). For ISI =1000 ms there was a significant decrease in R2 ratio from 0.80 to 0.67 at 3 months ($p=0.011$) and 0.66 at 6 months ($p=0.019$).

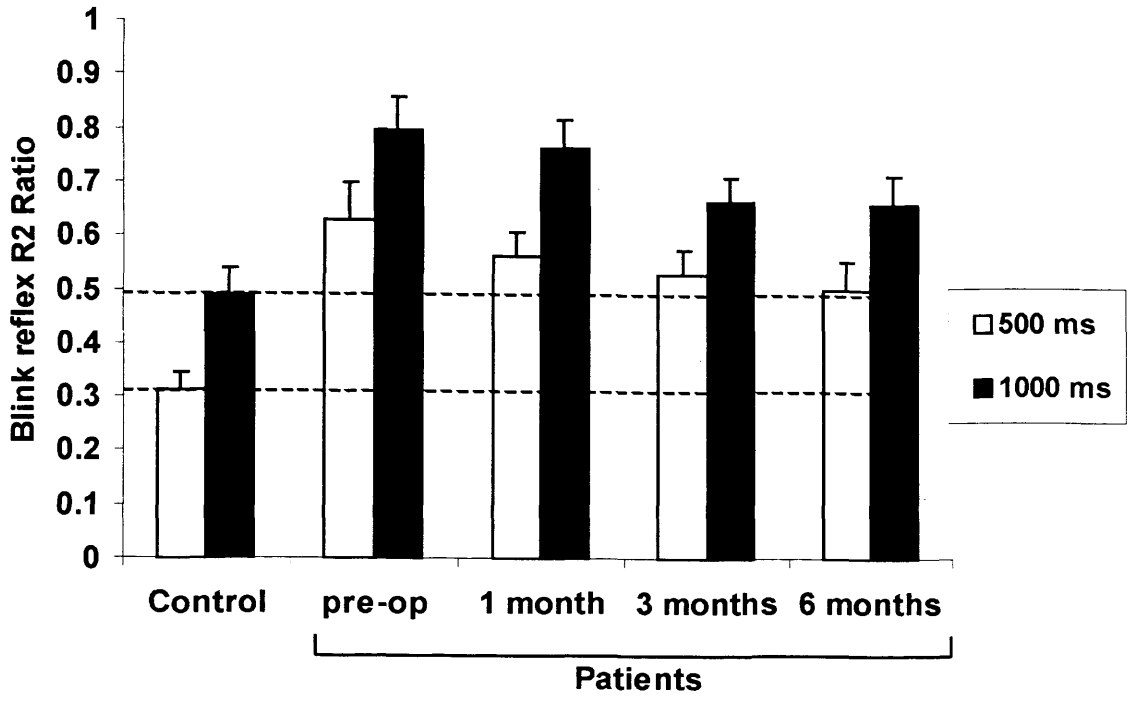


Figure 6.1. Grand average R2 ratio for ISI 500 and 1000 ms in control subjects and patients at all time-points with Y error bars of +/- 1 SEM. In patients the R2 ratio decreases significantly over time after GPi DBS but remains greater than control subjects at all time points.

6.4.2 Effects on latency and amplitude of R1 and R2 response

For patients, the latency of the unconditioned R1 (mean ± SEM, 11.02 ms ± 0.19 ms) and R2 (32.24 ms ± 0.71 ms) response did not alter after GPi DBS. The duration and amplitude of R1 and R2 response (R1: 10.4 ms ± 0.46 ms, 134 μV ± 56 μV, R2: 63.3 ms ± 3.42 ms, 122 μV ± 23 μV) were also unchanged after GPi DBS.

6.4.3 Effect of baseline R2 inhibition on changes after GPi DBS

To identify whether the degree of R2 disinhibition at baseline influenced the extent to which it changed after GPi DBS, patients were identified in whom the average baseline R2 ratio at ISI= 500 ms was more than two standard deviations above the control level

(i.e. greater than 0.61). The 500 ms ISI was chosen because previous work has suggested this to be the most discriminating between dystonia patients and healthy controls (Nakashima et al 1990). There were 4 patients in this category of "abnormal" ISI = 500 ms R2 at baseline (patients 2, 6, 8 and 9). The averaged rectified blink reflex recording for patient 9 is shown in Figure 6.2.

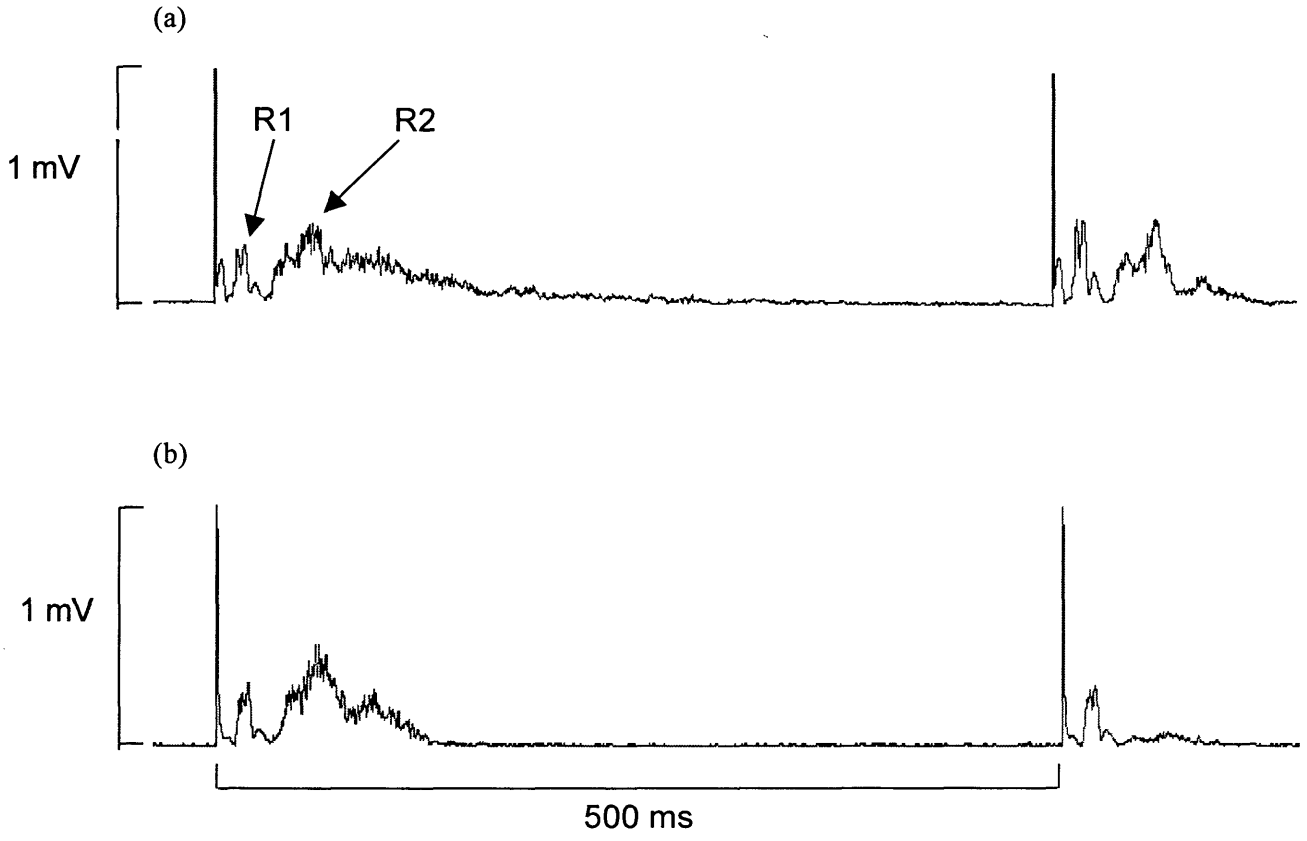


Figure 6.2. Mean rectified ipsilateral blink reflex recordings in patient 9 for right supraorbital nerve stimulation ISI=500 ms. (a) pre-op recording, R1 and R2 components of the blink reflex are marked for the unconditioned response (b) 6 months post GPi DBS recording. Note that the conditioned R2 response is smaller 6 months after GPi DBS.

Repeated measures ANOVA with main factors of TIME (1-4), INTERVAL (1-2) and GROUP (Normal vs Abnormal) showed significant effects of TIME [F(3,24)=13.5

p=0.006], INTERVAL [F(1,8)=37.3, P<0.0001] and TIME-GROUP interaction [F(3,24)=7.36, p=0.027]. The TIME-GROUP interaction indicates that the baseline level of R2 inhibition significantly influenced the extent to which R2 inhibition increased after GPi DBS. Across all patients, there was a significant correlation between percentage change in R2 ratio at 6 months with baseline value of R2 ratio for the 500 ms ISI (r= 0.58 p=0.008), Figure 6.3.

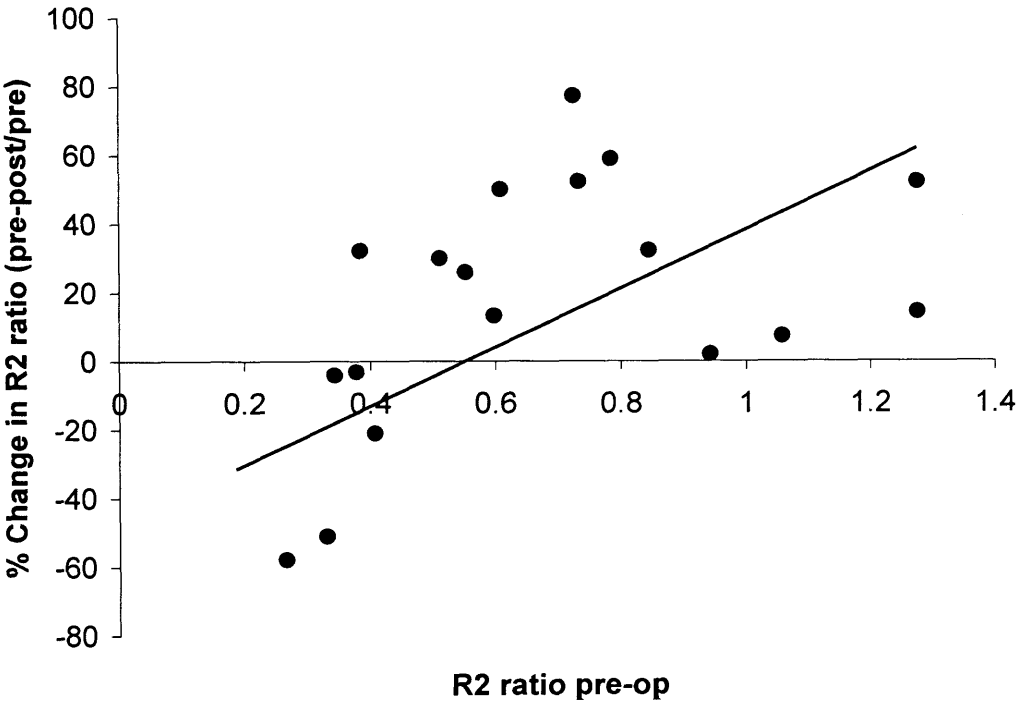


Figure 6.3. Relationship between percentage change in R2 ratio at 6 months with baseline value of R2 ratio for the 500 ms ISI.

6.4.4 Correlation of changes in R2 ratio and dystonia

The relationship between changes and clinical state was assessed using correlation analysis. There was a significant correlation between the change (pre – post) in BFM movement score and R2 ratio at the time points 1, 3, 6 months for ISI=500 ms, (Spearman correlation coefficient=0.48, p= 0.007), Figure 6.4.

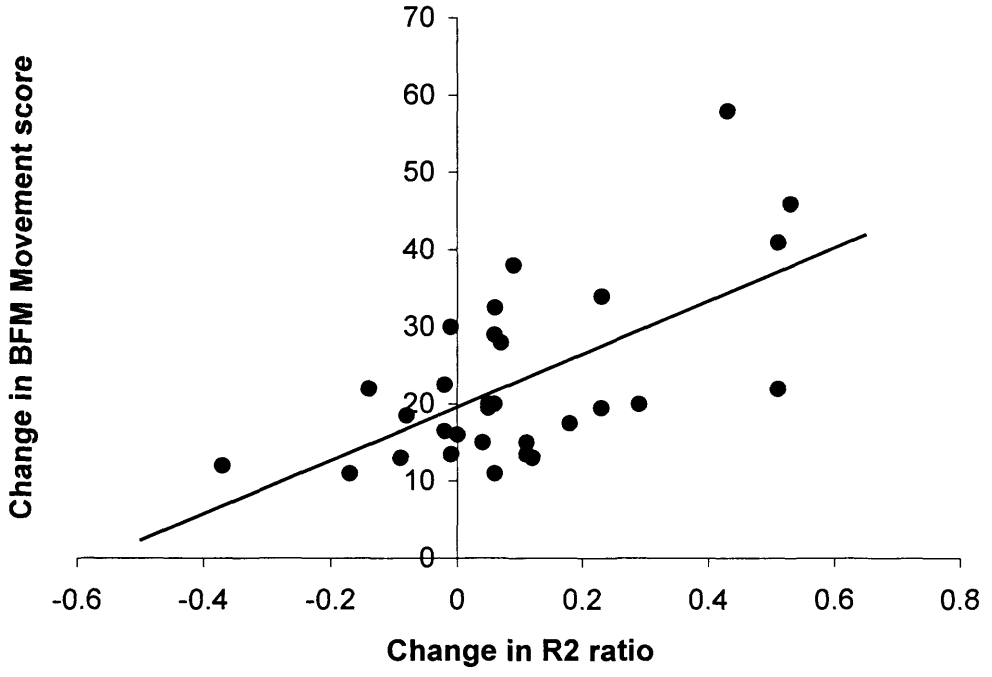


Figure 6.4. Relationship between change in BFM movement score and R2 ratio for ISI=500 ms.

6.5 Discussion

The main finding of the present study was that in patients with primary generalised dystonia, blink reflex R2 inhibition is abnormally reduced compared with healthy subjects, and that chronic therapeutic GPi DBS resulted in a progressive increase in blink reflex R2 inhibition towards normal levels. The magnitude of increase in R2 inhibition (decrease in R2 ratio) was related to degree of baseline disinhibition, in that those with the most disinhibition had the largest decreases following GPi DBS. Finally

the changes in R2 inhibition following surgery were significantly correlated with changes in clinical dystonia as measured by BFM score over the corresponding time course. These results demonstrate that chronic therapeutic GPi DBS partially reverses a well documented pathophysiological feature of dystonia, namely decreased inhibition of blink reflex circuits. Here it will be argued that the progressive nature of the changes in blink reflex excitability after GPi DBS point to neural reorganisation within basal ganglia and cortex.

6.5.1 Baseline abnormalities of R2 inhibition

In the present study, reduced blink reflex R2 inhibition was found in patients compared with healthy subjects. This finding confirms previous reports of reduced R2 inhibition in focal and segmental dystonia (Berardelli et al 1985, Tolosa et al 1988, Carella et al 1994) and primary generalised dystonia as were studied here (Nakashima et al 1990, Pauletti et al 1993). In the present study, only one patient had blepharospasm which emphasises that blink reflex disinhibition is often dissociated from clinical symptoms, a finding in agreement with an earlier study (Nakshima et al 1990). However, it should be remembered that these patients did have marked symptoms in body regions other than orbicularis oculi, so while dissociated from clinical symptoms in the territory of blink circuit motor output, the abnormalities were still linked to the presence of severe dystonia in the rest of the body. Blink reflex disinhibition can therefore be regarded as a physiological marker in generalised dystonia, even in the absence of blepharospasm. The dissociation between blink reflex disinhibition and dystonia in the target muscles of these circuits argues against a primary brainstem defect as their cause. Furthermore, apart from the finding of brainstem inclusion bodies in DYT1 patients (McNaught et al 2004) no pathology in the brainstem has been found in dystonia patients to explain the

finding of disinhibition. Instead, abnormalities of blink reflex inhibition in dystonia are more likely to be the result of abnormal descending control of blink circuits due to abnormal activity within basal ganglia-thalamo-cortical loop and its projections (Berardelli et al 1985, Nakashima et al 1990). This notion is aligned with the view that dystonia is fundamentally a disorder of the basal ganglia, leading to abnormal corticomotor function (Berardelli et al 1998). Basal ganglia influence on the blink reflex may involve GPi, thalamus and cortex, in turn projecting to the brainstem (Esteban et al 1999, Berardelli et al 1983). Animal studies have shown that 6-hydroxydopamine lesions of the SNc result in blink reflex R2 disinhibition via a nigro-collicular projection and the nucleus raphe magnus (Basso et al 1996, Schicatano et al 1997). From these studies, it can be inferred that basal ganglia influence on blink reflex circuits may follow thalamo-cortical or subcortical routes, this point being of particular relevance to the effects of GPi DBS.

6.5.2 Longitudinal effects of GPi DBS on R2 inhibition and potential mechanisms

In the present study, chronic therapeutic GPi DBS resulted in a progressive increase in R2 inhibition. Increases in R2 inhibition were proportional to the degree of disinhibition at baseline. These effects are likely to be the result of GPi DBS altering basal ganglia output and the descending influence from basal ganglia and cortex on blink reflex interneuronal circuits. The observation that the effect of GPi DBS was greatest in those with the greatest R2 disinhibition suggests the existence of a spectrum of blink hyperexcitability ranging from severe to minimal, which in turn would reflect the degree of dysfunction of descending influence from basal ganglia. In this model, patients with severe blink disinhibition would be expected to change greatly after major modification of basal ganglia output (GPi DBS), whereas those minimally affected

would not. These observations are consistent with the view that blink reflex disinhibition in dystonia is the consequence of basal ganglia dysfunction. There is evidence that GPi DBS may modify activity within the basal ganglia thalamo-cortical loop. GPi DBS in PGD patients has been shown to acutely alter motor cortical excitability to transcranial magnetic stimulation as evidenced by an upward shift of the stimulus response curve and reduction in motor thresholds (Kuhn et al 2003). GPi DBS also reverses abnormal overactivation in the premotor cortex seen on positron emission tomography (Detante et al 2004b). These studies suggest that GPi DBS alters cortical activity via the thalamo-cortical pathway but do not preclude the possible contribution of direct projections from basal ganglia to brainstem (Basso et al 1996, Schicatano et al 1997), which collectively would allow modification of descending influence on ponto-medullary blink reflex circuits.

6.5.3 Experimental limitations

A frequent problem encountered with physiological recordings in patients with generalised dystonia is involuntary muscle contractions interfering with EMG recordings. In this experiment, only one patient had dystonia involving orbicularis occuli which was mild, and did not interfere with recordings. Therefore it seems unlikely that involuntary muscle contractions influenced the experimental data. Habituation of the blink reflex is an inevitable consequence of repeated stimulation and results in a progressive diminution of blink reflex amplitude (Shahani 1970). To minimise habituation, subjects were kept alert and stimuli were delivered 10-20 seconds apart, the interval varied randomly which reduced the subjects' ability to predict the timing of stimuli. In the present study, healthy volunteers were recorded only once whereas patients were studied longitudinally at four time points. It was

assumed that blink reflex excitability in healthy subjects would not change over time. Confirmation of this, however, would require repeated recordings in the healthy subjects, which were not done. This potential limitation does not limit the comparison of patients and controls at baseline, nor of patients before and after surgery which provide the main results in this study. Finally, the possible effect of differences in stimulus intensity between assessments needs to be considered. It has been shown that larger intensities (19-26 mA) of supraorbital nerve stimulation decrease the degree of R2 inhibition in healthy subjects and patients with blepharospasm (Sommer and Ferbert 2001). Although the exact stimulus intensity used in each experiment was individualised to elicit the blink reflex, the intensity used ranged between 8-14 mA, and therefore stimulus intensity is unlikely to have influenced the observed changes in R2 inhibition. Finally the potential confounding effects of dystonia medications should be considered. Medications such as Baclofen are known to suppress the human blink reflex (Pellegrini and Evinger 1995) and other drugs enhancing GABAergic synapses such as the benzodiazepines might be expected to have similar effects. While some effect of anti-dystonia medications on blink reflexes seems likely, such effects were kept constant in both the pre and post-operative experiments by not changing medication during the study period. Therefore it seems very unlikely that effects of medication would explain the observed changes in R2 inhibition.

6.6 Conclusions

In the present study, patients with primary generalised dystonia showed abnormally decreased blink reflex R2 inhibition which progressively increased towards normal following GPi DBS. Changes in R2 inhibition and clinical scores of dystonia were significantly correlated. Since increased brainstem excitability is often dissociated from

clinical dystonia, changes in R2 inhibition are unlikely to account directly for clinical improvement. Instead changes in R2 inhibition probably reflect changes in basal ganglia and cortical function underlying clinical improvement, which would account for the correlation between R2 inhibition and clinical scores over time. Modification at the cortex and basal ganglia level seems likely since dysfunction in these regions is thought to underlie dystonia, and would be expected to change following effective treatment with GPi DBS. Further support for this notion comes from short-term ON/OFF stimulation studies which confirm that GPi DBS modifies cortical function, providing a pathway for long-term network alteration. The observed progressive time course suggests a progressive effect of GPi DBS, most likely involving synaptic plasticity within the cortex and basal ganglia. Reorganisation in the basal ganglia and cortex would alter the descending control of brainstem excitability. The present results provide evidence of long-term plasticity within the nervous system in dystonia patients after GPi DBS. This plasticity includes partial restoration of inhibition at the brainstem level which provides further support for the view that multilevel disinhibition represents an important physiological feature of dystonia.

Chapter 7. Cortical evoked potentials from pallidal stimulation in patients with primary generalised dystonia *

7.1 Summary

Deep brain stimulation (DBS) of globus pallidus internus (GPi) has emerged as an effective treatment for primary generalised dystonia; however the physiological mechanisms of improvement remain poorly understood. In the present study, cortical activity in response to GPi stimulation was recorded in 6 patients with primary generalised dystonia > 6 months after bilateral GPi DBS. Scalp electroencephalogram was recorded using 60 surface electrodes during 10 Hz bipolar GPi DBS at each bipolar pair on both sides sequentially. Anatomical position of the electrode contacts in relation to the GPi, internal lamina and GPe was determined from the post-operative stereotactic MRI. In all six patients, a potential was observed with onset latency 10.9 ms ± 0.77, peak latency 26.6 ms ± 1.6, distributed mainly over the ipsilateral hemisphere, maximal centrally. The mean amplitude of this potential was larger with stimulation in posteroventral GPi than in GPe (- 3.46 μV vs - 0.238 μV, $P<0.0001$). These results indicate that low frequency GPi stimulation produces an evoked potential distributed centrally over the ipsilateral hemisphere. The latency and distribution of this potential are consistent with stimulation of pallidothalamic neurons projecting to the sensorimotor cortex. Because this potential is larger and more consistently present with stimulation of posteroventral GPi than GPe, it may provide a physiological tool to identify contacts within the optimal surgical target.

* *This work was presented in poster form at the European Federation of Neuroscience Meeting, Glasgow, Scotland, UK September 2006*

7.2 Introduction

The emergence of GPi DBS as an effective therapy for primary generalised dystonia has provided another example of the dramatic improvement in movement disorders which may result from DBS therapy. Despite the growing acceptance of GPi DBS as treatment for dystonia, relatively little is known about its physiological effects. Its effects on the cortex are of particular interest since cortical dysfunction, possibly as the result of an underlying basal ganglia defect, has been implicated as a major site of abnormality underlying dystonia (Berardelli et al 1998). Moreover, defective basal ganglia output has been cited as the primary defect in dystonia (Vitek et al 2002), which emphasises the importance of the GPi output to thalamus and cortex in both the pathogenesis of dystonia and mechanisms of GPi DBS action. There is evidence that high frequency GPi DBS in humans can alter cortical excitability (Chen et al 2001, Kuhn et al 2003) and regional cerebral blood flow (Fukuda et al 2001, Detante et al 2004), and these effects have been attributed to modification of pallidothalamocortical activity. Whether this modification represents inhibition or excitation of the pallidothalamocortical pathway is difficult to ascertain from these studies. Neuronal excitation has attracted increasing attention as a potential mechanism of GPi DBS action (Garcia et al 2003, McIntyre et al 2004), however to date there has been no electrophysiological confirmation that GPi DBS activates neurons in the pallidothalamocortical pathway *in vivo.* Cortical evoked potentials in response to STN stimulation have been identified (Ashby et al 2001, MacKinnon et al 2004) and suggest that neural elements linking STN and cortex may be activated during low frequency DBS. Whether similar effects occur with GPi stimulation is unknown. In this experiment, cortical EEG was recorded during unilateral low frequency GPi DBS to explore the circuit interactions between GPi and cortex.

7.3 Methods

7.3.1 Subjects

Six patients with primary generalised dystonia were selected for this study, the clinical patient details are shown in Table 1. All patients had undergone bilateral GPi DBS as outlined in the General Methods. Patients were studied > 6 months after GPi DBS once stable improvement in dystonia had been achieved. Patients 3 and 5 underwent unilateral left and right thalamotomy 29 and 23 years ago. Subjects gave written informed consent and the study was approved by the Joint Research Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology.

Patient	*Gender*	*Age (years)*	*Disease duration (years)*	*DYT 1 gene status*	*BFM score pre/6 months post-op (0-120)*	*Medications*	*DBS parameters*
1	F	52	36	+	29 / 7	None	Rt: 5-, 3.4v, 60µsec, 130 Hz Lt: 1-, 3.0v, 60µsec, 130 Hz
2	F	63	4	-	23 / 1	L-dopa Trihexyphenidyl	Rt: 6-, 4.6v, 90µsec, 130 Hz Lt: 2-, 4.6v, 90µsec, 130 Hz
3	F	54	43	-	24 / 9	None	Rt: 4-, 3.7v, 60µsec, 130 Hz Lt: 1-, 3.7v, 60µsec, 130 Hz
4	F	36	25	+	20.5 / 1	Trihexyphenidyl	Rt: 4-, 4.6v, 90µsec, 130 Hz Lt: 0-, 4.2v, 90µsec, 130 Hz
5	F	53	43	+	41 / 22	Diazepam	Rt: 5-, 2.9v, 90µsec, 130 Hz Lt: 1-, 3.7v, 90µsec, 130 Hz
6	F	22	15	+	51 / 11	Trihexyphenidyl	Rt: 4-, 3.6v, 60µsec, 130 Hz Lt: 0-, 3.6v, 60µsec, 130 Hz

Table 7.1. Clinical patient data.

7.3.2 Recordings

The EEG was recorded using the Neuroscan EEG system (Compumedics Ltd, El Paso, Texas USA), and a modified 10-20 montage was used with 60 Ag/AgCl scalp electrodes. Recordings were referenced to linked ears. EEG signals were amplified, band pass filtered 0.05-200 Hz and analogue to digital converted at a sample rate of 2500 Hz and recorded on computer. EEG recordings were made during 10 Hz unilateral pallidal stimulation with an amplitude of 3.5-4 V and pulse width 60-90 μs. Recordings lasting 90-120 seconds were made during stimulation at each bipolar pair of the quadripolar electrode on both sides consecutively, with the other electrode set to zero amplitude. The detailed methodology for this experiment is described in the General Methods.

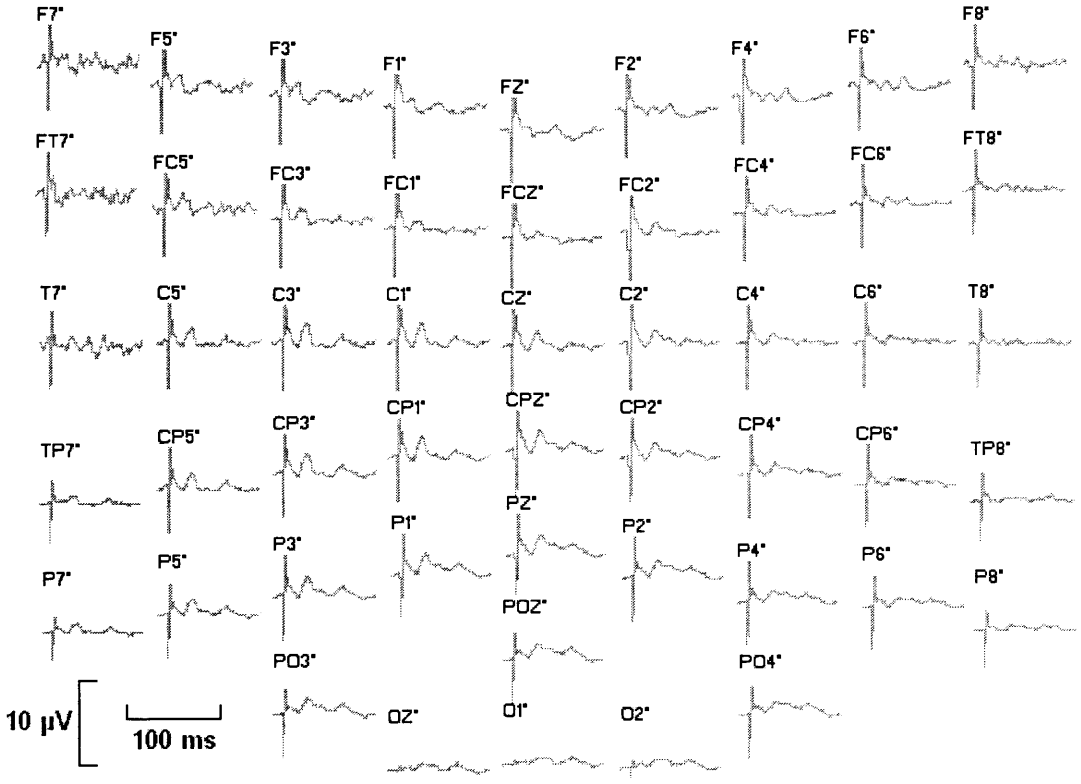
7.3.3 Statistical analysis

The continuous EEG was epoched to the stimulus artifact and averaged to derive the evoked potential. Each averaged EEG was baseline corrected with respect to the prestimulus interval and examined qualitatively for the presence of an evoked potential. Waveforms so identified were then subjected to quantitative analysis with manual marking of latency to onset and peak and measurement of peak amplitude using Neuroscan software (Compumedics Ltd, El Paso, Texas USA). The mean amplitude of the evoked potential was compared from contact pairs located in GPi or GPe using one-way ANOVA. Grand averages were also derived for contact pairs in GPi or GPe. The identification of position of contact in relation to GPi and GPe was made using the Stealth workstation (Framelink TM, Medtronic, Minneapolis USA) as described in Chapters 2 and 4. The investigator identifying contact location was blinded to the results of evoked potential recordings.

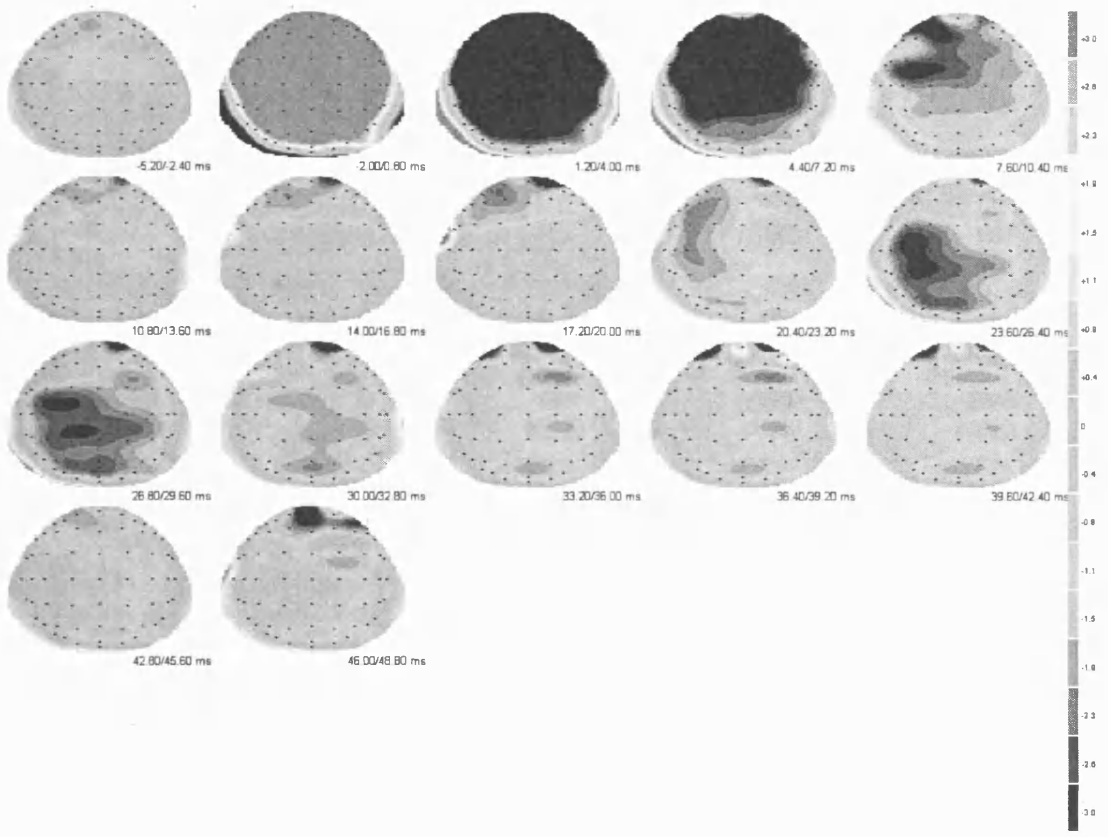
7.4 Results

7.4.1 Characteristics and topography of cortical evoked potential

In all six patients a distinct evoked potential was observed, distributed mainly over the ipsilateral hemisphere, maximal centrally (Figure 7.1). The evoked potential was present with both right and left pallidal stimulation in all patients except patient 5 where it was absent on the right side. When measured in leads C3 and C4, the average onset latency was 10.9 ms ± 0.77 and peak latency 26.6 ms ± 1.6. (Figure 7.2).



(a)



(b)

Figure 7.1. (a) Averaged EEG of patient 1 for stimulation of Left GPi (contacts 0-, 1+). Note the stimulus artifact followed by the evoked potential, a negative waveform seen predominantly ipsilateral to the side of stimulation, maximal centrally. (b) 2D map of the same record, again showing the transient negativity maximal ~26 ms after the stimulus, predominantly ipsilaterally and centrally.

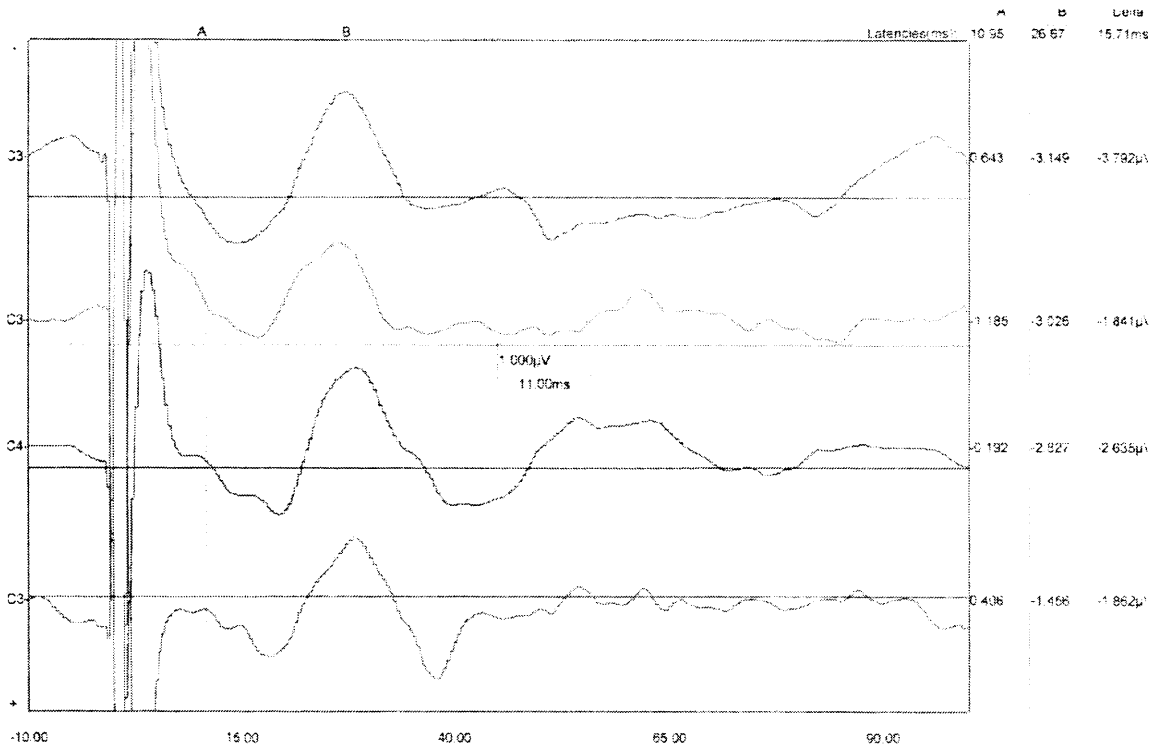


Figure 7.2. Evoked potential recordings from 4 patients recorded at C3 or C4 with stimulation of ventral contacts located in posteroventral GPi. Note the large stimulus artifact followed by the evoked potential. The cursors show the mean onset and peak latency determined for all patients.

7.4.2 Effect of location of pallidal stimulation on the evoked potential

Qualitative assessment of the averaged EEG records revealed that the largest and most consistent evoked potentials usually occurred with stimulation of ventral contact pairs. This observation prompted a formal comparison of the characteristics of the evoked potential with stimulation of contacts lying within the posteroventral GPi (the therapeutic target) and dorsal contacts in GPe. For this comparison the evoked potential was again quantified in C3 and C4. The mean amplitude of the evoked potential for posteroventral GPi stimulation was significantly larger than for GPe stimulation (-3.46 µV vs -0.238 µV, One-way ANOVA $p<0.0001$). The amplitude difference was also

reflected in the group average of actual waveforms, for GPi and GPe stimulation (Figure 7.3).

7.4.3 Relationship between clinically effective contacts and the evoked potential

In all patients the largest evoked potential was observed with stimulation of contact pairs including at least one of the therapeutically effective contacts. These contact pairs, in all patients, corresponded to stimulation of GPi rather the GPe. The contacts at which the largest EP was recorded, the clinically effective contacts and the contact location are shown in Table 7.2

Patient	*Right hemisphere*			*Left hemisphere*		
	Max EP		*Effective*	*Max EP*		*Effective*
1	4 GPi	5 GPi/MML	5 GPi/MML	0 GPi	1 GPi/MML	1 GPi/MML
2	5 GPi	6 GPi	6 GPi	1 GPi	2 GPi	2 GPi
3	4 GPi	5 GPi/MML	4 GPi	1 GPi	2 GPi/MML	1 GPi
4	4 GPi	5 MML/Gpe	4 GPi	0 GPi	1 GPi	0 GPi
5	EP absent		5 GPi	1 GPi	2 GPi	1 GPi
6	4 GPi	5 GPi/MML	4 GPi	0 GPi	1 GPi/MML	0 GPi

Table 7.2 Electrode contact pairs responsible for maximal EP and effective contact in use for chronic therapy. Contact location, in relation to pallidal anatomy, is stated beneath each contact. Note: in all sides the therapeutically effective contact was included in the bipolar pair subtending the largest EP and corresponded to GPi stimulation. Note that in patient 5 the EP on the Right side was absent, the same side as a previous thalamotomy. Patient one was effectively stimulated on contacts 4 and 0 but developed akinesia (see Chapters 3 and 4) and requiring change to contacts 5 and 1.

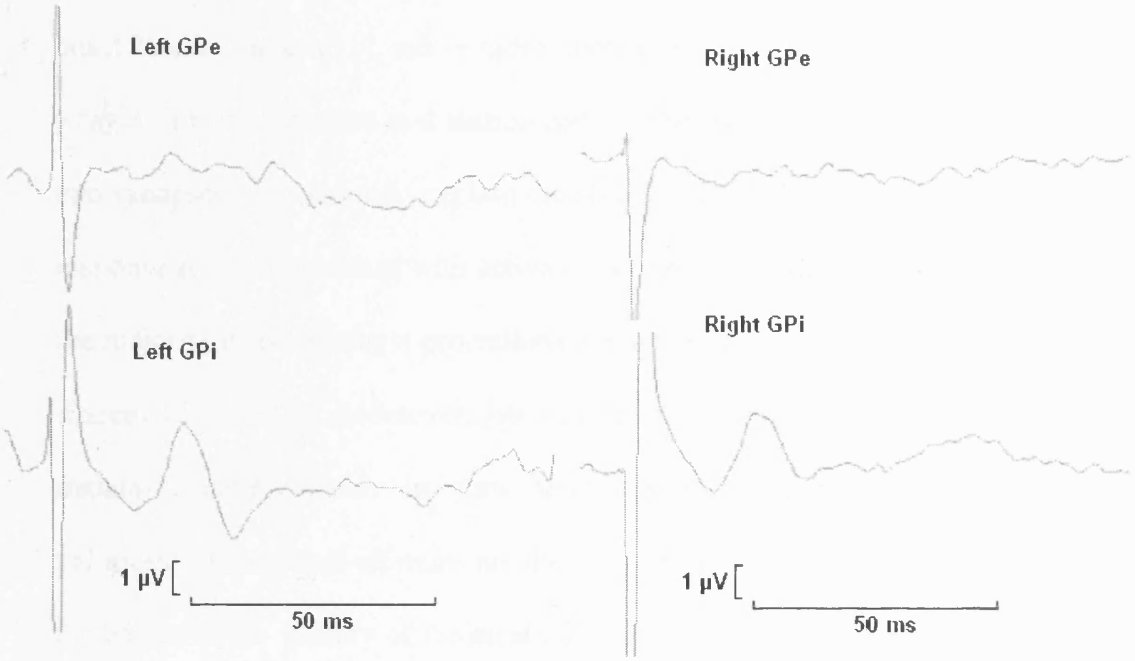


Figure 7.3. Grand average evoked potential from all patients at C3 and C4 for stimulation in GPi and GPe for left and right sides. Note the evoked potential is larger and more distinct for GPi stimulation, compared with GPe where it is almost absent.

7.5 Discussion

7.5.1 Neural pathways mediating the evoked potential

The main finding in the present study is the presence of a cortical evoked potential arising from low frequency pallidal stimulation. The latency, laterality and topography of this potential provide some clues as to the likely neural pathways involved. The average onset latency was around 11 ms, and is too slow for antidromic activation of myelinated cortical axons, where onset latencies in the vicinity of 3 ms would be

expected as observed by Ashby et al (1999) with STN stimulation while recording the scalp EEG. This makes antidromic stimulation of myelinated corticospinal axons of the internal capsule an unlikely candidate for mediating the observed evoked potential. The onset latency around 11 ms is more compatible with activation of pallidal efferents relaying in the thalamus and thence cortex. The pallidothalamocortical route involves two synapses, which would explain the observed latency. The laterality of the observed response is also consistent with activation of the pallidothalamocortical pathway, since the majority of pallidofugal projections are to the ipsilateral thalamus and thence cortex (Parent et al 1999). Moreover, because the GPi projects heavily to the ventral tier thalamic nuclei which in turn send massive projections to the cortex, the pallidothalamocortical efferents are the most abundant neuronal elements with access to the cortex in the vicinity of the electrode. The predominantly central topography of the evoked potential encompasses the sensorimotor cortices, which would be expected targets of pallidothalamocortical activation originating in the "sensorimotor" portion of the pallidum. In another study, using similar methodology, single STN stimuli produced cortical evoked potentials with latencies overlapping with the present data (onset 14 ± 3 ms and peak 23 ± 4 ms), and a similar distribution, ipsilateral and predominantly central (MacKinnon et al 2004). The evoked potential was larger and more consistent with stimulation of dorsal STN electrode contacts, the authors attributing the cortical evoked potential to stimulation of pallidothalamic fibres passing dorsal to the STN. These observations with regard to latency, topography and involved neural substrates for STN derived evoked potentials support the present findings and the putative role of pallidothalamcortical activation. A further possible clue to the involvement of the pallidothalamocortical route is that the only side in which the evoked potential was absent was in patient 5, on the same side as a previous

thalamotomy. This raises the possibility that the thalamic lesion disrupted the pathway, thereby abolishing the evoked potential. In the other patient with previous thalamotomy, the evoked potential was recordable on the thalamotomy side.

7.5.2 Effect of location of pallidal stimulation on the evoked potential: mechanisms and clinical implications

In the present study, the evoked potential was larger and more consistently present with stimulation of GPi compared with GPe. The likely explanation for this finding relates to pallidal anatomy; GPi projects heavily to the thalamus whereas GPe projects mainly to STN, GPi and SNr. Thus the pallidothalamic route, the putative pathway for the evoked potential, is of GPi origin. This explains the observed differences between the evoked potential for GPi and GPe stimulation and also supports the view that the evoked potential is mediated by the pallidothalamic route. As shown in Chapter 4, posteroventral GPi stimulation was the therapeutically more effective. In the present study, clinically effective contacts corresponded well to those in which the evoked potential was observed, which reflects that elicitation of the evoked potential and clinical benefit were both associated with posteroventral GPi site of stimulation. The congruence between the evoked potential and clinically effective sites of pallidal stimulation is consistent with presumed mechanisms of GPi DBS action in dystonia. A major putative mechanism of GPi DBS effect in dystonia is modification of pallidal output, which would entail activation of pallidofugal neurons and their targets in thalamus and brainstem. A further implication of the present results is that the evoked potential could be used as a physiological marker for stimulation in posteroventral GPi and a tool to identify electrode contacts within the optimal surgical target.

7.5.3 Experimental limitations

One aim of the present study was to delineate functionally operational circuits between GPi and cortex involved in therapeutic DBS. A limitation in the present study was that low frequency stimulation, required to elicit evoked potentials, has distinct and even opposing effects to high frequency stimulation (>100 Hz) used therapeutically. Therefore the observation of pallidothalamic activation at low frequencies does not automatically imply that the same circuits are operational during high frequency stimulation. Despite this caveat, however, there is some evidence that neurons of DBS targets can be activated at high frequencies by direct stimulation of the neuronal membrane (Garcia et al 2003). A recent study in a dystonic patient found that high frequency GPi stimulation produced inhibition or occasionally excitation of thalamic receiving neurons, time-locked to individual stimuli (Montgomery 2006). These data suggest that the pallidothalamocortical pathway, demonstrated at low frequencies in the present study, may also be operationally active under high frequency, therapeutic stimulation. Activation of the pallidothalamocortical pathway with high frequency GPi DBS is consistent with the observed short term changes in cortical excitability and regional cerebral blood flow with GPi DBS ON vs OFF (Kuhn et al 2003, Detante et al 2004b). In the present study, the finding of congruence between the evoked potential and therapeutic effective site of pallidal stimulation (posteroventral GPi) raise the possibility of using the evoked potential as a tool to identify contacts within the therapeutically efficient portion of the pallidum. The present results would need to be replicated in larger number of patients with blinded rating of evoked potential and contact location to validate this approach.

7.6 Conclusions

Low frequency GPi stimulation results in a characteristic medium latency evoked potential, which likely reflects activation of pallidothalamic neurons projecting the sensorimotor cortex. The demonstration of activation of this pathway during low frequency stimulation suggests this pathway is accessible to GPi stimulation and supports its putative role in GPi DBS action. However, the extent to which the apparent "driving" activation of pallidothalamocortical circuit observed at low frequencies occurs with therapeutic high frequency GPi DBS remains speculative. The present results raise interesting possibilities for further development of the cortical evoked potential during pallidal stimulation as a physiological marker for stimulation in the posteroventral GPi corresponding to the origin of sensorimotor pallidofugal efferents.

Chapter 8. The effects of GPi DBS on motor cortex plasticity

8.1 Summary

In this Chapter, the effect of globus pallidus internus (GPi) deep brain stimulation (DBS) on motor cortex plasticity in patients with primary generalised dystonia was studied. Ten patients with primary generalised dystonia (5 DYT1+, 5 idiopathic, 6 female, mean age 42) before and > 6 months after GPi DBS, and 10 healthy subjects were studied. Motor cortex plasticity was assessed using transcranial magnetic stimulation (TMS) paired associative stimulation (PAS) of motor cortex and median nerve. Thresholds and TMS intensity to produce a resting motor evoked potential (MEP) of 1mV were determined. Resting MEP amplitude and stimulus response curves were recorded before and after PAS. Patients were recorded ON and OFF DBS in separate sessions. The mean TMS intensity to produce a resting MEP of 1 mV was 54% of maximum stimulator output when OFF and 52% ON DBS. Fifteen minutes after PAS, the resting MEP amplitude increased in patients OFF DBS and in control subjects, whereas it decreased in patients ON DBS. Similarly, after PAS, the mean amplitude of the stimulus response curve increased OFF DBS, but this effect was abolished with DBS ON. Furthermore, patients who had the largest clinical response to chronic DBS also had the largest difference in the effect of PAS with DBS ON v OFF. After PAS, patients with primary generalised dystonia showed a similar pattern of increased motor cortex excitability as healthy subjects when GPi DBS was OFF but not with GPi DBS ON. These results suggest GPi DBS reduces LTP-like motor cortex plasticity, which may contribute to its mechanism of action in dystonia.

8.2 Introduction

As has been discussed in Chapter 1, the pathophysiology of primary dystonia is incompletely understood, but various lines of evidence point to a contributing role played by abnormal brain plasticity. Evidence for this comes from the demonstration of abnormal cortical sensorimotor representations in both animal models (Byl et al 1996) and human focal dystonia (Meunier et al 2001, Rosenkranz et al 2005). These studies suggest that abnormal cortical synaptic reorganisation may be an important feature of dystonia. Taking into account the documented abnormalities of neural inhibition and sensorimotor integration present in dystonia, it is easy to imagine how these factors could contribute to the development of abnormal cortical sensorimotor representations. The next important question is whether dystonia patients may be predisposed to abnormal reorganisation because of an excessive propensity for synaptic plasticity. Indeed, there is accumulating evidence that in dystonia such a defect of "excessive" plasticity exists. The most direct evidence for this has come from studies comparing dystonia patients and healthy subjects using TMS to experimentally induce motor cortex plasticity. Patients with focal dystonia have increased motor cortex plasticity in response to TMS PAS (Quartarone et al 2003, Weise et al 2006). Similarly, motor cortex plasticity following theta burst rTMS is increased in patients with DYT1 dystonia and sporadic cervical dystonia, but reduced in non-manifesting carriers of the DYT1 gene (Edwards et al 2006). These studies suggest that excessive plasticity within the motor cortex may be one factor that contributes to the occurrence of dystonia, and that less plasticity might even be protective for the development of dystonia (Edwards et al 2006). If excessive synaptic plasticity does contribute to dystonia, then it would follow that improvement in dystonia by effective therapy might be associated with reductions in motor cortex plasticity. To this end, the aim of the experiments presented

in this chapter was to determine the effect of GPi DBS on motor cortex plasticity measured using TMS PAS in patients with primary generalised dystonia.

8.3 Methods

8.3.1 Subjects

Ten patients with primary generalised dystonia (6 female, mean age 42 years range 18-64, five DYT1+) and 10 healthy participants (6 female, mean age 37 years, range 24-52) were enrolled in the study. The patient characteristics are shown in Table 1. Patient 5 underwent unilateral thalamotomy 23 years ago. All patients gave written informed consent. The study was approved by the Joint Research Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology

8.3.2 Surgical procedures

All patients underwent bilateral implantation of electrodes into GPi and chronic stimulation. The DBS electrode model 3389 and Kinetra model 7428 implanted pulse generator (Medtronic Neurological Division, Minneapolis USA) were used in all patients except in two where model 3387 electrodes were used. Surgery was performed using methods described in the General Methods section.

8.3.3 Stimulation parameters and clinical assessment

All patients received monopolar stimulation with one or two adjacent active contacts. Stimulation parameters were individualised in each patient and chosen for the best clinical effect in the absence of any side effects. Patients were assessed clinically using the Burke-Fahn-Marsden (BFM) dystonia rating scale (Burke et al 1985). The

stimulation parameters and BFM scores before and 6 months after DBS in each patient are shown in Table 1.

Patient	*Gender*	*Age (years)*	*Disease duration (years)*	*DYT 1 gene status*	*BFM score pre/6 months post-op (0-120)*	*Medications*	*DBS parameters*
1	M	47	37	+	52 / 23.5	Diazepam Tetrabenazine	Rt: 4-, 3.5v, 90μsec, 130 Hz Lt: 0,1-, 3.3v, 60μsec, 130 Hz
2	M	24	16	-	73 / 15	Clonazepam	Rt: 4,5-, 3.9v, 90μsec, 130 Hz Lt: 0,1-, 3.8v, 90μsec, 130 Hz
3	F	52	36	+	29 / 7	None	Rt: 5-, 3.4v, 60μsec, 130 Hz Lt: 1-, 3.0v, 60μsec, 130 Hz
4	F	63	4	-	23 / 1	L-dopa Trihexphenidyl	Rt: 6-, 4.6v, 90μsec, 130 Hz Lt: 2-, 4.6v, 90μsec, 130 Hz
5	F	54	43	-	24 / 9	None	Rt: 4-, 3.7v, 60μsec, 130 Hz Lt: 1-, 3.7v, 60μsec, 130 Hz
6	F	36	25	+	20.5 / 1	Trihexphenidyl	Rt: 4-, 4.6v, 90μsec, 130 Hz Lt: 0-, 4.2v, 90μsec, 130 Hz
7	M	47	26	-	25 / 12	None	Rt: 4,5-, 3.5v, 90μsec, 130 Hz Lt: 0,1-, 3.5v, 90μsec, 130 Hz
8	M	62	7	-	64 / 30	None	Rt: 4,5-, 3.5v, 60μsec, 130 Hz Lt: 1,2-, 3.5v, 60μsec, 130 Hz
9	F	16	7	+	20 / 1	L-dopa Trihexphenidyl	Rt: 4-, 2.5v, 90μsec, 130 Hz Lt: 0-, 2.5v, 90μsec, 130 Hz
10	F	22	15	+	51 / 11	Trihexphenidyl	Rt: 4-, 3.6v, 60μsec, 130 Hz Lt: 0-, 3.6v, 60μsec, 130 Hz

Table 8.1. Clinical patient data

8.3.4 Recordings

EMG recordings were made from abductor pollicis brevis (APB) using methods outlined in the General Methods. TMS was applied over the scalp using a 70 mm, hand-held figure-of-eight coil and Magstim 200 monopulse generator (Magstim UK). Thick physical shielding was fastened over the implanted pulse generator (IPG) to eliminate the risk of close range exposure of the IPG to damaging magnetic flux (Kumar et al 1999a). For median nerve stimulation, electrical stimulation was applied to the median nerve at the wrist using a constant current generator (Digitimer Ltd, Welwyn Garden City, Herts. UK).

8.3.4.1 Motor evoked potential (MEP) recordings

After localisation and marking of the "hotspot" for APB, the resting and active motor thresholds (RMT, AMT) were determined as the minimum stimulus to produce a 50 μV MEP in 5 out of 10 trials. AMT was determined during 20% maximum voluntary contraction of APB. The resting MEP amplitude was recorded over 30 trials, the stimulus intensity adjusted to produce an MEP amplitude of 1 mV. This intensity was then used throughout the experiment. The stimulus response curve (SRC) was recorded with 5 trials in 9 steps of intensity from 10-90% TMS output. Trials with any ongoing EMG artefact were rejected on line.

8.3.4.2 Paired associative stimulation (PAS)

Median nerve stimulation was applied at the wrist at 300% of perceptual threshold in the median distribution, stimulus duration 0.2 ms, delivered 25 ms before TMS over the APB "hotspot" at the intensity predetermined to yield a 1 mV resting MEP (Stefan et al 2000). Two hundred paired stimuli were delivered at a rate of 0.25 Hz. During PAS,

patients were instructed to concentrate on the APB muscle and silently count the stimuli felt in the thumb. The resting MEP amplitude was recorded before and 0, 15 and 30 minutes after PAS. The SRC was recorded before and 15 minutes after PAS. The entire experiment was performed with GPi DBS ON, with usual stimulation parameters, and OFF in two experimental sessions at least 48 hours apart. The medication was not altered during the study. The order of the ON and OFF was balanced between subjects so that approximately half had the OFF session first. For the OFF session GPi DBS was switched off at least 30 minutes prior to data collection.

8.3.5 Statistical analysis

Data were analysed off-line using custom-written software (Nucursor 2001). The peak-to-peak amplitude of individual MEP's were determined and then averaged within patients. Repeated measures ANOVA was used to identify significant effects and interactions. For post hoc comparisons, t tests and Tukey's multiple comparison test were used. Correlations between changes in MEP amplitude and clinical effect of DBS were examined using the Spearman correlation coefficient. All statistics were performed using SPSS for Windows version 11.5. A p value <0.05 was considered significant.

8.4 Results

8.4.1 Motor thresholds

Although there was a slight tendency for AMT, RMT and the 1mV MEP intensity to be higher with GPi DBS OFF (Figure 8.1), this difference was not significant. However, all values were higher than in healthy subjects ($p<0.05$ for all comparisons).

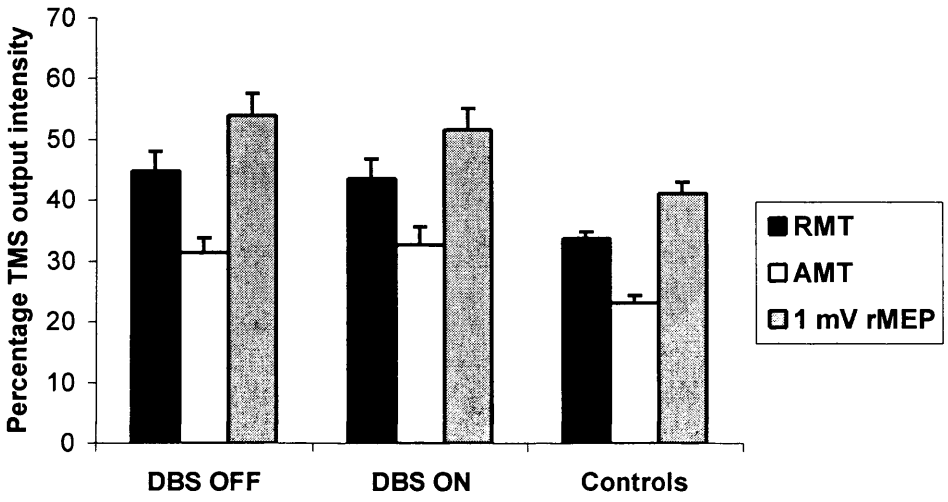


Figure 8.1. Average resting and active motor thresholds (RMT, AMT) and intensity for 1 mV resting MEP (1 mV MEP) in patients OFF and ON DBS and control subjects. Error bars show ± 1 SEM.

8.4.2 Resting MEP amplitudes

Figure 8.2 plots the change in the MEP amplitudes evoked before and at three times after the PAS intervention. We first compared the data ON and OFF DBS in the patients. A repeated measures ANOVA with main factors of TIME (pre, 0, 15, 30 mins post PAS) and STIM (DBS ON and OFF) showed a significant TIME*STIM interaction [$F(3,27)=3.49$, $p=0.029$] that was due to the fact that PAS increased MEPs

when the DBS stimulator was turned OFF, whereas MEPs decreased when it was ON. Post-hoc t-tests of MEP size after PAS with baseline values before PAS confirmed that when the DBS stimulator was OFF, MEP amplitude increased post-PAS ($p=0.016$ at 15 min), whereas it decreased post-PAS when ON ($p=0.026$ at 0 min). The fifteen minutes post-PAS MEP amplitude was significantly higher OFF DBS than ON ($p=0.01$), whereas the baseline MEP amplitude pre-PAS was not different in the two states.

Since the patients' results depended on whether the stimulator was ON or OFF, we compared each state separately with the control values. When patients were OFF stimulation, PAS had the same effect as in the control group, whereas this was not the case when ON stimulation. Thus two factor ANOVAS showed a significant TIME*GROUP interaction for the comparison of controls vs. ON DBS [$F(3,27)=8.41$, $p<0.001$], but not for controls vs. OFF DBS [$F(3,27)=0.62$, $p=0.58$]. Post hoc t tests revealed this effect was due to a significant reduction in MEP amplitude 15 minutes post PAS ON DBS compared with healthy subjects ($p=0.004$). There were no differences between patients OFF DBS and controls.

Finally, we also tested whether there was any difference in behaviour of patients with and without the DYT1 mutation. Mixed model ANOVAs failed to show any significant differences, although given the small numbers involved this needs to be confirmed in a larger study.

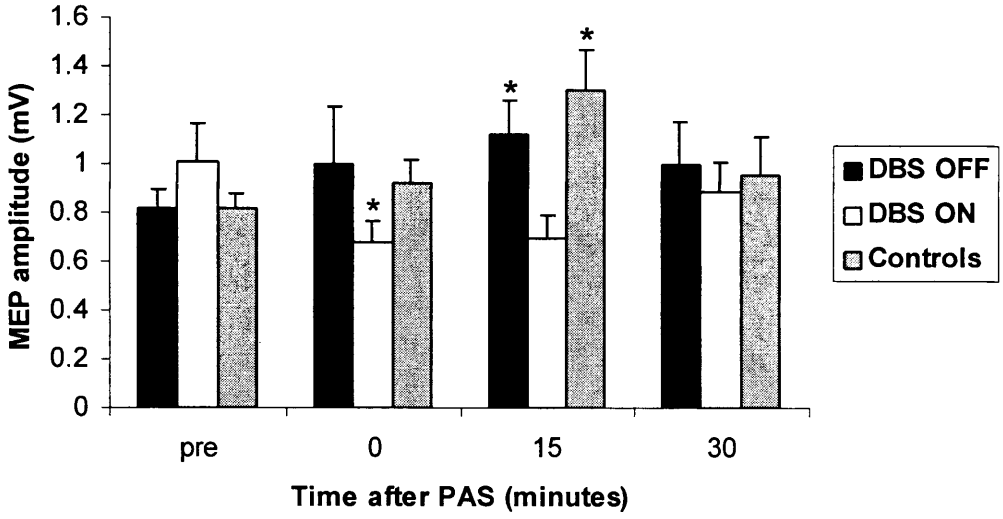


*Figure 8.2. Average resting MEP amplitude (mV) in patients OFF and ON DBS and control subjects before and after PAS. Error bars show ±1 SEM. ($p<0.05$ *).*

8.4.3 Stimulus response curves

The effects of GPi DBS on the stimulus-response curves before and after PAS were examined. This showed that PAS increased corticospinal excitability when patients were OFF stimulation, whereas excitability decreased when ON stimulation (Figure 8.3). This was confirmed in repeated measures ANOVA with main factors of TIME (pre vs post PAS), STIM (DBS ON vs OFF) and INTENSITY (9 levels, 10-90%) that showed a significant 3-way interaction [$F(8,72)=2.81$, $p=0.009$]. Subsequent One-way ANOVA revealed a significant difference in means between the 4 states ($F(3,24)=5.85$, $p=0.0038$). Tukey's Multiple comparison test showed a significant increase post-OFF compared with pre-OFF (mean difference = –0.28 mV, 95% Cl –0.51 to –0.048 mV, $q=4.72$, $p<0.05$) and that pre-OFF was smaller than pre-ON (mean difference = –0.26

mV, 95% CI –0.49 to –0.032 mV, q=4.44, p<0.05). Post-OFF was greater than post-ON (mean difference = 0.23 mV), and post-ON less than pre-ON (mean difference = 0.21 mV), but these differences did not reach significance.

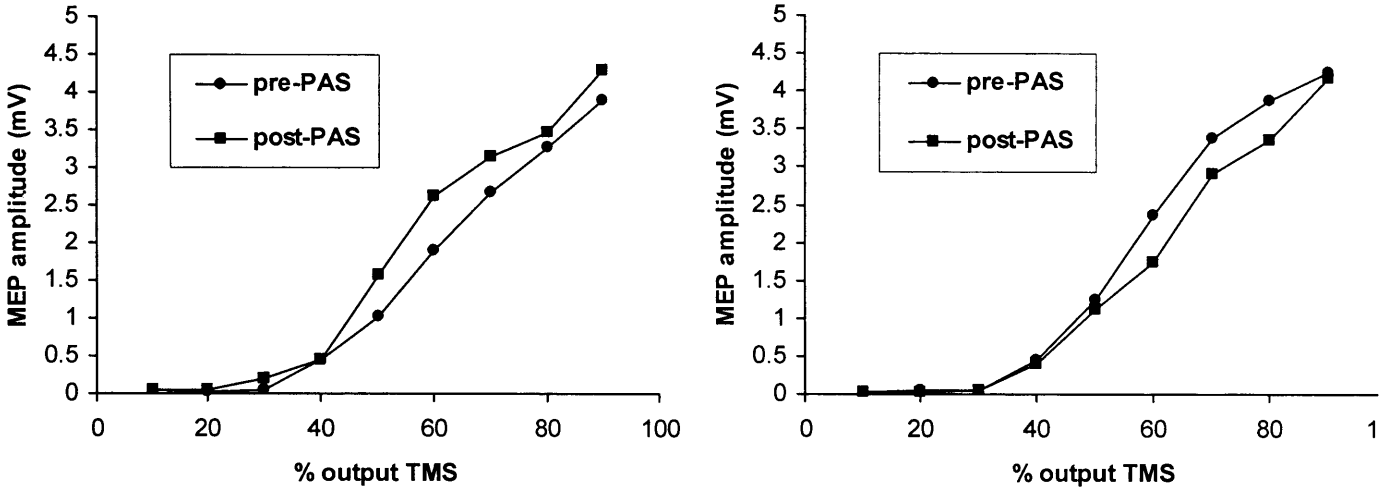


Figure 8.3. Stimulus response (input-output) curves before and after PAS (a) OFF DBS and (b) ON DBS. Note that OFF DBS (a) the stimulus response curve is shifted upwards after PAS (ie increased motor cortex excitability) whereas ON DBS (b) the curve shifts in the opposite direction. The pre-PAS curve ON DBS is also significantly upshifted compared with OFF DBS, indicating that GPi DBS increases motor cortical excitability.

8.4.4 Correlations of clinical outcome and physiological effects

To test whether the effect of DBS on PAS might be related to the clinical effect of chronic treatment, we examined the relationship between clinical improvement and the difference in the PAS effect ON and OFF DBS (Figure 8.4). There was a significant correlation between the change in clinical dystonia score (pre-op BFM - 6 months post-

op BFM) and the change in PAS effect with DBS ON vs OFF (maximal facilitation DBS OFF - maximum inhibition ON DBS), [Spearman's rho =0.69, p=0.026].

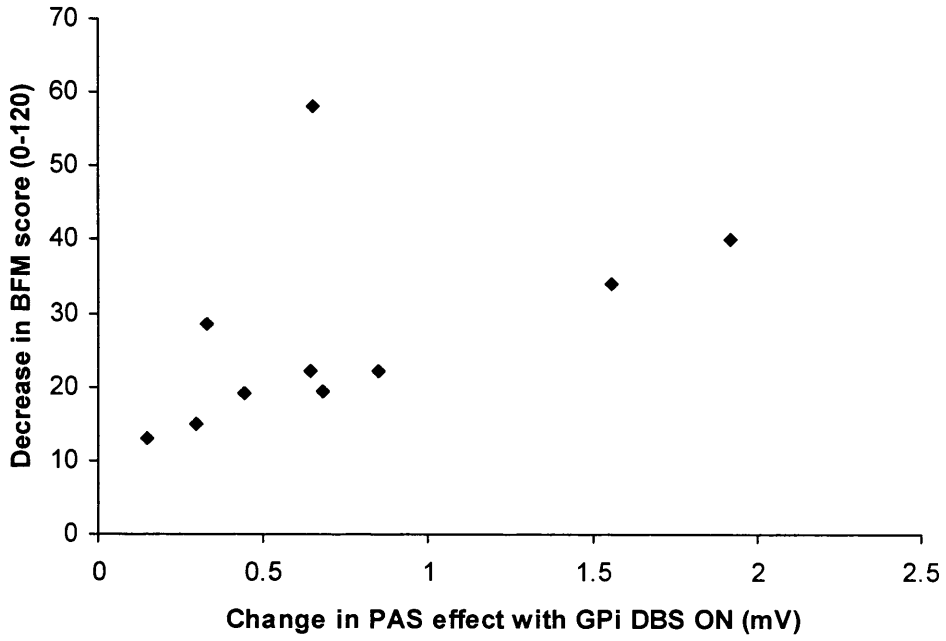


Figure 8.4. Correlation between change in clinical dystonia score (pre-op BFM – 6 months post-op BFM) and the change in PAS effect with DBS ON vs OFF (maximal facilitation DBS OFF -maximum inhibition ON DBS), [Spearmans rho =0.69, p=0.026].

8.5 Discussion

The main finding of the present study was that PAS produced the same effects as normal on MEP amplitude in patients with primary generalised dystonia when GPi DBS is switched OFF, but that the effect is reversed when stimulation is turned ON. Given that the after-effects of PAS are thought to reflect LTP-like plasticity at motor cortical synapses, this suggests that GPi DBS can modify the plastic response of motor cortical circuits to changes in their input. In addition, this effect may contribute to the

clinical effectiveness of DBS in dystonia. The merits of these considerations are now discussed.

8.5.1 Abnormalities of motor cortex plasticity in dystonia

As noted in the Introduction, here are several lines of evidence to suggest that brain plasticity may play a role in the pathophysiology of dystonia. Dramatic reorganisation of somatotopic domains in the sensorimotor cortex of monkeys that occurs after excessive hand training has been linked to the appearance of dystonia-like involuntary movements (Byl et al 1996). Similarly, abnormal patterns of cortical reorganisation have been found in patients who have developed task specific focal dystonia after overlearned tasks such as writing or playing musical instruments (Meunier et al 2001, Rosenkrantz et al 2005). Physiological evidence for abnormal plasticity in dystonia has come from TMS studies using PAS or theta-burst repetitive TMS protocols to probe motor cortex plasticity. Patients with writer's cramp show greater potentiation of MEP amplitude following PAS with 25 ms ISI than healthy subjects (Quartarone et al 2003, Weise et al 2006). Patients with sporadic cervical dystonia and DYT1 dystonia show more intense and longer-lasting inhibition of MEP amplitude following theta-burst repetitive TMS than healthy subjects or non-manifesting carriers of the DYT1 gene (Edwards et al 2006). These results suggest short-term synaptic plasticity is increased in dystonia patients and could contribute to the development of dystonia perhaps by promoting maladaptive reorganisation of the sensorimotor cortex (Quartarone et al 2006b).

8.5.2 Modification of motor cortex plasticity by GPi DBS

In the present study we observed that GPi DBS reduced or even reversed the normal facilitation of MEP amplitude following PAS. In contrast, when the DBS stimulator was turned OFF, facilitation returned to normal. This suggests that the chronic therapeutic GPi DBS results in reduced motor cortex plasticity, and that this effect is DBS dependant, because during arrest of stimulation (DBS OFF condition), plasticity returned to normal. This would normalise the "excessive" plasticity that has been described in dystonia patients. Indeed, long term suppression of neural plasticity during DBS in the present patients may explain why turning OFF DBS did not lead to a facilitated response to PAS. Perhaps chronic stimulation had produced long-term adaptation in these circuits that did not fully reverse when the DBS was transiently turned OFF. Finally it was noted that the clinical response after 6 months chronic stimulation correlated well with the ON/OFF difference in acute tests. We speculate that patients in whom the effects of DBS on synaptic plasticity are greatest are those who respond best to chronic stimulation.

We observed an inhibitory effect of PAS with DBS ON, which occurred immediately after PAS and was sustained at 15 minutes, then dissipated after thirty minutes. DBS ON altered not only the direction but also the time-course of the PAS effect, because it occurred earlier than DBS OFF post PAS facilitation. The fact that the inhibition occurred earlier than facilitation suggests differing mechanisms underlying the opposing effects. The bi-directional plasticity after PAS we have observed may be analogous to that which occurs with reversal of the temporal order of stimuli (Wolters et al 2003), but via a different mechanism: additional input of GPi DBS may orthodromically activate inhibitory pallidothalamocortical projections thereby altering the balance of excitation in the motor cortex, favouring sustained inhibition rather than

facilitation after PAS. In support of this, functional imaging studies in patients with primary generalised dystonia and GPi DBS have shown that during movement, pallidal stimulation reduces ipsilateral overactivity in premotor and primary motor areas, suggesting enhanced thalamocortical inhibition (Kumar et al 1999b, Detante et al 2004b). Recently, reversal of motor cortex facilitation after PAS has been shown to occur in healthy subjects with application of anodal transcranial direct current stimulation during PAS conditioning (Nitsche et al 2007). Anodal transcranial direct current stimulation increases background excitability, and it is reasoned that this increased background activity interferes with plasticity by increasing the signal to noise ratio. Put simply, motor cortex plasticity is favoured under "quiet" conditions when the level of background activity is low, so called homeostatic plasticity. There are clear parallels with this study and the present findings; bilateral GPi DBS like anodal direct current stimulation is a major diffuse input to the brain, which in the present and previous studies has been shown to increase motor cortex excitability. Therefore when GPi DBS is applied concurrently with PAS conditioning, it might interact in the same way as anodal direct current stimulation, and reverse PAS induced plasticity by increasing the background level of activation.

8.5.3 Effect of GPi DBS on measures of motor cortex excitability

In the present study, patients had higher RMT, AMT and 1 mV resting MEP intensity than healthy subjects, which contrasts with an earlier TMS study of dystonia patients with GPi DBS, which found no difference (Kuhn et al 2003). Methodological and surgical differences, including size and placement of burr hole and cap, course of connecting cables and the fact we recorded from APB rather than FDI may explain the differing results. Like Kuhn et al (2003), however, we found that motor cortical

excitability as measured by the stimulus response curve was significantly increased when GPi DBS was ON compared to OFF.

8.5.4 Study Limitations

An important part of the present hypothesis is that patients would have had excessive PAS-induced plasticity before operation. Although this has been described in patients with focal dystonia, there are no reports so far about PAS effects in generalised dystonia. Future investigations of this hypothesis would benefit from pre-operative assessment of patients. It would also be important to know whether the fact that DBS reverses the effect of PAS has any behavioural consequences, potentially even reducing the ability of patients to learn new tasks. Another important consideration in the present study is that an LTP-like mechanism for PAS effects has only been demonstrated in healthy subjects and not in dystonia patients. It therefore remains possible that pathophysiological features particular to dystonia such as decreased inhibition or abnormal sensorimotor integration could play a role in both mediating the PAS effect and also the effect of GPi DBS on PAS.

An additional methodological consideration worthy of discussion is the possible influence of dystonic contractions on the EMG recordings results. One potential concern is that recurrence of dystonia with GPi DBS OFF might lead to a spurious alteration of motor cortex plasticity. There are several reasons why this is unlikely to have influenced the results. Firstly, unrelaxed trials in all conditions were rejected online. Secondly, clinical recurrence of dystonia was mild during the period of GPi DBS OFF, and in no patient did strong dystonic contractions appear in APB that prohibited recordings. Lastly, if involuntary EMG had appeared with GPi DBS OFF then one would expect the pre-PAS cortical excitability to be increased with DBS OFF.

However, the opposite was observed, in that motor cortex excitability, as evidenced by stimulus response curves, was less with DBS OFF than ON, the same result as that observed in a previous study (Kuhn et al 2003).

8.6 Conclusions

The present findings of modification of short-term plasticity by GPi DBS may provide a potential mechanism for the observed neural reorganisation in spinal and brainstem excitability after GPi DBS described in Chapters 5 and 6. Existing evidence suggests that excessive short-term plasticity may be a contributing factor to dystonia. Reversal of LTP-like plasticity might be beneficial by reducing the strength of synaptic connections within aberrantly functioning networks, thereby partially normalising the "excessive plasticity", gradually resulting in the emergence of a physiologically more normal pattern. This proposed mechanism is consistent with our finding of a significant correlation between the change in LTP-like plasticity with DBS and eventual clinical improvement of dystonia. In conclusion, GPi DBS in patients with primary generalised dystonia modifies PAS induced LTP-like plasticity in the motor cortex, which may contribute to its mechanism of action.

Chapter 9. General Discussion

9.1 Therapeutic utility of GPi DBS for dystonia

The results presented in Chapter 3 confirm that GPi DBS is a safe and effective therapy in primary generalised dystonia and agree with previous studies (Coubes et al 2000, Tronnier et al 2000, Vercueil et al 2001, Bereznai et al 2002, Cif et al 2003, Katayama et al 2003, Yianni et al 2003, Krause et al 2004, Coubes et al 2004, Starr et al 2005, Vidailhet et al 2005, Kupsch et al 2006). Sustained improvement occurred in all body regions, with major functional benefit and reduction of disability. Speech was improved but not significantly, a finding in agreement with a previous study (Vidailhet et al 2005). The time course of improvement was progressive and followed a logarithmic distribution. Such a progressive time course is most compatible with neural reorganisation (plasticity) as has been previously proposed (Bereznai et al 2002, Yianni et al 2003, Vidailhet et al 2005). It was shown that the progressive time-course was not a by-product of serial increases in stimulation intensity, but rather a distinctive feature of dystonia in response to GPi DBS. It is important to note that similar progressive improvement has been observed after pallidotomy (Lozano et al 1997), suggesting that it is more a property of dystonia than GPi DBS per se. A progressive time-course of improvement following either type of pallidal intervention is still compatible with plasticity as the underlying mechanism. In Chapter 1 it was argued that dystonia can be viewed as a disorder of maladaptive plasticity in which there is an excessive propensity for synaptic reorganisation, which in the face of faulty processing of sensorimotor information by the basal ganglia leads to the development of abnormal cortical representations. Under this model, continued "misinformation" emanating from the GPi to thalamus and cortex might perpetuate the abnormal patterns of connectivity.

Therefore pallidal interventions which produce a major modification of GPi output might remove this "noisy" signal, allowing the sensorimotor cortex to reorganise into a more normal pattern. Such reorganisation would take time, accounting for the progressive time-course of clinical benefit.

The logarithmic time-course of improvement is steep initially, with almost 70% of eventual improvement achieved within the first 2 weeks, and then more gradual, leveling off at about 6 months. Why should improvement occur fast initially then slow in this logarithmic fashion? One possibility relates to the observation made in the present work and previous studies that mobile dystonia tends to improve more quickly than tonic aspects. Limitations of the BFM scale prevent quantification of the contribution of improvement of mobile dystonia to the early time-course however, based on the consistent clinical observations, such an attribution seems likely. Mobile and tonic aspects probably differ physiologically. Several studies have shown correlation between low frequency synchronised activity in GPi and EMG recorded from dystonic muscles (Chen C et al 2006a, Foncke et al 2007) with coherence between LFP and EMG occurring preferentially for mobile dystonia (Liu et al 2006). These studies support the notion that mobile aspects of dystonia may be preferentially mediated by abnormally synchronised low frequency oscillatory activity within the basal ganglia thalamocortical loop. The more rapid improvement of mobile aspects of dystonia could reflect disruption of this abnormal oscillatory activity that would occur quickly after the initiation of GPi DBS. This effect may be analogous to the immediate alleviation of mobile dyskinesias by GPi DBS, which can be observed in Parkinson's disease, where dyskinesias are associated with increased low frequency synchronised oscillatory activity (Silberstein et al 2003, Alonso-Frech et al 2006) that is rapidly "blocked" by DBS. The subsequent slower phase of improvement would be more

related to synaptic reorganisation which takes longer to occur. In the following sections, the physiological evidence which supports such a mechanism will be put forward.

9.2 Mechanisms of action of GPi DBS for dystonia

9.2.1 Short-term effects

Kuhn et al (2003) examined the effects of GPi DBS on TMS measures of cortical excitability and spinal excitability, as determined by forearm H-reflexes, in patients with severe primary dystonia. The patients were studied at least three months after implantation, with stimulation ON effective chronic stimulation parameters, and stimulation OFF. With GPi DBS ON, the resting motor threshold for TMS elicited cortical MEP was significantly reduced and the stimulus response curve of MEP amplitude was shifted upwards, such that larger MEPs were observed for a given TMS intensity. These effects were rapidly reversible when GPi DBS was switched OFF. Intracortical inhibition and facilitation, the duration of the cortical silent period and forearm H-reflex amplitude were unchanged with GPi DBS ON or OFF.

These results demonstrate that GPi DBS increases excitability of the motor cortex in a rapid and reversible manner, whilst the stability of spinal excitability measures suggest the effect is mediated at the cortical level. Direct activation of corticospinal axons in the internal capsule, which lies in close proximity medial to the GPi DBS electrode, could explain the observed cortical facilitation. Against this, however, the intensity of GPi DBS used was significantly less than required to produce observable motor responses, and facilitation was not observed with stimulation of the Vim thalamic nucleus, in which corticospinal stimulation might also be expected to occur. The observed cortical facilitation is more likely the result of DBS altering pallidal output to

thalamus and cortex. If GPi DBS increases cortical excitability, and the motor cortex is already disinhibited in dystonia, why is DBS beneficial? The explanation may relate to differences between short and long-term effects of GPi DBS. The ON/OFF paradigm used by Kuhn et al is only able to resolve short-term effects therefore it remains possible that motor cortex excitability may have decreased ON DBS compared with levels before surgery. Indirect evidence for this is that the stimulus response curves DBS ON were very similar to healthy control subjects, possibly suggesting some normalisation had occurred.

Two PET studies have examined the short-term effects of GPi DBS on regional cerebral blood flow. The first by Kumar et al (1999b), studied a single patient with primary generalized dystonia 12 months after surgery, ON and OFF DBS, during a free selection joystick task and rest. In this patient bilateral GPi DBS, during joystick movement, reduced activity bilaterally in the primary sensorimotor and prefrontal cortex. Detante et al (2004b) studied 6 patients with primary generalized dystonia using similar methods except that GPi DBS was switched on unilaterally. In this study, GPi DBS, during movement, reduced abnormal overactivation in ipsilateral prefrontal areas. At rest the pattern was quite different; GPi DBS reduced activity in the ipsilateral primary motor cortex and increased activity in the contralateral prefrontal cortex, ipsilateral pallidum and thalamus. The pattern at rest appears at odds with the findings of Kuhn in that primary motor cortex activity decreased rather than increased. As stated in Chapter 7, however, its is difficult to ascertain whether decreases in activation on PET correspond to inhibition or excitation, so caution is needed before considering these studies in conflict.

A consistent finding between the available PET studies is that GPi DBS, during movement, reverses abnormal overactivity in prefrontal areas, previously described in

dystonia patients (Ceballos-Baumann et al 1995a). Overactivity in these prefrontal areas suggests inappropriate recruitment of motor association areas during movement, possibly to compensate for inefficient processing in primary sensorimotor cortex. Reduced motor cortex activity, and increased thalamic activity at rest may reflect a shift in the balance of excitatory and inhibitory output from the thalamus, towards enhanced thalamocortical inhibition, with attendant improvement in clinical dystonia. During movement, the improved thalamocortical inhibition would facilitate focused motor selection and execution, and reduce the need for compensatory activation of prefrontal areas or allow them to be inhibited directly. With the caveats already mentioned concering ambiguity of sign in PET studies, the imaging results are congruent with physiological models of dystonia in which reduced thalamocortical inhibition plays a role and its reversal a potential mechanism of action of GPi DBS. A limitation of these studies is the lack of pre-operative imaging to assess the long-term effects of GPi DBS. The chronic effects of DBS may explain why in the study of Detante et al, patterns of cerebral activation in patients OFF DBS during movement differed from earlier studies, which showed additional abnormal activation in premotor cortex, cerebellum and lentiform nuclei (Ceballos-Baumann et al 1995b).

In the present study, short-term effects of GPi DBS on motor cortex function were studied further. Motor cortex excitability, as determined by TMS evoked resting MEP amplitude and stimulus response curves, was measured before and after PAS, a method shown in healthy subjects to produce plastic facilitation of motor cortex excitability. Measurements were made with GPi DBS under chronic stimulation (ON) or with chronic stimulation interrupted (OFF). The study confirmed the earlier finding of Kuhn et al (2003) of an increase in motor cortex excitability with GPi DBS ON, as evidenced by an upward shift of the stimulus response curve. More importantly, GPi DBS was

found to abolish the normal facilitation of motor cortex excitability following PAS. This suggests that GPi DBS may reduce LTP-like plasticity in the motor cortex, thereby reversing the tendency to excessive cortical plasticity found in dystonia. The results also suggest that LTP-like plasticity remains suppressed under chronic stimulation, but returns to more normal levels when stimulation is stopped. The lack of pre-operative recordings in these patients prevents the determination of when these effects occurred in the time-course after commencement of GPi DBS, but at the very least the results suggest that chronic clinically effective stimulation is associated with suppression of motor cortex LTP-like plasticity. Such an effect might be beneficial in dystonia by reducing the propensity to maintain abnormal patterns of connectivity, thereby allowing a more physiological pattern to emerge. It is well described that induction of LTP may be associated with axonal sprouting (Adams et al 1997) so conceivably an intervention which opposes LTP might reduce axonal sprouting, providing a possible mechanism for devolution of maladaptive synaptic connectivity.

In Chapter 7, it was shown that at low frequencies, GPi DBS is capable of activating the sensorimotor cortex, probably via the pallidothalamic route, generating an evoked potential over the sensorimotor cortex. It is conceivable that similar activation of sensorimotor cortex during therapeutic high frequency stimulation may also occur. This would be in keeping with increased motor cortical excitability during high frequency GPi DBS (Kuhn et al 2003, Tisch et al 2007) and changes in cortical activation seen with functional imaging (Detante et al 2004b, Kumar et al 1999b). Collectively, previous studies and the present work suggest that GPi DBS produces modification of cortical function. The likely general mechanism of these effects is major modification of pallidal output to the thalamus and thence cortex. Changes in motor cortex excitability and synaptic plasticity, and the overall topography of activation under GPi

DBS probably underlie the mechanisms of GPi DBS action. Although long-term studies of changes in cortical function are lacking, the effects demonstrated during interruption of chronic stimulation would provide a means of engendering long-term modifications of cortical-basal ganglia connectivity.

9.2.2 Long-term effects

In Chapters 5 and 6, the first longitudinal physiological studies in dystonia before and after GPi DBS are presented. The findings in both studies shared some similarities. At baseline, the primary generalised dystonia patients displayed abnormally reduced inhibition at the spinal cord and brain stem level, a finding in agreement with previous studies. After GPi DBS, progressive normalisation of excitability occurred for both spinal and brainstem reflex activity. For spinal reciprocal inhibition, levels returned to normal, while for blink reflex, reductions did not reach normal levels. Changes in both spinal and brainstem reflex excitability correlated with the magnitude of clinical improvement in dystonia, suggesting a link with clinical symptoms. These studies provide the first evidence that GPi DBS is capable of long-term reversal of a pathophysiological substrate of dystonia, namely defective inhibition. It is well established that abnormally reduced spinal reciprocal inhibition and brainstem blink reflex inhibition can be dissociated from clinical symptoms. As such these abnormalities are more likely to be a reflection of abnormal descending control from basal ganglia and cortex rather than a primary defect. It follows that the observed changes in spinal and brainstem excitability after GPi DBS are likely to be mediated by alteration of descending control from basal ganglia and cortex. This would explain why GPi DBS is able to exert an effect even though stimulation does not have direct access to brainstem or spinal levels. It also helps explain the correlation of changes in spinal

and brainstem excitability with clinical improvement. Rather than these changes being responsible for improvement, the two phenomena could be the mutual result of alterations occurring at the basal ganglia and cortical level.

9.2.3 Role of neural plasticity in GPi DBS action

Several lines of evidence point to a role for neural plasticity in mediating the effect of GPi DBS in dystonia. Firstly, dystonia itself is characterised by abnormal plasticity both in terms of excessive responsiveness to an external plastic force and the propensity to reorganise into abnormal functional representations. Therefore, it is reasonable to propose that any effective therapy for dystonia might be expected to impact on these abnormalities in some way to achieve a therapeutic response. Secondly, the progressive logarithmic time course of improvement after GPi DBS which is similar to that seen in settings where neural plasticity is thought to occur, such as stroke recovery. Thirdly, the progressive changes in spinal and brainstem excitability after GPi DBS suggest reorganisation of synaptic weightings to these circuits. Fourthly, the demonstration of reduced motor cortex LTP-like plasticity during chronic clinically effective GPi DBS suggests that alteration of synaptic plasticity may play a role in GPi DBS effect. Moreover, suppression of motor cortex LTP-like plasticity might provide one means by which long-term reorganisation within cortical-basal ganglia networks could occur. Lastly, the pattern of recurrence of dystonia when GPi DBS is stopped provide further clues to a long-term plastic effect. Although the clinical effects of DBS take weeks to reach a maximum after implantation, worsening of symptoms (by up to 70%) usually takes only hours if the DBS is then switched OFF (Vidailhet et al 2005, Grips et al 2007). Similarly, patients return to maximum benefit within hours of switching DBS back ON. Why is the initial response to DBS slow whereas the subsequent effects of

turning the stimulus ON and OFF are much more rapid? One possibility is that when DBS is started, there is a slow process of synaptic reorganisation that normalises function over several weeks. However, this normalisation takes place in the context of continuous DBS of the GPi. The outcome is that the activity within the "new" network is stimulation dependent so that when DBS is stopped, dystonia recurs quite rapidly. Similarly when DBS is recommenced, dystonia improves rapidly (rather than weeks to months) because the "new" network is already in place and can be functionally reinstated with the addition of the DBS input. Interestingly, the phasic mobile elements of dystonia recur more quickly than the tonic components (Grips et al 2007) which supports the notion that differing mechanisms may underlie these features, namely that the mobile aspects are more determined by abnormal oscillatory activity which reappears rapidly once stimulation is discontinued.

9.3 Future studies

Dystonia is both clinically and physiologically heterogeneous, making it a challenging disorder to study and understand. GPi DBS represents a major advance in the treatment of severe forms of primary dystonia, however its mechanisms of action are only beginning to be understood. A successful model of GPi DBS action must be able to explain the characteristic, progressive time course of clinical improvement, which occurs in dystonia. The available evidence suggests that GPi DBS exerts its effects by altering basal ganglia output, leading to modification of thalamocortical and subcortical activity. Chronic progressive changes in spinal and brainstem excitability following GPi DBS suggest brain plasticity may play an important role in GPi DBS action and provide a physiological explanation for progressive clinical improvement. Further longitudinal studies in these patients, using combinations of functional imaging and

TMS are needed to validate this model. Specifically, the demonstration of long-term changes in cortical excitability with TMS, and alteration in the pattern of regional brain activation with functional imaging studies would provide further evidence for the role of plasticity in the mechanism of GPi DBS for dystonia. It would also be important to validate the presumption that cortical synaptic plasticity is abnormally increased in patients with primary generalised dystonia, since this would lend further support to the notion that reversal of "excessive" plasticity in dystonia may be an important mechanism of GPi DBS action. In this regard it would be valuable in future studies to confirm the findings made with PAS, using an alternative TMS plasticity protocol, such as theta burst rTMS. Additional safety studies would be needed before using theta burst rTMS in patients with GPi DBS, however an advantage of this technique would be the ability to study LTD-like effects, a direction of plasticity which GPi DBS may favour, as suggested by the present PAS experiments. In future studies, baseline abnormalities before surgery, of cortical plasticity in dystonia should be correlated with eventual clinical improvement, to determine if measures of plasticity could be a useful predictive tool to identify patients likely to benefit. Such a biomarker would complement other predictive factors such as primary dystonia and DYT1, and potentially aid in patient selection. In this regard it would be interesting to compare motor cortex plasticity in primary and secondary dystonia to identify differences which might provide clues to the poorer response to GPi DBS in secondary dystonia. In those patients selected for DBS, the identification of superiority of stimulation in the more posteroventral GPi may assist in optimising both surgical targeting and choice of contacts for chronic stimulation. The evoked potential from low frequency GPi DBS may provide another means of identifying the contacts within GPi. It would be valuable in future studies to

record the evoked potential in a larger number of patients to determine its predictive value for identification of clinically effective contacts.

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