EFFECTS OF DEEP BRAIN STIMULATION ON SPEECH MOTOR PLANNING/ PROGRAMMING IN PATIENTS WITH PARKINSON'S DISEASE

By

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To my extraordinary wife Carlee – your steadfast love, support, and encouragement have allowed me to achieve my dreams

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LIST OF ABBREVIATIONS

CES	Communicativeness Effectiveness Survey
CMA	Cingulate motor area
DBS	Deep brain stimulation
GPe	Globus pallidus pars externa
GPi	Globus pallidus internus
IC	Internal capsule
MC	Motor cortex
MMSE	Mini-Mental State Examination
PD	Parkinson's disease
PET	Positron emission tomography
PMC	Premotor cortex
RT	Reaction time
SIT	Sentence Intelligibility Test
SLPs	Speech-language pathologists
SMA	Supplementary motor area
SNpc	Substantia nigra pars compacta
SNpr	Substantia nigra pars reticulata
SRB	Serial Response Box
SRT	Speech reaction time
STN	Subthalamic nucleus
UF	University of Florida
UPDRS	Unified Parkinson's Disease Rating Scale
WMS-III	Wechsler Memory Scale – 3rd Edition

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The primary purpose of this study was to measure the effects of deep brain stimulation (DBS) on maintaining and switching speech motor programs in individuals with Parkinson's disease (PD) and hypokinetic dysarthria. Recent literature suggests that at least a portion of the underlying mechanism of hypokinetic dysarthria in individuals with PD may be related to deficits in speech motor planning/programming, including maintaining and switching motor programs (Spencer & Rogers, 2005; Van der Merwe, 1997). Although the effects of DBS on speech motor planning/programming have not been previously explored, DBS has been shown to have a positive influence on these processes in the limbs and we posited that DBS would similarly benefit speech maintenance and switching.

A reaction time paradigm was employed to measure the effects of DBS on maintaining and switching of speech motor programs in individuals with PD. Double blind testing was completed in the 'on' and 'off' DBS conditions using a response priming procedure in which participants were provided with a prime word to supply information regarding target word. Over a series of targets, the prime was followed with a high probability by the primed target as

expected (‘no-switch’ condition) or with a low probability by an unexpected target word (‘switch’ condition). The primary dependent measure was SRT ‘on’ and ‘off’ DBS.

Twelve participants completed the study. Statistically significant differences ($p < 0.05$) were found in SRT between the ‘no switch’ and ‘switch’ conditions, regardless of DBS state. Significant differences were also found in SRT in the ‘no switch’ condition (i.e., subjects produced a word more quickly ‘on’ versus ‘off’ stimulation). No differences across stimulation conditions in the ‘switch’ condition were observed. These findings suggest that the greater complexity of the ‘switch’ condition requires increased speech motor planning/programming processes which can be measured temporally. DBS was also found to improve SRT in the ‘no switch’ condition, suggesting that maintenance of speech motor programs may be improved by DBS. No differences between DBS states were found in the ‘switch’ condition, suggesting that DBS has little influence on the multiple processes involved in a motor program switching task.

CHAPTER 1
INTRODUCTION

Primary Aims

The primary purpose of this study was to measure the effects of deep brain stimulation (DBS) on maintaining and switching speech motor programs in individuals with Parkinson's disease (PD) and hypokinetic dysarthria using a speech reaction time (SRT) paradigm. Recent literature suggests that at least a portion of the underlying mechanism of hypokinetic dysarthria in individuals with PD may be related to deficits in speech motor planning/programming, including maintaining and switching motor programs (Spencer & Rogers, 2005; Van der Merwe, 1997). Although the effects of DBS on speech motor planning/programming have not, to our knowledge been previously explored, DBS has been shown to positively influence maintaining and switching motor programs in the limbs and we posited that DBS would similarly improve motor speech program maintenance and switching. In order to test the influence of DBS on these processes, two priming conditions were tested (i.e., 'switch' or 'no switch') in both DBS states (i.e., 'on' and 'off' stimulation). The primary dependent variable was SRT.

The following null hypothesis was addressed:

There is no significant difference in SRT across DBS states (i.e., 'on' and 'off" stimulation) or priming condition (i.e., 'switch' and 'no switch').

Research Question 1

Are there significant differences in SRT when subjects with PD and DBS produce a word in the 'switch' and 'no switch' conditions?

It was predicted that SRT will be faster when producing a word in the 'no switch' versus 'switch' condition, regardless of DBS state. This was expected due to the increased complexity of the 'switch' condition on processes involved in speech motor programming/planning.

Research Question 2

Are there significant differences in SRT in the 'on' versus 'off' DBS state when participants with PD produce a word in the 'no switch' condition?

It was predicted that participants will have improved SRT in single words in the 'no switch' condition when 'on' versus 'off' DBS. This was expected due improved maintenance of the speech motor program in the 'on' stimulation condition.

Research Question 3

Are there significant differences in SRT in the 'on' versus 'off' DBS state when participants with PD produce a word in the 'switch' condition?

It was predicted that SRT will be improved in single words in the 'switch' condition in the 'on' versus 'off' stimulation condition. This was expected due to improved ability to switch speech motor programs in the 'on' stimulation condition.

Secondary and Exploratory Aims

The secondary aims of this study were to determine the effects of the experimental manipulations on speech response accuracy. It was expected that response accuracy would differ in response to priming condition. That is, more errors were anticipated in the 'switch' versus the 'no switch' condition. No difference in response accuracy was expected in response to DBS state. For exploratory purposes, measures of neuropsychological performance (i.e., verbal fluency and response inhibition) were conducted both 'on' and 'off' DBS.

CHAPTER 2
MATERIALS AND METHODS

Experiment Overview

A reaction time (RT) paradigm was employed to measure the effects of DBS on maintaining and switching of speech motor programs in individuals with PD and hypokinetic dysarthria. Double blind testing was completed in the 'on' and 'off' DBS states using a response priming procedure in which participants were provided with a prime to supply information regarding target. Over a series of targets, the prime word was followed with a high probability by the primed target as expected ('no-switch' condition) or with a low probability by an unexpected target word ('switch' condition). The task of the subjects was to speak the target word aloud as quickly and accurately as possible. The primary dependent measure was SRT.

Participants

Subjects

Twelve participants with PD and DBS completed the study. Subjects were recruited through the Movement Disorders Clinic at the University of Florida (UF) and the Speech and Hearing Center at UF based on the following criteria:

Inclusion Criteria

Inclusion criteria included patients age 25 – 85 years old with a diagnosis of "probable" idiopathic PD as determined by a neurologist with expertise in the evaluation of movement disorders, six months to two years status-post unilateral left or bilateral GPi or STN DBS, medically optimized and stable on anti-PD and psychotropic medications for at least 30 days at the time of the screening visit, the ability to read words and sentences aloud, and completion of the informed consent to participate in the study.

Exclusion Criteria

Exclusion criteria included history positive for previous neurosurgery for PD (e.g., pallidotomy or thalamotomy), DBS surgery completed at an outside institution, thalamic DBS, recent (less than three months previous) or significant stroke, Mini-Mental State Examination score (MMSE) < 26, and Wechsler Memory Scale – 3rd Edition (WMS-III) Spatial Span Forward or Backward Subtests standard score < 7, history or presence of aphasia, inability to discontinue anti-PD medication overnight and during the test session, inability to discontinue DBS for at least six hours, inability to perform the study tasks for reasons such as an incapacity to read words and sentences aloud or produce intelligible speech, severe motor symptoms causing extreme difficulty/inconvenience when medications are withheld and/or DBS device is turned off, or other significant medical illness that prevents meaningful participation in the study.

Screening Session

In order to determine eligibility and to further describe participants, a screening visit was first conducted. Screenings sessions were primarily conducted at the subject's homes and the Speech and Hearing Center at the University of Florida.

Eligibility Determination

During the screening visit, informed consent was first obtained. Next, participants were asked questions about their demographic information and current and past medical health status for inclusion/exclusion purposes. This was followed by administration of the MMSE and the WMS-III Spatial Span Forward and Backward Subtests to screen general cognitive function, attention and concentration, and working memory. Ability to read sentences aloud was determined during administration of the Sentence Intelligibility Test (SIT) (see "Participant description" below for more details).

Participant Description

A speech evaluation was completed including maximum performance testing of the speech mechanism (Kent, Kent, & Rosenbek, 1987), repetition of multisyllabic words and sentences, elicitation of a connected speech sample, and determination of intelligibility using the short form of the SIT. All components of the speech evaluation were recorded using a high-quality digital audio recorder (Marantz PMD671) and a head-mounted microphone (Shure SM10A) positioned two centimeters from the left corner of the subject's mouth. The Communicativeness Effectiveness Survey (CES), an eight-item questionnaire using a seven-point scale in which individuals make judgments about their ability to communicate effectively during everyday activities, was also administered (Donovan, Velozo, & Rosenbek, in press).

A speech diagnosis regarding the presence, type, and severity of dysarthria was later determined for each of the participants based on acoustic recordings of maximum performance testing, word and sentence repetition, and connected speech samples. Two speech-language pathologists (SLPs) (JR & HJ) experienced in the evaluation of neurogenic speech disorders used perceptual assessment to independently determine whether dysarthria was present and, if so, the type and severity based on a seven-point scale (see Table 2-1) using the Mayo Clinic classification terminology (Darley, Aronson, & Brown, 1969a, b, 1975; Duffy, 2005). Any differences in speech diagnosis or severity of dysarthria led to re-listening and debate to make a final consensus decision.

To determine intelligibility, acoustic recordings of sentences from the SIT were presented via headphone to two undergraduate students with normal hearing who served as intelligibility scorers. These individuals were inexperienced in communicating with individuals with dysarthria. Each sentence was presented at a fixed volume to each scorer two times with a three

second pause between presentations. They were asked to orthographically transcribe the sentences and enter them into the SIT program via a computer keypad. Scorers were encouraged to pause sentence playback as needed in order to accurately transcribe the sentences, although each sentence was heard only twice and no adjustments in volume were permitted.

A discourse analysis was completed by two SLPs experienced in discourse analysis (DK & HJ) based on acoustic recordings of repetition of multisyllabic words, repetition of sentences, and connected speech in order to determine linguistic competency. These productions were assessed for the presence of linguistic errors, specifically phonologic errors (i.e., substitutions, omissions, transpositions, etc.) and/or semantic or verbal errors. Any differences in analysis led to re-listening and debate in order to make a final determination regarding the presence and type of linguistic errors.

Experimental Sessions

Subjects who met all study criteria following completion of the screening session were scheduled for the experimental session one to 30 days later. Please see Figure 2-1 for an example of the typical experimental timeline. Subjects were tested ‘off’ their anti-PD medication, including levodopa. The ‘off’ medication condition was defined as at least 12 hours off anti-PD medications. Testing was conducted with left-brain DBS in the ‘on’ and ‘off’ states. If subjects had bilateral DBS, the right-brain DBS was turned ‘off’ for the duration of the experimental session. Two two-hour washouts of DBS were completed during each experimental session during which all DBS therapy was discontinued. Two test sessions in which a battery of tests was administered (see “Experimental Procedures” below) while subjects were ‘on’ and ‘off’ DBS were completed for each participant. Following the first DBS washout, subjects were quasi randomly assigned to the first stimulation condition (i.e., ‘on’ or ‘off’ DBS) in a counterbalanced

fashion. Using the Medtronic Access Review device, a trained research assistant turned subjects 'on' or 'off' allowing subjects and the principal investigator to remain blinded to the test condition. Thirty minutes later, the first test session was initiated and completed in approximately 30 minutes. The second two-hour DBS washout was then started and this was followed by implementation of the second stimulation condition by the research assistant. Subjects that were tested 'on' DBS during then first test session were tested 'off' DBS during the second test session, and vice versa. The second test session was also started 30 minutes after the condition was initiated and completed in approximately 30 minutes. Following completion of both test sessions, all subjects were turned 'on' DBS and took their anti-PD medications.

Experimental Procedures

Experimental sessions were conducted primarily at the homes of the participants, as well as the UF Speech and Hearing Center in select cases. A response priming procedure based on the work of Spencer (Spencer & Rogers, 2006; Spencer, 2006) was utilized. As shown in Figure 2-2, in this paradigm, participants are provided with a prime to supply information regarding a target. Over presentation of a series of target words for speech production, the prime word was followed with a high probability (75% of trials) by the primed target as expected in the 'no switch' condition, such as with the prime-target pair "shopper-shopper". In 25% of trials, however, the subject was presented with an incorrect prime, discovered upon presentation of the command for movement (i.e., the target word). In other words, the prime-target pair did not match in the 'switch' condition (i.e., "shopper-chopper"). Subjects were trained to read the target word aloud as quickly and accurately as possible and were further instructed to be prepared to say the prime word due to the high likelihood it would match the upcoming target. Each trial began with a signal (i.e., +) on a computer screen followed by visual presentation of the prime word for

1000ms. The prime was followed by a blank screen for 250ms and then the target word was presented for 1000ms. Response latency was measured temporally from the presentation of the target. Response accuracy was determined using broad phonetic transcription scored online with later verification and analysis of errors. Further details can be found under the "Scoring" and "Equipment" sections of this chapter.

Subjects were also administered two neuropsychological tests during each of the two test sessions: the FAS test of verbal fluency and the Stroop. Color and Word Test. During the FAS, participants were provided with one-minute to produce as many words as possible starting with each of the three letters F, A, and S (Benton & Hamsher, 1976). The Stroop has three sets of stimuli: color words printed in black ink, symbols (i.e., X) printed in color ink, and color words from the first set of stimuli printed with incongruous colors from the second set of stimuli. Subjects were asked to move through each set of stimuli reading words or naming colors as quickly as possible (Golden & Freshwater, 2002).

Training session

Prior to the first test session, participants were trained in the experimental task for approximately 10 minutes (see Appendix A for the training session stimuli). Following this training period, if a subject was unable to perform the experimental task, it was planned to discontinue testing, though this did not occur.

Stimuli

The prime and target words consisted of one- and two-syllable words (see Appendix B) from Spencer (2006) (adapted from Spencer & Rogers, 2005). Word rimes were maintained from prime to target. It was required that the onset of the prime needed to share two features with the target and be a highly marked phoneme. A balance for word frequency was maintained (Spencer

& Rogers, 2005). Stimuli were linguistically controlled so that all effects were due to the experimental manipulation.

Sixteen prime-target pairs were used in the experiment. Each of these sixteen prime-target pairs was presented four times. Three of the presentations for each of the prime-target pairs were the no-switch condition (i.e., shopper-shopper), while one of the four presentations was the switch condition (i.e., shopper-chopper). This ensured that subjects expected the prime to accurately provide information regarding the target.

Equipment

The equipment configuration is shown in cartoon format in Figure 2-3. A laptop computer (Compaq Presario V2000) was used to run the E-Prime computer software (Psychology Software Tools) used in the response priming procedure. Stimuli were presented on a separate 19" computer monitor (Planar PL1910M) placed in front of the subject. Presentation of stimuli and calculation of response latencies were managed by the E-Prime program and a Serial Response Box (SRB) (Psychology Software Tools). Registration of speech onset, as measured by the onset of voicing, was measured using an accelerometer (PCB Piezotronics 352C22) placed inferior to the thyroid cartilage with adhesive tape. The accelerometer was powered by a portable power source (PCB Piezotronics Model 480C02 ICP Signal Conditioner) and the signal captured by this transducer activated the Voice Key of the Serial Response Box to measure response latency.

High-quality acoustic recordings were made during administration of the response priming procedure, FAS, and Stroop using a high-quality digital recorder (Marantz PMD671) and a head-mounted microphone (Shure SM10A) positioned two centimeters from the left corner

of the patient's mouth. Digital video recordings (Sanyo VPC-C6) were also made during all experimental tasks.

Scoring

Speech Reaction Time

SRT was measured by E-Prime computer software and the voice key of the SRB. Only correct productions were used to calculate SRT. Subjects were trained to not produce a speech response until the target word was presented. SRT was measured starting with the command for movement (i.e., presentation of the target) until the onset of voicing registered for each response. Responses during the pause or less than 250ms after presentation of the target were scored as a premature response. Premature responses were considered to be incorrect and were combined with other errors from the response accuracy assessment to determine the total number of incorrect responses.

Response Accuracy

Acoustic recordings from the response priming test were used to determine the accuracy of responses over two sessions. During the first session, judge one (HJ) independently listened to all responses using high quality headphones (Sony MDR-V6). Each response was listened to as many times as necessary to be able to use broad phonetic transcription the record the responses and determine if a production was correct or incorrect. During the second session, a second judge (DK) was added and this process was completed with both judges simultaneously listening to the acoustic recordings with headphones. When the two judges did not agree on whether a response was correct or incorrect, a consensus decision was reached with further listening and debate. Agreement between the judges was not considered to occur in cases where further listening

and/or debate were required, although these final consensus judgments were used to determine accuracy of each response. Types of errors included the following:

Production of the prime – Responses in which participants do not "switch" their speech response. For example, "shopper-chopper" is the prime-target pair and the production is "shopper" rather than "chopper". Subjects may self-correct.

Partial production of prime – Responses in which participants partially produce the prime word such as the first sound or syllable. For example, the prime-target pair is "shopper-chopper" and the subject responds "sh…chopper". Subjects may self-correct.

Initial sound repetition – Responses in which participants repeat the initial sound or syllable of the target word. For example, in the case of the word pair "shopper-shopper", the subject responds "sh…shopper".

Production of previous target – Responses in which the subject produces a previously presented target.

No response – Subject does not produce a speech response upon command.

Phonological error **–** Single phoneme omission, deletion, substitution, transposition, etc.

Lexical/semantic error – Responses in which participants substituted a whole real word for the target word.

Multiple errors – Two or more errors from the above list were combined in a single response**.**

Reliability

Intra-rater Reliability

Judge one completed perceptual assessment to determine the accuracy of each response on two separate occasions. Point-by-point analysis was conducted for 100% of each subject's responses

during each of their two test sessions to determine whether agreement regarding accuracy was present. Intra-class correlation coefficients were determined.

Inter-rater Reliability

A point-by-point analysis was completed to compare the level of agreement between the two judges as to whether each individual response was correct or incorrect. Intra-class correlation coefficients were determined.

Data Analysis

Average response latency and number of errors were calculated for each participant by the stimulation condition (‘on’ and ‘off’ DBS) and by the prime-target relationship (‘switch’ and ‘no switch’ responses). Summary statistics are provided by the stimulation condition and by the prime-target relationship.

Furthermore, formal statistical inferences were conducted using nonparametric procedures. Separate Wilcoxon signed-rank tests were used to determine whether significant differences were present between the ‘on’ and ‘off’ stimulation conditions for ‘switch’ and ‘no switch’ speech responses in terms of SRT and response accuracy. Fisher's combination method was used to further analyze the data and combine results from the ‘on’ and ‘off’ stimulation conditions and the ‘switch’ and ‘no switch’ test conditions to obtain overall p-values.

Sample Size and Power Consideration

Power analysis was conducted based on data for participants with hypokinetic dysarthria published by Spencer and Rogers (2005). As the study population and experimental stimuli vary between the two experiments, a conservative approach was utilized whenever possible. The mean difference in log-transformed response latency (called speech reaction times in the published paper) is 0.0966 unit larger (i.e., 10% longer) for ‘switch’ versus ‘no switch’ speech

responses, with a standard deviation of 0.0805. If it assumed that the differences in log-transformed response latency have the same distribution in our study for each stimulation condition, then the Wilcoxon signed-rank sum test at the 0.05 Type-I error level has sufficient power to detect differences between ‘switch’ and ‘no switch’ speech responses as shown in Table 2-2.

On the other hand, for differences between ‘on’ and ‘off’ stimulation conditions, we did not have an estimate of effect size. Thus, a sensitivity analysis with regard to difference magnitude was completed with the assumption that the sample size would be 15 to test the hypothesis using the Wilcoxon signed-rank sum test at the 0.05 Type-I error level. Table 2-3 provides powers corresponding to r, ratio of mean SRT between the ‘on’ and ‘off’ stimulation conditions. This table suggests that even if the difference between the ‘on’ and ‘off’ stimulation conditions is only half of the difference between the ‘switch’ and ‘no switch’ responses observed in the Spencer and Rogers study from 2005, we will still have reasonable power.

Table 2-1. Auditory-perceptual dysarthria severity scale.

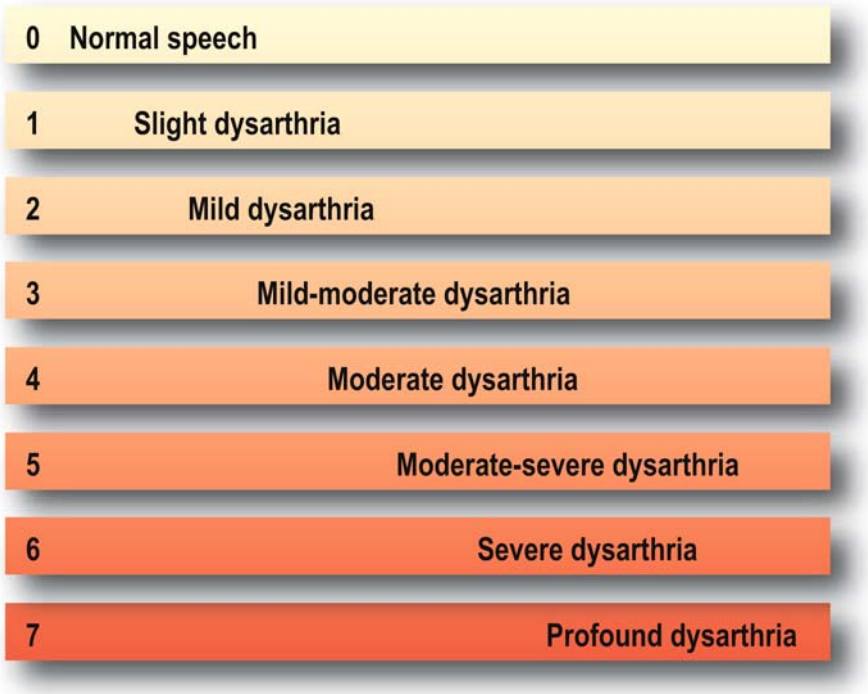

Table 2-2. Power analysis to detect differences between ‘switch’ and ‘no switch’ speech responses.

N	10	11	12	13	14	15
Power	0.9037	0.9286	0.9481	0.9696	0.9816	0.9875

Table 2-3. Powers corresponding to r, ratio of mean SRT between the ‘on’ and ‘off’ stimulation conditions, based on sensitivity analysis.

R	1.05	1.06	1.07	1.08	1.09	1.1
Power	0.5699	0.7193	0.8393	0.9217	0.9626	0.9856

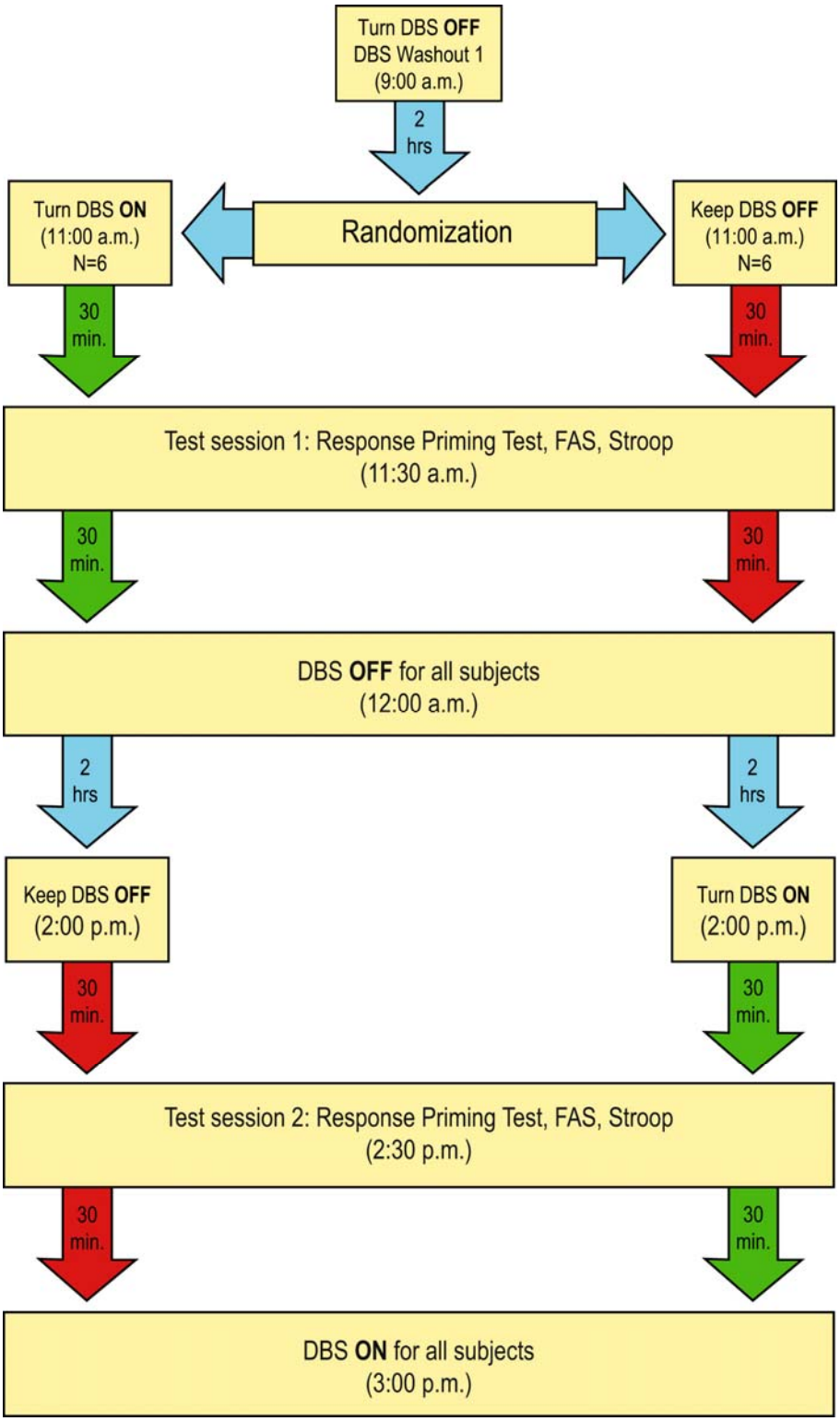

Figure 2-1. Typical experimental timeline.

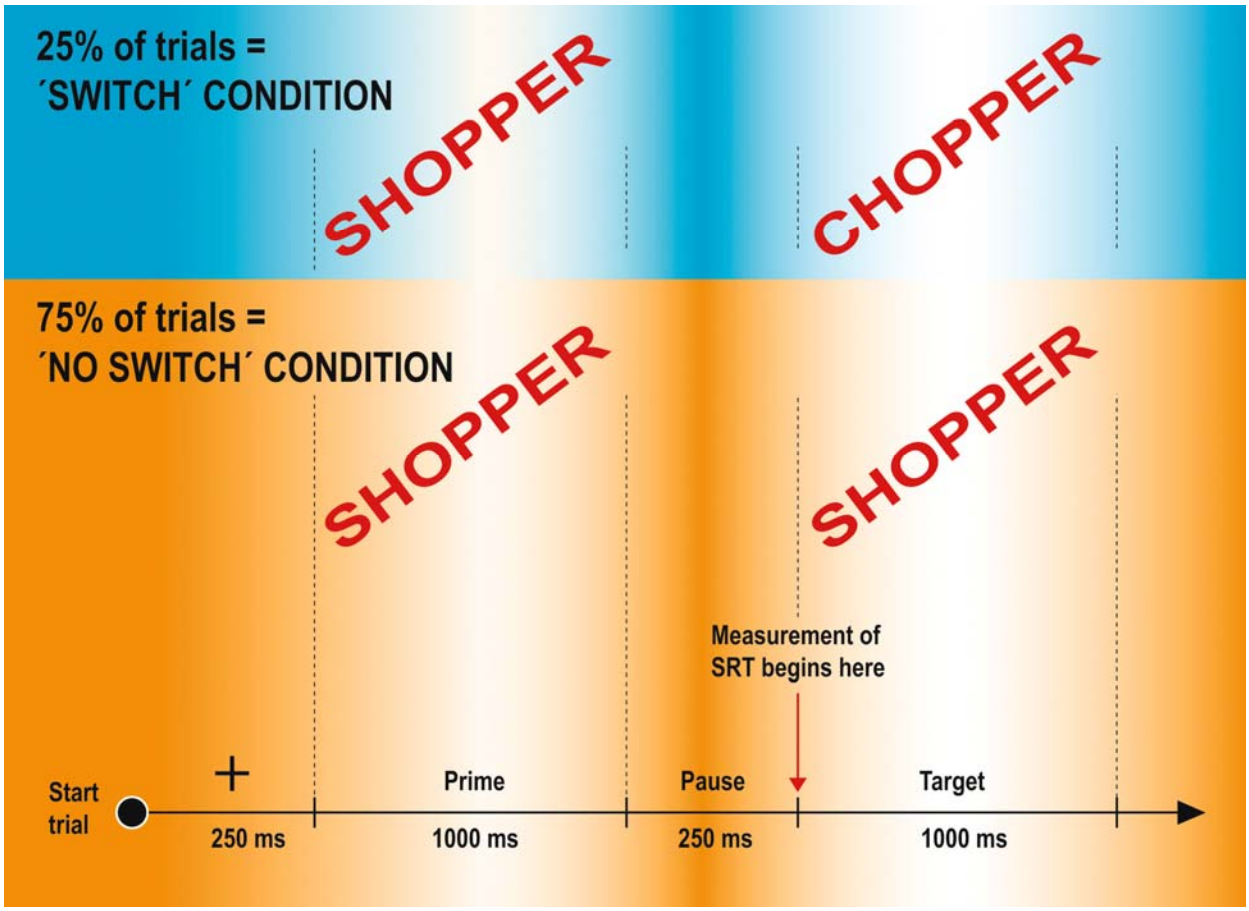

Figure 2-2. Response priming protocol.

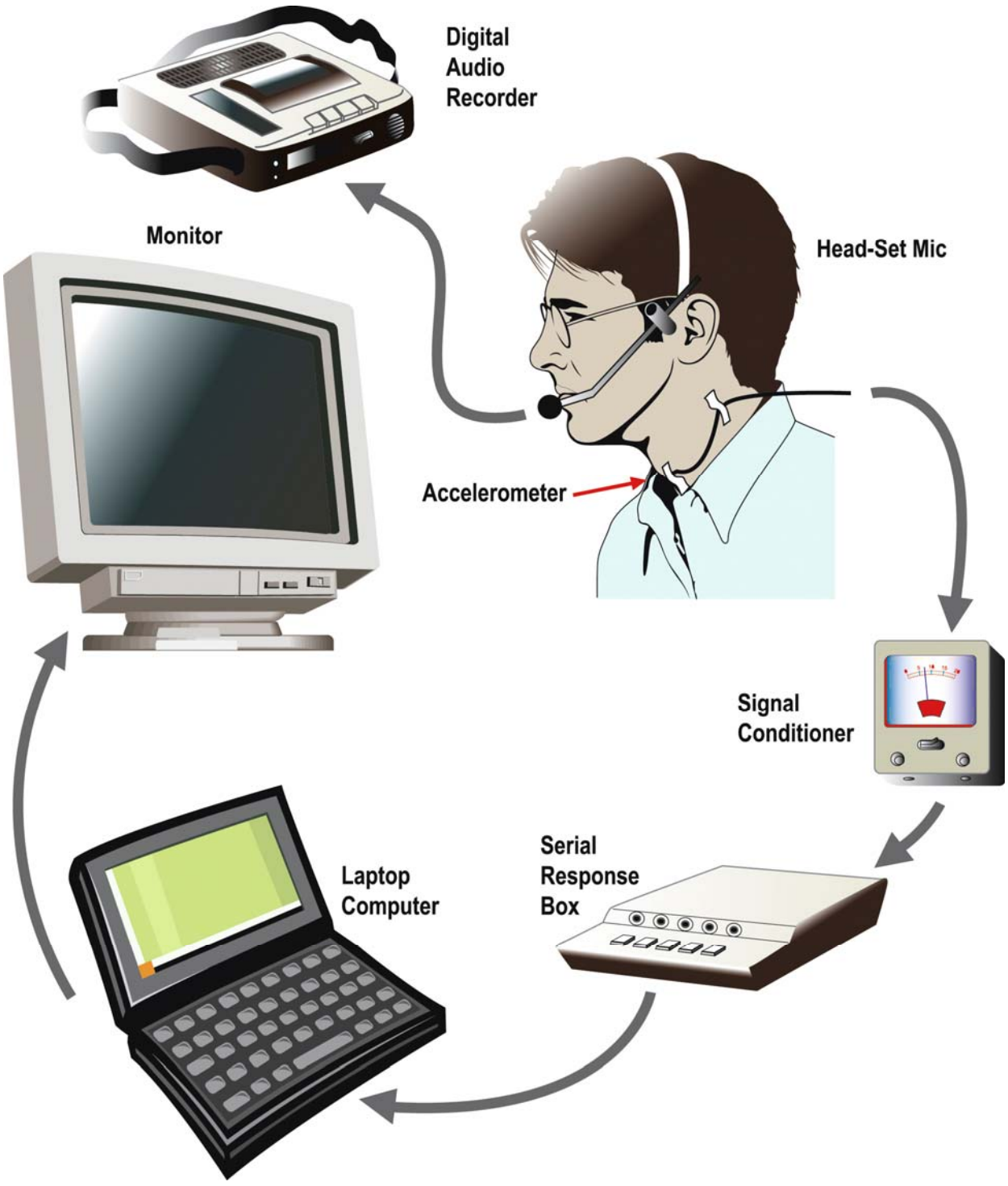

Figure 2-3. Equipment configuration

CHAPTER 3
LITERATURE REVIEW

This chapter will review the necessary literature to support the rationale of the study. This will include discussion of: (1) The basal ganglia and its internal and external circuitry; (2) DBS as treatment for PD and possible mechanisms of benefit; (3) Motor planning/programming with an emphasis on maintaining and switching motor programs, (4) The possibility of motor planning/programming deficits (including speech) in PD; and (5) The use of reaction time experiments to test aspects of motor planning/programming.

The Basal Ganglia

The basal ganglia comprise several subcortical nuclei critically involved in movement and posture. Although this study emphasizes the role of the basal ganglia in movement (specifically its planning/programming), it should be recognized that modern conceptualization of basal ganglia function emphasizes a number of functionally segregated circuits involved in a number of diverse motor, cognitive, and limbic functions (Alexander, DeLong & Strick, 1986). Due to the intrinsic/extrinsic basal ganglia circuitry, these structures have the opportunity to influence diverse cortical areas including those thought to be involved in speech motor planning/programming.

Anatomy

First, the normal basal ganglia anatomy will be described. The basal ganglia are often conceptualized as a group of input structures, output structures, and intrinsic nuclei. The two primary input structures are the striatum (comprised of the caudate and putamen) and the subthalamic nucleus (STN). The two primary output structures are globus pallidus internus (GPi) and substantia nigra pars reticulata (SNpr). The intrinsic nuclei of the basal ganglia include globus pallidus pars externa (GPe) and substantia nigra pars compacta (SNpc) (Mink, 1996).

Many of the structures of the basal ganglia, as well as other surrounding structures such as the thalamus and internal capsule (IC), are shown in Figure 3-1.

Normal Basal Ganglia Intrinsic/Extrinsic Circuitry

The extrinsic and intrinsic circuitry of the basal ganglia is of course complex and will only be briefly reviewed, with an emphasis on what some have begun to call the 'standard model' (Gale, Amirnovin, Williams, Flaherty, & Eskandar, in press) This model suggests a number of separate, functionally, and anatomically segregated corticobasal ganglion circuits, each of which has two pathways through the basal ganglia: the inhibitory direct pathway and the excitatory indirect pathway (DeLong & Wichmann, 2007). As shown in Figure 3-2, under normal conditions, the putamen receives excitatory input from multiple cortical areas, including the portions of the motor cortex (MC), premotor cortex (PMC), supplementary motor area (SMA), and cingulate motor area (CMA) (Alexander, DeLong & Strick, 1986; DeLong, 1990; DeLong & Wichmann, 2007; Mink, 1996). Output of the putamen is thought to be neuromodulated through the direct and indirect pathways. The direct pathway projects inhibitory signals to the output nuclei, mainly GPi and SNpr. The indirect pathway sends inhibitory signals from the striatum (primarily the putamen) to GPe and GPe in turn sends inhibitory projections to the STN. In addition receiving inhibitory projections from GPe, the STN also receives excitatory projections directly from the cortex. Finally, the STN projects excitatory signals to the main output nuclei (GPi and SNpr) where both the direct and indirect pathways to converge to deliver a balance of excitatory and inhibitory signals, resulting in tonic, rapid inhibitory GABAergic projections to the thalamus (Hikosaka, 2007). This finally results in excitatory projections back to cortical areas including MC, PMC, SMA, and CMA (Alexander, DeLong & Strick, 1986; DeLong, 1990; DeLong & Wichmann, 2007), as well as the dorsolateral prefrontal area, lateral orbitofrontal

cortex, and the anterior cingulate/medial orbitofrontal cortices. This arrangement allows the basal ganglia to influence multiple diverse processes of the frontal lobes including movement, behavior, cognition, language, and emotion (Alexander, DeLong & Strick, 1986). Indeed, as stated by Murdoch (2004), "(t)his anatomical arrangement (allows) the output from the basal ganglia (to gain) access to multiple areas of the frontal lobe…and provides a basic neuroanatomical mechanism whereby these subcortical structures can influence aspects of behaviour, cognition and language as well as motor function" (p. 235).

The focus of the present paper is on preparatory aspects of movement, specifically speech motor planning/programming. Van der Merwe's four phase model of speech production (1997; see full discussion below) suggests that many of the aforementioned neural regions are involved in these activities. Motor planning, for example, is suggested to be accomplished largely in PMC and SMA (i.e., the motor association area), while motor programming is thought to comprise areas such as the basal ganglia, cerebellum, SMA, and MC.

Circuitry in PD

Although the exact role of dopaminergic input to the striatum is not completely understood (Mink, 1996), the degeneration of dopaminergic cells in SNpc is a hallmark feature of PD (Bergman & Deuschl, 2002). Gale and colleagues (in press) state the at the neurophysiological level, loss of dopaminergic neurons in PD leads to the clinically observed manifestations of the disease due to derangements of firing rates, neuronal selectivity, and the firing patterns of (basal ganglia) neurons" (p. 2). Figure 3-3 illustrates the effect of PD on the circuitry of the basal ganglia as shown in the 'standard model'. In the indirect pathway, loss of striatal dopamine leads to excessive inhibition of GPe, leading to decreased inhibition of STN and the delivery of excessive excitatory drive to the basal ganglia output nuclei (i.e., GPi and SNpr). This is

reinforced by reduced inhibition to GPi/SNpr delivered through the direct pathway. Cumulatively, this "imbalance" between the indirect and direct pathways results in excessive thalamic inhibition, finally resulting in reduced excitatory projections back to the cortex and inhibiting intended movement (DeLong, 1990). Thus, the effect of striatal dopaminergic loss is "inhibition of cortically initiated movement, to cause akinesia (loss of movement), hypokinesia (reduction of movement) and bradykinesia (slowness of movement)" (Marsden & Obeso, 1994, p. 878).

Other work has continued to refine the role of the BG in movement. For example, Mink (1996; 2003; Mink & Thach, 1991) has proposed a model based on a series of experimental observations which suggests the role of the basal ganglia in normal movement is to facilitate desired motor programs while inhibiting other unwanted motor programs. According to this model of focused selection and inhibition of competing motor programs, voluntary movement is initiated by cortical mechanisms. The basal ganglia facilitate movement by decreasing inhibition of desired motor programs while simultaneously increasing inhibition of competing motor programs (Mink, 1996; Mink, 2003; Rubchinsky, Kopell, & Sigvardt, 2003) through GABAergic output influencing cortical (and brainstem) motor mechanisms (Hikosaka, 2007; Mink, 2003).

The standard model of basal ganglia circuitry continues to be influential but it has been suggested that this model requires substantial revision and refinement to account for advances in understanding (Gale et al., in press; Greybiel, 2005). Nevertheless, this model continues to have heuristic value and in particular, provides a logical rationale for surgical interventions.

Deep Brain Stimulation

A number of neurosurgical approaches to the treatment of PD have been developed over the last century, including ablative procedures (e.g., pallidotomy), and, more recently, DBS. DBS

is a surgical procedure in which electrical stimulation is delivered to neural targets through chronically implanted leads. Quadrapolar electrodes are connected to an internalized programmable neurostimulator usually placed below the clavicle as shown in Figure 3-4 (Benabid, 2003). Thalamic, pallidal, and STN DBS are all recognized to have a beneficial effect on the motor symptoms of PD (Benabid, 2003; Gross, 2004; Rodriguez-Oroz et al., 2005; Volkmann, 2004). After a period of intense use and then declining interest, neurosurgical treatments for PD have once again become popular, primarily due to limitations in the medical management of PD, advances in the understanding of the intrinsic and extrinsic circuitry of the basal ganglia, surgical technique, neuroimaging, and microelectrode recording techniques (Koller, Pahwa, Lyons & Albanese, 1999). In comparison to ablative procedures, DBS may have many advantages, including a decreased occurrence of adverse events, minimal permanent lesions, and an increased ability to perform bilateral procedures without adverse events such as speech and swallowing problems (Benabid et al., 1996; Ghika et al., 1998; Koller et al., 1999; Obwegeser et al., 2001; Pinto et al., 2004; Rodriguez-Oroz et al., 2005). Adjustments in the parameters of stimulation can also facilitate individualization in the treatment and minimize side effects.

DBS in PD

Although the optimal surgical target for DBS in PD remains unknown (Okun & Foote, 2005), the most common surgical targets are the thalamus, GPi, and STN. Influential early studies by Benabid and colleagues (1994) and Limousin et al. (1998) suggested significant benefit to STN DBS and this quickly became the surgical treatment of choice for most centers. However, it has been suggested that further trials comparing the benefit of GPi versus STN DBS need completion (and are in fact in progress) (Okun & Foote, 2005).

Surgical treatments are usually performed in those patients with advanced PD who have disabling motor symptoms that are insufficiently controlled with medical management. GPi and STN DBS are recognized to have a beneficial effect on symptoms such as tremor, rigidity, bradykinesia, dyskinesia, and postural/gait abnormalities in patients with PD who are insufficiently managed with pharmacological therapy (Benabid, 2003; Gross, 2004; Rodriguez-Oroz et al., 2005; Volkmann, 2004). Also important is the absence of significant cognitive impairments, an understanding of the surgical risks, and realistic post-operative expectations (Marks Jr., 2005; Vitek & Walter, 2005). For GPi or STN DBS, the best predictor of outcome seems to be a patient's response to levodopa (Benabid, 2003).

Mechanisms of DBS

The exact neurophysiological mechanisms for the improvement in motor symptomatology with DBS in PD are unknown. Due to the similarities in improvements in motor functioning following ablative lesioning procedures, it has been suggested that "DBS acts as a transient electrical inactivation or reversible lesion to block the output of dysfunctional targets" (Lozano, Dostrovsky, Chen, & Ashby, 2002, p. 226). However, current conceptualization of the mechanisms of DBS suggests that this is a vast oversimplification (Lozano et al., 2002; Desbonnet et al., 2004; Grill, Snyder, & Miocinovic, 2004). For example, Temel and colleagues (2005) state that "an increasing amount of data suggests that categorizing DBS as being 'inhibitory' and thus equating its effects to those of a lesion…is…an oversimplification of what is a highly complex and multi-faceted technique" (p. 397). Lozano and colleagues (2002) review multiple possible mechanisms of DBS including facilitative, inhibitory, and downstream effects. Facilitative effects likely include activation of large axons. Inhibitory effects may include partial or complete blocking of neuronal firing, possibly due to depolarization and/or the release of

inhibitory neurotransmitters. Neurons located downstream from the stimulation site are also likely to be influenced by DBS. This notion is supported by functional imaging studies revealing changes in cortical activity associated with improvements in motor function (Lozano et al., 2002). For example, Davis et al. (1997) used positron emission tomography (PET) to reveal an increase in regional cerebral blood flow in the PMC when GPi DBS improved motor symptomatology. Finally, when considering the mechanism of DBS, it is important to consider that DBS likely influences different neural targets in different ways (Lozano et al., 2002).

DBS and speech

Although speech disturbance in the form of hypokinetic dysarthria is common in individuals with PD, speech improvement is not specifically targeted by DBS surgery. The effects of neurosurgical treatments for PD on speech function have only recently begun to receive systematic attention, particularly STN DBS (for more detailed reviews see Jones, Kendall, Sudhyadhom, & Rosenbek, in press; Schulz, 2002; Schulz & Grant, 2000). To grossly simplify what is developing to be a fairly substantial body of work, the influence of STN DBS on speech has been studied using a variety of sophisticated measurement approaches, including instrumental approaches such as acoustic analysis and kinematic measurement. Gentil and colleagues (1999, 2000; 2001; see also Pinto, Gentil, Fraix, Benabid & Pollak, 2003) have been pioneers in the study of the speech effects of STN DBS and have conducted a program of research using perceptual, kinematic, and acoustic analyses. Considered overall, these data suggest a number changes ‘on’ versus ‘off’ STN DBS, including perceptual improvements in speech, improved lingual and labial strength and control, and improvements in the acoustic speech signal (e.g., increased fundamental frequency variability in sentences and decreased fundamental frequency variability during sustained vowel production). PET scan data from

Pinto et al. (2004) further suggest that the patterns of abnormal cortical activation in patients with PD and hypokinetic dysarthria appear to normalize with improvements in speech when 'on' STN stimulation. Other research also indicates that STN DBS has some benefit for speech (Dromey, Kumar, Lang, & Lozano, 2000; Hoffman-Ruddy, Schulz, Vitek & Evatt, 2001; Rousseaux, Krystkowiak, Kozlowski, Ozsancak, Blond, & Destee, 2004), though speech changes may be dependent on parameters of stimulation being applied (Tornqvist, Schalen, & Rehncrona, 2005) or the hemisphere be stimulated (Santens, De Letter, Van Borsel, De Reuck & Caemaert, 2003; Wang, Metman, Bakay, Arzbaecher,,& Bernard, 2003). However, dysarthria is also commonly reported as an adverse event in many surgical trials (The deep brain stimulation for Parkinson's disease study group, 2001; Esselink et al., 2004; Krack et al., 2003; Kumar et al., 1998a, b; Ostergaard, Sunde, & Dupont, 2002; Rodriguez-Oroz et al., 2005; Romito et al., 2003; Schupback et al., 2005; Thobois et al., 2002) and substantial improvement in speech would not be a surgical goal in most cases.

The aforementioned studies designed to evaluate the speech effects of surgery have primarily targeted measurement at the execution phase of movement, rather than preparatory motor processes such as planning/programming (see discussion of Models of Motor Control below). This is not surprising considering that the hypokinetic dysarthria encountered in PD has traditionally been conceptualized as a disorder of execution level processes (Darley, Aronson, & Brown, 1969a, b, 1975; Duffy, 2005; Yorkston, Beukelman, Strand, Bell, 1999). However, possible contribution of speech motor planning/programming deficits in PD are being increasingly recognized (Spencer, 2006; Spencer & Rogers, 2005; Van der Merwe, 1997), though little work has targeted processes involved in speech motor planning/programming to determine the possible influence of DBS. However, upon close inspection, data from Gentil and

colleagues (1999, 2000; 2001; see also Pinto, Gentil, Fraix, Benabid & Pollak, 2003) merit further scrutiny for those interested in the possible influence of DBS on speech motor planning/programming in PD.

Gentil and colleagues (1999) investigated the effect of bilateral STN DBS on speech and nonspeech oromotor function in 10 patients with PD and 14 healthy controls. Patients were tested off medication in both 'on' and 'off' stimulation conditions. The 'off' stimulation condition assessment occurred 1 hour after discontinuing stimulation. Perceptual and kinematic measurement approaches were utilized. Perceptual measurement was limited to using the score from item 18 of the Unified Parkinson's Disease Rating Scale (UPDRS). Kinematic assessment procedures utilized force transducers to determine ramp-and-hold force contractions and maximal strength of the lips and tongue. Kinematics revealed a number of improvements in lip and tongue function 'on' stimulation, including increased maximal strength, increased accuracy in reaching a target, increased precision during the hold phase, and decreased RT. Results of perceptual assessment also revealed improved speech function in the 'on' versus 'off' stimulation condition. It is the kinematic data which is most scientifically rigorous and which is of primary interest for the present discussion on speech motor planning/programming. These data which improvements in RT 'on' as compared to 'off' STN DBS for a nonspeech oromotor movement suggest that processes involved in speech motor planning/programming may be positively influenced by DBS. Indeed, the measure of RT (as discussed in detail later in this chapter) is an accepted measurement technique to quantify preparatory aspects of movement (e.g., motor planning/programming) and this study may reflect a pioneering effort to measure non-execution level speech changes with DBS in individuals with PD.

These RT data have been replicated by Gentil and colleagues. In 2000, they further investigated the influence of bilateral stimulation in 10 patients with STN DBS and used similar experimental procedures as described above. Improved RT in the 'on' STN DBS condition for a nonspeech oromotor movement was again reported. This group of researchers (Pinto, Gentil, Fraix, Benabid, & Pollak, 2003) continued to use their experimental protocol in their largest group to date – 26 patients with PD and bilateral STN DBS – and improved RT was again found in the 'on' stimulation condition.

A Model of Speech Motor Control

Numerous models of motor control which share many features including concepts consistent with the concept of motor programs have been proposed, including those from Schmidt (1975) and Brooks (1986). Speech specific models are also available, such as Van der Merwe's (1997) proposed four-phase framework.

Four Phase Model

Van der Merwe (1997) has proposed a model for speech motor control based on four phases: linguistic-symbolic planning, motor planning, motor programming, and execution. Let us consider each phase of the model in greater detail, with particular attention to motor planning and motor programming.

Linguistic Symbolic Planning

Linguistic symbolic planning is considered to be a non-motor stage during which the intent to communicate originates due to individual behavioral needs and environmental demands. A message in compiled during this level of processing, requiring semantic, syntactic, morphological, and phonological planning. For example, phonological planning involves selection and combination of phonemes "in accordance with the phontoactic rules of the

language, and it is portrayed as a linguistic-symbolic function within the proposed framework" (Van der Merwe, 1997, p. 9). These processes are thought to be accomplished primarily by temporal-parietal areas, including Broca's and Wernicke's areas. Errors attributed to the level of linguistic-symbolic planning are due to semantic, lexical, syntactic, morphological, and phonological errors associated with language based disorders (i.e., aphasia). For example, Van der Merwe suggests deficits in phonological planning will result in phoneme substitutions and transpositions.

Motor Planning

Motor planning, along with the next level of the model, motor programming, is the area of interest in the present experiment. Van der Merwe conceptualizes motor planning phase as being "mediated by the by the 'highest' level of the motor hierarchy" (p. 9). Motor planning involves "gradual transformation of symbolic units (phonemes) to a code that can be handled by a motor system" (p. 9). Van der Merwe (1997) suggests that speakers learn "core motor plans" during development and adaptation. These motor plans include goals in the form of spatial and temporal specifications for movement which are stored in sensorimotor memory. During acquisition of a core motor program, such as during development, this model suggests increased usage of external feedback, such as that from proprioception and audition. Following retrieval of the core motor plan, planning continues in order so that the "consecutive movements necessary to fulfill the spatial and temporal goals" can be met (p. 11). Motor plan subroutines such as velar lift and tongue placement are then specified for the planned production. Motor planning is thought be accomplished in multiple neural regions, particularly the motor association areas of PMC and SMA, as well as prefrontal and parietal association areas. Van der Merwe (1997) suggests the changes in speech that may be encountered due to deficits in motor planning to

include “slow, struggling speech with distortion and even apparent substitution” such as associated with apraxia of speech (p. 17).

Motor Programming

It should be acknowledged that differentiation between speech motor planning and motor programming is extremely challenging and has not, to our knowledge, been demonstrated experimentally. However, during this hypothesized level of speech production, motor programs are finally selected and sequenced for movements of the necessary muscles for speech production. Information regarding “spatio-temporal and force dimensions such as muscle tone, rate, direction, and range of movements” is controlled by muscle specific programs influenced by external feedback (Van der Merwe, 1997, p. 7). Motor programming involves multiple neural areas including the basal ganglia, SMA, lateral cerebellum, and MC. Speech change associated with deviant speech motor programming is hypothesized to include “sound distortion, defects in speech rate, and/or problems in the initiation of movement” (Van der Merwe, 1997, p.18).

Execution

At the level of execution, the plans and programs of the previous phases in speech production result in muscle movements and speech production. Feedback to higher levels in the motor system is an integral part of this phase, particularly during development. Feedback may take the form of tactile-kinematic and acoustic information, for example. Neural areas involved in execution include the “motor cortex, the lower motor neurones, peripheral nerves, and motor units in the muscles” (Van der Merwe, 1997, p. 16). Areas involved with preparatory aspects of speech movement (i.e., motor planning and motor programming) are also active during execution, including cortical (SMA) and subcortical regions (the basal ganglia and thalamus). Although not directly addressed by this model, execution level errors, for example, are often

associated with peripheral muscle changes such as impaired strength or tone. Current conceptualization of all dysarthria types, including the dysarthria of PD, suggests that these speech disorders and their resultant errors are due primarily (if not exclusively) from deviant processes of execution.

Motor Planning/Programming

Van der Merwe's four phase model of speech control provides useful theoretical constructs for research conducted in this area. In turn, notions about speech motor control will continue to be refined with experimental data. Data supporting differentiation between the processes of speech motor planning and speech motor programming would be particularly valuable, and, as noted by Spencer & Rogers (2005), has not yet occurred. Therefore, for the present discussion, we will combine these two phases of speech motor control into one – motor planning/programming.

The notion that preparatory activities consistent with processes involved in motor planning/programming which occur prior to movement execution are commonly encountered in the literature. Indeed, as noted by Schmidt in 1975, the notion of motor programs or "a set of stored muscle commands ready for action at any given time has probably been with us for a very long time" (p. 231). Early contributions from Lashley (1917) and Henry and Rogers (1960) have continued to be refined by a number of researchers who have proposed models consistent with concepts of speech motor planning/programming (Klapp, 2003; Levelt & Wheeldon, 1994; Schmidt, 1975; Sternberg, Knoll, Monsell, & Wright, 1988; Sternberg, Knoll, & Turock, 1990; Sternberg, Monsell, Knoll, & Wright, 1978; Sternberg, Wright, Knoll, & Monsell, 1980; Van der Merwe, 1997).

Subprogram Retrieval Model

The work of Sternberg and colleagues (1978, 1980, 1988, & 1990) has been particularly useful in attempting to define the theoretical underpinnings of the processes involved in speech motor planning/programming. In 1978, Sternberg et al. proposed a "subprogram retrieval" model (later renamed as the "subprogram-selection" model" by Sternberg et al., 1988) to explain their data on preparation of rapid movement sequences during speech and typewriting. In this model, a motor program or "representation of the entire response…is constructed before the response starts" (Sternberg et al., 1978, p. 133). The motor program comprises "a set of linked *subprograms*, one for each unit of the response" that are "retained in a special *motor-program buffer*…distinct from ordinary short-term memory" until the command for movement is received (Sternberg et al., 1978, p. 133). Subprograms are retrieved from the sensorimotor store and loaded into the buffer prior to movement. Keller (1987) suggests that the subprograms or "aggregates of muscle commands" are learned and are then to be found in the store ready for retrieval as needed, rather than freshly generated each time speech is to be produced (p. 135). Upon command for movement, the first subprogram is located in the buffer in order to initiate movement execution. Sternberg and colleagues (1978) further describe their proposed mechanism for retrieval of subprograms from the buffer: "The particular retrieval mechanism suggested by our results is *self-terminating* sequential *search* through a *nonshrinking* buffer, rather than, for example, a process of direct access…The search is presumably necessary because the necessary subprograms are not arranged in the buffer in the order in which they must be executed" (p. 147). Additionally, Sternberg and colleagues suggest the size or unit of the speech subprograms in their model is the "*stress group* or 'metric foot' (a segment of speech associated with a primary stress)" (1978, p. 136)

In 1988, Sternberg and colleagues continued to clarify and refine their model of they now call a “subprogram-selection model” in a paper emphasizing the concept that the motor program “is operated upon by a series of selection and command processes” (p. 184). Before a movement subprogram can be executed, it must first be accessed from the buffer. After the subprogram is accessed from the buffer, “The *command* process…causes it to be ‘executed’”. Speech production “is thus controlled by an alternating sequence of selection and command processes” (p. 184).

The model presented by Sternberg and colleagues has its limitations but it provides a sensible theoretical framework for research studying processes involved in motor planning/programming in general and speech more specifically. This model can be applied to concepts in the current motor control literature, such as motor programming maintenance and switching.

Motor Program Maintenance

Sternberg et al.’s notion that motor programs are held in the buffer until a command for movement is provided appears analogous to the ability to hold or maintain a motor program prior to movement execution. Maintenance of a motor program has been studied extensively in both normal and disordered populations. Hallett (1990) describes the common method for studying maintenance of a motor program using the delayed response paradigm. In this situation, “information about the movement is completely specified, but then the information is withdrawn for a period of time before the stimulus to move is delivered” (Hallett, 1990, p. 588). RT serves as an index of maintenance of the motor program in the buffer. In some disordered populations (including individuals with PD), the contents of the buffer have been found to decay over time, disrupting the maintenance of motor programs as measured by RT.

Motor Program Switching

The ability to rapidly switch motor programs has also received significant experimental attention. In such experiments, subjects are (often unexpectedly) presented with a prime stimulus that does not accurately or completely inform the target stimulus. Viewed through the model of Sternberg and colleagues, this task requires subjects to clear the prepared (and inaccurate) motor program in the buffer, search the sensorimotor store for the newly required motor subprograms, and load the motor program into the buffer before execution. Switching motor programs requires increased RT due to the increased complexity of this task. Difficulty switching has been hypothesized to be related to impairments inhibiting or modifying a motor program (Inzelberg et al., 2001; Kropotov & Etlinger, 1999; Mink, 1996) or in the activation of a new motor program (Haaland & Harrington, 1991).

Deviant Motor Programming in PD

In individuals with PD, deficits in aspects of motor programming are being recognized with increasing regularity, both in the limbs and, less commonly, the speech mechanism.

Limb Motor Programming Maintenance and Switching

A substantial literature supporting the concept of impaired maintenance of motor programs for limb movements in PD is available (Gentilucci and Negrotti, 1999a, b; Gueye, Viallet, Legallet & Trouche, 1998; Jones, Phillips, Bradshaw, Iansek, & Bradshaw, 1992; Pascual-Leone, Valiis-Sole, Brasil-Neto, Cohen & Hallett, 1994; Romero, Van Gemmert, Adler, Bekkering, & Stelmach, 2003; Sheridan, Flowers, & Hurrell, 1987; Stelmach, Garcia-Colera & Martin, 1989), though this finding has not been replicated by all studies (Labutta, Miles, Sanes, & Hallett, 1994). PD patients have also been found to have disordered ability to switch motor programs (Benecke, Rothwell, Dick, Day & Marsden, 1998; Contreras-Vidal & Stelmach, 1996;

Dirnberger, Reuman, Endl, Lindinger, Lang & Rothwell, 2000; Harrington & Haaland, 1991; Inzelberg, Plotnik, Flash, Schechtman, Shahar, & Korczyn, 2001; Kropotov & Etlinger, 1999; Robertson & Flowers, 1990; Roy, Saint-Cyr, Taylor, & Lang, 1993; Rubchinsky, Kopell, & Sigvardt, 2003; Stelmach, Garcia-Colera, & Martin, 1989; Weiss, Stelmach, & Hefter, 1997). Disordered maintenance and switching of motor programs has been proposed to explain some of the primary motor symptomatology of PD, such as akinesia.

Speech Motor Programming Maintenance and Switching

Deficits in speech motor planning/programming in patients with PD are being increasingly recognized (Van der Merwe, 1997). As noted by Van der Merwe (1997), "this complicates our traditional view of dysarthria as a motor execution problem" (p. 18). The fact that the basal ganglia appear to be involved "in both motor programming and execution suggests the possibility of dual symptomatology in certain types of dysarthria" (Van der Merwe, 1997, p. 18). The author then specifically suggests that the hypokinetic dysarthria of PD is one of the dysarthria types in which "Coexisting problems in both motor programming and motor execution would seem to be present…" (Van der Merwe, 1997, p. 18)

Spencer and Rogers (2005; see also Spencer 2006) have pioneered the study of speech motor planning/programming deficits in dysarthria types traditionally associated with execution level dysfunction. These authors suggest that the role of the basal ganglia in motor planning/programming has been "illuminated by converging evidence from limb RT studies of adults with Parkinson's disease" which show impairments in two primary areas: maintenance and switching (Spencer & Rogers, 2005, p. 348). Furthermore, the presence of motor planning/programming deficits in individuals with hypokinetic dysarthria is supported by specific speech symptoms commonly encountered in this population. Spencer and Rogers (2005)

suggest that disordered maintenance of speech motor programs may result in "abnormally placed pauses, difficulty with progression through an utterance and difficulty initiating articulation" (p. 348). Similarly, disordered switching of speech motor programs may be associated with "difficulty stopping an ongoing response, marked hesitations between movement segments, and occasional inability to switch from one to another movement" (Spencer & Rogers, 2005, p. 348).

To test the notion that speech motor planning/programming is disrupted in individuals with PD and hypokinetic dysarthria, Spencer and Rogers (2005) employed a RT paradigm. Ten participants with PD and hypokinetic dysarthria and 15 normal controls were tested using a response priming procedure in which participants were provided with a prime to supply information regarding target (see Chapter 2 - "Experimental Procedures" for more details). The primary dependent variable was SRT. Results provided preliminary evidence for the notion that maintenance and switching of speech motor programs is disordered in participants with PD and hypokinetic dysarthria.

Reaction Time/Speech Reaction Time

The use of RT experiments being used as an index of various underlying neural processes has a history that dates back to at least the mid-19th century (Smith, 2004). The basic RT paradigm (to which an infinite array of variables can be added) involves presentation of a stimulus to subjects who are then required to start a movement as quickly as possible (Hallett, 1990). RT is defined as the temporal duration between the presentation of the stimulus and the initiation in movement. Adaptations to the RT paradigm usually increase the complexity of the task in any number of ways, by methods such as demanding more complicated movements or adding a pause between presentation of the stimulus and the command for movement. Increased complexity invariably results in increases in RT. RT in individuals with PD has been studied

extensively and is generally found to be impaired in comparison to age-matched normal controls (Bloxham, Mindel, & Frith, 1984; Draper & Johns, 1964; Evarts, Teravainen, & Calne, 1981; Gueye, Viallet, Legallet, & Trouche, 1998; Labutta, Miles, Sanes, & Hallett, 1994; Montgomery, Baker, Lyons, & Koller, 2000; Muller, Eising, Khun, Buttner, Coenen, & Przuntek, 1999; Temel et al., 2006). There are two general types of RT conditions: simple RT and choice RT.

Simple and Choice Reaction Time

In the simple RT test paradigm, "the expected movement is described completely, without ambiguity" (Hallett, 1990, p. 587). This allows subjects to fully prepare (or plan and program) the required movements in advance of the command to execute movement. Simple RT experiments can still increase the complexity of the task, most often by adding a delay between stimulus and command. Using the model of Sternberg et al., this would require participants to maintain the motor program in the buffer until the command to execute movement is provided.

In the choice RT paradigm, subjects are not provided "a complete description of the required movement" until "the stimulus that calls for the movement initiation" (p. 587) is delivered. Since subjects are not able to plan/program movements in advance, choice RT is always longer than simple RT. Like simple RT, choice RT is also influenced by complexity factors. For example, providing incorrect information about the required movement in advance of the command for movement increases complexity (and thus RT). According to the model of Sternberg et al., the increase RT in the choice RT paradigm is explained by the additional required planning/programming processes required with this task. These processes include retrieving the appropriate motor subprograms from the sensorimotor store and loading them into the buffer.

SRT in the 'No Switch' Condition is a Measure of Speech Motor Program Maintenance

In the present experiment, SRT in the 'no switch' condition serves as a measure of the maintenance of speech motor programs 'on' and 'off' DBS. In this condition, subjects are visually presented with a prime word and instructed to speak this word as quickly and clearly as possible upon presentation of the command for movement (i.e., the target word). Although the experiment was not originally conceived in this manner, this paradigm satisfies the criteria for a simple RT experiment in that subjects are provided with complete information regarding the expected movement in advance. The subprogram retrieval model of Sternberg and colleagues suggests that this allows participants to retrieve subprograms from the sensorimotor store and load the motor program into the buffer prior to movement execution. Much like many other simple RT experiments, the complexity of this task in the present experiment was increased by adding a 250 ms delay between stimulus presentation (i.e., the prime word) and presentation of the command for movement (i.e., the target word).

SRT in the 'Switch' Condition is a Measure of Speech Motor Program Switching

In the present experiment, SRT in the 'switch' condition serves as a measure of the switching of speech motor programs 'on' and 'off' DBS. In this condition, subjects are visually presented with a stimulus (i.e., the prime word) which does not accurately inform the requested movement upon receipt of the command for movement (i.e., the target word). In other words, the prime unexpectedly does not match the target. This paradigm appears to generally satisfy the criteria for a choice RT experiment in that subjects are provided with incomplete information regarding the expected movement until the command for movement is presented. However, the complexity is again increased by the presentation of an incorrect prime. Presumably, according the model of Sternberg participants have already retrieved incorrect motor subprograms from the

sensorimotor store and loaded the motor program into the buffer. This task requires several processes to occur prior to movement execution. The incorrect motor program in the buffer must be inhibited, the correct motor subprograms must be retrieved from the store, and the motor program must be loaded into the buffer. Due to these additional processes and the increased complexity of the ‘switch’ versus ‘no switch’ condition, RT will be increased for these tasks.

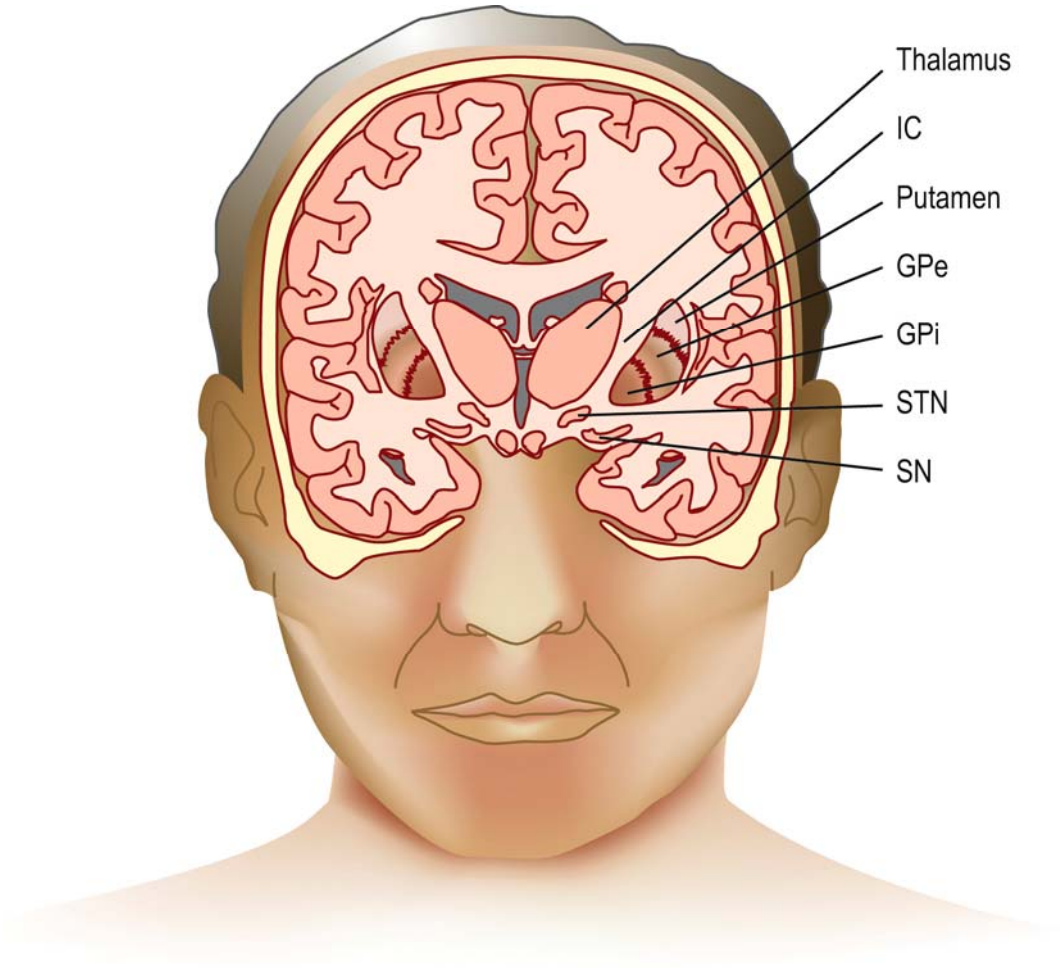

Figure 3-1. Basal ganglia structures and surrounding areas. IC = internal capsule, GPe = globus pallidus pars externa, GPi = globus pallidus internus, STN = subthalamic nucleus, SN = substantia nigra.

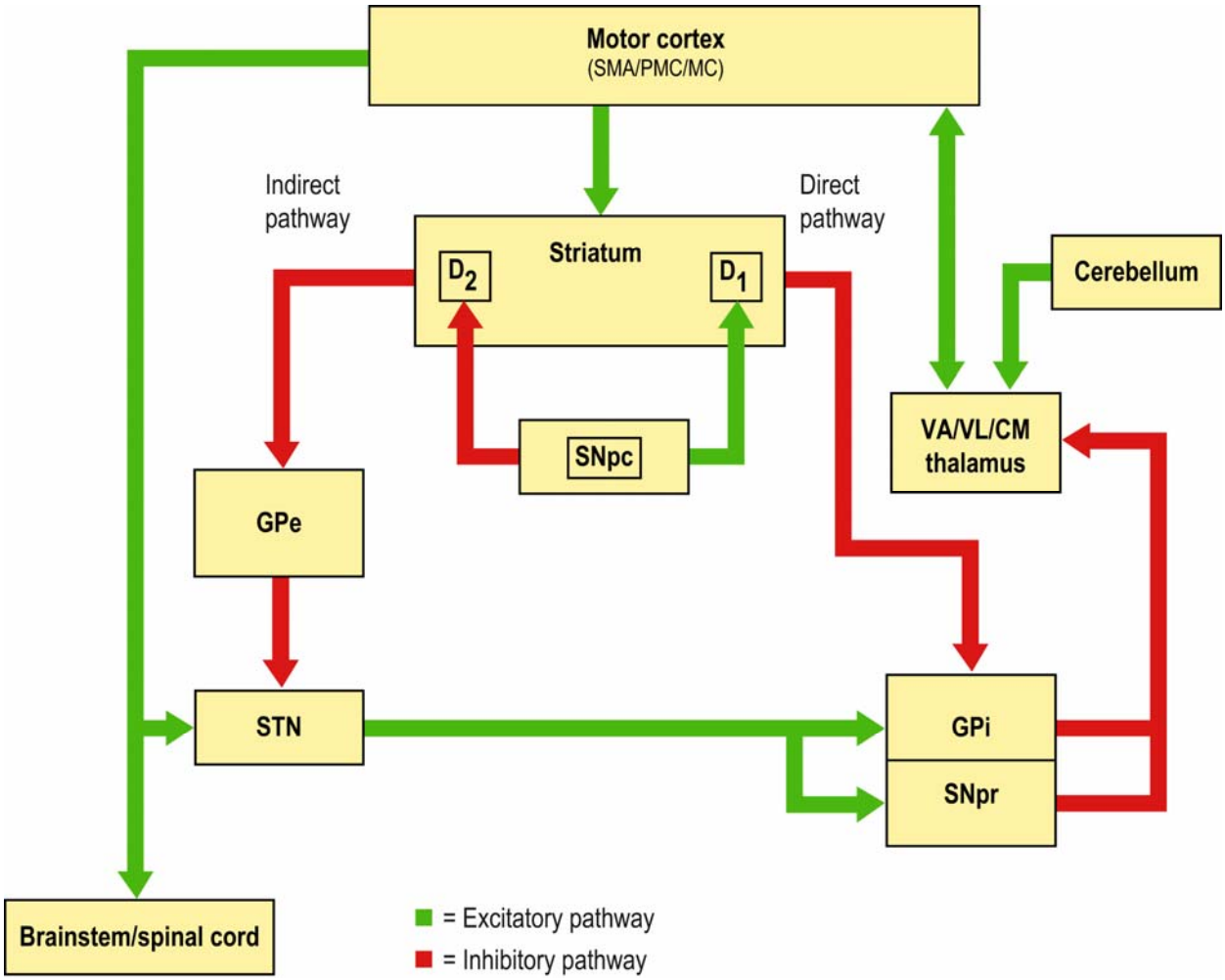

Figure 3-2. The intrinsic and extrinsic circuitry of the basal ganglia under normal conditions. SMA= supplementary motor area, PMC = premotor cortex, MC = motor cortex, SNpc = substantia nigra pars compacta, D1 = striatal output receptor type D1, D2 = striatal output receptor type D2, GPe = globus pallidus pars externa, STN = subthalamic nucleus, GPi = globus pallidus internus, SNpr = substantia nigra pars reticulata, VA = ventral anterior nucleus of the thalamus, VL = ventral lateral nucleus of the thalamus, CM = centrum medianum.

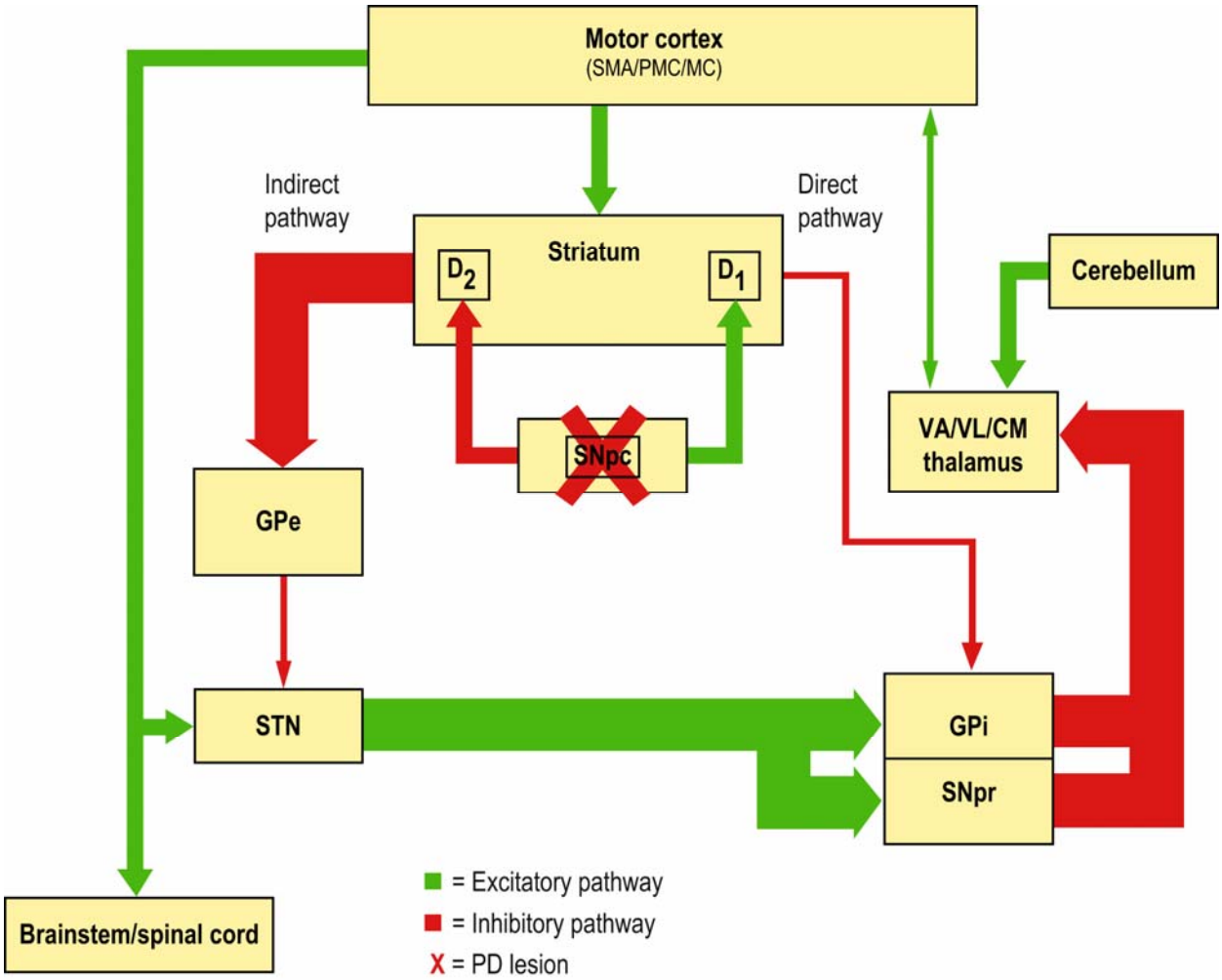

Figure 3-3. The intrinsic and extrinsic circuitry of the basal ganglia in Parkinson's disease. SMA = supplementary motor area, PMC = premotor cortex, MC = motor cortex, SNpc = substantia nigra pars compacta, D1 = striatal output receptor type D1, D2 = striatal output receptor type D2, GPe = globus pallidus pars externa, STN = subthalamic nucleus, GPi = globus pallidus internus, SNpr = substantia nigra pars reticulata, VA = ventral anterior nucleus of the thalamus, VL = ventral lateral nucleus of the thalamus, CM = centrum medianum.

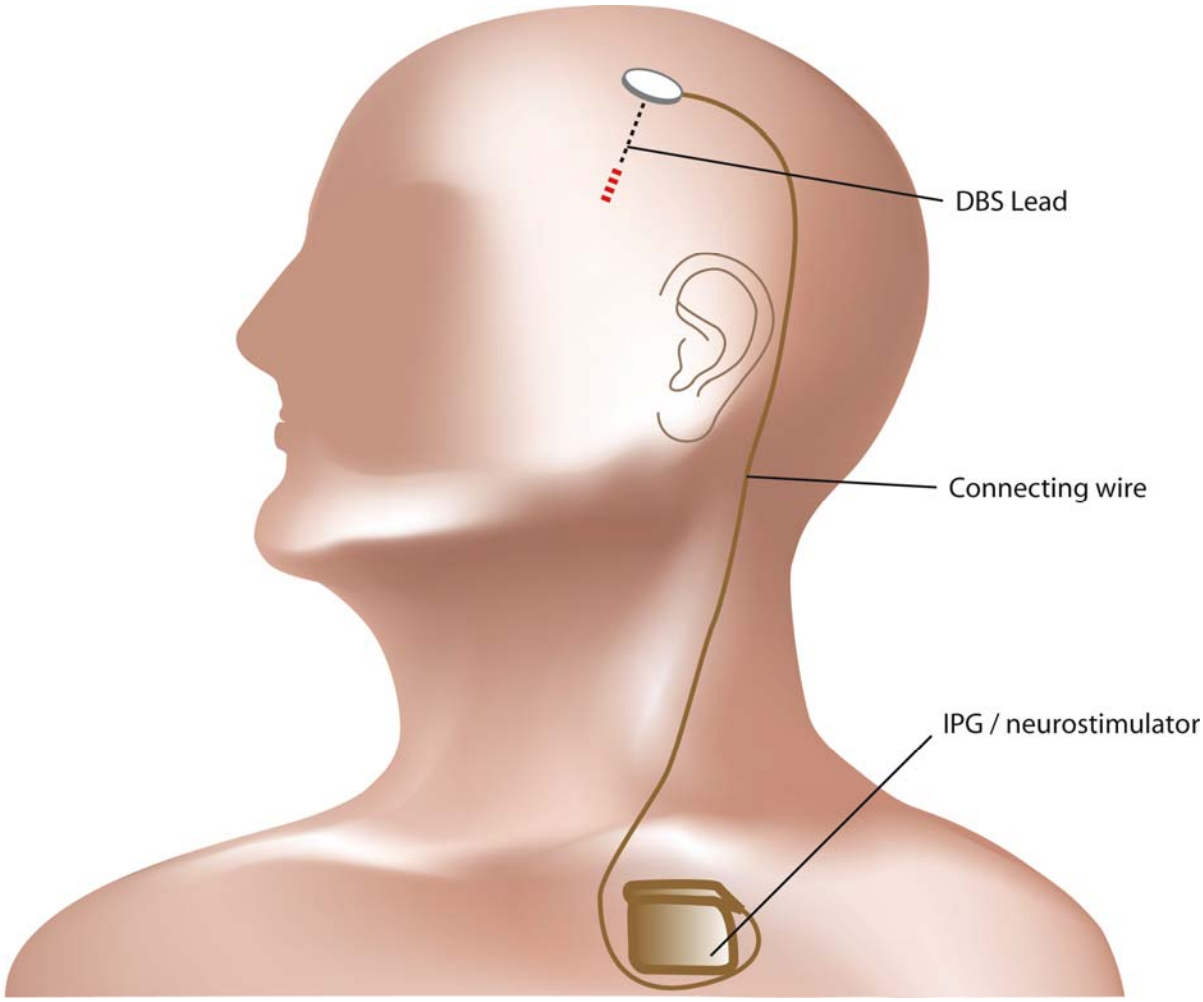

Figure 3-4. Unilateral deep brain stimulation (DBS). IPG = internal pulse generator.

CHAPTER 4
RESULTS

Participants

A total of 12 participated in the experiment. An additional eight individuals entered the screening process but did not meet inclusion criteria or were withdrawn (3 had surgery completed an outside facility, 2 failed screening due to a Spatial Span Subtest score < 7, 1 subject had severe tremor 'off' DBS, 1 subject was unstable on anti-Parkinson's disease medications, and 1 subject had a local skin reaction to the accelerometer).

Table 4-1 shows individual and group descriptive data for the 12 participants. Mean age was 61 years (sd = 8.28). Nine of the participants were male (75%) and three were female (25%). Three patients had undergone STN surgery (25%) and in 9 subjects the exact surgical site (GPi or STN) was unknown due to participation in a larger double-blinded study. Eight of 12 (67%) had undergone a unilateral DBS surgery and 4 (33%) had undergone bilateral DBS surgery. Mean duration status-post surgery in months following surgery at the time of screening was 13.5 months (sd = 5.45). Half of the participants (6/12) were first randomized to the 'on' stimulation test condition and the other half were first tested 'off' stimulation.

Mean years of education was 14.16 (sd = 3.69) with the mode being 12 years (i.e., a high school diploma). Mean MMSE was 28.67 out of 30 (sd = 0.98) Mean standard scores for the Spatial Span Subtests were a forward score of 10.17 (sd = 2.04) and backward score of 10.83 (sd = 1.99).

Perceptual judgment of dysarthria type was hypokinetic in all participants. The mean of dysarthria severity ratings was 3.08 (sd = 1.31) and the mode was 2. All participants reported an unremarkable speech and language developmental history. Mean intelligibility score across the two listeners was 93.25% (sd = .06). Mean CES score was 33.03 out of 56 (sd = 8.66).

Assessment of linguistic competency during repetition and connected speech suggested intact linguistic systems in eight of 12 (75%) participants. Four subjects produced a total of eight errors during repetition (n = 2) or connected speech (n = 6). Five errors were determined to be phonological and 3 were semantic.

Experimental Results

Table 4-2 presents the summary statistics for both the primary and secondary research questions. The mean and standard deviation for SRT and response accuracy are shown across priming (i.e., 'no switch' or 'switch') and stimulation (i.e., DBS 'on' or 'off') conditions. Mean SRT in the 'no switch' condition was 615.24 ms (SD = 96.77) 'on' DBS and 671.38 ms (SD =113.05) 'off' DBS. Mean SRT in the 'switch' condition was 717.09 ms (SD= 89.11) 'on' DBS and 728.67 ms (SD = 98.35) 'off' DBS. Mean number of errors (per 16 responses) in the 'no switch' condition was 0.69 (SD = 0.85) 'on' DBS and 1.06 (SD = 0.74). Mean number of errors in the 'switch' condition was 1.50 (SD = 1.17) 'on' DBS and 1.50 (SD = 1.98) 'off' DBS.

Primary Aims

Research question 1 ('no-switch' vs. 'switch')

Statistical significance was set at the 0.05 level for all analyses performed. Table 4-3 shows mean difference and p-values for all comparisons. Separate Wilcoxon signed-rank tests were conducted which revealed statistically significant differences in SRT in the predicted direction between 'switch' and 'no-switch' conditions in both the 'on' DBS (signed rank = 1, p = 0.0010) and 'off' DBS (signed rank = 12, p = 0.0342) states. Furthermore, Fisher's combination method revealed significant differences in SRT overall across DBS conditions (Fisher's combination test statistic = 20.57, p = 0.0040). In other words, subjects produced a speech response more quickly in the 'no-switch' versus 'switch' condition, regardless of whether DBS

was ‘on’ or ‘off’. As shown in Figure 4-1, when collapsed across stimulation conditions, mean SRT in the ‘no switch’ condition was 643.38 ms (SD = 106.83) and 722.88 ms (SD = 98.35) in the ‘switch’ condition.

Research question 2 (‘no-switch’ condition ‘on’ vs. ‘off’ DBS)

Separate Wilcoxon signed-rank tests were conducted which revealed statistically significant differences in SRT in the ‘no switch’ condition between ‘on’ and ‘off’ DBS states (signed rank = 10, p = 0.0210) in the predicted direction. That is, subjects produced a speech response more quickly in the ‘no switch’ condition when ‘on’ versus ‘off’ DBS. As shown in Figure 4-2, mean SRT in the ‘no switch’ condition was 615.24 ms (SD = 96.77) ‘on’ DBS and 671.38 ms (SD = 113.05) ‘off’ DBS.

Research question 3 (‘switch’ condition ‘on’ vs. ‘off’ DBS)

Separate Wilcoxon signed-rank tests were conducted which revealed no significant differences in SRT in the ‘switch’ condition (signed rank = 30, p = 0.5186) between ‘on’ and ‘off’ DBS states (i.e., no difference in SRT was observed in the ‘switch’ condition regardless of whether DBS was ‘on’ or ‘off’). As shown in Figure 4-2, mean SRT in the ‘switch’ condition was 717.09 ms (SD = 89.11) ‘on’ DBS and 728.67 ms (SD = 110.50) ‘off’ DBS.

Secondary Aims

Separate Wilcoxon signed-rank tests were conducted for both the DBS ‘on’ and ‘off’ conditions. In the ‘off’ DBS condition, no statistical difference (signed rank = 17, p = 0.5469) was found in response accuracy between ‘switch’ and ‘no-switch’ conditions. In the ‘on’ DBS condition, response accuracy was also not statistically significant (signed rank = 9, p = 0.0605), thought there was a trend toward significant response accuracy results in the predicted direction (i.e., subjects produced more errors on average in the ‘switch’ condition versus the ‘no switch’

condition under the ‘on’ DBS state but this difference was not significant). Fisher’s combination method was used to determine overall differences in response accuracy across DBS conditions and results were not significant (Fisher’s combination test statistic = 6.82, p = 0.1526).

Separate Wilcoxon signed rank tests revealed no significant differences in response accuracy in the ‘no switch’ (signed rank = 14, p = 0.1816) or ‘switch’ (signed rank = 11.5, p = 0.7188) conditions when ‘on’ versus ‘off’ DBS states were compared. In other words, no difference in response accuracy was observed in the ‘no switch’ or ‘switch’ conditions regardless of whether DBS was ‘on’ or ‘off’. Fisher’s combination was used to determine overall differences in response accuracy across DBS conditions and results were not significant (Fisher’s combination test statistic = 4.07, p = 0.3881).

Reliability

Intra-rater Reliability

Judge one completed perceptual assessment to determine the accuracy of each response on two separate occasions. Point-by-point analysis was conducted for each subject's responses during each of their two test sessions to determine whether agreement regarding accuracy was present. The kappa coefficient has the value 0.79, which indicates strong agreement between the separate rating sessions and the confidence interval of (0.70, 0.87) confirms that one can reject the null hypothesis of no agreement. Additionally, the percentage of task items agreed in the two occasions range from 86% to 100% for the twelve subjects. Intra-class correlation coefficient was determined to be 0.82 with a 95% confidence interval [0.71, 0.90].

Inter-rater Reliability

A point-by-point analysis was completed to compare the level of agreement between two judges as to whether each individual response was correct or incorrect. The kappa coefficient has

the value 0.68, which indicates strong agreement between the raters, and the confidence interval of (0.59, 0.77) confirms that one can reject the null hypothesis of no agreement. In addition, the percentage of task items agreed by the two raters range from 92% to 100% for the twelve subjects. Intra-class correlation coefficient was determined to be 0.82 with a 95% confidence interval [0.71, 0.90].

Table 4-1. Individual and group descriptive data.

Participant	Age	Sex	Procedure*	Months s/p surgery	Years of education	MMSE	Spatial span forward**	Spatial span backward**	Speech severity	CES***	Development history (per patient/family)	Linguistic competency	Intelligibility Judge 1	Intelligibility Judge 2	Overall Intelligibility score
1	78	F	B DBS	24	12	29	10	10	5	37	Unremarkable	No errors - intact	93%	94%	94%
2	65	M	B DBS	15	20	28	7	10	5	23	Unremarkable	Repetition - 1 phono error	99%	98%	99%
3	67	M	L DBS	17	20	30	13	10	4	25	Unremarkable	Connected speech - 1 semantic error	87%	79%	83%
4	63	M	L STN DBS	19	13	30	10	9	4	40	Unremarkable	No errors - intact	79%	79%	79%
5	55	M	L STN DBS	8	16	30	12	10	2	43	Unremarkable	Connected speech - 2 phono errors and 1 semantic error	97%	98%	98%
6	47	M	L DBS	10	12	28	13	15	2	28	Unremarkable	Repetition - 1 phono error; Connected speech - 1 phono error and 1 semantic error	95%	98%	97%
7	63	M	B STN DBS	12	14	28	10	12	3	38	Unremarkable	No errors - intact	90%	94%	92%
8	58	F	L DBS	13	16	28	10	9	1	39	Unremarkable	No errors - intact	99%	94%	97%
9	50	F	B DBS	17	12	29	9	12	2	35	Unremarkable	No errors - intact	98%	99%	99%
10	65	M	L DBS	6	12	27	7	12	4	15	Unremarkable	No errors - intact	95%	85%	90%
11	59	M	L DBS	15	16	28	9	8	3	32	Unremarkable	No errors - intact	95%	94%	95%
12	66	M	L DBS	6	7	29	12	13	2	42	Unremarkable	No errors - intact	95%	96%	96%
Mean	61.33			13.5	14.17	28.67	10.17	10.83	3.08	33.08			93.50%	92.33%	93.25%
SD	2.39			5.45	1.06	0.98	2.04	1.99	1.31	8.66			1.67	2.09	1.84
		9 males, 3 females										8/12 intact			
											12/12 unremarkable history	4/12 w/ errors - 5 phono, 3 semantic			

* Surgical site unknown in 9/12
** standard scores, x = 10, sd = 3
*** Maximum score = 56
phono = phonological

Table 4-2. Summary statistics for speech reaction time (SRT) and response accuracy by priming condition and stimulation state. SRT data is in milliseconds (ms) and the number of errors is per 16 responses.

	Priming condition	On DBS		Off DBS		Overall	
		Mean	SD	Mean	SD	Mean	SD
SRT	No switch	615.24	96.77	671.38	113.05	643.31	106.83
	Switch	717.09	89.11	728.67	110.50	722.88	98.35
Errors	No switch	0.69	0.85	1.06	0.74	0.88	0.8
	Switch	1.5	1.17	1.5	1.98	1.5	1.59

Table 4-3. Mean difference and p-values for speech reaction time (SRT) and response accuracy by priming condition and stimulation state.

	On vs Off				Switch vs No Switch	
	Priming condition	Mean Difference	P-value	Stimulation condition	Mean Difference	P-value
SRT	Switch	-11.58	0.519	On DBS	101.85	0.001*
	No switch	-56.14	0.021*	Off DBS	57.29	0.034*
	Overall	-33.86	0.075	Overall	79.57	0.004*
Errors	Switch	0.00	0.719	On DBS	0.81	0.061
	No switch	-0.36	0.182	Off DBS	0.44	0.547
	Overall	-0.18	0.388	Overall	0.63	0.153

*statistically significant, $p < 0.05$

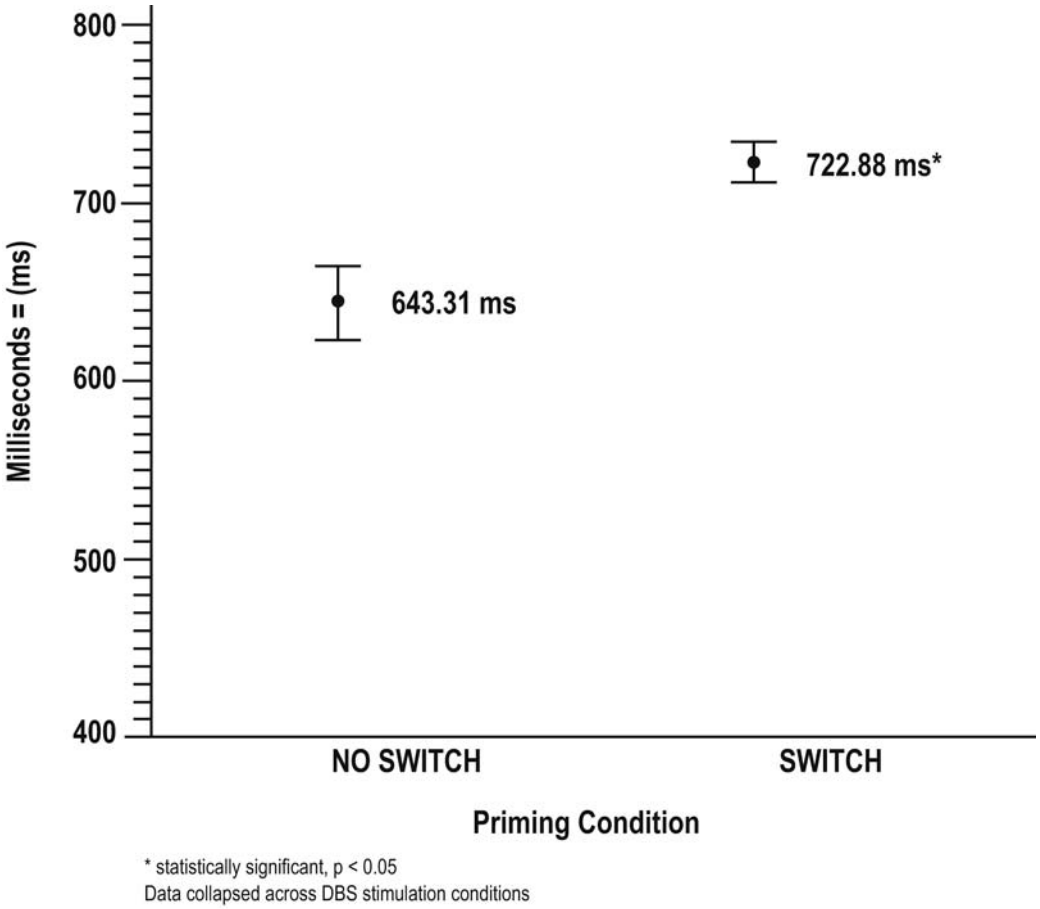

Figure 4-1. Mean speech reaction time (SRT) in milliseconds (ms) in the 'no switch' and 'switch' conditions.

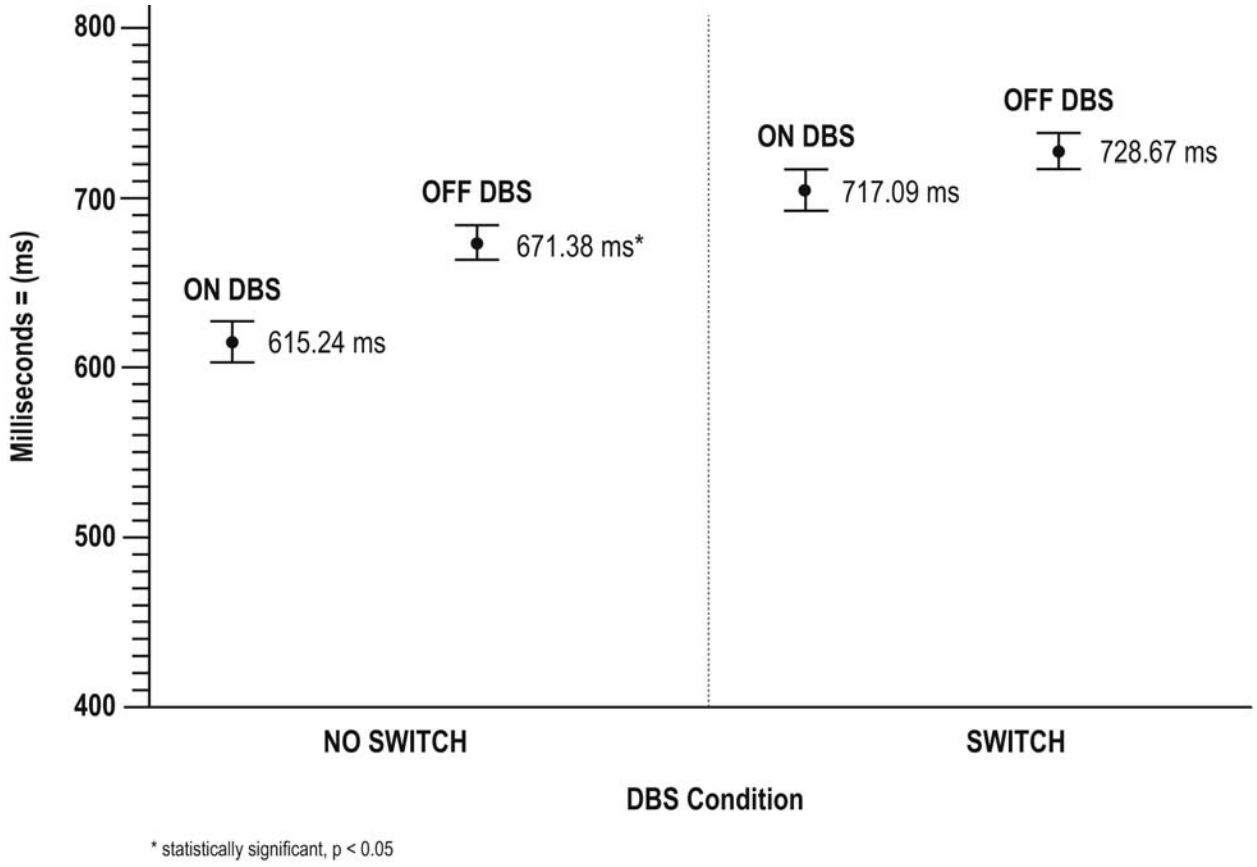

Figure 4-2. Mean speech reaction time (SRT) in milliseconds (ms) in the 'no switch' and 'switch' conditions 'on' and 'off' DBS.

CHAPTER 5
DISCUSSION

The following discussion of our research findings will be outlined as related to the primary, secondary, and exploratory research questions detailed in Chapter 1. This will be followed by a more general discussion including the strengths and weaknesses of the study and alternative hypotheses. Directions for future research will be covered in Chapter 6.

Primary Aims

Research Question 1

Research question 1 was designed to determine whether a significant difference exists in SRT between the 'switch' and 'no switch' conditions in patients with PD and DBS. While both conditions were hypothesized to target the level of speech motor planning/programming, the 'switch' condition was expected to require additional, more complex processes for successful completion (i.e., inhibition of the unwanted motor program, retrieval of new subprograms from the sensorimotor store, and the loading of these subprograms into the buffer in order to construct a new motor program). Consistent with our predictions, we found subjects responded significantly faster in terms of SRT in the 'no-switch' condition regardless of whether DBS was 'on' or 'off'. Collapsed across stimulation condition, mean SRT for the 'no switch' task was 643.31 ms and 722.88 ms. for the 'switch' task.

These data validate the response priming paradigm and support the critical notion that the 'switch' condition is more complex than the 'no switch' condition due to the increased demands of this task on processes involved in speech motor planning/programming. These data support use of this paradigm to measure processes involved in speech motor planning/programming. Additionally, these findings are consistent with the modern RT literature in which a variety of variables, including complexity, are known to influence reaction time (Henry & Rogers, 1960;

Smiley-Oyen, Lowry, & Kerr, 2007; Smiley-Oyen & Worringham, 2001; Sternberg et al., 1978). Indeed, as previously discussed, choice reaction time is always longer than simple reaction (Hallett, 1990). In the present experiment, results which did not support longer SRT for the 'switch' condition would cast great suspicion on the employed experimental paradigm. As the 'no switch' condition can be conceptualized as a simple RT experiment and the 'switch' condition can be regarded as a choice RT experiment, results which did not show increased SRT when switching speech motor programs would suggest a fatal flaw in the study as choice RT is invariably longer than simple RT.

To more explicitly describe the proposed underlying mechanisms involved in speech motor planning/programming, it is necessary to turn to the model proposed by Sternberg and colleagues (1978, 1980, 1988 & 1990). Based on this model, in the 'no switch' condition, subjects are hypothesized to retrieve subprograms for movement from the sensorimotor store. These subprograms are loaded into the motor buffer and comprise the motor program. Participants are able to prepare their speech responses prior to the command for speech execution and maintain them in the buffer. In contrast, in the more complex 'switch' condition, subjects are unable to prepare the desired motor program in advance, which requires that several additional processes must occur before speech can be produced when the command for execution is provided. These processes include inhibition of the previously prepared and now undesired motor program, retrieval of new subprograms from the sensorimotor store, and the loading of these subprograms into the buffer to construct a new motor program. Thus, as found in this experiment, SRT should be longer in the 'no switch' condition due to the additional processes required and the increased complexity of this task. It could further be argued that the temporal difference between the 'no switch' and 'switch' conditions is a measure of these additional

processes. In other words, the average difference across priming conditions of 79.57 ms may reflect the additional time required to inhibit the undesired motor program, retrieve new subprograms from the sensorimotor store, and load them into the buffer to construct a new motor program.

Research Question 2

Research question 2 was designed to determine whether a significant difference exists in SRT in the 'on' DBS versus the 'off' DBS state when participants with PD produce a word in the 'no switch' condition. The hypothesized theoretical level of processing of this question was maintenance of the motor program in the buffer at the level of motor planning/programming. We were interested in determining if DBS influences maintenance of the motor program in the buffer after retrieval from the sensorimotor store. As predicted, statistically significant differences in SRT were found which revealed faster performance 'on' DBS when compared to 'off' DBS. Mean SRT in the 'no switch' condition was 615.24 ms 'on' DBS and 671.38 ms 'off' DBS. This leads us to conclude that DBS directly influences speech motor program maintenance.

There are data available to suggest that motor program maintenance is impaired in PD (Gentilucci and Negrotti, 1999a, b; Gueye et al., 1998; Jones et al., 1992; Labutta et al., 1994; Pascual-Leone, Valls-Sole, Brasil-Neto, Cohen & Hallett, 1994; Romero et al., 2003; Sheridan, Flowers, & Hurrell, 1987; Stelmach, Garcia-Colera & Martin, 1989). Although sufficient detail regarding the theoretical underpinnings of many of these studies is not provided, the model of Sternberg et al. (1978, 1980, 1988 & 1990) suggests this deficit may occur while motor programs are held in the buffer prior to command for movement execution. Our findings suggest that maintenance of speech motor programs in the buffer may be enhanced by DBS in individuals with PD, at least in simple RT experiments. On average, SRT was improved by 56.14 ms in the

'no switch' condition when subjects were 'on' DBS. These data are supported by the limb movement literature in which GPi or STN DBS improves simple RT performance (Brown et al., 1999; Kumru, Summerfield, Valldeoriola, & Valle-Sole, 2003; Schubert et al., 2002; Temel et al., 2006; van den Wildenberg et al., 2006).

Of course, as reminded by Keller (1987) and Weismer (2007) among others, caution must be used when making inferences about speech movements based on other kinds of movements (e.g., limb movement). Thankfully, there is a burgeoning literature which may provide more direct support for the positive effects of DBS on maintenance of motor programs in the buffer in patients with PD. Data from the programmatic study of the effects of STN DBS on oromotor movements by Gentil and colleagues (1999, 2000; 2001; see also Pinto, Gentil, Fraix, Benabid & Pollak, 2003) have consistently shown improved labial and lingual RT when subjects are 'on' versus 'off' DBS. In the simple RT paradigm used by these researchers, subjects produce a target force level following presentation of a stimulus for response. Simple RT (along with a variety of other measurements) is measured using transducers affixed to the lower lip and tongue and has consistently been found to be improved by STN DBS. Of note, although participants in these experiments produced several different target force levels, this work appears consistent with a simple RT rather than a choice RT paradigm as subjects produced repetitions of each of the requested target force levels in block.

Research Question 3

Research Question 3 was designed to determine whether a significant difference exists in SRT in the 'on' DBS versus the 'off' DBS state when participants with PD produce a word under the 'switch' condition. The hypothesized theoretical level of processing of this question was switching of maintenance motor programs at the level of the sensorimotor store during the motor

planning/programming phase. Contrary to our prediction, no significant differences in SRT were observed in the 'switch' condition regardless of whether DBS was 'on' or 'off'. Mean SRT in the 'switch' condition was 717.09 ms 'on' DBS and 728.67 ms 'off' DBS.

This negative finding was unexpected considering previous data in the limb literature showing improvement in choice RT with DBS of GPi (Schubert et al., 2002) and STN in humans (Kumru et al., 2003; Temel et al., 2005; van den Wildenberg et al., 2006) and rodents (Temel et al., 2005). However, close inspection of these previous studies reveal the presence of at least two important differences in comparison to the present work. One, the choice RT paradigms utilized in previous work did not utilize use of a prime to prepare subjects for the upcoming movement command. This is in contrast to our study which utilized a presentation of a prime word in all trials. Additionally, in the 'switch' condition of our study, the prime word unexpectedly did not match the target word. This required subjects to activate the desired motor program and inhibit the unwanted motor program. This additional process of inhibition was not required by the simple RT paradigms in the previous work. The second important difference between this study and prior limb research concerns population differences. Subjects in the previous work almost invariably underwent bilateral procedures. In contrast, only one-third (4/12) of our participants had bilateral DBS and two-thirds (8/12) had underwent unilateral left only surgery. In participants who had undergone bilateral DBS and consequently had right DBS, the lead in this hemisphere was turned 'off' for the entire study and not manipulated experimentally. These two differences are particularly important because movement inhibition has been suggested to be a bilateral (Liddle, Kiehl, & Smith, 2001; Leung & Cai, 2007) but primarily right dominant process mediated by prefrontal cerebral circuits (Aron, Robbins, & Poldrack, 2004; Aron et al., 2003; Chambers et al., 2006; Garavan et al., 1999; Konishi et al., 1999; Leung & Cai, 2007;

Vink et al., 2005). Especially pertinent to the present discussion, Aron and colleagues (2004) assert that "Converging evidence the right frontal cortex might subserve inhibitory processes underlying switching" (p. 171). Since left DBS primarily influences the ipsilateral hemisphere, the lack of significance in SRT in the 'switch' condition found in our study may be due to a laterality effect precipitated by the inhibition demands of this task. In other words, if a large portion of the 'switch' task involves right hemisphere mediated inhibition mechanisms, it appears that left DBS would have little opportunity to influence these contralateral neural mechanisms.

The negative findings for this research question lead us to consider alternative explanations such as a lack of power. However, the study does not appear to be underpowered to answer this research question. Power was sufficient to answer research questions 1 and 2. The positive findings in research question 1 provide support for the experimental paradigm. All variables between research questions 2 and 3 remained constant except the priming condition and power was sufficient to answer research question 2. Furthermore, at a glance, mean SRT differed little between stimulation conditions (i.e., 717.09 ms 'off' DBS and 728.67 ms 'on' DBS) and the p-value of 0.52 do not suggest a trend in the data. Of course, the participation of additional subjects would increase the likelihood of detecting statistically significant group differences, but in this case, if such differences were found, they would be unlikely to be meaningful.

Perhaps the most parsimonious explanation for these findings is that stimulation only had a positive influence on maintenance of motor programs in the buffer rather than on the additional processes necessary for switching. The 'switch' condition was designed to be a more complex test of motor planning/programming due to these additional processes. To again turn to the

model proposed by Sternberg and colleagues (1978, 1980, 1988 & 1990), the hypothesized levels of processing that must occur in the 'switch' condition before movement can be executed include inhibition of the unwanted motor program held in the buffer, retrieval of the appropriate subprograms from the sensorimotor store, and the loading of a new motor program into the buffer. When results from research questions 2 and 3 are both considered, the data suggest that DBS improves performance at the level of the buffer, but not retrieval of subprograms from the store and/or inhibition of the unwanted motor program.

Secondary Aims

The secondary aims of this study were to determine the effects of the experimental manipulations on response accuracy. Overall, errors were infrequently encountered. We anticipated that response accuracy would be significantly decreased in the 'switch' versus 'no switch' condition. Contrary to this expectation, response accuracy was not significantly influenced by the priming condition ($p = 0.15$). When collapsed across DBS conditions, subjects produced a mean of 1.50 errors per 16 responses in the 'switch' condition compared to 0.88 errors in the 'no switch' condition. Consistent with our expectations, stimulation condition also did not significantly influence response accuracy in either priming condition. In the 'no switch' condition, subjects produced a mean of 0.69 errors per 16 responses 'on' stimulation and 1.06 errors 'off' DBS ($p = 0.18$). In the 'switch' condition, subjects produced a mean of 1.50 errors per 16 responses both 'on' and 'off' DBS ($p = 0.72$).

These non-significant differences in response accuracy are likely due to a lack of power due to the low number of errors observed. Quite simply, errors did not occur frequently enough or there were an insufficient number of stimuli to elicit a sufficient number of errors to find significant group differences. Of note, power analysis was conducted based on SRT data rather

than response accuracy and a low number of errors are typically encountered in RT experiments, so perhaps this finding is not surprising.

Once again, the limb literature in on RT in PD may be informative, particularly with regard to the lack of effects of DBS on response accuracy. For example, Schubert et al. (2002) report no statistical difference in response accuracy across stimulation conditions in a variety of RT paradigms, including a visual simple RT task, a visual choice RT task, and an auditory choice RT task. Other researchers have reported similar findings in simple (Temel et al., 2006) and choice RT (van den Wildenberg et al. 2006) experiments in individuals with PD and DBS. These previous studies, along with our present findings, suggest that DBS may have little influence on response accuracy in simple and choice RT experiments. Again, this is likely explained by the relatively low frequency of errors encountered in RT experiments. For example, we found an error rate of 6.5% on all trials completed by our study participants. Temel and colleagues (2006) report errors occurred in "about 5%" of trials, while Van den Wildenberg et al. (2006) found a 2% error rate. Due to the low occurrence of errors, the current study was likely underpowered to detect differences in response accuracy.

Our participants made ninety-nine errors in a total of 1,526 trials. Our error rate of 6.5% is similar to the error rate of 6.4% reported by Spencer and Rogers (2005) in their participants with dysarthria (both hypokinetic and ataxic types). Of course, as previously discussed in Chapter 3, the response priming procedure we utilized was based on this and subsequent work (Spencer, 2006), so the consistency of error rates in subjects with dysarthria is reassuring. Figure 5-1 shows the distribution of errors in the present study. Out of the 99 total errors, 64 (65%) were either a premature response (32) or a phonologic error (32). The other 35% included the following error types: lexical/semantic (7), production of a previous prime (6), production of a

previous target (6), initial sound or syllable repetition (5), no speech response (3), and production of the prime in a 'switch' task (2). A combination of two or more of these error types was also encountered in five trials. Please see Chapter 2 for methods and operational definitions used in determining error type.

These errors in response accuracy are likely best explained by a variety of hypothesized mechanisms. Premature responses are generally the most common type of errors described in RT studies and they are generally accepted to reflect decreased inhibition of movement execution and these types of errors comprised approximately one-third (33%) of the total errors in our study. Spencer & Rogers (2005) reported that premature responses (or "early responders") occurred in 25% of the total errors produced by subjects with hypokinetic dysarthria.

The next two most frequently occurring error types, phonological (33%) and lexical/semantic errors (7%), comprised approximately 40% of the total errors. As defined in Chapter 2, phonological errors include single phoneme omissions, deletions, substitutions, and transpositions, while lexical/semantic errors consist of whole real word substitutions. These two errors types are best considered to be linguistically based errors, rather than errors occurring at the motor level. Using the model of Van der Merwe (1997), the hypothesized level of disruption would be at the level of linguistic symbolic planning, rather than the level which is the focus of this study, motor planning/programming. Although the relatively high number of language based errors was unexpected, disorders of language function in PD such as subtle declines in expressive language function are being recognized with increasing regularity (Ellis et al., 2006; Ellis & Rosenbek, 2007). Additionally, in our group of participants, we conducted discourse analysis of repetition of multisyllabic words, repetition of sentences, and connected speech in order to determine linguistic competency. Some evidence of language disturbance was found in

one-third (4/12) of our participants. As shown in Table 4-1, of these four participants, subject 2 produced one phonological error in repetition, subject 3 made one semantic error in connected speech, subject 4 produced a total of three errors in connected speech (two phonological and one semantic error), and subject 6 was found to produce one phonological error in repetition and two errors in connected speech (one phonological and one semantic). The influence of DBS on language function in individuals with PD and DBS has received little attention other than with verbal fluency tasks which "represent an almost exclusively applied index of linguistic proficiency…in this population (Whelan, Murdoch, Theodoros, Silburn, & Hall, 2005, p. 93). Whelan et al. (2005) provide some of the only available data on the language specific effects of STN DBS in two patients. Although language changes varied with time in both the positive and negative directions, they primarily report changes in "divergent language production proficiency" and "lexical-semantic manipulation skills" (Whelan, Murdoch, Theodoros, Silburn, & Hall, 2005, p. 99). Further studies of the language effects of DBS and PD await completion.

The other 27% of errors produced included a variety of error types, including production of a previous prime (6%), production of a previous target (6%), initial sound or syllable repetition (5%), multiple errors (5%), no speech response (3%), and production of the prime in a 'switch' task (2%). Many of these error types can be hypothesized to occur at the level of motor planning/programming. For example, errors such as production of a previous prime or target both seem to reflect an inability to inhibit previous motor programs. Production of the prime in the 'switch' condition occurred infrequently, but provides a direct example of disordered switching of speech motor programs. Van der Merwe (1997) suggests that errors such as initial sound repetitions (i.e., neurogenic dysfluency) may also be due to deficits at the level of motor planning/programming.

Exploratory Aims

For exploratory purposes, two measures of neuropsychological performance, the FAS test and the Stroop Color and Word Test, were administered both 'on' and 'off' DBS. The FAS is a test of phonemic verbal fluency in which an individual's ability to generate words beginning with the letters F, A, and S is counted. The FAS and other tests of phonemic verbal fluency are commonly encountered in the neuropsychological literature, as are similar tests such as tests of semantic verbal fluency (e.g., animals). Normative data is available from Tombaugh, Kozak, and Rees (1999) from a large group stratified by age and education level are available for these particular stimuli.

The Stroop Color and Word Test has three sections – the word section, the color section, and the color-word section. The word section has randomly ordered stimulus items comprising three different color words (i.e., red, green, and blue) printed in black ink. Subjects are instructed to correctly read aloud as many of the printed words as possible in 45 seconds. Similarly, the color section comprises symbols (i.e., XXXX) printed in red, green, and blue ink and subjects are instructed to correctly read aloud as many of the printed colors as possible in 45 seconds. Finally, the color-word section comprises the color words from the word page printed in incongruent colors from the color page. For example, the word "red" is shown printed in blue ink. Subjects are again provided 45 seconds and instructed to name as many of the colors the words are printed in as possible (rather than the word that is printed). The Stroop Color and Word Test is thought to be a test of an individual's ability to volitionally inhibit automatic word reading to produce the required response. Our findings on these tests and their interpretation follow.

FAS Test

Separate Wilcoxon signed-rank tests were conducted for each stimuli item of the FAS (i.e., the letters F, A, and S) in the 'on' versus 'off' DBS condition. No statistical differences in phonemic verbal fluency between DBS conditions were found for any of the three stimuli letters (F, $p = 0.36$, A, $p = 0.25$; S, $p = 0.99$), or across all stimuli ($p = 0.99$). For the stimulus letter F, the mean number of correct response across subjects was 10.92 (SD = 4.34, range = 15) in the 'on' DBS condition and 11.92 (SD = 4.54, range = 16) 'off' DBS. Mean number of correct productions for the stimulus letter A was 9.75 (SD = 4.85, range 18) 'on' DBS and 8.58 (SD = 3.63, range = 12) 'off' DBS. A mean of 10.92 (SD = 5.16, range = 19) correct productions were observed 'on' DBS compared to 11.42 (SD = 4.38, range = 15) 'off' DBS for stimulus letter S. When these values were combined across all three stimulus letters, the mean number of correct productions 'on' DBS was 31.58 (SD = 13.12, range 51) and 31.92 (SD = 11.40, range = 41) 'off' DBS.

A pre-post decline in phonemic and semantic verbal fluency is perhaps the most common neuropsychological finding after GPi and STN DBS surgery (Daniele et al., 2003; De Gaspari et al., 2006; Morrison et al., 2004; Parsons, Rogers, Braaten, Woods, & Troster, 2006; Rothlind, Cockshott, Starr, & Marks, Jr., 2007; Saint-Cyr, Trepanier, Kumar, Lozano, & Lang, 2000; Trepanier, Kumar, Lozano, Lang, & Saint-Cyr, 2000). In contrast to this well-established, persistent decline in verbal fluency pre-post DBS surgery, the influence of post-operative DBS state (i.e., 'on' and 'off' stimulation) on this measure has received very little attention. However, Schroeder and colleagues (2003) provide some guidance in their study of phonemic verbal fluency in seven subjects 'on' and 'off' stimulation. Phonemic verbal fluency was found to significantly decline in the 'on' versus the 'off' DBS condition. PET results revealed this decline

was accompanied by decreased regional cerebral blood flow in several areas including "the right orbitofrontal cortex, the left inferior temporal gyrus, and the left inferior frontal/insular cortex" (Schroeder et al., 2003, p. 447). The neurophysiological mechanism proposed by these authors for this decline with STN DBS was "decreased activation of a left-sided network…incorporating the inferior frontal cortex, the insular cortex, and the temporal cortex" (Schroeder et al., 2003, p. 447). Our data are not consistent with these findings but other recent work supports our findings. Witt et al. (2004) studied the effects of STN DBS on verbal fluency (including phonemic fluency) in 23 subjects with PD and found no change in verbal fluency between the 'on' and 'off' DBS states. The differences between these two previous studies might be explained by differences in the cognitive status of the participants. That is, Schroeder et al. (2003) did not appear to screen or assess cognitive status, while Witt and colleagues (2004) excluded participants with evidence of cognitive dysfunction, as did our current study. Regardless, the effects of DBS state on verbal fluency in individuals with PD demands further systematic attention.

Stroop Color and Word Test

Separate Wilcoxon signed-rank tests were conducted for each of the subtests of the Stroop in the 'on' versus 'off' DBS conditions. No statistical differences in t-scores were found for the word section ($p = 0.49$), the color section ($p = 0.30$), or the color-word section ($p = 0.28$). Further, no significant differences in interference score were found ($p = 0.56$). Overall, GPi and STN DBS have generally been found to be well tolerated procedures in terms of associated cognitive decline besides the common and persistent decline in verbal fluency described above (Daniele et al., 2003; Limousin et al., 1998; Pillon et al., 2000). However, meta-analysis has revealed "significant, albeit small, declines in executive functions and verbal learning and

memory" associated with STN DBS (along with "moderate declines…in semantic and phonemic verbal fluency" (Parsons et al., 2006, p. 578). Studies which attempt to determine the effects of the 'on' and 'off' DBS state are emerging. Jahanshahi et al. (2000) reported that bilateral GPi and STN DBS improved Stroop control trial performance 'on' versus 'off' DBS, while the 'on' STN DBS state worsened performance on the interference portion of the Stroop. Pillion and colleagues (2000) found that bilateral STN DBS improved performance in the word and the color portions of the Stroop, though more errors were noted 'on' DBS in the interference condition of the Stroop color test. Comparing the exact findings between these two studies and our own is made challenging by the fact that each study used a different version of the Stroop. Insufficient power does not appear to explain our nonsignificant findings as Pillon et al. found significant group differences in a similar group of 13 subjects (six with GPi DBS & with seven with STN DBS). Regardless, many more data are needed understand he effects of DBS state on measures of cognitive function, including response inhibition.

Strengths/Weaknesses

This study has several strengths which allow it to make a contribution to the understanding of the speech effects of DBS in PD, particularly at the level of motor planning/programming. The experimental design was rigorous and controlled for many threats to internal and external validity. Particular strengths of the design include the use of double blind testing, a thorough washout for both stimulation and medication effects, rigid inclusion/exclusion criteria, and the use of an objective measurement approach for determining speech effects (i.e., SRT).

These strengths are not insignificant. To our knowledge, double blind testing has not previously been conducted in the literature which has been focused on the speech effects of DBS

in patients with PD. The use of thorough washouts of DBS is also an important aspect of this work. Many previous data are collected from studies with inadequate washouts and we utilized two two-hour washouts before the DBS condition was implemented. The strict inclusion/exclusion criteria allowed us to obtain a homogenous and representative sample of individuals with PD. Finally, our use of a SRT paradigm allowed us to measure the primary variable of interest using an instrumental, objective measurement tool.

Weaknesses of the study are also present. The small sample size (n = 12) is a clear limitation which highlights the preliminary nature of our findings. However, the sample size appeared to be sufficient to answer the primary research questions. The strength of the study is also compromised by the fact that the exact implantation site is unknown in 75% (9/12) of participants. Although all participants underwent unilateral or staged bilateral procedures, three-quarters of participants were recruited from a larger surgical trial which seeks to compare the effects of GPi and STN DBS in a blinded fashion. Although the exact surgical sites will be known upon completion of the larger trial, at the present, determining differential effects of GPi or STN DBS on SRT is impossible. Our incomplete knowledge regarding the exact processes involved in speech motor planning/programming and their neurophysiological correlates is another limitation. For example, the anatomical locations of the speech sensorimotor store and buffer have not been established experimentally. Another limitation of the study is the quality of the digital recordings obtained during the appropriate portions of the screening and test sessions. These recordings were sufficient for the purposes of the present study, which include aiding in the description of study participants by determining linguistic competency, intelligibility scores, and speech diagnosis and severity, as well as for determining response accuracy. However, due to the fact that the recordings were made during screening and testing sessions conducted at

patient's homes or in a clinic environment, they are of insufficient quality to use for additional, more precise analyses of the speech signal, such as temporal measurement of word length or acoustic analyses.

Alternative Explanations

Alternative explanations for our findings must be considered. Chief among these alternative considerations must be the notion that the findings are due to a different process than speech motor planning/programming. A variety of cognitive influences could be used to explain our findings including global cognitive function, attention and concentration, and working memory. However, the MMSE was used to screen for global cognitive dysfunction and participants with MMSE < 26 were excluded. Mean MMSE was 28.67 (SD = 0.98). Changes in overall cognitive function thus appear unlikely to explain our findings for SRT as global cognitive function was intact for our participants. The forward and backward portions of the WMS-III Spatial Span were used to screen for disorders of attention and working memory. Individuals with standard scores < 7 on either subtest were excluded. Mean Spatial Span forward standard score was 10.17 (SD = 2.04) and Spatial Span backward standard score was 10.83 (SD = 1.99). These means are both within the normal range and thusly, changes in attention or working memory appear unlikely to explain our findings.

The response priming procedure we utilized also does not seem to support cognitive mechanisms such as working memory to explain our findings. This testing procedure was designed to make little demand on cognitive function in general. Additionally, we argue that this paradigm is not a test of working memory, as subjects were provided with the target immediately upon command for execution.

Another alternative explanation for these findings is that the differences we found are due to execution level speech deficits, rather than the deficits in speech motor planning/programming. This explanation does not appear plausible, as the primary dependent measure of SRT was calculated *before* speech was executed. The response accuracy data also support deficits primarily at the level of motor planning/programming, although deficits at the level of execution also appeared to be present. This notion is based on the perceptual assessment that sound distortions occurred during production of words in the response priming test on 4% of all trials. Sixty-five sound distortions were perceived in 1,526 trials, 38 while subjects were 'on' DBS and 27 'off' DBS. Although Van der Merwe (1997) suggests that distortions may occur due to programming level deficits, it is traditional to attribute this type of error to execution level deficits. Therefore, it appears plausible that the hypokinetic dysarthria of our subjects was influenced by deficits in both planning/programming and execution.

Discussion Conclusion

We conducted an experiment in subjects with DBS and PD in which participants completed a response priming protocol in two priming conditions (i.e., 'switch' and 'no switch') both 'on' and 'off' DBS. SRT was found to be significantly different across the priming conditions in that subjects produced a word more quickly in the 'no switch' versus the 'switch' condition. Our participants were also found to produce a word more quickly in the 'no switch' condition when 'on' versus 'off' DBS. The proposed mechanism of this improvement is an increased ability to maintain the motor program in the buffer prior to the command for execution. SRT was not significantly different in the 'switch' condition across DBS states, suggesting that DBS has little influence on mechanisms involved in switching of speech motor programs (i.e.,

inhibition of unwanted motor programs or retrieval of new subprograms from the sensorimotor store).

Traditionally, the speech deficits in individuals with hypokinetic dysarthria (and indeed all dysarthria types) have been considered to be execution level deficits (Darley, Aronson, & Brown, 1969a, b, 1975; Duffy, 2005; Yorkston et al. 1999). However, this conceptualization of dysarthria as strictly an execution level disorder has been questioned by Kent and associates (Kent & Rosenbek, 1982; Kent et al. 1997), as well as more recent experimental findings from Spencer & Rogers (2005; see also Spencer 2006). Our present findings also support the notion that individuals with PD and hypokinetic dysarthria have speech deficits at the level of motor planning/programming. Furthermore, our findings suggest that these planning/programming deficits can be measured using a SRT paradigm. Finally, DBS of the GPi and/or STN appears to differentially influence the motor planning/programming processes required in the different priming conditions of our experiment. In other words, our findings suggest that DBS is associated with an improvement in the maintenance of the speech motor program in the buffer but not the multiple processes involved in switching of speech motor programs.

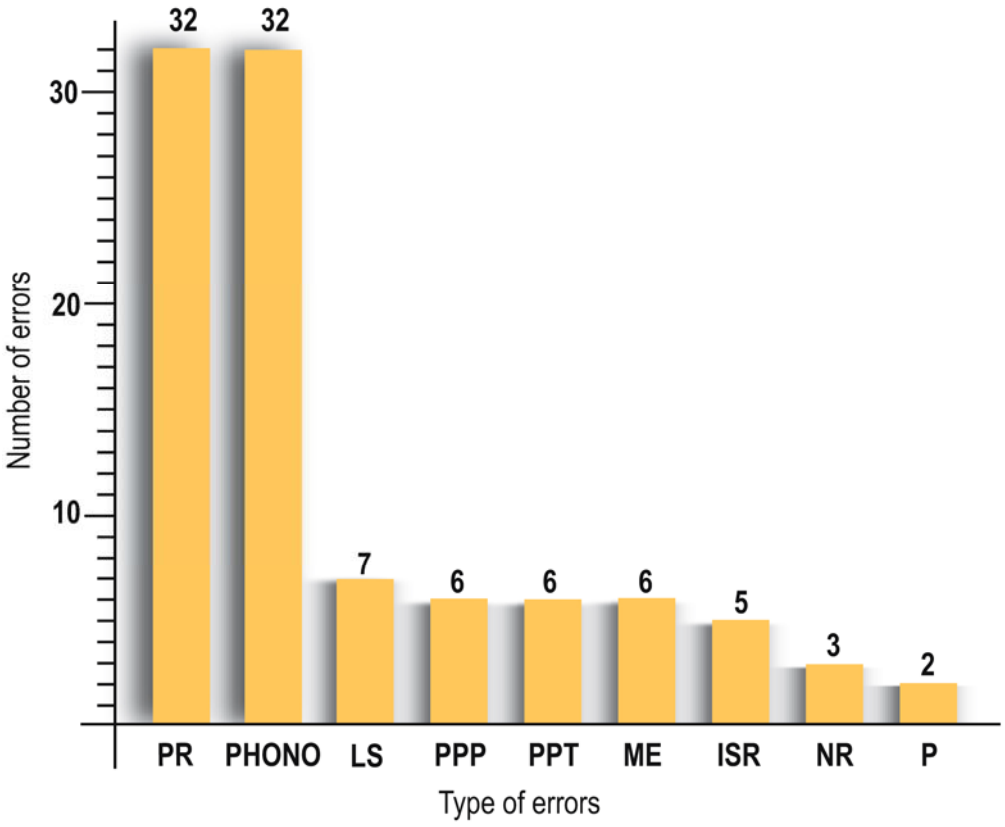

Figure 5-1. Distribution of errors differentiated among error type. PR = premature response, PHONO = phonological error, LS = lexical/semantic error, PPP = production of previous prime, PPT = production of previous target, ME = multiple errors (i.e., two or more of other error types), ISR = initial sound repetition, NR = no response, P = production of the prime in 'switch' trial.

CHAPTER 6
FUTURE WORK

Our experience with this research project suggests many avenues for future work in this area. Experiments to further determine how robust the positive influences of DBS on maintaining speech motor programs in the buffer are warranted. This can be accomplished in a number of ways, such as by varying the length of delay or with the use of articulatory suppression between presentation of the prime and target.

Further investigations into the laterality effects of DBS in PD on speech motor program maintenance and switching are also warranted. As previously discussed in Chapter 5, our lack of significant differences in the 'switch' condition between the 'on' and 'off' DBS states may have been due to the fact that subjects with unilateral left DBS were targeted for recruitment due to the critical nature of the left hemisphere in speech and language. Although subjects with bilateral DBS also participated, right DBS was turned 'off' for the entirety of the experiment. Since the inhibition process involved in the 'switch' condition may rely heavily on right hemisphere cerebral circuitry, a comparison between PD subjects with right and left DBS may assist in further determining the effects of DBS on the switching of speech motor programs. It might be expected that right hemisphere DBS would improve performance in the 'switch' condition due to an improved ability to inhibit unwanted motor programs. Such a paradigm would also allow a comparison on the effects of left and right DBS on maintenance of speech motor programs.

Subsequent work in this area may be improved by collecting execution level speech data in addition to the motor planning/programming variables studied in the present experiment. For example, data such as the duration of movement during target speech productions would target the level of execution and complement the SRT planning/programming data we collected. We attempted to complete post-hoc analysis of movement time in the present experiment, but were

unable to reliably make these measurements due to the presence of extraneous noise in the acoustic signal. This was presumably due to the environments the digital recordings were made (i.e., subject's homes and clinical environments). Although this was convenient for participants and aided in recruitment, it would be a significant improvement to make acoustic recordings in a sound treated room to more purely capture the speech signal. This would also provide the high-quality digital recordings necessary for acoustic analysis of the speech signal which would allow for additional insights at the level of execution. Although acoustic analysis of the speech effects of DBS in subjects with PD has been completed previously (Dromey et al., 2000; Hoffman-Ruddy et al. 2001, Wang et al., 2003), these studies suffer methodological limitations such as unspecified stimulation washouts and small sample sizes.

Another interesting area for future study would be modification of the paradigm in order to compare limb planning/programming with speech planning/programming. This is important because of the differential responses across the corticospinal and corticobulbar systems to treatments for PD (e.g., DBS, levodopa) that are commonly reported in the literature. However, data from Adams and colleagues (2004) suggest that the reported differential response of these systems to levodopa, for example, may be due to differences in the measurement approaches used rather than true differences. If appropriately modified, the employed experimental paradigm would allow for comparisons across these two systems using the same measurement approach (i.e., RT). Such an approach could facilitate further understanding of how treatments for PD influence different movements.

Finally, overall, the participants in our study were judged to have only mild-moderate dysarthria on average. Only two of the 12 were on the more severe end of the severity spectrum with moderate-severe dysarthria. This may have caused a ceiling effect in terms of speech

improvements with DBS. Further study in patients with more severe dysarthria would be beneficial to more completely understand the speech effects of DBS in individuals with PD.

APPENDIX A
TRAINING SESSION STIMULI

Stimuli	Set 1	Set 2
1	Hill-Hill	Nut-Nut
2	Lame-Shame	Howing-Howing
3	Beat-Beat	Heat-Heat
4	Hum-Hum	Char-Jar
5	Lady-Lady	Dill-Dill
6	Wrecker-Checker	Cherry-Sherry
7	Mall-Mall	Ship-Ship
8	Nut-Cut	Men-Men
9	Heat-Heat	Rowing-Showing
10	Rowing-Rowing	Sheet-Sheet

= Switch = No switch

APPENDIX B
EXPERIMENTAL STIMULI

Stimuli	SET 1	SET 2
1	Jump-JUMP	Zipper-ZIPPER
2	Shopper-SHOPPER	Chatter-SHATTER
3	Cheer-JEER	Shining-SHINING
4	Jealous-JEALOUS	Thug-THUG
5	Shake-SHAKE	Shake-SHAKE
6	Rowing-SHOWING	Jealous-JEALOUS
7	Zipper-ZIPPER	Jump-JUMP
8	Ramp-RAMP	Veal-VEAL
9	Jingle-JINGLE	Rowing-ROWING
10	Liver-SHIVER	Jade-JADE
11	Cheer-CHEER	Jealous-ZEALOUS
12	Thug-THUG	Shining-LINING
13	Rowing-ROWING	Cheer-CHEER
14	Veal-VEAL	Jingle-JINGLE
15	Chatter-CHATTER	Zipper-CHIPPER
16	Shining-SHINING	Chatter-CHATTER
17	Jump-JUMP	Sheep-SHEEP
18	Jealous-JEALOUS	Zipper-ZIPPER
19	Shake-SHAKE	Ramp-RAMP
20	Jade-JADE	Liver-LIVER
21	Sheep-SHEEP	Jump-JUMP
22	Jade-SHADE	Shake-RAKE
23	Liver-LIVER	Cheer-JEER
24	Veal-VEAL	Jingle-SHINGLE
25	Jump-LUMP	Shopper-SHOPPER
26	Shopper-CHOPPER	Thug-RUG
27	Ramp-RAMP	Shining-SHINING
28	Jade-JADE	Sheep-JEEP
29	Jingle-JINGLE	Jealous-JEALOUS
30	Chatter-SHATTER	Liver-SHIVER
31	Rowing-ROWING	Ramp-CHAMP
32	Cheer-CHEER	Rowing-ROWING

Stimuli	SET 1	SET 2
33	Shining-SHINING	Thug-THUG
34	Thug-THUG	Rowing-SHOWING
35	Zipper-CHIPPER	Shake-SHAKE
36	Shopper-SHOPPER	Veal-VEAL
37	Jingle-SHINGLE	Cheer-CHEER
38	Jump-JUMP	Liver-LIVER
39	Zipper-ZIPPER	Jade-SHADE
40	Liver-LIVER	Shopper-SHOPPER
41	Sheep-SHEEP	Jingle-JINGLE
42	Chatter-CHATTER	Shining-SHINING
43	Jealous-ZEALOUS	Rowing-ROWING
44	Ramp-CHAMP	Sheep-SHEEP
45	Jade-JADE	Jump-LUMP
46	Shake-RAKE	Ramp-RAMP
47	Veal-ZEAL	Jade-JADE
48	Sheep-JEEP	Zipper-ZIPPER
49	Shake-SHAKE	Jealous-JEALOUS
50	Chatter-CHATTER	Chatter-CHATTER
51	Rowing-ROWING	Veal-VEAL
52	Shining-LINING	Thug-THUG
53	Veal-VEAL	Shopper-SHOPPER
54	Thug-RUG	Liver-LIVER
55	Shopper-SHOPPER	Cheer-CHEER
56	Liver-LIVER	Ramp-RAMP
57	Jingle-JINGLE	Sheep-SHEEP
58	Shining-SHINING	Veal-ZEAL
59	Thug-THUG	Jump-JUMP
60	Zipper-ZIPPER	Shake-SHAKE
61	Sheep-SHEEP	Shopper-CHOPPER
62	Jealous-JEALOUS	Chatter-CHATTER
63	Ramp-RAMP	Jade-JADE
64	Cheer-CHEER	Jingle-JINGLE

= Switch = No switch

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BIOGRAPHICAL SKETCH

Harrison N. Jones completed his B.A. in communication disorders at North Carolina State University in 1996, followed by his M.A. in communication disorders at Appalachian State University in 1998. Upon completion of his master's degree, Mr. Jones started his clinical fellowship as a speech-language pathologist, which he completed in 1999. Since beginning his fellowship, he has continued to practice as a speech-language pathologist with expertise in the evaluation and treatment neurogenic communication and swallowing disorders in adults. He has practiced at a variety of institutions including Duke University Medical Center and Shands Hospital at the University of Florida. Mr. Jones enrolled at the University of Florida in pursuit of his Ph.D. in rehabilitation science in 2004. His broad area of research interest is in motor speech disorders in patients with neurological disease. He is particularly interested in preparatory aspects of speech production (e.g., motor planning/programming) and speech disorders in individuals with Parkinson's disease. Following completion of his Ph.D., Mr. Jones will return to Duke University to join the academic faculty as an assistant professor. His primary responsibilities will be to conduct a programmatic line of research in his areas of scientific interest and provide evaluation and treatment services to adults with neurogenic speech and swallowing disorders.