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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.

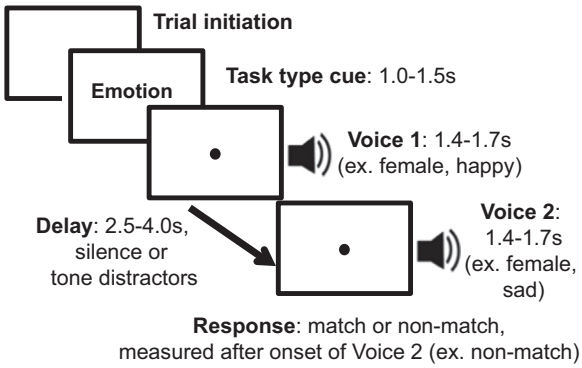

Fig. 1. Auditory delayed match to sample task design. Subjects initiated each trial with a keypress, after which a task type cue (emotion or gender) was displayed for 1–1.5 s. This indicated the feature of the nonverbal voice clip to be remembered. A fixation spot appeared and the first voice stimulus 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.