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BRIEF COMMUNICATION

Subthalamic stimulation affects homophone meaning generation in Parkinson's disease

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Abstract

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) in individuals with Parkinson's disease (PD) has often been associated with reduced verbal fluency performance. This study aimed to directly assess semantic switching as a function of STN stimulation in PD participants with the Homophone Meaning Generation Test (HMGT). Seventeen participants with PD who had received STN DBS completed the HMGT in on and off stimulation conditions. Twenty-one non-neurologically impaired participants acted as controls. PD participants (in both on and off stimulation conditions) generated significantly fewer meanings than control participants and consistent with the previous reports of verbal fluency impairment, PD participants produced fewer definitions in the on stimulation condition. PD participants (in both on and off stimulation conditions) also had greater difficulty generating definitions for nonhomographic homophones compared with homographic homographs. The results of this study indicate that STN stimulation exacerbates impairment in semantic switching. (*JINS*, 2008, *14*, 890–894.)

Keywords: Deep brain stimulation, Verbal fluency, Semantic switching, Basal ganglia, Subthalamic nucleus, Homophones

INTRODUCTION

Over the past decade, deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become a widely accepted treatment for medically intractable Parkinson's disease (PD). Numerous studies have now associated STN DBS with significant improvements in the motor complications of PD (see Kleiner-Fisman et al., 2006, for a review), yet changes in neuropsychological status as a function of STN stimulation are not as clearly defined. Whereas STN DBS has generally been considered as a cognitively safe procedure, declines in verbal fluency have frequently been reported (e.g., Cilia et al., 2007; De Gaspari et al., 2006;

Saint-Cyr et al., 2000; Schroeder et al., 2003; Smeding et al., 2006).

Saint-Cyr and colleagues (2000) in a comprehensive study of the neuropsychological consequences of STN DBS, compared preoperative semantic and phonemic verbal fluency scores, including measures of switching (number of switches from one semantic subcategory to another) and clustering (mean number of words per semantic subcategory) with postoperative scores in 10 patients who received STN DBS. Verbal fluency performance declined postoperatively for the majority of patients and the subcomponent process of switching similarly declined, suggesting that STN DBS surgery is associated with greater difficulties switching from one semantic subcategory to another. This pattern of verbal fluency decline has since been replicated in a study including a larger sample size (De Gaspari et al., 2006).

As an alternative test of verbal generation, Warrington (2000) proposed the use of a Homophone Meaning Gener-

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ation Test (HMG) which requires the generation of multiple definitions to words that have many meanings (e.g., *slip*). The HMG, therefore, assesses the ability to switch between one independent semantic representation and another, linked at a lexical level by a common word form. In contrast to verbal fluency paradigms, the HMG is an un-timed measure. As suggested by Warrington (2000), the use of an un-timed measure is advantageous when applied to a population with speech production difficulties and in the case of the present study this allows for the consideration of the presence of dysarthria or bradykinesia associated with PD or alterations in motor speech impairment as a result of DBS. Therefore, more accurate comparisons can be made between PD and control performance and also between on and off stimulation assessment if the test used is less dependent on measures of vocal (or speech) performance or speed of response. Furthermore, the HMG is advantageous over verbal fluency measures as it directly targets semantic switching capacity rather than the many subcomponent measures (such as response initiation, strategy formation, and attention) that may influence outcomes in verbal fluency performance. The HMG is also reported to be highly sensitive to frontal lobe dysfunction (Warrington, 2000) and highly correlated with phonemic and semantic verbal fluency tests (Kave et al., 2007).

Whelan and colleagues (2003) first assessed the ability to generate definitions from homophones in PD as a function of STN DBS surgery. The results were not consistent with verbal fluency declines reported elsewhere, as four of the five participants improved in their ability to provide definitions to homophones when receiving STN stimulation compared with preoperative results. However, the results of this study should be interpreted with caution considering the small sample size and potential shortcomings of the assessment.

The purpose of the present study was to investigate homophone meaning generation in a larger cohort of PD participants who had received surgery for bilateral subthalamic DBS. Homophone meaning generation skills were also measured in on- and off-stimulation conditions, providing a direct measure of the effects of STN stimulation on semantic switching unconfounded by the effects of DBS surgery.

METHODS

Participants

Seventeen participants (13 males) diagnosed with PD were assessed at least 4 months after receiving bilateral STN DBS surgery (refer to Coyne et al., 2006, for details of the surgical procedure). All PD participants had undergone extensive neurological and psychiatric evaluation before surgery for DBS. They met the strict inclusion criteria for admission to the DBS program, which included no evidence of significant psychiatric symptoms. Each participant was tested with their stimulators turned on and again with their stimulators turned off. The order of test condition was counterbalanced with at least 6 weeks separating the two testing sessions. The stimulators were turned off for at least 1 hr before the commencement of assessment in the off stimulation condition. Four participants were no longer taking levodopa medication and the remaining 13 participants were tested while taking their usual medication and levodopa dosage remained constant for each testing session. Demographic and disease characteristics of the PD participants are presented in Table 1.

Twenty-one normal control participants (13 males) were matched for age and education to the PD participants (Table 1). All control participants were right handed, had no history of neurological impairment, were not taking any medication deemed to affect neurological functioning, had no self-reported hearing loss, and had self-reported normal or corrected-to-normal vision. All participants provided informed consent for participation, which was obtained according to the Declaration of Helsinki, and this project was approved by the appropriate University and Hospital Ethics Committees.

Procedure

PD and control participants completed the HMG (Warrington, 2000) which consists of a total of eight homophones (*tick, tip, slip, form, plain, bored, right, and sent*). Four of the eight homophones were also homographic (e.g., *slip*) and the remaining four had more than one possible

Table 1. Demographic and disease characteristics of Parkinson's disease participants and controls

	PD Participants		Control Participants	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Age (years)	61.18	9.42	62.29	9.04
Education (years)	13.29	4.75	13.33	4.13
Disease Duration (years)	12.59	4.57	—	—
Time post-DBS surgery (months)	6.47	3.95	—	—
Severity (H & Y)	2.76	0.69	—	—
UPDRS III (On score)	11.76	5.84	—	—

Note. DBS = Deep Brain Stimulation; UPDRS = Unified Parkinson's Disease Rating Scale; H & Y = Hoehn and Yahr.

spelling (e.g., *right/write/rite*). Each word was presented auditorily, and participants were required to generate as many definitions as possible. Responses to each homophone were un-timed and participants were required to indicate when they had exhausted all possible meanings for each item.

Homophone definitions were considered correct if they were representative of any definition considered appropriate in Australian English according to the 2001 Macquarie Dictionary. Each correct definition was awarded one point and summed to create a total for same spelling and different spelling homophones.

RESULTS

Mean and standard deviations for same and different spelling homophones for PD participants and controls are presented in Table 2. In addition, the distribution of individual PD participant total scores is presented in Figure 1.

An analysis of variance (ANOVA) was first conducted on homophone meaning generation scores with session order, session type, and homophone type as factors, to determine the presence of assessment order effects for the PD participants. Order effects did not reach significance [$F(1,60) = 7.767$; $p = .263$] and there were no significant interactions between order effects and other factors of interest ($p > .5$); therefore, assessment order effects were not included in further analyses.

To determine the effects of STN stimulation on homophone meaning generation for PD participants, a repeated measures 2×2 ANOVA was performed on homophone meaning generation scores as a function of homophone type (same vs. different spelling) and stimulation condition (on vs. off stimulation). A significant main effect for stimulation revealed that STN stimulation was associated with an overall decline in the number of definitions provided compared with the off stimulation condition irrespective of homophone type [$F(1,16) = 5.633$; $p < .05$]. There was also a main effect for homophone type [$F(1,16) = 12.712$; $p < .005$], suggesting the presence of a greater number of definitions generated for same spelling homophones ($M = 12.706$; $SD = 2.714$) compared with different spelling homophones ($M = 11.265$; $SD = 2.274$). An interaction between homophone type and stimulation condition did not reach

significance [$F(1,16) = .983$; $p > .05$]. For control participants, a paired samples t test revealed no significant difference between the number of meanings generated for same or different spelling homophones [$t(20) = 1.105$; $p = .282$].

DISCUSSION

The results of the present study reveal a general deficit in the generation of meanings of homophonic words by PD participants in both on- and off-stimulation conditions, thereby suggesting that homophone meaning generation is similarly affected by frontal–subcortical dysfunction associated with PD. Furthermore, STN stimulation resulted in a further decline on the HMGT, suggesting that STN stimulation acts to further impair semantic switching in PD.

Impaired performance on the HMGT is consistent with the numerous studies that have linked STN stimulation with impaired performance on verbal fluency tests (e.g., Cilia et al., 2007; De Gaspari et al., 2006; Saint-Cyr et al., 2000; Schroeder et al., 2003; Smeding et al., 2006). While performance on both semantic and phonemic fluency tests is related to performance on the HMGT (Kave et al., 2007), there are some distinct differences between them. The HMGT requires the generation of a series of independent semantic meanings from a homophone, whereas category fluency requires switching within a single semantic domain. Therefore, HMGT is likely to require a greater capacity to switch between semantic domains than category fluency. Whereas phonemic fluency potentially engages cognitive switching to a similar extent to the HMGT, reliance on lexical knowledge is not as high (Kave et al., 2007).

Behaviorally, verbal fluency deficits associated with STN stimulation have been hypothesized to be influenced by motor speech impairment subsequent to STN stimulation, impairment in lexical retrieval, or cognitive switching from one semantic concept to another (Warrington, 2000). The use of the HMGT in the present study substantially eliminates the influence of speech production demands or bradykinesia. The HMGT stresses semantic switching skills but performance might also be affected by the lexical retrieval demands of providing definitions. Category fluency tasks require switching semantic subdomains within a larger semantic domain according to strict semantic criteria, phonemic fluency tasks require switching between semantic

Table 2. Mean (*SD*) scores on the Homophone Meaning Generation Test for PD participants and controls

	PD Participants					
	On stimulation		Off stimulation		Control Participants	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Same spelling homophones	12.177	2.404	13.235	2.969	15.952	2.312
Different spelling homophones	10.412	2.213	12.118	2.147	15.191	3.558
Total score	22.589	3.922	25.353	4.782	31.143	5.102

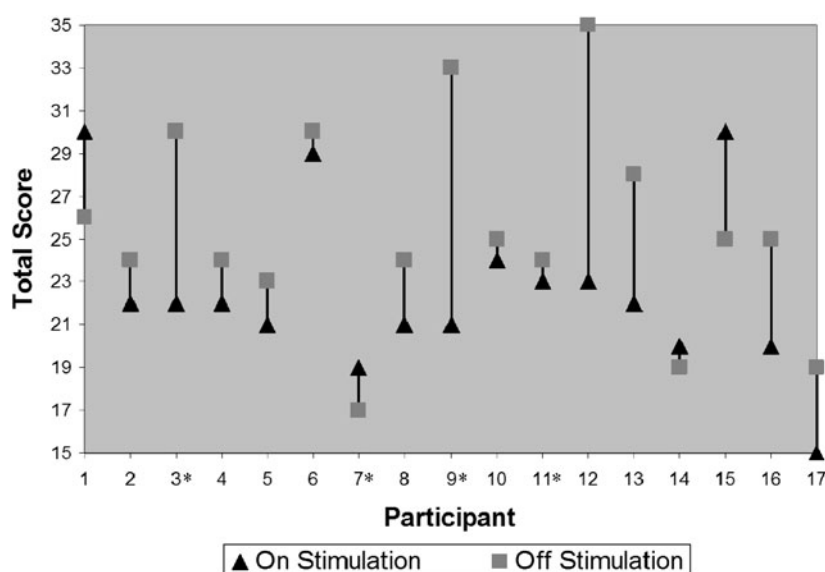


Fig. 1. Distribution of total Homophone Meaning Generation Test scores for patients with Parkinson's disease in on and off stimulation conditions. * indicates that the participant was no longer taking levodopa medication.

domains on the basis of lexical search (Troyer et al., 1998); and both tasks require an ability to suppress habitual responses (Perrett, 1974; Ross et al., 2007). STN stimulation has previously been reported to improve the ability to inhibit dominant semantic meanings (as measured by the Hayling Test) (Castner et al., 2007). Therefore, it is unlikely that the impairment in semantic switching associated with STN stimulation is related to difficulties in inhibiting habitual responses.

Why DBS facilitates movement but impairs semantic switching is unknown. STN stimulation might impair semantic switching by at least two mechanisms: the spread of current to adjacent neural regions (Perriol et al., 2006), and the spread of current within the STN itself to directly affect nonmotor basal ganglia–thalamocortical circuits (Perriol et al., 2006; Schroeder et al., 2003). It is also possible that basal ganglia–thalamocortical circuits are not as segregated as originally believed (Parsons et al., 2006).

An unexpected result of the present study was a relatively greater deficit in ability to generate definitions for homophones that could be spelled multiple ways. This deficit was seen in PD participants only, and in both on- and off-stimulation conditions. This finding contrasts with the results of Warrington's study (2000) of subjects with focal frontal pathology, in whom there was no evidence of a homophone type effect. It also contrasts with the results of the study by Kave et al. (2007) in which normal subjects achieved higher scores for Hebrew nonhomographic homophones. These disparate findings may reflect statistical limitations of the studies, the effect of different pathologies, or language-specific differences.

The greater difficulty with differently spelled homophones exhibited by PD subjects may reflect the larger cognitive switches required in generating definitions for this

type of homophone. For example, performing well on different spelling homophones (such as scent/sent/cent) requires a shift from one orthographic lexical representation to another in addition to a semantic switch to enable the generation of the various meanings across and within lexical representations.

In conclusion, our study suggests that subjects with PD have impaired lexical–semantic switching ability relative to age- and education-matched control subjects, reflected in their impaired performance on the HMG. This impairment is increased with STN DBS, and it is greatest with homophone definition involving differently spelled homophones. These results extend and clarify the results of prior studies using phonemic and semantic fluency tests because the use of the HMG substantially eliminates confounds attributable to the potentially deleterious effects of bradykinesia and dysarthria on word fluency.

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