Effects of deep brain stimulation on speech in patients with Parkinson's disease and dystonia.

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I, Elina Tripoliti, confirm that the work presented in this thesis is my own. Where information has been derived form other sources, I confirm that this has been indicated in the thesis.

Abstract

Disorders affecting the basal ganglia can have a severe effect on speech motor control. The effect can vary depending on the pathophysiology of the basal ganglia disease but in general terms it can be classified as hypokinetic or hyperkinetic dysarthria. Despite the role of basal ganglia on speech, there is a marked discrepancy between the effect of medical and surgical treatments on limb and speech motor control. This is compounded by the complex nature of speech and communication in general, and the lack of animal models of speech motor control. The emergence of deep brain stimulation of basal ganglia structures gives us the opportunity to record systematically the effects on speech and attempt some assumptions on the role of basal ganglia on speech motor control.

The aim of the present work was to examine the impact of bilateral subthalamic nucleus deep brain stimulation (STN-DBS) for Parkinson's disease (PD) and globus pallidus internus (GPi-DBS) for dystonia on speech motor control. A consecutive series of PD and dystonia patients who underwent DBS was evaluated. Patients were studied in a prospective longitudinal manner with both clinical assessment of their speech intelligibility and acoustical analysis of their speech. The role of pre-operative clinical factors and electrical parameters of stimulation, mainly electrode positioning and voltage amplitude was systematically examined. In addition, for selected patients, tongue movements were studied using electropalatography. Aerodynamic aspects of speech were also studied. The impact of speech therapy was assessed in a subgroup of patients.

The clinical evaluation of speech intelligibility one and three years post STN-DBS in PD patients showed a deterioration of speech, partly related to medially placed electrodes and high amplitude of stimulation. Pre-operative predictive factors included low speech intelligibility before surgery and longer disease duration. Articulation rather

than voice was most frequently affected with a distinct dysarthria type emerging, mainly hyperkinetic-dystonic, rather than hypokinetic. Traditionally effective therapy for PD dysarthria had little to no benefit following STN-DBS.

Speech following GPi-DBS for dystonia did not significantly change after one year of stimulation. A subgroup of patients showed hypokinetic features, mainly reduced voice volume and fast rate of speech more typical of Parkinsonian speech.

Speech changes in both STN-DBS and GPi-DBS were apparent after six months of stimulation. This progressive deterioration of speech and the critical role of the electrical parameters of stimulation suggest a long-term effect of electrical stimulation of basal ganglia on speech motor control.

Acknowledgements

My heartfelt and warmest thanks go to my supervisor Dr Patricia Limousin. Without her steadfast support and trust this work would not have been completed. I have benefited enormously by her experience, knowledge, clarity of thought, and above all her true care for the patients. I am equally thankful to Professor Marwan Hariz, whose constant encouragement, inspiration and integral, meticulous approach have set the highest clinical and research standards.

This study is the result of teamwork. I'm gratefully indebted to Mr Ludvic Zrinzo for his practical help, enthusiasm and confident dynamism, to Dr Tom Foltynie for his organised and persistent approach to data analysis, Mr Joseph Candelario and Ms Ellie Borrell, Dr Irene Martinez-Torres and Dr Iciar Aviles, to Dr Diane Ruge for our discussions, to Dr Stephen Tisch and to Professor Marjan Jahanshahi. I would also like to thank Professor John Rothwell and Dr Serge Pinto who supported the study at the very beginning; Sue McGowan and the Speech & Language Therapy Team at the National Hospital for our friendship and encouragement; Ms Laura Strong, Ms Eleanor Frost and Ms Freya Hickey for all the hours of listening to recorded speech they provided. I was also very fortunate to work with Mr Michael Roughton, Senior Statistician at UCL, who supported me with positive and clear advice on the data analysis.

I owe a lot to my husband Mark who made it all possible with his strong belief, his persistence, his sense of humour and the joy of our conversations. I also owe a lot to my late grandmother Stamatia who first impressed on me the value of "logos" – the Greek word for both speech and nous.

Most of all I would like to thank the patients who took part in this study over the last six years. I hope this is the beginning and that one day someone will be able to resolve the mystery of speech and electrical stimulation of deep brain structures.

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Abbreviations

AAC	augmentative and alternative communication
AIDS	assessment of intelligibility of the dysarthric speech
AL	Ansa Lenticularis
BFM	Burke-Fahn-Marsden (dystonia rating scale)
BOTOX	Botulinum Toxin
CD	cervical dystonia
CP	cerebral palsy
CT	cricothyroid
CSL	Computerised Speech Lab
dB	decibel
DDK	diadochokinesis
DLPF	dorsolateral prefrontal cortex
EEL	end expiratory level
EMG	electromyography
EPG	electropalatography
FCT	fasciculus cerebellothalamicus
FEV1	forced expiratory volume in one second
F_0	fundamental frequency
FVC	forced vital capacity
GPe	GLobus pallidus externus
GPi	Globus pallidus internus
IA	interarytenoid
IC	internal capsule
LCA	lateral cricorytenoid
LEDD	Levodopa equivalent daily dose
LSVT	Lee Silverman voice treatment
LTAS	long term average spectra
LV	lung volume
LVP	levator veli palatine
MAP	mean subglottal air pressure
MFR	mean flow rate
MPT	maximum phonation time
MRI	Magnetic resonance imaging
OMD	oromandibular dystonia
PAG	periaquaductal grey
PAP	peak subglottal air pressure
PCA	posterior cricoarytenoid
PET	Positron Emission tomography
PMd	dorsal premotor cortex
PP	palatopharyngeus
PPN	peduculopontine nucleus
rCBF	regional cerebral blood flow
RN	red nucleus
SD	standard deviation
SLM	sound level meter
SLT	Speech and Language Therapist
SMA	supplementary motor area
SN	substantia nigra

SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
SPL	sound pressure level
STF	slow muscle fibres
STN	subthalamic nucleus
SVP	sustained vowel phonation
TA	thyroartenoid
TMS	transcranial magnetic stimulation
TVP	tensor veli palatine
TWSTRS	Toronto Western Spasmodic Torticollis Rating Scale
U	uvular
UPDRS	Unified Parkinson's disease Rating Scale
VHI	voice handicap index
VOT	voice onset time

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“No subject of late years has occupied the attention of physiologists in all parts of the world as the attempt to localize the grand attribute of humanity, the faculty of speech.”

Bateman (1870, as in Lorch MP, 2008) on the logomachy between Broca and Hughlings Jackson in Norwich.

CHAPTER 1: INTRODUCTION

1.1 Basal ganglia structure and function

The basal ganglia consist of four main nuclei: the striatum, the globus pallidus, the subthalamic nucleus and the substantia nigra. Other nuclei, such as the central complex of the thalamus and the penduculopontine nucleus also play a major role in basal ganglia functioning.

There are four determinants of basal ganglia functional properties: the anatomy of the four nuclei, the neuronal morphology, the dopaminergic control and their connectivity.

1.1.1 Anatomy

The striatum consists of two macroscopic nuclei, the caudate nucleus and the putamen. The caudate nucleus has a curved shape, with the rostral portion referred to as the head being far more voluminous than the body. The tail is very small in humans (Figure 1.1).

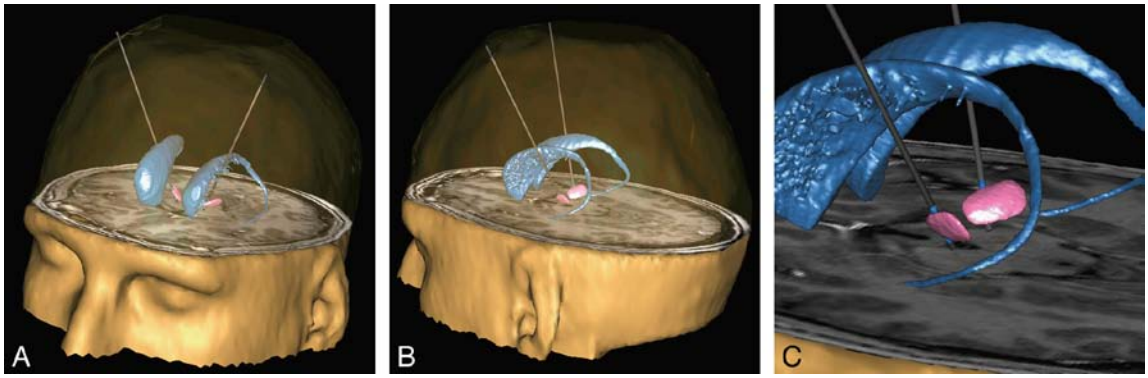

Figure 1.1: *Three-dimensional view of the caudate nuclei (blue) in relation to the STN (pink) from a postoperative MR acquisition in a patient with bilateral implantation of electrodes (grey) in the STN for the treatment of advanced PD using the atlas from Yelnik et al (2007). A, Anterior oblique view. B, Posterior oblique view. C, Zoom on the electrodes showing that their contacts are located inside the STN from Dormont, 2010.*

The putamen, together with the globus pallidus, constitute the lenticular nucleus (Figure 1.2). The shape of the lenticular nucleus is triangular when seen on axial sections but more elongated, like a banana (Yelnik, 2002) when seen on coronal sections.

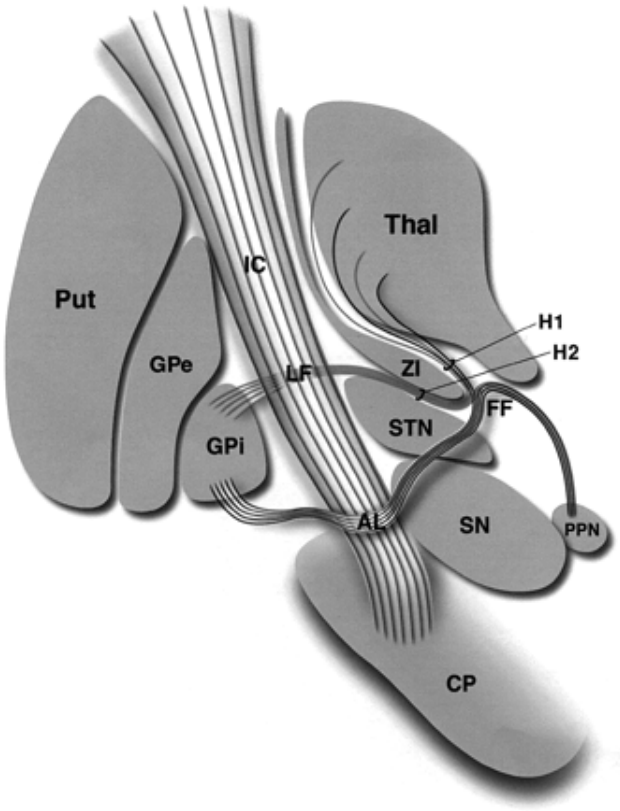

Figure 1.2: *Representation of the major anatomical structures and fibre tracts associated with the subthalamic nucleus. AL = ansa lenticularis; CP = cerebral peduncle; FF = Fields of Forel; GPe = globus pallidus externus; GPi = globus pallidus internus; H1 = H1 Field of Forel (thalamic fasciculus); IC = internal capsule; LF = lenticular fasciculus (H2); PPN = pedunculopontine nucleus; Put = putamen; SN = substantia nigra; STN = subthalamic nucleus; Thal = thalamus*
ZI = zona incerta. From Hamani et al (2004).

The globus pallidus is subdivided into an external (GPe) and an internal (GPi) segment (Figure 1.3). The subthalamic nucleus (STN) is located under the thalamus and above the mesencephalon. Its shape is that of a biconvex lens (3x 5 x 12 mm in humans) which is obliquely oriented to the three anatomic planes. Thus the anterior pole of the STN is much more inferior (ventral) than the posterior pole. It is also much more medial

than the posterior pole (Figure 1.1). The substantia nigra is a mesencephalic structure that comprises two main subdivisions: the pars compacta (SNc) and the pars reticulata (SNr) (Figure 1.3).

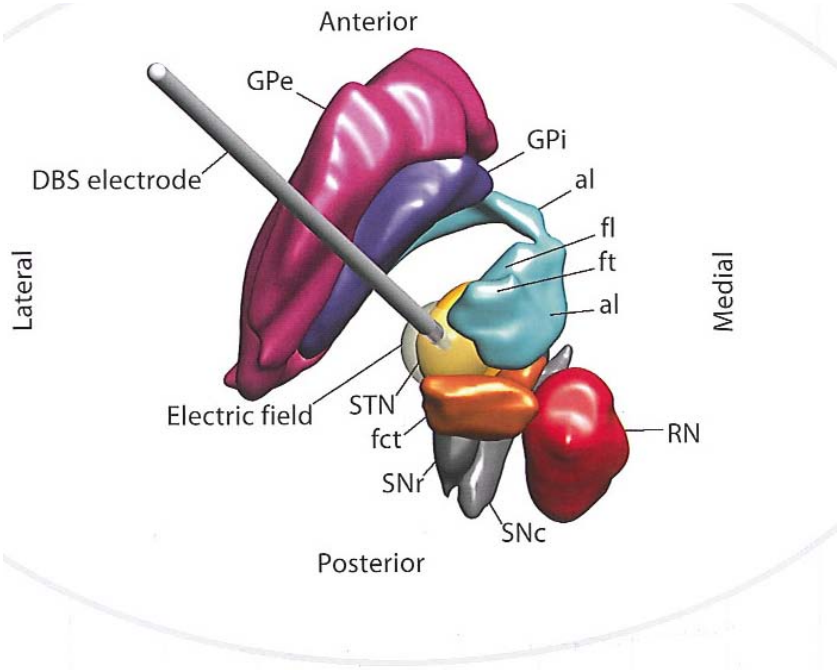

Figure 1.3: *Superior view of a three-dimensional atlas model of the STN, Red Nucleus (RN), fct, al, fl, ft, substantia nigra pars reticulate (SNr), substantia nigra pars compacta (SNc), internal segment of the globus pallidus (GPi), and external segment of the globus pallidus (GPe), together with a DBS electrode placed in the posterodorsal area of the STN. From Astrom, 2010.*

1.1.2 Neuronal morphology

Striatal neurons consist mainly of spiny neurons whose dendrites are densely covered with dendritic spines (Figure 1.4). They use GABA as their neurotransmitter, while afferent cortical neurons use glutamate. Cortical information is received on the spines of the spiny neurons, which are in turn submitted to the inhibitory control of the local circuit motorneurons, the disinhibitive control of the cholinergic neurons and the excitatory control of dopamine afferents.

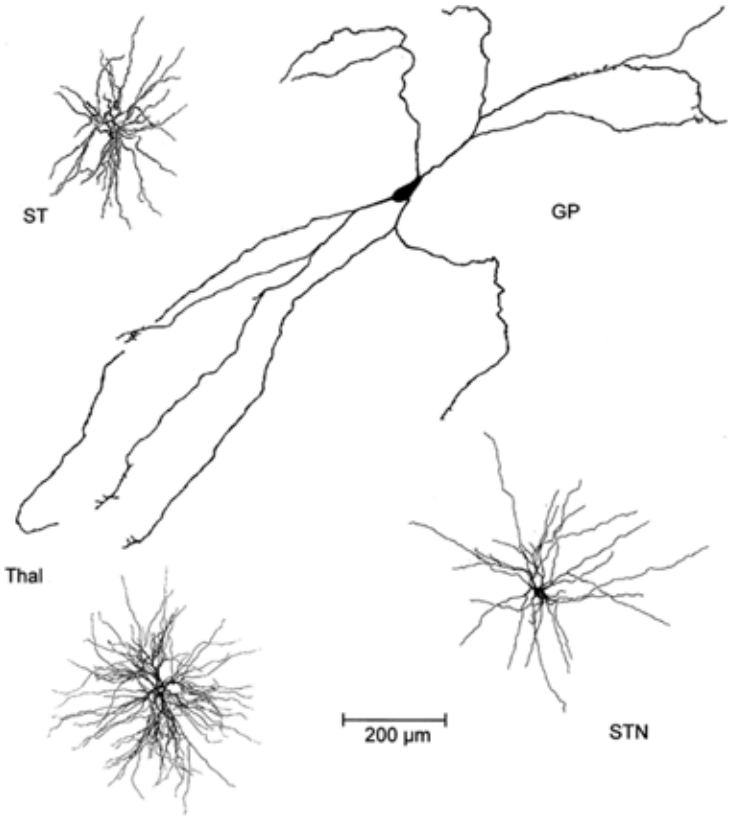

Figure 1.4: *Four main neuronal types of the basal ganglia as they appear after reconstruction from serial sections and camera lucida drawing. All neurons are shown at the same magnification. Note the long and sparsely ramified dendrites of pallidal neurons (GP) compared with the short but densely ramified dendrites of spiny striatal (ST), subthalamic (STN) and thalamocortical (Thal) neurons. From Yelnik, 2002.*

Pallidal and nigral neurons, which receive striatal input, have a different morphology than the striatal spiny neurons: their dendrites are long (up to 1 mm), thick, smooth and sparsely branched (Francois et al, 1984). They are covered with synaptic boutons 90% of which are coming from the striatum, 10% of which are coming from other sources including the STN and the PPN. Pallidal neurons are GABAergic neurons, which suggests they have an inhibitory effect on their thalamic target neurons (Penney et al, 1981). They are 100 times fewer in number than the striatal neurons, which suggests a numeric convergence (Yelnik et al, 2008). Nigral neurons have the same dendrites as pallidal neurons. Anatomically the striatopallidal system is characterised by a volumic, numerical and geometrical convergence (see below). According to Yelnik (2008) the

GP could be viewed as a keyboard on which various behavioural repertoires could be coded from the simple movement of a single joint (which would be coded by a small number of pallidal neurons of the sensorimotor territory) to the most complex motor sequence involving the entire body and expressing an emotional content in a cognitive context (e.g. conversational speech, or movement of a dancer, or playing a musical instrument; this would involve a larger sample of neurons of the sensorimotor, associative and limbic territories).

The subthalamic neurons have dendritic arborizations that are intermediate, in number of branching points and length of dendritic branches between those of striatal and pallidal neurons. They use glutamate as their neurotransmitter and have thus an excitatory effect on their pallidal and nigral targets. Neurons of the STN have the same branching pattern (number of branching points and length of dendritic branches) in rats, monkeys and humans. They are identical throughout the nucleus, which means that the nucleus is cytologically homogenous. In monkeys and humans the STN is a closed nucleus that receives and processes only afferences that are specifically devoted to it (Yelnik, 2008). For this reason it represents a target that is perfectly delimited, both anatomically and functionally. The STN has two major projection sites, the external globus pallidus and the output nuclei of the basal ganglia, internal globus pallidus and SNr. In the STN pallidal information is submitted to a volumic compression since the nucleus is five times smaller than the GPe (Yelnik, 2002). The GPe inhibits the STN, while this latter activates the former, making the pallidosubthalamic system a closed loop submitted to a autoinhibition process the role of which is not fully understood (Yelnik, 2008) (Figure 1.5).

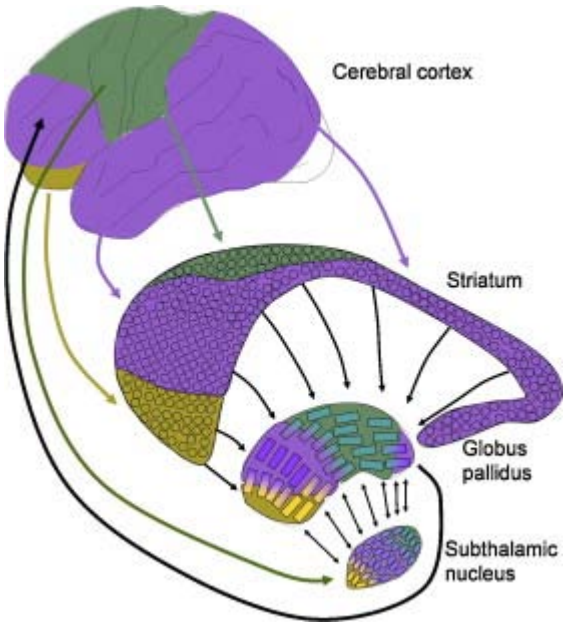

Figure 1.5: *A diagrammatic representation of the basal ganglia organisation. The basal ganglia receive information from three functional territories of the cerebral cortex, sensorimotor (green), associative (violet) and limbic (yellow), that are transmitted to separate regions of the striatum. Information is received by spiny-striatal neurons, which have small spherical dendritic arborizations (spheres), which preserve functional specificity. In the globus pallidus, neurons are 100 times less numerous and have flattened and large dendritic arborizations (rectangles), which makes transmission of striatal information onto pallidal neurons highly converging. In the subthalamic nucleus, information comes from the three functional territories of the globus pallidus, but also directly from motor cortices, which confers to this nucleus the role of a nexus in the circuit. From Yelnik, 2008.*

The role of the projection of the STN to the output nuclei is clearer: it provides a tonic excitatory permanent drive in these nuclei, which results in a permanent inhibition of the thalamocortical projection. However the way information is processed in the STN remains unclear: it is a small nucleus (3,000 times smaller than the cortex and with 4,000 times smaller number of neurons), which implies that information coming from the sensorimotor, associative and limbic regions converge into a nucleus only a few mm large (Yelnik, 2002). The afferents from the GPe respect the functional division (Karachi, 2005). The STN receives two strikingly different inputs – one from the GPe, which is inhibitory and one from the cerebral cortex which is excitatory. (For the

functional implications of this dual system see section 1.4). Thus the STN can be viewed as a thermostat, whereby in the normal state with an appropriate level of activity it enables normal execution of cortical commands, neither too impulsive nor too slow. When hyperactive it slows down all cortical programmes, like in Parkinson akinesia, which can be released by its inactivation by lesion (Bergman et al, 1990) or stimulation (Limousin et al, 1995). At a territorial level the STN can process separately motor, associative and limbic information. At a neuronal scale a much finer organisation probably exists since it is possible to modify a behaviour with one particular contact but not with an adjacent contact, only 2 mm apart (Mallet, 2007).

1.1.3 Dopaminergic control

The dual model of direct and indirect pathways (Albin et al, 1989) is based on the observation that the striatum is not a uniform structure but a heterogeneous one, including the distribution of dopamine terminals. It was based on two concepts: the existence of subpopulations of striatal projection neurons and a differential effect of dopamine onto these two populations. Neurons that contained the neuropeptide substance P were supposed to project mainly upon the GPi and the SNr, the direct pathway, whereas those containing enkephalin would project to the GPe, the indirect pathway. Activation of the direct pathway has an excitatory effect on the thalamocortical projection, which facilitates movement; activation of the indirect pathway leads to an activation of the STN and then to an increased inhibition of the thalamocortical pathway. Dopamine had an excitatory role on the direct pathway and an inhibitory role on the indirect pathway, thus decreasing the inhibitory effect of the system and making possible the execution of movement. In the parkinsonian state the absence of dopamine results in the disinhibition of the output nuclei (GPi and SNr) and an increased inhibition of the thalamocortical projection, which leads to a reduction or

absence of movement (brady or akinesia). The model also suggests that the two populations of the striatal neurons bear different dopaminergic receptors (D1 receptors for the direct pathway and D2 for the indirect pathway) and that dopamine has an excitatory effect on the D1 receptors and an inhibitory effect on the D2 receptors.

This model has received some criticism: it supposes that striatal neurons project to either the GPe or the GPi and not to both target nuclei. A single neuron tracing study has shown striatal neurons that project to GPe, GPi and SNr (Parent, 1995). Also a large number of pathways that may have a crucial control in normal and pathologic functioning of the circuit are not considered in the model: e.g. the pallidopallidal projection, the dopaminergic innervation of the STN (Francois et al, 2000), and globus pallidus (Jan et al, 2000) the afferent projection of the parafascicular nucleus and the PPN to the STN and the projections from the PPN to the basal ganglia.

1.1.4 Connectivity and functional organisation

Whilst our understanding of the morphological and biochemical properties of the basal ganglia system is increasing, its exact functioning in normal and pathological conditions remains quite enigmatic. This has led to various interpretations from which different models have been construed.

1.1.4.1 The box and arrows models

In the box and arrows model each nucleus of the basal ganglia is considered as a unique and homogenous structure, “the box” that communicates with the other nuclei by connections, characterised by their excitatory or inhibitory nature, the “arrows”.

The dual circuit model was proposed by Albin et al (1989) to provide a simplified description of the basal ganglia circuits and the pathophysiology of both hypokinetic and hyperkinetic disorders. There is a direct pathway that has an excitatory effect and

thus a positive effect on movement and an indirect pathway that has an inhibitory effect on movement. The main information to the basal ganglia system comes from the cortex. Striatal information is transferred to the GPi and the SNr and then to the thalamus and from there to the frontal cortex, the supplementary motor area (SMA) for pallidal input and the dorsolateral prefrontal cortex (DLPF) for nigral input. This cortico-cortical loop passes through the direct pathway. The indirect pathway involves the GPe, then the STN and from there the GPi and the SNr. The central complex of the thalamus (centre median parafascicular complex) has strong links with the basal ganglia system in primates. The GPi projects to the central part of the complex (centre median nucleus), which projects back to the sensorimotor putamen. The SNr projects back to the medial part (the parafascicular nucleus), which projects back to the caudate nucleus.

Mink (1996) put forward the triple-circuit model, adding a hyperdirect pathway, a most rapid cortico-subthalamopallidal projection that first inhibits all motor programmes in a reset-like fashion. Then the direct cortico-striapallidal pathway activates the motor sequence to be executed and finally the slow indirect cortico-stiato-subthalamopallidal pathway inhibits the motor sequence to terminate the execution (Nambu, 2002 and 2004) (Figure 1.6).

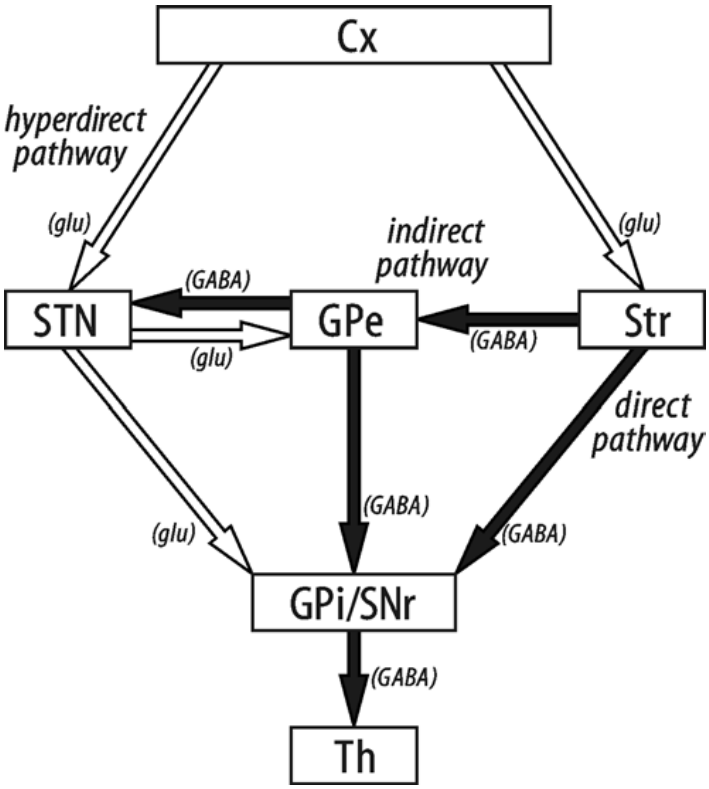

Figure 1.6: *A schematic diagram of the cortico-STN-GPi/SNr "hyperdirect", cortico-striato-GPi/SNr "direct" and cortico-striato-GPe-STN-GPi/SNr "indirect" pathways. Open and filled arrows represent excitatory glutamatergic (glu) and inhibitory GABAergic (GABA) projections, respectively. Cx cerebral cortex; GPe external segment of the globus pallidus; GPi internal segment of the globus pallidus; SNr substantia nigra pars reticulata; STN subthalamic nucleus;*
Str striatum; Th thalamus (modified from Nambu et al, 2005).

Alexander (1986) and Delong & Wichmann (2007) proposed the five-circuit model.

It represents five different circuits from the frontal cortex, namely oculomotor, motor, dorsolateral, prefrontal, lateral orbitofrontal and anterior cingulated, which cross through the basal ganglia direct and indirect pathways. They also remain segregated up to their projection up to the frontal cortex from where they arise. This model supposes a parallel processing of cortical information and it has been challenged for the lack of integration between motor, oculomotor and nonmotor information in the basal ganglia.

1.1.4.2 The three functional territories

Parent (1990) proposed a more functional subdivision of basal ganglia activity, namely the sensorimotor, associative and limbic territories (Figures 1.5, 1.7 and 1.8).

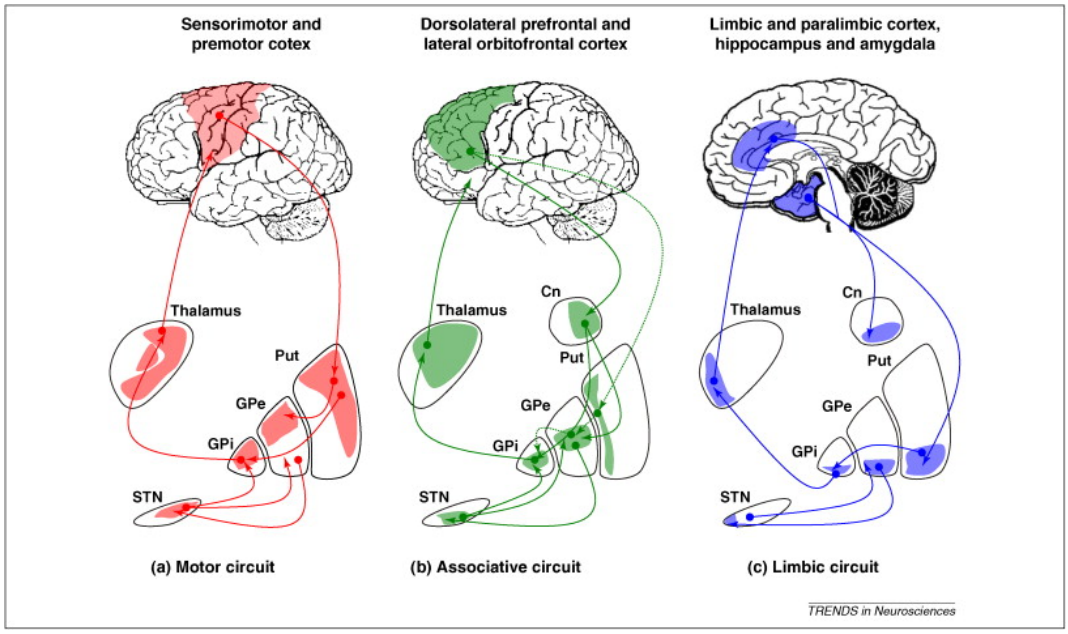

Figure 1.7 *Schematic diagram illustrating the main cortico-basal ganglia-thalamocortical circuits within human brain. This figure shows a pseudo-anatomical arrangement of the motor, associative and limbic pathways.* ***(a)*** *Motor circuit. Neurons from the sensorimotor cortex project to the posterolateral putamen (Put). From the putamen there are two main projections topographically organised onto the posterolateral region of the target nuclei: (i) the direct circuit to the GPi and (ii) the indirect circuit connecting the posterior putamen to the globus pallidus pars externa (GPe), the STN and the GPi. The GPi is the primary output nucleus of the basal ganglia to the cortex via the ventrolateral thalamus.* ***(b)*** *Associative circuit. This circuit originates in the dorsolateral prefrontal and lateral orbitofrontal cortices, which project to the caudate nucleus (Cn) and anteromedial portion of the putamen. From the striatum (Cn + Put) it projects to the dorsomedial region of the GPi and anteromedial parts of the GPe and STN to converge onto the GPi and back to the cortex via the ventral anterior nuclei of the thalamus.* ***(c)*** *Limbic circuit. This loop starts in the hippocampus, amygdala and paralimbic and limbic cortices and projects to the ventral striatum (ventral portion of the caudate and putamen, including NAcc). The ventral striatum projects to the limbic portion of the GPe and medioventral STN and ventral GPi and to the cortex via the mediodorsal nucleus of the thalamus. From Krack et al, 2010.*

The sensorimotor comprises the primary motor, the premotor cortices, supplementary motor area and the oculomotor area. It processes motor and somesthetic information. The associative territory comprises the prefrontal dorsolateral and lateral orbitofrontal

cortices as well as the temporal, parietal and occipital cortices. It processes cognitive information. The limbic territory comprises the anterior cingulated and medial orbitofrontal cortices, as well as the hypocampus. It processes emotional and motivational information. These three functional territories project to different parts of the basal ganglia nuclei: the sensorimotor territory to the dorsolateral portions, the medial territory to the ventromedial portions and the associative territory to the central intermediate portions. The validity of this model has been demonstrated in both primate research (Francois et al, 2004) and in human clinical research (Mallet, 2002; 2007).

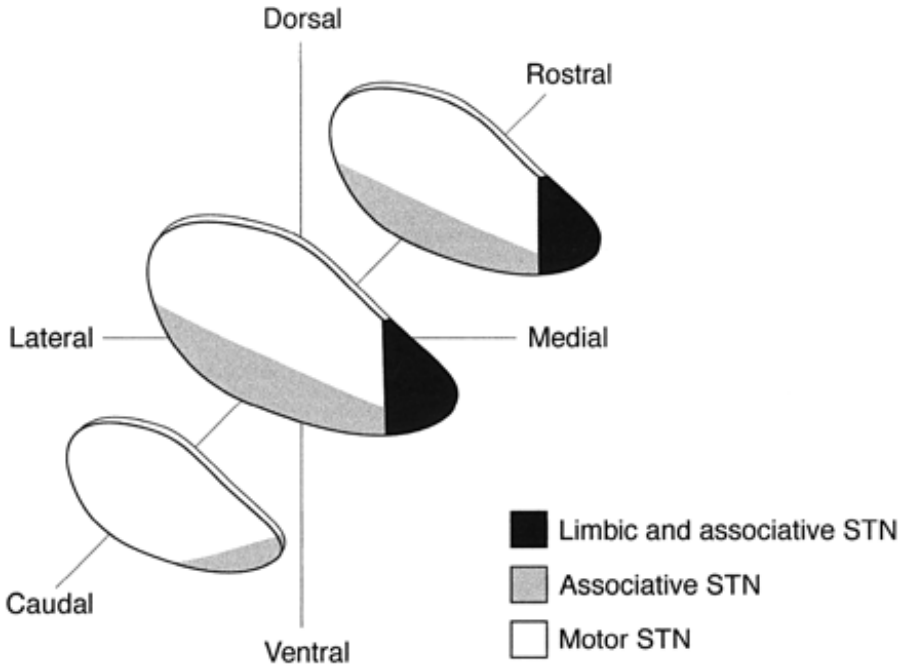

Figure 1.8: *Schematic representation of the intrinsic organisation of the subthalamic nucleus (STN) according to the tripartite functional subdivision of the basal ganglia. From Hamani et al, 2004.*

1.1.4.3 The integrative properties of the basal ganglia (Yelnik, 2008)

In contrast to the segregated parallel-circuit, the anatomical organisation of the basal ganglia exhibits a strong convergence at several levels: first the volumes of the successive nuclei that the circuits cross through are decreasing in dramatic proportions: cortex 500,000 mm3, striatum 10,000 mm3, pallidum 500 mm3, STN 150 mm3; hence

3,000 times less than the emitting cortex (Yelnik, 2002a and 2002b). Also the number of neurons in each of these nuclei also exhibits a dramatic decrease due to the decrease of both the volumes and the cell density (Parent, 1996; Levesque & Parent, 2005). The integrative properties of the basal ganglia have been considered in a model based on the anatomical properties of the dopaminergic pathways which do not form closed independent loops but rather provide ascending connections between the sensorimotor, associative and limbic striatal subdivisions (Yelnik, 2008; Flaherty & Graybiel, 1993) (Figure 1.5).

1.2 Speech motor control in healthy adults and the role of basal ganglia

Fluent articulation is perhaps man's most complex motor skill. It involves the coordinated use of many muscles, such that speech sounds are produced at a rate of about 15 per second (Levelt, 1989). These muscles are distributed over three anatomically distinct structures: the respiratory, the laryngeal and the supralaryngeal. The respiratory system with the lungs as its central organ regulates the flow of air, the source of energy for speech production. The laryngeal structure, including the vocal folds, is responsible for the alternation between voicing and non-voicing. The supralaryngeal structure, the vocal tract, with the velum, the tongue, the jaw and the lips, as its major moving parts, exercises two functions in articulation. The first is to constrict or interrupt the airflow in particular ways so as to produce speech sounds and the second is to serve as a resonator, modulating the timbre of the successive speech sounds. The timbre depends in particular on the shape of the oral, pharyngeal and nasal cavities (Levelt, 1989, chapter 11, p 413).

As compared to other areas of motor control, e.g. upper limb movement, rather sparse data of the cerebral organisation of speech motor control is available so far. This discrepancy is due, among other reasons, to the absence of an animal model of human

verbal communication and the biomechanical complexities of the vocal tract, together with restricted opportunities for kinematic and electormyographic (EMG) measurements (Ackermann, 2005, chapter 4). Prior to the introduction of brain imaging techniques, analyses of the neural network subserving speech had to rely on detailed perceptual descriptions of dysarthria in patients suffering from relatively focal lesions or degenerative disorders bound to a distinct functional component of the nervous system, e.g. PD or cerebellar atrophy. Some further data of speech motor control have been obtained by means of electrophysiological recordings during brain surgery. Functional brain imaging techniques such as PET and fMRI provide more detailed information on the neural correlates of speech motor control. However there are methodological difficulties in studying speech production, mainly because it involves mouth movements that can cause artifacts in the imaging signal as well as increasing head movement.

1.2.1 Imaging data

In the pioneering work carried out in the 1940s at the Montreal Neurological Institute, Penfield (1954) established a functional map of the sensorimotor areas along the central sulcus. In particular they found that electrical stimulation of the precentral gyrus (motor cortex) produced individualised movement. Stimulation of the lateral surface evoked movements of the lips, the tongue and the jaw. Imaging studies on speech production have shown activation mainly in motor and premotor cortex, the cerebellum, the supplementary motor area (SMA) the superior temporal gyri, the tempoparietal cortices, and the anterior insula with left lateralised activation in the putamen (Brown et al, 2009; Price 2010).

With respect to the left anterior insula Brown and colleagues (2009) speculate that it is involved in generalised orofacial functions, including lip movement, tongue movement

and vocalisation. The fact that activation is not dependent on whether speech is overt (Riecker et al, 2002) or covert (Watkins et al, 2008) speech production and not reported to depend on number of syllables being produced (Papoutsi et al, 2009) is consistent with the previous claims from lesions studies (Dronkers et al, 1996) that the anterior insula is involved in the planning rather than the execution of speech sounds (for review see also Ackermann & Riecker, 2010).

The initiation and execution of movement increases activation in bilateral premotor/motor cortex, the pre-SMA, and the left putamen. With respect to the function of the premotor cortex, Brown and colleagues (2009) distinguished the areas that control larynx movement (dorsal region) from those that involve tongue and lip movements (ventral region).

The SMA is one of the few brain areas which when lesioned can give rise to mutism and stimulation in this area can lead to vocalisation in humans but not in monkeys (Jürgens, 2002). In the meta-analysis of 82 studies by Indefrey & Levelt (2004), they concluded that the SMA plays a role in motor planning, motor sequencing but its exact role in vocalisation is not well understood (Riecker et al, 2002; Price, 2010).

The two areas found to be more involved with articulation of speech than non-speech orofacial movements are the anterior cingulate and bilateral head of caudate (Chang et al, 2009).

Soros et al (2005) found that speech sounds of increasing complexity (monosyllabic consonant versus vowel and trisyllabic consonant versus vowel) are associated with an increased task demand and an increased recruitment of additional brain regions. Their experimental tasks included overt speech production of the vowel ah, the syllable /pa/ or /ta/ or /ka/, the /pataka/, and simple facial movement (kiss) using clustered MRI

acquisition. They found that more complex polysyllabic utterances were associated with additional activation in the bilateral cerebellum and the bilateral temporal cortex. Speaking a single vowel and performing a simple oral movement involved almost identical activation of the pyramidal and extrapyramidal tract (Figure 1.9). The production of more complex /pataka/ utterances involved activation in the left inferior frontal gyrus (Broca's area), the left cerebellum (involved in timing), the left caudate nucleus (timing of sequential movements) and the bilateral superior and middle temporal gyri.

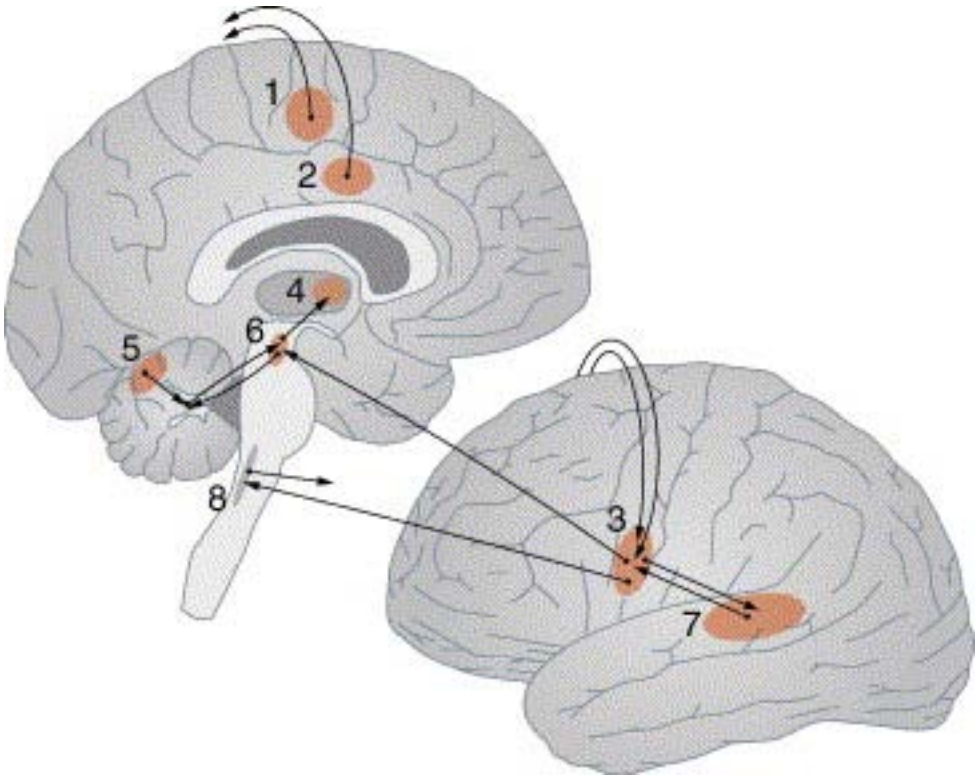

Figure 1.9: *The neural network of speech production. Schematic fibre tracts connecting those areas are represented by black arrows. Only main areas of activation and main fibre tracts are shown. The supplementary motor area (1) and the cingulated motor areas (2) are connected with the primary motor cortex (3). Several connections exist between the cortical and the subcortical motor system. Subcortical activation was found in the thalamus (4), the basal ganglia (not shown), the red nucleus (6) and in the vermal and paravermal cerebellum (5). In addition, the bilateral posterior superior temporal gyrus (7) was activated. The brain stem nuclei innervating the articulatory organs, such as the nucleus hypoglossus, were outside the field of view (8). From Soros et al (2006).*

1.2.1.1. Role of basal ganglia on speech motor control in healthy adults

The differential contribution of basal ganglia and cerebellum in timing of speech motor control has been investigated by Wildgruber et al (2001) using silent repetition of /ta/ at three different rates (2.5, 4.0 and 5.5 Hz). Lower rates (2.5 and 4.0 Hz) gave rise to higher magnitude of activation in the left putamen, whereas cerebellar activation was restricted for higher rates (5.5 Hz). The observed asymmetry of activation at the level of basal ganglia towards the left putamen is in good accordance with clinical observations of articulatory impairment and reduced voice volume after left-sided subcortical infarction (Alexander, 1987, Brain) as well as PET studies investigating repetition of single words. The decreased activation within the putamen during the fastest production rate might indicate this structure to be specifically involved in the control of articulatory movements during lower frequencies. The clinical observation of accelerated speech tempo in patients with dysfunction of the basal ganglia supports this assumption (Ackermann et al, 1993 & 1997). This was the opposite of the pattern of activation of the cerebellum: absence of cerebellar activation during slow syllable rate is in line with the clinical observation that maximum production rate does not seem to drop below 3 Hz in patients suffering from ataxic dysarthria (Hertrich & Ackermann, 1997). Riecker et al (2005) repeated the same experiment but with overt speech production, synchronised to clic trains (from 2 Hz to 6 Hz) versus a passive listening task. Two different time series patterns were detected (Figure 1.10). Peak activation of the left SMA, left dorsolateral pre-frontal cortex (including Broca's area), left anterior insula and right superior cerebellum emerged three to five seconds after the onset of acoustical stimulation; and by contrast the left sensorimotor cortex, left thalamus, left putamen/pallidum, left caudate nucleus and right inferior cerebellum achieved the maximum activity eight to nine seconds after the onset of speech production. The authors interpreted these data as two distinct cerebral networks subserving speech motor

control – one for motor preparation and one for motor execution. It is of note that the left basal ganglia and left thalamus and inferior aspects of the right cerebellum were found to be involved in the motor execution of speech.

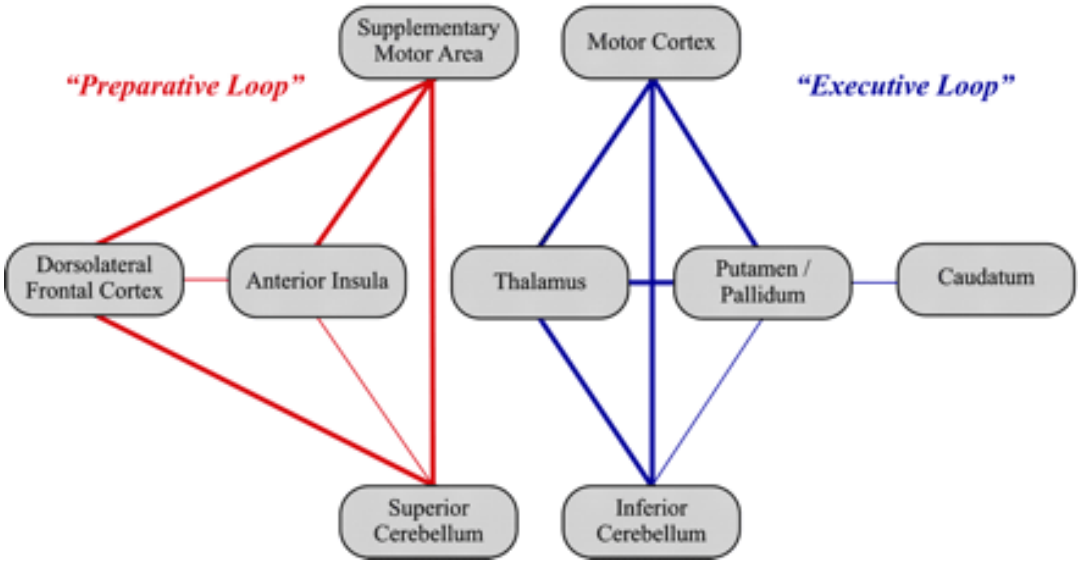

Figure 1.10: *Preparative and executive speech loop from quantitative functional connectivity analyses: computed correlation coefficients across the time series of the blood oxygen level-dependent (BOLD) signal within the volumes of interest. Only very high (_0.9, bold lines) and high correlations (0.75– 0.9, thin lines) are depicted. Low and intermediate correlations are not displayed. From Riecker et al, 2005, p 704.*

Watkins (2008) examined the brain activation during both overt and covert production of stutterers and found overactivity in the midbrain, at the level of substantia nigra, the pedunculopontine nucleus, red nucleus and subthalamic nucleus. The role of putamen in speech production becomes even more complex, when comparing phonation versus articulation and reading versus speaking. According to Brown et al (2009) there was no activity for the phonation task whereas there was a strong left hemispheric focus for speech. One could surmise that putamen is more important for articulation than phonation. However, clinical damage to the basal ganglia circuit gives rise to severe dysphonia (low vocal volume) (see section 1.4). The only therapy that seems to ameliorate voice and speech in PD, namely the Lee Silverman Voice Treatment

(Ramig et al, 2001) is based on phonation with benefit on articulation as a by-product. Activation in the putamen co-occurs with activation in the ventral thalamus, mainly in the syllable singing (Wildgruber et al, 1996).

In summary neuroimaging studies of speech motor control (Bohland & Guenther, 2006; Riecker et al, 2008; Soros et al, 2006) using a variety of speech tasks have roughly converged on a "minimal network for overt speech production" including the "mesiofrontal areas, intrasylvian cortex, pre- and post-central gyrus, extending rostrally into posterior parts of the left inferior frontal convolution, basal ganglia, cerebellum and thalamus" (Riecker, 2008). However when it comes to speech versus singing, studies have found an opposite pattern of lateralisation in the sensorimotor cortex during speech production and production of tunes (i.e. "la" while singing a melody) with the former eliciting predominantly left-sided activity and the latter right-sided one (Wildgruber, 1996). Similarly, Riecker et al (2000) and Callan et al (2006) found opposite laterality in the insula, motor cortex and cerebellum. That could explain the clinical observations of many aphasic right-handed patients with left inferior frontal lobe (Broca's area) damage, having severe deficits in their ability to speak but being able to sing words without much effort (Hebert, 2003). Equally TMS to the left inferior frontal cortex in right-handed individuals causes speech arrest but singing even of the same words is relatively spared (Stewart 2001).

1.2.2 Neural control of human vocalisation

Apart from the linguistic/semantic versus motor control of speech, the elements of motor speech can be decomposed in yet another way, by isolating the neural substrates for phonation and differentiating these from those that regulate articulation. Animal studies suggest that in lower mammalian species, from rat, to cat, to monkey (Kuypers, 1958; Larson, 1991) there exists a midline network of brain regions dedicated to

phonation, controlling the species-specific calls. It includes the anterior cingulate cortex, the periaquaductal grey (PAG) the nucleus retroambiguus and nucleus ambiguous (Jürgens, 2002). The main area of this circuit is the mesencephalic periaqueductal grey (PAG) which regulates activity of the lower brainstem that control vocal fold tension and respiration. The PAG itself is regulated by limbic-related regions of the forebrain and it encodes information about the emotional status and behaviour in a repertoire of vocal calls over which voluntary control – in non-human species – appears to be slight (Jürgens & Zwirner, 1996). In humans this system may be involved in emotional expression such as laughter or crying but appears to be less important for volitional expression, which appears to be more under cortical control. There are two competing hypotheses (Jürgens & Zwirner 1996; Jürgens, 2002); one suggests that only involuntary emotional vocalisations, such as laughter or crying, are controlled by the PAG whereas voluntary phonation during speech is under the control of an autonomous neocortical system; the other suggests that both these systems operate in concert during production of spoken language, with a hierarchical control maintained by neocortical motor systems. From the literature it seems that comparative animal versus human studies of anatomical connections provide evidence supporting the first hypothesis, whereas functional imaging studies support the second. Kuypers compared the corticobulbar pathways in humans (1958a) with those in monkeys (1958b) and found sparse labeling in the nucleus ambiguous after cortical injection of a tracer in a patient, suggesting that there are some direct corticobulbar projections from the motor cortex to the laryngeal motor neurons in the nucleus ambiguous in the humans. He found no evidence of a similar direct corticobulbar projection in the monkey and chimpanzee. This has been confirmed more recently by Simonyan & Jürgens (2003). They used electrical stimulation to identify the laryngeal motor cortex producing bilateral vocal fold closure in Rhesus monkeys and injected an anterograde tracer into the effective site

to label subcortical projections. Dense projections with ipsilateral predominance were found in the putamen and thalamus (in the ventral nuclei) with heavy bilateral projections to the brain stem nuclei in the nucleus tractus solitarius. In 2005 the same authors found dense projections into the laryngeal motor cortex from the ventrolateral thalamus in Rhesus monkeys, demonstrating dense reciprocal connections between the basal ganglia and the laryngeal motor cortex. These results support the conclusion that many of the laryngeal muscle functions for swallowing, cough respiration and vocalisation are controlled by subcortical connections for non-human primates and that direct corticobulbar projections to the nucleus ambiguus may be exclusively human. Although the study in four human brains of Kuypers has not been replicated, TMS studies of latencies of laryngeal muscle responses (12ms) support the possibility of direct projections from the cortex to the recurrent laryngeal nerve innervating the intrinsic laryngeal muscles (Ludlow et al, 1996). Clinically evidence of this dissociation can be seen in spasmodic dysphonia, where involuntary muscle spasms only interfere with voice production for speech and not during crying, laughing (Izdebski et al, 1984; Nash & Ludlow, 1996).

Although anatomical connections provide evidence on regions of connectivity, only functional neuroimaging can provide information on active systems for laryngeal muscle control during respiration and voice production in humans. Schulz et al (2005) compared brain activation of voiced and whispered speech (using voiced narrative speech and an identical whispered narrative) in 20 healthy adults. They observed activation of the PAG and paramedian cortices only with voiced and not whispered speech, which provided evidence that, as in lower mammalian species, these midline regions may operate as an integrated system during human vocalisation. However since linguistic information was also conveyed with the narrative they observed coactivation

of additional regions during voiced speech: premotor regions including the SMA and subcortical projection areas in the basal ganglia and thalamus. Stimulation in the pre-SMA has been reported to elicit vocalisations in humans (Fried et al, 1991) but not in lower species. It appears that there are no direct links with the PAG (Jürgens, 1984). Activity in the SMA is regulated to some degree by its interaction with the basal ganglia (Alexander et al, 1986; Parent et al, 1995). The putamen, where they found maximal increases in activation, is part of the motor circuit which conducts neural information from the striatum through to the ventral thalamus through to the SMA. This motor circuit might enable more precise voluntary control over the timing and sequencing of laryngeal, respiratory and articulatory activity during voiced speech. Thalamic activations were maximal in the region of the centromedian (CM) nucleus, a major source of input to the basal ganglia and with projections in the SMA and the PAG (Jürgens, 1984). The authors interpreted activation in the cerebellum and the perisylvian areas of the temporal lobe as related to self-monitoring and processing of own voice that makes possible the continuous online correction of laryngeal and oral articulatory movements. Thus basal ganglia and thalamic structures and premotor structures provide the degree of voluntary control over phonation in humans. In a more recent study of 34 healthy adults, Chang et al (2009) compared the neural control of speech and non-speech production (defined as “volitional vocal tract gestures, such as whistle, cry, sigh and cough) and found that they share the same network as speech and same left cortical laterality. They concluded that the brain regions involved in both speech and non-speech gestures seem to support “a larger domain of vocal tract gestures requiring sensory-motor mapping” (p 321).

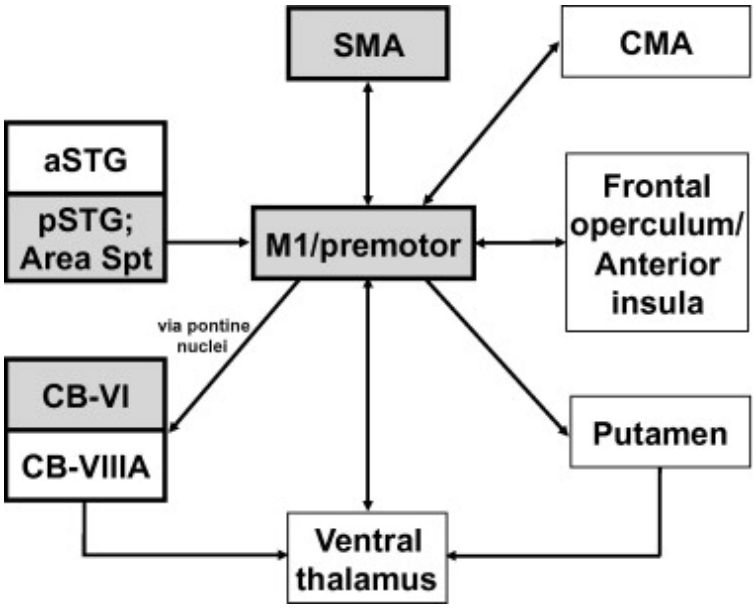

Figure 1.11: *Key brain areas of the vocal circuit. Shaded boxes represent "primary" areas that are principal regions for the control of phonation in speaking and singing. White boxes represent "secondary" areas that are less reliably activated during phonation and that might be more important for articulation. See text for details.*
This is not meant to be a comprehensive connectivity diagram. The focus is placed on the connectivity between these multiple areas and the primary motor/premotor cortex, rather than on connections among the other areas. Connectivity data is based principally on the afferent and efferent connections of the M1 larynx area of the Rhesus monkey, as described in (Simonyan & Jürgens, 2003,2005, Simonyan et al, 2008). The projection from the motor cortex to the cerebellum is via the pontine nuclei. As described in the text, lobule VIII of the cerebellum may turn out to be a primary area, but many imaging studies, especially PET studies, have not included this part of the cerebellum in their field of view. Abbreviations: SMA, supplementary motor area; CMA, cingulated motor area; pSTG, posterior part of the superior temporal gyrus; aSTG, anterior part of the superior temporal gyrus; Spt, cortex of the dorsal Sylvian fissure at the parietal-temporal junction. From Brown et al, 2009.

Brown et al (2009) used fMRI to compare an overt speech task with tongue, lip movement and vowel phonation in an attempt to differentiate the activation areas for phonation to those for articulation (Figure 1.11). Their results showed that the strongest motor activation for speech was the somatotopic larynx area of the motor cortex, thus reflecting the significant contribution of phonation to speech production.

1.2.3 Neural control of facial muscles

Hughlings Jackson first noted that the muscles of the lower face, and not those of the upper face, were adversely affected unilaterally following common localised brain trauma. In an attempt to explain this pattern of facial paralysis, Jackson suggested that unilateral movements like those performed by the arm, leg and lower face were more voluntary and it was this "voluntary" nature of these movements that formed the basis of their underlying vulnerability (Jackson as reported in Morecraft et al, 2004). It was further speculated that bilateral movements such as those commonly expressed by the upper face were retained, as they represent a more automatic class of movements. Recent experimental data (Morecraft, 2001) reveal the existence of multiple cortical facial representation of the primary motor cortex (M1), ventral lateral premotor cortex, supplementary motor cortex (M2), rostral cingulate motor cortex (M3) and caudal cingulate motor cortex (M4). These diverse cortical areas are part of limbic and prefrontal regions (M3 and M4), which suggests a role in emotional expression attention and cognition. Functional correlates of face/head regions of M2 may include the control of eye movements, speech (Paus, 1993) and laughter (Fried, 1998). Speech and laughter are distinctly human abilities and share the same musculature. Fried et al (1998) applied electrical stimulation in the anterior part of the anterior SMA of a patient undergoing monitoring by intracranial subdural electrodes to locate the focus of epileptic seizures. They identified a small area on the left superior frontal gyrus where stimulation consistently produced laughter, accompanied by a sensation of merriment or mirth. It was interesting that each trial was accompanied with a different explanation offered by the patient, attributing the laughter to whatever external stimulus was present at the moment. They concluded that speech and laughter are closely represented in the rostral part of the SMA, just anterior to the representation of manual activity. Clinically the recognition of multiple cortical facial representations is reflected in the dual control

of facial movements, such as the dissociation of voluntary (i.e. for speech) and emotional facial movements. The most common clinical profile is in patients presenting with impaired lower face voluntary movement with intact ability to overcome the paralysis when emotional facial expression is needed. In contrast, emotional facial paralysis (also described as amimia) has been reported to occur in patients with damage to the midline cortex, insula, thalamus striatocapsular region and pons and is characterised by a disturbance in smiling on one side of the face in the presence of complete voluntary control over the same set of facial muscles (Morecraft, 2004). In summary, cortical projections from the lateral facial representations (M1 and LPMC) and the caudal cingulated motor cortex (M4) might exert their influence primarily on contralateral lower facial muscles. Medial motor areas including the supplementary (M2) and rostral cingulated (M3) motor cortices may exert influence on the upper facial muscles, possibly bilaterally. Also the cingulated corticofacial projections may exert an influence on emotional facial expression. However despite the marked paucity of facial expression from diseases of basal ganglia there is limited literature on the role of subcortical structures in the control of facial muscles.

1.3 Muscle control for speech

The speech related muscles in humans appear to differ from analogous tissues in mammalian and non-mammalian species, as well as from limb muscles. This is the case of the inferior pharyngeal constrictor (Mu & Sanders, 2001), the vocalis muscle (Han et al, 1999) and the masseter muscle (Korfage et al, 2005a and 2005b). The muscle properties of the human craniofacial and laryngeal systems are suited to motor performances that are continuous, precise and highly coordinated. This can be true cross-culturally: Levelt et al (1989) have argued that the normal syllable rate in the world's languages of five to six syllables per second is a consequence of the

biomechanics of the vocal tract, especially the movements of the mandible. Some of the muscles involved in speech have properties of fatigue resistance. Thus compared with limb and trunk muscles, the jaw muscles are highly unusual: in addition to the normal slow type I and fast type II fibres, they contain fibre types which are typical for cardiac muscle. Korfage et al (2000) reported that the temporalis, masseter and pterygoid muscles (mandibular elevators) have a large number of hybrid fibres, but mylohyoid, geniohyoid and digastric muscles (mandibular depressors) have fewer hybrid fibres. Hybrid fibres are thought to be those that are in transition from one fibre type to the other since they are predominantly found during disuse or during extreme usage of the muscle (Korfage, 2005). This relatively high quantity of hybrid fibres provides a mechanism that produces a very fine gradation of force and movement.

1.3.1 Laryngeal muscles involved in the production of speech, swallowing, respiration and cough

For each of these laryngeal functions different vocal fold movement is required. Voice is produced as the vocal folds are held in the midline of the glottis and airflow from the lungs causes increases in the subglottal air pressure for opening the vocal folds. As the vocal folds open, the airflow passes between the folds reducing the pressure between them (the Bernouilli effect) and the muscle tension in the vocal folds returns to the midline for closure, allowing the cyclic process to continue (Titze, 1994). Thus the speaker has to maintain adequate respiratory airflow during exhalation and use adequate muscle activity to keep the vocal folds in the midline for vibration to occur (Figure 1.12). Speech requires a rapid and precise muscle control for voice onsets and offsets within a few milliseconds to make linguistic distinctions between voiced and unvoiced sounds such as /t/ and /d/.

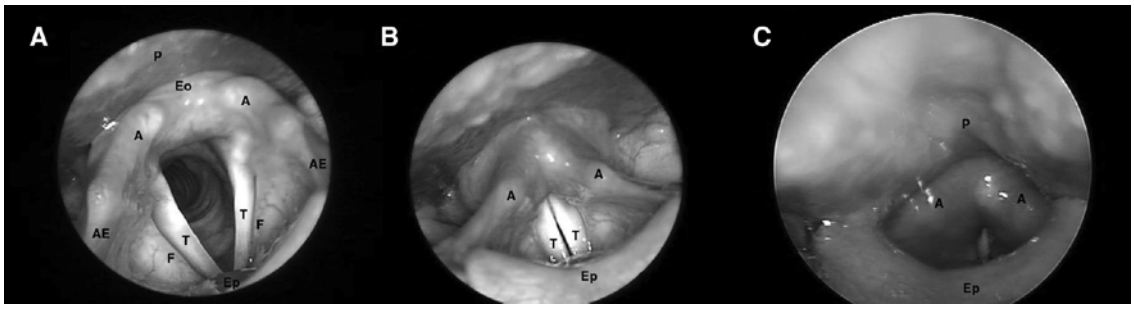

Figure 1.12: *This shows a normal larynx in the abducted or open position for breathing. Notice that it is very easy to see into the trachea. B, This is the larynx in the adducted position for phonation. Only the true vocal folds are opposed. C, This is a gag and shows the larynx in a protective position – notice that the false vocal folds have closed over the true vocal folds and the epiglottis and aryepiglottic folds are constricting in a sphincteric manner. T indicates true vocal folds; F, false vocal folds; A, arytenoids; AE, aryepiglottic folds; Ep, epiglottis (anterior); P, posterior pharyngeal wall; Eo, esophageal inlet. From: Meyer, 2009*

The laryngeal muscles are classified as either intrinsic (confined in the larynx) or extrinsic (attaching the larynx to other structures within the neck). Vocal fold movements are described as adductor (closing) or abductor (opening).

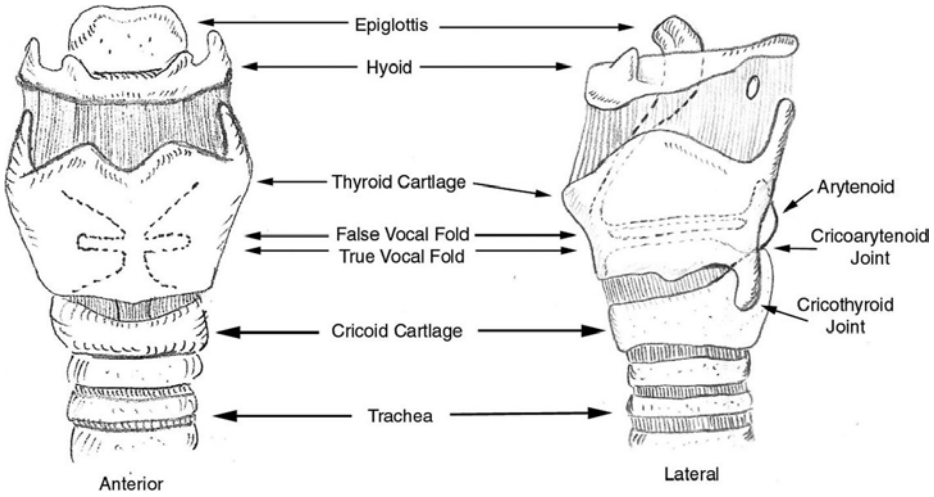

Figure 1.13: *Cartilaginous structures of the larynx. From: Meyer, 2009.*

Intrinsic laryngeal muscles are classified as either having an adductor action (thyroarytenoid (TA), lateral cricoarytenoid (LCA), interarytenoid (IA), or abductor

function (posterior cricoarytenoid (PCA). The cricothyroid (CT) muscle can elongate the vocal folds.

The extrinsic laryngeal muscles are the thyrohyoid and the sternohyoid change the position of the larynx in the neck by raising or lowering the thyroid cartilage respectively. The thyrohyoid muscle raises the larynx during swallowing while the sternothyroid lowers voice pitch (Ludlow, 2005).

In the laryngeal system, Han et al (1999) have identified a large population of slow tonic muscle fibres (STF) in the vocalis muscle compartment of the thyroarytenoid muscle. STF differ from most other muscle fibres in that they do not exhibit a twitch contraction but rather have contractions that are prolonged, precisely controlled and fatigue resistant. Because STF have not been observed in the vocal folds of other mammals, Han et al suggested that STF may be a unique specialisation for human speech (p 146). The physiological study of the laryngeal musculature in humans is challenging due to the difficulty in obtaining accurate EMG recordings from these inaccessible muscles. Most investigators use percutaneous insertions of hooked or needle electrodes. Placement is verified by using gestures that would elicit accurate location of the recording electrode (Hirano & Ohala, 1969). For example, a sniff will elicit increased activity in the PCA while throat clear will activate the TA muscle. These methodological difficulties may partly account for the differences in results between studies of swallowing, respiration, voice and speech. However individual differences in use of the laryngeal musculature to produce the same task are particularly evident during speech. In a study of four young healthy adults and five old ones Baker et al (2001) found a striking variability in the amount of muscle activation of the TA, CT and LCA muscles during three different loudness levels. Finnegan et al (1999, 2000) recorded from the laryngeal muscles while recording tracheal (subglottal) air pressure

during speech. They found a complex but independent interaction between variations in laryngeal muscle activity and tracheal pressures, demonstrating that speakers control the laryngeal muscles independently from subglottal air pressure to produce changes in voice intensity and fundamental frequency. This is possibly why breathing exercises have no effect on vocal loudness (Yorkston et al, 1996).

1.3.2 Lingual and palatal muscles

Lingual and palatal muscles have not been examined as extensively as jaw and laryngeal muscles. Sokoloff (2000) has identified motor units in the rat tongue that are fatigue resistant. In humans the production of most vowels depends on the positioning of the tongue body by means of the extrinsic muscles – in particular the genioglossus. Most consonants that involve the tongue in particular the alveolars, /t/, /d/, /s/, /z/) are articulated by means of the intrinsic muscles, which affect the shape rather than the body of the tongue. Thus the movements between vowels and consonants can be produced without interference (Levelt, 1989, Chapter 11, p 453).

The palatal muscles also resemble facial muscles more than limb muscles: Stal & Lindman (2000) have studied the palatopharyngeus (PP), the uvular (U), levator veli palatini (LVP) and tensor veli palatini (TVP). PP and U were found to have some of the highest proportions of type II fibres ever reported in human muscles, while LVP and TVP contained primarily type I fibres. The authors concluded that PP and U are equipped for rapid movements whereas LVP and TVP are more adapted to slow and continuous contractions. The lingual and palatal muscles have shared respiratory-related activity. The tongue is central to a variety of reflexes and orofacial movements that contribute to complex motor responses in feeding, chewing, swallowing, speech and respiration. Intersystem coordination that links mandibular, lingual and laryngeal

movements to respiratory patterns serves speech well by ensuring efficient and well-timed movement.

This difference between the muscle fibre composition of speech versus limb muscles could partly account for the discrepancy between limb and speech motor response to medical and surgical interventions, especially in PD. Although it is not known exactly how the neural control of speech differs from that of the limbs, it may be important to consider both peripheral factors (e.g. differences in muscle fibre composition) and central factors (neural circuits controlling movement).

1.4 Perceptual and acoustical characteristics of speech in Parkinson's disease

James Parkinson in his 1817 essay on the "shaking palsy" mentioned some distinguishing features of the disease. He reported that in the late stages of the disease patients' words are "scarcely intelligible" and "that speech is very much interrupted". In presenting the "pathognomonic symptoms" Parkinson listed "a propensity to bend the trunk forwards and to pass from a walking to a running pace". He quoted an earlier observer Gaubius, "cases occur in which the muscles duly excited into action by the impulse of the will, do then, with an unbidden agility, and with the impetus not to be repressed, accelerate their motion, and run before the unwilling mind. It is a frequent fault of the muscles belonging to speech, nor yet of these alone: I have seen one who was able to run but not walk" (p 24). Parkinson himself added: "a similar affection of the speech, when the tongue thus outruns the mind is termed volubility". He also quoted a Dr Maty who described the case of Count de Lordat: what began as a small impediment in uttering some words increased in severity until later "it was with difficulty he uttered a few words"; still later, "what words he could still utter were monosyllables, and these came out, after much struggle, in a violent expiration, and

with such low voice and indistinct articulation, as hardly to be understood but by those who were constantly with him. He fetched his breath rather hard."

More modern discussions of Parkinsonism uniformly describe speech changes as an integral part of the syndrome. For the era before levodopa, descriptions are quite similar: Walshe (1955) mentions "the loss of inflections in the voice, the weakness of phonation, and the blurring of articulation". De Jong (1967) calls the speech problem bradylalia and lists its characteristics as weakness of voice, dysprosody, lack of inflection, indistinctness of articulation, hesitations, stoppages and bursts of speed". Nielsen (1958) describes the phenomenon of repetitious speech known as palilalia: "palilalia is a repetitive disturbance encountered in parkinsonism and encephalitis (as representatives of the organic causes) and in schizophrenia. This condition is characterised by a repetition of sentences or fractions of sentences."

At the beginning, the main purpose of studying the physiological support for speech in PD seemed to be to investigate the motor rather than the motivational/linguistic aspects of speech impairment in PD in order to inform therapy. Thus, on one hand, Zimmerman (1959, as reported in Canter, 1965a, p 48) stresses that the primary goal of speech therapy should be to increase motivation so that the patient would make maximum use of his abilities. On the other hand, through the pioneering work starting with Canter in 1963, and culminating with Darley Aronson Brown (1969), the physiologic basis of the speech deficit in PD was established.

Perhaps the most comprehensive descriptions of the dysarthria of parkinsonism is presented by Selby (1968): "in the great majority of cases of paralysis agitans, disorders of speech become obvious as the disease advances. The shades of inflection to emphasise a point disappear, the volume of the voice is reduced, pronunciation of consonants is defective and the sentence often ends in a mumble. From a monotonous,

soft voice without variation in pitch there is a gradual progression of dysarthria until the patient's diction might become neither audible nor intelligible. Whereas the general slowness of movement finds its expression also in the rate of speech in some cases, others talk fast, running words into each other, as if they wanted to conserve their energies and get it over and done with. A few exhibit progressive acceleration of words toward the end of the sentence similar to the festination of gait" (p 188). In a large series of patients Selby (1968) found speech to be impaired in most patients, although almost half considered their speech to be unimpaired. Darley et al (1969) in their seminal work on motor speech disorders examined the perceptual characteristics of various types of dysarthrias. They determined the salient pitch, loudness, respiration, prosody and articulation characteristics as well as overall general impressions for each of the dysarthria classifications. The authors served as listeners and ranked the perceptual prominence of 38 speech characteristics after listening to speech samples from 212 patients of various aetiologies. The parkinsonian group consisted of 32 unmedicated patients. The characteristics associated with hypokinetic dysarthria were monopitch, reduced stress, mono-loudness, imprecise consonants and inappropriate silences. Other perceptual characteristics were short rushes of speech and a harsh voice quality. We will review the pertinent characteristics of dysarthria in PD based on the three anatomically distinct yet functionally linked components – the subsystems of respiration, phonation and articulation and prosody.

1.4.1 Respiration

Several features of the total picture of hypokinetic dysarthria, namely decreased loudness, short phrases, fast rate, could be partly linked to the respiratory impairment. Methodologically the studies could be classified according to whether they examine non-speech breathing function, mainly measures of vital capacity, or speech breathing

functions, mainly chest wall kinematics (Hixon et al, 1973), mean flow rate (evaluation of the phonatory function by dividing the total volume of air used by the duration of phonation: lt/sec), phonation quotient (the greatest vital capacity divided by the max phonation time: ml/sec) and voice efficiency measurements, (oral pressure, equal to the subglottal air pressure during the articulation of an unvoiced plosive where the lips are closed and the vocal folds are fully opened e.g. /p/: cm H_2O) (Yiu et al, 2004).

Some aspects of non-speech breathing function, mainly the vital capacity, have been found to be abnormal in PD. Laszewski (1956, as reported in DAB, 1969, p 180) reported that in most cases of PD there is a marked decrease in vital capacity with little measurable thoracic excursion during either inhalation or exhalation. She attributed parkinsonian speech impairment more to rigidity of the articulatory muscles than to restriction of vital capacity. Equally, reduced amplitude of chest wall movements during breathing, irregularities in breathing patterns and increased respiratory rates have been documented (Solomon & Hixon, 1993).

Generalisation of non-speech breathing characteristics to breathing for speech is difficult because the total range of speech capacity is not needed for speech production (Kent et al, 1987), and there are other systems involved in the production of speech that interact with breathing (Netsell, 1975). Two primary methodologies have been used in studying the speech breathing mechanism. The first method evaluates features of the airstream (e.g. air pressure, airflow) and the second examines measures of chest wall movements or kinematics.

1.4.1.1 Chest wall kinematics

Direct measurements of speech breathing via assessment of chest wall kinematics have been employed infrequently in studies of PD. The technique involves measuring movement of the rib cage and the abdomen from the surface (Hixon et al, 1973).

Murdoch et al (1989) measured chest wall kinematics in 19 PD patients and 19 healthy controls. Rib cage and abdominal circumference was assessed using strain gauge belt pneumographs. However their method of attaching the belt above the umbilicus raised some criticism of their results (Solomon & Hixon, 1993). Solomon & Hixon (1993) examined speech breathing in people with PD using kinematic, spirometric, acoustic and pressure data in 14 patients and 14 healthy controls, during resting, reading aloud and monologue at the middle and the end of their drug cycle. There were no significant differences between the data from the two drug cycles. During resting tidal breathing, PD patients had a faster breathing rate and smaller relative contribution of the rib cage to lung volume change than did normal controls. Patients with PD produced fewer words per breath group and tended to have faster interpause speech rate than did the controls. Oral pressure was lower for patients with PD but estimated tracheal pressure did not differ between the two groups. The authors concluded that there is "inadequate valving of the air stream for patients with PD". Huber et al (2004) reported increased reliance on the abdomen for changing lung volume compared to controls as well as increased variability in respiratory movements compared to controls. Equally, Vercueil et al (1999) studied the breathing pattern in 11 patients with PD on- and off-levodopa. They found abnormal rib cage/ abdomen plots in four out of six patients, suggesting normal diaphragmatic activity, but impaired activity in other intercostal muscles.

1.4.1.2 Studies of air stream

Lower than normal air pressure during consonant production has been demonstrated in people with PD (Netsell et al, 1975). Oral pressure can be a good estimate of the driving pressure delivered to the larynx and upper airway structures for sound generation. However the influence of the oral structures on the air stream makes it difficult to determine whether the lower than expected oral pressure seen in patients with PD is due

to the respiratory system or to the laryngeal or upper airway valving. Solomon & Hixon (1993) reported oral pressure to be lower in patients with PD but estimated tracheal pressure to be equal to this in the controls. This difference suggests that in PD poor oral closure and/or velopharyngeal valving problems affects measures of oral pressure, thus it is not a good indicator of respiratory impairment (Bunton, 2005). DePandis et al (2002) examined the Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1) in 12 PD patients during on- and off-medication. They found reduced FEV1 and FVC in both medication states but more severe in the off state. They concluded that the respiratory dysfunction in those patients is due to abnormal activity of respiratory muscles, resulting directly from their state of rigidity and reduced range of movement. Similarly Weiner et al (2002) found reduced respiratory muscle strength and endurance more during off- medication as measured by FVC and FEV1.

Regarding airflow during speech there are contradictory reports and few normative data. Warren and Wood (1969, as reported in Bunton, 2005) report 0.040 lt per syllable for men and 0.053 lt per syllable for women. Mueller (1971, as reported in Bunton, 2005, p 332) found no difference from controls in a sustained phonation task. Bunton (2005) analysed speech production per the breath groups in seven PD patients using a free monologue. She used chest wall kinematics and linguistic and acoustic analysis. She concluded that there was a great variability between PD speakers: “three out of seven PD speakers initiated speech at low starting lung volumes and continued speaking below the end expiratory level (EEL). This subgroup ended breath groups at agrammatical boundaries” (p 331). Intraoral air pressure has been reported to vary as a function of linguistic variables, age (Hiss et al, 2001) and to a lesser extent, gender (Stathopoulos, 1986). However Hiss et al (2001) studied the intraoral air pressure in 60 adults of three different age groups, males and females, using /ipipi/. They found no

statistically significant difference of age or gender. The mean intraoral air pressure across age and gender was 6.20cm H_2O (0.08 standard error). Intraoral air pressure has not been investigated in PD (see also Chapter 7).

Indirect measures of respiratory function concern deficits in phonation, articulation and phrasing. Thus some studies imply respiratory capacity from measures of voice, mainly maximum phonation time (MPT) and ability to vary intensity. PD speakers have been found to have overall lower intensity levels (Ramig et al, 2001) difficulty in maintaining intensity level (Ho et al, 2001) and deficits regulating intensity in response to external cues (Ho et al, 1999). Sadagopan et al (2007) studied the effects of implicit and explicit cues in increasing vocal loudness on respiratory support in PD patients and they found that speaking in background noise resulted in the largest increase in loudness with the most efficient respiratory patterns, rather than a more explicit cue (i.e. speak at 10 dB SPL above your comfortable loudness or speak at double your comfortable loudness). They concluded that PD dysarthria is not related to disease-related physiologic limitations in increasing loudness since they can produce normal loudness with cueing. In a recent study De Letter et al (2007) investigated the effects of levodopa medication on vital capacity, sustained vowel phonation (SVP) and phonation quotient and the speech intelligibility (as measured by the Words subtest of the AIDS, Yorkston et al, 1981). They found reduced vital capacity in 18/25 patients at the off-medication condition and 15/25 at the on-medication condition. Phonation quotient and SVP were within normal limits. All three respiratory parameters, as well as intelligibility, improved with levodopa. However there was no correlation between the respiratory measures and speech intelligibility.

This lack of correlation between respiratory parameters and articulatory/laryngeal measures has been discussed in the literature in terms of overlapping neural control and

muscular coordination. Thus because the larynx plays a vital role in regulating airflow during metabolic respiration, it shares some neural structures with the control of both respiratory and laryngeal muscles, namely neurons in the nucleus ambiguous and the nucleus retroambiguus with their axons projecting via the recurrent laryngeal nerve to the intrinsic muscles of the larynx (Dromey, 1998). Even though rest breathing with its medullary rhythm generation differs from speech breathing (Sakamoto et al, 1996), the central nervous system facilitates integration of these separately descending neural drives at the level of spinal motorneuron. This allows the same respiratory muscles to be driven automatically by the brain stem or to be enlisted by the cortex for the more specialised requirements of spoken communication. Despite this shared neural control for respiration and laryngeal activity, little is known about the coordination of respiration and articulation. Given the therapy modification techniques based on respiratory control, it would be of clinical interest to understand whether working respiratory variables such as airflow and air pressure could affect articulation. Davis et al (1996) concluded that "the fine and rapid changes in orofacial muscle activity associated with the production of speech consonants are highly coordinated with but also independent of the patterned laryngorespiratory activities" (p 34). Dromey et al (1998) examined the effect of lung volume on phonatory and articulatory variables in five men and five women using the phrase "I sell a sapapple again". They used five lung volume conditions: speaking normally; speaking after exhaling most of the air of the lungs ("immediately after taking a very deep breath"); speaking at the end of expiratory level (EEL) ("after a sigh without taking any air first"); speaking at a low lung volume (LV) ("after breathing out most of your air first"); and speaking at maximum LV while speaking normally ("immediately after taking a very deep breath but concentrating on saying the sentence as normal as possible") (p 494). They first measured vital capacity with a spirometer and then they used plethysmograph bands around the rib cage (but

secured on participants' clothing), to calculate the percentage of VC used for speech. They then correlated these measures with measures of phonatory activity (mean SPL, mean F_0 and lip displacement in mm from /p/ to /ae/ and from /ae/ to /p/ as calculated by a strain-gauge cantilever system (Barlow et al, 1983). They found that the sentence was spoken faster in the lowest LV condition. Sound Pressure Level (SPL) was increased at the high LV condition. There was no effect of LV on lower lip displacement and upper lip velocities generally decreased for anything but normal lip velocities. Thus there doesn't seem to be a clear relationship between respiratory and articulatory control unlike the positive relationship of respiratory and laryngeal parameters (see also McClean & Tasko, 2002). This is reflected in the results from PD patients' therapy studies, where breathing exercises have little to no effect on articulatory parameters of speech (Ramig, 1998).

1.4.2 Phonation

Phonation abnormality is one of the main symptoms of the disease. Logemann (1978) attempted to characterise the voice and speech abnormalities in 200 PD patients representing all stages of the disease. Two expert listeners performed the phonetic analysis during reading of a paragraph and conversation. They reported that 89% of the patients had abnormal voice and 45% had abnormal articulation. Of the patients with voice abnormality 45% had only voice whereas the others had an additional articulatory disorder. They concluded that the progression of dysfunction begins with voice and gradually extends to include the articulation and other aspects of speech. Sapir et al (2001) repeated the same speech protocol for 41 medicated PD patients and correlated disease severity (as measured by the Unified Parkinson's Disease Rating Scale, motor part III-UPDRS-III), depression, age and gender variables. They found 85.6% prevalence of voice and speech abnormalities. Abnormal voice was present even with

short duration or low UPDRS-III scores. Patients with high UPDRS-III scores tended to have significantly more voice and speech abnormalities, primarily related to abnormalities in articulation and prosody. There was no significant correlation between age, gender and depression scores.

The main study areas of phonation problems in people with PD concern four areas: studies on fundamental frequency (F_0) and vocal intensity, studies on voice quality, studies on laryngeal motor control and studies on laryngeal structure and vocal fold function (as suggested by Darley et al 1969, and Duffy, 2005).

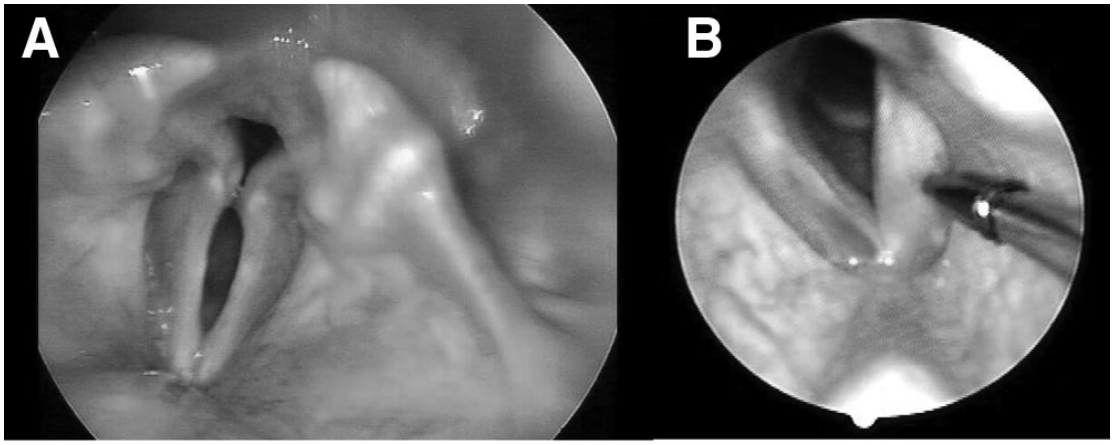

Figure 1.14: *Bowing of vocal folds from Parkinson's disease. A, Notice the spindle shaped defect in the closure of the true vocal folds. B, The vocal folds are injected bilaterally with collagen. From: Meyer (2009).*

1.4.2.1 Fundamental frequency and vocal intensity

Fundamental frequency (F_0) can vary across the course of a syllable and can contribute to vowel identification in dysarthric speech (Bunton, 2006). Vowel identification is thought to be dependent on the location of the first three formant frequencies (F1, F2, F3). Fundamental frequency (F_0) is believed to primarily influence perception of speaker-specific qualities (e.g. age, sex).

Canter (1963), investigated the voice characteristics of 17 people with PD, unmedicated and 17 age-matched controls. He found that although vocal intensity was not

significantly lower than the controls (only 1.6dB on average) the average pitch levels were higher in the patient group and "the parkinsonian subjects were found to be deviant with respect to the range of fundamental vocal frequencies used in the reading of the sample material" (p 226). Thus the median F_0 for Canter's 17 patients was 126 Hz compared to 106 Hz for age-matched controls. Similarly Doyle et al (1995) found higher F_0 for 12 PD patients off medication, in sustained vowel production. On the other hand, Metter & Hanson (1986) found F_0 to fall mostly within the normal range of their seven PD patients although they noted a tendency for the F_0 to increase with increased disease severity. This tendency for the F_0 to be increased is in contrast to the perceptual findings of Darley and colleagues (1969) who found a tendency for pitch to be perceived generally as lower in PD. According to Duffy (2005) the reasons for this discrepancy between acoustic and perceptual data on this dimension are not very clear. It may be that there is a considerable intersubject variability or that monopitch, monoloudness and reduced loudness could lead to perceptions of lower pitch. Hence Duffy advises against using F_0 and pitch levels as a sensitive distinguishing feature of hypokinetic dysarthria. Additionally work in the area of synthetic speech and by Bunton (2006) in PD speech has shown that even though flattening of F_0 does not affect vowel identification in normal controls, modification of the F_0 for PD speakers affected the accuracy with which speakers identified certain vowels. This resulted in reduced intelligibility in PD patients. This result supports the perception of monopitch in PD dysarthria and the perceptual contribution of F_0 variation to sentence-level intelligibility (see also Laures & Weismer, 1999: reduced sentence intelligibility by synthetically flattening F_0 in two normal speakers).

In PD speech measures of F_0 and intensity variability are much more revealing: findings consistently demonstrate a reduction of pitch and loudness variability in PD

patients (Duffy, 1995). As Canter (1965b) noted, he was unable to measure DDK measures in some of his patients due to “flattened intensity peaks” during DDK tasks. One factor that varies in the literature is the selection of appropriate speech and non-speech tasks, that are sensitive to the disease. Although decreased vocal intensity is a common finding (Fox et al, 1997; Dromey, 2003; Ho et al, 1999; Schulz, 2000) it is not consistently replicated in acoustic or perceptual studies (Canter, 1963; Metter & Hanson, 1986; Ludlow & Bassich 1984). Ho et al (1999) found that speakers with PD had reduced conversational loudness at various distances from the listeners but they could increase the loudness as distance increased. These results were interpreted as a reflection of normal loudness regulation but within a context of a damaged “motor set” for loudness, analogous to the reduced limb movement associated with PD. It is also interesting that PD patients overestimated the speakers’ loudness as distance increased, thus raising the possibility that perceptual deficits played a role in their ability to set loudness for themselves. The same group (Ho et al 2001, 2002a) investigated intensity decay (the tendency of the voice to trail off) and found that patients with PD have consistently larger intensity decay than healthy speakers in sustained vowels and reading text. In a later study (Ho et al, 2002b) the same group found that PD patients had difficulty maintaining vocal intensity while performing a concurrent visual-motor task, which indicates that maintenance of vocal intensity requires greater attention for patients with PD. This implies that complex tasks may be more sensitive than others to the impaired motor control, either because they are less automatic or because they demand more attention. Rosen et al (2006) examined intensity decline (measured in dB/sec) across tasks, sustained phonation and syllable repetitions (termed “quasi-speech”) and isolated sentences and conversation (termed “speech”) in 20 medicated male patients with PD, and compared them to six healthy controls. The task that yielded the greater amount of intensity decay was the DDK

rates, and there were no differences between PD and controls in sentence and conversation tasks with regards to maintaining intensity. Thus they concluded that rapid intensity decline is not a robust feature of PD dysarthria, but they noted a large intersubject variability. They thus replicated previous results by Ho and colleagues of no significant difference in intensity decline between patients and controls. However the same group (Rosen et al, 2005) published the results from the acoustic analysis of conversational speech in 20 PD patients compared to 20 controls. They analysed speech-pause ratio, intensity variation, median and max formant slope, formant range and range of the spectral envelope. Their aim was to identify which measures were sensitive to PD speech. They defined acoustic contrastivity as the "degree of spectrotemporal variation in the acoustic signal of speech. The variability of acoustic characteristics, such as formants, intensity and spectral shapes contributes to our ability to produce distinguishable speech sounds (…) thus it is not surprising that reduced variation in prosody, resonances and spectral envelopes has been shown to be associated with perceived severity or reduced speech intelligibility" (p 396). They found that intensity variation and spectral range in both sentence repetition and conversational speech can consistently distinguish PD speech from normal control.

In contrast to the reduced variability of F_0 and intensity in connected speech, studies have shown that PD speakers tend to have abnormally large standard deviations (SD) of F_0 in sustained vowel phonation and that this is correlated with perceptual judgements of dysphonia (Zwirner, 1991, 1992). Larson et al (1994) found abnormally high long-term amplitude perturbation in two speakers with PD which they assigned to slow innervation fluctuations to laryngeal abductory and adductory muscles[1]. A promising new measure for capturing some of the abnormalities perceived in PD speech,

[1] Also high SD of F_0 in our data was linked with dysphonia.

especially in connected speech, may lie in long-term average spectrum (LTAS) measures, which capture the shape of the distribution of energy in the acoustic spectrum. Dromey (2003) compared dysarthric speakers with PD to age-matched controls and found that LTAS measures distinguished the two groups on vowel prolongation, reading and monologue tasks, when other acoustic measures such as SPL level and variability of F_0 did not. Duffy (2005, p 200) comments that this suggests that some of the prominent qualitative deficits perceived in PD speech may be more readily detectable by the spectrum of voice rather than the "simpler" measures of frequency and intensity variability.

1.4.2.2 Voice quality and voice motor control

There are few acoustic investigations of voice quality, mainly due to the inherent methodological difficulties of correlating perceptual and acoustical data (Bunton, 2007). Lehiste (1965) as reported in Duffy (1995, p 178) found spectrographic evidence of laryngealisation (slow or irregular vocal fold activity or biphasic phonation) and breathiness in parkinsonian speakers. Ludlow & Bassich (1984) found abnormal average amplitude perturbations (shimmer) that were correlated with perceptual measures of breathiness; they noted that this abnormality could be related to vocal fold bowing, with subsequent increased airflow turbulence and intensity variations. However Kent (1993) found that measures of jitter and shimmer fail to discriminate PD males from healthy males. He concluded that there would be reason to question the sensitivity of acoustic perturbation measures (such as jitter and shimmer) to voice function in dysarthria, at least for the general purposes of identifying abnormality and classifying clinical groups.

The area that links perceptual and acoustical measures most is that of the onset and offset of voicing. Voice Onset Time (VOT) is defined as the duration of time from

articulatory release of a consonant to the onset of voicing of the following vowel (Goberman & Blomgren, 2006). So far, examination of VOT in PD speech as yielded varied results: there have been reports of increased VOT in PD patients compared to age-matched controls (Forrest et al 1989; Ozsancak et al, 1997) attributed to difficulties initiating movement, i.e. bradykinesia, at the level of the larynx (Forrest et al, 1989). Bunton & Weismer (2002) found no clear differences between PD patients and normal geriatric controls. And finally Flint et al (1992) and Weismer (1984) reported decreased VOT in PD speech, attributed to the rigidity of the laryngeal musculature causing a reduction in vocal fold opening. Recently, Goberman & Blomgren (2008) investigated the acoustical correlates of the perception of laryngeal tension at the initiation of voicing, or else the difficulty with offset of voicing before and after a voiceless consonant. They found that PD patients stop vocal fold vibration through vocal fold adduction (without adding tension). This tension was lowest for patients off-medication and highest for age-matched participants and patients on-medication. They assign this laryngeal tension to laryngeal rigidity in PD speech. In summary the VOT literature in PD speech shows deficits with the onset of voicing but the direction of this difference is still undetermined. This is perhaps illustrated by the fact that the same researcher made two opposing conclusions: Weismer (1984) showed a decrease in VOT and five years later an increase (Forrest et al, 1989). Goberman & Blomgren (2008) examined the VOT and voice offset times in nine PD patients on- and off-medication, compared to eight controls. They studied the phrase “one finds” by analyzing the F_0 before and after the voiceless consonant. They found a great variability especially at the off-medication state, with patients overall having difficulty with rapid onset of voicing, not significantly improved with medication. They assigned these deficits in either articulatory (accuracy of phoneme production) or phonatory (tension and abduction of vocal folds) or aerodynamic (decrease airflow rate) variables in speech but not the result

of timing deficits. Apart from acoustical examination of voice onset and offset, a number of studies have examined similar measures physiologically. Gallena et al (2001) performed EMG analysis of laryngeal muscle activity during the offset and onset of voicing in PD patients. They found increased laryngeal muscle activity (i.e. tension), which was reduced with medication. Earlier, in a comprehensive telescopic cinelaryngoscopy study of 32 unselected patients, Hanson et al (1984) studied the laryngeal abnormalities of PD speech: of the 32 patients only two had normal voices and no voice complaints and were free of "abnormal phonatory posturing". The remaining 30 patients exhibited vocal cord bowing during phonation, represented by a significant glottic gap. This increased glottic gap was correlated with perceived breathiness and reduced intensity (Figure 1.13). Tremulousness of the arytenoids cartilages was apparent during quiet breathing in some patients but the perception of voice tremor was more closely related to the secondary effects of head tremor. Laryngeal structure asymmetries were apparent in many patients, in terms of vocal fold length, degree of bowing and ventricular fold movements. The authors noted that the vocal folds appeared solid, in spite of bowing, in contrast to the hypotonicity that may be present in lower motor neuron paralysis. They concluded that the abnormalities in phonatory postures are related to muscle rigidity. Similarly Jiang et al (1999) used electroglottographic analysis and found that PD patients had increased laryngeal rigidity, improved with medication.

1.4.3 Articulation and resonance

Plowman-Price (2009) analysed the speech of 16 PD patients on- and off-medication and applied the 35 perceptual dimensions of Darley et al (1969). They found that reduced intelligibility was most strongly correlated with imprecise articulation (sound imprecision), followed by mono-loudness and mono-pitch.

Studies on articulation in PD speech can be grouped according to the methodology they use (acoustic analysis, EMG, microbeam, force transducer), the area of articulation motor control they investigate (muscle function, rate of movement with DDKs) or the articulatory organ they examine (tongue, lips, jaw). They provide support for the perception of imprecise articulation, rate abnormalities and the reduction in range of articulatory movement.

Articulatory imprecision is usually termed articulatory "undershoot". The failure to completely reach articulatory targets or sustain contacts for sufficient durations has the perceived effect of reduced acoustic contrast and detail, and it contributes to imprecise articulation (Weismer, 1984). This undershooting could be explained by reduced range of movement or rigidity.

1.4.3.1 Lips

Leanderson et al (1972) examined the articulatory EMG activity of lip muscles in 12 PD Swedish patients and compared with normal speakers and the effects of levodopa using needle electrodes (see also Leanderson (1971), where he describes the needle EMG method for the first time). He found increased resting activity between utterances, which progressed to a sustained hypertonic background activity. He found no signs of reciprocal inhibition of labial muscles when patients were off-medication. levodopa medication was followed by a reduction of background activity and reestablishment of reciprocal activation. He concluded that there was an obvious relationship between this disturbed activity pattern and misarticulation of bilabial consonants, as well as rigidity. These conclusions have been confirmed by Forrest et al (1989) and Hirose (1981), who used an X-ray microbeam system together with the EMG measures from the anterior digastric and mentalis muscles in two patients. Similarly, Caligiuri (1989 as reported in Goberman, 2002b, p 250) examined labial stiffness, displacement and velocity in five

PD patients. Recordings were made of the syllable /va/ before taking levodopa and at the beginning, half-way point and end of the drug cycle. The investigator found that PD patients showed increased labial stiffness, which decreased immediately after taking medication. Amplitude and velocity of labial movements also improved immediately after medication. Labial velocity and stiffness continued to improve throughout the drug cycle, while labial amplitude did not change. Caligiuri (1989) acknowledged a limitation to this study, in that the labial changes reported may not necessarily reflect on speech intelligibility. Netsell et al (1975) used the term acceleration and weakness to describe the underlying neuromuscular mechanisms responsible for the articulatory undershoot that they studied in 22 PD medicated patients using lip surface EMG aerodynamics and audio recordings. Hunker et al (1982) suggested that such persistent abnormal muscle contractions – reflecting difficulties with reciprocal adjustments of antagonistic muscles or a loss of reciprocal suppression between functionally antagonistic muscular pairs – may represent the physiological basis of rigidity and hypokinesia (see also Leanderson, 1972).

1.4.3.2 Tongue

In examining articulation in PD a number of researchers have reported that stop consonants (p,t,k,g,b,d) were imprecise and produced as fricatives (Logemann, 1981; Weismer, 1984). Logemann (1978) studied the frequency and co-occurrence of speech deficits in 200 medicated patients with PD and reported that five main groups of misarticulations: 45% of patients presented with laryngeal dysfunction as their only vocal tract symptom, 13.5% presented with laryngeal and back of the tongue involvement (k,g sounds), 17% of patients presented with laryngeal, back tongue and tongue blade dysfunction (k,g,s,z), 5.5% presented with additional lip involvement and finally 9% presented with additional tongue tip involvement. This consistent pattern

was interpreted as a result of the incomplete contact of the articulators, i.e. an articulatory undershoot phenomenon. Tongue muscle weakness has rarely been detected during neurologic examination of people with PD (Yanagawa et al, 1990). Solomon et al (2000) examined tongue strength endurance and stability during a sustained submaximal effort using a pressure transducer that senses pressure exerted on an air-filled bulb. Patients were asked to talk for 10 minutes and then the effortful tongue endurance tasks were performed. Tongue endurance was found to be significantly lower in the PD patients rather than the controls. However there was no significant correlation between tongue strength and endurance, interpause speech rate, articulatory precision and overall speech impairment. They thus question the influence of modest degrees of tongue weakness and fatigue on perceptual speech deficits. Ackermann & Zeigler (1991) compared the intensity of stop consonant production in 12 PD patients and they found that whereas normal speakers showed a decreased intensity at the moment of stop closure (i.e. oral closure) the PD patients did not show any decrease in intensity, therefore complete closure may not have been achieved. This may be another example of reduced amplitude of articulatory movement leading to an inability to close off the oral cavity.

Rate is the other area that has received a lot of attention due to the increased rate often perceived in PD speech. It can be measured as words per minute (with normal of 180 wpm, Yorkston, 1981) or syllables per second. Canter et al (1967) showed a great variability across patients ranging from abnormally slow to abnormally fast. Another method of evaluating articulatory skills and rate in particular is the oral diadochokinetic tasks (DDK), i.e. the production of syllable trains containing consonant-vowel combinations with bilabial, alveolar and velar places of articulation /papapa/tatata/kakaka/ following the instruction “repeat the syllables…as fast as

possible in a single breath". They are used to examine the patient's ability to make rapidly alternating articulatory movements. Patients with cerebellar atrophy, Friedreich's ataxia, spastic dysarthria or Huntington's chorea show decreased syllabic rates (Ludlow et al, 1987; Ackermann et al, 1995a). In contrast the performance of most PD patients is similar to the normal subjects (Ackermann, 1991, 1997). The explanation of this phenomenon is that PD patients may produce normal syllabic movements at the expense of movement amplitude (Ackermann et al, 1997). Hence Caligiuri (1989) compared sequences of repetitions of the syllable /va/ at 3 to 5 Hz and at 5 to 7 Hz and found hypokinesia, i.e. reduced range of movement with faster oral diadochokinesis in the PD patients. Ackermann et al (1995b) reported similar results for 17 patients, who used articulatory undershoot to successfully compensate for bradykinesia; however the more severe patients were unable to fully compensate and produced abnormally slow speech. This trade off between tempo and articulatory precision is made possible by the fact that reduced articulatory precision may still be compatible with the requirements for intelligible speech. In this respect speech is different from other motor acts like grasping or finger tapping where a similar trade off cannot be made without compromising the requirements of the task.

1.4.4 Speech intelligibility and people with PD

Speech intelligibility is of paramount concern in both the evaluation and management of dysarthria. The definition of speech intelligibility for this study is "the degree to which a speaker's message can be recovered by the listener" (Kent et al, 1989, p 483). Current clinical methods for measuring speech intelligibility reflect the interaction between a speaker and a listener under given communication conditions. Factors that can influence intelligibility measures include: a) severity of the intelligibility impairment (Yorkston & Beukelman, 1978b), b) speech rate (Yorkston & Beukelman, 1981; Canter, 1965c), c)

type of speech stimulus, d) scoring method (Beukelman & Yorkston, 1980), e) predictability of stimuli (Duffy & Giolas, 1974), f) listener familiarity with the speech disorder and/or individual speaker (Beukelman & Yorkston, 1980; Platt et al, 1980). Studies of clear versus conversational style speech offer insight into speech production changes that speakers make when asked to produce speech clearly. Specifically, clear speech was characterised by decreased articulation rates and increased frequency and length of pauses (Bradlow et al, 2003; Goberman, 2005; Canter, 1969). Bradlow (2003) compared speakers who differed in intelligibility and found that a highly intelligible speaker would have a relatively wide range of fundamental frequency, a relatively expanded vowel space, precise articulation of the point vowels (/i/ /a/ /u/) and high precision in intersegmental timing. Dysarthric speech analysis of the relative contribution of speech subsystems (voice, quality, articulation, nasality and prosody) showed that articulation was the strongest contributor on speech intelligibility (DeBodt et al, 2002). Barreto & Ortiz (2009) reviewed the methods of measuring speech intelligibility. Because speech intelligibility is defined as the amount of speech understood from the acoustic signal alone, most current clinical measurement tools for speech intelligibility allow listeners access to only signal-dependent information. The most common measurement protocol for intelligibility involves audiotape-recording the speaker and then asking the listener to transcribe words and or sentences (Tikofsky & Tikofsky 1964; Yorkston & Beukelman, 1980). The resultant intelligibility score is the percentage of words correctly transcribed or selected. Information other than that provided by the acoustic signal is referred to as signal-independent. Hustad et al (2003) have described three types of communicative knowledge that may be used by listeners to decode a spoken message. They include: a) linguistic knowledge, which defines a listener's expectations for semantics, syntax and phonology, b) paralinguistic knowledge, such as that related to gestures, facial expression and speech related

movements, and c) experiential knowledge, which refers to shared knowledge of culture and experiences between the listener and the speaker. Keintz et al (2007) investigated the influence of visual information on speech intelligibility for eight PD patients with dysarthria. Twenty listeners transcribed sentences while watching and listening to videotapes of the speakers (audio-visual mode) and while only listening to the speakers (auditory-only mode). They found that auditory-visual scores were significantly higher than auditory-only scores for three speakers with the lowest intelligibility scores. Kent et al (1994) have suggested that each speaker has a range of potential intelligibility that is influenced by factors related to the speaker, the listener and the conditions in which communication takes place. They suggested that given that visual cues are commonly available to listeners in most everyday situations, it may be appropriate to include visual information when evaluating a patient's intelligibility and when managing a communication disorder.

Goberman (2005) studied the strategies patients with PD use when they are instructed to use clear speech (i.e. "to speak as clearly as possible") compared to conversational speech (i.e. "to speak in a manner similar to ordinary conversation"). They found that people with PD use the same strategies as non-impaired speakers, namely decreased articulation rate, increased mean fundamental frequency, and increased speaking F_0 SD compared to conversational speech. However they doubt how much these strategies could be generalised outside the clinical setting.

The strategy of rate manipulation (i.e. speaking at a slower or faster rate) has been further tested. Tjaden & Wilding (2004) compared the effects of rate and loudness manipulations on speech intelligibility of 12 people with PD. Ten listeners scaled intelligibility for reading passages. Intelligibility for people with PD improved with the loud condition as opposed to the slow condition. Rate manipulation and its effects on

speech intelligibility were studied earlier by Hammen et al, (1994). They examined the difference between paced temporal alteration, i.e. the slowing down of speech rate by 60%, and synthetically altered speech, i.e. modifying the rate of speech samples using digital signal processing, in six PD patients. They found that the greater impact on speech intelligibility was achieved with the paced alteration, i.e. slowing down the habitual speaking rate, rather than synthetically altered speech rate. Loudness manipulations have been used more successfully to improve speech intelligibility in people with PD, hence the success of treatments based on increase loudness, such as the Lee Silverman Voice Treatment (LSVT, Ramig et al, 2001). Dromey & Ramig (1998) found that for talkers with normal speech, loud speech is characterised by greater displacement and velocity of jaw and lip movements than normal speech. Physiological changes associated with people with PD using loud speech include increased tongue strength and endurance, increased lip displacement and velocity (Dromey, 2000), and greater stability of lip movement patterns (Kleinow et al, 2001). Acoustic changes such as increases in vowel duration, decreased in fricative duration and increased in formant transition duration and extent (Dromey et al, 1998), increased in vowel space area (Bunton, 2006; Sapir et al, 2007) and reduced rate of speech with increased distinctiveness between stop consonants (Tjaden & Wilding, 2004) have also been described. Recently Neel (2009) examined the effects of loud speech and amplification on people with PD and found that loud speech resulted in greater intelligibility improvement than amplification, mainly due to phonatory changes (as measured by improvements in fundamental frequency and spectral tilt) and not so much articulatory ones (measured as articulatory rate and pause time). In terms of amplification, Neel (2009) findings agreed with the scarce evidence regarding their efficacy for people with PD. Sarno (1968) was the first to observe that amplification may improve communication for “occasional cases” of speakers with PD, but that in her experience

amplification “exaggerates” the dysarthria. Equally Greene & Watson (1968) reported their clinical experience that benefit is gained from amplification only when reduced vocal volume is the only symptom present, but there is no benefit when the speaker has slurred articulation. Adams (1997) commented that despite widespread use of voice amplification for people with PD little data is available on their effectiveness. The prevalence of speech intelligibility problems in the parkinsonian population has been estimated at 70-90% in five studies that used various methodologies. The most recent one is by Miller (2007) and it is the only one using a diagnostic test (the Assessment of Intelligibility of the Dysarthric Speaker, AIDS, Yorkston et al, 1984) in a large sample (N=125) of PD patients off-medication with controls and 99 naïve listeners. They found that 70% of people with PD fell below the control mean of unaffected speakers, of which 51% by more than one standard deviation. Thirty-eight percent placed speech changes amongst their top four concerns regarding their PD. Intelligibility level did not correlate significantly with age or disease duration and only weakly with stage and severity of PD. They found no significant differences between tremor dominant versus balance/gait disorder motor phenotypes of PD. Previous surveys gave similar estimates of speech and voice problems in PD. Logemann et al, (1978) was the first to assess 200 PD patients by two expert listeners listening to tapes of their conversational speech and reading samples. By examining the co-occurrence of speech deficit a progression of impairment was hypothesised beginning with voice followed by articulation, progressing from posterior tongue involvement to lip involvement. Ho et al (1998) replicated the study and had similar findings. Hartelius (1994) surveyed a large sample of patients with PD and Multiple Sclerosis (MS) and found that 70% of PD patients had experienced impairment of speech and voice after the onset of the disease (compared to 40% of people with MS) and 41% had some swallowing problems. Of those affected patients only 3% had received some form of speech therapy. Coates & Bakheit (1997)

assessed 48 patients using a modified version of the AIDS, rated by a single Speech and Language Therapist (SLT). They found that two-thirds of patients had reduced speech intelligibility. They also examined the impact on their lifestyle and they found that none of the patients reported that their speech difficulties interfered with their lives. This study was later criticised for its methodology.

The issue of the impact of reduced intelligibility on the lives of people with PD has occupied relatively few studies. Miller et al (2006) performed a qualitative study with interviews of 37 people with PD and four impact themes emerged: i) interaction with others, ii) problems with conversations, iii) feelings about intelligibility and iv) voice. They also identified four corresponding coping themes a) helping others understand, b) managing conversations, c) monitoring and adjusting and d) physical changes. Of interest is the passive approach that people with PD adopt when they need to manage conversations, i.e. not speaking unless directly addressed. When it comes to hospital care or other vital communication people with PD ask their relatives to be present:
"I don't speak unless I have to as I'm frightened I don't get my words out, and if I go to the hospital my wife comes and does all the talking". In conclusion speech and language changes in PD impact upon individual and family life long before frank impairment on intelligibility is apparent.

The same group (Walshe et al, 2008) tried to compare speaker and listener reception of the intelligibility of dysarthric speech and in particular to examine the relationship between speaker perceptions of intelligibility and formal clinical intelligibility ratings. They compared the intelligibility ratings between 20 people with dysarthria, 10 SLTs and 20 naïve listeners and found no significant difference between the three listener groups. They also compared the ratings of patients' own speech compared to those of the SLTs and the naïve listeners and they found no relationship between the two.

1.4.5 Prosody

According to Pell et al (2006) prosody refers to an equilibrium between temporal (duration, pause) dynamic (intensity) and melodic aspects (pitch) of speech.

A combination of these features allows speakers to communicate their emotions and attitudes to listeners. Disturbances in the rate of speech, pitch variation and intensity in PD patients may alter listeners' perceptions of the social and linguistic competence of the speaker with PD in a negative manner (McNamara & Durso, 2003). Listeners judge people with PD to be more "cold, anxious, unhappy and less likeable" than healthy adults, based on impressions from their speaking voices (Pitcairn et al, 1990). Thus prosody is the intersection between the acoustic and the perceptual aspects of speech. Acoustic analysis of intensity and pitch variation, speech rate and speech intelligibility may be used towards characterising prosodic aspects of speech. Skodda (2009) investigated the progression of dysprosody in 50 patients with PD over at least seven months (mean 25 months) using syllable rate, pause rate, frequency variation. They found no correlation between these prosodic aspects of speech and disease duration or UPDRS motor score. In a previous study (Skodda, 2008) the same group calculated the speech rate and pause time in 121 patients with PD and compared that to 70 healthy controls. They found no significant difference in overall articulatory rate, but the PD patients had higher speech acceleration at the end of the sentence than did the controls.

De Letter et al (2007) investigated the effects of levodopa on prosody and comprehensibility in 10 PD patients, using non-instrumental, perceptual rating of the speech samples by four speech and language therapists. They used a 100 mm, 10 point scale on four aspects of speech production: variations in pitch, variations in loudness, variations in reading rate and comprehensibility. They found a significant improvement in pitch variation, loudness variation and comprehensibility. However Goberman et al (2005) found no significant changes in pitch variation after levodopa intake, possibly

due to the different methodology and stage of disease. Prosody was rated as the most severely affected speech subsystem in Darley's et al (1969) seminal investigations.
In those studies three raters performed perceptual assessments of speech of 212 neurologically impaired patients as they read the "Grandfather Passage". They used a 36 speech dimensions and two general dimensions (intelligibility and bizarreness) using a seven-point scale. The classification of hypokinetic dysarthria of the 32 PD patients was based on the monotony of pitch and loudness, reduced stress and imprecise consonants speech dimensions.

These results were recently replicated by Plowman-Prine et al (2009) with the same methodology in 16 PD patients on- and off-medication. They found monopitch, monoloudness, reduced stress and imprecise consonants to be the most prominent speech dimension. Neither intelligibility nor the affected speech dimensions changed significantly with medication, as opposed to the significant improvement in the motor scores.

Perhaps most eloquently Kent & Rosenbeck (1982) have provided a useful summary of the acoustic "signature" of hypokinetic dysarthria. They labelled the pattern in which the contour across syllables within utterances is flattened or indistinct as fused. This fused or altered profile is characterised by 1) small and gradual F_0 and intensity variations within and between syllables, 2) continuous voicing, 3) reduced variations in syllable durations, 4) syllable reduction, 5) indistinct boundaries between syllables because of faulty consonant articulation and 6) spread of nasalization across consecutive syllables. In summary these features represent a reduced ability to use the full range of pitch, intensity, articulatory and durational options that are used in normal speakers.

Mobes et al (2008) conducted an interesting study on emotional speech in PD using prosodic measures of pitch and intensity variation. They compared 16 PD patients and

16 healthy controls in the following tasks: 1. intensity and pitch range (max and min values of loudness and fundamental frequency) of non-emotional speech (phonatory capacity), 2. intensity and pitch range when saying “Anna” in emotional intonation (neutral, sad and happy), and 3. intensity and pitch range when imitating a professional speaker. They found no differences in the phonation capacity and the imitation task between groups, but a significantly reduced pitch and intensity range in the production task. These patients had mild motor symptoms as measured by the UPDRS and no dysarthria. They interpreted these results as a result of a difficulty in emotional processing but they did not provide further arguments. The inability to internally self-cue a behaviour has also been postulated.

1.4.5.1 Perception of emotional prosody

Scott and colleagues (1984) were among the first to investigate the perception of emotional prosody in PD, an area that has received scant interest. They reported that PD patients were able to discriminate sentences with non-emotional prosodic contrast (e.g. I can run, versus I can run) but were impaired in judging the meaning and certain emotional features of those sentences (similar results from Pell et al (1996). There may be at least two confounding factors when analyzing emotional processing either through recognition of facial expression or prosody: the effect of higher cognitive processes in the comprehension of emotional aspects of speech has been shown by Benke et al (1998). Depression is another factor that could be implicated as a confounding variable. However there is increasing evidence that emotional processing of both facial expression and prosody can be affected in PD. In 1998 Breitenstein et al published their data on the emotional perception of 32 patients with focal cortical lesions and 14 patients with PD. They found that only patients with advanced PD and those with focal damage to the right frontal lobe differed significantly from controls in both facial

expression and affective prosody recognition. They thus conclude that there is an involvement of the fronto-striatal circuitry in emotional processing. Velez et al, (2008) found that PD patients with depression had heightened perception of negative emotions (indifference and anger). Contrarily, recently Dara et al (2008) found the opposite i.e. reduced sensitivity to negative emotions. They compared 16 non-demented PD patients to 17 healthy controls and they found that the PD group was significantly impaired in categorizing emotional prosody, especially for expressions of anger, disgust and fear. Similarly Ariatti et al (2008) used the Facial Emotion Recognition Battery and the Emotional Prosody Recognition Battery and they found that PD patients (n=27) had significant impairment in selecting, recognising and matching facial effects, in particular sad and fearful faces. Bach (2008) using fMRI found activation of the basal ganglia and the right anterior cingulated cortex in response to explicit processing of emotional versus neutral sentences. Additionally, Paulmann (2008) found impaired explicit recognition of emotional processing in a group of patients with focal basal ganglia lesions. In 1998 Scott et al presented a case study of a lady with lesion confined to the amygdala complex through stereotactic neurosurgery for her epilepsy. She had severely affected recognition of fear and sadness despite normal hearing. These studies argue that basal ganglia provide a critical mechanism for reinforcing the behavioural significance of prosodic/emotional aspects of speech. However the above observations have not been tested clinically: indeed Yoshimura et al (2005) conclude that "corticostriatal connections may be variably affected by a lack of dopamine or by pathological changes in the amygdala, but somatosensory recruitment may overcome the mild cognitive emotional deficits that may be present in PD patients".

1.4.6 Correlation of speech with motor symptoms

Speech response to medical and surgical treatments in PD rarely follows the pattern of improvement of the other limb motor symptoms (Pinto et al, 2004), despite the fact that speech is affected in the majority of PD patients at some stage of the disease process (Logemann, 1978). This has led investigators to examine the pattern of change of motor and speech symptoms and assign the latter to non-dopaminergic basal ganglia lesions. Midi et al (2008) evaluated the changes in perceptual and acoustic parameters of voice in patients with PD and the relationship with UPDRS motor score. They found only few significant correlations between UPDRS subcomponents and speech measures, mainly with diadochokinetic (DDK) tasks: they found no association between finger tapping DDK rate as well as a negative correlation between DDK and rigidity, indicating a lower speech DDK rate with increased severity of rigidity. Goberman (2005) studied nine PD patients and Gamboa (1997) 41 patients and found the same lack of association between speech and motor symptoms (see also Plowman-Prine, 2009, as cited above). On the other hand, Sapir et al (2001) found a positive correlation between higher UPDRS scores (i.e. worse motor functioning) and disease duration with voice and speech abnormalities in 42 PD patients. These voice abnormalities did not correlate with age, depression or gender.

Another interesting motor area is that of festination and freezing of gait, i.e. the tendency to speed up and lose normal amplitude during quick, repetitive movements (gait, speech and tapping). Gait festination was described as a propensity to lean forward while taking rapid small steps whereas freezing of gait refers to sudden motor block. Moreau et al (2007) correlated oral festination with gait and freezing in 40 patients recruited according to their gait disorder, off-medication. They used an orofacial DDK task the repetition of the syllable /pa/ at different frequencies (from 1 to

7.5 Hz) and patients were asked to synchronise their performance with a metronome. Jaw movements were recorded using an optoelectronic movement analysis system.
They found a high correlation between oral festination and gait but not freezing. Oral festination was not correlated with the severity of dysarthria and it was present in 45% of their sample.

A task similar to speech, in terms of linguistic expression, can be handwriting with a typical symptom of micrographia in PD. Micrographia resembles hypokinetic speech in that small movement excursions compensate for the inability to execute high velocity strokes (Ackermann, 1991). Poluha et al (1998) examined the effects of medication on handwriting and speech in 10 PD patients. The handwriting measures include /l/ and /e/ upstroke duration and size, whereas the speech measures included duration of the vowels /i/, /u/, /ae/ and /o/. Levodopa improved significantly handwriting upstroke duration but not size. Speech measures did not show any significant change across levodopa cycle.

Perhaps the most interesting comparative study of motor effects of PD on speech and movement is that of the finger spelling of deaf signers with Parkinson's disease. Since movements of the articulators in sign, unlike speech, are directly observable, one can investigate signing not only as a linguistic behaviour but also as a motor behaviour. Brentari et al (1995) contrasted aphasic and parkinsonian signing and found the equivalent of a phonetic impairment in the PD signers manifested as a disturbance in the temporal organisation and coordination of hand shape and movement, with no disruption in the underlying representation and syllabification processes of the language as in the aphasic signers. They also describe the equivalent of monotone speech, in the lack of difference between hand shape changes that occur as syllable peaks and those that occur during the transitional movements between signs. The underlying strategy is

that of lessened motor programming load. It is also in accordance with earlier results from Benecke et al (1987) who showed that PD patients exhibit a longer inter-onset latency for preparation of the second of the three movements within a sequence.

Tyrone and colleagues (1999) examined the production of the ASL finger spelling, a more sequential and rapid motor behaviour than signing, with a linguistic structure. They found that signers with PD showed segmentation of individual segments of finger spelling sequence (holding them for longer), blended adjacent segments into a single segment (sequential blending). The movements for the independent articulators for finger spelling (thumb, fingers and wrist) were markedly further apart in time and they had fewer wrist movements. They assigned these deficits to lack of interarticulator coordinator. One could however argue that they are merely symptoms of bradykinesia and rigidity. The similarities of parkinsonian signing and speaking point towards a common underlying neural deficit affecting all movement of articulators which is not confined to the oral area. There are no imaging studies on deaf signers with PD. If sign language stands at the intersection of how the brain controls arm/hand movement and how it controls language expression, then the interest would be in investigating the effect of stimulation on non-linguistic hand movement (i.e. joystick) and linguistic hand movement (signing) and speech. That could elucidate the role of basal ganglia and perhaps point to an oromotor speech specific neural network.

1.4.7 Patient perceptions and complaints

Patients with PD frequently report that others tell them that their voice is quiet or weak, and they often deny or minimize such changes themselves (Duffy, 2005). Complaints that rate is too fast or that words are indistinct are common. They also report that it can be hard to get speech started and that they have hesitations or stutter.

Patients' perception of their speech problems is directly linked to sensory processing of their own speech, and particularly their speech volume. Fox et al (1997) showed that PD patients were able to rate their speech and volume more severely impaired than healthy controls. In other studies though, specifically focusing on volume, patients consistently perceived their speech when reading and in conversation to be louder than the actual volume (Ho et al, 2000). This suggests that the voice disorder experienced by PD patients may be compounded by an impaired perception of its true characteristics. There have been two types of cueing the implicit and explicit. Ho et al (1999) investigated the effect of implicit cueing for loudness using background noise ("the Lombard effect") as well as the provision of instantaneous auditory feedback at various intensities (the reverse "Lombard effect"). They found that PD patients had overall reduced intensity and reduced ability to modulate their volume using implicit cueing. Under explicit instructions to increase their volume they were able to do so but they were still below the control levels. This difficulty in maintaining the amplitude of movement without constant explicit cueing had been investigated in the early 1980s with the provision of a portable auditory feedback device. Thus Rubow et al (1985) published their "microcomputer-based wearable biofeedback device to improve transfer of treatment in parkinsonian dysarthria" which gave visual feedback on intensity following treatment. There was little further research in the technology in this biofeedback area, despite the promising results and the sound scientific argument. There has been more interest in Delayed Auditory Feedback (DAF) devices mainly for palilalia (or festinating speech). This technique is not equally effective on all patients and it is still unclear who can be helped (Downie et al, 1981).

However, despite the difficulty in self-perception of speech loudness, patients with PD seem to have intact perception of the communication and speech intelligibility changes

associated with PD (Miller, 2008, 2006) when this is compared to their carers' perception.

1.4.8 Neural control of speech in Parkinson's disease

There are four published studies of functional imaging and the neural correlates of parkinsonian speech. Pinto and colleagues (2004) used H_2 15O PET to measure the effects of subthalamic nucleus (STN) stimulation on speech production and silent articulation of one sentence. Patients when on- and off-stimulation showed lack of involvement of the right orofacial primary motor area (M1) and the cerebellum, and increased regional cerebral blood flow (rCBF) in the SMA, dorsolateral prefrontal cortex (DLPFC), right superior premotor and left insula. Stimulation normalised the pattern of rCBF to that of the healthy controls, mainly for the M1, the SMA and the cerebellum, concurrently with improvement in speech.

Liotti and colleagues (2003) used the same PET technique and both paragraph reading and sustained phonation tasks to investigate the effects of a speech treatment, the Lee Silverman Voice Treatment (LSVT) on PD patients with medication on. Results showed an increase in rCBF post LSVT compared to pre-LSVT in the right caudate, right putamen, right anterior insula and right DLPFC in the phonation and reading tasks.

In contrast there were CBF decreases in all motor and pre-motor areas, including right orofacial M1, SMA and left Broca's area. The response in the primary motor cortex and cerebellum appears variable with both decreases (Pinto et al, 2004) and increases (Liotti et al, 2003) reported. The authors of these studies interpreted these findings as pre-treatment abnormalities. Another difference is the abnormal hyperactivity in bilateral DLPFC during speech tasks that was reversed following STN-DBS (Pinto et al, 2004). They concluded that the combined hyperactivity of the DLPFC and the rostral SMA is a compensatory phenomenon due to the disease process, which becomes normalized with

STN-DBS. In the Liotti study the opposite was observed: hyperactivity of the DLPFC was noted only post-treatment. Therefore the authors concluded that activation of DLPFC post LSVT-LOUD undergoes normalisation similar to the limb motor system in PD, due to the re-establishment of the basal ganglia-thalamic inputs to the prefrontal cortex. However DLPFC activation is not observed during speech in normal controls[2]. Thus the only common area in the two studies was the increased activation of the SMA when patients are without medical or surgical treatment or before behavioural treatment and the increase in the right orofacial sensorimotor cortex (SM1) after the STN stimulation and when reading in patients before LSVT, on-medication. The differences in medication status and disease-speech severity should be considered when interpreting these findings.

Rektorova et al (2007) used fMRI to assess the response to the overt reading of emotionally neutral sentences in medically treated female patients (N=9) with mild to moderate PD and compared them to eight age and sex matched healthy controls. They found increased activity in the left orofacial sensorimotor cortex (SM1), which was involved in all aspects of speech (including initiation, duration, speech loudness and prosody)[3]. However between group analysis revealed higher signal in the right orofacial SM1 for the PD patients. They speculated that this might be a compensatory strategy for the impaired recruitment of subcortical structures or indeed the result of medical treatment, as it contradicts earlier finding by Pinto et al (2004) on decreased right SM1 activity in PD patients when off-medication and off-stimulation.

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[2] A challenging hypothesis would be: DLPFC activation is used as a compensatory strategy for speech in PD patients. **STN-DBS reduces** the need for DLPFC activation only in patients where speech is improved by stimulation. LSVT increases activation as it improves speech. So there is a competing activation of the DLPFC when it comes to speech post STN-DBS and LSVT.

[3] See also Dias et al (2006): one session of high frequency rTMS in the left orofacial SM1 may lead to improvement of fundamental frequency and voice intensity in PD patients.

It is of note that the quality of speech of their sample is described as similar to that of the control group (i.e. very mild dysarthria). In the above studies the observed activations during PD speech do not parallel the activation associated during hand movements: Haslinger et al (2001) reported increased SM1 overactivity in advanced PD patients when off-medication while studying simple or complex motor tasks.

Sachin et al (2008) studied 22 PD patients off-medication using fMRI and compared the results with 18 PSP patients and 10 healthy controls. They found PD patients to have the least consistency of activated areas. They found increased activation in the SMA (as in Pinto et al, 2004) and in the pre frontal cortex, namely the DLPFC and the insula (as in Pinto 2004 and Narayana 2009, see below).

In a case study, Narayana et al (2009) used PET to investigate changes in neural activation during paragraph reading in a medicated PD patient with speech deterioration following bilateral STN-DBS. They compared activation and speech effects of left and right stimulation alone. They concluded that speech production was worst during left STN stimulation compared to no stimulation. This was accompanied with increased activity in the left dorsal premotor cortex (PMd). Then they used rTMS to "lesion" the PMd with patient off stimulation and they observed perceptually similar speech, characterized by decreased speech intelligibility. Activation of the PMd in normal speech has been reported before (Schultz et al, 2005), as well as in stuttering (Brown et al, 2005). Lesion studies indicate that PMd is important for speech programming (Watkins & Dronkers, 2002). In contrast studies on limb motor control and STN-DBS report decrease of activation in the left PMd when DBS is on (Haslinger, 2005). Pinto et al reported abnormal activation in PMd during speech, normalised with STN-DBS. In Narayana (2009) speech disruption seen during STN-DBS as well as TMS on the PMd was interpreted as a "direct result of disynchronisation of ongoing activity in the left

PMd" (p 158). Aravamathun et al (2007) used MR tractography to map the connections between STN and cortex. They found that STN regions connected to the cortex (i.e. motor cortex, SMA, PMd) are located in close proximity and are more lateral and anterior to the STN regions connected to the thalamus and basal ganglia. Thus motor cortical regions (M1, SMA and PMd) all connect to the most superior portion of the STN while associative regions are connected to the inferior and medial portions of the STN, as in the STN topography of non-human primates (Hamani, 2004). The STN regions connected to the GP, midcerebellum, SN, and PPN were located in the inferior and medial STN. However the STN region connected to the thalamus was distinctly segregated, located superior and posterior to the STN regions connected to other subcortical regions. Therefore DBS can directly stimulate areas in the STN connected to the premotor cortices and the primary hand, limb and trunk areas. So while improving motor function by "lesioning" the connections of the STN to the motor cortex, DBS might incidentally "lesion" its connections to the premotor area, needed for speech. This could also explain the variability in speech response seen in STN-DBS patients.

1.4.9 Effects of medication on speech in PD

Initial reports on the effects of levodopa on speech noted the less dramatic effect than on physical symptoms. Rigrodsky & Morrison (1970) first examined the effects of optimum dose levodopa on reading and spontaneous speaking in consecutive patients and in a double-blind fashion. They found no significant difference but a trend towards improvement during levodopa therapy with a considerable individual variation. They pointed out the need for a more long-term study with appropriate tasks. Interestingly Mawdsley & Gamsu (1971) found the opposite, i.e. that speech of six patients became more intelligible after treatment with levodopa. They also noted that "there is a suggestion that needs further study, that in those patients with the postencephalic

disease and in those who have undergone stereotactic thalamotomy, levodopa is less effective in improving speech" (p 316). They followed on from that to propose a hypothesis on the relative contribution of the malfunction of the striatum, which leads to reduced kinesthetic information from the speech organs and consequently to what is perceived as prolonged phonation. "Restoration of the inhibitory striatal action by activation of dopaminergic neurons restores a more rapid selection of the cues for the next stage of motor activation thus shortening the phonation time of individual words and lengthening the pauses" (p 316). Marsden & Parkes (1976) observed the co-occurrence of peak-dose akinesia with dysphonia, and without tremor or rigidity. Subsequently, Critchley (1976) in a letter to the Lancet describes his experience of a similar discrepancy between motor improvement and speech deterioration without dyskinesias. Leandersen et al (1971, 1972) demonstrated through EMG of the lips that coordination of labio-oral musculature improved with levodopa. Similarly, in a double-blind study by Nakano et al (1973) parkinsonian patients treated with levodopa showed a significant improvement in movement and coordination of labial muscles. Logemann (1973, as reported in Wolfe et al, 1975), had commented that although near normal motor state can be achieved through levodopa therapy, speech may not be helped. Wolfe et al (1975) found that out of 17 patients nine achieved minimal or poor improvement, with only two patients showing 50% or more improvement. They also found that age and duration of the disease did not reliably predict the speech response result replicated recently by Sapir et al (2001) and Skodda et al (2008). This variability in response has since been documented in all levels of speech motor control and overall speech intelligibility. Perhaps the area where medication has more beneficial effect is that of lip movement (Leanderson, 1971, 1972; Nakano, 1973; Caligiuri, 1989). At the laryngeal level, levodopa can have a beneficial effect (Mawdsley, 1971; Jiang et al, 1999; Sanabria, 2001; Galena, 2001; Goberman, 2002). Larson et al (1994) conducted

the most detailed recording study on two patients with drug-related dyskinesias. They recorded voice and EGG signal during two full-day sessions one week apart. During each day, data were collected every hour for 10 consecutive hours. They found no systematic and consistent relationship between drug cycle fluctuations and phonatory measures.

Recently Plowman-Prine (2009) examined drug related fluctuations in speech using the Darley et al (1972) scale (henceforth "DAB scale") and found no significant differences in any speech dimension, despite beneficial effect on movement. De Letter et al (2007a- Clin Neurology and Neurosurgery, and 2007b- Clinical Linguistics and Phonetics) examined the effect of levodopa on respiration (thoracic mobility) and word intelligibility as well as prosody in 10 patients with advanced PD. They found medication results in improvement of thoracic mobility but not normalisation and improvement in intelligibility not correlated to the respiratory change. They also found improvement of variability in pitch and loudness after medication intake, which had a beneficial effect on comprehensibility as scored by four SLTs.

Studies on the effects of apomorphine on speech are limited (Kompoliti, 2000) and they showed that although non-speech motor functions may improve overall speech intelligibility doesn't. It is thus apparent that the effects of medication on speech are not as dramatic as those on movement, despite the symptomatology of tremor, rigidity and akinesia that seemingly affects the oral musculature and the possible alleviation of these symptoms by medical treatment.

1.4.10 Effects of deep brain stimulation on speech in PD

1.4.10.1 Initial studies on electrical stimulation and lesions of deep brain structures and speech

In 1908 Sir Victor Horsley (1857-1914) and Robert Henri Clarke (1850-1926) applied the stereotactic instrument and electricity to study cerebellar structures and functions in monkeys (Horsley & Clarke, 1908). In 1947 Spiegel & Wycis became the first to apply Clarke's idea for human stereotaxis by performing a thalamotomy in a depressed man (Spiegel et al, 1947). Stimulation of deep cerebral structures was used initially to guide lesioning procedures in the early years of surgical treatment of PD. This development of basal ganglia lesioning and then stimulation procedures gave rise to an interest in the role of thalamus and basal ganglia on speech. Very early in the course of stereotactic neurosurgery it was observed that "improvement in speech should not be the prime goal in selecting patients for surgical treatment of parkinsonism. Rather patients should be selected on a basis of the degree of incapacitation due to rigidity and tremor. They should be informed that whereas 70% of patients obtain material alleviation of tremor and rigidity following operation on the globus pallidus, less than 20% experience a similar degree of improvement in speech" (Buck & Cooper, 1956, p 122). Initially the role of the thalamus in speech motor control was explored through stimulation and lesioning procedures. Guiot (Guiot et al, 1961) was the first to describe speech phenomena in the course of stereotactic procedures, in each of the three areas, thalamus, internal capsule and pallidum, traversed by the needle for stimulation, before destroying the selected region. The point stimulated was situated in the ventrolateral nucleus of the thalamus near the thalamocapsular boundary. He described two distinct speech modifications, one was total arrest and the other was speech acceleration, coupled with "progressive weakening of the voice and an enunciation which ends in a kind of incomprehensible jumbling of several figures or the last figure uttered" (p 367). He

hypothesised that diffusion of the current mainly in the internal capsule was the cause of these speech phenomena. He also noted “stimulation by a volley of impulses can excite a number of positive responses which vary according to individual patients and of which the origin may be quite remote from the point stimulated” (p 367). However he also observed that the speech modifications might not be a purely motor phenomenon, but a psychomotor one. Van Buren (1975) and Hassler (Hassler et al, 1960) described similar observations from stimulation in the head of the caudate nucleus, the pallidum and the frontal limb of the internal capsule.

In 1969, Samra and colleagues (Samra et al, 1969) reported their experience from the surgical treatment of 6,000 individuals who underwent thalamic surgery for the relief of parkinsonian tremor and rigidity. They were routinely referred for language and speech evaluations before and after surgery. Speech overall deteriorated in 35% of unilateral and 75% of bilateral surgeries. It was not clear however why some patients developed language and speech difficulties and others did not. The surgical target was the ventrolateral nucleus of the thalamus in all cases. Results from the correlation of the site of the lesion from 27 brains of deceased parkinsonian patients – out of the initial 6,000 – and any language and speech deficit that may have resulted from thalamic surgery showed that partial involvement of the subthalamic nucleus, the red nucleus or even the internal capsule could be tolerated so long as the pyramidal tract remained intact. Language deficits seemed related to left thalamic unilateral surgery but no definite relationship was found between laterality of surgery and motor speech deficits. There was no relationship between the site or size of lesion and postoperative speech deficits. They conclude that “the motor processes associated with “speech” – mainly rate and rhythm of articulation – might be related more directly and exclusively to motor cortex-ventrolateral thalamus modulation than to thalamic influences in general” (pp 538-539).

Bell (1968) on the other hand could not find any relationship between the pre and postoperative speech deficits in PD dysarthria and concluded that the speech deterioration following thalamic surgery is due to lesions in the internal capsule.

Schaltenbrand (1975) summarised his observations from thalamic stimulation using a bipolar electrode on the tip of a stereotactic needle and stimulation of 32 Hz and 8 volts and 10-20 μsec pulse width. He described mainly silencing and slowing of speech with thalamic stimulation, monosyllabic yells and exclamations, some stammering, repetition of syllables and words and "compulsory speech". He concluded that the function of the thalamus cannot be that of initiating speech but of releasing and silencing preformed patterns, therefore of timing and time giving. He warns against the production of large lesions in this area since the effects on speech can be lasting.

In summary, the debate of the role of thalamus in speech production started with the interest of the pioneers of stereotactic neurosurgery on the overall effects of their treatments. The exact role of the thalamus in speech deterioration following surgery for the alleviation of parkinsonian rigidity and tremor was debated due to the variability and high occurrence of speech deficits. The role of and the involvement of the internal capsule in the postoperative speech problems was a topic of debate.

1.4.10.2 Effects of STN-DBS on speech in PD

After the introduction of levodopa in the late 1960's, stereotactic surgery for PD went into a worldwide hibernation (Hariz, 2003). Following the initial satisfactory response to levodopa many patients develop motor fluctuations that are difficult to control. The patients alternate between a state of severe parkinsonism (the "off-medication" period) and a state of improved mobility (the "on-medication" state) when movement is often

impaired by dyskinesias. In 1991, Benabid and colleagues (Benabid et al, 1991) published the long-term results of thalamic DBS with emphasis on its reversibility and adaptability compared to destructive lesions. Thalamic stimulation is effective mainly for tremor and therefore is useful to only a small proportion of people with PD (Limousin et al, 1998). Advances in the knowledge of basal ganglia pathophysiology and neurosurgical procedures have led to the development of high frequency stimulation in the GPi (Siegfried & Lippitz, 1994) and the STN (Limousin et al, 1998; Limousin et al, 1995) as a treatment of choice for the majority of parkinsonian signs.

Studies on the effects of STN-DBS on speech, using clinical scales, have shown a variable response to stimulation (Limousin et al, 1998). Hariz and colleagues (2000) illustrate the barrier speech deterioration can become towards fully utilising the motor benefits from the procedure. They described a patient following one year of STN stimulation and good motor effect, with worsening of pre-operative dysphonia and drooling. They concluded that "improvement in motor function may not be sufficient alone to improve the overall disability of a patient in whom cognitive decline and speech problems are present pre-operatively" (p 138). In recent reports of long-term follow-up, using the UPDRS-III scale, dysarthria has been reported as a common stimulation-induced side effect of STN-DBS with a prevalence ranging from 4% to 17% (Deuschl et al, 2006). Speech is the only function not improved following five years of STN stimulation (Deuschl, 2006; Krack et al, 2003) with some patients reporting unequivocal worsening of speech over time and after surgery, and displaying a progression of speech difficulties that was not modifiable with adjustment of medication and stimulation (Kleiner-Fisman et al, 2004). At six months after bilateral STN-DBS Herzog and colleagues (2003) reported a 4% incidence of speech problems in their results from 48 consecutive patients. At one year, Tir et al (2007) reported a 12%

incidence of speech problems, only for patients with disease duration longer than 12 years. Thobois et al (2002) reports a 5% incidence in 18 patients and Herzog et al (2003) a 6% in 32 patients. Higher incidence is reported by Pahwa et al (2003) with 28%, and Volkmann and colleagues (2001) who noted a 56% incidence of speech problems in 16 patients. Some groups do not report any speech problems following STN-DBS (Jaggi et al, 2004; Romito et al, 2003; Vesper et al, 2002). At three and five years the reported incidence of speech problems tends to increase: Schupbach (2006) reported a 35% incidence at five years of STN-DBS and Gan et al (2007) reported a 52% incidence in 36 patients at three years. The highest incidence is reported by Piboolnurak (2007) with 69.7% (23 patients in 33). Krack et al (2003) and Rodriguez-Oros (2005) reported a progressive deterioration of speech over five years' follow-up, particularly for the on-medication/on-stimulation condition.

However initial reports, using electrophysiological measures of speech, showed a marked improvement of non-speech oral motor tasks with STN-DBS. Gentil and colleagues (Gentil et al, 1999) studied the oral force control of ten selected patients using load sensitive devices to measure the compression forces generated by the upper and lower lip and tongue. STN stimulation improved speech as measured with the UPDRS-III speech item 18, and increased the maximal strength, accuracy and precision of the articulatory organs. The same group reported the beneficial effects of stimulation on acoustical data of 26 PD patients. They found longer duration of sustained vowels, shorter duration of sentences, more variable fundamental frequency in sentences and more stable fundamental frequency in vowels. Relative intensity was unchanged (Gentil et al, 2001, 2003). These studies were on selected patients and selected non-speech motor tasks with no reference to speech intelligibility. They also compare the off- and on-stimulation conditions without reference to the pre-operative state.

Dromey and colleagues (2000) measured the STN stimulation effects on acoustical variables of speech in seven consecutive patients compared to their pre-operative state. They found modest increases in vocal intensity and in fundamental frequency variability in the on-medication condition. They also note the wide variability in speech response, with decline in functional communication in some patients and great disparity between the motor and speech outcomes. Rousseaux and colleagues (Rousseaux et al, 2004) were the first to assess speech intelligibility and compare the results with perceptual indices of voice and articulatory quality in seven patients. They observed reduced intelligibility in the on-stimulation and on-medication condition for two patients who also exhibited increased facial and trunk dyskinesias, whilst the rest remained the same. At a group level the non-significant decrease in speech intelligibility was not associated with oromotor difficulties, or with the pre-operative speech level or surgical parameters.

Pinto and colleagues (Pinto et al, 2005) illustrated this variability in four case studies. Response to STN stimulation varied from improvement with medication and stimulation to deterioration with increased voltage intensity. They also noted that "motor speech subcomponents can improve like other limb motor aspect but that complex coordination of all speech anatomical substrates is not responsive to STN stimulation" (p 1507). They conclude that diffusion of the current outside the target may be responsible for speech deterioration.

Laterality of stimulation and its effects on speech have been investigated. Santens and colleagues (2003) analysed the effects of left and right STN separately on different perceptual aspects of speech in seven patients. All patients reported subjective decrease of the speech intelligibility following bilateral STN stimulation. There was a significant

deterioration of prosody, articulation and intelligibility when stimulating the left STN compared to the right STN alone. Wang and colleagues (2006) investigated the effect of unilateral STN-DBS on speech in 20 PD patients, 10 operated on the left STN and 10 on the right. They presented the results from articulatory accuracy and syllable rate of diadochokinetic tasks. Left STN stimulation decreased articulatory accuracy and speaking rate.

One case report (Burghaus et al, 2006) so far describes a PD patient treated with bilateral STN-DBS and with severe deterioration of his childhood stuttering under effective stimulation. Positron emission tomography (PET) of regional cerebral blood flow (rCBF) in stimulation on and off conditions showed overactivation of cerebral and cerebellar motor systems in line with other studies on brain activation during stuttering. The abnormal rCBF pattern was increased in the stimulation- on condition and was associated with a marked worsening of stuttering.

Klostermann et al (2007) have investigated the effect of STN-DBS on acoustic measures of speech and speech intelligibility in 19 patients on medication and on- and off-stimulation. They conclude that speech intelligibility declines, despite an improvement in glottic tremor, increased sustained phonation time and faster rate of reading. They hypothesise that the discrepancy is due to the nature of the voice measures and the difficulty in measuring prosodic changes of connected speech. This dissociation between improvement in acoustic parameters related to glottal vibration and voice tremor and lack of effect on speech intelligibility is discussed in a study by D'Alatri et al (2008). They assessed 12 selected patients two to five years post bilateral STN-DBS in all medication and stimulation conditions. They analysed sustained phonation, one set sentence for intonation and diadochokinesis for rate control.

Perceptual speech evaluation was conducted using the UPDRS-III speech item. Similarly Putzer at al (2008) studied the effect of STN-DBS in nine consecutive patients on- and off-stimulation with no pre-operative data. They collected EGG (electroglottograph) data together with acoustic recording of syllable repetition /pa/ta/ka/ as fast as possible. They observed a varied response in both the phonation and supraglottal system of speech. No data on speech intelligibility is given.

1.4.10.3 Effects of GPi-DBS on speech in Parkinson's disease

Speech difficulties following GPi-DBS have been infrequently reported. Initially, Gross and colleagues (Gross et al, 1997) reported improvement in speech following one year GPi stimulation in six patients as measured by the Unified Parkinson's Disease Rating Scale-motor part III (Fahn et al, 1987). Ghika and colleagues (Ghika et al, 1998) reported dysarthria as a side effect that was controlled by modulation of stimulation. They do not however give any more details of the nature of this modulation. Lyons et al (2002) reported dysarthria in six out of nine patients. Volkmann et al (2004) followed-up 11 patients with GPi-DBS who did not have a significant speech change after five years of stimulation.

Solomon and colleagues (2000) examined the effects of pallidal stimulation on aerodynamic and intelligibility data. They measured airflow and air pressure during slow syllable repetitions and speech intelligibility before surgery on- and off-medication, and six months and 12 months after. There is a variable response to speech intelligibility. Speech improved in one patient, through the alleviation of painful oromandibular dyskinesias, and deteriorated in the other two. They also concluded that it is laryngeal rather than respiratory dysfunction that contributes to the speech impairment. Maruska and colleagues (2000) described the changes in speech

intelligibility of four patients on- and off-medication and on- and off-stimulation. Stimulation and medication were beneficial to speech intelligibility. Increase of intelligibility was coupled with decreases in the numbers of errors, increases in speaking rate and loudness.

1.4.10.4 Comparison of GPi and STN effects on speech

Krack et al (1998) compared the effects of STN and GPi DBS on speech and reported two out of five GPi patients having speech problems but no STN-DBS patients. Burchiel et al (1999) reported only one out of five STN-DBS patients having transient speech problem. In a multicentre study of bilateral DBS with four-years' follow-up Rodriguez-Oroz and colleagues (2005) report that speech and postural stability showed significant worsening for both the GPi and the STN group, but more commonly for the STN group. Volkman and colleagues (2001) compared one year results of bilateral DBS of the STN and the GPi and found equal improvement in the motor symptoms apart from a significant worsening of speech and swallowing items only in the STN patients (nine out of 16 STN-DBS patients (56.3%). A recent large multicentre study on adverse events following deep brain stimulation (Hariz et al, 2008) compared adverse events following four years of STN versus GPi stimulation. They reported nine out of 49 patients with STN-DBS (18.5%) to have speech problems compared to one out of 20 (5%) with GPi-DBS. Similarly Moro et al (2010) reported the effects of five years of GPi versus STN-DBS and found 10 out of 35 (28.5%) STN patients with speech problems compared to two out of 16 (12%) GPi patients.

1.4.10.5 Treatment of speech problems arising from surgical treatment

Neurosurgeons were strongly involved in earlier studies with peri-operative observations and descriptions of long-term results of their operations on speech. Cooper

(Cooper et al, 1968) founded the multidisciplinary approach to management of surgical patients with emphasis on vocational rehabilitation. The aim of the two-to-four weeks' postoperative rehabilitation was to restore vocational function. Most parkinsonian patients who underwent surgery were given speech therapy. The postoperative techniques were directed towards the difficulties of voice volume. "Since difficulties in volume are paramount we emphasize strengthening of the voice. One of these methods is essentially a "boosting" technique and involves various means of using the entire body to support the tone of voice" (p 1215). In order to ensure generalisation, family and friends of the patient are "instructed not to respond to the patient unless he speaks with sufficient volume. This is sometimes a tedious and frustrating task but experience has shown that only constant attention to his own voice and constant awareness of his difficulties can produce the desired results." The programme involves techniques for rate control through reading and singing, but mainly free conversation in groups of six to eight and individual sessions. The intensity and the voice focus of these techniques remind one of the Lee Silverman Voice Treatment (LSVT) (Ramig et al, 2001). There are no recent studies on the treatment of speech problems following bilateral STN-DBS (see also Chapter 6).

1.5 Dystonia

Dystonia has been defined as a "syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures" (Fahn at al, 1998).

It is characterised by excessive movement which leads to involuntary movements and abnormal postures. Depending on the affected body site dystonia may affect speech musculature and motor speech production. Oppenheim first used the term dystonia in 1911 when he described a childhood-onset syndrome that he called dystonia musculorum deformans. Almost a century later, many different types of dystonia are

been described and the classification is continuously updated. Although a detailed discussion of the numerous forms and types of dystonia goes beyond the scope of this chapter, a description of the types that can affect speech in a direct or indirect way will be attempted.

1.5.1 Definition and classification

Marsden and his colleagues (1976), based on clustered clinical phenomenology, described three basic approaches to classification: age at onset, body regions or distribution affected and etiology.

They stressed that the age at onset is the single most important feature in determining outcome. The earlier the age at onset the more likely symptoms will be severe, with dystonia spreading to involve multiple regions. In terms of speech muscles early-onset dystonia (onset before 26 years of age as described by Jarman et al, 1998) usually first involves a leg or arm and less commonly starts with the neck or vocal folds (Hallett, 1998). Conversely, late-onset (onset after 26 years of age) primary dystonia commonly affects the neck or cranial muscles and less frequently involves an arm at onset. It also tends to remain localised as focal or segmental dystonia.

In terms of distribution, focal dystonia tends to involve a single body area, frequently affecting motor speech production: blepharospasm (upper face), oromandibular (jaw opening or jaw closing), vocal cords (spasmodic dysphonia) and neck area (spasmodic torticollis).

In segmental dystonia two or more continuous areas are affected, namely cranial (face, jaw, tongue and vocal cords), cranial and cervical, or axial (neck and trunk). In multifocal two or more non-contiguous regions are involved either as hemidystonia (ipsilateral arm and leg) or as generalised, when it affects both legs and trunk and at least one more region (Bressman, 2004). However, establishing discrete groups for age at onset and affected body distributions cannot fully reflect the complex relationship between muscles involved at onset and spread of symptoms and cause (Greene, 1995).

1.5.2 Pathophysiology of dystonia and implications for speech

Historically the causes of dystonia have been divided into two main groups: idiopathic (or primary) and symptomatic (or secondary) (Fahn, 1998).

Primary dystonia includes early onset dystonia with onset in a limb and a tendency to generalise, and late-onset dystonia which most commonly occurs in focal (blepharospasm, oromandibular dystonia, cervical dystonia, laryngeal dystonia and arm dystonia) or segmental forms. Primary dystonia is the most common cause of dystonia with prevalence estimates from two to 50 cases per million for early onset and from 30 to 7,320 per million for late onset dystonia (Defazio et al, 2004). Primary dystonia is thought to be partly genetic in origin, mainly because of its aggregation within certain families and the identification of specific genetic loci. Ozelius (2004) reports at least 13 different loci identified for various forms of inherited dystonia. DYT1 was the first gene mapped. Focal dystonias, most commonly cranial and cervical dystonia, can affect the most commonly performed, automatic and unconscious motor acts – blinking, mimicking, voice performing, speaking, turning or tilting of the head.

Possible underlying mechanisms of these multiple motor abnormalities have implications both for interpreting the clinical presentation and for treatment planning. Basal ganglia are involved in the control of surround inhibition as evidenced by studies on bradykinesia and dystonia. Yoshida et al (2003) in a study in patients with oromandibular dystonia showed that novel and unfamiliar lateral jaw movements strongly reduce movement related potentials in central and parietal areas compared to normal subjects, whereas familiar mouth closing movements do not. They thus suggest that execution of familiar movement in the cranial area (for muscles involved in speech and mastication) might predominantly involve subcortical mechanisms.

Basal ganglia have been involved in sensorimotor integration, the continuous modulation of motor tasks based on on-line sensory input. For patients with cranial and cervical dystonia the most striking evidence of impaired sensorimotor integration is the use of the “sensory trick” (or geste antagoniste). Sensory tricks can be observed in up to 70% of patients with cervical dystonia (Deuschl et al, 1992). It is defined as a tactile or proprioceptive sensory input applied to a nearby body part which improves the abnormal posture. Although traditional opinion regarded the “sensory trick” as a sort of psychological manoeuvre to distract attention, later physiological and PET studies showed that it could actually modify EMG recruitment (Schramm et al, 2004) by inducing a perceptual dysbalance between primary and secondary motor and sensory areas (Naumann et al, 2000).

1.5 3 Speech disorders associated with primary and secondary dystonia

1.5.3.1 Primary dystonia and speech

The typical features associated with DYT1 dystonia are early limb onset and spread to the trunk, which rarely affects craniofacial muscles (Jarman, 1999).

The clinical presentation of the DYT6 locus is mixed with an early age of onset and progression to involve multiple body regions, mainly orofacial (Ozelius, 2004). DYT13 is also characterised by prominent cervical-cranial and upper limp involvement with early onset, similar to the DYT6 dystonia but with less significant laryngeal and leg involvement.

Adult onset primary dystonia usually remains focal or spreads only to one contiguous body region. In a meta-analysis of published studies to date O'Riordan and colleagues (2004) investigated age as the single factor in determining the phenotype of primary dystonia. They report that in a total of 13 studies on spasmodic dysphonia the mean age at onset was 43 years, compared to 55 years for the 21 studies on blepharospasm/oromandibular dystonia. They thus concluded that with increasing age there is a caudal-to-rostral shift of the site of onset in the order: leg-onset dystonia, writer's cramp, cervical dystonia, spasmodic dysphonia and blepharospasm/oromandibular dystonia. The authors speculate that this spread of symptoms from the limbs to the face area may reflect a somatotropic organisation of the putamen.

Cervical dystonia, also known as spasmodic torticollis, is the most common focal dystonia (Defazio, 2004). It usually begins between the ages of 30 and 50 years, often with initial neck stiffness and restricted head mobility. Abnormal head postures follow,

sometimes associated with head tremor, neck and shoulder pain. Speech can be affected at a later stage, and swallowing abnormalities at the pharyngeal level can also occur.

Blepharospasm, a focal dystonia whose main feature is involuntary eye closure, is the most common cranial dystonia. Symptoms usually begin with excess eye blinking and sore eyes and develop into periods of complete eye closure that can be triggered by bright light, reading, watching TV or stressful situations. Suppression of unwanted eye closure is possible in some patients by touching the periorbital area or some other points of the face (Valls-Sole & Montero, 2004). Blepharospasm may be accompanied by oromandibular dystonia (OMD), in which case the condition is referred to as Meige's syndrome.

OMD can also occur as an adverse effect of chronic administration of certain drugs, known as tardive dystonia, or as an accompanied manifestation of neurodegenerative disease or focal or brainstem lesions (Tolosa, 1988). The most common form of presentation of OMD is that of an adult with idiopathic focal dystonia. The patients show bizarre, irregular, somewhat chaotic movements of the jaw, lips, platysma and sometimes tongue. These disturbed perioral movements can interfere with basic functions, such as chewing and swallowing as well as speech, with the consequence of social embarrassment. Yoshida et al (2002) studied 44 patients with OMD and the effect of local injection of ethanol and lidocaine. They distinguished four groups, according to the pattern of incisal movement and involuntary contraction: spastic group, in which the patients showed spastic contraction but no remarkable movement, rhythmic group in which the patients showed rhythmic or involuntarily repeated muscle contractions, dyskinetic group in which the patients showed oral dyskinesia or hyperkinetic jaw movement and task-specific group in which the involuntary contraction appeared only

at the time of speech or mastication, with no symptoms at rest. Difficulty in speech was the major complaint, followed by tenderness and pain of muscle. Difficulty in swallowing and communicating are the main factors influencing quality of life in OMD patients (Bhattacharyya & Tatsy, 2001). Dystonia is rarely life-threatening; however there have been reports of respiratory failure due to involvement of the larynx (Hamzei et al, 2003). The pathophysiology of OMD is still unknown and despite the wealth of studies on blepharospasm there is a paucity of studies on OMD.

1.5.3.2 Secondary dystonia and speech

Secondary dystonia is a large and diverse group of disorders with many causes, including acquired brain lesions, heredodegenerative disorders and drug-induced dystonia. Speech and swallowing mechanism can be affected to a greater or lesser degree depending on the site of the lesion and the age of onset. From the heredodegenerative disorders the ones involving speech are Huntington's disease, Wilson's disease and Pantothenate kinase-associated neurodegeneration, formerly known as Hallervorden-Spatz syndrome. Primary Focal Lingual Dystonia is a rare form of focal dystonia affecting the tongue muscles and induced by speaking. There have been four cases reported in the literature so far: two with tongue protrusion and two with tongue retraction, all induced by speaking and with symptoms not present during mastication and swallowing. These cases all responded well to anticholinergic therapy and sensory tricks (Papapetropoulos & Singer, 2005; Baik et al, 2004).

1.5.4 Examination findings

1.5.4.1 Non-speech oral mechanism

In terms of non-speech oral mechanism, examination can show normal strength, size and symmetry at rest, with dystonic movements triggered only by speech (Duffy, 2005). Blepharospasm and temporomandibular movements may be present intermittently. The main non-speech oromotor examination finding is slow and sustained co-contractions of the muscles of the lips, jaw, mouth-tongue and neck and respiratory muscles that can interfere with voluntary control of movement and presentation at rest. Use of sensory tricks are common, mainly use of a pipe, or a stick for mouth-closing dystonia and pressure or light touch at the jaw or neck.

1.5.4.2 Examination findings: speech

Two main studies summarize observations from dystonic speech examination, namely the Darley et al (1975) and Golper et al (1983). Depending on the pathophysiology and main presentation of dystonia, nearly all aspects of movement during speech can be disturbed. Dystonic movements may alter direction and rhythm of movement with generally slow rate and impact on precision. Fatigue is another factor influencing repetitive movements.

The most prominent feature of the dysarthria in dystonia is the variable presentation of deviant speech characteristics, both between patients and within the same patient with dystonia. This variability is more prevalent in the phonatory and articulatory subcomponents of speech. Speakers often try to compensate or avoid the involuntary co-contraction of a neck-facial muscle which results in irregular, slower rate speech with imprecise consonants, unexpected pauses and disordered prosody of speech.

More specifically, phonation may be affected depending on the degree of cervical dystonia and spasmodic dysphonia. Harsh or strained and strangled voice quality with excess loudness variations and voice stoppages are often observed (Duffy, 2005). These difficulties lead to short phrases with occasional audible inspiration, probably due to involuntary vocal fold adduction during inhalation. This is a feature rarely encountered in other dysarthria types (Darley et al 1975). In the most detailed study of speech in people with cervical dystonia La Pointe et al (1994) report reduced intelligibility despite the overall impression of "functional and intelligible speech even if subtly different along some parameters". In general speech in people with cervical dystonia may be perceived as slowly initiated, with short phrases, reduced pitch variability and reduced in rate.

Articulation is particularly affected in patients with OMD, with or without blepharospasm. Imprecise consonants and distorted vowels are the effect of involuntary jaw, lips and tongue movements and of various efforts to compensate. Patients with predominantly jaw-opening dystonia present with more sensory tricks and spread of symptoms in different regions than those with predominantly jaw-closing dystonia (Singer et al, 2006). The combination of articulatory and phonatory distortions leads to prosodic disorders and the overall impression of slow and effortful speech.

1.5.4.3 Investigating speech in patients with dystonia

The variability in the clinical presentation of speech in dystonia and the dynamic nature of its progression warrant multiple sources of information gathering. Duffy (2005) stresses the importance of "careful visual observation of the patient during speaking",
in order to describe the speech difficulties at every level and the likely triggers of co-contractions and sensory tricks. Videotaping can facilitate observations of movements

of the trunk and neck, especially when their influence on speech may not be immediately obvious. It also serves as a record of changes through time in the disease process and the treatment effects.

Due to the variable presentation of respiratory-phonatory-articulatory features of speech in dystonia there is no expected acoustic and perceptual profile with very few studies of limited and diverse population. Respiratory dynamics in six patients with generalized dystonia have been investigated by LaBlanche & Rutherford (1991) using respiratory inductive plethysmography to assess breathing rate, periodicity of the breathing pattern and inspiratory lung volume. They found faster breathing rate, less rhythmic breathing pattern and decreased lung volume. LaPointe et al (1994) in their study of 70 patients with cervical dystonia found reduced speech DDK rates, reduced maximum phonation reduced phonation reaction time and reduced pitch variability.

In terms of observational scales Yoshida et al (2002) use a 4-point rating scale for OMD for mastication, speech, pain and discomfort. The speech subcomponent ranges from inaudible (over 50%) to normal. Equally, the most widely used scale for dystonia Fahn-Marsden rating scale (Burke et al, 1985) groups together in one item (SS) both swallowing and different speech abnormalities (spasmodic dysphonia and dysarthria) which limits its sensitivity and specificity.

There is a need for more descriptive data following medical or surgical interventions in order to appreciate the changes and to maximise the benefits of such procedures.

1.5.5 Treatment of communication disorders in dystonia

Dystonia can affect muscles of the face, neck and trunk areas and consequently affect communication and swallowing. Depending on the affected body site dystonia may affect speech musculature and motor speech production. The face is a very active part of the body involved in many spontaneous movements such as blinking, swallowing and expression of emotions.

Treatment of communication disorders of people with dystonia can be a challenge for the speech clinician not only due to the wide variability of the disease presentation, the sometimes unpredictable progression to other body parts, and the effect of environmental factors on the dystonia but also the effect of other medical and surgical treatments on the disease.

Timing of intervention largely depends on diagnosis and referral to the speech clinician rather than evidence. Medical and surgical treatments throughout the disease course can also be a significant factor on communication intervention. Speech management could be deferred until after the planned intervention, but often the provision of an Augmentative and Alternative Communication Aid can facilitate the treatment process and decision making.

Dystonic symptoms can vary depending on environmental and personal factors such as anxiety, pain, fatigue and stress, all of which can exacerbate the symptoms of dystonia. The general principle of every communication intervention of considering the environment and the people where communication takes place applies to treatment of dystonia. Family, employment and social support can be positive factors in any intervention.

1.5.5.1 Behavioural management

The role of the speech clinician when working with patients with dystonia is to observe and describe as accurately as possible the changes induced by the treatment in the whole body. This is best achieved by videotaping before and after intervention. Speech being so variable in different dystonia types, it requires a multitude of speech and non-speech tasks. Subjective accounts of change are also valuable. The aim of any communication intervention should be to maximise the benefit of the procedure for communication.

When working with OMD and lingual dystonia the speech clinician needs to consider the fact that these focal dystonias are usually task-specific. The abnormal, involuntary and sustained co-contractions of the facial, jaw and tongue muscles occur when the patient wants to speak and/or chew and swallow. Breathing and voice can also be affected, with tight and strained phonation or some vocalisation. It is thus very difficult to apply a set of drills or repetitive exercises of non-speech motor tasks in the hope of generalising into speech. Additionally writing can be impaired especially in cases of primary generalised dystonia with early onset and limb progression.

Disease progression usually means deterioration of function. Patients have to adapt to a continually changing and unpredictably moving body. Because of the variable effect of pharmacological and surgical function and the effects of correct posture and sitting, working in a multidisciplinary setting is paramount for maximum effect in dystonia intervention.

Dwarkin (1996) investigated the impact of a bite block or other acceptable object in the mouth to limit the involuntary movements during speech, which had a resultant improvement in articulation and intelligibility (Dwarkin et al, 1996).

Equally sensory tricks for oromandibular dystonia, blepharospasm and other facial dystonia can inhibit involuntary movements and facilitate speech. It is worth exploring different sensory tricks with patients who haven't discovered their own. Another area with very limited evidence (Duffy, 2005) is the use of EMG biofeedback for the treatment of orofacial dystonia.

McGuire et al (1988) report on the rehabilitation of three patients with "dystonia musculorum deformans". Communication work consisted of maximising their hand function for use of a communication board. They stress the need for a total team approach.

Similarly Shahar et al (1987) report on the rehabilitation of communication impairment of three patients with dystonia using Augmentative and Alternative Communication (AAC). It is also stressed that every AAC method requires support and training of the family/social setting and a relaxing environment.

1.5.5.2 Pharmacological treatment in dystonia and effects on speech

The symptomatic treatment of dystonia has markedly improved, particularly since the introduction of Botulinum Toxin. Many patients with dystonia require a combination of several medications and treatments. Thus anticholinergic therapy has been found to be useful in the treatment of generalised and segmental dystonia (Greene et al, 1988). Oral

Baclofen may be helpful in the treatment of OMD (Jankovic, 2004). Intrathecal Baclofen can be used in cervical and truncal dystonia.

Botulinum Toxin has been a major advance in the treatment of dystonia.
It was first introduced in 1981 by Scott to correct strabismus and he later began using it for blepharospasm. It acts presynaptically at peripheral nerve terminals to prevent calcium-dependent release of acetylcholine (Fahn & Marsden, 1998) and thus weakening the hyperactive muscle fibres involved in the involuntary movement.
It is useful in the treatment of focal dystonias, cranial and cervical. Numerous reports have shown the efficacy of Botulinum Toxin in treating dystonia (and it can be regarded as a first line of treatment for primary cranial (but not oromandibular) or cervical dystonia, (Albanese, 2006). OMD is the most challenging of the focal dystonias to treat with Botulinum Toxin, which can possibly complicate swallowing problems. The masseter muscles are injected in patients with jaw-closing dystonia and the lateral pterygoid or submental muscles which can occasionally cause rhinolalia or nasal regurgitation (Yoshida et al, 2002). These are groups of muscles directly involved in mastication. In cases of OMD that do not respond to Botulinum Toxin, either due to antibodies or weakness of the muscles, Yoshida et al (2003) have reported a method of blocking muscle afferents using a local injection of lidocaine and ethanol. They reported significant improvement in patients with the spastic type of OMD but not those with the hyperkinetic/dyskinetic type. Complications include tenderness, stiffness or swelling of the injected muscle, limited mouth opening and dysphagia.

Similarly patients with cervical dystonia can expect improvement in function of their head and neck movements and pain. However there have been only a few longitudinal studies of Botulinum Toxin injections in cervical dystonia (Jankovic, 2004 as reported

in Duffy 2005). Patients with longstanding dystonia have been found to respond less than those treated relatively early in their disease process. Complications such as swallowing problems and neck weakness are probably related to local spread of activity into adjacent muscles.

The response of lingual dystonia to Botulinum Toxin is more variable, with a high risk of dysphagia (up to 50%) and aspiration pneumonia. The tongue is solely composed of muscle and thus plays an important and delicate role in chewing, speaking and swallowing. Therefore it is hard to control the task-specific dystonic muscle contraction of tongue by local injections of Botulinum Toxin.

Spasmodic dysphonia is a primary task specific focal dysphonia affecting the laryngeal muscles during speech (Ludlow C, 2009). Adductor spasmodic dysphonia (ADSD) affects close to 90% of spasmodic dysphonia patients and it is characterised by voice breaks during vowels during speech due to intermittent hyperadduction of the vocla folds (Parnes et al, 1978). Abductor spasmodic dysphonia (ABSD) is relatively rare and involves intermittent voiceless voice breaks due to prolonged voiceless consonants before initiation of the following vowel (Edgar et al, 2001). Treatment of spasmodic dysphonia with botulinum toxin has been the subject of two evidence-based reviews: Watts and colleagues (2008) concluded that botulinum toxin injection is an effective treatment for spasmodic dysphonia. However, Simpson and colleagues (2008) concluded that botulinum toxin injection is probably effective for the treatment of ADSD but that there is insufficient evidence for the use of botulinum toxin injection for ABSD.

In summary, pharmacological therapy in focal dystonia is centred on Botulinum Toxin. Swallowing problems can arise as a complication of injections in the cranial and cervical muscles treated. A thorough assessment before and after treatment, preferably with videotaping, can assist the speech clinician in measuring change and maximising the benefit from the treatment. Advice and careful monitoring of swallowing and speech complications following treatment is warranted.

1.5.5.3 Surgical treatment

Peripheral denervation therapy and Botulinum Toxin injections cannot be used to treat segmental and generalised dystonias because of the greater number of muscles involved. Bilateral stereotactic Deep Brain Stimulation of the Globus Pallidus internum (GPi-DBS) is most commonly performed.

Victor Horsley in 1909 was the first to carry out ablative lesions of brain tissue in an attempt to treat hyperkinetic disorders. He excised the motor cortex in a boy with hemi-athetosis, dramatically relieving the involuntary movements. This work was a milestone in understanding motor physiology and anatomy. Stereotactic surgery in animals was developed around the same period by Horsley & Clark. Several decades after (1946) Spiegel and his colleagues were the first to apply the principles of stereotactic surgery to humans. Cooper (1969) then developed the idea of carrying out chemopalidectomies in patients with dystonia based on the observation that a relief of a fixed dystonic flexion of a Parkinson's disease patient can improve with stereotactic lesions of the pallidum. He operated on approximately 226 and he reported some benefit in 70% of his patients. He agreed that this type of surgery is more effective for limb dystonia than axial dystonia and that dysarthria occurred in 11% of patients with unilateral lesions and

56% of bilateral lesions. Dysphonia has been reported to occur in 18% of cases by Cooper and 33% of cases by Ojemann (1982).

The first GPi-DBS for dystonia was attempted in 1996 by Coubes (2004) for an eight-year old girl, based on the established efficacy of the technique for the treatment of levodopa-induced dyskinesia in patients with Parkinson's disease. In 2004, Coubes reported the results of 31 patients with primary torsion dystonia bilaterally implanted in the GPi with improvement of 79±19%. Children displayed greater improvement in clinical scores than adult patients.

However although limb and trunk dystonia is improved by DBS the benefit on speech intelligibility is more critical and less predictable (Vidailhet & Pollak, 2005b). These differential effects of neurostimulation should be considered when selecting patients for surgery. Speech may not be directly affected by GPi-DBS but improvement of other involuntary movements mainly of the trunk for breathing control and of limbs may provide more flexibility in the choice of communication modality. For patients with anarthria due to severe dystonia the option of a communication aid using their improved hand function or head control is a significant gain to their quality of life. Additionally frequent reassessments of overall function and possibilities of augmenting communication are warranted following GPi-DBS due to the observed progressive improvement of the dystonia, following more than two years after surgery.

1.5.5.3.1 Primary generalised dystonia

Two large studies have confirmed the beneficial effect of GPi-DBS for patients with primary generalised dystonia: Vidailhet et al (2005b) studied 22 patients and found a 54% improvement at the BFM movement score and a 44% at the BFM disability score

at 12 months with chronic stimulation relative to baseline. Motor improvement occurred in most segments of the body (neck, trunk and limbs) with the exception of facial movement and speech, which remained unchanged. This improvement was maintained at 36 months (Vidailhet et al, 2007). In 2006, Kupsch et al reported the results from a randomised control trial in primary dystonia, with 40 patients, comparing 20 who received sham stimulation (off-stimulation) with 20 who received stimulation, at three months, and then the whole group versus baseline at six months. At three months, stimulation led to an improvement of 39% in movement and 38% in disability, both superior to the ones from sham stimulation. Speech and swallowing was the only item in the BFM scale that didn't change significantly. Dysarthria was the most common adverse event occurring in five patients (12%) and manifesting as slurred but understandable speech. The most beneficial results with pallidal DBS were reported in children with DYT-1 positive generalised dystonia. Coubes et al (2000) described a mean 90% improvement in the BFM motor scores at one year follow-up (also Cif et al, 2003; Tisch et al, 2007). Tisch et al reported the development of delayed-onset akinesia with gait slowing, difficulty rising from chair and turning in bed in two out of 15 DYT-1 positive patients. In terms of speech, Isaias (2009) reported the long-term effects (up to four years) of 30 consecutive patients with speech and swallowing abnormalities being the least responsive to DBS and with one-quarter of symptomatic patients showing no improvement or worsening. They commented that this might be due to the inadequacy of the BFMDRS scale which lumps together in one item (SS) both swallowing and different speech abnormalities (spasmodic dysphonia and dysarthria). "the SS symptoms should be further evaluated in dedicated studies" (p 469). Allert et al (2010) have recently reported a case of a patient with generalised dystonia, and Vim DBS mainly to treat dystonic tremor who developed reversible stuttering following the replacement of the battery. The fluency disorder disappeared after adjustments.

1.5.5.3.2 Cervical dystonia

Idiopathic cranial-cervical dystonia (CD) is an adult-onset segmental dystonia affecting orbicularis oris, facial, oromandibular and cervical musculature (Ostrem et al, 2007). It is the most frequent dystonic movement disorder, hence DBS may be of special interest in this group. Bilateral pallidal stimulation produces both symptomatic and functional improvement including marked long-term relief of pain in patients with complex CD (Krauss, 1999, 2002). Krauss et al (2002) reported a gradual improvement of CD over time as reported on the modified Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) of 63%, and 69% improvement in the disability score and 50% improvement in the pain score. Similarly Yianni et al (2003) reported similar amelioration for severity (64%), disability (60%) at 19 months follow-up. Kiss et al (2007) reported the results from the Canadian multicentre study in 10 patients with severe cervical dystonia using the Toronto Western Spasmodic Torticollis Rating Scale (TWISTRS). They reported 43% improvement over one year of stimulation and 59% in disability scores. The reported that two patients had mild difficulties with swallowing and two patients had mild improvement but they do not discuss any details. Ostrem et al (2007) were the first to report worsening in non-dystonic body regions with stimulation in four out of their six CD patients treated with bilateral GPi-DBS. Speech and swallowing were the only subscores of the BFMDRS that did not improve significantly. The same group recently reported induction of bradykinesia in 10 out of 11 CD patients, despite of significant improvement in dystonia. They used a questionnaire to rate changes in various upper and lower limb motor activities e.g. handwriting, dressing, walking, buttoning shirts and they correlated with lead placement. They found no correlation with leads nearer the internal capsule. Furthermore patients who received most benefit from the treatment tended to have more difficulty with stimulation-induced

bradykinesia, indicating a common neural circuit mediating the antidystonic effect rather than a spread to neighbouring structures. In terms of speech there are two case reports in the literature so far suggesting the induction of dysarthria and dysfluency: Nebel (2009) reported on two patients, one with DYT-1 positive and one with CD both of which developed stuttering after GPi-DBS under conditions that optimally suppressed the dystonic symptoms, which suggests a shared neural control pathway. The description of speech difficulties in Case 2 (DYT-1) resembles hypokinetic-parkinsonian speech more so than stuttering ("dysarthria was characterised by a very soft voice, imprecise articulation, and very small amplitudes of articulatory movements. His fluency was disturbed by blocks, iterations and intermittent rushes of unintelligible utterances. By using a pacing board he could slow down his speech, increase speech volume and improve intelligibility" p 168). A recent case study of hypophonia amongst other parkinsonian symptoms was reported by Zauber et al, (2009), in a patient with craniocervical dystonia. There have been no reports of electrical parameters and their effects on speech/hypophonia in relation to CD and GPi-DBS (Moro et al, 2009).

1.5.5.3.3 Oromandibular/orofacial

Woerhrle (2009) et al published their results on 14 consecutive patients with segmental dystonia, 12 primary, with segmental dystonia affecting larynx, oromandibular and cervical muscles. They reported a mean relative improvement of 57% with the effect of DBS being more pronounced for the extremities and less pronounced in axial and facial regions. They also report that dysarthria was limiting the therapeutic voltage amplitude in four patients.

However despite the improvement in segmental dystonia, it is not clear which parts of the facial musculature improve most and what is the functional impact on speech and

swallowing. A long-term follow-up of 11 segmental dystonia patients (Sensi et al, 2009) shows that dysarthria can still be a stimulation-related side effect despite overall improvement in the orofacial dystonia. They report that there was a delayed positive effect on speech at three year follow-up "of around 60% that was more evident in the most anarthric patients where language was not intelligible". So the controversy between improvement in segmental dystonia involving head and face and possible stimulation-related deterioration of speech points towards a threshold of stimulation above which dysarthria is a side effect and below which dystonia is not well controlled. This threshold and any predictive factors associated are worth investigating.

1.5.5.3.4 Secondary dystonia

DBS for the treatment of secondary dystonia appears to be much more complex than that of primary dystonia. Vidailhet et al (2009) have recently reported on the treatment of cerebral palsy (CP). The dystonia-choreoathetosis forms of CP with basal ganglia dysfunction are mainly due to neonatal hypoxic ischaemic encephalopathy in term or near term infants (Bax et al, JAMA, 2006). The group conducted a multicentre prospective pilot study in 13 adults with dystonia-choroathetosis CP improvement in the BFMDRS scale of 24% as well as improvement in functional disability and pain. They do note however the inherent difficulties of this population, namely the heterogeneity due to the injury in a developing brain and the complex movement disorder.

CHAPTER 2: GENERAL METHODS

2.1 Participants

The work presented in this thesis is derived from a consecutive series of 54 PD patients and 25 dystonia patients, who were all studied clinically before and after deep brain stimulation surgery.

2.1.1 PD patients

For the first 32 consecutive PD patients data were collected before, one month, six months, one year and three years (N=15) after the operation. For the following 22 patients data were collected before and one year after the operation (total of 54 PD patients with before-one year post data). A group of 12 non-operated PD patients, randomised for medical treatment as part of a larger study (PD-SURG) were also studied as control participants to the surgical PD group. A subgroup of the PD patients underwent further studies, using aerodynamic recordings (N=12) and electropalatography (N=2).

2.1.2 Dystonia patients

Twenty five patients with dystonia were assessed before and 12 months after bilateral GPi-DBS. The aetiology of dystonia was as follows: eleven were primary generalised (six DYT-1 positive, five DYT-1 negative), seven were cervical/cranial dystonia, two myoclonic dystonia, one tardivedystonia plus Tourette's, one hemidystonia, two dystonia following stroke and one dystonia following a post-anoxic episode. Data for the dystonia patients were collected before and one year after surgery.

The description of the participants included in each study is outlined in the methods section of each chapter. All participants gave written informed consent and the studies were approved by the joint Ethics Research Committee of the National Hospital for Neurology and Neurosurgery, and the Institute of Neurology.

2.2 Surgical procedure

2.2.1 Bilateral STN-DBS for PD patients

Surgery was usually performed under local anaesthesia, in the off-medication condition, to allow clinical evaluation during electrode placement. If the patient was unable to tolerate prolonged periods off-medication, surgery was performed under general anaesthesia (N=7). The STN was visualised in each patient using specifically selected pre-operative stereotactic MRI sequences (Ashkan et al, 2007; Hariz et al, 2003) following attachment of a Leksell frame (Elekta Instrument AB, Stockholm, Sweden). Our standard technique is that two experienced neurosurgeons independently select the optimal target within the STN and then compare co-ordinates that are calculated both manually on enlarged film copies, and using commercially available planning software (FrameLink, Medtronic, Minneapolis). This is performed to ensure that optimal target selection is reviewed in detail for every patient and the possibility of human error or miscalculation is minimised. A trajectory was calculated during planning to avoid sulci and the ventricular system as this has been shown to reduce complications and improve targeting accuracy (Elias et al, 2009; Zrinzo et al, 2009). In addition, the trajectory was modified to maximise the number of quadripolar electrode contacts within the three-dimensional structure of the nucleus. Impedance monitoring was performed while introducing a 1.5 or 2.2 mm blunt-tip radiofrequency (RF) electrode to the target (Leksell RF electrodes, Elekta, Stockholm). After withdrawal of the RF electrode, a quadripolar DBS electrode (Model 3389 DBS lead, Medtronic®, Minneapolis) was

soft-passed down the same track. In those patients undergoing surgery under local anaesthesia, symptoms were assessed for the presence of a micro-lesion introduction effect. Monopolar stimulation through the contacts of the DBS electrode was then sequentially performed to assess for additional therapeutic effect and/or the presence of side effects such as dysarthria, oculomotor, sensory or capsular responses (~10 minutes per side).

Immediately following implantation of the DBS leads, all patients had a stereotactic MRI scan with the frame still on the head to confirm the electrode positions before implantation of the pulse generator. The perpendicular scalar (Euclidean) distance between the intended MRI target and the actual position of the implanted electrode was calculated on the post-operative MRI for each patient.

2.2.2 Bilateral GPi-DBS for dystonia patients

The surgery for dystonia patients is carried out under general anaesthesia following the MRI guided technique described above (2.A). By convention the electrode for the right hemibody (left brain) is connected to channel 1 (contacts 0, 1, 2, 3) and the left hemibody (right brain) to channel 2 (contacts 4, 5, 6, 7).

2.3 Clinical evaluation

2.3.1 Study design: prospective longitudinal assessment

In all patients clinical evaluations were performed before and serially after surgery: postoperative evaluations were undertaken at the following time points: one month, six months, one year and three years. The clinical scoring of motor symptoms was carried out by a neurologist. The collection of the speech data was performed by the author.

The clinical scoring of speech intelligibility was carried out by a trained SLT, native speaker, independent of the study according to the instructions of the speech intelligibility assessment (see methods below) and as directed by the author. The acoustical analysis of the speech samples was carried out by the author. The aerodynamic data were analysed by the author. The Electropalatography (EPG) analysis was carried out jointly by Dr M. Hartinger and the author, under the guidance of Prof W. Hardcastle at Edinburgh University.

2.3.2 Clinical scoring of motor symptoms for dystonia: Burke-Fahn-Marsden dystonia rating scale (BFM)

The BFM was used for the evaluation of motor symptoms of the dystonia patients (Burke et al, 1985). The BFM is divided into two parts, the movement scale and the disability scale. 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 to 4) and a severity factor (0 to 4), multiplied by a weighing factor, where zero represents no dystonia. The provoking factor ranges from dystonia present with a 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 weighing factor for eye, mouth and neck regions is 0.5 reflecting their lesser impact on disability and 1 for the 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 to 4) except walking which is (0 to 6). 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). It has however been criticised for having a single item dedicated to both speech and swallowing, which may not reflect accurately the effects of various treatments of dystonic movements associated with speech and swallowing.

2.3.3 Clinical scoring of motor symptoms for PD: Unified Parkinson's Disease Rating

The UPDRS is the most widely used scale for measuring symptoms and signs of patients with PD in clinical practice (Siderowf et al, 2002). The UPDRS consists of 42 items in four sections assessing (I) mentation and mood (4 items), (II) activities of daily living based on historical information (13 items), (III) motor function based on clinical examination (14 items) and (IV) complications in patients on dopaminergic therapy based on historical information (11 items). Each of the 14 items of the motor part (III) is given a rate between 0 – no abnormality and 4 – severe abnormality. Some of the items (symptoms) are rated for the different body parts, for example tremor at rest (item 20) is rated for the head and neck, right and left upper and lower limbs respectively. As a consequence, the maximum score (all items rated as severe) is 108. Maximum points for the different parkinsonian symptoms are as follows: speech (4), facial expression (4), tremor (28), rigidity (20), akinesia (32), axial symptoms and gait (20). High internal consistency (Martinez-Martin et al, 1994), inter-rater reliability (Richards et al, 1994) and test-retest reliability (Siderowf, 2002) have been shown for the part III UPDRS, not though for the speech and facial expression item (Richards, 1994).

2.4 Speech recording set up

The speech lab at the Unit of Functional Neurosurgery was set up according to the guidelines of the National centre for Voice and speech. The room was sound-treated and the ambient noise of no more than 50 dB at the centre of the room. All efforts were made to minimise noise from the computers, and the room does not have air

conditioning or other source of noise (according to Titze, (1995, p 29); given that 120 Hz is very close to the average normal male speaking F_0 special care should be given to the removal of noise sources in the room that create a 60 Hz hum and its associated harmonics). The equipment comprised:

- a Shure SM48 unidirectional dynamic microphone with a wide frequency response of 55 to 14,000 Hz
- The Computerised Speech Lab (CSL), Kay Pentax 4150, with its recording software
- A B&K class I Sound Level Meter (SLM), model 2100, calibrated
- A Sony HD camcorder and a tripod
- Chair without wheels and no arms
- A DAT machine for recordings outside the speech lab
- The Aerophone II, Kay Pentax for aerodynamic recordings
- EPG software for analysis of EPG data (not acquisition) and the dongle
- Backup of all files though the back up system of Sobell department.

2.4.1. Set-up and computerised acquisition

The recordings of all speech samples were made according to the recommendations from the Workshop on Acoustic Voice Analysis (Titze, 1995, NCVS) and Kent et al, 1999. All recordings were made in a sound-treated room about 4m x 3m x 2m with the participants seated on a chair with no arms. The audio signal was picked up by a Shure SM 48 dynamic microphone kept at a constant distance of 15 cm from the mouth in an

off-axis positioning (45 to 65 degrees from the mouth axis) to avoid respiratory sounds. We did not use a head mounted microphone for two reasons: 1. patient comfort: some of the immediate post-operative recordings were done with the head bandages still on. Winholz & Titze (1997) advise that the microphone cable of the head mounted microphone should have a strain relief to eliminate motion noise that can be conducted through the cable, which would have been uncomfortable for newly operated patients. 2. There is a possibility of electromagnetic interference because the electrical output of the microphone is unbalanced from the microphone to the connector (at the time of starting our recordings Medtronic advised against the use of head mounted microphones). 3. The effect of aerodynamic artefacts with consonants and rapid voice onset-offset at close mouth-to-microphone distances awaits further study: Winholz & Titze (1997) do not recommend the head mounted microphone for connected speech tasks. The sampling frequency was at 22 kHz. For the aerodynamics and EPG data acquisition the methodology is described in the relevant chapters.

2.4.2 Calibration for loudness data

Measurement of speech intensity (and its subjective correlate loudness) can be made directly by placing a sound level meter at a specified distance from the speaker's mouth (Ramig et al, 2001), or by indirectly converting the microphone signal to a decibel (dB) level (e.g. Winholz & Titze, 1997). The purpose of the calibration procedure is to obtain a decibel equivalent for the output voltage of the microphone. We used a steady vocalisation of the patient instead of an external sound source for ease of reference. Patient was positioned at 15 cm from the recording microphone and the calibrated sound level meter (SLM) (they are mounted alongside on the stand, at the same distance form the patient, see figure 2.1). The distance was checked periodically to ensure stability. This signal (patient vocalisation) was used during the computerised data

measurement to obtain calibrated intensity measurements of the speakers' voices. The level shown on the sound level meter was then announced and recorded onto the CSL to allow a conversion of the CSL dB values to dB SPL (Dromey et al, 2002). The analysis is then based on the difference between the known reference value of the sound source (patient vocalisation) as recorded in the calibrated sound level meter and the processed value of the calibration tone (Winholz & Titze, 1997).

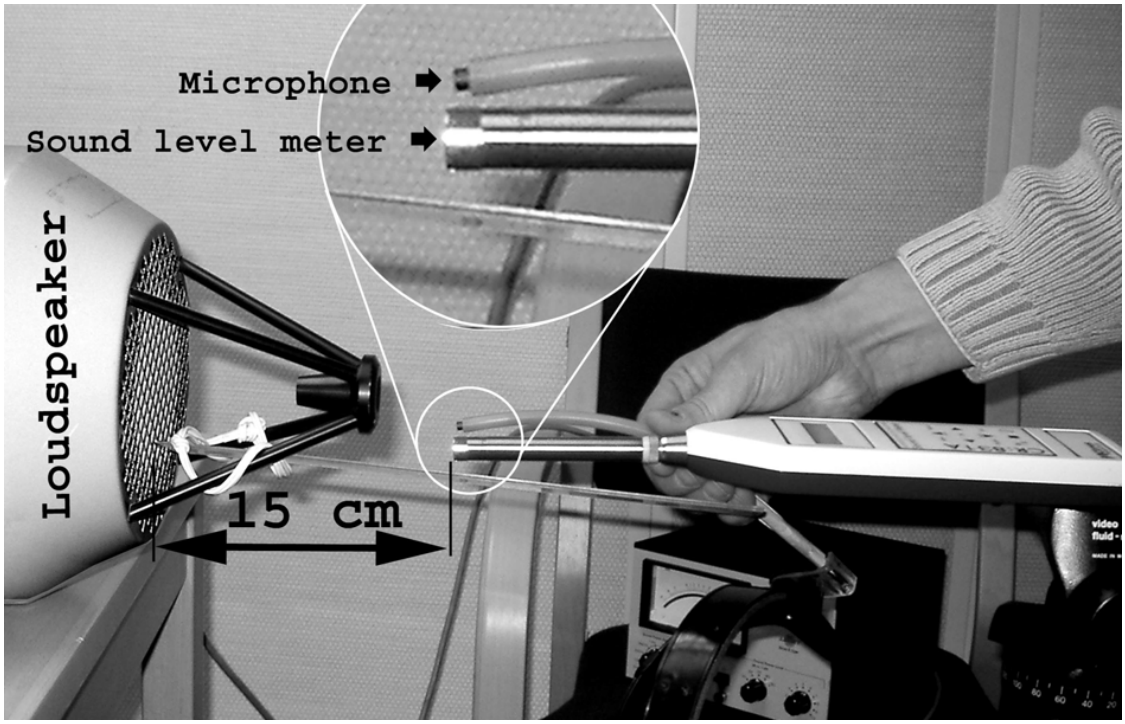

Figure 2.1. *Photograph of calibration method for collection of loudness data. From Asplund A, How loud was it? A calibration system for voice recording in clinical and research situation.*

2.5 Speech tasks

Following the calibration method the patients were instructed to "take a deep breath and say /aaaa/ for as long and as loud as you can". They were instructed to say the /aaa/ three times. Then they were instructed to read aloud the sentences from the Assessment of Intelligibility of the Dysarthric Speech (Yorkston et al, 1988). The sentences are printed in a single A4 page with font size 18 from the computerised version of the test. Then patients were asked to "talk for one minute about anything they want to talk

about" and they were given a topic (e.g. "what did you have for breakfast?", "how did you come here?", "how has it been since the operation?" etc), only if they could find nothing to talk about themselves. The sequence of instructions was the same for each speaker. The 15 cm mouth-to-microphone distance was checked periodically. At no time were tasks modelled by the experimenter because it was felt that this could influence the speaker's performance.

2.6 Speech acoustic analysis

The contemporary understanding of vocal tract acoustics is based on the linear time-invariant source-filter model (Fant, 1970). The source-filter concept proposes that acoustic energy generated by a sound-source is passed through a frequency dependent transmission system. The task of speech analysis therefore is to identify the sound source and to describe the corresponding filter function. There are three major sources to be considered: 1. laryngeal voicing source for the vowels, 2. turbulence noise source for the fricatives, and 3. transient source for the release of stop consonants.

Acoustic analyses may be classified broadly as time-domain, frequency-domain and time-frequency domain analyses. A waveform or an energy envelope is time-domain analysis; a Fast Fourier Transform (FFT) spectrum or Linear Predictive Coding (LPC) spectrum is frequency-domain analysis. A spectogram is a time-frequency domain analysis (Kent 1993, Vocal tract acoustics). Another way to interpret speech data is according to their function: deterministic data focus on individual spectral-temporal features that relate to an aspect of speech production. For example, formant-frequency values pertaining to a particular vowel may be used to infer features of lingual articulation during that segment. Thus the objective of deterministic analysis is to infer some property of speech from individual events in the acoustic record. Stochastic data are statistical features typically collected over long samples. The Long Term Average

Spectrum (LTAS) may be used to characterise the overall energy patterns for a particular speaking task. The LTAS may not say anything about a specific event of speech but it describes the average energy calculated for a relatively long duration of the sample. It is similar to a histogram of vocal fundamental frequency (F_0) determined from a long sample of speech which does not indicate how F_0 varies with individual segments such as vowels and consonants but it portrays the distribution of values over a defined sample. Thus the assumption for using the LTAS is that the influence of various vocal tract resonances on spectral shape will average out across the sample (typically more than 40 seconds) yielding a measure that approximates the overall source contribution (Kreiman, 2007).

2.6.1 Trimming of data files

All data files (from sustained phonation, speech intelligibility and monologue) were inspected for non-speech vocal sounds such as loud cough or laughing that could interfere with speech intensity measurements. These were carefully trimmed so as not to remove any speech sounds as well.

2.6.2 Loudness analysis for phonation and connected speech

In order to calculate the mean sound pressure level of the sustained phonation the middle four seconds of the second trial were anlysed, using the CSL, energy contour. For the analysis of connected speech the maximum value was taken and the mean was calculated from the voiced peaks.

2.6.3 Calculation of long-term average spectra

The CSL LTAS algorithm was used for the analysis of the mean and standard deviation of both read sentences and connected speech samples. For the LTAS analysis the window length was 8192 points and the statistical moments were calculated

automatically by CSL for the entire frequency range of 0 to 22 kHz.

2.7 Auditory-perceptual evaluation of voice quality

Darley et al (1975, 1969) performed the seminal investigations that defined perceptual features of dysarthrias. In those studies three raters performed perceptual assessments of the speech of 212 neurologically impaired patients as they read the "Grandfather passage". Thirty six individual speech dimensions and two general dimensions (intelligibility and bizarreness) were assessed on a seven-point scale. Of the sample 32 patients had IPD and were classified as demonstrating a hypokinetic dysarthria. This dysarthria classification was based upon the most striking perceptual phenomena that consisted of monotony of pitch and loudness, reduced stress and imprecise consonants. In addition the single speech dimension of imprecise consonants was most highly correlated with the overall dimensions of intelligibility and bizarreness. Though nearly four decades have ensued, the Darley et al classification system of dysarthria has remained relatively intact (Kent et al, 2001) and is widely used by clinicians for diagnosis and treatment planning. Recently Plowman-Prine (2009) and colleagues have replicated this early work in 16 IPD patients on- and off-medication. They grouped the 35 speech dimensions listed by Darley et al (1975) under six speech clusters. Our study follows the same methodology. The AIDS intelligibility sentences were used for rating both the speech intelligibility and the perceptual dimensions. Each speech dimension was assessed on a seven-point interval scale, where "one" represented the greatest deviation from normalcy and "seven" represented normalcy. So a score of 42 denotes "normal" sounding speech and a score closer to 0 denotes a greatest deviation. Perceptual analysis was performed independently in the same quiet speech lab, and with the same equipment so as to minimize variability across raters and listening tasks. The rater was blinded as to the patient and the stimulation/medication status as well as the

time of assessment. Speech samples were played using the CSL with Sennheiser HD500 headphones. Assessment of overall intelligibility was determined at the beginning, so as to eliminate familiarity effects from re-reviewing a given sample. Thus the rater listened to 220 speech samples of the AIDS sentences (four samples for each of the 55 patients, two pre-operative ones and two at one year). Each sample could be looped for a maximum of six times in succession, one for each dimension. The rater completed the assessment in six 5-five hour sessions (total of 30 hours to complete the evaluation). Mean speech ratings were calculated individually for each of the 35 speech dimensions and collectively for the six speech clusters across medication/stimulation states.

2.7.1 Rating speech intelligibility

Intelligibility is a measure of the effectiveness of speech and it is usually expressed as the percentage of a message that is understood correctly. Intelligibility of speech depends both on audibility and clarity. Comprehensibility is defined as "contextual intelligibility" or intelligibility when contextual information is present in different forms, such as semantic cues, syntactic cues, orthographic cues and gestures (Yorkston et al, 1996). Improved intelligibility is often a primary goal of speech therapy (Yorkston et al, 1999). Ways to assess intelligibility vary. Scaling methods include equal appearing interval scale (EAIS) (e.g. UPDRS), Visual Analogue Scale (VAS); transcription is when the listener transcribes the words produced by the talker. Scoring is typically done by counting the number of words correctly transcribed. However when applied in conversation it must be assumed that the talker's intent is known. There are Single Word Identification Tests and Sentence Intelligibility Test (e.g. Assessment of Intelligibility of the Dysarthric Speaker, Yorkston & Beukelman, 1981). The AIDS is the most widely used intelligibility assessment (Duffy, 2005) and it is based on the transcription of random sentences of varied length from five to 15 words (total words

110). Sentence samples are generated by randomly selecting one sentence (for the short version we used in this study) from a master pool of 100 sentences of each length from the computerised version of the test (Sentence Intelligibility Test). All of the sentences were selected from adult level reading material and have the following characteristics:

1) phrases and sentences containing five to 15 words with contractions counted as single word,

2) words chosen from the 30,000 most frequently occurring (Thorndike & Lodge, 1944),

3) phrases and sentences containing no quotations, parentheses, proper names, hyphenated words or numbers larger than 10.

In our study we followed the instructions in the AIDS manual, namely that "the number of judges required for reliable results depends on the purposes of the intelligibility measurements. If the purpose is the monitoring of change in an individual dysarthric speaker over time, a single judge is sufficient, provided that the judge is the same individual each time" (pp 5-6).

There is no consensus in the literature as to how many raters are needed for intelligibility or whether experience with dysarthric speech makes a difference. Hammen et al (1994) provided a guide, which seems ideal. They used a 5 x 5 Latin square (Listeners x Sentences) for each of their subjects, with the five conditions counterbalanced under the rows and the columns of the square (as suggested in Edwards 1985, Experimental design in psychological research. New York: Harper and Row). Thus, for five sentences of each of five conditions spoken by six patients one would need 30 listeners. The advantage of this design is that a reduced number of listeners are required to obtain measures of intelligibility. Because each listener is presented a

different sentence for each condition, the problem of listener familiarity confounding the intelligibility measure is avoided. This design would also eliminate the need to determine the reliability of the listeners using correlation methods. Therefore relative homogeneity of the variables assigned to the rows and columns (i.e. listeners and sentences) is assumed. However this design has not been replicated since. The majority of the studies on speech intelligibility in PD have from five patients (Neel, 2009) to 10 (De Letter et al, 2007; De Letter et al, 2005; Yunusova, 2005; Tornqvist, 2005; Keinz et al, 2007; Goberman & Elmer, 2005) and they recruit from three expert listeners (De Letter, 2007) to 60 (Yunusova, 2005). Miller et al (2008) had 104 PD patients and 45 carers to assess self perception of speech changes. For a previous study looking at the prevalence of intelligibility problems Miller et al (2007) had 125 patients rated by 99 unfamiliar listeners.

The methodology for the studies on aerodynamic measures and electropalatography are described in the relevant chapters.

CHAPTER 3: LONGITUDINAL STUDY OF THE EFFECTS OF STN-DBS ON SPEECH IN CONSECUTIVE SERIES OF PATIENTS.

3.1 Summary

Studies on speech outcome following bilateral STN-DBS have focused on selected patients and selected speech tasks with lack of pre-operative data. Similarly there was no detailed description of perceptual speech changes following STN-DBS. There was also a lack of information on surgical factors that could affect speech, (i.e. active contact location and amplitude of electrical parameters of stimulation) as well as clinical factors (i.e. age, disease duration, speech before surgery, speech response to medication and stimulation) that could predict speech outcome. Patients' own perception of how these speech changes affect their quality of life has not been investigated either.

The aims of this study were: i) to prospectively examine the short- and long-term response to STN-DBS on speech intelligibility in a consecutive series of patients, ii) to analyse speech changes using a wide range of perceptual and acoustical measures, iii) to identify clinical and surgical factors associated with speech changes, and iv) to examine their impact on quality of life using the Voice Handicap Index.

Study 1: Thirty-two consecutive patients with PD were assessed before surgery on- and off- medication, then one month, six months and one year after STN-DBS in four conditions on- and off-medication with on- and off-stimulation. Fifteen of these patients were followed up for three years. A control group of 12 PD patients, randomly assigned to medical treatment, were followed up for one year. The speech evaluation protocol

consisted of a standardised speech intelligibility scale, maximum sustained phonation and a one-minute monologue. Movement was assessed using the motor part (III) of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Data are presented as in means ± standard deviations.

Speech intelligibility significantly deteriorated following one year of STN-DBS by an average of 14.2±20.15% off-medication and 16.9±21.8% on-medication compared to respectively 3.6±5.5% and 4.5±8.8% in the medical group. Seven patients showed speech amelioration after surgery. Loudness increased significantly in all tasks with stimulation. Medially placed electrodes on the left brain were associated with a significantly higher risk of speech deterioration than electrodes inside the nucleus. There was a strong relationship between high voltage in the left brain and poor speech outcome at one year.

Study 2: A further 22 patients (total N=54) were assessed, before and one year after surgery, with the same speech protocol, in order to analyse in more detail the perceptual speech changes and any associated clinical or surgical predictive factors. There was a significant decline mainly in articulation and prosody. Multivariate regression with left brain contact position as covariate showed that the strongest predictors of speech intelligibility off-medication/on-stimulation at one year were the pre-operative on-medication speech intelligibility, the pre-operative on-medication motor score, the disease duration, and the left brain active contact location (medial vs inside).

Study 3: In order to assess the self perception of speech changes, a subgroup of 20 patients were asked to rate current post-surgery speech difficulties using the Voice Handicap Index (VHI) and used the same measure to retrospectively rate their pre-

surgery voice. A control group of non-surgical PD patients also completed the VHI. VHI scores deteriorated equally in the two groups. However the variability of the change in the surgical group was significantly greater than the one in the non-surgical group. Correlations between VHI scores and speech intelligibility were significant, both before and after surgery, suggesting good validity for both measures. Influence of STN-DBS on speech is variable and multifactorial, with most patients exhibiting some deterioration of speech intelligibility. Both medical and surgical factors need to be taken into account when managing these patients.

3.2 Study 1: Effects of bilateral STN-DBS on speech intelligibility and movement in consecutive PD patients over time

Study 1 aimed at describing the speech changes following bilateral STN-DBS over time in consecutive PD patients, using a wide range of speech tasks and methods of acoustical analysis, and to appraise the role of electrode position and voltage amplitude.

3.2.1 Patients and methods

Thirty-two consecutive patients (23 men) were implanted with bilateral STN-DBS electrodes between 2005 and 2006 and were included in the study (henceforth surgical group). Their mean age was 58.8 years (±6.3, range: 42 to 69). Mean disease duration at the time of surgery was 12.5 years (±4.7, range: 6 to 25). The levodopa equivalent daily dose (LEDD) (calculated as in Williams-Gray et al. 2007) was 1556 (±671) mg/day. Their mean motor score (UPDRS-III) before surgery, without medication was 48.1 (±17.9, range: 20-89) and with medication 12.4 (±7.8, range: 2-31).

All 32 patients were followed up for one year, and 15 of them were followed up for three years after surgery. Twelve patient candidates for DBS, who had been randomised

to one year medical treatment as part of a separate study, were used as a control group (henceforth “medical group”). Their mean age was 55 years (±9.7, range: 36-69); mean disease duration at the time of baseline assessment was 13.2 years (±6, range: 7-26). Their mean motor score (UPDRS-III) before surgery without medication was 48.9 (±10.6, range: 28-62) and with medication 14.1 (±5.2, range: 5-20).

Surgical procedure and contact localisation

Surgery was performed as previously described (Hariz et al, 2002; Hariz et al, 2003; Chen et al, 2006 and Chapter II-Methods). Preoperative stereotactic MR images using T2-weighted, fast-acquisition sequences were obtained in all patients[12]. The subthalamic target was visualized on MR images and directly targeted using planning software (FrameLink4™, Version 2003, Medtronic®, Minneapolis). Dynamic impedance monitoring and electrical stimulation combined with clinical assessment were used to provide an indication of the target. Patients were thus implanted bilaterally with a quadripolar DBS electrode (Model 3389 DBS lead, Medtronic®, Minneapolis). Post-operative stereotactic MR images were imported into the planning software allowing three-dimensional reconstruction of the images along the electrode trajectory (Framelink, Medtronic, MN). Stereotactic localisation of the four electrode contacts was performed using a template superimposed on the electrode artefact. The coordinates of each contact were transposed onto the pre-operative stereotactic MR images. The targeting accuracy, the Eucledian error, defined as the perpendicular distance from the electrode trajectory to the intended target coordinates, was calculated geometrically from the stereotactic images (Chen et al, 2006; Yelnik et al, 2003). Three neurosurgeons (LZ, EH, EP), blinded to the results of STN-DBS on speech, independently assessed and agreed on the anatomical position of each contact in relation to the visualised STN in the axial and coronal planes. The visualised STN was subdivided into five segments:

superior (A), anterior-medial (B), central (C), posterolateral (D) and inferior (E) (Figure 3.5). Each contact was localised in relation to the closest STN segment and classified as being inside, superior, medial, inferior or lateral to that segment. Each contact was given two ratings: one based on the anatomical localisation around the STN and its surrounding structures; and one based on the STN segment.

3.2.1.1 Patient evaluation

Patients were assessed after overnight withdrawal of medication at baseline, two weeks post-operatively, and six months, one year (N=32) and three years (N=15) post bilateral STN-DBS in all four medication and stimulation conditions. Evaluations were carried out on the same day for each patient and in the same order. For the off-medication/on-stimulation condition drugs were withdrawn for at least 12 hours. The on-medication/on-stimulation assessment took place one hour after the administration of a supra-threshold dose of levodopa. For the off-medication/off-stimulation condition stimulation was withdrawn for 20-30 minutes before the evaluation, depending on the patient's tolerance. One patient could not be assessed without medication at one year, and three patients were not taking any medication at one year.

Speech assessment consisted of three tasks: sustained vowel phonation /a:/ for three repetitions, the Assessment of Intelligibility for Dysarthric Speech (AIDS) (Yorkston & Beukelman 1981) and a 60-second monologue about a topic of the speaker's choice (see Chapter 2). The Computerised Speech Lab (CSL, 4150, Kay Pentax) was used for recording and analysis of all samples. Following speech recordings, movement was assessed in all conditions using the UPDRS-III (Fahn and Elton, 1987).

3.2.1.2 Data analysis

Acoustic recordings and analysis were performed as previously described (Methods section). The 256 files from the sentence intelligibility test for the 32 patients of the surgical group, the additional 30 for the 15 patients followed up for three years and the 48 files for the medical group were rated blindly, and a percentage of words correctly identified was derived. For the acoustical analysis of intensity of sustained phonation, reading and monologue we calculated the mean vocal sound pressure level (SPL dB) measure from the speech recording of each condition. After obtaining the mean SPL for each individual phonation, data were averaged across all maximum duration sustained vowel phonations to obtain an overall average mean SPL for sustained phonation (as per Ramig, 1995). The long-term average spectrum (LTAS) is a fast Fourrier transform-generated power spectrum of frequencies represented in the acoustic voice signal. By averaging across all speech sounds the LTAS provides insights into the function of the voice and the movement of the articulators in connected speech (Dromey, 2003; Duffy, 2005). For the LTAS analysis the window length was 8,192 points and the statistical moments were calculated automatically by CSL for the entire frequency range of 0 to 22 kHz.

UPDRS-III subscores were divided as follows: rigidity (item 22, range 0-20), tremor (item 20-21, range 0-28), axial symptoms (item 27-30, range 0-16), speech (item 18, range 0-4) and akinesia (item 23-26, range 0-32).

3.2.1.3 Statistical analysis

The primary outcome was the change in speech intelligibility from baseline to 12 months in the surgical group. In addition, a linear regression mixed effects model was used to assess the overall effect of time on the measurements. For this analysis patients

were declared as random effects, with time as the fixed effect to be estimated. Independent t-tests were used to compare the change in speech and motor scores between the surgical and medical groups. Acoustic data and motor scores were the secondary outcomes. Continuous variables are presented using mean (SD). Univariate analysis of variance (with two factors: anatomical description and STN segment) was used to explore the impact of contact location on speech outcome. Statistical analysis was performed on SPSS-16 for Mac (SPSS, Chicago, IL) and Prism 5 for Mac (GraphPad software, Inc.) and was supervised by a statistician (Mr Michael Roughton, Senior Statistician at the Cancer Research UK & UCL Cancer Trials Centre).

3.2.2 Results

3.2.2.1 Surgical group: speech and motor function at one year

Speech intelligibility (using the AIDS) deteriorated on average by 14.2 ±20.1% ($p<0.001$) after one year of STN stimulation when the patients were off-medication/on-stimulation compared to off-medication state preoperatively, and by 16.9±21.8% ($p<0.01$) when the patients were on-medication/on-stimulation compared to on-medication state pre-operatively (Table 3.1 and Figure 3.1). There was substantial variability. Speech intelligibility deteriorated in 25 patients (range: -77% to -3%) and improved in seven patients (range: 2% to 17%). UPDRS-III speech item 18 identified only 12 patients with speech deterioration. There was a significant change of speech intelligibility between six months and one year but not between baseline and six months. When off-medication/off-stimulation speech intelligibility deteriorated on average by 12.6±16.6% ($p<0.001$) compared to off-medication pre-operatively. Switching the stimulation off improved speech intelligibility by 1.5% (n.s.) compared to the off-medication/on-stimulation condition.

Table 3.1: *Speech intelligibility (% of words understood) for the surgical (N=32) and medical (N=12) groups at baseline, one month, six months and one year follow-up (the surgical group: on-stimulation) (mean ± SD).*

Time	Surgical group		Medical group	
	Off-medication	On-medication	Off-medication	On-medication
Baseline	75.3 ± 18	77.6 ± 15	74.2 ± 5.6	76.3 ± 5.8
One month	70.4 ± 19	71± 17		
Six months	70.2 ± 18	69.4 ± 19		
One year	62.7 ± 27 ** §	61.7 ± 26**	70.5 ± 7.9*	71.8 ± 8.4

*p<0.05, ** p<0.001 for overall effect of time § N=31

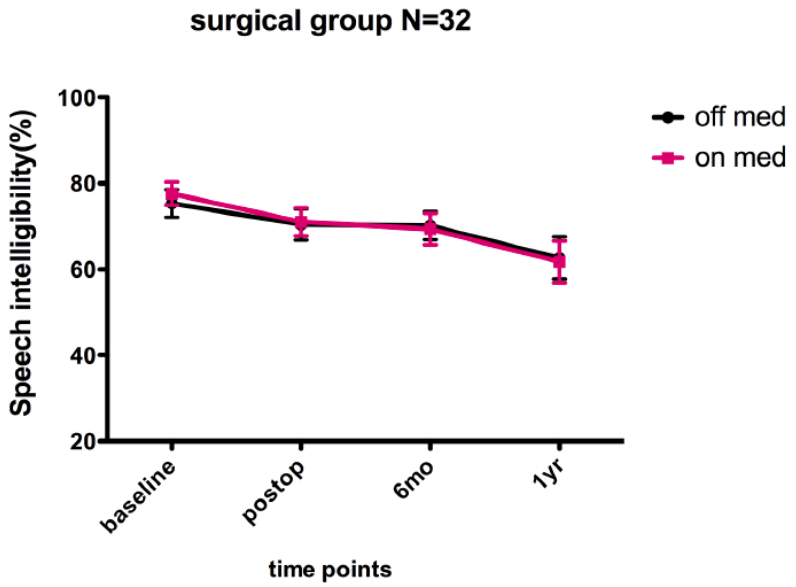

Figure 3.1: *Speech intelligibility (% of words understood) for the surgical group (N=32) at baseline, post-operatively, six months and one year post bilateral STN-DBS (on-stimulation) (mean +/- sem).*

In terms of speech subsystems, loudness (SPL dB) increased by 7.4 dB for read sentences (p<0.0001), by 7.2 dB for monologue (p<0.0001) and by 9.9 dB for phonation (p<0.0001) in the off-medication/on-stimulation condition at one year (table 3.2 and figure 3.2). There was an increase of the LTAS means for reading (p<0.05) and phonation (p<0.001) for the one-year off-medication/on-stimulation condition (table

3.3).

Table 3.2: *Sound Pressure Level (SPL in dB) means (SD) for the surgical group at baseline on- and off-medication, six months and one year.*

	dBSPL sentences	dBSPL monologue	dBSPL phonation
Baseline off-medication	64.8 (5.7)	64.2 (5.5)	66 (8.1)
on-medication	69.1 (5.8)	69.4 (5.8)	69.3 (6.9)
six months off-medication/on-stimulation	70.3 (6.8) **	70.5 (7) **	70.4 (8.8) **
Six months on-medication/on-stimulation	70.6 (6.1)	70.7 (5.5)	73.8 (7) *
one year off-medication/on-stimulation	72.2 (6) **	71.4 (6.9) **	75.2 (6.9) **
one year on-medication/on-stimulation	74.3 (6.7) **	74.7 (6.8) *	78 (5.6) *

* denotes p<.05 and ** denotes p<.001.

Table 3.3: *Long Term Average Spectra (LTAS) means (SD) for the surgical group at baseline on- and off-medication, six months and one year.*

	LTAS sentences	LTAS monologue	LTAS phonation
Baseline off-medication	252 (97.1)	267.2 (108)	440 (202)
on-medication	289 (100.9)	276 (105.7)	491 (220)
six months off-medication/on-stimulation	299.2 (129.7)	287.1 (120.1)	548 (221) *
six months on-medication/on-stimulation	302.2 (113.8)	304 (135.1)	567 (229)
one year off-medication/on-stimulation	289.7(121.8)*	278.1 (115.5)	621 (233) **
One year on-medication/on-stimulation	318 (121)	316 (115.4)	638 (196) *

*denotes p<.05 and ** denotes p<.001.

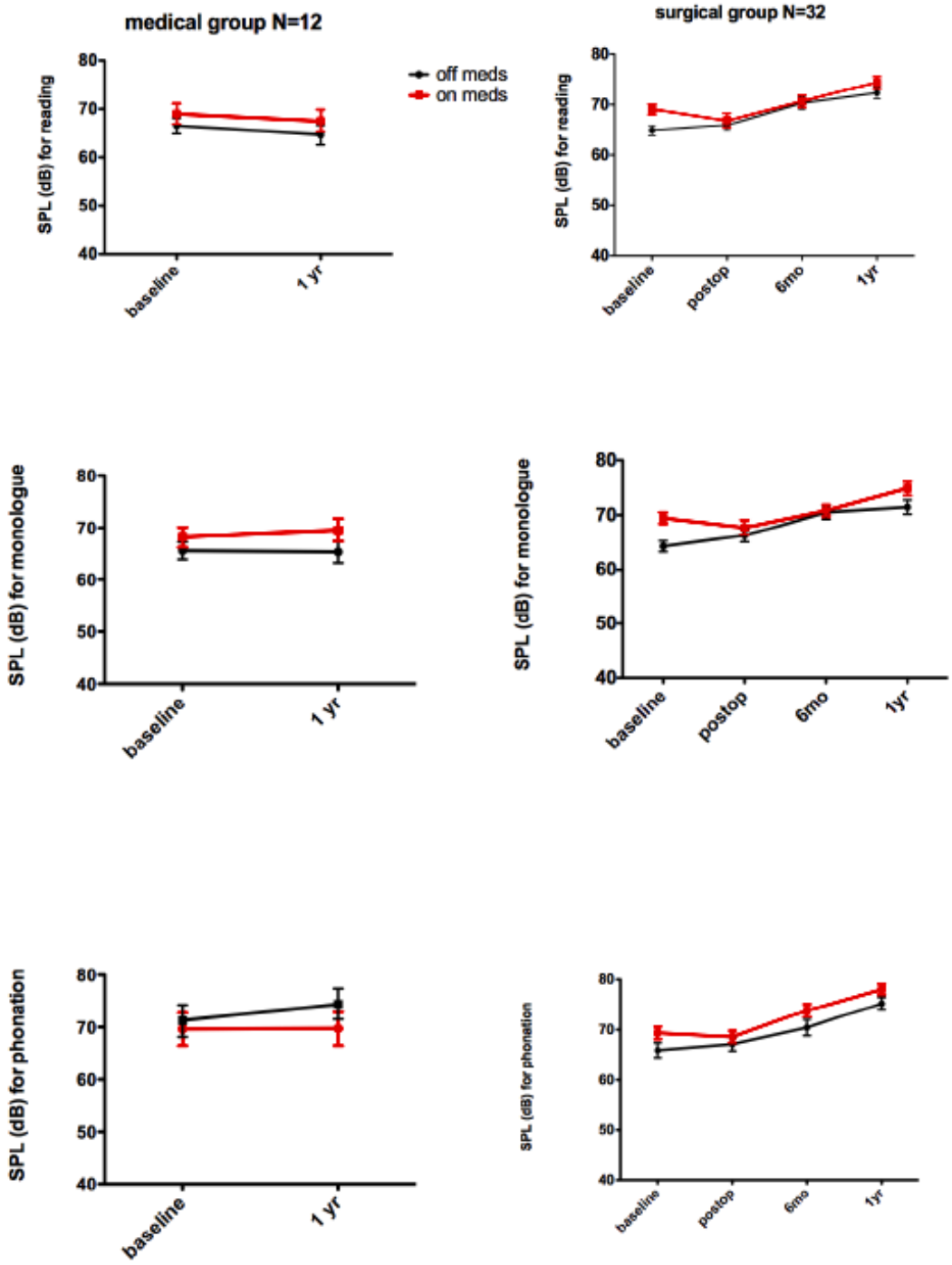

Figure 3.2: *Sound Pressure Level (dB) for reading, monologue and phonation for the surgical and medical groups (mean +/- sem).*

Mean off-medication motor score as measured by the UPDRS-III improved with STN stimulation from 47.3±17.8 before surgery to 20.5±11.19 at six months ($p<0.0001$) (56.6% improvement) and 23.3±11.6 at one year ($p<0.0001$) (50.7% improvement). On-

medication scores did not significantly change over one year. UPDRS-III score was 12.4±7.8 pre-operatively, 10.1±7.4 at six months and 13.9±9.6 at one year. The levodopa equivalent daily dose (LEDD) was reduced over one year from 1556±671 mg to 744±494 mg (52%, $p<0.0001$). The mean (SD) targeting electrode accuracy was 1.3 (0.6) mm. The mean amplitude of stimulation at six months was 2.9±0.7 V for the left electrode and 3.0±0.6 V for the right electrode with mean frequency 133 Hz and mean pulse width 61μsec. The mean amplitude at one year was 3.1±0.8 V for the left electrode and 3.2±0.5 V for the right electrode with the same frequency and pulse width. There was no significant difference between right and left electrode settings at six months and one year.

3.2.2.2 Medical group: speech function at one year

Speech intelligibility in the medical group (N=12) declined by 3.6±5.5% ($p<0.05$) in the off-medication condition and 4.5±8.8% in the on-medication condition (Table 3.1 and Figure 3.3). This decline was not significantly smaller than the one of the surgical group ($p=0.06$ for the change on-medication and 0.08 for off-medication). Eight out of 12 patients (66%) had some degree of speech worsening (range: -13% to -2%). For the medical group, loudness did not change significantly at one year with or without medication in any of the speech tasks. Similarly, LTAS means did not significantly increase over one year apart from the off-medication reading task.

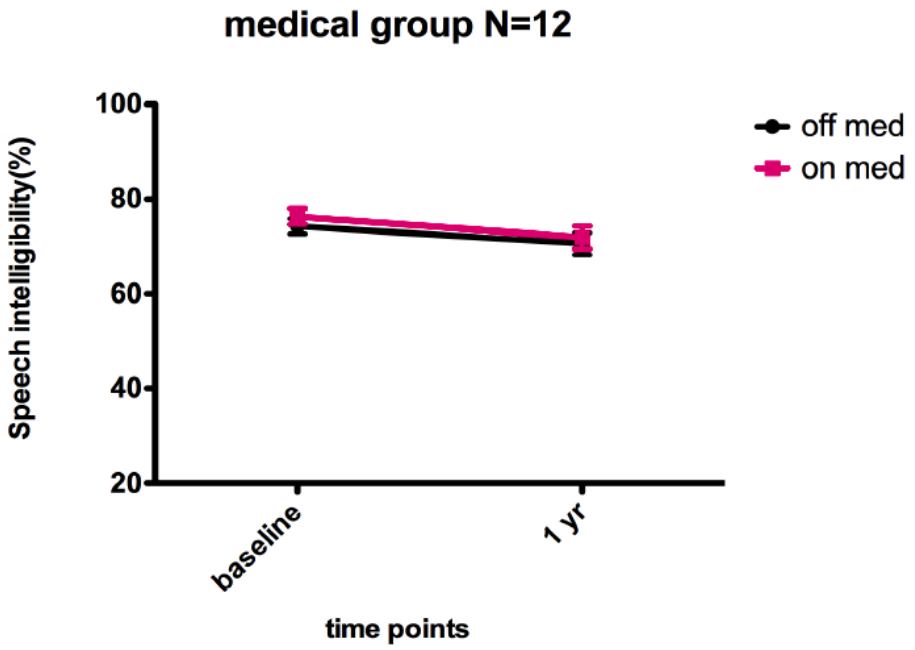

Figure 3.3: *Speech intelligibility (% of words understood) for the medical group (N=12) at baseline and one-year post (mean +/- sem)*

3.2.2.3 Surgical group: speech function at three years

Fifteen patients out of the 32 initial patients were followed up for three years (table 3.4). Out of these, one patient could not be assessed without medication and one patient did not take any medication at three years. In this subgroup, speech intelligibility deteriorated from 76.2% (±19.4, N=15) pre-operatively in the off-medication condition to 59.5 (±36.8, N=14) in the off-medication /on-stimulation condition three years after (p=0.019) (figure 3.4). On-medication speech intelligibility deteriorated from 75.7% (±16.8, N=15) at baseline to 59.8% (±32.9, N=14) (p=.03) at three years. The average deterioration in the off-medication/on-stimulation condition from year one (69.07±26.1%) to year three (59.5±36.8%) was 10% (figure 3.1). Detailed examination showed six patients improving slightly over three years of stimulation (mean improvement +3%) and six patients deteriorating (mean deterioration -44.6%). The amplitude of stimulation at three years (3.2 V left, 3.5 V right) was not significantly different from year one. Four patients deteriorated more than the average. Two of those

patients changed their contacts from monopolar to double monopolar with increased amplitude. The other two patients had increased voltage. Six patients improved from year 1 to year 3 by 7.1% and their improvement was associated with reduced amplitude (Volts) of stimulation.

Table 3.4: *Baseline characteristics of the surgical group followed-up for one year compared to the surgical group followed-up for three years (mean ± SD).*

Baseline characteristics (N=32)	Patients followed-up for one year (N=17)	Patients followed-up for three years (N=15)	P value
Age	57.5 ± 7.4	60.2± 4.6	ns
Time since diagnosis	10.5 ± 3.1	14.4 ± 5.3	0.02
male	15	7	
UPDRS-IIIoff-medication	47.4 ± 17.7	48.9 ± 18.8	ns
UPDRS-III on-medication	12.6 ± 8.0	12.1 ± 7.9	ns
Speech intelligibility off-medication	74.5± 17.1	76.2 ± 19.4	ns
Speech intelligibility on-medication	79.2 ± 13.7	75.7± 16.8	ns

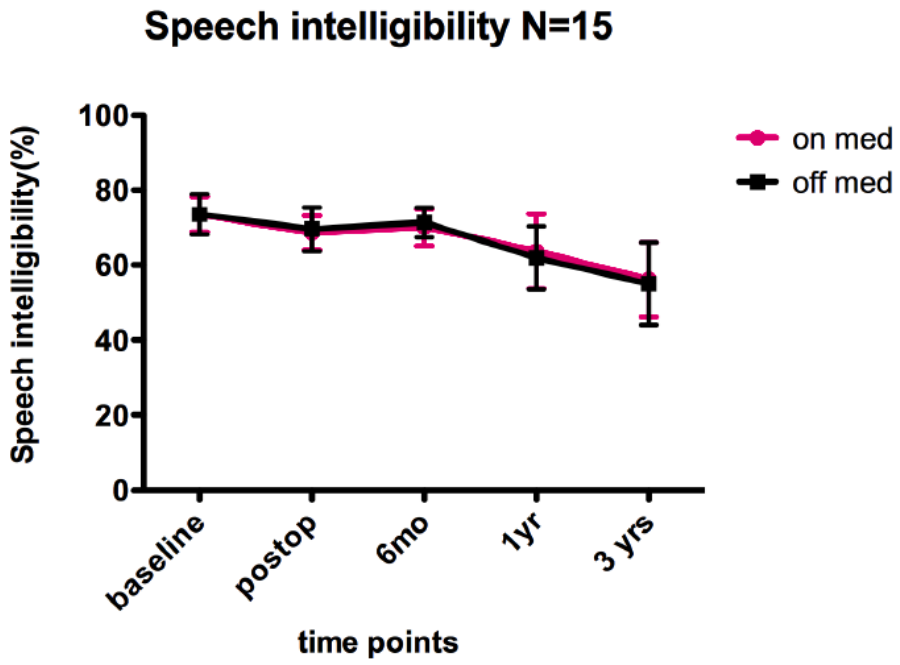

Figure 3.4: *Speech intelligibility (% of words understood) for the surgical group (N=15) at baseline, one month, six months, one year and three years post bilateral STN-DBS (on-stimulation) (mean ± sem).*

3.2.2.4 Effect of active electrode position on speech intelligibility

A univariate analysis of variance was used to assess the impact of the position of the stimulated contact (see methods) for the left and the right brain, on speech response over one year of STN-DBS. In 19 patients the left stimulated contact was inside the STN [mean speech change -7.89%, (16.1)], in 11 patients it was medial [mean change -22.4% (22.4)] and in one patient it was lateral (-45%) (Table 3.5).

Table 3.5: *Mean speech change (sd) (off-medication/on-stimulation at one year minus off-medication pre-operatively) per contact classified according to anatomical localisation around the STN area and the STN segment for the left and right brain (N=31: one patient could not be assessed without medication at one year).*

Anatomical localisation	**STN segment**	**Left brain**		**Right brain**	
		Mean speech change (sd)	Number of contacts	Mean speech change (sd)	Number of contacts
Inside the STN	A	6.6 (11.2)	5	-7.2(21.4)	7
	B	-5	1	2	1
	C	-11.8 (12)	10	-15 (12.9)	6
	D	-31 (22)	2		
	E	2	1		
	Total	-7.8 (16.1)	19	-9.9 (17.4)	14
Superior to the STN	A			-7	1
	Total			-7	1
Medial to the STN	A	-15.7(14.2)	4		
	B	-31(35.4)	4	-77	1
	C	-22	1	-14.2(16.7)	9
	D			-16.8(20.3)	5
	E	-19 (12.7)	2		
	Total	-22.4(22.4)	11	-19.2(23.1)	15
Lateral to the STN	A				
	B				
	C	-45	1		
	D				

	E			-7	1
	Total	-45	1	-7	1
Total	A	-3.3 (16.6)	9	-7.2(19.8)	8
	B	-25.8(32.8)	5	-37.5(55.8)	2
	C	-15.4(14.6)	12	-14.5(14.8)	15
	D	-31(22.6)	2	-16.8(20.3)	5
	E	-12(15.1)	3	-7	1
	Total	-14.2 (20.1)	31	-14.2 (20.1)	31

Anatomical localisation and the STN area are divided into inside the STN, superior, medial and lateral to the STN. There were no electrodes inferiorly to the STN. The segments of the STN are A: superior, B: anterior-medial, C: central, D: postero-lateral, and E: inferior. For further information refer to Figure 1.

Speech deterioration was significantly less for the electrodes positioned inside the STN than those positioned medially or laterally to the STN (p=.016). The difference of speech change in different segments inside the STN on the left brain was not significant (p=.082). However, pairwise comparison showed that speech was on average improved for the contacts in the superior part of the STN [+6.6% (11.2)] rather than the posterolateral part [-31% (22.3)] (p=.014). A p-value of .05 was taken to be significant for all analyses, although this should be viewed in the context of the number of tests performed. For the right brain, 14 patients had the stimulated contact positioned inside the STN [mean change -9.9% (17.4)], one patient superiorly (mean change -7%) and 15 patients medially [mean change -19.2%, (23.1)] (Table 3.5 and Figure 3.5). There was no significant difference between STN segment or anatomical localisation and speech change for the right brain.

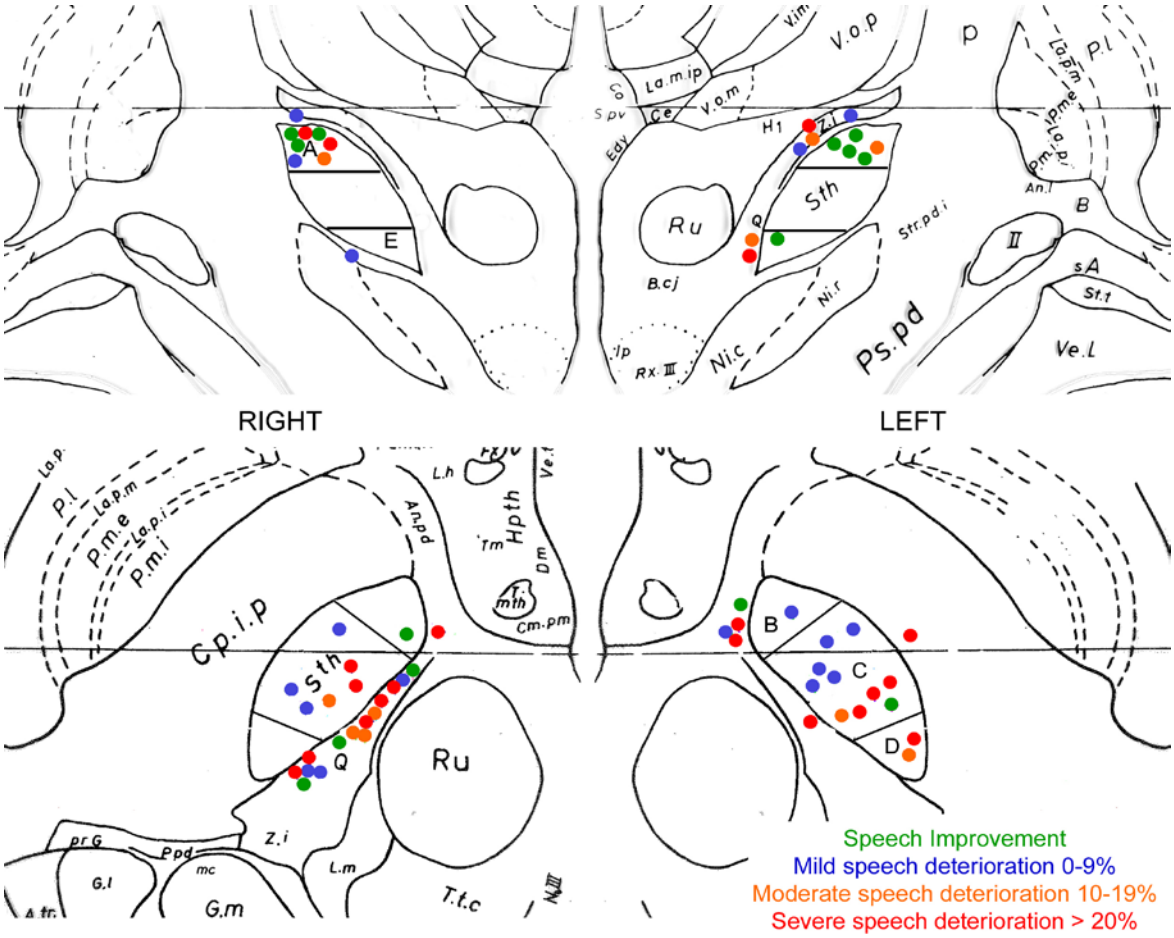

Figure 3.5: *Location of the active contacts in all patients (N=31) at one year post bilateral STN-DBS as transposed onto the Schaltenbrand atlas adopting the radiological imaging convention (right STN on the left side of the image). Top: coronal view adapted from plate 27, f.p. 3.0. Contacts related to the superior (A) and inferior (E) segment of the STN are shown. The middle section of the STN in coronal view is further subdivided into three segments in the axial plane shown below. Bottom: axial view adapted from plate 55, H.v. 4.5. Contact location is shown in relation to the Anterio-medial (B), central (C) and postero-lateral (D) segments of the STN. Selected abbreviations: Ru: red nucleus, Sth: subthalamic nucleus, Z.i.: zona incerta.*

Linear regression analysis was used to assess the association between voltage and speech at one year, as well as speech change over a year. There was a strong relationship between the amplitude of stimulation in the left brain and speech intelligibility in the off-medication/on-stimulation condition at one year (coefficient -16.1, 95% CI -26.8 to -5.4, p=.007, R squared 0.24), as well as the mean speech change over one year of stimulation (coefficient -11.3, 95% CI -19.3 to -3.2 p=.007, R squared 0.22). The higher the voltage needed in the left brain the worse speech was at one year

and the worse the speech change over one year. Similarly, higher voltage was associated with worse speech in the on-medication/on-stimulation condition (p=0.02, r squared 0.1871 for the speech change over a year and p=.0076, r-squared 0.2521 for speech at one year). There was a less strong relationship between the amplitude of the right electrode and speech at one year in the off-medication/on-stimulation condition (-18.7, 95% CI -36.7 to -0.6, p=.042, r squared 0.13) and no relationship with speech change over a year. There was no relationship between the reduction in levodopa (LEDD at one year minus LEDD pre-operatively) and speech outcome and no relationship between LEDD at one year and speech in the on-medication/on-stimulation condition.

3.3 Study 2. Perceptual speech characteristics in 54 consecutive PD patients following one year bilateral STN-DBS and impact of clinical and surgical factors on speech outcome

Following on from the results of the acoustical analysis (Study 3.1) it was evident that the type of dysarthria from STN-DBS stimulation had different perceptual characteristics than that of hypokinetic dysarthria, mainly in respect of vocal loudness. A more detailed description of the perceptual characteristics of speech following stimulation in the STN would inform not only hypotheses on speech motor control but also possible therapy approaches (see Chapter 6-LSVT). Study 2 aimed at analyzing the perceptual speech changes and the clinical and surgical factors in order to identify predictive factors.

3.3.1 Patients and methods

An extra 22 patients, consecutively recruited following the initial 32 (total of 54 patients), participated in this study (Table 3.6). They were assessed before and at one year following surgery.

Table 3.6: *Patient characteristics (N=54)*

Baseline patient characteristics	
Male/Female	34/20
Age mean ± SD (range)	58.8 ± 6.3 (42 to 69)
Disease duration mean ± SD (range)	12.5 ± 4.7 (6 to 25)
Levodopa equivalent daily dose (LEDD) (mg/day)	1556 ± 671
UPDRS-III off medication	48.1 ± 17.9 range 20-89
UPDRS-III on-medication	12.4 ± 7.8 range 2-31

Surgical procedure, contact localisation and patient evaluation were performed as previously described (Study 1).

3.3.1.1 Data analysis

For the perceptual rating the same 22 intelligibility sentences were used. A native English trained SLT with three years' experience, independent to the study and blinded to the conditions, rated the 22 sentences from AIDS using the Darley et al (1972) scale (henceforth "DAB scale"). The 35 speech dimensions listed by Darley et al (1972) were grouped under six clusters as described in Plowman-Prine (2009). Each speech cluster was assessed on a seven-point interval scale where one represented the greatest deviation from normal speech and seven represented normal speech. Mean speech ratings were calculated individually for each of the six speech clusters (articulation, respiration, resonance, phonation, prosody and rate) and collectively for the whole scale across medication and stimulation settings. All perceptual analysis was performed in the same quiet speech laboratory with identical equipment so as to minimize variability across listening tasks. Assessment of overall speech intelligibility was always determined first so as to eliminate familiarity effects from re-reviewing a given sample. After the speech intelligibility rating, each sample of the AIDS sentences was played up to six times so that the rater could listen to the sample once while rating the particular speech cluster with the specific speech dimensions. Thus a total of 220 speech samples were rated. The rater needed approximately ten 6-hour sessions with breaks in between to complete the task.

Speech intelligibility was assessed using the sentence task of the AIDS as previously described (Methods section). Sound pressure level (dB SPL) for the read sentences was extracted using the CSL software program, as previously described (Methods section

and study 3.1). Speaking rate was obtained by dividing the total number of words (220) by the duration of the sentence sample in minutes, as instructed in the AIDS manual (Yorkston & Beukelman, 1984, p 11).

3.3.1.2 Statistical analysis

Primary outcomes were the change in speech intelligibility and perceptual rating (total of the DAB scale) from baseline to one year off-medication (one year off-medication/on-stimulation minus baseline off-medication) and on-medication (one year on-medication/on-stimulation minus baseline on-medication). Secondary outcomes were the loudness measures and the subscores of the DAB scale (respiration, articulation, phonation, resonance, prosody and rate). To assess the impact of STN-DBS and medication on acoustic and perceptual data across times we used one-way ANOVA with Bonferroni's multiple comparisons post tests. In order to assess the impact of pre-operative clinical factors on speech outcome we used first a univariate regression and then a multivariate regression on the significant factors. The primary outcomes for the regression were the change in speech intelligibility (in %) over one year of STN-DBS (one year off-medication/on-stimulation minus baseline off-medication) and the change in the total perceptual scale (/42). Statistical analysis was performed on SPSS-18 for Mac and Prism 5 for Mac (Graphpad software, Inc).

3.3.2 Results

3.3.2.1 Effects of STN-DBS on speech intelligibility and perceptual speech features at one year (N=54)

Speech intelligibility deteriorated on average by 14.4% ($p=0.0006$) after one year of STN-DBS when the patients were off medication and by 12.7% ($p=0.001$) when the patients were on-medication. Both these percentages were similar to the previous cohort of patients (N=32). In terms of perceptual ratings the total of the DAB scale (with a

score of 42 marking near normal speech) deteriorated by 5.1 points (p=0.001) when patients were off-medication and by 6 points (p=0.0001) when patients were on-medication. When comparing on-medication conditions, analysis of the perceptual subscales scores showed a more significant decline in the subscale of articulation (mean decline of 1.2 points, p=0.0001), followed by prosody (mean decline of 1.18 points, p=0.001), phonation (mean decline of 1.01, p=0.0001), respiration (mean decline of 0.94, p=0.001), rate (0.90, p=0.001) and finally resonance (0.76, p=0.05). When comparing off-medication conditions, analysis of the perceptual subscales showed a more significant decline in the subscale of articulation (mean decline of 1.5 points, p=0.0001), followed by respiration (mean decline 0.92, p=0.001) and then rate of speech (mean decline 0.86, p=0.01) and resonance (mean decline 0.6, p=0.01). There was no significant decline for the subscales of prosody and phonation when off-medication (Table 3.7).

Table 3.7: *Changes in intelligibility (% of words understood) and perceptual speech characteristics (as per Darley, Aronson & Brown, 1975) in 55 consecutive PD patients following one year of bilateral STN-DBS (mean ± SD)* .

	Baseline off-medication	Baseline on-medication	one year off-medication/on-stimulation	one year on-medication/on-stimulation
Speech intelligibility	98% (4.3)	97% (7.7)	83.9% (28)	84.3% (26.6)
dB max reading	69.3 (6.9)	73.4 (7)	74.8 (6)	76.2 (6.5)
Rate (words per minute)	149.3 (26.8)	147 (26)	150.2 (36.3)	140.5 (37.9)
Total perceptual score (/42)	32.4 (4.6)	32.5 (5.2)	27.3 (8.8)	26.5 (8.9)
articulation (/7)	5.9	5.6	4.4	4.4
respiration (/7)	5	4.9	4.1	3.9
resonance (/7)	5.6	5.6	4.9	4.9
phonation (/7)	4.8	5.1	4.4	4.1
prosody (/7)	4.9	5.3	4.1	4.1
Rate control (/7)	6	5.8	5.2	4.9

The speech characteristics of the patients with laterally placed left electrode were imprecise articulation mainly caused by tongue weakness and lack of precision of the alveolar and velar sounds, fatigue with speaking which manifests in faster rate of speech and reduced voice volume. Patients with electrodes positioned medially (the majority of

the cohort) presented with slower rate of speech, imprecise articulation mainly affected by reduced lip movement and with difficulties controlling volume of speech, which is usually explosive but more often reduced and breathy. Rate is variable. Patients often complained of not being able to control their breathing with speaking and to “run out of breath”. Voice often sounds more nasal and their voice becomes strained-strangled with prolonged speaking.

3.3.2.2 Predictive value of pre-operative data

The potential predictive value of pre-operative clinical factors was initially assessed using a univariate analysis. The primary outcomes for the regression were the change in speech intelligibility (in %) over one year of STN-DBS (one year off-medication/on-stimulation minus baseline off-medication and on-medication respectively) and the change in the total perceptual DAB scale (/42). The main clinical predictive factors were: pre-operative speech intelligibility off- and on-medication, pre-operative UPDRS-III score off- and on-medication, disease duration and age at surgery. Of those, duration of PD and UPDRS-III off-medication were consistently predictive of speech outcome after one year whereas age was not predictive of any speech outcome (Table 3.8).

Table 3.8: *Univariate analysis of pre-operative clinical predictive factors on speech intelligibility change off- and on-medication and perceptual rating (DAB scale) change one year after STN-DBS (N=54).*

Outcome Variable	*Predictive Variable*	*B-coefficient*	*P<*
Change in speech intelligibility AIDS pre-off to one year off/on	**AIDS pre-on**	-1.8	0.0001
	AIDS pre-off	-2.5	0.01
	UPDRS-III pre-on	0.75	0.23
	UPDRS-III pre-off	0.78	0.004
	Duration of PD	2.77	0.001
	Age at surgery	0.08	0.87
Change in speech intelligibility AIDS pre-on to one year on/on	AIDS pre-on	0.31	0.52
	AIDS pre-off	-3.99	0.0001
	UPDRS-III pre-on	0.68	0.24
	UPDRS-III pre-off	0.51	0.03
	Duration of PD	1.99	0.004
	Age at surgery	0.30	0.51
Change in DAB scale pre-off to one year off/on	**AIDS pre-on**	-0.43	0.001
	AIDS pre-off	-0.99	0.41
	UPDRS-III pre-on	0.23	0.18

	UPDRS-III pre-off	0.23	0.001
	Duration of PD	0.47	0.042
	Age at surgery	0.02	0.86
Change in DAB scale pre-on to one year on/on	AIDS pre-on	0.13	0.2
	AIDS pre-off	-0.94	0.0001
	UPDRS-III pre-on	0.32	0.025
	UPDRS-III pre-off	0.16	0.007
	Duration of PD	0.43	0.014
	Age at surgery	-0.05	0.63

A multivariate regression of the most significant variables from the univariate regression, with left brain active contact as a covariate showed that the most significant predictive factors for speech intelligibility change when off-medication/on-stimulation were the pre-operative speech intelligibility on-medication, the longer disease duration and medially placed left brain active contact. For the speech intelligibility change when on-medication/on-stimulation only the pre-operative speech off-medication was significant (Table 3.9).

Table 3.9: *Multivariate regression of pre-operative clinical predictive factors with left electrode contact anatomical description (medial versus inside) as covariate, on speech intelligibility change off- and on- medication and perceptual rating (DAB scale) change one year after STN-DBS (N=54).*

Outcome variable	Predictive variable	B-coefficient	P<
Change in speech intelligibility AIDS pre-off to one year off/on	**AIDS pre-on**	-1.73	0.000
	AIDS pre-off	-0.74	0.398
	UPDRS-III pre-on	-0.28	0.614
	UPDRS-III pre-off	0.00	0.990
	Duration of PD	2.35	0.002
	Left active contact position	9.25	0.006
Change in speech intelligibility AIDS pre-on to one year on/on	AIDS pre-on	0.67	0.147
	AIDS pre-off	-3.05	0.002
	UPDRS-III pre-on	-0.88	0.172
	UPDRS-III pre-off	0.29	0.360
	Duration of PD	1.33	0.060
	Left active contact position	6.65	0.063

3.4 Study 3: Self perception of speech changes in patients with PD following bilateral STN-DBS

Patients' own perceptions of speech changes following STN-DBS and how these impact their quality of life was the topic of this study. Non-surgical PD patients rated their voice and speech as more severely impaired than healthy controls (Fox et al, 1997), indicating some awareness of their difficulties. However PD patients rarely report difficulties with their voice clinically (Duffy, 2005), perceiving their speech when reading and in conversation to be louder than its actual volume (Ho et al, 2000). The aim of this study was to assess the self-perception of speech changes following bilateral STN-DBS and how it correlates with the clinician's speech intelligibility ratings.

3.4.1 Patients and methods

Twenty-three patients between six and 12 months post STN-DBS and 28 patients who were also severely affected by the disease and were potential candidates for future surgery, were invited to participate.

3.4.1.1 Study design

The questionnaire "Voice Handicap Index" (VHI, Jacobson, 1997) was used in this study. It was developed and validated with patients with a wide range of disorders, including neurological disorders and has good test-retest reliability (Jacobson et al, 1997). It is self-administered and quantifies the patients' perceptions of the handicap they experience in everyday life due to voice disorder. It asks patients to rate 30 statements about their voice and daily living on a scale of 0 to 4. Ten of each relate to the functional, physical and emotional aspects of the disorder. It is the most commonly used measure in peer-reviewed studies and has been used as a measure of treatment

effectiveness (Sewall et al, 2006; Spielman et al, 2007). Using an adapted version for conversation partners, Zraick et al (2007) found good agreement between patients and their partners.

Two copies of the Voice Handicap Index (VHI) were sent to the patients. Those who had received surgery were asked to rate their speech difficulties as they perceived them now and, retrospectively, how they perceived them before surgery. The same questionnaire was sent to the non-surgical Parkinson's patients, asking them to rate their speech difficulties now and at the time of their last clinic visit. Clinic visits occurred every six months to a year and were used to provide a reference point for the patients, allowing them to assess their speech over a similar period as those undergoing surgery. The questionnaires gave two scores (with a maximum of 120), with higher values indicating a greater perceived handicap resulting from the voice disorder. The VHI scores were analysed to assess the patients' perception of changes in their voice over time (since surgery or since the time of their last clinic).

Additional data was available on the patients who underwent surgery. UPDRS-III scores were taken as routine procedure before surgery (off-medication) and after surgery at six month follow-up (off-medication/on-stimulation). These were available for 18 of the 20 patients who received surgery. In addition, surgical patients were asked to make a voice recording before (off-medication) and after surgery (off-medication/on-stimulation) using the Computerized Speech Lab (Kay Elemetrics, Kay Pentax, Model 4150). Each sample consisted of reading randomly generated sentences from the Assessment of Intelligibility of Dysarthric Speech (AIDS, Yorkston & Beukelman, 1981). Both recordings were available for 18 of the patients and were rated for intelligibility by a naïve listener as previously described (Chapter 2 and Chapter 3.1).

3.4.1.2 Statistical analysis

The main analysis examined the changes in VHI scores for the two groups of patients. A two factor mixed ANOVA with subjects (non surgical/surgical) as a between subjects variable and time (pre-surgery/now for the surgical group; 6-12 months ago/now for the non-surgical group) was a within subject variable.

Additional analyses compared the pre- and post-surgical UPDRS-III and intelligibility scores for the surgical group using related t-tests. Correlation was used to examine the relationship between VHI and intelligibility scores for this group to assess whether patients self perceptions and their rated intelligibility were related.

The correlation between the changes in VHI scores and in UPDRS-III scores was also examined.

3.4.2 Results

The questionnaire return rate for post-surgical patients was 20 out of 23 (10 male/10 female; mean age: 58; range: 35-69). The return rate for non-surgical patients was 20 out of 28 (11 male/9 female; mean age: 55; range: 43-74).

In both groups, 14 out of 20 participants scored their current voice difficulties higher than previously (i.e. they perceived the impact of their voice difficulties before surgery or at the time of their last clinic visit to be less than currently). The ANOVA gave a significant effect of time ($F(1, 38) = 6.339$, $p < .05$) showing that the patients generally perceived a deterioration in their speech (Table 3.10). Although the surgical group have

higher scores, the difference between the groups fell just short of significance ($p = .06$). As the table shows, the VHI scores for patients in both groups were very variable.

Table 3.10: *VHI scores for surgical and non-surgical groups pre and post surgery. Higher score denotes greater handicap.*

		Before	Present
DBS patients	Mean	30.35	45.95
	SD	34.76	27.47
Non DBS patients	Mean	20.20	27.35
	SD	22.82	24.02

The interaction between groups and time was not significant, indicating that neither group deteriorated more than the other over time. Changes with time were also highly variable across patients. This was particularly apparent in the surgical group. The absolute values (ignoring deterioration or improvement) for each group were compared with an independent t-test. This revealed a highly significant difference ($t = 3.50$ (d.f. = 21.41; adjusted for unequal variances), $p < .01$) between the groups.

A comparison of the surgical groups UPDRS-III scores before and after surgery showed a highly significant improvement ($t(17) = 6.85$, $p < .001$). A similar comparison for the intelligibility scores showed that the deterioration in these scores was not significant ($t(17) = 1.52$, n.s.) (Table 3.11)

Table 3.11: *Mean UPDRS-III and intelligibility scores pre- and post-surgery for the surgical group.*

		Before	Present
UPDRS scores	Mean	43.89	22.55
	SD	15.35	13.72
% Intelligibility	Mean	79.05	72.44
	SD	15.85	22.86

There was a significant negative correlations between VHI scores and intelligibility for both the pre-surgery ($r = -0.506$, $p < .05$) and post-surgery scores ($r = -0.749$, $p < .001$). Thus high intelligibility scores corresponded with low VHI scores (i.e. low handicap). There was a non-significant, positive correlation between VHI scores and UPDRS-III ($r = 0.192$), suggesting that lower scores on both scales were associated, albeit weakly.

3.5 Discussion

3.5.1 Short- and long-term effects of STN-DBS on speech

In our series of 32 consecutive patients, speech intelligibility deteriorated by 14.2% one year after STN-DBS, when off-medication, whereas movement measured with UPDRS-III improved by 50.7%. Twenty-five patients (78%) experienced some degree of worsening of speech intelligibility. This was disabling for 13 patients (40%) who experienced speech deterioration larger than the average 14.2%. At three years 53% (95% CI: 25,81) of patients showed speech deterioration in the off-medication/on-stimulation condition and 73% (95% CI: 42,92) of patients in the on-medication/on-stimulation condition, in line with other reports (Piboolnurak et al, 2007; Schupbach et al, 2006; Gan et al, 2007; Krack et al, 2003; Rodriguez-Oroz et al, 2005).

This percentage is higher than most clinical series in the literature. Nevertheless, most

series have focussed on the motor benefit and speech has mostly been assessed by item 18 of the UPDRS which shows poor sensitivity to detect speech problems (Richards et al, 1994 and our data, Study 3.1). It is therefore likely that speech worsening is under-reported in most series of the literature. In a meta-analysis of 34 papers (from 1993 to 2004) Kleiner-Fisman et al (2006) estimated 9.3% of speech deterioration from reported data. At six months after bilateral STN-DBS Herzog and colleagues (2003) reported a 4% incidence of speech problems in their results from 48 consecutive patients.

At one year, Tir et al (2007) reported a 12% incidence of speech problems, only for patients with disease duration longer than 12 years. Thobois et al (2002) reports a 5% incidence in 18 patients and Herzog et al (2003) a 6% in 32 patients. Higher incidence is reported by Pahwa et al (2003) with 28%, and Volkmann and colleagues (2001) who noted a 56% incidence of speech problems in 16 patients. Some groups do not report any speech problems following STN-DBS (Jaggi et al, 2004; Romito et al, 2003; Vesper et al, 2002). At three and five years the reported incidence of speech problems tends to increase: Schupbach et al (2006) reported a 35% incidence at five years of STN-DBS and Gan et al (2007) reported a 52% incidence in 36 patients at three years. The highest incidence is reported by Piboolnurak (2007) with 69.7% (23 patients in 33). Krack et al (2003) and Rodriguez-Oros (2005) reported a progressive deterioration of speech over five years follow-up, particularly for the on-medication/on-stimulation condition. In our series, at three years, eight out of 15 patients (53%) showed speech deterioration in the off-medication/on-stimulation condition and 11 patients in the on-medication/on-stimulation condition (73%). Interestingly in some patients speech deterioration was partly reversible and improvement was linked to amplitude reduction and/or change of contacts from medial to inside. The numbers though are too small to make any more substantial claims.

The incidence of speech problems seems higher with STN-DBS than GPi-DBS. Volkmann et al (2001) reported a 56% incidence of speech problems only in the STN group, with speech worsening further with medications. Rodriguez-Oroz (2005) reported 18% of patients with speech problems following STN-DBS compared to 5% following GPi-DBS.

Disease progression in the medical group accounted for only a 3.6% deterioration of speech intelligibility off-medication and 4.5% on-medication over one year. Despite the small size of the medical group, the clear difference between the two groups makes it unlikely for the worsening in the surgical group to be related only to disease progression. One study that has compared the outcome of a DBS group and a medical group reported a 10% deterioration of speech in the DBS group and 1% in the medical group at six months follow-up; however they had no specific measure of speech (Deuschl et al, 2006). Weaver et al (2009) and Williams et al (2010) do not report data on speech progression following one year of medical therapy versus one year of STN-DBS.

3.5.2 Role of medication and stimulation parameters on speech response

Speech response was not significantly improved by administration of levodopa before or after STN-DBS. Indeed, for some patients, speech was worse on-medication/on-stimulation, as reported earlier (Krack et al, 2003; Rodriguez-Oroz et al, 2005; Volkmann et al, 2001), especially in patients with residual orofacial dyskinesias (Rousseaux et al, 2004). The amount of reduction of levodopa was not associated with speech deterioration either.

The majority of the speech deterioration in the surgical group occurred between six months and one year. This was not alleviated by switching the stimulation off. Also voltage was not significantly increased between six months and one year.

Systematic evaluation of the anatomical location of the electrode contact and its effects on speech showed that electrodes placed medial to the left STN were worse for speech intelligibility than electrodes inside the STN, confirming results from other studies. Plaha and colleagues (2006) reported that stimulation in contacts dorsomedial or medial to the STN have resulted in reversible, hypophonic and slurred speech, despite marked improvement in limb movement. In the same study contacts in caudal zona incerta and the one inside the STN did not induce dysarthria as a side effect. Stimulation of the prelemniscal radiation has also been reported to cause dysarthria despite improvement in tremor and rigidity (Velasco et al, 2001). Paek and colleagues (2008) investigated the clinical outcome from bilateral STN-DBS in 53 patients. Speech, as measured with the UPDRS-III, item 18, improved only in the patients whose electrodes were positioned within the STN as opposed to the red nucleus or the area between the STN and the red nucleus. In our study the limited number of electrodes in each area (for example, one lateral electrode for each side) makes any assumptions tentative.

Equally information on the particular STN segment where the active contact is and speech outcome is scarce. In our study stimulation in the left superior segment of the STN improved speech by 6.6% over a year compared to a deterioration of 31% from stimulation in the left posterolateral segment (D). Despite the different methodology of electrode localisation, stimulation of this same superior segment (A) is reported to be more effective for limb motor control (Yelnik et al, 2003; Hamel et al, 2003; Yokoyama et al, 2006). Improvement in both speech and motor control from stimulation of this

segment compared to improvement predominantly in motor control with stimulation of the posterolateral segment may have implications for surgeons when targeting the STN. However there was too limited a number of electrodes in each of the five segments inside the STN to make firm assumptions on their effects on speech. Additionally, there is scarce evidence on the somatotopy of the STN and speech. In a study of PD patients, neurons corresponding to the oromandibular musculature were found in the middle of the STN (Rodriguez-Oros, 2002). In the monkey, neurons in the dorsolateral and lateral part of the STN and in the substantia nigra were particularly active during oral movements for feeding (DeLong et al, 1983; Mora et al, 1977; Wichmann et al, 1994; Nambu et al, 1996). These reports may not be relevant to the effects of STN stimulation in humans and on speech in particular.

Higher voltage on the left STN at one year was also associated with speech deterioration. The worsening effect of higher voltage has been described before (Krack et al, 2003; Tornqvist et al, 2005; Tripoliti et al, 2008). Some studies have attributed this deterioration to the spread of current in the internal capsule (Benabid et al, 2009; Krack et al, 2003; McIntyre et al, 2004; Tommasi et al, 2007). In our study the strong association of a medial contact and higher voltage with poor speech outcome points towards a different mechanism. A spread in the cerebellothalamic tract has been proposed by our group and others (Gallay et al, 2008; Plaha et al, 2006; Tripoliti et al, 2008; Astrom et al, 2010; see also Chapter 4).

The stronger association of the left STN contact with speech response conforms to the findings from other studies (Santens et al, 2003; Wang et al, 2006). Santens and colleagues (2003) analysed the effects of left and right STN separately on different perceptual aspects of speech in seven patients. There was a significant deterioration of

prosody, articulation and intelligibility when stimulating the left STN compared to the right STN alone. All patients reported subjective decrease of speech intelligibility following bilateral STN stimulation. Wang and colleagues (2006) investigated the effect of unilateral STN-DBS on speech in 20 PD patients, 10 operated only on the left STN and 10 only on the right. Patients with left STN stimulation decreased their articulatory accuracy and speaking rate.

3.5.3 Acoustical data and speech response

Higher LTAS means in both reading and monologue when on-medication was a predictive factor of good speech outcome. Dromey (2003) examined the use of a number of acoustical variables to describe PD speech and concluded that lower LTAS means was the variable that differentiated PD speech most from that of normal controls. Perceptually lower LTAS means would suggest a weakness in the upper harmonics (i.e. consonants and mainly fricatives), with the main acoustic power concentrated towards the lower frequencies (mainly vowels). High frequency consonants are more important for comprehending speech (Horwitz, 2008). However, the relationship between these acoustic measures and perceptual judgements is still not clear (Lofqvist & Mandersson 1987; Tanner et al, 2005). Thus lower LTAS means can represent the breathy phonation of vocal fold palsy (Hartl et al, 2003) or indeed higher LTAS means can represent the "overpressured phonation" of spastic dysphonia (Izdebski, 1984).

There was a discrepancy between deterioration in speech intelligibility and improvement in loudness, which is contrary to other studies in PD dysarthria where increased loudness is associated with increased speech intelligibility (Rosen et al, 2006; Tjaden & Wilding 2004; Neel, 2009). This discrepancy is part of an ongoing debate in

the speech motor control literature. Connor & Abbs (1991) examined the variations in amplitude and velocity of movement in three jaw lowering tasks: 1) single, rapid, visually guided movement, 2) equivalent movement associated with a single speech syllable (/da/) and 3) well-learned speech movement produced in a natural sequence ("say /da/ again"). PD jaw movements were characterised by reductions in velocity/ amplitude only when performed under visual guidance. There was no such impairment during speech actions. This dissociation in performance of speech versus non-speech motor tasks may be a reflection of the different neural control. Riecker et al (2000) showed that non-speech lateral tongue movements were associated with bilateral cerebellar activation whereas speaking was accompanied by unilateral (right-sided) activation of the cerebellum. Ziegler (2003) postulated that there is a case for task-specificity in oromotor control, based on dissociations between speech and non-speech tasks.

Our finding supports similar findings from the limb motor literature on the effects of STN-DBS, which show increase in force production but deterioration on more complex movement (Brown & Eusebio, 2008; Chen et al, 2006; Vaillancourt et al, 2004). So far evidence of impaired performance following STN-DBS has been limited to selected cognitive tasks (Brown et al, 2006; Hershey et al, 2004; Jahanshahi et al, 2000) and complex manual tasks (Brown et al, 2006). Recently Alberts et al (2008, 2010) showed that complex cognitive and motor performance declined significantly with bilateral STN-DBS. Human conversation is a unique complex task of cognitive and motor nature, requiring fast and precise movement under constantly changing circumstances.

3.5.4 Perceptual characteristics of speech following one year of STN-DBS in 54 consecutive patients

In our cohort of 54 consecutive patients we used the DAB scale to identify the perceptual changes on speech after one year of STN-DBS. In their original studies of 1969, Darley et al analysed the speech of 32 PD patients, without medication and using the same scale, and they described the characteristics of hypokinetic dysarthria. In order of severity their patients presented with impaired prosody (monopitch, reduced stress, monoloudness), articulation (imprecise consonants), respiration (inappropriate silences, short rushes), phonation (harsh voice, breathy voice) (p 257).

In our study patients pre-operatively without medication seem to present with the similar characteristics, i.e. more severely affected prosody, followed by phonation, and respiration (Study 2, Table 3.7). However the pattern was different at one year post STN-DBS. The characteristics that seem to deteriorate more significantly when off-medication/on-stimulation are articulation, followed by respiration (which reflects patient's complaint of difficulty breathing). There is no effect of stimulation alone on phonation and prosody. When on-medication/on-stimulation however the pattern changes and the impact on articulation, prosody and phonation become significant, reflecting again the more severe overall deterioration of speech when on-medication/on-stimulation.

3.5.4.1 Comparison with dysarthrias from lesions in the area of internal capsule

Stimulation in the deep brain structures provides the opportunity to study their role in speech motor control in a more precise manner than the dysarthria caused by lesions in the same areas and to hypothesise on the relative role of each structure on speech motor control. The most common description of dysarthria following lacunar strokes (in the

areas of putamen, caudate, thalamus, pons, and internal capsule) is limited to vague terms such as “slow dysarthria, slurred, unintelligible or thick”.

The corticobulbar fibres for head and neck occupy the genu of the internal capsule. Electrodes positioned laterally to the STN would affect the posterior part of the internal capsule. Pure dysarthria syndrome has been described by Ichikawa et al (1991) in nine patients caused by infarcts at the superior limb of the anterior portion or corona radiata or the superior portion of the genu of the internal capsule: “The most prominent speech abnormalities were a “thick” tongue or slurring with incomplete articulation, some patients showed mild slowness of their speech but speech was not scanning, explosive, hypophonic or dysprosodic” (Ichikawa, 1991, p 809). Kim (1994) described the same syndrome in 13 patients with infarcts in the area of corona radiata. Takahashi et al (1995) described the lesions in 40 patients with dysarthria mainly from lesions in the left corona radiata/junctional zone. Ozaki et al (1986) described five cases with sudden onset of dysarthria in the anterior internal capsule, “impaired articulation with slurred speech with nasal features, but no dysphagia. Weakness of the tongue was not detected. Soft palate movements were well preserved. No facial palsy”. Urban et al (1999) describes five patients with pure dysarthria due to extracerebellar lacunar strokes in the area of internal capsule and corona radiata.

Focal ischaemic lesions in the genu of the internal capsule have been reported to cause orofacial and laryngeal paresis due to massive disruption of the corticobulbar tract which is broadly described as unilateral upper motor neuron (UUMN) dysarthria, with pyramidal signs, unless the lesion is bilateral when dysarthria is spastic (Tredici et al, 1982 but assessed with early CT scanning). The involvement of the genu of the right internal capsule in spasmodic dysphonia (SD) was revealed in a study by Simonyan et

al (2008) using DTI and post-mortem histopathology. They also found involvement of the posterior limb of the internal capsule, putamen, globus pallidus and cerebellum. However the type of voice impairment and the microstructural abnormalities in the internal capsule in the SD patients suggest a different pathological process than that of a lesion. Noda (1994) also reported micrographia as a concomitant symptom of lacunar infarctions involving the putamen or the genu of the internal capsule.

3.5.4.2 Lesions in the cerebellothalamic tract

The cerebellum is involved in the motor control via the ventrolateral thalamus and has a modulatory role in coordinating voice and speech production (Günther, 2006). Arboix (2007) compared the presentation of thalamic haemorrhage versus internal capsule/basal ganglia haemorrhage and found that speech disturbances are more frequent in patients with the latter (44%) rather than the former (21%) but they do not provide any further description. There is also a case of Horner's syndrome due to ipsilateral posterior hypothalamic infarction with contralateral faciobrachial weakness and dysarthria (Austin & Lessell, 1991). Urban (2006) studied the lesion location of 62 consecutive patients with dysarthria due to a single non-space occupying infarction. Of the 85.5% extracerebellar lesions, 46.8% were in the striatocapsular region with dysarthria mainly caused by left-sided lesions. Cerebellar lesions were characterised by articulatory problems (consonant articulation, speaking rate slowed over time, prolonged phonemes and syllables, articulatory inaccuracy, reduction or elision of phonemes and syllables, repetition of phonemes and syllables and vowels imprecise or distorted") more so than voice problems.[4]

[4] Both the putamen and the thalamus are shown to be involved in reading at the level of speech production, they are more activated when subjects read meaningless written syllables (Bohland & Guenther, 2006) or completed stem words (Rosen et al, 2000) when performed aloud rather than silently. The left thalamus (and not the putamen)

3.5.5. Pre-operative predictive factors

One of the main aims of this study was to provide clinicians and patients with information on the possible effects of STN-DBS on their speech prior to surgery. Speech outcome was not linked to either age or pre-operative motor scores, unlike motor outcome (Welter, 2002; Charles, 2002; Guehl, 2006). Indeed, speech problems may arise at any stage of the disease process and are not necessarily related to the degree of motor disability (Metter & Hanson, 1986). The best predictive factor for speech response after one year of STN-DBS when off-medication/on-stimulation was the residual speech problem after medication before surgery. Thus, the better the speech on-medication pre-operatively, the better the outcome one year post, off-medication/on-stimulation. Or inversely, the fact that the severity of the residual parkinsonian speech score when "on-medication" was predictive of a poor post-operative outcome is probably explained by the presence of non-dopaminergic lesions within the basal ganglia, (Agid, 1991) which would not respond to stimulation. The reason why longer disease duration is predictive of poorer speech outcome may be also related to the severity of speech problems pre-operatively. The only predictor of poor speech outcome at the on-medication/on-stimulation condition was the pre-operative off-medication speech. This could reflect the residual ability to compensate and mediate the combined effects of medication and stimulation on the motor control of speech following STN-DBS.

3.5.6 Self-perception of speech changes following one year of STN-DBS

This study investigated the perception of patients' speech difficulties following STN-DBS. Speech difficulties were assessed using the VHI which is a measure of

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plays a consistent role in name retrieval (Price & Friston, 1997). (See also Seghier & Price, 2009 for the role of the putamen in reading aloud).

participants' self perceptions of their voice. Patients were also required to score their speech difficulties retrospectively over a period of six to 12 months. The main analysis showed that both surgical and non-surgical groups perceived their voice as deteriorating over the period of the study. Fourteen out of 20 members of each group reported deterioration. However the VHI changes in the surgical group were more variable than those in the non-surgical group. A comparison of the changes showed a highly significant difference between the groups. The analysis also showed that the overall difference between the groups was close to significance. Its failure to show a more striking difference may reflect the high level of variability between patients in both groups.

Relationship of motor, intelligibility and VHI scores in the STN-DBS group

UPDRS-III scores were only available for the surgical group of patients. These show a strongly significant improvement after surgery and are in contrast with the decrease in patients' satisfaction with their speech as assessed by the VHI. The correlation between these two was not significant, however. This suggests there is no close relationship between the improved UPDRS-III scores and the decline in VHI scores. This inconclusive result owes much to the variability in speech changes after DBS. Whereas UPDRS-III scores improved strongly and fairly consistently, changes in the VHI scores, as seen above, were very inconsistent and not always negative.

On the other hand, the high correlation between the intelligibility scores and the VHI was a very important finding. Objective speech assessment, such as the speech intelligibility rating, precludes evaluation of the impact of speech disorders on everyday life. Therefore the VHI, which is used to measure the influence of voice problems on one's quality of life, offers unique information for the multidimensional diagnosis of

dysarthria. In the literature opinions on the possible correlation between the objective and subjective parameters of speech assessment differ widely and they are mainly limited to acoustic measures The correlation with speech intelligibility, a measure of percentage of words understood by a naïve listener, shows that the VHI can be used with patients with PD to evaluate the impact of their speech impairment on their quality of life.

Two aspects of this study are novel. Firstly, it uses the VHI as a means of obtaining a patient's own estimation of their voice problems. This reflects a patient's own experience of speech difficulties in everyday situations and the effect of their dysarthria on their quality of life. The study also investigated the accuracy and validity of retrospective evaluation of speech changes over time. In view of reports of patients' poor awareness of their speech (Duffy, 2005; Ho et al, 1999a, 1999b, 2000) there may be doubts as to whether retrospective assessments are reliable. In our study patients' ratings of their speech changes, including those made retrospectively, were significantly correlated with the blind assessment of their intelligibility by an independent listener. This suggests that the patients' own assessments are valid and accurate; moreover they may be more sensitive than the intelligibility scores.

The results of this study are consistent with previous findings and suggest that the VHI can be used with patients with Parkinson's disease. To assist the patients they were given a clear reference point at which to recollect their voice (before surgery for the surgical group and their last clinic visit for the non-surgical group). While this appeared to help them, the retrospective element of the methodology is not generally recommended. Clinically, however, it may be useful. Patients are often seen at relatively lengthy intervals (six months in the present case) and enquiries about changes

in their symptoms are likely to be made at these times. The findings here suggest that some reliance may be placed on their perceptions of changes in their voice over such periods.

CHAPTER 4: EFFECTS OF CONTACT LOCATION AND VOLTAGE AMPLITUDE ON SPEECH AND MOVEMENT IN BILATERAL SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION

4.1 Summary

Contact site and amplitude of stimulation have been suggested as possible factors influencing the variability of speech response to STN-DBS.

In this double-blind study we assessed 14 patients post bilateral STN-DBS, without medication. Six conditions were studied in random order: stimulation inside the STN at low voltage (2V) and at high voltage (4V); above the STN at 2V and 4V, usual clinical parameters and off-stimulation. The site of stimulation was defined on the post-operative stereotactic MRI data. Speech protocol consisted of the Assessment of Intelligibility of the Dysarthric Speech, maximum sustained phonation and a one-minute monologue. Movement was assessed using the UPDRS-III. Stimulation at 4V significantly reduced speech intelligibility (p=.004) independently from the site of stimulation. Stimulation at 4V inside the nucleus significantly improved the motor function (p=.0006). A subgroup of patients (N=10) was studied further using patient-specific finite element computer models and the electric field generated during the various electrical settings could be visualized. The aim of this study was to relate the anatomical aspect of the simulated field to acute effects of speech intelligibility and movement. The results showed that a current spread in the pallidofugal and cerebellothalamic pathways, medially to the STN, could be responsible for the

stimulation induced speech deficits.

The significant improvement in movement coupled with significant deterioration in speech intelligibility when patients are stimulated inside the nucleus at high voltage indicates a critical role for electrical stimulation parameters in speech motor control.

4.2 Introduction

Speech motor outcome following STN-DBS could be dependent on both clinical factors such as speech impairment before surgery and speech response to medication and surgical factors such as contact site and electrical parameters of stimulation[15;16]. The aim of the present study is to evaluate the role of the voltage amplitude on speech of the location of the stimulated contact and the role and motor function. Study 1 aimed at exploring the relative contribution of voltage amplitude and contact location (inside versus outside the STN) and Study 2 aimed at exploring the spread of current in the fasciculus cerebellothalamicus (fct) medially to the STN.

4.3 Study 1: Effects of voltage amplitude and contact location (inside versus outside the STN) on speech and movement in bilateral subthalamic nucleus deep brain stimulation

4.3.1 Patients and methods

Fourteen patients diagnosed with PD and treated with bilateral STN-DBS for at least six months were recruited consecutively, as they were coming for their routine clinical follow-up. All patients had at least one contact on each side within the STN, as determined by localization on post-operative stereotactic MRI. No patients had previously been treated surgically for their PD. Their mean age (SD) at the time of surgery was 60 (6.5) years, the mean duration of PD before surgery was 15.6 (5) years

and the mean duration of STN stimulation at the time of this study was 13.6 (8.6) months. Their mean Unified Parkinson's Disease Rating Scale (UPDRS-III) score off-medication pre-operatively was 40.1 (11) and on-medication 11.7 (6.8). The mean speech intelligibility off- medication was 86.3% (9.7) and on-medication 87.8% (9.3) (Table 4.1).

Table 4.1: *Settings of usual clinical contacts at the time of evaluation and effect on motor and speech (% of words correctly understood) symptoms (all evaluations off-medication).*

	UPDRS-III		Speech intelligibility (%)		Contact (Volts)	
Patient	**ON stim**	**OFF stim**	**ON stim**	**OFF stim**	**Left brain**	**Right brain**
1.	28	52	80%	93%	2 (3.6V)	5 (4.4V)
2.	16	57	73%	75%	1 (2.4V)	4 (3.5V)
3.	20	50	60%	70%	1 (3V)	5 (3V)
4.	36	62	15%	30%	2 (3.5V)	5 (3.5V)
5.	41	71	50%	60%	0 (3.5V)	4 (2.6V)
6.	20	51	71%	76%	1 (3.8V)	5 (3.8V)
7.	12	49	78%	74%	1 (3.5V)	5 (3V)
8.	26	48	70%	60%	2 (3.1V)	6 (3.1V)
9.	33	64	54%	45%	0 (3V)	5 (4V)
10.	17	42	86%	83%	1 (1.8V)	4 (2.7V)
11.	32	42	45%	52%	2 (3.5V)	5 (3.5V)

12.	21	41	65%	85%	1 (2.8V)	5 (3.3V)
13.	19	45	60%	62%	1 (3V)	5 (3.6V)
14.	27	59	10%	55%	1 & 2(3.2V)	5 (3.5V)
Mean (SD)	24.8 (8.4)	52.2 (9)	58.3% (22.6)	65.7% (16.9)	3.1V	3.3V

4.3.1.1 Surgery and contact localisation

Surgery was performed as previously described (See Methods). For this study, a neurosurgeon (LZ) independently assessed the anatomical position of each contact in relation to the visualised STN in the axial and coronal planes. The contact closest to the centre of the STN (henceforth "inside") and that furthest from the centre of the STN (usually the uppermost one-henceforth "outside") were thus identified. These were not always the active contacts used for chronic stimulation (Table 1). Based on the mean amplitude of stimulation at the time of assessment (3.1V for the left brain, 3.3V for the right) we defined low voltage as 2 Volts and high voltage as 4 Volts. The pulse width and frequency were kept at the clinical setting of the time of stimulation (for all patients in this study frequency was 130 Hz and pulse width was 60 μsec).

4.3.1.2 Patient evaluation

This is a double blind within-subjects study. Both assessors (PDL and ET) and the patients were blinded as to the stimulation condition. Stimulation parameter changes were performed by a trained collaborator, independent to the assessments.

Patients were studied after overnight withdrawal from their anti-parkinsonian medication. Six conditions were assessed in a random order, the four experimental conditions: inside the nucleus at 2V; inside the nucleus at 4V; outside the nucleus at 2V; outside the nucleus at 4V, as well as DBS OFF and DBS ON with usual clinical parameters. Following each change of parameters patients had a 15 minutes waiting before the evaluation.

The speech evaluation consisted of three tasks: sustained vowel phonation "ah" for three repetitions, the Assessment of Intelligibility for the Dysarthric Speech[20] (AIDS) and a 60-seconds monologue about a topic of the speaker's choice. The AIDS is the most widely used standardised test for measuring speech intelligibility (see Methods). The intelligibility score is the percentage of words correctly transcribed after two exposures to the sentences[21] by a native English speaker, blinded of the conditions.

The Computerised Speech Lab (CSL, Kay Pentax, 4150) was used for recording and analysis of all samples. Acoustic recordings were obtained using a calibrated Shure SM 48 dynamic microphone, with a 15 cm mouth-to-microphone distance, at a 22 kHz sampling rate in a sound treated room. For the measurement of the intensity-Sound Pressure Level (SPL dB) of the sustained phonation, calibration occurred at the beginning of each recording session using a 600 Hz tone at 15 cm, measured with a Quest 2100 SPL meter to allow for the conversion of CSL values to SPL[22]. Following speech recordings, movement was assessed using the UPDRS-III.

4.3.1.3 Data analysis

The 84 files from the AIDS sentences were rated blindly (EF) and a percentage of words correctly identified, was derived. For the acoustical analysis of intensity of sustained phonation, reading and monologue we calculated the mean vocal SPL dB measures from the speech recording of each condition.

To explore the impact of contact location and voltage amplitude for the four experimental conditions we used two factors within subjects ANOVA with factor A electrode contact site (with two levels: inside and outside) and factor B voltage amplitude (with two levels: high – 4 V and low – 2 V). Paired t-tests were used for post-hoc means comparisons.

For the comparison of speech and motor scores at the ON versus OFF STN-DBS conditions we used paired t-tests. The two-tailed level of significance was set at 5%. Statistical analysis was performed on SPSS-12 for Windows (SPSS Inc., Chicago, IL, USA) and Origin 7.5 (OriginLab Corporation, Northampton, MA 01060, USA).

4.3.2 Results

4.3.2.1 Speech intelligibility

High voltage had a significantly worsening effect on speech intelligibility in comparison to low voltage [F (1,52)=9.05, p=0.004]. The mean speech intelligibility score for the “inside/high” condition was 53.4% (SD 26.09), “outside/high” 53.42% (SD 26.93), “inside/low” 72.2% (SD 14.07) and “outside/low” 69.21% (SD 15.6) (Fig 4.1). Post hoc comparisons indicate that the mean speech intelligibility for the inside/high condition was significantly lower than the inside/low condition (p=0.02) with a mean deterioration of 18.7%. There was no main effect of contact location [F (1,52)=0.068, p=0.79]. The interaction effect between contact site and voltage was not statistically significant for speech or movement [F (1,52) = 0.06, p=0.79] and [F (1,52) = 0.59, p=0.44] respectively.

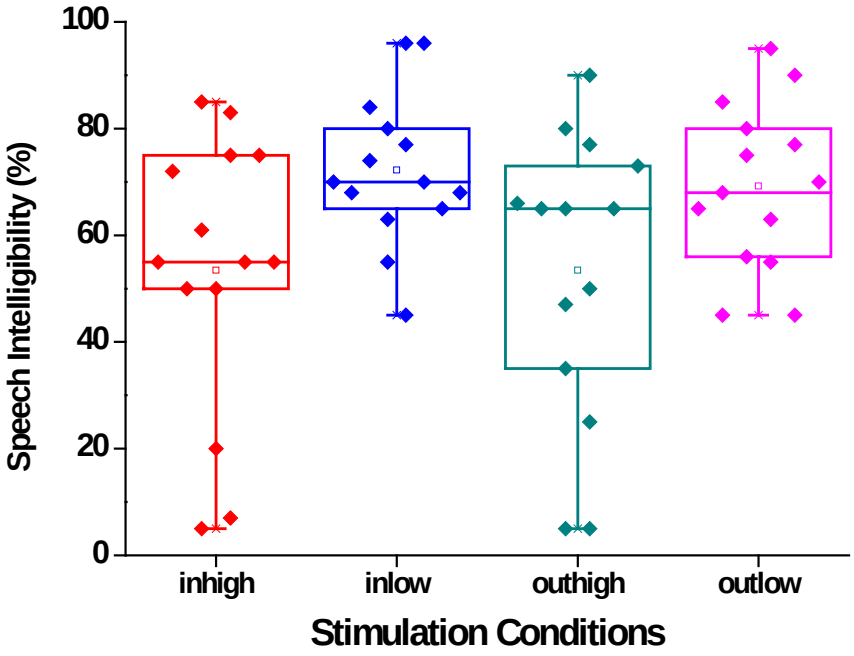

Figure 4.1: *Median (inside horizontal line), Means (small square), quartiles (first and third) and range of data points of speech intelligibility scores (in % of words understood) per stimulation condition.*

The average deterioration when stimulated at high voltage (inside and outside the STN) compared to low voltage was 16.5%. Detailed examination of individual patients' data reveals two distinct subgroups of patients, one group not or less affected by the increased amplitude of stimulation and one group showing a higher than the average deterioration of speech with increased amplitude. A blinded assessor (MIH) examined the electrode location of the patients in these two subgroups in more detail. Patients whose speech was less affected had electrodes positioned more posteriorily in the STN area (Figure 4.2a). Patients showing marked deterioration had electrodes positioned more medially or anteriomedially to the STN (Figure 4.2b).

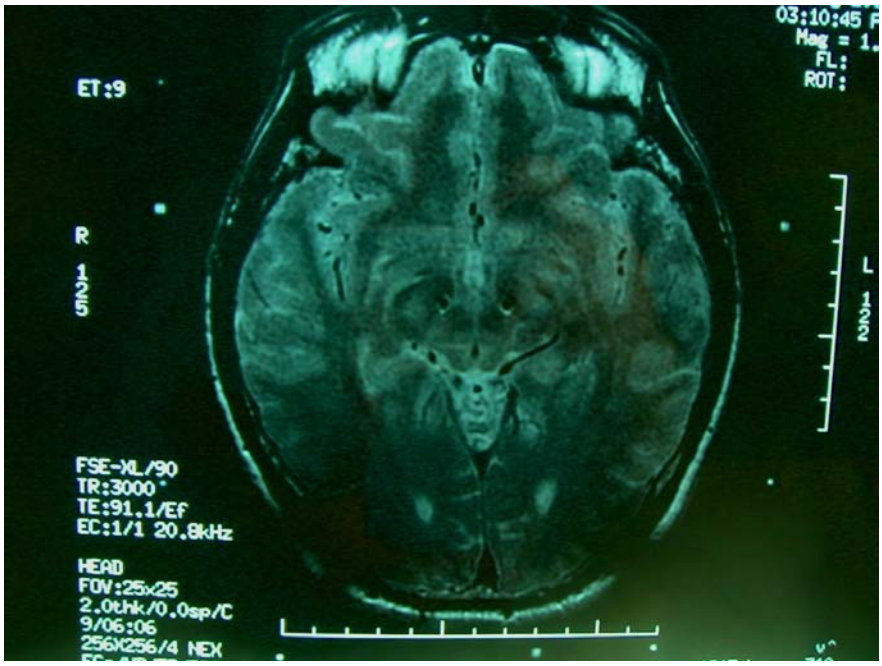

Figure 4.2a: *Example of electrode location of a patient whose speech did not change with high voltage stimulation.*

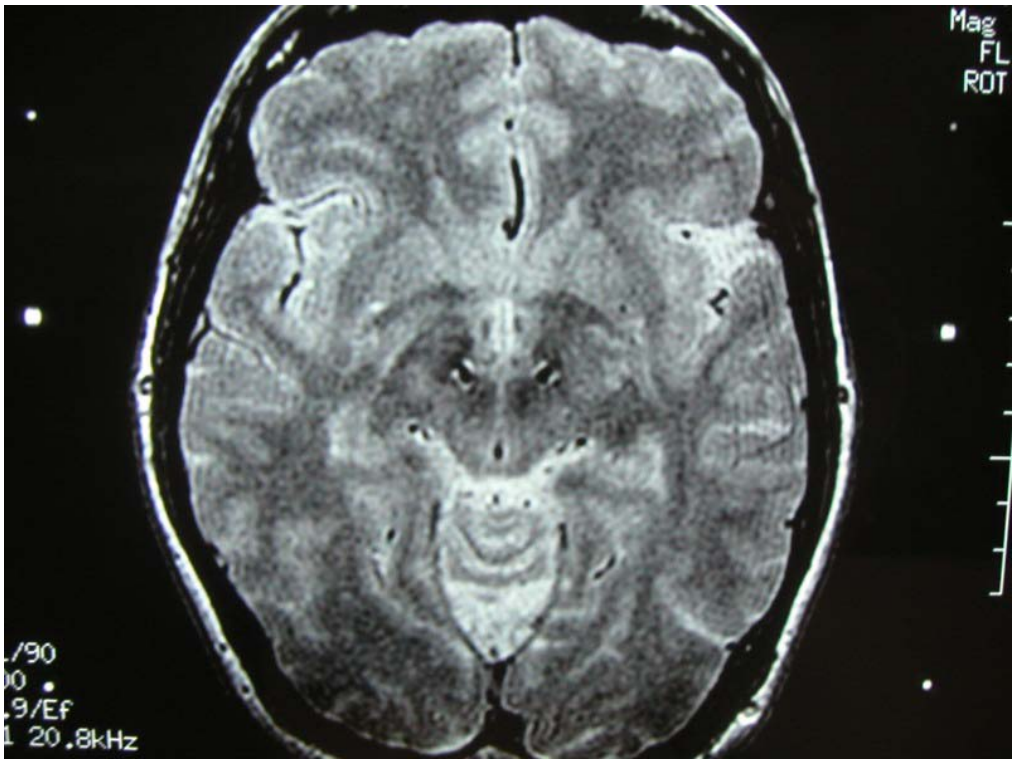

Figure 4.2b: *Example of electrode location of a patient with marked speech deterioration when stimulated at high voltage.*

4.3.2.2 Acoustic measures

We used a two-factor within-groups analysis of variance to explore the impact of contact location and voltage amplitude on intensity (SPL dB) for sustained phonation, the one minute monologue and the read sentences. The interaction effect between contact location and voltage amplitude was not statistically significant for either speech task. The main effects for contact location [F (1,52)=0.61, p=0.43] and voltage amplitude [F (1,52)=0.22, p=0.63] did not reach statistical significance for intensity (SPL dB) measures of sustained vowel phonation. Similarly the main effects for contact location [F (1,52)=3.25, p=0.07] and voltage amplitude [F (1,52)=0.0005, p=0.98] for the intensity (SPL dB) of the one-minute monologue were not significant. The main effects for contact location [F (1,52)=0.61, p=0.43] and voltage amplitude [F (1,52)=0.22, p=0.63] for the intensity (SPL dB) of the read sentences were not significant either (Table 4.2).

Table 4.2: *Mean and standard deviation of dB SPL (15cm) during sustained phonation /aa/, reading AIDS sentences and monologue at each stimulation condition.*

Stimulation condition	*SPL (dB) for sustained phonation Mean (SD)*	*SPL (dB) for AIDS read sentences Mean (SD)*	*SPL (dB) for one minute monologue Mean (SD)*
Inside/high	71.5 (5.7)	73.7 (5.6)	73 (6.6)
Inside/low	71.1 (6.6	72.2 (6.1)	71.35 (5.8)
Outside/high	68.9 (5.9)	70.2 (5.9)	68.5 (6)
Outside/low	69.7 (4.3)	73.2 (5.9)	70.14 (5.44)
OFF stimulation	69.4 (6.3)	71.8 (6)	71 (6.5)
clinical settings	70.8 (7.8)	72 (6.4)	71.64 (7.8)

4.3.2.3 Motor scores

High voltage had a significantly more beneficial effect on movement than low voltage [F (1,52)=13.33, p=0.00061] (mean UPDRS-III "inside/high": 23.7, (SD 7.2), "inside/low": 35.4 (SD 13.6), "outside/high": 31.4 (SD 7.4) and "outside/low": 39 (SD 9.7)). Contacts inside the STN had a significantly more beneficial effect on movement than contacts outside the STN [F (1,52)=4.54, p=0.03] (Figure 3). The interaction between contact site and voltage was not statistically significant [F (1,52) = 0.59, p=0.44] for the UPDRS-III. Post hoc comparisons indicate that the mean UPDRS-III for the inside/high condition was significantly lower (i.e. better function) than the inside/low condition (p=0.0088). Equally the UPDRS-III score for the outside/high condition was significantly lower than the outside/low condition (p=0.029). Post-hoc comparisons indicate also that the mean UPDRS-III score for the inside/high was significantly lower (i.e. better function) than the outside/high. There was no statistically significant difference between the inside/low and outside/low conditions (p=0.114).

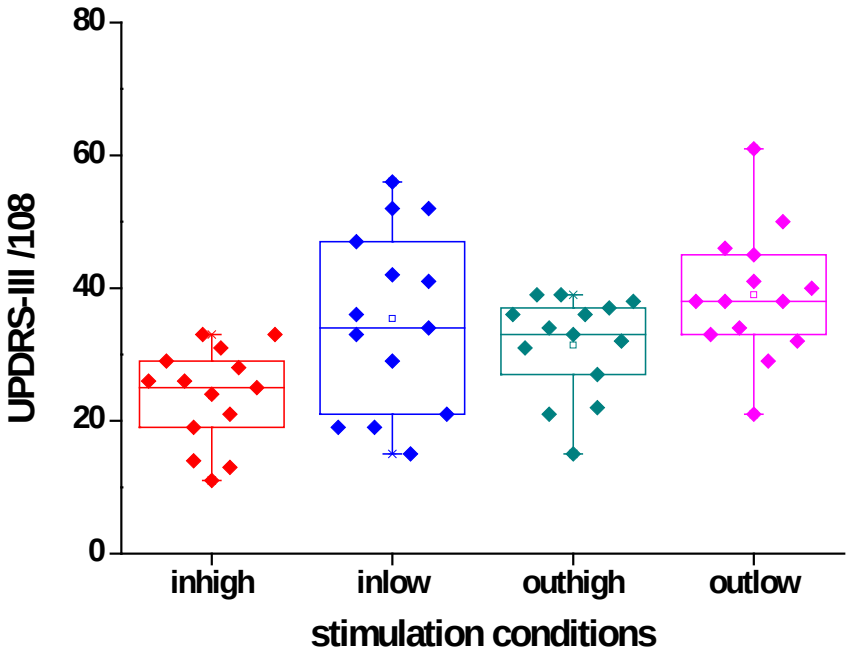

Figure 4.3: *Median (inside horizontal line), Means (small square), quartiles (first and third) and range of UPDRS-III scores per stimulation condition.*

4.3.2.4 Speech and motor score with stimulation-on at clinical parameters versus off-stimulation.

A paired samples t-test was conducted to evaluate the impact of stimulation-on at clinical settings and off-stimulation on speech intelligibility (AIDS) and on UPDRS-III motor score. The difference between speech intelligibility on- (mean=58.3% SD=22.63) and off-stimulation (mean=65.78%, SD=16.99), [t (26) = 0.98, p=0.33] was not significant. The mean decrease in speech intelligibility when on-stimulation was 7.4%. There was a statistically significant improvement in UPDRS-III motor scores when patients were stimulated at clinical parameters (mean 24.8, SD 8.4) versus off (mean=52.28, SD=9), t (26) = 8.31, p=.000, with a 95% confidence interval ranging from 20.65 to 34.2.

4.4 Study 2. The role of the cerebellothalamic tract on speech intelligibility: a patient-specific model-based investigation of speech intelligibility and movement during deep brain stimulation.

In order to investigate further the variability of speech response with high voltage stimulation, in particular the spread of current medially to the STN, we studied a subgroup of patients further. Patient specific finite element computer models were set up for each patient and the electric field generated during various electrical settings was visualized. The overall aim of this study was to relate the anatomical aspect of the simulated electric field to acute effects of speech intelligibility and movement. This study was a collaboration with the department of Biomedical Engineering, Linköping University, Sweden (Astrom et al, 2010).

4.4.1 Patients and methods

4.4.1.1 Patient selection

Ten out of the 14 patients of Study 1 were included in this study (Table 4.3) based on their stimulation-induced effects on speech intelligibility. The patients fell into three groups: Group A (patients 1-2) included patients with substantially impaired speech intelligibility during 4 Volt (V) amplitude settings compared to off stimulation. Group B (patients 3-6) included patients with slightly impaired speech intelligibility during 4V amplitude settings compared to off-stimulation, and group C (patients 7-10) included patients whose speech intelligibility was not impaired during 4V amplitude settings. The stimulation-induced impairment of speech intelligibility was considered substantial if a reduction of ≥ 30% was present, slight if a reduction of 7-10% was present, and not impaired if a reduction of ≤ 1% was present (Table 4.3).

Table 4.3: *Speech intelligibility and UPDRS-III scores during 4V, 2V, and off-stimulation for the subgroup of 10 patients who were studied further.*

Patients	Group	Speech 2 V	Speech 4 V	Speech Off	UPDRS-III 2 V	UPDRS-III 4 V	UPDRS-III Off
1	A	45%	7%	60%	52	28	71
2	A	84%	55%	85%	19	21	41
3	B	70%	20%	30%	33	33	62
4	B	65%	50%	60%	34	26	48
5	B	63%	61%	70%	29	31	50
6	B	68%	55%	62%	52	32	45
7	C	74%	75%	76%	47	14	51
8	C	77%	83%	75%	42	24	57
9	C	68%	55%	53%	21	29	42
10	C	55%	50%	45%	56	25	64

4.4.1.2 Patient specific simulations and visualisation

Electric field simulations were performed for all patients with 2V and 4V electric potential settings which were used during the assessments. The electric field was visualised in three dimensions with isolevels at 0.2 V/mm together with the anatomy on two-dimensional colour-coded axial and coronal slices. The contours of the electric field isolevels were traced onto the axial and coronal slices where they were colour-coded according to the assessment scores on speech intelligibility. Red colour indicated substantially impaired speech intelligibility (≥30% impairment), orange colour indicated slightly impaired speech intelligibility (7-10% impairment), and white colour indicated no reduction of speech intelligibility (<7% impairment) (Figure 4.4). Surrounding structures of the STN e.g. the pallidofugal fibres and fct, were identified and traced onto the model images with help from atlases presented in Gallay et al, (2008) and Morel (2007).

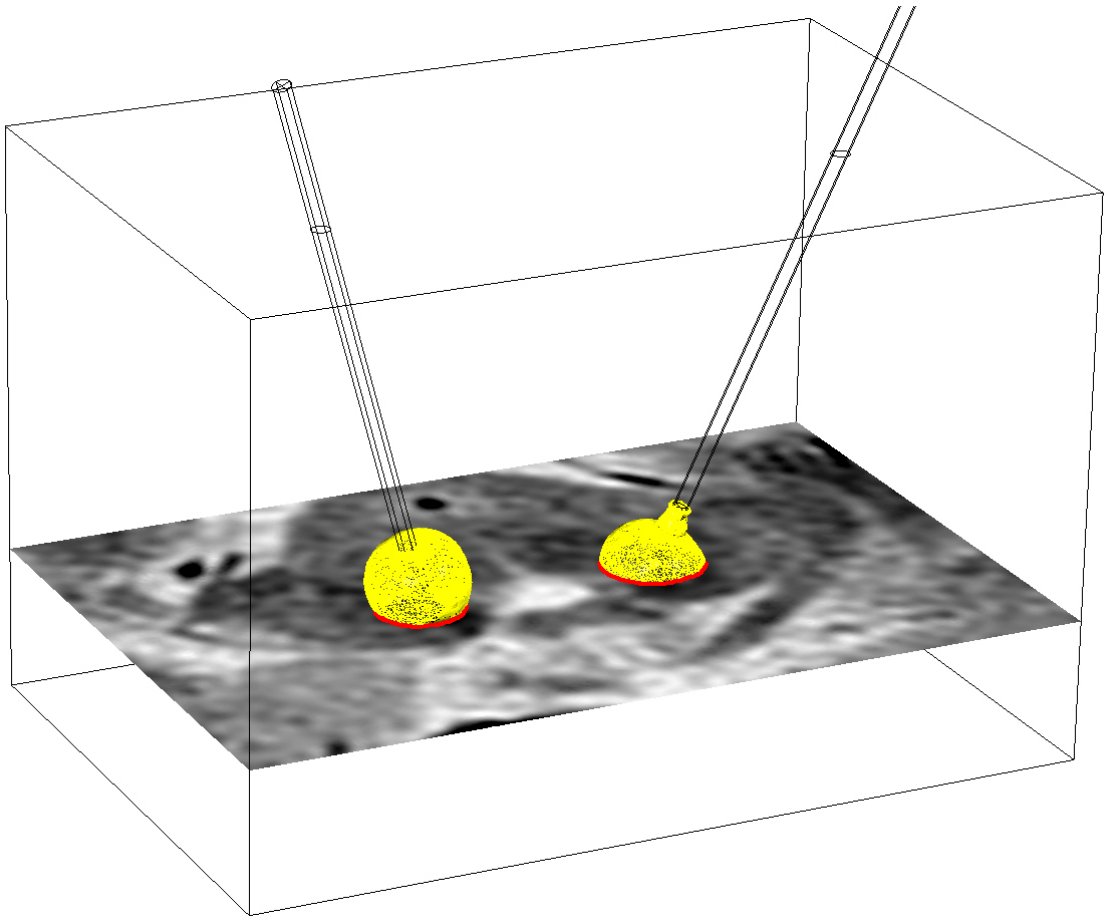

Figure 4.4: *Patient-specific simulation of DBS in the STN. The electric field was visualized with isolevels at 0.2 V/mm. The isolevels were traced onto axial and coronal images. In this figure the trace was coloured in red, which indicates substantially decreased speech intelligibility.*

4.4.1.3 Atlas model

In order to improve the understanding of the anatomical relation between the STN and its surrounding structures, a 3D atlas model of the STN, red nucleus (RN), fct, al, fl, fasciculus thalamicus (ft), substantia nigra pars reticulata (SNr), substantia nigra pars compacta (SNc), globus pallidus interna (GPi), and the globus pallidus externa (GPe) was created in Matlab 7.0 (The MathWorks, USA). The anatomical model was based on axial images from a stereotactic atlas of the human thalamus and basal ganglia by Morel (2007). The atlas model also included a modelled DBS electrode positioned in the posterodorsal part of the STN with an animated electric field at contact 2.

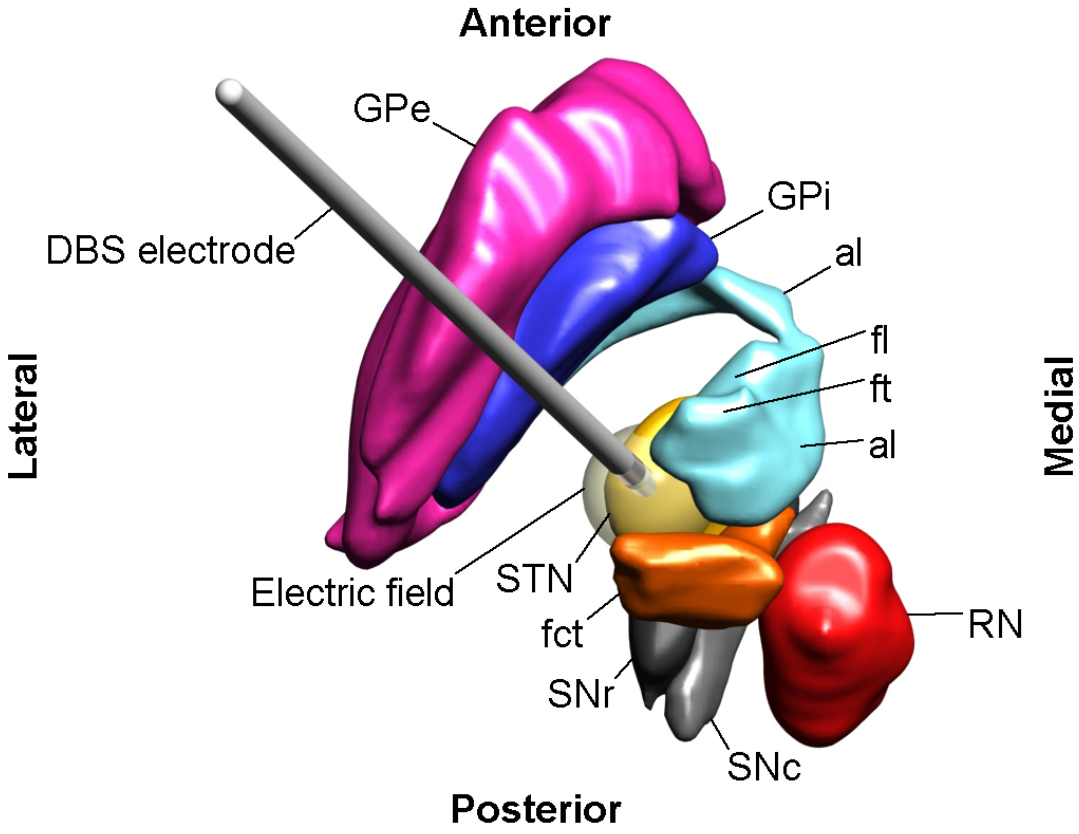

Figure 4.5: *Three-dimensional atlas model. A three-dimensional atlas model of the STN, RN, fct, al, fl, ft, SNr, SNc, GPi, and GPe together with a modelled DBS electrode placed in the posterodorsal area of the STN. An electric field was visualized with a transparent isolevel in white colour. (From: Astrom et al, 2010).*

4.4.2 Results

4.4.2.1 Speech intelligibility and the fct

The patients in group A (patients 1-2) suffered from substantial stimulation-induced impairment of speech intelligibility during high amplitude stimulation (i.e. 4V) (Table 4.3). These two patients had at least one active electrode contact positioned in the posterior part of the STN. The simulated electric field isolevel covered except for the STN also a major part of the fct during high amplitude stimulation. Patient 1 suffered from stimulation-induced impairment of speech intelligibility also during low amplitude stimulation (i.e. 2V). The electric field isolevel in relation to the fct, al, fl, and ft is presented in Table 4.4.

The speech intelligibility in group B (patients 3-6) was noticeably impaired during high amplitude settings, although to a smaller degree than the patients in group A (Table 4.3). The patients of group B had at least one electrode contact positioned in the posterior and/or medial part of the STN. In patient 3, 4 and 6 at least one of the active contacts were also positioned ventral to the centre of the STN. At least one of the electric field isolevels covered part of the fct during high amplitude stimulation. In patient 5, speech intelligibility was reduced also during low amplitude stimulation. The electric field isolevel in relation to the fct, al, fl, and ft is presented in Table 4.4.

The patients in group C (patients 7-10) did not suffer from stimulation-induced speech impairments during high or low amplitude stimulation (Table 4.3). Patient 7-9 had electrode contacts positioned in the dorsal part of the STN area, while the left electrode contact in patient 10 was located more ventral. This electrode was pulled up ~2.5 mm one week after the post-operative images were acquired. Despite the fact that this was compensated for in the model, the position of this electrode is uncertain. The distribution of the electric field isolevels during high amplitude stimulation did not cover part of the fct in patient 7-9, and slightly covered part of the fct in patient 10.
The electric field isolevel in relation to the fct, al, fl, and ft is presented in Table 4.4.

Table 4.4: *The position of the left (L) and right (R) active electrode contacts were described in relation to the centre of the STN. The spatial distribution of the electric field isolevels during high amplitude stimulation (4 V) were described in relation to the fct, al, fl, and ft, where N = did not cover, S = slightly covered, and C = considerably covered the structure.*

Patients		Electrode contact position	Electric field isolevel covered:			
(L/R side)			fct	al	fl	ft
1	L	dorsal, posterior	C	N	C	C
	R	dorsal	N	S	C	C
2	L	centre	S	N	C	N
	R	posterior	C	N	C	N
3	L	ventral, medial	C	N	C	C
	R	ventral, medial, posterior	C	N	C	C
4	L	medial	N	N	C	C
	R	ventral, medial, posterior	C	N	C	S
5	L	medial	S	N	C	C
	R	medial	S	S	C	C
6	L	ventral	S	N	S	N
	R	posterior	S	N	S	N
7	L	dorsal	N	N	C	C
	R	dorsal	N	N	C	C
8	L	dorsal	N	C	C	C
	R	dorsal	N	C	C	C
9	L	dorsal, medial	N	S	C	C
	R	dorsal, medial	N	C	C	C
10	L	ventral, medial	S	N	C	S
	R	dorsal, anterior	N	N	C	C

4.4.2.2 Movement

Movement as scored by the UPDRS-III was improved in all patients to various degrees during both low and high amplitude settings compared to off-stimulation (Table 4.3). Patients 2, 3 and 5, had similar motor scores during both low and high amplitude stimulation, while patient 1, 6, 7 and 10 showed large differences in the UPDRS-III between low and high amplitude stimulation. The electric field isolevel in relation to the fct, al, fl, and ft is presented in Table 4.4. High amplitude stimulation was more consistent in improving the motor scores than low amplitude stimulation. This was also the case in patients whose speech intelligibility was substantially impaired by the stimulation. No general differences were found in the acute stimulation-induced effects on movement between groups A, B, and C.

4.5 Discussion

4.5.1 The role of high voltage on speech intelligibility

We have demonstrated in this study that speech intelligibility can deteriorate with high voltage for contacts both inside and outside the STN. Deterioration in speech intelligibility was not linked to a significant deterioration of vocal loudness. High voltage stimulation of contacts inside the STN can have a beneficial effect on motor scores and at the same time induce a significant deterioration of speech intelligibility. The degree to which speech is affected by high voltage stimulation was variable between patients.

The role of high voltage on speech confirms previous reports. Tornqvist et al (2005) found an impairment of speech following a 25% increase in voltage or with frequencies 185 Hz and 130 Hz, compared to 70 Hz. Krack et al (2002, 2003) and Tommasi et al

(2007) have also reported speech deterioration with increased electrical parameters such as frequency and voltage.

In our study speech motor deficits subsequent to high voltage STN-DBS include breathy and hypernasal voice quality, intermittently continuous voicing of a hyperfunctional character, and slowed lip, tongue and jaw movements, leading to imprecise articulation. In addition, dystonic contractions of the laryngeal and velar muscles may emerge during connected speech, but not in association with laughing/crying or production of isolated vowels. These characteristics are not typical of the syndrome of hypokinetic dysarthria as initially described by Darley and co-workers (1969) in patients with Parkinson's disease. Rather, the observed profile of speech motor deficits must be considered a variant of mixed dysarthria, encompassing bradykinetic and dystonic features. Further evidence for a mixed dysarthria type emerging from STN stimulation is the lack of change in vocal intensity despite the decreased intelligibility. This is contrary to other studies in PD dysarthria where increased loudness is associated with increased speech intelligibility (Tjaden et al, 2004; Rosen et al, 2006).

Several hypotheses could explain the worsening effect of STN-DBS on speech. STN could have a different role or a different somatotopy for speech and body motor control. Another hypothesis is that the current could spread to other pathways in the area.

The somatotopy of the STN with respect to speech is very poorly understood, mainly due to lack of animal models. In monkeys, neurons in the dorsolateral part of the STN and the substantia nigra have been identified to be particularly active during oral movements for feeding (Mora et al, 1977; DeLong et al, 1983). Mouth movements have

been elicited by electrical stimulation applied in the STN area (Mora et al 1977). In the non-parkinsonian monkey the face was represented in the most lateral zone of the STN (Wichmann et al, 1994).

4.5.2 Stimulation-induced speech impairment and spread of current to neighbouring structures

The electric field generated by DBS electrodes is capable of spreading to a large volume of tissue (McIntyre et al, 2004). Guiot and colleagues (1961) had first hypothetised that the spread of current to the cortico-bulbar tract during intraoperative electrical stimulation could be responsible for speech impairment. This has recently been suggested by Krack et al (2003). Tommasi and colleagues (2007) analysed the pyramidal tract side effects (PTSEs) induced by increased voltage of stimulation. They also studied the relationship between the voltage threshold for the PTSEs and the distance from the centre of the used contact to the medial border of the pyramidal tract as measured on MRI in 14 patients treated with bilateral STN-DBS (i.e. for 28 electrodes). They differentiated between stimulus-dependent contractions of muscles referred to as speech organs and dysarthria defined as a) the subjective effort to speak reported by the patient and the objective observation by the physician of the qualitative speech changes time-locked to the stimulus, b) the worsening of speech disturbances in parallel with the voltage increase and c) the reproducibility of these effects. They found increased contractions in the forehead, eyebrow, eyelid, cheek, lip and chin with progressive increase in voltage. Contractions of the lower face were opposite to the stimulation site for all the electrodes and bilaterally for the upper face. Dysarthria was observed for seven out of 28 electrodes and it was characterised by hypophonic, slurred speech, rapid fatiguing and hesitation with frequent, long pauses. However dysarthria

was rarely involved as the initial PTSE. Initial PTSEs were located in the face. They also found a linear correlation between the distance from the chronically used contact and the medial pyramidal tract border and the voltage threshold for motor contractions. This confirmed their hypothesis that the observed motor contractions were induced by spread of current to the pyramidal tract. However they report no correlation between the motor contractions of the face observed as early signs of PTSEs in the majority of the electrodes and dysarthria, observed in a small number of patients and with increased stimulation voltage. However if the effects on speech were caused by the spread of current to the internal capsule, and the corticobulbar pathways for laryngeal motor control, we would expect a significant change on sustained phonation and other acoustical parameters of connected speech, which is not observed in our data.

Spread into other pathways, namely the pallidofugal and the cerebellothalamic fibres could affect speech and it is especially likely from patients with medially placed electrodes (Morel, 2007). Results from the simulations showed that patients with stimulation-induced speech impairments had electrodes placed medial and/or posterior to the centre of the STN. In these patients the electric field isolevel during high amplitude stimulation only slightly extended laterally into the corticobulbar fibres. Thus, it is not likely that the speech impairments were attributed to stimulation of corticobulbar fibres.

4.5.3 Stimulation-induced speech impairment and the fasciculus cerebellothalamicus

In a study by Plaha and co-workers (Plaha et al, 2006) stimulation related dysarthria was noticed in patients with active electrode contacts positioned medially to the STN. The authors believed that stimulation of fibres from the fct that control movements of

the vocal cords was likely the cause of the dysarthria. In addition, Velasco et al (2001) found that three out of ten patients suffered from stimulation-induced dysarthria from electrodes placed in the prelemniscal radiation which run medially to the STN and contain cerebellar fibres. These results are in agreement with the present findings. In addition, the fct projects to the motor thalamus with primary projections to the ventral intermediate nucleus (VIM) (Gallay et al, 2008). Thus, current spread into the fct may constitute a possible cause of the well-known stimulation-induced speech impairments during VIM DBS. In addition in the present study it was shown that speech intelligibility was impaired only when the 0.2 V/mm electric field isolevel covered part of the fct and not when the electric field isolevel covered a major part of the pallidofugal fibres without covering the fct. This is the important finding of this study.

4.5.4 Limitations of the simulation study

It is important to recognize that the patient specific models and electric field simulations presented in this study only provide a rough estimation of the electric field generated by DBS (Astrom et al, 2009). Most importantly, the 0.2 V/mm electric field isolevel should be interpreted as a boundary wherein the electric field is 0.2 V/mm or larger, and not as the volume of tissue influenced by the stimulation. Various neural components (soma, axons and dendrites) are affected differently depending on their size and orientation in the electric field, and the volume of tissue influenced by DBS is still not known. The 0.2 V/mm isolevel was used in this study for visualization of relative changes of the electric field between high and low amplitude stimulation. The uncertainty of the volume of influence exists in parallel with the uncertainty of the brain anatomy and physiology on a detailed level. Atlases presented by Gallay and colleagues (2008) and Morel (2007) were used to identify and trace the contours of structures and fibre-paths

in the surrounding of the STN onto the axial and coronal images. However, these traces only provide an approximation of the true locations of these structures and fibre paths due to e.g. slight misplacement of the atlas, the MRI not being aligned with the anterior commissure – posterior commissure (AC-PC) plane, and patient individual anatomical variability.

The results indicate that movement can be improved by DBS for a wide range of electrode contact locations and electrical settings within the STN area. Stimulation of the fct may be a possible cause of stimulation-induced dysarthria during STN-DBS. Special attention to stimulation induced speech-impairments should be taken in cases when active electrodes are positioned medial and/or posterior to the centre of the STN. However, only the acute effects were assessed which is not always equivalent with the long-term effects. Assessments during unilateral stimulation of the STN have suggested that the effect on speech intelligibility is hemisphere specific (Santens et al, 2003; Wang et al, 2003). Although highly relevant, unilateral assessments were not performed in this study in order to keep the examination time reasonable. Moreover, the small sample size of the present study accentuates carefulness when interpreting the results.

CHAPTER 5: EFFECTS OF MEDICATION AND SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION (STN-DBS) ON TONGUE MOVEMENTS IN SPEAKERS WITH PARKINSON'S DISEASE USING ELECTROPALATOGRAPHY (EPG): A PILOT STUDY.

5.1 Summary

Speech problems in PD following STN-DBS can be due, in part, to articulatory breakdown. Timing and accuracy of tongue movement can affect articulation. The aim of this pilot study was to quantify the effects of bilateral STN-DBS and medication on articulation, using Electropalatography (EPG).

Two patients were selected to participate for their contrasting speech response to STN-DBS: PT1 showed deterioration of speech intelligibility with stimulation whereas PT2 showed improvement. They were studied under four conditions: on- and off-medication and on- and off-stimulation. The EPG protocol consisted of a number of target words with alveolar (/t/, /d/) and velar (/k/, /g/) stops, repeated 10 times in a random order. The results illustrated the variable effects of stimulation and medication on articulation and the role of tongue movements on speech intelligibility. The study quantified more articulatory imprecision for alveolar stops than velars. Furthermore, the findings provided evidence that stimulation with medication has a more detrimental effect on articulation than stimulation alone in both patients.

This pilot study illustrates the variability of response to STN-DBS, the way stimulation can affect the timing and amount of tongue movements as well as the role of tongue movements on speech intelligibility. It is also the first study to use EPG to quantify tongue articulation during speech following STN-DBS.

5.2 Introduction

A number of studies on PD articulation have reported that stop consonants (/p,t, k,g,b,d/) were imprecise and sound like fricatives (/f, θ, χ, v, γ, δ/) (Logemann, 1981; Weismer, 1984). So far initial reports on the effects of STN-DBS on speech have showed a marked improvement of lip and tongue force, as measured with non-speech oral motor tasks. Gentil and colleagues (Gentil et al, 1999) studied the oral force control of ten selected patients using load-sensitive devices to measure the compression forces generated by the upper and lower lip and tongue. STN stimulation improved speech performance as measured with the UPDRS-III speech item 18, and increased the maximal strength, accuracy and precision of the articulatory organs. The same group reported the beneficial effects of stimulation on acoustical data of 26 PD patients (Gentil et al, 2001; Gentil et al, 2003). Pinto and colleagues (Pinto et al, 2005) illustrated a variable effect on speech in four case studies. Response to STN stimulation ranged from improvement with medication and stimulation to deterioration with increased voltage intensity. More recent studies point out this dissociation between improvement in acoustic measures of speech and decline in speech intelligibility (Klostermann et al, 2007; D'Alatri et al, 2008; Pützer et al, 2008). Putzer et al, (2008) reported the presence of articulation problem, mainly fricated stops in five out of nine patients when on-stimulation. Most of the studies mentioned so far are based either on acoustic measures, or on non-speech oro-motor tasks (with load-sensitive devices), with limited indication of the underlying articulatory problem during speech. In comparison

to the studies mentioned above we wanted to use a method that enables quantification of changes in consonant production during speech. Electropalatography (EPG) was the technique of choice for this articulatory analysis, because it can detect articulatory undershoot (Hardcastle et al, 1985) and thus reflects levels of articulatory precision. EPG is a technique that measures the amount of tongue to palate contact during speech. McAuliffe et al (2006a; b) investigated consonant production in nine patients with PD (non-operated) with a mild to moderate dysarthria using EPG. Contrary to expectations, they found no differences between their subjects and healthy controls in terms of segment duration, spatial characteristics or variability (McAuliffe et al, 2007). At the same time, perceptual ratings revealed impaired speech rate and target undershoot, which could not be quantified with EPG.

The aim of this pilot study was to use EPG to study the movements of the tongue to the palate in two patients with bilateral STN-DBS. We aimed to focus on velar and alveolar stops (/t/, /k/) because from clinical observation we anticipated most articulatory problems in tongue tip and back-of-the tongue sounds.

This study was a collaboration with Dr M. Hartinger and Prof. William Hardcastle from University of Edinburgh.

5.3 Patients and methods

5.3.1 Patients

Two patients (PT1 and PT2) were selected for the pilot study, on the basis that DBS produced contrasting effects on their speech. Both patients were assessed pre- and post-operatively using the Assessment of Intelligibility of Dysarthric Speech (AIDS, Yorkston & Beukelman, 1984) and the Unified Parkinson's Disease Rating Scale, Part

III (UPDRS-III), as part of their routine clinical testing off- and on-medication and off- and on-stimulation. STN-DBS improved the motor symptoms of both patients (Table 5.1A).

Speech intelligibility was rated as described before (Chapter 2 and 3). PT1's speech intelligibility deteriorated with STN-DBS, especially when on medication, whereas PT2 had the opposite effect, his speech intelligibility was improved following one year of stimulation (Table 5.1B). Speech for PT1 when off-medication/on-stimulation was characterised by imprecise consonants, reduced voice volume, monopitch, monoloudness, rapid rate and reduced stress. This pattern deteriorated with medication, mainly the articulatory imprecision and the strained-strangled voice quality. Conversely the pattern was improved when the patient was off-medication/off-stimulation. PT2's speech was characterised by some consonant imprecision and mildly strained voice with the opposite effect of medication and stimulation.

Table 5.1A: *Patient details*

patient	**age**	**disease duration**	**UPDRS-III baseline**	**UPDRS-III post-operative**
PT1	57	15	21 (on)	16 (off/ON)
				11 (on/ON)
PT2	55	9	60 (off)	16 (off/ON)
			10 (on)	2 (on/ON)

Table 5.1B: *Speech intelligibility data of the participants as measured by the Assessment of Intelligibility of Dysarthric Speech (Yorkston et al, 1981) before the operation on- and off-medication and one year after (nearest time point to the EPG experiment) off-medication/on-stimulation, off-medication/off-stimulation and on-*

medication/on-stimulation. The data is the percentage of words understood per hundred.

patient	Baseline on-medication	Baseline off-medication	post-operative off-meds/on-stim	post-operative off-meds/off-stim	post-operative on-meds/on-stim
PT1	82%	90%	45%	72%	55%
PT2	90%	75%	92%	82%	95%

5.3.2 Electropalatography

EPG is a safe and non-invasive technique. Individual artificial palates were manufactured for each speaker. The artificial palate incorporates 62 touch-sensitive electrodes (see Figure 5.1) and records details of the location and timing of tongue contacts with the hard palate during speech. The speakers practiced using the artificial palate at home and then took part in the experiment. According to McAuliffe et al (2006a) after wearing the palate for 45 minutes speakers generally produce normal speech articulation (consistent with the no palate condition).

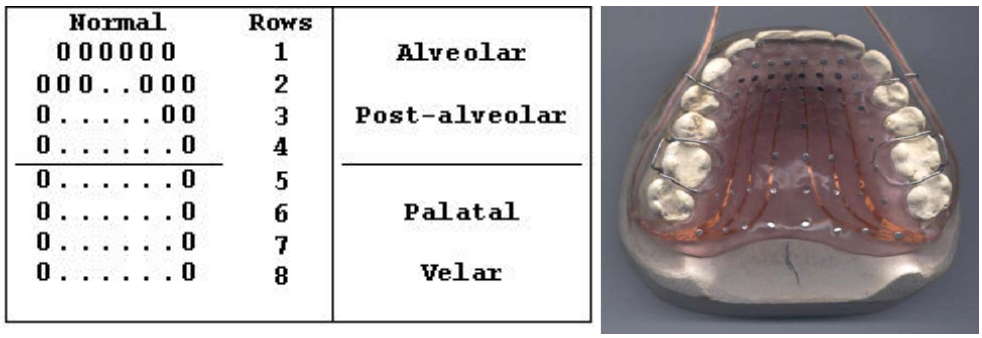

Figure 5.1: *EPG palate (left) and computerised EPG frame EPG frame (right).*

5.3.3 Stimuli

In order to keep co-articulatory and prosodic effects constant the test material was recorded in a highly controlled manner. The EPG protocol consisted of a number of monosyllabic target words with alveolar and velar stops, repeated up to 10 times in random order.

The words (take, Tate, cake, Kate) contained a CVC structure where C = /t/ or /k/ and V = /ei/. The four words were embedded in the frame sentence 'It's a ___ again' to keep the co-articulatory effects on the initial and final sounds constant. Stops were chosen because most speech errors in parkinsonian dysarthria occur on these sounds (McAuliffe et al, 2006a). Furthermore, we were interested in the comparison of tongue tip (alveolar) versus tongue back (velar) movements, since some authors propose that back of tongue movements are more impaired in PD speech (Logemann et al, 1978, Logemann & Fisher, 1981).

Because speech production is known to be highly variable generally, and even more so in parkinsonian dysarthria, (McAuliffe et al, 2007), we aimed to record 10 repetitions of each target in a random order to measure the variability of articulation patterns. During the recording the speakers were asked to read the sentences from a monitor in a normal and habitual way while wearing the EPG palate. Data presented here focus on the production of sounds in initial position only.

5.3.4 Experimental conditions

The WinEPG system was used to record EPG (100 Hz) and acoustic data simultaneously (44,100 kHz). The recordings were carried out on one day in four

conditions, lasting a maximum of 10 minutes each, in the following order: 1. off-medication/on-stimulation 2. off-medication/off-stimulation 3. on-medication/on-stimulation 4. on-medication/off-stimulation.

The on-medication recordings were started one hour after the oral intake of the patients' anti-parkinsonian medication. Following the on-medication/on-stimulation recording the stimulator was switched off for the on-medication/off-stimulation recording. The delay before starting the on-medication/off-stimulation recording was 10 minutes for PT1 and less than two minutes for PT2, who showed rapid deterioration and discomfort when the stimulator was switched-off. PT2 recorded a maximum of five repetitions of each word in these conditions.

5.3.5 Data analysis

Articulate Assistant software (version 1.16) was used to analyse the EPG data. The alveolar zone was defined as the first four rows of the palate, where the electrodes are relatively close together.

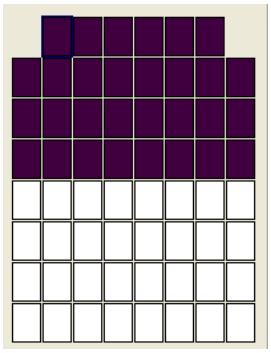

Figure 5.2: *Defined alveolar zone in the EPG palate.*

The velar zone comprised the last four rows. Our definition of velar closure does not necessarily presuppose full contact across the EPG palate, because actual articulatory closure may occur posterior to the last row of electrodes.

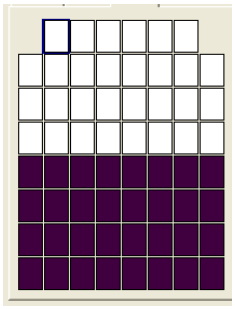

Figure 5.3: *Defined velar zone in the EPG palate.*

The data analysis was undertaken in two parts, segmentation of data and measurement of temporal and spatial characteristics.

5.3.5.1 Segmentation of closure phase

Because of the articulatory differences in the four conditions we devised consistent segmentation criteria that applied to accurate as well as impaired articulation (for example in the case of frication of stops, where no closure and release phase was produced).

The alveolar zone consists of 30 electrodes (figure 5.2). The defined onset of the closure phase marks the time point where a clear increase of tongue contacts in this region could be determined. For example for the initial alveolar stop /t/ in 'take' or 'Tate' the onset of the alveolar closure was the EPG frame where 12 out of 30 electrodes (40%) were activated. Figure 4 illustrates how the onset of the closure phase coincides with the abrupt increase of alveolar contacts in the middle trace where the EPG frames are displayed. This increase of activated contacts is displayed in the bottom trace of the figure and is marked as “onset”. Where it was not possible to use this criterion (i.e. in

cases of frication) we used the onset of acoustic energy to define the beginning of the consonant (Figure 5.4).

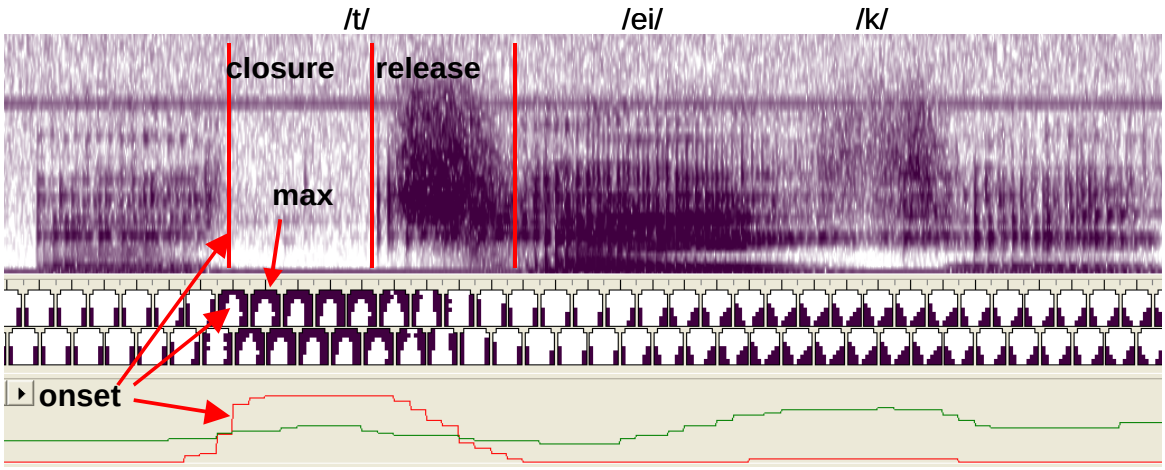

Figure 5.4: *Segmentation points for the target word 'take'. The segmentation lines mark the on- and off-sets of the different articulatory phases. The upper trace shows a spectrogram where the left annotation line marks the onset of the closure. The middle trace shows the succession of EPG frames every 10ms. The individual palate diagrams are staggered in two rows. In the bottom trace two lines are shown: one for the total number of contacts in the alveolar zone (red) and the other for the totals in the velar zone (green). The onset of the closure phase coincides with the time point in the bottom trace showing an abrupt increase in the number of alveolar contacts. This time point refers to the first EPG frame which shows a complete closure in the alveolar zone.*
The segmentation of the release is the synchronized time point of the burst in the spectrogram and where in the EPG frame the number of alveolar contacts decreases.

5.3.5.2 Temporal measurement

Consonant duration, i.e. the duration of contact for each segment measured in msec was used to describe the temporal characteristics of articulation. In the case of frication, only one time interval, namely that of the frication phase, was measured (see Figure 5.5).

5.3.5.3 Spatial measurement

Spatial characteristics were calculated based on the mean number of contacts at the frame of maximum contact during the closure phase (alveolar, velar) or, in cases such as the ones shown in Figure 5, during the frication phase.

In the case of abnormal stop production where no clear closure and release phase was produced (Figure 5.5), we measured the duration of the frication phase and identified the EPG frame with the maximum number of contacts to analyse the precision of articulation.

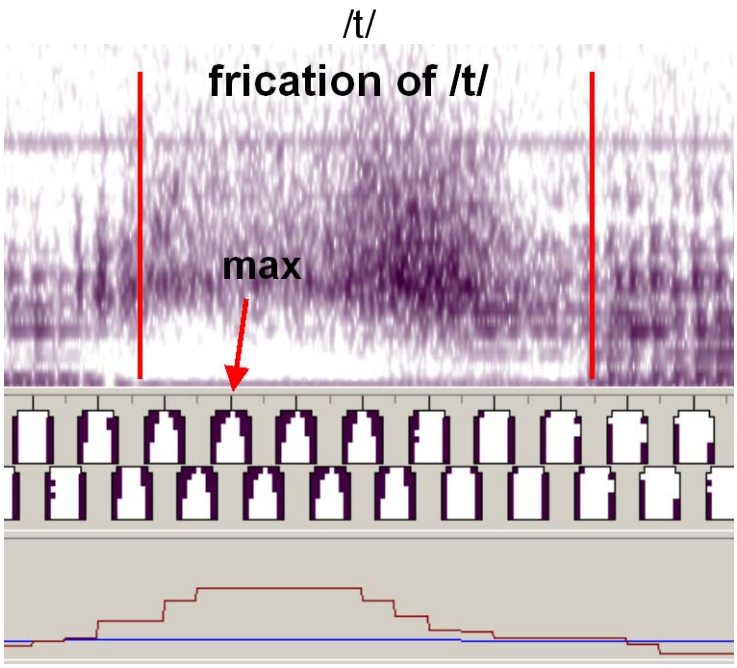

Figure 5.5: *Example of frication of the stop /t/ in 'take'. The EPG frames in the middle trace show an incomplete closure in the alveolar zone and a more /s/-like sound is produced. In the spectrogram no decreases of energy after the previous vowel can be seen and no burst which marks the beginning of a release ephase. The absence of these characteristics coupled with the presence of spatial noise indicates frication.*

Each target word was analysed separately, this means that “take” was not combined with “Tate” because the initial stops were in two different environments (with possible effects of the final consonant). In the off-stimulation stimulation condition of PT2 only three to five repetitions were recorded due to the deteriorating disease symptoms. Therefore the mean values of those symptoms are based on smaller numbers.

5.3.6 Statistical analysis

Two-way ANOVAs were conducted with the independent factors medication and stimulation and the dependent variables segment duration and maximal contact.

Statistical comparisons of articulation across the four recording conditions were undertaken using a two-way analysis of variance (ANOVA). The calculations were based on mean values of the 10 repetitions of each target word. In order to quantify imprecise consonant articulation, descriptive statistics were used to count the cases where stops were produced without a complete constriction in any one of the rows in the defined articulatory region.

Spearman r correlation coefficient between temporal and spatial data was calculated in order to determine any relationship between these two different parameters.

Due to the fact that the patients were selected on the basis of their different response to STN-DBS the results will be reported separately.

5.4 Results

5.4.1 Patient PT1

PT1's speech when on-stimulation was reduced in intensity, with fast rate and indistinct articulation. Intelligibility ratings showed a decrease from 72% intelligible speech when off-medication/off-stimulation to 55% when on-medication/on-stimulation.

Overall reduced speech intelligibility was linked with imprecise articulation in the form of fricated stops (Table 5.2). This phenomenon occurred mainly at the on-

medication/on-stimulation condition. In the off-medication conditions, stimulation clearly caused more frication. The stops sounded spirantised (similar to /s/). The frication seems to be influenced by the place of articulation (Table 5.2): frication occurred in velar but not in alveolar stops when on-medication/off-stimulation. Furthermore, higher numbers of frication of the initial stops /t/ and /k/ could be seen in words including final /t/ in comparison to final /k/ words, when on-medication/on-stimulation. Anticipatory tongue-tip (alveolar) gestures seemed to result in more frication than velar gestures.

Table 5.2: *Absolute frequency of normal and fricated (in brackets) production of closure phase for PT1 and PT2.*

		medication off		**medication on**	
word	**speaker**	**Stim- off**	**Stim- on**	**Stim- off**	**Stim- on**
take	PT1	10	7(3)	10	8(2)
	PT2	0(6)	10	1(9)	10
Tate	PT1	10	9(1)	10	1(9)
	PT2	0(5)	10	0(10)	8(2)
cake	PT1	10	8(2)	5(5)	6(4)
	PT2	0(4)	10	1(9)	8(2)
Kate	PT1	10	8(2)	7(3)	2(8)
	PT2	0(3)	10	1(9)	8(2)

5.4.1.1 Temporal characteristics

Consonant duration, i.e. the duration of contact for each segment measured in ms, was used to describe the temporal characteristics of articulation. When PT1 was off-stimulation he showed an increase in segment duration. As the ANOVA results show

(Table 5.3) there were significant temporal effects of stimulation on the segment duration (except for "cake"). Medication had no effect on the duration of alveolar or velar stops.

Table 5.3: *Means and standard deviations for the consonant duration split by articulatory region (alveolar-velar) for PT1.*

PT1								
	alveolars				velars			
	take		Tate		cake		Kate	
cond	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**
med/stim								
off/OFF	166.6	24.0	159.7	15.1	158.4	18.9	157.8	27.3
off/ON	132.1	11.3	122.3	18.0	146.6	49.1	131.5	14.0
on/ON	134.9	17.9	129.2	14.4	134.6	9.2	130.5	13.3
on/OFF	145.8	17.1	142.2	17.3	145.9	14.8	139.2	17.1
ANOVA	F(1,36)=		F(1,36)=		F(1,36)=		F(1,36)=	
med	2.5; p=.126		1.1; p=.304		1.9; p=.171		2.7; p=.108	
stim	15.6; **p=.000***		24.0; p=**.000***		1.7; p=.195		8.7; **p=.006***	
med*stim	4.3; **p=.046***		5.6; **p=0.23***		0.0; p=.973		2.2; p=.149	

The interaction of medication and stimulation was significant for alveolars but not for velars. In the alveolar stop production stimulation affected the durations when the patient was off-medication (166.6±24.0ms when off-medication/off-stimulation versus 132.1±11.3ms when off-medication/on-stimulation) but not on-medication (145.8±17.1ms when on-medication/off-stimulation versus 134.9±17.9ms when on-medication/on-stimulation) (Figure 5.6). The same tendency can be seen in the example of "cake" (Figure 5.7), where PT1 produced longer durations when off-stimulation.

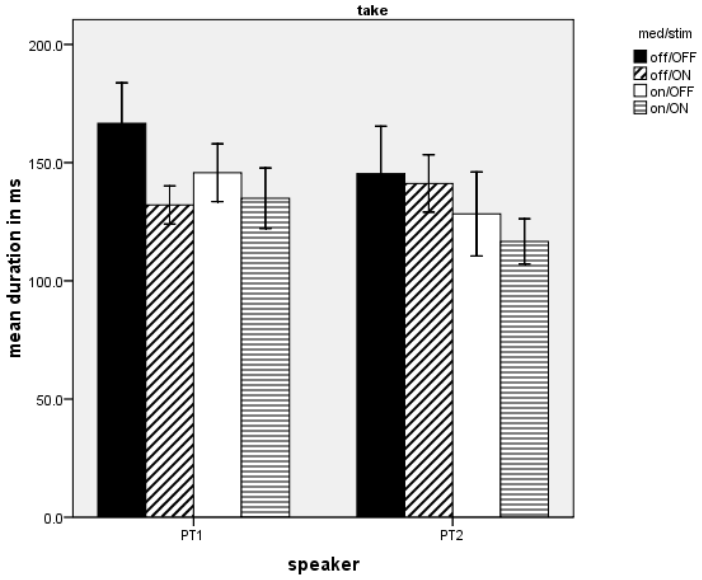

Figure 5.6: *Means and standard deviations of the stop duration (in ms) in the word "take" for PT1 and PT2.*

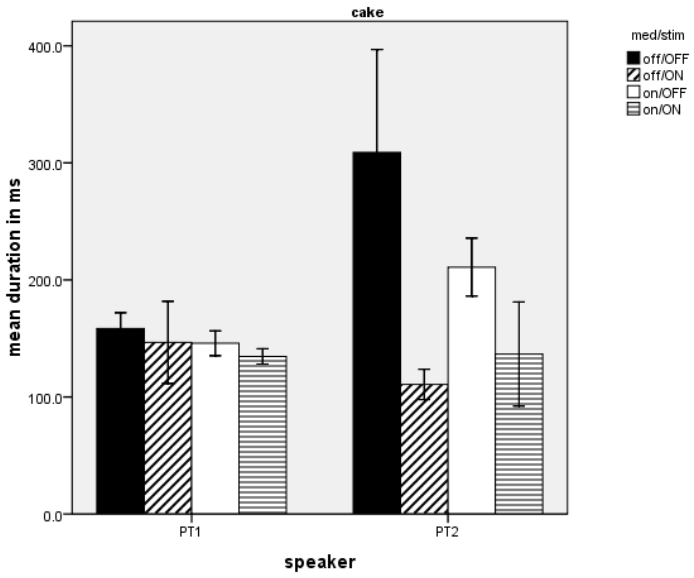

Figure 5.7: *Means and standard deviation of the stop duration (in ms) of "cake" in PT1 and PT2.*

5.4.1.2 Spatial characteristics

PT1 produced higher number of contacts for the alveolar closure of "take" in the off-stimulation condition in both on- and off-medication (Figure 5.8). Articulation for PT1 became less precise when stimulation was on. The results of the two-way ANOVA revealed a significant main effect of stimulation on the precision of tongue movements

in all the target words (Table 5.4). The main effect of stimulation was significant for alveolar but not for velar stops.

Table 5.4: *Means and standard deviations for the number of activated contacts of the tongue with the hard palate in the relevant articulatory region.*

PT1								
	alveolars				velars			
	take		Tate		cake		Kate	
cond	mean	SD	mean	SD	mean	SD	mean	SD
med/stim								
off/OFF	80	2.2	79	5.5	63.4	2.1	63.7	2.2
off/ON	65.3	12.2	70.7	8.6	55	2.2	55.6	3.2
on/ON	54.3	15.1	49.3	13.8	54.4	3.7	54.7	3.7
on/OFF	78	4.5	75.7	8.2	63.1	2.4	64	3.0
ANOVA	F(1,36)=		F(1,36)=		F(1,36)=		F(1,36)=	
med	4.2; p=**.048***		18.3; p=**.000***		0.3; p=.595		0.1; p=.760	
stim	36.7; p=**.000***		31.5; p=**.000***		103.1; p=**.000***		81.1; p=**.000***	
med*stim	2.0; p=.164		8.0; p=**.008***		0.0; p=.865		0.4; p=.534	

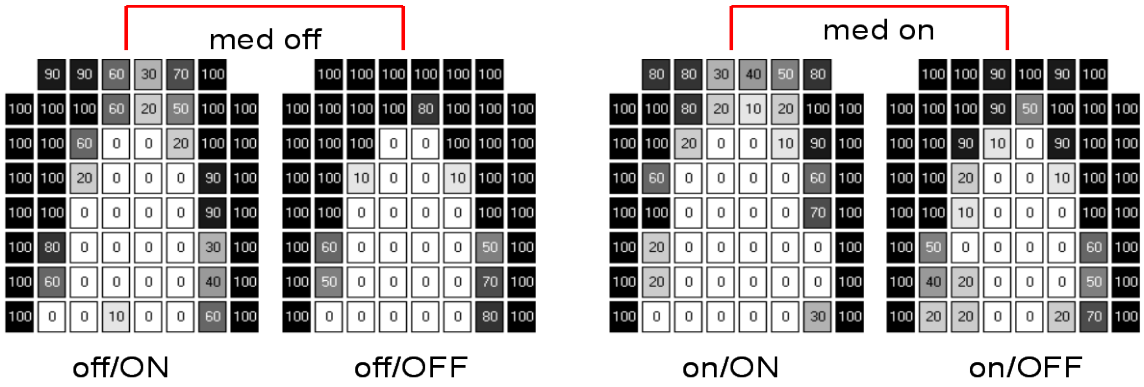

Figure 5.8: *Mean number of contacts during the closure phase of /t/ in 'take' in % for PT1. 100% means contact in 10 out of 10 repetitions in the relevant EPG zone. In cases where stops were fricated, the frame with the maximum number of contacts was included in the mean values as well. The numbers and different shadings refer to percentage values that show the mean number of activated electrodes for the multiple repetitions of the word. The black shading and a '100' in figure 10 mean that this electrode was touched in all of the repetitions (= 100% activated electrode) while '0' means that there was no contact in any of the repetitions.*

5.4.1.3 Correlation

In order to explore the relationship between timing (duration of contact) and articulatory precision (number of contacts), correlation coefficients were calculated. The results showed that prolonged durations do correlate with improved articulatory accuracy in PT1 (r2=0.61for "take", 0.40 for "tate"; 0.52 for "cake"; 0.99 for "Kate"). Thus it seems that deterioration of articulation in PT1 when on-stimulation was related to a decrease in

consonant durations, which resulted in what perceptually we describe as articulatory undershoot.

5.4.2 Patient 2 (PT2)

PT2 intelligibility improved from 90% pre-operatively on-medication to 95% post-operation (on-medication/on-stimulation). Speech when off-stimulation was reduced in intensity and slowed in rate (Table 5.1B).

Overall PT2 produced fricated stops in both the velar and the alveolar targets. Frication was found in both off-stimulation conditions. In terms of medication effects, articulation was more imprecise when on-medication compared to off-medication.

5.4.2.1 Temporal characteristics

Medication with stimulation significantly influenced segment durations in speaker PT2: when off-stimulation articulation was slower with longer durations, mainly for the velar sounds (Table 5.5) (mean segment duration= 308ms for “cake” off-medication/off-stimulation versus 110ms off-medication/on-stimulation). Such a large difference was not observed in the alveolar sounds. The 2-way ANOVA results also showed a significant main effect of medication (“take”: $F=10.2$. $p<0.01$, “Tate”: $F=8.7$, $p<0.01$, “cake”: $F= 70.1$, $p<0.001$, Kate: $F=73.8$, $p<0.001$). The interaction effect of medication and stimulation was significant in velar tongue movements (“cake”: $F=14.5$, $p<0.001$; “Kate”: $F=5.7$, $p<0.05$) but not in alveolar stops (“take”: $F=0.3$, n.s.; “Tate”: $F=0.9$, n.s.). Figures 5.6 and 5.7 illustrate the relative long duration for the velar stops, in the off-medication/off-stimulation condition. Thus medication for PT2 seems to increase the rate of speech, however in comparison with the on-stimulation conditions

medication alone (i.e. at the on-medication/off-stimulation condition) does not normalise speech rate.

Table 5.5: *Means and standard deviations for the consonant duration split by articulatory region (alveolar-velar) for PT2.*

PT2								
	alveolars				velars			
	take		Tate		cake		Kate	
cond	mean	SD	mean	SD	mean	SD	mean	SD
med/stim								
off/OFF	145.4	19.1	175.3	43.9	308.9	55.3	283.6	10.1
off/ON	141.2	16.9	140.8	16.4	110.7	18.1	122.4	9.7
on/ON	116.7	13.4	122.8	23.8	136.7	62.2	126.4	31.0
on/OFF	128.3	24.9	139.8	24.1	210.9	34.6	217.4	57.5
ANOVA	F(1,32)=		F(1,31)=		F(1,30)=		F(1,29)=	
med	10.2; p=**.003***		8.7; p=**.006***		4.9; p=**.034***		4.5; p=**.043***	
stim	1.5; p=.232		8.1; p=**.008***		70.1; p=**.000***		73.8; p=**.000***	
med*stim	0.3; p=.569		0.9; p=.341		14.5; p=**.001***		5.7; p=**.024***	

5.4.2.2 Spatial characteristics

While stimulation and medication showed noticeable temporal effects on velar articulation, there were no significant effects in terms of spatial characteristics (main effect of medication for “cake”: F=2.6, n.s; “Kate”: F=3.9, n.s.; main effect of stimulation for “cake”: F=0.8, n.s.; “Kate” F=1.2, n.s.). There were however effects on alveolar targets (main effect of medication for “take”: F=28.9, p<0.001; “Tate”: F=12.9, p=0.001; main effect of stimulation for “take”: F=39.7, p=0.001; “Tate” F=112.0, p=0.001) (Table 5.6). In terms of interaction effects between medication and stimulation on the precision of tongue movements there was no consistent difference between alveolar and velar stops (“take”: F=0.0, n.s, “Tate”: F=4.9, p<0.05, “cake”: F=14.4, p<0.001, “Kate”: F=3.1. n.s.). (Table 5.5).

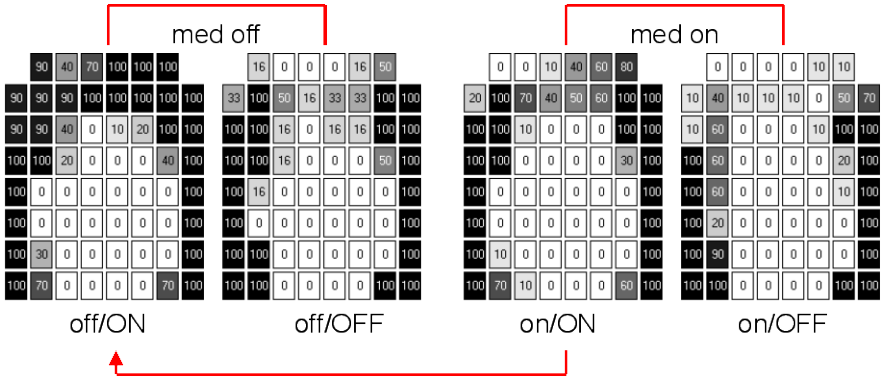

Figure 5.9: *Mean number of contacts during the closure phase of /t/ in 'take' in % for PT2. It shows that most precise articulation could be found off-medication/on-stimulation, whilst on-medication/on-stimulation PT2 produced less alveolar contacts. When the stimulator was switched off, the negative medication effects in comparison to articulation without medication can be seen again. Another interesting observation about this speaker is that in the off-stimulation conditions, when speech intelligibility deteriorated, additional velar contacts were noticeable. Thus, target undershoot in the alveolar region and overshoot in the velar region could be detected.*

Table 5.6: *Means and standard deviations for the number of activated contacts of the tongue with the hard palate in the relevant articulatory region.*

PT2								
	alveolars				velars			
	take		Tate		cake		Kate	
cond	mean	SD	mean	SD	mean	SD	mean	SD
med/stim								
off/OFF	80	2.2	29.3	6.4	34.4	0.0	35.4	4.8
off/ON	65.3	12.2	75.7	6.3	38.4	1.5	39.7	2.9
on/ON	54.3	15.1	54.7	14.5	36.6	2.1	40	3.5
on/OFF	78	4.5	24.3	9.7	39	3.3	40.9	4.3
ANOVA	F(1,32)=		F(1,31)=		F(1,30)=		F(1,29)=	
med	28.9; p=**.000***		12.9; p=**.001***		2.6; p=.114		3.9; p=.058	
stim	39.7; p=**.000***		112.0; p=**.000***		0.8; p=.373		1.2; p=.270	
med*stim	0.0; p= .919		4.9; p=**.035***		14.4; p=**.001***		3.1; p=.088	

5.4.2.3 Correlations

Calculation between timing and articulatory precision in speaker PT2 resulted in higher coefficients for velars (r2=0.42 for “cake”; 0.48 “Kate) than for alveolar stops (r2= 0.10 for “take” and 0.20 for “Tate”). Thus in PT2 slowing in speech production was not an indicator of improved articulatory precision in general.

5.4.3 Comparison of the two patients

As anticipated from the selection of the patients, the results for the EPG were able to show both the contrasting effects of stimulation on stop articulation for the two speakers and the contrasting effects of medication and stimulation together.

In both patients stimulation had a significant effect on segment duration. Medication changed the timing significantly in PT2 but not in PT1. A decrease of speech rate improved the articulatory precision of PT1 as documented by means of correlations between spatial and temporal data. By contrast the speech of PT2 was only improved when on-stimulation. When PT2 was off-stimulation velar sounds were significantly slower, but without any change at the number of EPG contacts. The number of contacts for the alveolar sounds was significantly influenced by both stimulation and medication.

The differences in target control between the two speakers can be seen clearly in the EPG frames in Figures 5.8 and 5.9. While PT1 showed complete closures in one of the first rows in the alveolar region off-medication and off-stimulation, speaker PT2 produced the best closures off-medication/on- stimulation. Articulatory precision in these examples was better off-medication.

5.5 Discussion

In this pilot study we used EPG to quantify the timing as well as the articulatory-spatial effects of deep brain stimulation and medication on the speech of two selected patients.

5.5.1 Spatial characteristics

The two speakers differed in their EPG contact patterns in that PT1 produced incomplete closures for /t/ in the on-stimulation condition (signifying articulatory undershoot) while PT2 showed no such effects when on-stimulation. In PT2 speech rate was slowed and the longer the stimulator was off the weaker the speech output became in the spectrogram. More frication and co-articulatory effects were characteristic of the off-stimulation conditions.

For both speakers, velar movements were affected in a similar way to alveolars. In Putzer et al (2008) frication was noted most frequently in the alveolar stop /t/ and never on velar or labial stops. The authors argued that fine motor control of the tongue tip is more differentiated and more influenced by vowels than tongue back movements. This argumentation confirms the findings of McAuliffe et al (2006a) and Gurd et al (1998) but is contrary to Logemann & Fisher (1981) and Weismer (1984) who described a particular impairment of tongue back movements. EPG provides the possibility to quantify tongue movements that are normally hidden from view. The detected articulatory target undershoot is evidence for reduced amplitudes of movement, which could be the reason for the imprecise consonant articulation (e.g. Ackermann et al, 1997; McAuliffe et al, 2006a).

5.5.2 Temporal characteristics

While both medication and stimulation had significant effects on the accuracy of articulation (spatial information), the effects on segmental durations were variable. In PT2 medication but not stimulation had a significant effect on consonant durations. The reverse effect could be found in PT1. An increase in the durations for PT1 was coupled

with an improvement of speech in the off-stimulation condition, whereas for PT2 off-stimulation led to an abnormal slowing of speech. Interestingly, stimulation had the greatest influence on alveolar durations in PT1 and on velar movements in PT2. Thus different timing influences on the place of articulation for both speakers can be assumed.

5.5.3 Medication and stimulation effects

The speakers were chosen for the pilot study because of their contrasting response to stimulation. However, we found similarities when on-stimulation/on medication: In both speakers the precision of alveolar stops was worse when on-medication/on-stimulation compared to off-medication/on-stimulation. Most precise articulation (using presence or absence of frication of stops as a criterion; see Figure 5.5) could be found in the off-medication/off-stimulation condition in PT1 and off-medication/on-stimulation in PT2. Their on-medication counterparts (on-medication/off-stimulation for PT1 and on-medication/on-stimulation for PT2) showed frication. It can be concluded that administration of dopaminergic medication caused deteriorating articulation in both patients. This finding may suggest that the fine motor control of lingual movements during speech is considerably more sensitive to the changed cortico-striatal circuits caused by stimulation and medication than gross motor control of limb movements. Rousseaux et al (2004) also noted that intelligibility of spontaneous utterances and sentence reading was slightly reduced not solely in the on-stimulation condition but coupled with the effect of levodopa medication.

In other EPG studies on parkinsonian dysarthria it has been observed that articulatory errors may be related to temporal aspects of speech (e.g. McAuliffe et al, 2006a).

McAuliffe et al (2006a) also detected target undershoot in their EPG studies. They assumed that undershoot of the target consonant was not the cause of articulatory errors. They argued that reduced tongue pressure resulted in impaired articulation. Pinto et al (2003) measured the force of articulators but not during speech. They provided evidence that deep brain stimulation improved the force control of the upper lip, lower lip and tongue in comparison to movements without stimulation.

5.5.4 Methodological issues

The background aim of this pilot study was to investigate the effects of stimulation and medication on tongue articulation using EPG. The limited number of patients limits the generalisation of the results. However, EPG showed changes of articulation in terms of spatial as well as temporal features. In their methodologically comparable studies, McAuliffe et al (2006a, b, 2007) detected articulatory undershoot in individual speakers, but not as a significant group difference to the control group. They also observed a discrepancy between perceptually identified articulatory undershoot in patients with PD and the lack of difference in the EPG data. They argued that EPG possibly failed to detect lingual movement impairment, because it only measures contacts of the tongue with the hard palate and not the approach to the palate. The authors also discussed the role of timing as a potentially important indicator of precise articulation. In our study, EPG detected significantly different articulatory patterns in the four recording conditions. On the other hand, specifying reliable and consistent segmentation criteria was a challenging task because of the considerable differences in speech production in the four recording conditions. In the literature, reliable methods of EPG data segmentation are described for normal speakers by Byrd et al (1995). But these methods could be used for the dysarthric speakers. For further qualitative and

quantitative measurements of lingual fine motor control of articulation in disordered speech, the methods of data segmentation have to be applied to a larger scale of patients in order to examine more generally the effects of medication and stimulation on parkinsonian dysarthria.

5.6 Conclusion

This pilot study provided evidence that EPG is a suitable experimental phonetic technique to quantify spatial and temporal aspects of articulation in patients with Parkinson's disease. We observed 1) contrary effects of stimulation and medication on tongue articulation in both speakers, 2) different timing effects on alveolar and velar stop production and 3) deteriorating effects on speech accuracy in on-medication compared to off- medication conditions.

On the basis of the results of this pilot study it would be worthwhile investigating the issues in a larger EPG study to verify how stimulation changes articulatory patterns in more detail and to find out more about the underlying processes of speech motor control. In terms of speech therapy, evidence is needed as to whether and how speech which is negatively affected by stimulation can be improved using articulation, rather than voice, as a target, and EPG biofeedback.

CHAPTER 6: TREATMENT OF DYSARTHRIA FOLLOWING SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE

6.1 Summary

This study aimed to examine the efficacy of an existing, intensive speech treatment (the Lee Silverman Voice Treatment, LSVT) on dysarthria after STN-DBS.

The LSVT was administered in ten patients with STN-DBS (surgical group) and ten patients without (medical group). Patients were assessed before, immediately after and six months following the speech treatment using sustained phonation, a speech intelligibility scale and monologue. Vocal loudness, speech intelligibility and perceptual ratings were the primary outcome measures.

Vocal loudness and perceptual scores improved significantly across tasks for the medical group only. Speech intelligibility did not significantly change for either group. Results in the surgical group were variable with four out of ten surgical patients deteriorating after LSVT.

Investigating the efficacy of existing speech treatments following STN-DBS could inform on the nature of speech impairment as well as attempt to improve speech.

6.2 Introduction

The aim of this study was to assess whether an established behavioral treatment for parkinsonian dysarthria has a beneficial effect on speech problems following STN-DBS. Treatment of speech following STN-DBS has not been investigated so far.

The Lee Silverman Voice Treatment (LSVT) is a very intensive treatment (four hourly sessions per week for four consecutive weeks) that has been developed to treat speech problems for patients with PD. The five essential concepts of the LSVT include: 1. Focus on voice (increase amplitude of movement, increase vocal loudness), 2. Improve sensory perception of effort depending on the situation, what they call "calibration", 3. Administer treatment in a high effort style, 4. Intensity of treatment (four times per week for 16 sessions in one month), and 5. Quantify treatment related changes (mainly using the decibel scale). The LSVT is based on the hypothesized features underlying the voice disorder in PD (Ramig, 1995), namely the overall reduced amplitude of the speech mechanism that leads to "soft voice that is monotone". Thus the whole approach centres on a specific therapeutic target: increasing vocal loudness (increasing amplitude of movement). This key target of loudness acts as a "trigger" to increase effort and coordination across the speech production system. Another feature of PD dysarthria is the reduced sensory perception of actual reduced voice volume and the effort needed to produce "normal" loudness. By incorporating sensory awareness training with motor exercises, LSVT facilitates acceptance and comfort with increased loudness, and the ability to self-monitor vocal loudness (Trail, 2005). Findings from initial treatment studies (Ramig et al, 1995) on 40 patients with PD (26 treated with LSVT and 19 with respiratory treatment) showed post LSVT increases in loudness ranging from 8-13dB SPL across a variety of speech tasks. Follow-up studies showed that these gains were maintained for one year (Ramig et al, 1996) and two years follow-up (Ramig et al, 2001). The main outcome measure in these studies was the change in dB SPL across sustained phonation, reading the "Rainbow passage" and a monologue. All patients in these studies were PD patients treated with best medical (pharmacological) therapy.

6.3 Patients and methods

6.3.1 Participants

Ten patients with PD treated with bilateral STN-DBS ("surgical group" mean age 59.4±4.5 years, mean disease duration 13.6±5.3 years, mean H&Y stage when on-medication and on-stimulation 2.1±0.2) and 10 patients with only medically treated PD ("medical group" mean age 63±9.7 years, mean disease duration 8.6±6.5 years, mean H&Y stage when on-medication 1.7±0.3) participated in this study. All patients were referred by the Movement Disorder Consultants of the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK. There were no changes of patients' stimulation or medication during the treatment. The mean amplitude of stimulation at the time of the treatment in the surgical group was 3.09 V (±0.28) for the left brain and 3.26 V (±0.58) for the right brain. For the surgical group (N=9, one patient was operated in France so no pre-operative data were available) pre- and post-operative data on speech intelligibility were available through routine clinical assessment. Speech intelligibility declined from 97.38% (±4.9) pre-operatively on-medication to 83.67% (±30.5) post-operatively on-medication/on-stimulation. There was a great variability of speech response to stimulation within the surgical group (as evidenced by the high standard deviation) with one patient improving, three remaining the same, and five deteriorating.

6.3.2 Treatment

The LSVT was delivered by a trained and experienced SLT (ET) in the same way to all patients as instructed by the LSVT Foundation protocol[4]. The main goal of LSVT is "to maximize phonatory efficiency by improving vocal fold adduction and overall laryngeal muscle activation and control"[8] (LSVT Training Manual, p 495). The treatment is

intensive (four hourly sessions per week for four weeks) and requires high effort to increase vocal loudness.

6.3.3 Speech assessment

All patients were assessed pre, post and six months after the treatment (FU). The tasks included sustained phonation /a/ for three repetitions, the Assessment of Intelligibility for the Dysarthric Speech (AIDS), and a 60-seconds monologue about a topic of the speaker's choice. The Computerized Speech lab was used for recording and analysis of all samples. Acoustic recordings were obtained using a calibrated Shure SM 48 dynamic microphone, with a 15 cm mouth-to-microphone distance at 22 kHz sampling rate in a sound treated room. For the measurement of intensity (SPL dB) of the sustained phonation, AIDS sentences and monologue calibration occurred at the beginning of each recording using a Quest 2100 SPL meter at 15 cm, as described before (Chapter 2 and 3).

6.3.4 Data analysis

For the acoustical analysis of intensity of sustained phonation, reading and monologue we calculated the mean vocal sound pressure level (SPL dB) measures from the speech recording of each condition. The AIDS sentences were rated blindly by an independent speech and language therapist (LS), blinded to the patients' treatment (surgical or medical) and the timing of the assessment (pre-post-FU). The percentage of words correctly identified was derived from the AIDS sentences according to the instructions of the manual. To explore the impact of the LSVT on perceptual characteristics of speech we used the 35 speech dimensions listed by Darley et al (1975) grouped under six speech clusters (Plowman-Prine et al, 2009) (Table 6.2). Each speech cluster was assessed on a seven-point interval scale, where seven represented normal speech and one represented the greatest deviation from normal. Mean speech ratings were

calculated for each of the speech-sign clusters across the groups in the three time points with a maximum total of 42 representing a near-normal speech. All perceptual analysis was performed in the same quiet speech laboratory with the same equipment. Assessment of overall intelligibility was always determined first. Then the rater could listen to the monologue file up to six times, one for each speech cluster to determine the perceptual rating.

6.3.5 Statistical analysis

The primary outcome was the change in mean SPL dB across the three tasks. Secondary outcomes were the change in speech intelligibility (% of words understood) and the change in the total perceptual rating of monologue between baseline and follow-up in the medical and surgical groups. A two-way ANOVA with factor 1 time (pre-post and FU) and factor 2 group (medical vs. surgical) was used to compare the effect of the LSVT in the two groups of patients across time points. Bonferroni post tests were used to explore the change between baseline and follow-up within groups. The relationship between impact of STN-DBS on speech intelligibility and the effect of LSVT was examined using Spearman r correlation coefficient, with change from LSVT in both speech intelligibility and perceptual measures as dependent (outcome variable). Similarly we examined the relationship between voltage amplitude and change in speech post LSVT.

6.4 Results

Patients in the two groups did not differ significantly at baseline in any of the measures. Mean vocal loudness increased significantly across all tasks for the medical group between baseline and FU but not for the surgical (Table 6.1).

Table 6.1: *Means (SD) of SPL dB at 15cm mouth-to-microphone distance for phonation, reading and monologue in the surgical and medical groups across time points.*

LOUDNESS	**PRE LSVT**	**POST LSVT**	**FU LSVT**
Phonation			
DBS	77.2 (7.3)	81.7 (8.7)	79.9 (7.2)ns
MED	76.6 (11.1)	84.1 (8.5)*	86.5 (3.5)**
Reading			
DBS	76.4 (5.8)	80.9 (5.7)	79.5 (6.2)ns
MED	74.5 (6.6)	81.3 (8.1)*	85.3 (2.9)**
Monologue			
DBS	77.4 (4.1)	76.1 (6.5)	79.3 (5.7)ns
MED	75.2 (7.0)	78.9 (6.3)	81.9 (3.5)*

*p<.05, **p<.001 for time

Speech intelligibility did not significantly change in the two groups between baseline and follow-up (surgical group 88.5±23.4% at baseline and 83.1±21.7% at FU and medical group 95.1±7.9% and 98.2±2.9% respectively).

Results from the perceptual rating of the monologue showed significant main effect for group in the subsections of articulation ($F(1,36) = 10.1$, $p=0.0051$) respiration, ($F(1,36)=8.4$, $p=0.009$), phonation ($F(1,36)=4.9$, $p=0.038$), and the total score ($F(1,36)=8.1$, $p=0.01$), with only the medical group showing an improvement. There was also a significant main effect for time for the respiration ($F(2,36)=4.5$, $p=0.01$) prosody, ($F(2,36)=7.1$, $p=0.002$), and the total score ($F(2,36)=6.1$, $p=0.004$) showing that over time the medical group improved. There was an interaction effect for

respiration (F (2,36)=5.07, p=0.01), phonation (F(2,36)=5.77, p=0.006) and the total score (F(2,36)=6.3, p=0.004). Post hoc Bonferroni tests showed that these measures improved in the medical group both post and at FU whereas respiration deteriorated in the DBS group (Table 6.2).

Table 6.2: *Means (SD) of perceptual rating for the monologue task in the medical and surgical groups across time points. Mean ratings are calculated for each cluster (scale of 1 to 7). Total of 42 is the maximum and denotes near normal speech.*

PERCEPTUAL SCALE	**PRE LSVT**	**POST LSVT**	**FU LSVT**
Resonance (/7)			
DBS	5.4 (1.1)	5.7 (1.1)	5.8 (1.4)
MED	5.9 (0.5)	6.2 (0.4)	6.2 (0.4)
Prosody (/7)			
DBS	5.2 (1.0)	5.5 (1.5)	5.4 (1.6)
MED	5.6 (1.0)	6.7 (0.6)***	6.4 (0.8)*
Articulation (/7)			
DBS	4.5 (2.1)	4.5 (1.6)	3.6 (1.8)
MED	5.9 (1.6)	6.2 (0.7)	6.3 (0.6)
Rate (/7)			
DBS	4.8 (1.9)	5.0 (1.4)	4.4 (1.9)
MED	5.5 (1.2)	6.3 (0.9)	6.1 (0.8)
Phonation (/7)			
DBS	5.0 (1.3)	4.8 (1.5)	4.4 (1.1)
MED	5.1 (0.9)	6.1 (0.7)**	5.9 (0.7)*
Respiration (/7)			
DBS	4.5 (1.3)	4.8 (1.3)	4.0 (1.5)*
MED	5.1 (1.2)	6.2 (0.6)**	6.1 (0.5)**

Total (/42)			
DBS	29.4 (7.0)	30.4 (6.9)	27.9 (7.5)
MED	33.0 (4.6)	37.8 (3.2)***	37.3 (2.9)**

*p<.05, **p<.01, ***p<.001

A more detailed analysis of the perceptual ratings of monologue showed that four out of ten patients in the DBS group deteriorated following LSVT, three remained the same and three had a transient only improvement. The speech of the patients who deteriorated was characterized by a strained-hoarse voice quality, an excess loudness variations, monoloudness, monopitch, reduced stress, imprecise consonants, distorted vowels insufficient breath support leading to short phrases. These features worsened with effort for increased loudness.

There was no relationship between the effect of STN-DBS on speech intelligibility and the impact of LSVT (post-treatment) on speech intelligibility and perceptual ratings of the monologue. Also there was no relationship between voltage amplitude and the impact of LSVT on perceptual ratings.

6.5 Discussion

Our study shows that LSVT has a significant effect on vocal loudness and perceptual ratings of speech in patients with PD treated medically and not in patients with PD following STN-DBS. Patients with STN-DBS presented with a variable response to LSVT treatment, with no sustained improvement and with four out of ten patients showing worsening of their perceptual ratings at FU.

The rationale for the treatment goals and tasks of the LSVT is based on the perceptual characteristics of hypokinetic speech and the hypothesized oral and laryngeal motor impairment, mainly the reduced amplitude of vocal fold adduction[3] observed in PD.

LSVT also targets the abnormal sensory processing of the reduced amplitude output. Patients commonly report that they are using sufficient effort for loud speech but their friends and spouses are losing their hearing rather than consider that they are speaking softly (Fox et al, 1997; Spielman et al, 2007). LSVT directly addresses this sensory mismatch and teaches patients with PD to recalibrate the amount of effort needed for normal loudness. Apart of the motor (hypokinesia) and sensory (lack of immediate feedback) aspects of PD speech, LSVT also targets motor learning, by using treatment strategies that incorporate cueing and repetition. Overlearning a new motor task through intensive practice and repetition can improve task automaticity and create a stronger memory (habit) for the motor behavior (Schmidt & Lee, 1999, as reported in Spielman et al, 2007). This intensive, high effort work on vocal loudness can bring significant improvement, as reported in clinical studies so far[4] and observed in our medical group.

The limited gains on speech of patients with STN-DBS observed in our study can be due to differences in the pathophysiology of dysarthria, the sensory processing (self perception of speech deficit) or the ability for motor learning. Speech following STN-DBS can be perceptually different from the hypokinetic dysarthria initially described by Darley and colleagues (1975). Voice can occasionally sound strained, strangled and breathless, resulting in scanning, "one-word-at-a-time" speech. Articulation can be affected mainly in alveolar and velar sounds (Putzer, 2008) (and Chapter 7, EPG study). Klostermann and colleagues (2007) examined acoustic measures of speech and patient self-reports on- and off-stimulation and found that despite an improvement in the acoustical measures both patients and their clinicians rated speech as worse when on-stimulation. Speech can be affected by voltage amplitude and contact location (Tripoliti et al 2008) as well as clinical pre-operative factors. The neural correlates of speech

following STN-DBS may be different from that of non STN-DBS treated PD patients (Liotti et al, 2003; Pinto et al, 2004, see also Chapter 1).

The effects of STN-DBS on sensory processing of speech and motor learning have not been examined systematically so far. Alberts et al (2008) and Frankemolle et al (2010) have used a dual task cognitive-motor task to show that DBS can compromise performance, mainly due to the spread of current in the non-motor regions of the subthalamic nucleus. They also observed that the greatest dual-task cost or loss in performance was observed in the motor task (a force-tracking task) rather than the cognitive task. Speech can be described as a complex cognitive-motor task and the LSVT heavily relies on training both. Thus the limited effect of LSVT on surgical patients might be partially due to the stimulation effect on motor learning and ability for dual processing. However, we would need a non-speech control task (e.g. drumming) to examine whether the limited effect of LSVT is due to the effect of STN-DBS on cognitive–motor learning or on speech.

In our study, the small number of patients in the two groups limits the generalisation of the results. Larger numbers could allow an analysis of the characteristics of the surgical patients who benefit from LSVT versus those who don't, mainly with regards to active contact localisation. As the LSVT is based on principles of motor learning (Trail et al, 2005; Nieuwboer et al, 2009) it would be interesting to investigate any impairment in motor learning for the subgroup of surgical patients who did not maintain the gains, or indeed to compare the two groups.

The studies on the efficacy of the LSVT so far have reported data mainly on vocal loudness (Trail et al, 2005). Thus it is difficult to compare our data on speech intelligibility and the perceptual aspects of speech. Perceptual ratings from the Ramig group have concentrated on use of a Visual Analogue Scale for a pair of read sentences

(Spielman et al, 2007), “better-worse” judgement of the “Rainbow Passage” (Sapir et al, 2002 and 2003), and perceptual rating of vowels (Sapir, 2007). Recently, the Ramig group (Halpern, 2010) has presented the results from an extended version of LSVT. Patients during the two extra weeks of treatment worked either with articulation or with carryover into all communication settings. Their results show that all patients increased in SPL dB from pre- to post-treatment but they do not report follow-up data. Further investigations are needed into the efficacy of tailoring therapy to the particular speech problems post STN-DBS or of providing therapy before STN-DBS in order to maximize the benefits of the procedure.

CHAPTER 7: AERODYNAMIC STUDY ON SPEECH IN PATIENTS WITH PD FOLLOWING BILATERAL STN-DBS

7.1 Summary

Adequate respiratory motor control is essential for speech but may be impaired in PD. The aim of this study was to examine the impact of STN-DBS on respiratory control for speech and its relationship to speech intelligibility and loudness.

Five consecutive patients (one female) were tested pre-operatively on- and off-medication and at six months post STN-DBS off-medication and on- and off-stimulation. Three extra patients were assessed at six months only, off-medication, on- and off-stimulation. The Aerophone II was used to measure vital capacity, mean flow rate during phonation, a syllable repetition task /ipipipi/ and a sentence repetition task ("buy bobby a puppy"). Mean and peak intraoral air pressure was also calculated for the syllable and sentence repetition tasks. Data were correlated with changes in speech intelligibility and loudness for read sentences.

Mean and peak air pressure for speech increased significantly between pre- and post-surgery for both medication conditions. Vital capacity increased significantly when on-stimulation compared to off-stimulation. No other measure changed significantly between off- and on-stimulation. None of the aerodynamic measures were correlated with speech intelligibility or loudness at six months. Loudness pre-operatively off-medication was correlated with peak air pressure post-operatively
off-medication/on-stimulation. Data from this study were also compared to normative values.

Mean and peak air pressure for speech may increase following STN-DBS. This is not correlated with changes in speech intelligibility or loudness.

7.2 Introduction

Respiratory impairment may be linked to several features of hypokinetic dysarthria, namely decreased loudness, short phrases and fast rate of speech. Studies of vital capacity, intraoral air pressure and airflow during speech show that patients with PD tend to have lower scores than healthy controls (Netsell et al, 1975; Solomon & Hixon, 1993). However the degree to which these measures influence speech intelligibility and vocal loudness is still uncertain. Furthermore there is only one study examining the effect of STN-DBS on respiratory control (Hammer et al, 2010). They reported increased respiratory driving pressure (i.e. intraoral air pressure) with stimulation.
The authors did not report changes from pre-operative data, and they did not correlate speech intelligibility or acoustic measures to these changes.

The aim of this study was to investigate the effect of bilateral STN-DBS on respiratory speech function in consecutive patients and its impact on speech intelligibility and loudness.

7.3 Patients and methods

7.3.1 Patients

Five consecutive patients were assessed before and at six months following bilateral STN-DBS. A further three patients were assessed only at six months (total of eight patients). Their mean age was 59.5 years (±5.1), mean time since diagnosis was 11.6 years (±4.4), UPDRS-III pre-operatively off-medication was 54.8 (±25.5) and on-medication 11.25 (±10.02) and at six months UPDRS-III off-medication /on-stimulation was 23.8 (±12.5) ($p=0.0094$ for UPDRS-III pre-operative off-medication to post-

operative off-medication/on-stimulation). Their mean speech intelligibility pre-operatively off-medication (N=5) was 67.75% (±22.31) and on-medication 72.0% (±20.79) and at six months off-medication/on-stimulation (N=8) 70.0% (±15.15%), and off-medication/off-stimulation 61.6% (±30.2%).

7.3.2 Aerodynamic measures and data analysis

The aerodynamic measures were obtained following the methods described in Yiu et al (2004) using a Kay Elemetrics Aerophone II model 6800. Airflow and pressure calibration were carried out according to the manufacturers' instructions. The recordings were carried out in a sound-treated room with each patient seated in an upright position in a straight backed chair. Each patient was required to undertake four tasks: measurement of vital capacity, production of most comfortable sustained vowel phonation, production of strings of vowel-consonant syllables (/ipipi/) and production of a sentence ("Buy Bobby a puppy"). The choice of the syllable and sentence repetition tasks was based on the recommendations from Smitheran & Hixon (1981). Each recording session took approximately 20 minutes. For the vital capacity the patient was instructed to make a good seal around the carbon tube, connected to the transducer of the Aerophone II, and the recording setting was 0-5ml for females and 0-10 ml for males. The instruction was "breathe in as deep as possible and breathe out all the air through the tube until the lungs are completely empty". The task was repeated three times and the highest value of the three was taken as representative of the patient's VC. The task gives information about the maximum volume of air which can be exhaled following a maximum inhalation. It thus provides an estimate of the amount of air potentially available for phonation. It is measured in ml. Normative values vary in the literature but we considered 4.9 L for males and 2.3 L for females.

For the remaining tasks the Rothenberg face mask was used, which was connected to the transducer of the Aerophone. The mask was held tightly against the face by one of the investigators, due to possible movement problems. In this task the patient was instructed to sustain the vowel /a/ at a comfortable pitch and loudness for approximately five seconds following a normal inspiration. This task was preferred over the maximally sustained vowel because the latter is not generally representative of the normal expiratory duration or volume during phonation (Terasawa et al, 1987). The /a/ phonation was repeated three times and the mean flow rate was obtained for each production. The task gives information about the phonatory function, and it represents the total volume of air used for phonation divided by the duration of phonation and the unit is ml/sec. The normal values depend on height (there is no significant male/female difference) and range between 100-160 ml/sec. Below 80 ml/sec voice could be hyperfunctional and above 200 ml/sec hypofunctional.

In the vowel-consonant string production each patient was asked to produce the vowel /i/ followed by a bilateral plosive /p/ repeated consecutively for minimum seven times (/ipipipi/) at a comfortable pitch and loudness. The mask was tightly held over the patient's face by one of the investigators and a 12 cm long polyethylene tube, with 2.5 mm diameter, was placed on top of the tongue for each production. The production was repeated three times and the mean and peak intra-oral air pressure was measured. The task gives information for voice efficiency. It is based on the assumption that oral pressure is equal to subglottal air pressure during the articulation of an unvoiced plosive where the lips are closed and the vocal folds are fully opened (as in /p/). This task is based on the work by Smitheran & Hixon (1981) who examined the air pressure from different combinations of consonants and vowels. Since then the /ipipi/ utterance has been routinely used for the measurement of intraoral air pressure. Hiss et al (2001)

examined the effect of age, gender and repeated measures on intraoral air pressure on 60 adults comprised of ten males and ten females in each of the three age groups (i.e. 20-39, 40-59 and 60-83 years) and found that there is no statistically significant difference in intraoral air pressure as a function of age, gender or repeated measures. Thus intraoral air pressure was chosen as the primary outcome of this study. The sound pressure level setting was at 50-100dB SPL, the pressure range at 0-10cm H_2O, the flow range at 0-500 ml/sec. The same procedure was repeated for the production of /buy Bobby a puppy/ sentence, repeated three times. Data on healthy adults show that there is no statistically significant difference in intraoral air pressure as a function of age or gender (Hiss, 2001). Thus normal values range from 5.55 to 6.70 cm H_2O, with a mean of 6.20 cm H_2O.

Four types of analysis were carried out:

From the vital capacity task the highest score of the three trials was retained for analysis. From the vowel phonation task the mean flow rate (ml/sec) was calculated by including the lowest point of the rising slope (i.e. the beginning of phonation) and the lowest point of the falling slope (i.e. the end of phonation) on the sound pressure level waveform display. From the /ipipi/ the peak intraoral pressure measurement was based on the middle five /pi/s in each string. These five /pi/s were extracted by identifying the lowest point of the rising slope of the second peak and the lowest point of the falling slope of the sixth peak on the sound pressure display. From the sentence production the airflow and intraoral pressure measurements were carried out by extracting the lowest point of the first rising slope (i.e. the beginning of the sentence) and the lowest point of the falling slope of the last peak (i.e. the end of the sentence) in the sound pressure display. With these analyses the following aerodynamic measures were extracted:

- Mean flow rate (MFR) for the /a/ phonation sustained for a comfortable period of time (measured in ml/sec).

- Mean (MAP) and peak (PAP) subglottal air pressure estimated from the syllable repetition task /ipipi/ (measured in cm H_2O).

- MFR for the above syllable repetition task.

- MAP and PAP and MFR for the sentence task[5].

- Vital capacity (VC) (measured in L).

Data were inspected for inclusion based on the method described by Higgins & Saxman (1991). In their study participants whose minimum flow went below 0.05 l/sec were considered to have had mask leaks serious enough to jeopardize the validity of their data. In our study there were no data excluded, possibly because leaks were avoided by an experimenter holding the mask on the face, rather than the patient.

Speech intelligibility was measured routinely before the operation (N=5) on-and off medication and at six months (N=8) as described previously (Chapter 3). Loudness data (SPL dB) for the read sentences were collected and analysed as described before (Chapter 3).

Statistical analysis

Primary outcome was the change in MAP and PAP of syllable and sentence repetition task at six months post STN-DBS (N=5) at the off- and on-medication/on-stimulation conditions. Secondary outcomes were: 1.the change in VC and MFR in phonation,

[5] Healthy speakers in the upright position produce conversation using between 40-60% of their vital capacity (20-40% when supine); this amounts to approximately 20% of the average adult male five litre vital capacity (Hixon et al, 1973). Thus conversational speech usually consumes only a moderate portion of the mid-range lung volume.

syllable and sentence repetition; 2.the change with stimulation at six months (off-medication/off-stimulation minus off-medication/on-stimulation) in all measures (N=8); 3. the relationship between PAP and speech intelligibility as well as average loudness (SPL dB) of read sentences was examined using Spearman's r correlation coefficient;
4. comparison with normative data. Paired t-tests were used for comparisons across conditions at six months and across time (pre-six months).

7.4 Results

The MAP for the sentence task changed significantly from 1.37 cm H_2O pre-operatively on-medication and 1.59 cm H_2O pre-operatively off-medication to 2.01 cm H_2O post off-medication/on-stimulation. The PAP increased significantly for the sentence task, from 6.13 cm H_2O pre-operatively on-medication and 6.11 cm H_2O off-medication, to 7.79 cm H_2O post-operatively off-medication/on-stimulation. The PAP also increased significantly for the syllable repetition task from 5.95 cm H_2O pre-operatively on-medication to 9.27 cm H_2O post-operatively off-medication/on-stimulation. There was no significant change in VC and MFR of any task between pre-operative and six months (Table 7.1).

Table 7.1: *Mean (±sd) of aerodynamic measures, before (N=5) and 6 months after (N=8), off- and on-medication and off- and on-stimulation.*

Measure	Pre-operative on-med	Pre-operative off-med	6 months off-med/on stim	6 months off-med/off-stim
VC (L)	3.67 (0.83)	3.64 (0.57)	3.76 (1.11)	3.30 (0.94)**
MFRphon (ml/sec)	200.0 (155.9)	230.4(147.7)	204.6 (146.2)	215.5 (174.1)
MFR /ipipi/	83.2 (40.4)	96.6 (103.6)	178.4 (107.5)	134.6 (93.1)
MFR sentence	107.3 (36.2)	118.8 (50.7)	122.4 (64.7)	120.0 (82.45)
MAP /ipipi/ (cm H_2O)	3.55 (3.4)	2.83 (1.21)	2.88 (2.54)	3.75 (4.18)
MAP sentence	1.37 (0.35)	1.59 (0.42)	2.01 (0.97)*	2.25 (1.08)
PAP /ipipi/ (cm H_2O)	5.95 (4.71)	10.53 (6.65)	9.27 (4.29)*	8.71 (3.06)
PAP sentence	6.13 (1.76)	6.11 (1.57)	7.79 (1.61) **	7.12 (2.08)

*VC=vital capacity (normal values 4.9L), MFR=mean flow rate (normal values 100-160 ml/sec), MAP=mean intraoral air pressure, PAP=peak intraoral air pressure (normal values 6.2cm H_2O). *p<0.05, **p<0.01.*

Comparison of data off-medication/on-stimulation with off-medication/off-stimulation at six months showed that the only measure that significantly increased with stimulation was the vital capacity (Figure 7.1). Spearman's r correlation between speech intelligibility and aerodynamic measures at six months showed no relationship between the two measures. Loudness of read sentences was not correlated to MAP or PAP of the sentence or syllable repetition task at six months. Loudness (SPL dB) of read sentences pre-operatively off-medication was positively correlated with the PAP of syllable repetition task off-medication/on-stimulation (Spearman r 0.85, p=0.023).

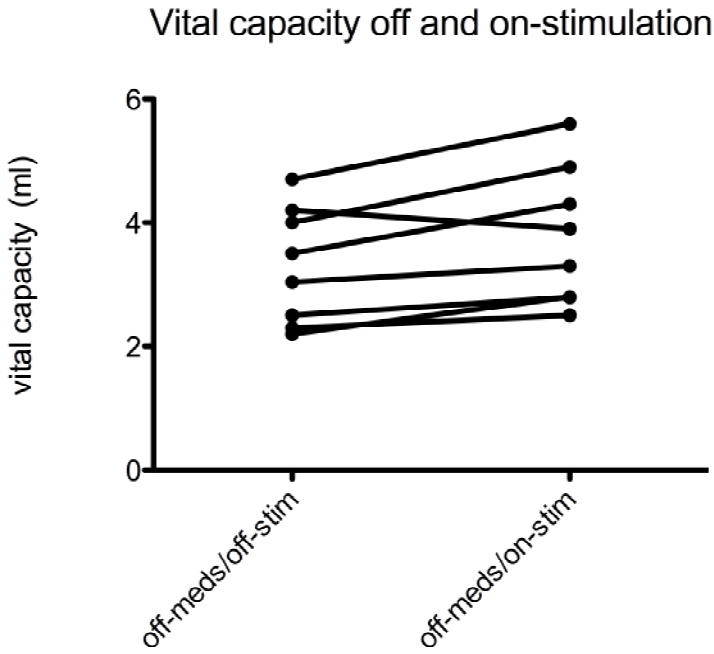

Figure 7.1: *Vital capacity (in L) off- and on-stimulation at six months, off-medication*

Comparison of normal values of VC showed that patients with PD scored below the normal values of 4.9ml across all time point and conditions, with the lowest being the off-medication/off-stimulation condition at six months. Equally MFR for phonation is much above the average 100-160ml/sec, and at levels above 200ml/sec it could be linked to hypofunctional voice. Normal values of PAP for the syllable repetition task

are around 6.2 cm H_2O.Values pre-operatively were within the normal limits, but they exceed those post-operatively.

7.5 Discussion

The aim of this study was to investigate the role of the aerodynamic function on speech difficulty after STN-DBS. Many patients report becoming more "short of breath" after STN-DBS, with breath support enough only for three to four word phrases. Perceptual analysis of the speech from a group of patients at one year post STN-DBS also showed that respiration was one of the components that deteriorated significantly (Chapter 3). Deterioration of respiratory function can have an effect on both phonation and prosody. The primary outcome was the impact of bilateral STN-DBS on mean and peak intraoral air pressure of speech in consecutive patients. One of the secondary outcomes was to investigate the relationship between changes in respiratory function with vocal loudness and speech intelligibility. A strong relationship could point towards a therapy strategy involving respiratory control.

Peak oral pressure values were chosen as a primary outcome due to the stability they show in repeated measurements, different age groups and between genders (Hiss, 2001). There was a significant increase of MAP and PAP for speech and syllable repetition at six months compared to the pre-operative values. Lower than normal air pressure has been reported in people with PD previously (Netsell et al, 1975; Solomon & Hixon, 1993). Oral pressure can be a good estimate of the driving pressure delivered to the larynx and the upper airway structures for speech. However the influence of the oral structures on intraoral pressure (mainly the larynx and the velopharyngeal valving) makes it difficult to determine whether the higher than expected oral pressure post STN-

DBS is due to the airway system or the upper airway valving[6]. The fact that in our study, higher air pressure was not accompanied by higher mean flow rate suggests a laryngeal/velopharyngeal valving basis, rather than purely respiratory. Additionally VC measures were lower than the normal values even post-operatively, in accordance with the literature on PD (De Pandis, 2002; Weiner et al, 2002). Increased intraoral air pressure has been linked with increased laryngeal resistance and increased vocal loudness (Stathopoulos, 1986) in healthy controls. However in our study air pressure was not linked to vocal loudness for the sentence task. This is in accordance with Ramig & Dromey (1996), who examined the link between cued increased air pressure and vocal loudness in 20 patients with PD and found no relationship. Thus most of the changes with stimulation point towards increased vocal fold and /or velopharyngeal closure (air pressure) and not increased respiratory driving pressure (air flow). This is consistent with the observation of tight-strained voice quality and occasional hypernasality observed in speech following STN-DBS (Chapter 3). Hammer et al (2010) also found that post-DBS PD patients showed changes consistent with increased respiratory driving pressure and increased vocal fold closure. They also found that most participants exceeded a typical operating range for these respiratory and laryngeal control variables, which is in agreement with our data. However they do not provide any acoustical or perceptual information on speech changes and they do not make any assumptions about the reasons for these changes.

[6] During the /ipipi/ utterance the two types of sounds (/i/ and /p/) involve different combinations of valving adjustments. For the /p/ there is a closed phase and the release phase. The closed phase requires the laryngeal valve open and the velopharyngeal and oral valves closed. The release phase (for the initiation of /i/) maintains the open larynx and the closed velopharynx but involves an abrupt opening of the oral valve. Additionally the larynx needs to vibrate for the vowel /i/ sound. (from Smitheran & Hixon, 1981).

Speech intelligibility was not correlated to any of the aerodynamic measures. However the pre- to post-operative decline for the five patients was not significant either. This could be due to the small number of participants (N=5). Additionally, in the longitudinal study (N=32, Chapter 3.2) the majority of speech decline occurred between six months and one year. There are no reports in the literature on the relationship of speech intelligibility and aerodynamic measures in PD. Studies on hearing impaired speech (Itoh & Horii, 1985) show that more frequent inspirations were linked to poorer speech intelligibility but they only report air flow measures.

Limitations of this study include the small number of participants and the lack of pre-operative data for all of them. A longer follow-up (more than 6 months) would possibly show some deterioration in speech intelligibility and could eb correlated with more marked changes in aerodynamics. However the reported initial data are an indication that patients' reports and the observed respiratory problems post STN-DBS may be due to laryngeal/velopharyngeal valving problems rather than purely respiratory.

CHAPTER 8: EFFECTS OF BILATERAL GPI-DBS ON SPEECH IN PATIENTS WITH DYSTONIA

8.1 Summary

GPi-DBS is an effective treatment for patients with dystonia. The effects on speech have not been systematically reported. The aim of this study was to prospectively evaluate the effect of GPi-DBS on speech in a series of dystonia patients.

Twenty five patients with dystonia were assessed before and 12 months after bilateral GPi-DBS. The aetiology of dystonia was as follows: eleven were primary generalised (six DYT-1 positive, five DYT-1 negative), seven were cervical/cranial dystonia, two myoclonic dystonia, one tardive dystonia plus Tourette's, one hemidystonia, two dystonia following stroke and one dystonia following a post-anoxic episode. The speech protocol consisted of sustained phonation, reading sentences from the AIDS, and one minute monologue. Post-operative recordings were made with patients being on-stimulation and on their usual medications. Analysis consisted of loudness (SPL dB) across all tasks, rate of speech (measured in words per minute) and speech intelligibility.

Speech intelligibility did not significantly change. Rate of speech increased significantly for reading. SPL dB did not change significantly for any task. Detailed examination of data revealed a subgroup of eight patients whose speech changed perceptually from normal/hyperkinetic to hypokinetic, mainly characterised by fast rate of speech, indistinct articulation and reduced volume.

Speech following GPi-DBS can show a wide variability. The presence of hypokinetic-parkinsonian features warrants further investigation.

8.2 Introduction

The benefit of GPi-DBS on speech for patients with dystonia has not been investigated prospectively and in detail. However speech changes as measured by the BFM scale have been reported in the literature.

8.3 Patients and methods

8.3.1 Participants

Twenty five patients with dystonia were assessed before and 12 months after bilateral GPi-DBS. The aetiology of dystonia was as follows: eleven were primary generalised (six DYT-1 positive, five DYT-1 negative), seven were cervical/cranial dystonia, two myoclonic dystonia, one tardivedystonia plus Tourette's, one hemidystonia, two dystonia following stroke and one dystonia following a post-anoxic episode. They were assessed before the operation and at 12-36 months after (mean 21.5±10.6 months). Their average age was 46.1±14.6 years and average time since diagnosis was 18.3± 6.3 years. Their BFM score pre-operatively was 35.2 (±17.02) and post-operatively 12.07 (±9.07) ($p<0.0001$).

8.3.2 Tasks

The tasks included sustained phonation /a/ for three repetitions, the Assessment of Intelligibility for the Dysarthric Speech (AIDS), and a 60-seconds monologue about a topic of the speaker's choice. The Computerized Speech lab was used for recording and analysis of all samples. Acoustic recordings were obtained using a calibrated Shure SM 48 dynamic microphone, with a 15 cm mouth-to-microphone distance at 22 kHz

sampling rate in a sound treated room. For the measurement of intensity (SPL dB) of the sustained phonation, AIDS sentences and monologue calibration occurred at the beginning of each recording using a Quest 2100 SPL meter at 15 cm, as described before (Chapter 2 and 3). One patient with secondary dystonia was anarthric, so he couldn't participate at the speech recordings, but video recordings were made instead. Post-operative recordings were made with patients being on-stimulation and on their usual medications.

8.3.3 Analysis

Primary outcome was the change in speech intelligibility, loudness (SPL dB) and rate of speech (words per minute) in the read sentences of the AIDS. Secondary outcomes were the change in loudness and rate of speech for the monologue and the change in loudness for the sustained phonation. T-tests were used for the comparison of pre- and post-surgery outcomes. The subgroups of primary DYT-1 positive, primary DYT-1 negative and cervical/cranial dystonia patients were examined in greater detail due to the large variability observed, based on the following criteria: a. patients whose speech loudness deteriorated across all tasks and speech rate increased, b. patients whose speech loudness increased across tasks and c. patients who remained the same.

8.4 Results

Speech intelligibility as measured by the AIDS did not significantly change (baseline 97.08±10.4% post-operative 97.2±9.7%). The change in loudness of read sentences showed a great variability but there was no significant difference overall (Figure 8.1) (mean SPLdB pre-operative: 74.2±7.6; mean SPLdB post-operative: 73.2±7.3, p=0.44). Rate of speech (words per minute) was significantly increased (Figure 8.2) (mean rate pre-operative: 122.3±27.3; mean rate post-operative: 130.6±25.0, p=0.03).

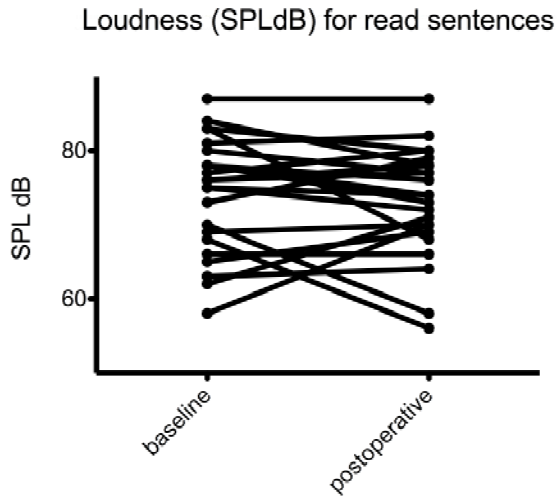

Figure 8.1: *Loudness of read sentences (the AIDS) in SPL dB for 25 patients with dystonia.*

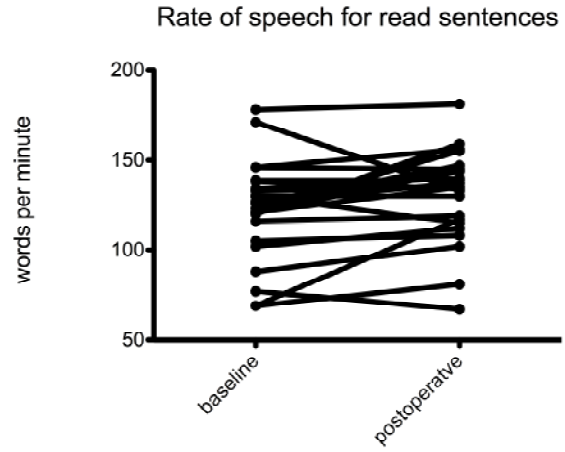

Figure 8.2: *Rate of speech (words per minute) for read sentences (AIDS).*

Loudness did not significantly change in sustained phonation (mean SPLdB pre-operative: 72.7±9.3; mean SPLdB post-operative: 74.3±7.6) or monologue (mean SPLdB pre-operative: 73.0±9.3; mean SPLdB post-operative: 74.4±6.7). Rate of speech did not significantly change for monologue either (mean rate pre-operative: 131.9±30.4; mean rate post-operative 130.9±32.3). The patient with generalised secondary dystonia who was anarthric was able after DBS to operate a Lightwriter (a typewriter with the

facility of artificial speech) which gave him a way to communicate. That was due to improvement in upper limb function.

The average amplitude of stimulation at the post-operative assessment was 3.5±0.45V for the left brain and 3.56±0.46V for the right brain; mean pulse width for the left was 78.9±17.9μsec and 83.3±16.4μsec for the right; mean frequency for the left was 124.2±25.2 Hz and 130±0 Hz for the right.

8.4.1 Primary DYT-1 positive

Two out of six patients developed signs of hypokinetic dysarthria, mainly reduced volume across all tasks and increased speech rate in both reading and monologue. Three patients showed increased volume across all tasks and no sign of hypokinetic dysarthria, and one patient complained of “slurred and more difficult” speech mainly linked to increased voltage. Two more patients complained of mouth and lips pulling with increased voltage that was remedied with reduced amplitude. The complaint in these cases was immediately following the increase of stimulation. However they did not show signs of hypokinetic dysarthria.

8.4.2 Primary DYT-1 negative

Two out of five patients with primary generalized DYT-1 negative dystonia developed signs of hypokinetic dysarthria. One of them had laryngeal dystonia as well, treated mainly with BOTOX. The speech symptoms might have been influenced by the timing of his injections. Two patients complained of voltage related face and mouth pulling which was relieved with change of parameters.

8.4.3 Cervical/cranial

Four out of seven patients with cervical dystonia showed signs of hypokinetic dysarthria, and three remained the same. The hypokinetic signs were more pronounced in these patients. They were typically not aware of their more quiet voice and they commented how other people complained about it. One patient with tardive cervical and Tourette's complained of softer voice but this was not transient, related to stimulation parameters.

8.5 Discussion

Speech intelligibility following GPi-DBS did not significantly change in our series of 25 patients. There was however a variable response to stimulation. Eight patients out of the 18 in the above subgroups showed signs of hypokinetic dysarthria, as characterized by reduced voice volume, fast rate of speech and indistinct articulation. A separate group of patients complained of face/mouth/lip pulling when adjusting stimulation parameters, a symptom relieved with change of these parameters and not accompanied by signs of hypokinetic dysarthria.

Both clinical and surgical factors could have affected the speech outcome in dystonia. From the clinical factors, speech before surgery and type of diagnosis could possibly have affected the presence of hypokinetic signs in speech post-surgery. From the eight patients who presented with these signs post-operatively, only one had signs of dysarthria pre-operatively, and those were of the hyperkinetic type due to laryngeal dystonia, treated with BOTOX. These features were not observed in patients with secondary or myoclonic dystonia, however the numbers are small. The majority were patients with cervical dystonia. Ostrem et al (2007) reported induction of bradykinesia in 10 out of 11 patients with cervical dystonia, but with no detailed description of speech changes.

The origin of these speech symptoms could be either corticospinal, through the spread of current in the internal capsule or extrapyramidal, due to modification of basal ganglia output. The hypothesis of spread of current to the corticospinal pathway is corroborated by the tension and stiffness (often described as “pulling”) that is occasionally observed around the mouth following stimulation adjustment. However this was transient and was relieved by change of stimulation parameters. It was not accompanied by persistent hypokinetic dysarthria.

The delayed onset of hypokinetic dysarthria following adjustment of stimulation, argues against direct capsular effect for this specific symptom, which tends to be immediate once threshold is reached. Thus the most probable explanation is the modification of the basal ganglia output through inactivation of the pallidothalamic outflow from the ventral GPi. Krack (1998) and Bejjani (1997) made similar observation during pallidal stimulation of PD where akinesia could be elicited with ventral GPi (lower contact) stimulation and relieved with dorsal GPe (higher contact) stimulation. Ventral contacts also led to pronounced improvement in rigidity, which would suggest a different pathophysiology for the two symptoms. The explanation of these findings may also relate to pallidal anatomy. Anatomical and physiological studies in primates have shown that the sensorimotor territory of the GPi is ventral and posterior, with the face and the arm being ventral and posterior and the leg more dorsal (Iansek et al, 1980; Parent et al, 1995; Delong et al, 1985). With the posteroventral GPi being also the preferred site for stimulation (Tisch et al, 2007) it would be logical to assume that the akinetic effect of the preferred ventral GPi stimulation is more pronounced in the face-upper limb area (Figure 8.3).

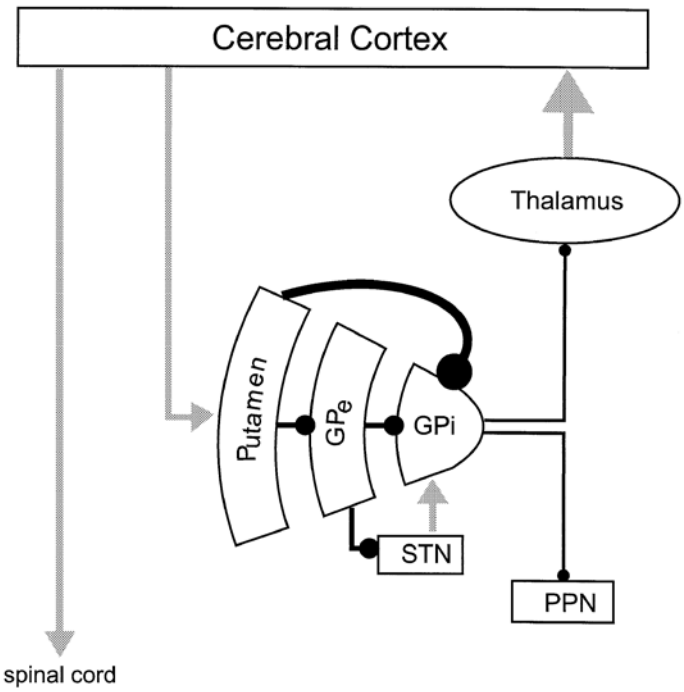

Figure 8.3 Highly simplified schematic summary of the basal ganglia circuitry in dystonia. Note the overactivity of the direct putamenopallidal direct pathway leading to reduced output of the medial globus pallidus and increased thalamic input to the cortex. GPi medial globus pallidus; GPe lateral globus pallidus; STN subthalamic nucleus; PPN pedunculopontine nucleus. From: Berardelli et al,l 1998, Brain.

Limitations of this study include the small and, by the nature of dystonia, not homogeneous sample and the lack of multiple data points for each patient to observe the change through time and the change in the degree of hypokinesia. Having more detailed movement data for bradykinesia would have given more information on the nature of hypokinetic speech.

8.6 Conclusion

Speech intelligibility following GPi-DBS is not significantly affected in patients with dystonia. Hence speech improvement should not be the primary criterion when considering surgery. There was a delayed onset hypokinetic effect on speech in some patients with primary dystonia which warrants further investigation.

CHAPTER 9: GENERAL DISCUSSION

9.1 Effect of STN-DBS on speech in patients with PD.

This work includes the first large series of consecutive patients with detailed speech evaluation before and after bilateral STN-DBS (PD) and GPi-DBS (dystonia). The aim was to systematically observe and describe the speech changes following DBS and to analyse the surgical and clinical factors associated with it in order to advise patients and to form hypothesis on the role of high frequency electrical stimulation on speech.

In our series of 32 consecutive PD patients speech intelligibility deteriorated by 14.2% one year after STN-DBS and by 16.7% three years after (N=15), whereas movement measured with UPDRS-III improved by 50.7%. The control group of medical therapy alone (N=12) showed a 3.6% deterioration of speech intelligibility over a year, so disease progression alone would not explain the deterioration of the surgical group. Seven patients showed some amelioration of speech after surgery illustrating the variability of the impact of STN-DBS on speech. A further 22 consecutive patients (Total N=54) were assessed in order to analyse in more detail the perceptual speech changes. Articulation and prosody were primarily affected, and a non-typically parkinsonian speech pattern emerged. Two case studies illustrated the variability of speech response, using electropalatography: stimulation affected the precision and amplitude of tongue movement only for the patient whose speech deteriorated with stimulation. A subgroup of STN-DBS patients (N=20) were asked to complete a questionnaire on the effect of speech changes on their quality of life and the results were compared with a subgroup of non-surgical PD patients. Patients' reports on speech changes correlated highly with the independent speech intelligibility ratings, and reflected the variability of speech response following STN-DBS.

Speech deteriorated in the majority of patients (78%) one of the highest percentages reported in the literature. The use of UPDRS-III speech item 18, in the majority of studies, to measure speech change might have contributed to this symptom being under-reported so far. Recent studies with longer follow-up have reported speech as a side effect more frequently and with a higher incidence. Thus similar percentages are reported by Piboolnurak (2007) with 69.7% and by Fasano (2010) with a 70% incidence of speech problems after 5 years of STN-DBS, and hypophonia being the most frequent motor side effect. In parkinsonian patients following GPi-DBS speech deterioration is not so frequently reported following GPi-DBS (Volkmann et al 2001; Rodriguez-Oroz et al, 2005, Rouaud et al 2010). Nevertheless, GPi-DBS has been less extensively studied than STN-DBS. There are no control groups with long follow-up to compare the effect of disease progression to stimulation. In our study speech deterioration was not correlated to any other motor subscale of the UPDRS-III nor to the amount of medication before and after surgery. It was gradual, more often beginning at 6 months and becoming progressively worse.

9.2 Factors associated with speech deterioration

The risk factors associated with speech deterioration have been assessed. The pre-operative clinical factors predictive of speech deterioration at one year of STN-DBS were a poor pre-operative score of speech intelligibility on-medication and a longer disease duration. The fact that the severity of the residual parkinsonian speech score when on-medication was predictive of a poor postoperative outcome is probably explained by the presence of non-dopaminergic lesions within the basal ganglia (Agid, 1991). Better speech pre-operatively could also mean greater ability to compensate for the disruption of speech through stimulation. Longer disease duration could also be linked with more extensive non-dopaminergic degeneration (Agid 1991).

However the variability of speech response, some patients with good speech intelligibility pre-operative were greatly affected by stimulation, was indicative of other factors for the speech outcome. Contact position and amplitude of stimulation are important factors. In our study speech deterioration was more frequently linked to medially placed left active contact. Our acute study also showed that increased voltage (4V) significantly reduced speech intelligibility both with contacts inside and outside the STN. The role of amplitude or frequency of stimulation has been shown in other studies (Tornqvist et al 2006). This could suggest a spread to other pathways. So far in the literature (Krack et al 2003, Tommasi et al 2008) speech deterioration was assigned to current spread to the internal capsule. In order to visualize the electric field generated during the various electrical settings a patient-specific computer model was generated. This showed that the increase in voltage of medially placed electrodes could affect the cerebellothalamic tract, and this could account for the speech deficit.

9.3 Possible mechanisms underlying speech change after STN-DBS

The basal ganglia and cerebellum have been assumed to be anatomically separate and to perform distinct functional operations. Recent studies have provided evidence for anatomical link between basal ganglia and cerebellum in monkeys, and specifically between the STN and dentate nucleus of the cerebellum (Bostan et al 2010). The role of cerebellum in speech production has not been extensively discussed in the literature of speech motor control (Price 2010) even though it is clearly activated during articulation (Brown et al 2009) and auditory self-monitoring during speech production (Zheng et al 2009). Lesions in cerebellum can cause dysarthria mainly characterised by reduced articulatory precision (both imprecise consonants and prolonged vowels), slurred pronunciation, exaggerated stops, slowed rate of speech and rough voice quality (Ackermann et al 1992, Urban et al, 2003). In our study, patients with left active contact

medially to the STN presented with similar perceptual characteristics, namely imprecise articulation, slurred pronunciation and prosodic insufficiency (slowed rate of speech and inappropriate pauses). The additional speech characteristic was a marked dystonic quality in the voice, sounding tight, strained and strangled, becoming worse with prolonged use, not present with cough or laugther, and in most cases being associated with oromandibular or neck and upper limb dystonic posture, made worse with speaking. This tight voice quality was reflected in the increased mean and peak air pressure for speech as assessed with aerodynamics. These dystonic features could still be a sign of cerebellar – thalamic involvement. Thalamic lesions can cause limb dystonia and the responsible lesions occur more frequently in the nuclei linked to the cerebellum, rather than the basal ganglia (Jinnah & Hess, 2006; Lehericy et al, 2001). The cerebellum has also been involved in verbal fluency tasks (Eickhoff et al 2009). Decline in verbal fluency is the most prominent neuropsychologic impairment following STN-DBS (Fasano 2010), with still unknown pathogenic mechanism. Increased activity in the cerebellum and the right anterior insula has also been implicated in the speech motor control of developmental stuttering, along with overactivity bilaterally in the basal ganglia (Watkins et al 2008). Re-emergence of childhood stuttering following STN-DBS has been reported in the literature (Burghaus et al, 2006) and was apparent in one of our patients.

A further hypothesis on the pathophysiology of speech impairment following STN-DBS could be the disruption of the cortical pathways utilized for speech. An early imaging study of PD patients showed that STN-DBS performed during a motor task involving decision making and motivational aspects induced metabolic activation of the SMA, the dorsolateral prefrontal cortex and the anterior cingulated cortex (Limousin et al 1997). This metabolic activation of cortical areas involved in motor, cognitive and

motivational functions implies that STN-DBS can affect all three functional territories of the basal ganglia (Krack et al 2010). Areas that are more specific to speech production in normal adults are the left middle frontal gyrus, left anterior insula, left putamen, bilateral head of caudate, anterior cingulated, pre-SMA, SMA, motor cortex and cerebellum (Price 2010). These areas are shared among the three functional territories of basal ganglia activity: the SMA and pre-SMA from the sensorimotor territory, the prefrontal dorsolateral cortex from the associative territory and the anterior cingulated from the limbic territory. A prolonged disruption of these pathways through electrical stimulation could contribute to the delayed onset of speech problems and their gradual deterioration.

9.4. Management of speech problems following STN-DBS

Managing the speech problems post bilateral STN-DBS can be challenging due to the unpredictability of the symptoms, the gradual progression over time, and the sensitivity to voltage and contact parameters. The speech profile following surgery can be different from that of the typical hypokinetic parkinsonian dysarthria. The LSVT is an effective speech treatment for people with PD. However when administered to PD patients post STN-DBS the results were not as positive as with non-surgical PD patients. Comparison with a control medical group showed that patients either did not maintain the effect of this intensive treatment or they deteriorated. Thus other ways for preventing and managing speech must be found. Team work, for detailed assessment of the contact and voltage effects on speech, has been more successful clinically, along with appropriate selection of patients and pre-operative advice. The use of biofeedback, as in the immediate self-monitoring of tongue movements during electropalatography, could be another way of treatment that requires further investigation.

9.5 Effects of GPi-DBS on dystonia patients

Speech intelligibility did not significantly change in the 25 dystonia patients, of diverse aetiology, who were assessed before and after GPi-DBS. However detailed examination of data showed a subgroup of patients whose speech changed from hyperkinetic to hypokinetic, with reduced volume, fast rate and indistinct articulation. The most probable explanation is the modification of the basal ganglia output through inactivation of the pallidothalamic outflow from the ventral GPi. However further studies are needed, in particular more electrophysiologic and limb motor data to make a firm hypothesis.

9.6 Methodological issues and limitations of the study

There are inherent difficulties when trying to evaluate the effects of stereotactic stimulation procedures on speech. These procedures target the triad of parkinsonian symptoms, tremor, rigidity and bradykinesia. Patient selection for surgery is mostlybased on potential limb motor improvement and not speech.

Most of the studies so far on the speech effects of GPi and STN-DBS were on small samples of selected patients. Comparison was between off-stimulation and on-stimulation at varied post-operative timings and without pre-operative data. There was also a lack of a large control sample to compare speech changes induced by neurosurgical interventions to those induced by the disease process and pharmacological intervention over time. A larger control sample of medical therapy alone, with longer follow-up, would have given greater power in our study.

The choice of a speech protocol that adequately reflects the complexity of speech, through the respiratory, phonatory and articulatory systems and can represent the

changes in functional communication is an ongoing debate (Weismer, 2006; Ziegler, 2003). The need to accurately assess speech problems led to the development of speech and language specific protocols. Buck and Cooper (1956) developed perhaps the most comprehensive speech scale for the speech examination of pre and postoperative parkinsonian patients. Despite the fact that the main speech tasks remain the same, namely counting, diadochokinesis, reading of set sentences and conversation, there seems to be a wide variability of measures. There are no studies so far evaluating the changes in conversational speech despite the fact that patients tend to report increased speech difficulties following neurosurgery. This is partly due to technical issues, mainly controlling the rate of speech, the order and choice of words used. Still, this is a limitation of this study. Analysing the narrative speech not only acoustically but in terms of speech intelligibility would give us a more naturalistic perspective of speech changes.

9.7 Hypotheses and future studies

The main hypotheses concern the mechanism of action of deep brain stimulation on speech and the understanding of the variability in speech response. Speech could be affected by the disruption of the cerebellothalamic pathway or the re-organisation of mainly cortical pathways involved in speech production. In order to investigate these hypotheses further first we need to continue the collection of consecutive prospective speech data along with information from the anatomic location of the active contacts and electrical parameters. Increasing the sample would also allow for a more detailed analysis of the somatotopy of the STN in respect of speech.

The most valid way of testing our hypothesis would be an imaging study, preferably before and one year after STN-DBS. This would allow us to observe the individual changes in activated pathways and it might help to understand the variability.

Verbal fluency is another area that hasn't been addressed in this study since the primary aim was the investigation of motor speech changes. The fact that it is one of the consistent areas of deterioration along with speech makes it an interesting topic for further study.

Unilateral stimulation of STN and the effects on speech need further investigation as well. There are technical issues in measuring speech activity due to the variability of electrode positioning in the left and right brain and the compensation inherent in the speech mechanism from the axial speech muscles. EMG could be used in tandem with perceptual and acoustical ratings in order to examine the effect of unilateral stimulation on speech motor control.

In the dystonia patients speech intelligibility did not significantly change following GPi-DBS. At an individual patient level, the appearance of hypokinetic features following at least one year of stimulation warrants further investigation.

The ultimate aim is to understand the nature of speech changes in order to either avoid them or bypass them using a successful therapy strategy. Further investigation of biofeedback methods, like the electropalatography, with articulation as main aim should be the next step, in order to develop a new treatment for speech problems after stimulation.

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Appendices

Appendix 1: Unified Parkinson's Disease Rating Scale

III. MOTOR EXAMINATION

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression.
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair
(Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.
29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.
30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders
while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.
31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal.
Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

Appendix 2: Burke-Fahn and Marsden Dystonia Scale

Patients name: _____
Date of examination: _____
Examiners name: _____

Stimulation parameters:				
	+	-	V	PW	Hz
R					
L					
Stimulator :	ON		OFF		

1) Burke-Fahn-Marsden Dystonia movement scale

Region	Provoking Factor (0-4) ×	Severity Factor (0-4) ×	Weight	Product
Eyes	0. No dystonia at rest or with action 1. Dystonia only with particular action 2. Dystonia with many actions 3. Dystonia on action of distant part of body or intermittently at rest 4. Dystonia present at rest	0. No dystonia 1. Slight. Occasional blinking 2. Mild. Frequent blinking without prolonged spasms of eye closure 3. Moderate. Prolonged spasms of eyelid closure, but eyes open most of the time 4. Severe. Prolonged spasms of eyelid closure, with eyes closed at least 30% of the time	0.5	
Mouth	0. No dystonia at rest or with action 1. Dystonia only with particular action 2. Dystonia with many actions 3. Dystonia on action of distant part of body or intermittently at rest 4. Dystonia present at rest	0. no dystonia present 1. Slight. Occasional grimacing or other mouth movements (e.g., jaw opened or clenched; tongue movement 2. Mild. Movement present less than 50% of the time 3. Moderate dystonic movements or contractions present most of the time 4. Severe dystonic movements or contractions present most of the time	0.5	
Speech, swallowing	0. Occasional, either or both 1. Frequent either 2. Frequent one and occasional other 3. Frequent both	0. Normal 1. Slightly involved; speech easily understood or occasional choking 2. Some difficulty in understanding speech or frequent choking 3. Marked difficulty in understanding speech or inability to swallow firm foods 4. Complete or almost complete anarthria, or marked difficulty swallowing soft foods and liquids	1	
Neck	0. No dystonia at rest or with action 1. Dystonia only with particular action 2. Dystonia with many actions 3. Dystonia on action of distant part of body or intermittently at rest 4. Dystonia present at rest	0. No dystonia present 1. Slight. Occasional pulling 2. Obvious torticollis, but mild 3. Moderate pulling 4. Extreme pulling	0.5	
R arm	0. No dystonia at rest or with action 1. Dystonia only with particular action 2. Dystonia with many actions 3. Dystonia on action of distant part of body or intermittently at rest 4. Dystonia present at rest	0. No dystonia present 1. Slight dystonia. Clinically insignificant 2. Mild. Obvious dystonia, but not disabling 3. Moderate. Able to grasp, with some manual function 4. Severe. No useful grasp	1	
L arm			1	
Trunk	0. No dystonia at rest or with action 1. Dystonia only with particular action 2. Dystonia with many actions 3. Dystonia on action of distant part of body or intermittently at rest 4. Dystonia present at rest	0. No dystonia present 1. Slight bending; clinically insignificant 2. Definite bending, but not interfering with standing or walking 3. Moderate bending; interfering with standing or walking 4. Extreme bending of trunk preventing standing or walking	1	

Patients name: _____
Date of examination: _____
Examiners name: _____

R leg	0. No dystonia at rest or with action 1. Dystonia only with particular action 2. Dystonia with many actions 3. Dystonia on action of distant part of body or intermittently at rest 4. Dystonia present at rest	0. No dystonia present 1. Slight dystonia, but not causing impairment; clinically insignificant 2. Mild dystonia. Walks briskly and unaided 3. Moderate dystonia. Severely impairs walking requires assistance 4. Severe. Unable to stand or walk on involved	1	
L leg			1	

Total (max=120) _____

2) Burke-Fahn-Marsden Dystonia disability scale.

Speech (0-4)	0. Normal 1. Slightly involved; easily understood 2. Some difficulty in understanding 3. Marked difficulty in understanding 4. Complete or almost anarthria	
Writing (0-4)	0. Normal 1. Slight difficulty; legible 2. Almost illegible 3. Illegible 4. Unable to grasp to maintain hold on pen	
Feeding (0-4)	0. Normal 1. Uses "tricks"; independent 2. Can feed, but not cut 3. Finger food only 4. Completely dependent	
Eating (0-4)	0. Normal 1. Occasional choking 2. Chokes frequently; difficulty swallowing 3. Unable to swallow firm foods 4. Marked difficulty swallowing soft foods and liquids	
Hygiene (0-4)	0. Normal 1. Clumsy; independent 2. Needs help with some activities 3. Needs help with most activities 4. Needs help with all activities	
Dressing (0-4)	0. Normal 1. Clumsy; independent 2. Needs help with some activities 3. Needs help with most activities 4. Helpless	
Walking (0-6)	0. Normal 1. Slightly abnormal; hardly noticeable 2. Moderately abnormal; obvious to naïve observer 3. Considerably abnormal 4. Needs assistance to walk 6. Wheelchair bound	

Total (max=30)_____

Appendix 3: "The 35 perceptual dimensions from Darley et al (1972) scale"

Speech sign-cluster	Speech dimension	Definition
Articulation	Sound imprecision	Phonemes lack precision. They show slurring, inadequate sharpness, distortions, and lack of crispness. There is clumsiness in going from one sound to another
	Sounds prolonged	There are prolongations of phonemes
	Sounds repeated	There are repetitions of phonemes
	Irregular articulatory breakdown	Intermittent nonsystematic breakdown in accuracy of articulation
	Sound omissions	Vowel or consonant sounds omitted
Respiration	Forced inspiration-expiration	Speech is interrupted by sudden, forced inspiration and expiration sighs
	Audible inspiration	Audible, breathy inspiration
	Grunt at end of expiration	Grunt at end of expiration
	Phrases short	Phrases are short (possibly due to fact that inspirations occur more often than normal). Speaker may sound as if he / she has run out of air. They may produce a gasp at the end of a phrase
	Excess loudness variation	Voice shows sudden, uncontrolled alterations in loudness, sometimes being too loud, sometimes too weak
	Loudness decay	There is a progressive diminution or decay of loudness
Resonance	Hypernasality	Voice sounds excessively nasal. Excessive amount of air is resonated by nasal cavities
	Hyponasality	Voice is denasal
	Nasal omission	There is nasal emission of air stream
Phonation	Voice tremor	Voice shows shakiness or tremulousness
	Harsh voice	Voice is harsh, rough, and raspy
	Breathy voice – continuous	Continuously breathy, weak, and thin
	Breathy voice – transient	Breathiness is transient, periodic, intermittent
	Strained – strangled voice	Voice (phonation) sounds strained or strangled (an apparently effortful squeezing of voice through glottis)
	Hoarse voice	Wet, "liquid sounding" hoarseness
	Voice stoppages	There are sudden stoppages of voiced air stream (as if some obstacle along vocal tract momentarily impedes flow of air)
	Pitch breaks	Pitch of voice shows sudden and uncontrolled variation (falsetto breaks)
	Low pitch level	Pitch of voice sounds consistently too low for individuals age & sex
	High pitch level	Pitch of voice sounds consistently too high for individuals age & sex
Prosody	Reduced stress	Speech shows reduction of proper stress or emphasis patterns
	Inappropriately placed stress	Excess on usually unstressed parts of speech, e.g. (1) monosyllabic words and (2) unstressed syllables of polysyllabic words
	Monopitch	Voice is characterized by a monopitch or monotone. Voice lacks normal pitch and inflectional changes. It tends to stay at one pitch level
	Monoloudness	Voice shows monotony of loudness. It lacks normal variation
Rate	Slow rate	Rate of actual speech is abnormally slow
	Rapid rate	Rate of actual speech is abnormally rapid
	Increase overall rate	Rate increases from beginning to end of sample
	Increase rate across segments	Rate increases progressively within given segments of connected speech
	Short rushes of speech	There are short rushes of speech separated by pauses
	Inappropriate silences	There are inappropriate silent intervals
	Variable rate	Intermittent non-systematic breakdown in regular rate

Appendix 4: Example from the "Assessment of Intelligibility of the dysarthric speaker"

Sentence Intelligibility Test

File:
Date: 09/12/2010
Examiner:
Agency:
Comment:

5A. That plant needs more water.
5B. It's beauty that surrounds you.
6A. The old gentleman's coat was threadbare.
6B. Four people work in the restaurant.
7A. I just try to do my best.
7B. The marriage went well from the start.
8A. You can easily make discoveries of your own.
8B. It can lead to any number of adventures.
9A. It cannot live in animals or elsewhere in nature.
9B. Why is yours the greatest choir in the world?
10A. Why would such a man be fired from his job?
10B. Hundreds of tools and inventions are now on the market.
11A. Some of us give assurance, while others do quite the contrary.
11B. Finding someone willing to trade with you takes a little courage.
12A. Where is the wilderness that was to be preserved for all generations?

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Sentence Intelligibility Test

12B. According to the rules, you shouldn't end a sentence with a preposition.
13A. Adoring fans reached out to touch the players, who sat atop open vehicles.
13B. I never asked for more in this life than a patch of grass.
14A. Only a few friends of the three refused to take part in the benefit.
14B. I know two women who learned to fly, and have since become licensed pilots.
15A. It was the first step aimed at winning wages comparable to those paid other workers.
15B. He bought everything he needed to start drawing and painting, but then changed his mind.

Appendix 5: The Voice Handicap Index (Jacobson et al, 1997)

Voice Handicap Index

Instructions: These are statements that many people have used to describe their voices and the effect of their voices on their lives. Circle the response that indicates how frequently you have the same experience **in your life now.**

Key: 0 = Never 1 = Almost never 2 = Sometimes 3 = Almost always 4 = Always

Part 1a – Functional

1. My voice makes it difficult for people to hear me.	0	1	2	3	4
2. People have difficulty understanding me in a noisy room.	0	1	2	3	4
3. My family have difficulty hearing me when I call them throughout the house.	0	1	2	3	4
4. I use the phone less often than I would like to.	0	1	2	3	4
5. I tend to avoid groups of people because of my voice.	0	1	2	3	4
6. I speak with friends, neighbours, or relatives less often because of my voice.	0	1	2	3	4
7. People ask me to repeat myself when speaking face-to-face.	0	1	2	3	4
8. My voice difficulties restrict personal and social life.	0	1	2	3	4
9. I feel left out of conversations because of my voice problem.	0	1	2	3	4
10. My voice problem causes me to lose income.	0	1	2	3	4

Part 2a – Physical

1. I run out of air when I talk.	0	1	2	3	4
2. The sound of my voice varies throughout the day.	0	1	2	3	4
3. People ask, "What is wrong with your voice?"	0	1	2	3	4
4. My voice sounds creaky and dry.	0	1	2	3	4
5. I feel as though I have to strain to produce voice.	0	1	2	3	4
6. The clarity of my voice is unpredictable.	0	1	2	3	4

7. I try to change my voice to sound different.	0	1	2	3	4
8. I use a great deal of effort to speak.	0	1	2	3	4
9. My voice sounds worse in the evening.	0	1	2	3	4
10. My voice "gives out" on me in the middle of speaking.	0	1	2	3	4

Part 3a – Emotional

1. I am tense when talking to others because of my voice.	0	1	2	3	4
2. People seem irritated with my voice.	0	1	2	3	4
3. I find that other people don't understand my voice problem.	0	1	2	3	4
4. My voice problem upsets me.	0	1	2	3	4
5. I am less outgoing because of my voice problem.	0	1	2	3	4
6. My voice makes me feel handicapped.	0	1	2	3	4
7. I feel annoyed when people ask me to repeat.	0	1	2	3	4
8. I feel embarrassed when people ask me to repeat.	0	1	2	3	4
9. My voice makes me feel incompetent.	0	1	2	3	4
10. I am ashamed of my voice problem.	0	1	2	3	4

Thank you for taking the time to complete this questionnaire. If you require any further information, please feel free to contact Mrs Elina Tripoliti, Sobell Department of Motor Neuroscience and Movement Disorders, Box 146 Institute of Neurology, 33 Queen Square, London, WC1N 3BG