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Subthalamic nucleus deep brain stimulation affects distractor interference in auditory working memory

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ABSTRACT

Computational and theoretical accounts hypothesize the basal ganglia play a supramodal "gating" role in the maintenance of working memory representations, especially in preservation from distractor interference. There are currently two major limitations to this account. The first is that supporting experiments have focused exclusively on the visuospatial domain, leaving questions as to whether such "gating" is domain-specific. The second is that current evidence relies on correlational measures, as it is extremely difficult to causally and reversibly manipulate subcortical structures in humans. To address these shortcomings, we examined non-spatial, auditory working memory performance during reversible modulation of the basal ganglia, an approach afforded by deep brain stimulation of the subthalamic nucleus. We found that subthalamic nucleus stimulation impaired auditory working memory performance, specifically in the group tested in the presence of distractors, even though the distractors were predictable and completely irrelevant to the encoding of the task stimuli. This study provides key causal evidence that the basal ganglia act as a supramodal filter in working memory processes, further adding to our growing understanding of their role in cognition.

1. Introduction

The ability to preserve working memory from external interference is critical for daily life, and two key regions of the brain thought to support this are the prefrontal cortex (PFC) and the basal ganglia (BG). The prefrontal cortex is thought to be critical in processes such as working memory (WM) maintenance, and a number of computational and theoretical accounts hypothesize a "filtering" role of the basal ganglia in preservation of WM from distractors (e.g. Hazy et al., 2006). Anatomically, the basal ganglia are well placed to affect prefrontal function, being extensively connected via fronto-striatal loops (Alexander et al., 1986) – this circuitry has long been implicated in the selection and filtering of competing motor plans (see Nambu (2008)). Key support for an analogous filtering role in working memory comes from studies in patients with basal ganglia lesions, in which they demonstrate an impaired ability to preserve visuospatial WM from distractors. Intriguingly, this impairment appears to be distractor-specific, and distinct from WM deficits resulting from prefrontal lesions (Baier et al., 2010; Voytek and Knight, 2010) suggesting the basal ganglia act as a filter or "gatekeeper" to the maintenance processes of the prefrontal cortex during WM.

Two elements of this intriguing hypothesis remain untested. First, the filtering role of the basal ganglia is hypothesized to be supramodal, and should extend to WM in other sensory systems and modalities (e.g. auditory and/or non-spatial). Yet, dominant psychological models of WM posit separate, modality-specific storage and processing pathways for auditory and visual WM representations (Baddeley, 2007; Baddeley and Hitch, 1974). Indeed, attentional processes, core to working memory function, have both modality specific and independent functions (see Tamber-Rosenau and Marois (2016) for review) and a recent study suggests that the prefrontal cortex may have spatially specific regions for auditory and visual attentional processes (Michalka et al., 2015). Thus, it may be overly simplistic to assume that the "gatekeeper" role of the basal ganglia, shown in the visuospatial domain, will generalize to a nonspatial, auditory modality. If it is instead specific to the visuospatial domain, it poses a significant challenge to accounts of basal ganglia function as a mechanism supporting global WM.

A second untested element is that the nature of the supporting evidence has been correlational, as it is difficult to causally and reversibly manipulate deep subcortical structures, such as the basal ganglia, in humans. In this study, we test the role of the basal ganglia in distractor suppression during a non-spatial, auditory WM (AWM) task. To examine the effects of basal ganglia manipulation, we employ a reversible modulation approach afforded by deep brain stimulation of

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the subthalamic nucleus (STN-DBS) a common therapy for Parkinson's disease (PD). In STN-DBS, high frequency electrical stimulation is applied, disrupting some aspects of basal ganglia transmission and ameliorating motor symptoms (see Kringelbach et al., 2007; Wichmann and DeLong, 2016). The effects are rapidly reversible once stimulation is turned off – motor symptoms return within minutes (Hristova et al., 2000). The STN is an important modulatory node in basal ganglia circuitry, and is powerfully poised to affect basal ganglia function. By selectively affecting the basal ganglia using STN-DBS, we are able to address their causal role in human WM processes. Because of this, STN-DBS has been used as a unique, reversible, approach to study the role of the basal ganglia in cognitive functions (e.g. in reversal learning: Frank et al., 2007).

This approach affords a uniquely powerful within-subject approach to study whether the basal ganglia's gating role could extend to non-spatial auditory WM processes. To evaluate the hypothesis that the basal ganglia are involved in auditory distractor suppression, we contrast auditory memory performance on and off STN-DBS in two groups: one in which the maintenance portion of the AWM task contains distractors and one without distractors. For comparison, we also establish performance with and without distractors in a cohort of healthy aged, replicating effects seen in an earlier study (Chao and Knight, 1997). If modulation of the basal ganglia impairs WM processing, then we would expect response slowing or decreased accuracy in the ON-DBS condition relative to OFF-DBS. If this effect is specific to preservation of the mnemonic trace from distractors, as would be predicted by the accounts described above, then we should see the impairment *specifically* in the group presented with distractors. If modulation of the basal ganglia does not affect AWM performance, we must then consider that these effects may be domain specific to visual, or visuospatial working memory.

2. Methods

2.1. Task design

To examine auditory non-spatial memory, we used a variant of a well-characterized auditory delayed-match-to-sample task (after Chao and Knight (1998)). In this task, participants initiated each trial with a keypress, after which a feature cue (emotion or gender) was displayed for 1–1.5 s (s), indicating the feature of the nonverbal voice clip to be remembered. A fixation spot then appeared, and the first vocal stimulus was presented. After a variable delay of 2.5–4 s, the second vocal stimulus was played, and subjects determined whether the second stimulus did or did not match the first stimulus based on the cued feature (see Fig. 1). Subjects were instructed to be as fast and accurate as possible. Responses were indicated by a left hand key press for a "non-match" response and right hand keypress for "match". Before the experiment began, all subjects had at least 8 practice trials to become familiar with the stimuli, button responses, and task requirements, and were given feedback on their performance to ensure clarity. Each session contained 64 trials, fully counterbalanced for task type (gender or emotion) and response (match or nonmatch).

There were two distractor groups in each cohort (PD or HEC). In the first "no distractor" group, the delay period contained silence. In the second "distractor" group, the delay period was filled with irrelevant 100 millisecond (ms) long, 4 kHz tone pips, with an inter-pip interval varying from 75 to 100 ms. The frequency of the tone pips was selected such that there was no spectral overlap with the stimuli, and thus any change in performance seen would not be due to low-level acoustic interference.

The use of two task types (the feature cue) allowed us to make distinctions between encoding and other stages of memory, thus better specifying effects. We predicted that if one feature was more difficult to perceive/encode than the other (i.e. emotion is more difficult/slower to perceive than gender), it would help determine whether DBS differentially affects encoding vs other components of the mnemonic process. We saw no selective interactions of task type and distractor, the focus of this study (see results), so the conditions are combined in the figures.

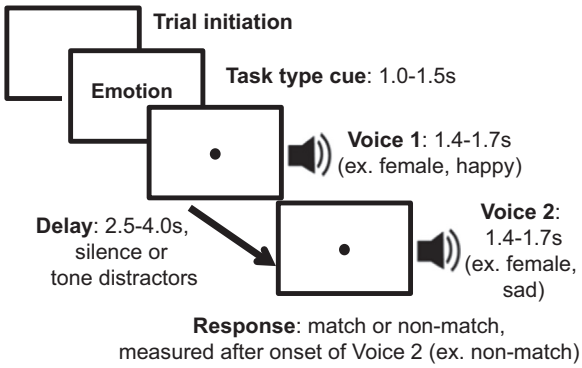

Fig. 1. Auditory delayed match to sample task design. Subjects initiated each trial with a keypress, after which a task type cue (emotion or gender) was displayed for 1–1.5 s. This indicated the feature of the nonverbal voice clip to be remembered. A fixation spot appeared and the first voice stimulus was presented. After a variable delay of 2.5–4.0 s, the second voice stimulus was played and subjects were instructed to decide if the two stimuli did or did not match based on the cued feature. In the first "no distractor" group, the delay period contained silence. In the second "distractor" group, the delay period was filled with irrelevant 100 ms long, 4 kHz tone pips, with an inter-pip interval varying from 75 to 100 ms. In the example illustrated here, the feature to be compared is "emotion", the first voice stimulus is a female laughing, the second is a different female crying, and the correct response is "non-match".

2.2. Subjects

Two cohorts of subjects participated in this experiment: 1) Parkinson's disease patients undergoing therapeutic STN-DBS (PD: n=28), and 2) Age- and education-matched healthy elderly controls (HEC: n=28) with no history of neurological deficits. Parkinson's patients were recruited from the Vanderbilt University movement disorders clinic, and healthy elderly controls were recruited from the local community or were occasionally family members (e.g. spouses) of PD patients. Written informed consent was acquired from each participant and all procedures were in accordance with and approved by the Vanderbilt Institutional Review Board (IRB #111730, 171210). Current IQ was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Participants were screened for dementia by a comparison of the current IQ (WASI) to the estimated premorbid IQ estimated by the Weschler Test of Adult Reading (WTAR; Wechsler, 2001) – if the difference between current and premorbid IQ was greater than 25 points, the subject was not included. Full demographic information for the 56 participants is listed in Table 1 and discussed in results.

2.3. DBS ON/OFF stimulation testing protocol

Each subject from the PD cohort was tested with bilateral STN-DBS stimulators both on and off ("ON" vs "OFF" conditions). All patients were tested with stimulation settings at those used to achieve optimal clinical benefit, determined by their Vanderbilt movement disorders neurologist. Patients were tested on medications. Information on disease duration, time since lead implantation, stimulation settings, and levodopa equivalent dose listed in Table 2. Order of testing was counterbalanced across subjects and within each group (distractor/no distractor), and the time in between the change of stimulation settings and testing was at least 15 min. Total testing time, including time to change parameters, was approximately 1–1.5 h. Due to this long testing protocol, PD patients were split into either a distractor or no distractor group (n=14) to avoid effects due to exhaustion. Consistent with this, the HEC were also split into two distractor conditions.

Table 1
Demographic data for the PD and HEC cohorts, split by distractor group (standard deviations in parentheses). Separate groups of distractor conditions (no distractor vs distractor) are not different for age, IQ, and years of education. Cohorts (PD vs HEC), are matched for age and years of education, and IQ in the PD cohort is lower than that of HEC (see text).

	PD		HEC	
	No distractor	**Distractor**	**No distractor**	**Distractor**
# Participants	14	14	14	14
Age (yr)	60.1 (6.9)	61.1 (5.0)	63.4 (9.3)	62.7 (6.6)
Current IQ	104.8 (10.3)	108.8 (10.8)	118.5 (9.4)	119.3 (13.9)
Education (yr)	14.8 (2.1)	14.7 (2.6)	15.2 (2.4)	15.6 (2.2)

Table 2
Average disease duration, time since DBS implantation surgery, daily Levodopa equivalent dose (LDOPA), AC-PC coordinates of center of active contact of STN-DBS lead, and stimulation settings for the PD cohort, split by distractor group (standard deviations shown in parentheses). LDOPA equivalency conversion after (Tomlinson et al., 2010). All location and stimulation characteristics are not different for participants in different groups (no distractor vs distractor).

		PD	
		No distractor	**Distractor**
	Time since surgery (mo)	37.3 (27.1)	43.0 (34.1)
	Time since diagnosis (yrs)	9.8 (4.4)	13.3 (6.6)
	LDOPA equivalency (mg)	1256.3 (550.8)	1496.4 (803.3)
DBS settings	**L Voltage (V)**	2.7 (1.0)	2.3 (0.8)
	L Pulse width (μsec)	79.3 (19.0)	75.0 (15.6)
	L Frequency (Hz)	131.8 (25.8)	125.4 (18.9)
	R Voltage (V)	2.4 (0.8)	2.2 (0.8)
	R Pulse width (μsec)	72.9 (15.4)	75.7 (21.4)
	R Frequency (Hz)	131.8 (25.8)	125.4 (18.9)
Center of active contact (AC/PC corr, in mm)	**L Lateral, from left**	11.1 (1.1)	10.8 (1.4)
	L Posterior	2.2 (1.6)	1.8 (0.9)
	L Superior	−2.6 (1.9)	−2.5 (1.9)
	R Lateral, from left	−11.2 (1.6)	−11.0 (1.8)
	R Posterior	1.9 (1.8)	2.1 (1.4)
	R Superior	−3.1 (2.0)	−1.6 (4.6)

2.4. Data analyses

Accuracy (as % correct) and reaction times (RTs) were computed for each subject and each condition. RTs were measured from the onset of the second stimulus, and only correct trials were included. Trials with RTs greater or less than 4 standard deviations from the mean were discarded (less than 3% of trials). For the PD cohort, accuracy and RTs were analyzed for effects using a four-factor mixed between/within subject ANOVA (stimulation (2)×distractor present (2)×task type (2)×stimulation order (2)). For the HEC cohort, the analysis involved a two factor mixed between/within subject ANOVA (distractor present (2)×task type (2)). Level of statistical significance was set to be α=0.05. For all statistical comparisons, we used appropriate transformations of the data to conduct ANOVAs. As the accuracy score is essentially a proportion, accuracy data were arcsin transformed prior to statistical tests. As an additional control, we analyzed accuracies using logistic regression and results did not change. RTs were log-transformed prior to statistical analyses (Ratcliff, 1993). Again as an additional control, RT data were also analyzed using medians, and results did not change.

3. Results

3.1. Participant characteristics

Table 1 summarizes demographic data for the PD and HEC cohorts, split by distractor group. The PD and HEC cohorts were matched for age and years of education. Current IQ was higher in the HEC than the PD cohort by 11.9 points, an expected consequence of disease processes. Within each cohort, an equal number of participants were in the distractor or no distractor groups (n=14), and there were no significant differences between these groups for age, years of education, or IQ. This was confirmed by a two factor between subject ANOVA (cohort (PD/HEC)×distractor group (no distractor/distractor)) separately for IQ, education and age. For IQ, there was a main effect of group ($F(1,52)=16.0$, $p < 0.01$). All other main effects and interactions did not reach significance ($p > 0.2$).

Since the most important comparison was whether DBS stimulation differentially affects performance in the distractor vs no distractor groups, Table 2 summarizes disease and treatment factors such as disease duration, time since lead implantation, stimulation settings, and levodopa equivalent dose for the participants of the two distractor groups in the PD cohort. There were no significant differences for any measures between the two groups (two tailed *t*-tests, all $p > 0.2$), suggesting that any differences in performance seen in the distractor vs no distractor groups are not due to baseline differences in disease characteristics, lead location, stimulation settings, Levodopa dose, etc.

3.2. Effects of distractors on AWM performance in healthy elderly controls

As useful baseline data, we examined AWM task performance in a cohort of healthy elderly participants with no reported neurological deficits and no history of neurosurgery. Fig. 2A and B summarizes accuracies and reaction times for the healthy elderly control cohort. For visualization in this and all graphs, accuracies are collapsed across type (emotion/gender). There is no effect of distractor presence on either measure, consistent with the block design and relatively short delay used here, as well as the completely task-irrelevant nature of the distractor, consistent with a previous auditory working memory study in the elderly using a nearly identical design (see discussion; Chao and Knight (1997)). These effects were confirmed by a 2-way mixed within/between subjects ANOVA, task type×distractor group for both accuracy and RT. There was no main effect of distractor group on accuracy or RT ($p > 0.15$, $p > 0.80$ respectively). There was also no significant main effect of task type on accuracy or RT.

3.3. Effects of distractors and STN-DBS on AWM performance

Fig. 3A summarizes AWM accuracies for the PD STN-DBS group for each DBS state (ON vs OFF) and distractor group. Consistent with effects seen above in the HEC cohort, overall accuracy was high, greater than 90% for both the distractor and no distractor groups, and was not significantly affected by stimulation or distractor group. Again, this was probably due to the relatively short maintenance durations used. This

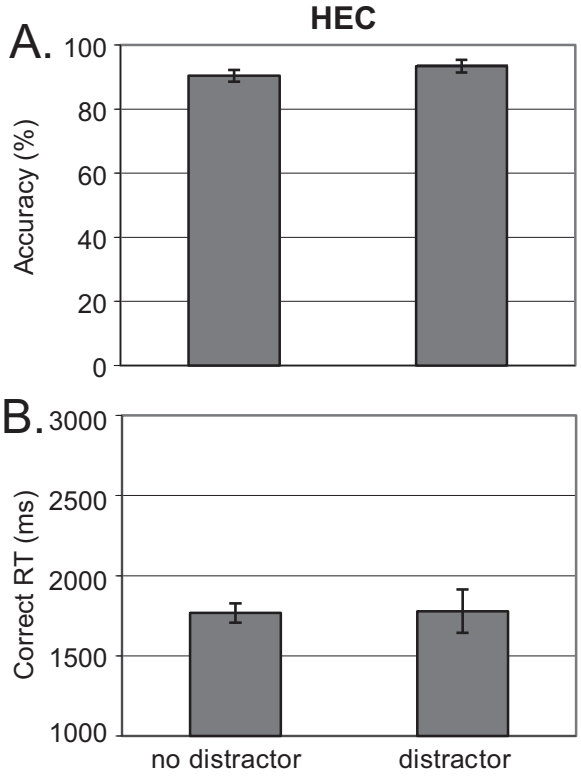

Fig. 2. Auditory working memory performance of the healthy elderly control cohort, divided by distractor group. Performance for the no distractor group is displayed on the left, and for the distractor group is displayed on the right. A. Mean accuracy, in %. B. Mean correct RT from beginning of second stimulus, in ms. No comparisons reach significance. Error bars reflect standard error of the mean.

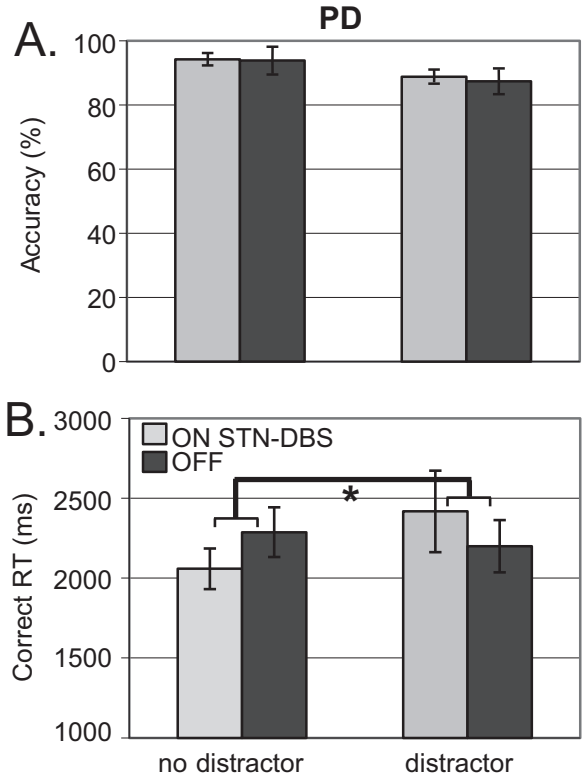

Fig. 3. Auditory working memory performance of the Parkinson's disease cohort ON and OFF STN-DBS. Performance for the no distractor group is displayed on the left, and for the distractor group is displayed on the right. A. Mean accuracy, in %. B. Mean correct RT from beginning of second stimulus, in ms. The star represents the significant interaction of stimulation×distractor presence on RT, no other comparisons reach significance. Error bars reflect standard error of the mean. Error bars in this reflect standard error of the mean, and are computed across individuals to describe variability – the important statistical comparison is within an individual (see text).

was confirmed by a 4 way mixed within/between subjects ANOVA, task type×DBS stimulation×distractor group×stimulation order. There were no main effects of DBS stimulation, distractor group, or stimulation order ($p > 0.2$). A main effect of task type was also not significant. No interactions reached significance except the interaction of stimulation×stimulation order ($F(1,24)=6.62$, $p=0.017$). There was no significant interaction of this with distractor ($p > 0.7$), this effect did not change with distractor presence and was unrelated to the effect of distractors. No other main effects or interactions reached significance.

Fig. 3B summarizes average AWM reaction time performance for the PD STN-DBS cohort for each DBS state (ON vs OFF) and distractor group. In contrast to the accuracy data, there were significant effects of distractor and stimulation on RTs. In the group in which no distractors were present, RTs were generally faster ON STN-DBS, an expected motor benefit of STN-DBS therapy, especially in tasks requiring bimanual responses such as this one (e.g. Klostermann et al., 2010). However, in the group that had distractors during the maintenance period, this speeding is absent and responses are *slower* than OFF STN-DBS. This effect was confirmed by a 4 way mixed within/between subjects ANOVA, task type×DBS stimulation×distractor group×stimulation order. There was a significant interaction of DBS stimulation×distractor group ($F(1,24)=5.46$, $p=0.028$), illustrated with a star in Figs. 3B and 4. Neither stimulation nor distractor group reached significance as a main effect ($p > 0.4$). There was a significant main effect of task type, in which the emotion condition was generally slower than the gender condition ($F(1,24)=14.65$, $p=0.001$). No other main effects or interactions reached significance. Since there were no significant interactions with task type, particularly no interactions with stimulation or distractor group ($p > 0.4$), task type did not affect whether distractors or DBS stimulation (or their interaction) affected response times. Thus, RT performance is affected similarly regardless of task type, and data across types were collapsed for visualization.

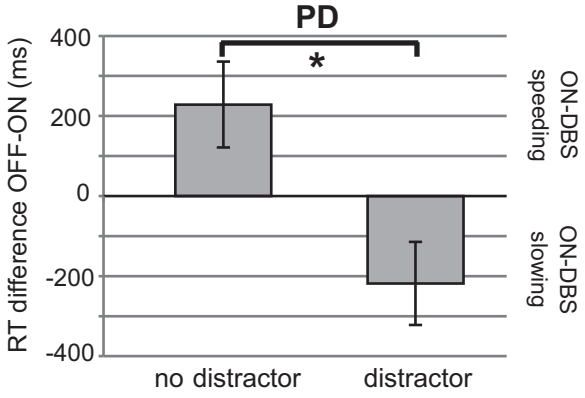

Fig. 4. Mean of individual-based RT differences between ON and OFF STN-DBS. Values above 0 indicate RT speeding ON-DBS relative to OFF-DBS, an expected therapeutic effect of STN-DBS. The star represents the significant interaction of stimulation×distractor presence on RT. Error bars reflect standard error of the mean.

One advantage of STN-DBS to assay basal ganglia function is that it allows an examination of effects in the ON-DBS relative to the OFF-DBS condition *within an individual*. To better visualize these effects, Fig. 4 shows the mean and SEM of individual subject's RT differences in the ON vs OFF-DBS conditions as a function of distractor group. The star indicates the significant interaction of distractor group and stimulation, described above. In the no distractor group, there is an average speeding of 200 ms (positive values), consistent with the therapeutic effects of STN-DBS on motor processes in PD. However, when distractors are introduced during the delay of an otherwise

identical task, speeding is abolished and responses are slowed relative to the OFF-DBS condition, indicating that processing in this AWM task is slowed down by distractors.

4. Discussion

In this study, we find that modulation of the basal ganglia using STN-DBS has an effect on auditory WM performance, specifically in the group presented with distractors during the maintenance period. This effect is seen as a marked slowing of RTs in the presence of distractors in the ON-DBS condition. This is in contrast to the well-established speeding of RTs seen for the ON-DBS condition in both the no distractor group and in other studies involving choice tasks. The observation that the simple addition of predictable, task irrelevant distractors abolished normal RT speeding is indeed surprising, and suggests that the distractors impaired WM processing by lengthening processing time needed to complete the decision. These distractor-specific effects nicely mirror results from studies examining visuospatial WM in patients with lesions of the basal ganglia (Baier et al., 2010; Voytek and Knight, 2010). Taken together, disruptions of the basal ganglia appear to render WM processes susceptible to distractors in both the visuospatial and non-spatial auditory domains.

In addition to demonstrating basal ganglia involvement in distractor interference in AWM, these results suggest the locus of the impairment most likely involves maintenance of the mnemonic trace, and not at other stages, such as encoding or response execution. Both the task type manipulation, as well as the nature of the distractor, suggest the distractor-based interference of AWM is unlikely to affect the encoding stage. The emotion condition was slower than the gender condition, no doubt because a gender judgment can be made rapidly based on the frequency of the exemplar, especially in a restricted set such as this. Thus the manipulation of task type allowed us to selectively affect the relative timing of the encoding stage. Since task type effects were dissociated from the effect of basal ganglia modulation (i.e. no interaction of task type with distractor×stimulation), the distractor based interference is unlikely to be at the encoding stage. In addition, the nature of the distractor in this study minimizes its potential effects on encoding. In previous studies examining basal ganglia effects on WM performance in the visuospatial domain, distractors were introduced at the same time as the to-be-encoded stimulus, potentially introducing interference at multiple stages (Baier et al., 2010; Voytek and Knight, 2010). Here, the distractors are introduced after the first stimulus presentation during the delay, when presumably encoding and categorization are mostly complete.

Moreover, this distractor-based interference on AWM is unlikely to be an effect at the response mapping or execution stages. First, it is unlikely that these decision-related stages would be affected by completely predictable, task-irrelevant distractors that disappear before the second stimulus is presented and a decision must be made. Second, the nature of RT effects in the ON-DBS condition suggests the distractor-based interference effect is unlikely at the response execution phase. In studies examining the RT consequences of STN-DBS, RT effects in the ON-DBS condition are typically attributed to speeding of the motor preparation stage (Ellrichmann et al., 2008; Klostermann et al., 2010; Temel et al., 2006; van den Wildenberg et al., 2006). Logically, if the encoding portion appeared untouched by the distractor manipulation in the ON-DBS condition, and RTs would be expected to be *faster* at the motor preparation stage in the ON-DBS condition, then the increase in RTs is most likely due to interference of the distractors on an intervening stage. We therefore believe the deleterious effect of basal ganglia pertubation on performance in the presence of distractors is most likely during maintenance of the memory trace. That the effects of distractors manifest as RT slowing and not accuracy impairment is most likely due to the blocked design and relatively short maintenance durations used. Based on a previous study, accuracy decrements would only be expected with longer delays, at least twice as long as what was used in this task (Chao and Knight, 1997). Even with the longer delays used in that study, accuracy decrements are minor, so we chose to avoid limiting confounds due to exhaustion from task length in the PD population. Thus, we did not expect, nor see, accuracy deficits, and the use of RT effects to index interference in the WM domain is a robust measure entirely consistent with its use in other studies of interference in visuospatial WM (e.g. Cools et al., 2010).

The strength of our approach is to the ability to compare basal ganglia effects within a single subject via reversible STN-DBS, rather than relying on different groups of lesion patients, but there remain caveats to this approach that are also shared by lesion studies. Similar to lesion studies, STN-DBS has significant effects across the brain, inducing changes in activation both in the basal ganglia as well as downstream areas such as motor, premotor, and also the prefrontal areas implicated in memory maintenance (Hershey et al., 2003; Min et al., 2012; Sestini et al., 2005; Stefurak et al., 2003). However, STN-DBS avoids previous limitations inherent in lesion studies such as heterogeneities in lesion location, and confounds due to brain plasticity during recovery. This within subject approach also accounts for confounding factors such as medication or disease state, as these factors are controlled for under these experimental conditions.

Unfortunately, the burden placed on the PD patients by task length prevented us from running all distractor conditions within a single subject. Therefore, we report the relative speeding of RTs within individual subjects, which differs for two groups exposed to distractors vs no distractors. A number of reasons suggest these effects are due to the presence of distractors and not group differences. First, the RT effects in the no distractor group mirror the well-established ON STN-DBS speeding of RTs seen in choice tasks, particularly when bimanual responses are used (Ellrichmann et al., 2008; Klostermann et al., 2010; Temel et al., 2006; van den Wildenberg et al., 2006). In addition, the relative slowing in the presence of distractors in the ON-DBS condition is unlikely to be due to considerable group differences in disease status, electrode location, stimulation parameters, or medication, as the groups are matched for these factors.

The current study expands earlier work on visuospatial memory (Baier et al., 2010; Voytek and Knight, 2010) in two important dimensions. First, it demonstrates basal ganglia involvement in WM along a non-spatial feature domain. Second, it confirms the supramodal nature of the basal ganglia involvement in WM, until now only hypothesized. Though subjects were not explicitly instructed to use auditory memory in this study (vs another approach such as visuospatial mental imagery), these distractor most likely act upon auditory-verbal rehearsal process either of the stimulus itself or its label (e.g. “happy”), since encoding and recall of phonological information in a short-term phonological store appears to be relatively automatic. Indeed, the pervasive and automatic nature of auditory rehearsal for short term recall in humans is thought to explain why irrelevant tones or speech interfere with memory, even when items are presented visually (Jones and Macken, 1993; Salame and Baddeley, 1982).

In addition to supporting the basal ganglia's role as a domain-general WM resource, these results additionally shed light on the currently contentious question of whether the clinical application of STN-DBS affects visuospatial WM. Though PD patients generally show mild to moderate deficits in visuospatial WM compared to aged-matched controls (e.g. Lee et al., 2010), there have been conflicting accounts of the effects of STN-DBS state on spatial WM performance (Hershey et al., 2008; Mollion et al., 2011; Selzler et al., 2013; Ventre-Dominey et al., 2014), though even in the absence of behavioral effects, ERP components indexing WM processes are affected by STN-DBS (Selzler et al., 2013). Across these studies, the effect of distractors was not specifically or systematically examined, which may help in part to explain the inconsistencies in finding clear spatial WM deficits. Indeed, STN-DBS effects on visuospatial WM performance appear to be strongest when distractor suppression is necessary, and this should be taken into account when designing future studies. These distractor-

dependent effects are intriguingly similar to the increased distractor susceptibility of visual WM seen in PD patients ON Levodopa replacement medication vs OFF medication (Cools et al., 2010; Moustafa et al., 2008), though the differences between STN-DBS and levodopa replacement therapy make direct comparison of mechanisms difficult.

This account of basal ganglia filtering of distractors from working memory gives support to the hypothesized role of the basal ganglia in modulating prefrontal function, but specific mechanisms need to be established. The basal ganglia are extensively connected to the prefrontal cortex via fronto-striatal loops (Alexander et al., 1986), and have been hypothesized to be critical in the updating of WM processes in computational models (e.g. Hazy et al., 2006). In an AWM task very similar to the one used in this study, patients with prefrontal lesions had trouble maintaining inhibition of tone distractors during the delay (Chao and Knight, 1998). Based on this, we speculate that the AWM impairment seen in the current study results from improper updating of prefrontal representations. The delay-period distractors are somehow not suppressed appropriately, either at the level of sensory or prefrontal cortex, and are accidentally gated into WM, disrupting the mnemonic trace. Future studies need to explore exactly how and where this “gatekeeper” role is instantiated, and whether this mechanism is conserved across sensory systems.

In conclusion, our finding of deficits in auditory WM performance in STN-DBS participants expands our understanding of the role of the basal ganglia in distractor suppression, a core cognitive mechanism. Using a powerful reversible modulation approach afforded by deep brain stimulation of the subthalamic nucleus, we find that basal ganglia pertubation selectively impairs auditory WM performance in the presence of task-irrelevant distractors. Combined with recent observations of the role of the basal ganglia in visuospatial processing, this suggests the basal ganglia filtering mechanism is modality independent. This dovetails nicely with dominant accounts of working memory that posit the existence of amodal “central” resources that operate on both visual and auditory working memory processes such as Baddeley's central executive (Baddeley, 2007) and Cowan's focus of attention (Cowan, 1999). Our results suggest that the filtering by the basal ganglia may play a central role in supporting these central, executive resources. These data add to our growing appreciation of the role of the basal ganglia in a broad array of cognitive processes. This circuitry has long been implicated in the focused selection of movements, particularly selection and filtering out unnecessary competing motor plans (e.g. Nambu, 2008). Given the basal ganglia's rich interconnections with frontal cortex, and our growing understanding of their role in nonmotor processes, they seem ideally placed to mediate a wide variety of suppressive/inhibitory processes, and may prove to be a critical node in both movement and psychiatric disorders.

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