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Thalamic cholinergic innervation makes a specific bottom-up contribution to signal detection: Evidence from Parkinson's Disease patients with defined cholinergic losses

Kamin Kim[1], **Martijn L.T.M. Müller**[3,5], **Nicolaas I. Bohnen**[3,4,5,6], **Martin Sarter**[1,2,5], and **Cindy Lustig**[1,2,5]

[1]Department of Psychology, University of Michigan, Ann Arbor, MI, 48109

[2]Neuroscience Program, University of Michigan, Ann Arbor, MI, 48109

[3]Department of Radiology, University of Michigan, Ann Arbor, MI, 48109

[4]Department of Neurology, University of Michigan, Ann Arbor, MI, 48109

[5]University of Michigan Morris K. Udall Center of Excellence for Parkinson's Disease Research, Ann Arbor, MI, 48109

[6]Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, MI, 48109

Abstract

Successful behavior depends on the ability to detect and respond to relevant cues, especially under challenging conditions. This essential component of attention has been hypothesized to be mediated by multiple neuromodulator systems, but the contributions of individual systems (e.g., cholinergic, dopaminergic) have remained unclear. The present study addresses this issue by leveraging individual variation in regionally-specific cholinergic denervation in Parkinson's disease (PD) patients, while controlling for variation in dopaminergic denervation. Patients whose dopaminergic and cholinergic nerve terminal integrity had been previously assessed using Positron Emission Tomography (Bohnen et al., 2012) and controls were tested in a signal detection task that manipulates attentional-perceptual challenge and has been used extensively in both rodents and humans to investigate the cholinergic system's role in responding to such challenges (Demeter et al., 2008; McGaughy and Sarter, 1995; see Hasselmo & Sarter 2011 for review). In simple correlation analyses, measures of midbrain dopaminergic, cortical and thalamic cholinergic innervation all predicted preserved signal detection under challenge. However, regression analyses also controlling for age, disease severity, and other variables showed that the only significant independent neurotransmitter-related predictor over and above the other variables in the model was

Address correspondence to: Cindy Lustig, Psychology Department, University of Michigan, Ann Arbor, MI 48109, Phone: 734-647-6925, clustig@umich.edu, Kamin Kim, University of Texas Medical School at Houston, 6431 Fannin Street, MSB Suite G550D, Houston, TX 77030, Phone: 713-500-5208, um.kaminkim@gmail.com.
Present affiliation: Kamin Kim is currently affiliated with University of Texas Medical School at Houston, Houston, TX, 77030.

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thalamic cholinergic integrity. Furthermore, thalamic cholinergic innervation exclusively predicted hits, not correct rejections, indicating a specific contribution to bottom-up salience processing. These results help define regionally-specific contributions of cholinergic function to different aspects of attention and behavior.

1.1 Introduction

Successful behavior, especially in challenging conditions, requires both the top-down guidance of perception and action in accordance with current goals and successful bottom-up processing of the incoming stimuli relevant to those goals. Imagine driving in an unfamiliar neighborhood, trying to find the house of a colleague who has invited you to a dinner party. You will likely devote more attention and cognitive control to your task if a thunderstorm breaks out than if it is a bright and sunny day, perhaps even turning off the radio or stopping conversation to do so. Regardless of the weather or how focused you are finding that address, you will have better success if your host's house number is indicated by a large black sign with white numbers hanging below the mailbox than if it is indicated by small white numbers painted on the silver-colored metal of the mailbox itself – especially if you're not wearing your glasses. While attention to our goals is important for guiding behavior, so is our ability to efficiently process stimuli relevant to those goals. The present study leverages individual variation in the denervation of cortical and thalamic cholinergic pathways in patients with Parkinson's disease (PD) to examine the contributions of those pathways to goal-driven (top-down) versus stimulus-driven (bottom-up) processing.

The progressive decline of dopaminergic neurons in the striatum leading to motor symptoms is a defining feature of PD. However, there is increasing recognition that declines in other neuromodulatory systems likely underlie many of the non-motor symptoms that are not remediated by dopaminergic treatments (see Brichta et al., 2013; Müller and Bohnen, 2013 recent reviews). In the cognitive domain, the dual-syndrome hypothesis of cognitive impairment in PD suggests that dopaminergic denervation primarily leads to executive deficits, and cholinergic decline leads to visuospatial deficits and dementia (Kehagia et al., 2013). However, cortical cholinergic deficits have been shown to predict reduced executive, attention, and verbal learning scores in PD patients without dementia (Bohnen et al., 2012, 2015), suggesting that cholinergic denervation may be associated with PD-related executive deficits more directly. An additional subset of PD patients also has denervation of brainstem-thalamic cholinergic nerve terminals. In contrast to the cognitive deficits seen with cortical cholinergic denervation, thalamic cholinergic denervation does not appear to contribute to poor performance on cognitive neuropsychological batteries. Instead, it is linked to an increased incidence of falls and risky driving, hypothesized to reflect poor integration of sensory cues (Bohnen et al., 2012; Müller et al., 2013; Weathers et al., 2014).

The differences in the behavioral deficits associated with cortical versus thalamic cholinergic denervation suggest that the cortical subsystem may be more involved in cognitive control and top-down processing, whereas the thalamic system may be more involved in sensory processing and bottom-up attention. Indirect support for the idea that the cholinergic system makes important contributions to both top-down and bottom-up processing, also comes from

studies of healthy humans, although most such investigations have tended to focus on the top-down component (e.g., Boucart et al., 2015; Breckel et al., 2015; Danielmeier et al., 2015; Sarter et al., 2016; Silver et al., 2008; Vossel et al., 2014; see reviews by Nees, 2015; Newhouse & Dumas, 2015; Thiele, 2013; van Amselsvoort & Hernaus, 2016). For example, a recent Activation Likelihood Estimation (ALE) meta-analysis by Sutherland et al. (2015) found that nicotinic acetylcholine receptor agonists increased activity in lateral frontoparietal regions associated with cognitive control, as well as thalamus and cuneus, decreased activity in other regions more associated with task implementation, and increased the (below-baseline) de-activation of typical default-network regions. Most of these studies involved visual attention or working memory. The authors suggested that, in correspondence with the behavioral effects, the patterns they found likely reflected increased engagement of top-down, executive control paired with increased efficiency of task processing, potentially enhanced by a reduction in distraction from task-unrelated default-mode processes.

More detailed insight into the temporally- and spatially-specific ways in which the cholinergic system acts to impact top-down processing and bottom-up processing and their interactions derives from recent rodent studies suggesting a distinction between a relatively long timescale (seconds-to-minutes) frontoparietal subsystem mediating top-down processing and cognitive control versus more transient (milliseconds to seconds) thalamocortical glutamatergic-cholinergic signaling that is more directly involved in signal detection (see reviews by Hasselmo and Sarter, 2011; Lee and Dan, 2012; Sarter et al., 2014; Zaborszky et al., 2015). The frontoparietal system has been demonstrated to be especially important for maintaining performance under challenging conditions (Gill et al., 2000; St. Peters et al., 2011), and is thought to help support goal-driven attention and cognitive control via the reinforcement of relevant task (e.g., Paolone et al., 2013b; Sarter et al., in press). In contrast, transient thalamocortical glutamatergic-cholinergic signaling mediates trial-level shifts from monitoring for the signal to the processes involved in successfully detecting and responding to it (Hirata and Castro-Alamancos, 2010; Howe et al., 2013; Parikh et al., 2007; see Gritton et al., 2016 for causal evidence from optogenetics).

To test the link between the rodent and human findings, we have previously used a signal detection and perceptual-challenge manipulation task that closely corresponds to that used in the rodent studies described above to test both healthy young adults (Berry et al., in revision; Demeter et al., 2008; Demeter et al., 2011; Howe et al., 2013) and a genetic population thought to have a reduced ability to sustain the longer-timescale frontoparietal cholinergic signals (Berry et al., 2015; see Lustig et al., 2013 for discussion of psychometric properties, correspondence between rodent and human findings, and relation to other translational tasks). In healthy young adults, fMRI studies consistently find right-lateralized fronto-parietal increases in activation in response to the challenge manipulation that parallel the rodent findings of right-lateralized fronto parietal cholinergic activity and correlate with behavior (Berry et al., in revision; Demeter et al., 2011). The hypothesis that the fMRI activation patterns seen in humans correspond to the increases in acetylcholine (ACh) release seen in rodents is further supported by demonstrations that both mice genetically modified to reduce expression of the choline high affinity transporter (CHT) and humans with a genetic polymorphism thought to reduce the efficiency of the CHT fail to show the

typical performance-associated increases in right prefrontal acetylcholine (mice) and activation (humans) (Berry et al., 2015; Paolone et al., 2013b; Parikh et al., 2013).

Intriguingly, although mice and humans with reduced CHT function fail to show challenge-related increases in frontoparietal ACh (mice) and fMRI activation (humans), they do not show impaired signal detection (Berry et al., 2015; Paolone et al., 2013b; Parikh et al., 2013). This contrasts with the increased vulnerability to distractors with strong bottom-up salience demonstrated in humans with genetically-reduced CHT function (Berry et al., 2014; see also Neumann et al., 2006). Genetic variation in the CHT is thought to primarily affect the ability to sustain a cholinergic response, as it impacts the rate at which ACh can be synthesized and released (Bazalakova & Blakely, 2006; Ferguson & Blakely, 2004), and may leave the transient response that is more strongly associated with the thalamus relatively unaffected. Thus, these data suggest that basal forebrain-cortical pathways may be more strongly associated with the sustained top-down control needed to resist salient bottom-up distractors, whereas the more transient thalamic response may be more important for detecting and responding to salient inputs such as the sudden-onset signal used in the rodent and human studies described above.

While these previous studies are suggestive, both behavior and fMRI measures of activation are multiply determined, both drugs and genetics typically have systemic effects throughout the brain and periphery, making it difficult to isolate how different pathways contribute to specific cognitive outcomes. Therefore, in the present study we leveraged individual differences in the degree of cortical and thalamic cholinergic denervation in Parkinson's patients taking dopaminergic medication (and also controlling statistically for measures of both dopaminergic denervation) to determine the contributions of these different systems to signal detection under challenge. Specifically, we hypothesized that the thalamic pathway should be more associated with preserved signal detection, and specifically with hits (correct detections of the target signal). We first provide a comparison of the performance of the patients versus healthy controls, to provide a sense for patients' function/level of impairment, and then use multiple regression analyses to estimate the independent contributions of caudate-dopaminergic, cortical-cholinergic, and thalamic-cholinergic pathways.

2.1 Materials and Methods

2.1.1 Participants

All experimental procedures were approved by the University of Michigan's Institutional Review Board, and were fully described to the participants before they consented to take part in the study. PD patients were recruited from an existing pool who had previously undergone cholinergic and dopaminergic PET scanning within one year of the present study (see description below; Bohnen et al., 2012). Healthy control (HC) participants were recruited from the Ann Arbor community to be age-, gender-, and education-matched to the PD patients and did not undergo PET scanning. PD patients were compensated for their time at a rate of $25/hour and HC participants were compensated at a rate of $10-12/hour (the payment rate went up for HC during data collection).

Inclusion criteria for the present study included the absence of a history of seizures, severe brain injury, and neurological disorders other than PD. The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) was used to screen for dementia. The Extended Range Vocabulary Test Version 3 (ERVT; Educational Testing Services, 1976) was used to screen out participants who might be unable or unwilling to understand and follow instructions; all participants scored above the minimum threshold of 9/48 correct responses. All participants reported normal or corrected-to-normal vision and hearing.

A total of 19 PD patients and 19 healthy age-, gender-, and education-matched controls (healthy controls, HC) completed the study. Age and education matches were within a +3-year margin of error within a pair. Two patients and their counterpart control subjects were eliminated from final analysis due to outlying (ceiling/floor) performance that distorted the results, especially for the regression analyses: First, one patient reported being an extraordinary case in attention skill due to prior training as a Morse-code decoder, and showed ceiling performance across all conditions. Second, one patient failed to follow instructions and treated the response tone as the target signal, resulting in very long reaction times and a high percentage of omissions and false alarms. Thus, final analyses included 17 PD patients (6 female; mean age = 63.12 age range 52-85) and 17 healthy older adults (6 female; mean age = 64.24; age range 54-83).

On average, motor symptom duration of PD patients was 5.0 years (SD = 3.78), and the median Hoehn and Yahr PD severity score, assessed in the dopaminergic “off” state, was 2.5 (SD = 0.43; 1-5 scale, scores of 4 or more indicate severe disability; median reported as it is an ordinal scale; Hoehn and Yahr, 1967). All patients except one were on dopaminergic treatment (average levodopa equivalent daily dose (LEDD; Tomlinson et al., 2010) for those on dopaminergic treatment was 615 mg, range: 100-1596 mg). No patient was taking any cholinergic or anti-cholinergic medications. Three patients were also being pharmacologically treated for anxiety, 1 for depression, 2 for comorbid anxiety and depression, and 1 for comorbid anxiety, depression, and panic disorder. We did not exclude these patients because depression and/or anxiety are frequently co-morbid with PD, occurring in 40-50% of patients (Cummings, 1992; Tandberg et al., 1996), and thus can be considered typical of the disorder. One HC reported a previous diagnosis of depression but was not currently in treatment.

Participants also completed standardized self-report and neuropsychological tests evaluating the ability to maintain independent function in everyday life and affective, cognitive, and motor function. The measures included the Instrumental Activities of Daily Living scale (IADL; Lawton and Brody, 1969), Apathy Evaluation Scale (AES; Glenn, 2005), Beck Depression Inventory II (BDI-II, Beck et al., 1961), and Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS; copyright: Movement Disorder Society; Goetz et al., 2007).

2.1.2 SAT/dSAT Task

The task and procedures were similar to those used in our previous papers with healthy and patient populations (e.g., Berry et al., 2015; Demeter et al., 2008, 2011, 2013; Howe et al., 2013; see Lustig et al., 2013 and Nuechterlein et al., 2009 for discussion of psychometrics

and translational validity). Stimulus presentation and response recording were conducted on a HP laptop (Probook 6570b) with a 34.5×19.5 cm screen (1024×768 screen resolution, 60Hz refresh rate), using E-prime software (Psychology Software tools; http://www.pstnet.com/eprime.cfm; Version 2.0).

The task and conditions are outlined in Figure 1. Each task trial consisted of a variable-duration (1-3 sec) monitoring period, at the end of which a variable-duration (17-67 ms) signal did (signal event) or did not (nonsignal event) occur. The durations of the monitoring period and signal were varied unpredictably to increase uncertainty and demands on attention (Demeter et al., 2008; McGaughy and Sarter, 1995). On standard, no-distractor (SAT) trials, the background was a static whole-field display of the "silver" color in E-prime. For trials in the challenge (dSAT) condition, the silver background alternated with a black background at a 10 Hz rate, creating a global distractor. Regardless of condition (SAT or dSAT), the signal event was presented against the silver background and consisted of a 3.5 × 3.5 mm centrally-presented square in the standard "gray" color in E-prime. The signal was presented on 50% of trials in both the SAT and dSAT conditions. 500 ms after the non/signal event, participants were cued to respond by a 700 ms low-frequency auditory tone marking the beginning of the 1000 ms response window. During this window, participants were to respond with one key if a signal had occurred on that trial, another key if it had not. (Left or right index finger keypresses to 'z' or '/' keys on the standard laptop keyboard; left/right key assignments to non/signal events were counterbalanced across participants within a group.) Requiring responses for non-signal trials allowed us to distinguish true "misses" (failures to detect the signal) from "omissions" (failures to respond). Correct responses were given positive feedback in the form of a 700 ms high-frequency tone signaling an increase in the monetary reward; no feedback was given for incorrect or late responses. Participants received one cent for each percentage of correct responses, and were penalized 5 cents for each percentage of miss trials.

Consistent with our recent event-related fMRI and ERP studies (Berry et al., 2012a, 2012b, 2015), SAT and dSAT trials were presented intermixed with fixation trials that did not require an overt response. Fixation trials consisted of a gray fixation cross presented on the alternating silver/black background, similar to distractor trials, and were of variable duration, like task trials. Participants were instructed to relax and keep their eyes on the fixation cross during these trials.

Before beginning the runs used for data analyses, participants were first given task instruction and practice. The experimenter explained what a trial would be like with the aid of a printed-out diagram of the sequence of events in a single SAT trial. Once participants understood what a trial involved, they were shown examples on the computer screen and the performance-based reward was explained. Next, participants completed a one-minute long practice block with SAT trials intermixed with fixation trials on a static background. The practice block was repeated until they reached at least a 60% accuracy rate. Once participants met this criterion, the experimenter explained the distractor condition and showed an example on the screen. Participants then completed a slightly longer practice block (about 1.5 minutes) that included all trial types – SAT, dSAT, and fixation trials - until they reached at least 60% accuracy. Patients and controls did not differ from each other in

the number of trials to reach criterion for either the SAT (HC mean = 1.6, PD mean = 1.8) or mixed-trial (HC mean = 1.5, PD mean = 1.4) conditions, both $t < 1$.

Participants then completed 9 task runs, each consisting of 75 trials and lasting approximately 5 minutes. Runs 1, 5, and 9 were SAT runs consisting of 50 SAT trials (25 signal and 25 non-signal trials) and 25 fixation trials. These runs were used to investigate a separate question about sequence effects (cf., Howe et al., 2013) and are not reported here. The other six runs are the focus of the present paper and included both SAT and dSAT trials, allowing us to investigate the impact of the challenge imposed by the dSAT condition. Each run consisted of 15 trials each of SAT signal, SAT nonsignal, dSAT signal, dSAT nonsignal, and fixation (75 trials total). Trial types were pseudorandomly intermixed within each run so that each trial type followed each trial type an equal number of times.

2.1.3 Positron Emission Tomography (PET)

For the PD patients, Positron Emission Tomography (PET) scan data on dopaminergic and cholinergic nerve terminal integrity were obtained from previous studies (Bohnen et al., 2012). (HC were not scanned, but were chosen to be closely matched to patients in age, gender, and education.) Patients came in for dopaminergic PET scanning in the dopaminergic off-state, i.e. after abstaining from dopaminergic drugs overnight. The PET scans were obtained prior to the behavioral testing session (median .83 yrs; SD = .55).

The integrity of dopaminergic nigrostriatal nerve terminals was measured with [^{11}C]dihydrotetrabenazine (DTBZ), a vesicular monoamine transporter type 2 analogue (VMAT2; see Bohnen et al., 2012 for details on DTBZ preparation, injection, and scanning parameters). The primary outcome parameter is DTBZ distribution volume ratio (DVR, Bohnen et al., 2009). Greater DVR indicates better dopaminergic terminal function. DTBZ DVR was measured for caudate and putamen. Mean DVR values for PD patients in the present study were M = 2.2974, SD = .3579 for caudate, M = 1.9054, SD = .3057 for putamen; M = 2.102, SD = .3058 for striatum (average over caudate and putamen). Values reported from a larger sample in Bohnen et al., 2012 were striatum (average over putamen and caudate) DVR M = 1.93, SD = 0.27 for PD patients and M = 3.03, SD = 0.31 for HC.

Cholinergic function was estimated using radio-labeled acetylcholine analogue [^{11}C]methyl-4-piperidinyl propionate (PMP) PET, which measures acetylcholinesterase (AChE) activity. PMP PET scans were performed in the dopaminergic medication ‘on’ state. Details on PMP preparation, injection, and scanning parameters have been described previously (Bohnen et al. 2012). The primary outcome parameter is AChE hydrolysis rate (k_3; min^{-1}), with a higher k_3 indicating higher cholinergic nerve terminal integrity. Although PMP PET is an indirect measure of cholinergic activity, it has been validated in both rodent and primate models (e.g, Kilbourn et al., 1996; Selden et al., 1998) as well as in humans (e.g., Kuhl et al., 1996; 1999). We are not aware of any evidence suggesting that dopaminergic therapy affects brain AChE hydrolysis rates. To the extent that dopaminergic therapy may affect cholinergic activity, its effects may be more likely to be on the availability of nicotinic or muscarinic receptors rather than AChE, given its long half-life of approximately 2.8 days (Wenthold et al., 1974).

AChE k_3 was measured for the cortex and thalamus separately. Cortical measures are used to index cholinergic nerve terminal integrity of the basal forebrain (including the nucleus basalis of Meynert), whereas thalamic measures primarily (though not exclusively) reflect integrity in the brainstem pedunculopontine nucleus (Bohnen and Albin, 2011; Bohnen et al., 2012; see review by Varela, 2014). Mean k3 values for PD patients in the present study were cortical M = .0246, SD = .0031; thalamic M = .0541, SD = .0064. For comparison, the values reported by Bohnen et al. (2012) were HC: cortical M = .0263, SD = .0027; thalamic M = .0599, SD = .0074; PD: cortical M = .0236, SD = .0027; thalamic M = .0542, SD = .0056).

3.1 Procedure

At the beginning of the experimental session, participants first completed informed consent procedures and a health and demographic information questionnaire. Then they completed the dSAT and another computerized task that was part of a different study and took approximately one hour. The order of the two computerized tasks was counterbalanced across subjects. After completing the two computerized-tasks, participants were given the ERVT, the Edinburgh handedness Inventory (Oldfield, 1971), and 36 items from the Imaginal Processes Inventory (IPI) questionnaire (Singer and Antrobus, 1970). The IPI items included the Poor Attentional Control (PAC) scale (Huba et al., 1982) and its subscales for boredom, mind-wandering, and distractibility.

In a separate session, participants completed the IADL (Lawton and Brody, 1969), AES (Glenn, 2005), BDI-II (Beck et al., 1961), MoCA (Nasreddine et al., 2005), and MDS-UPDRS (Goetz et al., 2007). PD participants were additionally examined for H&Y severity scale by the neurologist (NB). Motor examination of the PD patients by the neurologist, which was performed in a separate session, was performed in the dopaminergic “off” state and included H&Y staging and MDS-UPDRS rating. One limitation of the study is that we do not have motor and cognitive scores collected both at the time of the PET scan and this behavioral session. This might have allowed us to assess changes in those scores that would add noise to the relationship between the PET values and behavioral performance. However, Lawson et al. (2016) did not find systematic changes in either motor or cognitive scores at either 18 or 36 months in patients with similar MoCA (26.2 vs 27.2) scores as in the current study. This suggests these scores likely stay stable during the time period in question here.

4.1 Statistical Analysis

In keeping with previous work in both humans and animals, SAT score was used as the primary behavioral measure of signal detection (SAT score = (H – FA) / [2× (H + FA) – (H + FA)^2], e.g., Berry et al., 2015; Demeter et al., 2008, 2011, 2013; St. Peters, 2011). The advantage of SAT score over other signal-detection indices such as d' is that it does not rely on assumptions about the variance of positive and negative responses. In contrast, d' assumes equal variance of positive and negative responses, an assumption which is frequently violated (Frey and Colliver, 1973). The SAT score ranges from -1.0 (100% incorrect performance; all misses and false alarms) to +1.0 (100% correct performance; all hits and correct rejections).

To test the potential effects of the distractor condition and/or disease status (HC vs. PD) on signal detection, mixed-design ANOVAs were conducted on the SAT score with condition (SAT, dSAT) as the within-subject variable and the group (PD/HC) as the between-subject variable. To illustrate the contrast between patients with and without cholinergic deficits relative to healthy controls, we also conducted follow-up ANOVAs adding low versus high cholinergic status as an additional factor.

Bohnen et al. (2012) suggested using the lowest 5th percentile of the k3 values from their healthy older adult participants to establish the cut off for “normal” versus “low” cholinergic innervation. For the cortical ANOVA, the PD patients (and their counterpart controls) were divided into “normal” or “low” cortical cholinergic groups based on the cutoff value (cortical k3 = 0.022645) as derived from the healthy controls reported in Bohnen et al. (2012). Thus, in the present sample, PD patients with cortical k3 values of 0.022645 or above and their healthy control counterparts (13 pairs) were assigned to the “normal cortical cholinergic” group, whereas PD patients with cortical k3 values smaller than 0.022645 and their healthy control counterparts (4 pairs) were assigned to the “low cortical cholinergic” group. For the thalamic ANOVA, only one patient fell below the 5th percentile (thalamic k3 = 0.049001) cutoff used by Bohnen et al. Therefore, to provide an equitable and similarly-powered comparison with the cortical ANOVA, for this analysis we likewise used the 13-highest vs 4-lowest split to define the groups. It should be noted that, since several of the “low” patients fall above the 5th percentile cutoff, this provides a conservative test of the hypothesis that low thalamic cholinergic innervation leads to performance impairment. All ANOVA analyses in the study met the sphericity assumption. Independent-sample t-tests were used for follow-up comparisons.

As effect sizes, we report Cohen's d for t-tests, and generalized eta squared (η^2_G, Olejnik and Algina, 2003) for repeated measures ANOVAs. Generalized eta squared typically provides smaller values than the eta squared (η^2) or partial eta squared (η^2_p) values that are automatically generated by SPSS and other statistical packages (and which are thus more frequently reported), but is considered preferable as it as it allows comparison of effect size across studies, including across between-subjects and within-subjects designs (Bakeman 2005; Fitz et al., 2012).

The categorical comparisons provided by the ANOVA analyses illustrate how patients of different cholinergic status compare to healthy controls. However, these are presented primarily for descriptive purposes and potential clinical relevance. Our main hypotheses regarding the contribution of cortical versus thalamic cholinergic pathways to signal detection under challenge were tested using continuous (correlation, regression) analyses within the patient group. Bivariate correlation analyses were used to provide an initial picture of the relationships between the behavioral and neural measures, followed by hierarchical multiple regression to evaluate how specific neural measures uniquely predicted performance over and above potentially shared variance with other measures (e.g., to evaluate whether thalamic k3 made unique contributions over and above any shared contributions with cortical k3). Effect sizes are reported as Pearson's r for bivariate correlations, standardized beta coefficient for multiple regression. G*power software (v 3.1., Faul et al., 2007; 2009) was used to estimate the power of multiple regression.

5.1 Results

5.1.1 Demographic, questionnaire, and neuropsychological data

Table 1 provides the demographic information, neuropsychological test results, and overall performance of the PD patients and healthy controls (HC). The PD and HC groups were comparable in age, years of education, verbal ability (ERVT), general cognitive function (MoCA), instrumental activities of daily living (IADL), and the apathy evaluation scale (AES). However, PD patients had significantly higher scores on the Poor Attentional Control (PAC) scale, depression scale (BDI) and PD-related motor symptoms (MDS-UPDRS III). The higher BDI scores are expected, as mild to moderate depressive symptoms occur in 40-50% of PD patients (Cummings, 1992; Tandberg et al., 1996).

Based on Edinburgh handedness inventory measure, one participant was left-handed, 26 right-handed, and the remaining 7 were ambidextrous. A comparison of results for the right-handed subjects indicated that the assignment of the “signal” response to the left versus right hand did not influence performance, $t < 1$.

5.1.2 PD vs HC group comparison: Only hypocholinergic PD patients differ from controls

Both the HC and PD groups showed robust performance declines in response to the perceptual challenge (SAT vs. dSAT), $F(1,32) = 53.88$, $p <. 0005$, $\eta^2_G = .29$, but the size of the dSAT effect did not differ between the groups, $F < 1$. Follow-up t-tests confirmed that the decline in performance was large and significant within each group (both $p < .0005$, both Cohen's $d = 1.18$ for HC, 1.40 for PD). The two groups also did not differ in overall performance (no main effect of group), $F(1,32) = 1.62$, $p = .21$, $\eta^2_G = .04$, or within either condition tested separately (Table 1). When the groups were divided into normal-cholinergic vs low-cholinergic categories (please see Methods: Statistical Analyses for a description of category classification), only low-cholinergic patients significantly differed from healthy controls (3-way interaction between diagnostic group, cholinergic group, and SAT/dSAT condition: cortical $F(1, 30) = 4.30$, $p = .047$, $\eta^2_G = .03$); thalamic $F (1, 30) = 6.29$, $p = .018$, $\eta^2_G = .05$; see Supplementary Figure 1 for details). The low cortical cholinergic group exhibited lower depression scores than the normal cholinergic group ($t = -2.5$, $p = .02$, Cohen's $d = -1.55$), and otherwise the normal- and low- cholinergic PD groups did not differ in age or in the cognitive/behavioral measures (MoCA, AES, IADL, PAC, all $|t| (15) < 1.5$, $p > .1$). See Supplementary Table 2 and 3 for means, standard deviations, and effect sizes. Controlling for numerical differences between the groups in age, AES, BDI, and MDS-UPDRS III by including these factors as covariates only increased the strength of the 3-way interaction between diagnostic group, cholinergic group, and SAT/dSAT condition: cortical $F(1, 26) = 5.50$, $p = .027$, $\eta^2_G = .05$; thalamic $F(1, 26) = 9.55$, $p = .005$, $\eta^2_G = .08$.

In summary, these data suggest that for PD patients on dopaminergic medication, signal detection even under a perceptual-attention challenge is preserved unless they also have cholinergic declines. However, while separating patients into categorical groups can be of interest from a “clinical threshold” perspective, relations between cholinergic integrity and performance are more likely to be continuous. Furthermore, and directly relevant to our conceptual question, the categorical approach does not allow the relative contributions of

cortical or thalamic integrity to be assessed independently from each other (or other measures) after the other has been controlled for. To better understand the relation between cholinergic disruption and attention, we next performed a series of correlation and regression analyses within the PD group.

5.1.3 Within-group PD correlation and regression analyses of cortical and thalamic cholinergic measures and attention: Thalamic cholinergic integrity uniquely predicts preserved performance under challenge

In simple (Pearson's r) correlations, performance in both conditions as well as the drop in performance (SAT – dSAT) resulting from the perceptual-attention challenge imposed by the dSAT condition showed moderate to large correlations (absolute r values between .33 and .56) with age, cortical k3, thalamic k3, and caudate DVR, but not with BDI score or putamen DVR (See Supplementary Table 1 for full correlation tables). However, there were also significant correlations between age and the PET measures that were related to performance, and the PET measures were also correlated with each other. Simple correlations do not allow one to separate how different predictors (e.g., age and each PET measure) may be related to the outcome variable (in this case, preserved signal detection under challenge; see discussion by Cohen et al., 1983, and many others).

Therefore, to disentangle the independent contributions of age, caudate-dopaminergic, cortical-cholinergic, and thalamic-cholinergic measures to preserved performance during the challenge condition, we conducted a series of hierarchical regression analyses. In all of the analyses reported here, collinearity statistics were well within acceptable ranges (all tolerance values above .47; values above .10 are typically considered acceptable; all VIF values below 2.1; values below 10 are usually considered acceptable; Field et al., 2012).

As our primary question was whether greater cholinergic denervation might increase vulnerability to the perceptual challenge imposed by the distractor condition, we first used the distractor effect (SAT – dSAT performance scores) as the criterion variable. Age was entered in the first step, followed by cortical k3, thalamic k3, and caudate DVR in a single step (See Table 2). Critically, in the final model, only age and thalamic k3 remained significant predictors of the challenge effect over and above the other variables. Greater age was associated with a larger drop in performance in the challenge condition ($b^* = .64$, $t = 2.65$, $p = .021$), whereas greater thalamic k3 was associated with a smaller decline ($b^* = -.59$, $t = 2.32$, $p = .039$; See Figure 2A). Neither cortical k3 nor caudate DVR approached significance, both $|t| < 1$.

In response to a reviewer's question we included the number of days between the PET scan session and the behavioral testing session as an additional control variable, entered in the first step with age. There was no relationship between this variable and performance ($b^* = .07$, $p = .30$), and more importantly, the relationship between thalamic k3 and performance remained (from $b^* = -.59$ without this additional control variable to $b^* = -.58$ when it is included). We also tested a model in which LED was entered in the first step as an additional control variable along with age. LED was not a significant predictor ($b^* = -.19$, $t = -.80$, $p = .44$); nor did its inclusion in the model substantially change the contributions of either caudate DVR (from $b^* = .01$ to $b^* = -.11$) or thalamic k3 (from $b^* = -.59$ to $b^* = -.54$).

The finding that thalamic (rather than cortical) cholinergic measures predicted the degree to which participants were able to maintain performance under challenge suggested that rather than top-down control (at least in a strategic, effortful sense), thalamic cholinergic integrity might instead contribute to preserved signal detection by supporting signal salience. If so, then thalamic k3 should be related to changes in hits (i.e., detection of signals), but not changes in correction rejections (where there is no signal to be "salient" or detected). This was indeed the case (Table 3).

When the decline in hit rates between the SAT and dSAT conditions was used as the predicted variable, the results for both age and thalamic k3 were even stronger than when the predicted variable was the difference in SAT score (age: b* = .81, t = 4.12, p = .001; thalamic k3: b* = -.78, t = - 3.81, p = .002; Figure 2B). In other words, over and above the other variables in the model, a one standard deviation increase in thalamic k3 was associated with a .78 standard deviation decrease in the drop in performance associated with the dSAT condition. In contrast, thalamic k3 was not a significant predictor of correct rejections (thalamic k3: b* = -.15, t = -.43, p = .68; Figure 2C; age: b* = .23, t =.92, p = .37). Thus, our findings suggest that (thalamic) cholinergic denervation in PD patients is more strongly associated with reduced signal saliency and detection than with declines in top-down control.

A potential concern is whether low thalamic cholinergic integrity simply reflects greater overall deterioration. The specific relationship with hits, as well as the significant contribution of thalamic k3 after controlling for age, cortical k3, and caudate DVR, argues against this possibility. In order to provide an even more rigorous test, we ran an expanded model also controlling for MoCA score, PAC score, disease duration, AES, BDI, and MDS-UPDRS III, entered into the first step along with age. This had miniscule effects on the ability of thalamic k3 to predict resistance to the challenge effect (from b* of -.59 to -.60 for the SAT score measure, from b* of -.78 to -.71 for hits). The robustness of the relation between thalamic k3 and preserved performance even after controlling for these other variables argues strongly for a specific contribution to signal saliency and detection.

6.1 Discussion

The present study examined variations in dopaminergic and cholinergic denervation in PD patients to determine those systems' contributions to signal detection under both standard and perceptually-challenging conditions. Measures of caudate nucleus dopaminergic integrity, cortical cholinergic integrity, and thalamic cholinergic integrity all correlated approximately equally (r values between .42 - .54) with signal detection levels under both standard (SAT) and perceptually-challenging (dSAT) conditions. However, only thalamic cholinergic integrity remained a significant predictor, over and above the other variables in the model, of preserved signal detection under challenge. Furthermore, in the perceptually-challenging condition, thalamic cholinergic integrity was specifically related to hits, not correct rejections. These results suggest that thalamic cholinergic signaling plays a particularly important role in sustaining signal detection under challenging conditions, perhaps by maintaining the saliency of bottom-up sensory signals (cf., Kobayashi and Isa, 2002; Langner and Eickhoff, 2013; Morris et al., 1997).

To our knowledge, this is the first report linking thalamic cholinergic function to signal detection under perceptual noise in humans. As noted earlier, compared to the system-wide effects of genetic comparisons or pharmacologic manipulations, the ability to assess pathway-specific (cortical vs thalamic) patterns of cholinergic decline in the present patient population provides a significant advantage for understanding their function. Our findings and interpretation receive indirect support from previous patient studies in humans as well as animal studies that allow more detailed examination and experimental manipulation of cortical and thalamic cholinergic circuits.

As described previously, cortical but not thalamic cholinergic deficits predict reduced executive, attention, and verbal learning scores in PD patients without dementia (Bohnen et al., 2012, 2015), as well as freezing-of-gait symptoms associated with increased demand on and failure of cognitive control and reduced function of cognitive control-associated cortical networks (Bartels & Leenders; 2008; Bohnen et al. 2014; Giladi & Hausdorff, 2006; Shine et al., 2013; Tard et al., 2015a,b). In contrast, thalamic cholinergic denervation has been linked to falls, with Bohnen et al. noting that compared to other patients, those with a history of falls had an approximately 12% reduction in thalamic AChE activity. Likewise, driving requires continuous monitoring of the environment for sensory cues, and Weathers et al. (2014) found that PD patients with a history of risky driving had reduced thalamic cholinergic integrity. These deficits were specific to thalamic cholinergic deficits; neither cortical cholinergic nor nigrostriatal dopaminergic denervation differentiated safe and risky drivers. Difficulties integrating sensory information into perception and action provide a likely mechanism for these associations with thalamic cholinergic denervation: Müller et al. (2013) found that even after controlling for dementia ratings and general motor function, thalamic cholinergic integrity predicted the ability to use sensory feedback to maintain postural integrity, especially in conditions that degraded sensory information. Consistent with the present findings, this relationship was specific to thalamic cholinergic integrity; neither cortical cholinergic integrity nor striatal dopaminergic integrity measures showed such correlations.

Dissociations between other patient populations provide additional supporting evidence. Cortical cholinergic loss is a hallmark of Alzheimer's dementia, with very minor thalamic denervation (less than 1%) relative to age-matched controls. Alzheimer's patients correspondingly have primarily cognitive symptoms, with relatively low fall rates (Kotagal et al., 2012). In contrast, patients with progressive supranuclear palsy, which severely affects cholinergic pedunculopontine nucleus (PPN) pathways to thalamus but by comparison spares cortical cholinergic innervation (e.g., Gilman et al., 2010), have relatively spared cognition at early stages of the disease but show an increased vulnerability to falls, with strong links to thalamic volume and function (e.g., Zwergal et al., 2011; see discussion by Sidiropoulos and LeWitt, 2011). These two patient populations thus provide a double dissociation supporting the specific importance of thalamic cholinergic integrity. Our findings provide a potential mechanistic explanation for the link between thalamic cholinergic function and fall propensity.

Evidence from basic neuroscience research in animals corresponds with the conclusions drawn from the patient studies. In addition to the rodent studies described above, in vivo and

in vitro evidence points to acetylcholine's contribution to thalamic and thalamic-cortical stimulus processing and signal detection (Castro-Alamancos, 2002a; 2002b; 2004; Runfeldt et al., 2014; see Beierlein, 2014 for recent reviews). Using slice preparations, Runfeldt et al. (2014) found that stimulation of thalamic cholinergic inputs re-organized sensory circuits in a way that would be expected to promote accurate signal detection. Specifically, such stimulation reduced spontaneous circuit activity and pruned weak functional connections (both of which would be expected to contribute to noise), but prolonged temporally precise activity more likely to represent an incoming signal (see also Avery et al., 2014 for related computational modeling work). Furthermore, Sun et al. (2013) found that rather than diffuse neuromodulatory effects (though these may also play a role in modulating signal to noise ratios, e.g., Wester and Contreas, 2013), cholinergic stimulation of somatosensory thalamic reticular nucleus slices triggered spike activity and entrained neuronal firing to support fast and precise firing of the type likely to support processing of individual stimulus events.

The present findings thus join with and help interpret previous evidence suggesting that although the basal forebrain-cortical cholinergic system supports top-down control and (normal populations) increases activity in response to challenges, it does not implement the specific processes required to support signal detection per se. Instead, cortical, and especially fronto-parietal, cholinergic activity are hypothesized to support “attentional effort” – the motivated activation of top-down attention to stabilize task representations, especially when performance is challenged (Lustig & Sarter, 2016; Raizada & Poldrack, 2008; Sarter et al., 2006). Fronto-parietal cholinergic activity increases reliably from baseline to the SAT, and further in response to the dSAT condition or other challenges (see Kozak et al., 2006); even placing trained animals in the operant chamber or simply testing them at the same time every day can lead to increases in frontoparietal cholinergic activity suggesting a readiness to engage in the task (Paolone et al., 2012). However, evidence from both the rodent and human studies suggests that, given the bottom-up nature of the target signal in the dSAT, this increased engagement is more strongly associated with attempts to recover performance after it has been impaired by the challenge than the ability to maintain it (e.g., Demeter et al., 2011; Berry et al., 2015, in revision; Howe et al., 2010; Kozak et al., 2006; 2007; Parikh et al., 2013). Instead, the critical factor for detecting this brief, sudden-onset signal is preserved bottom-up salience (Posner, 1978).

It is important to note that thalamic cholinergic loss occurs in the context of the dopaminergic losses typically associated with PD, and in many patients is also accompanied by basal forebrain-cortical cholinergic declines. Our regression analyses point to a unique contribution of thalamic cholinergic integrity to salience processing and signal detection, but one limitation of the current study is that the sample size is not large enough to support tests for potential interaction effects. This should be tested in larger studies, and in patients in both the “on” and “off” dopaminergic-medicated states. It is also important to note that an increased reliance on bottom-up salience processing, associated with preserved signal detection in the present situation, may contribute to performance deficits in situations with low-salience targets and high-salience distractors. While this hypothesis remains to be tested in PD, an increased susceptibility to bottom-up salience has been found in the genetic group thought to have reductions in sustained cortical cholinergic activity supporting top-down control (Berry et al., 2014; Neumann et al., 2006), and in rodents, reduced cortical

cholinergic function is associated with an increased tendency to “sign-track” rather than “goal-track” in Pavlovian conditioning paradigms (Paolone et al., 2013a; see Haight & Flagel, 2014; Haight et al., 2015, submitted, for evidence of thalamic involvement).

In summary, the data presented here suggest that thalamic cholinergic circuitry makes a unique and important contribution to signal detection, especially under conditions of perceptual noise. The specific association with hits, and lack of relationship to correct rejections, supports the idea that the thalamic contributions are related to bottom-up signal salience, rather than top-down control of attentional selection. These findings point to potential pathways of both compensation and vulnerability in low-cholinergic populations, as well as the need for understanding subgroup differences that may underlie vulnerability to falls in patients with PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance statement

An essential aspect of interacting effectively with the environment is detecting the cues that require action to support goal-directed behavior. Detecting such signals is especially important but also especially difficult in challenging environments. The cholinergic system mediates both stimulus-driven (bottom-up) and goal-driven (top-down) processes involved in signal detection, but defining its region-specific contributions in the human brain has been difficult. Using medicated Parkinson's disease patients with regionally-specific patterns of cholinergic and dopaminergic denervation, we demonstrate that thalamic cholinergic integrity makes a specific contribution to the bottom-up mechanisms supporting signal detection in the face of perceptual challenge. These results provide a more precise understanding of the neural mechanisms underlying attention, particularly the respective contributions of different branches of the brain's cholinergic system.

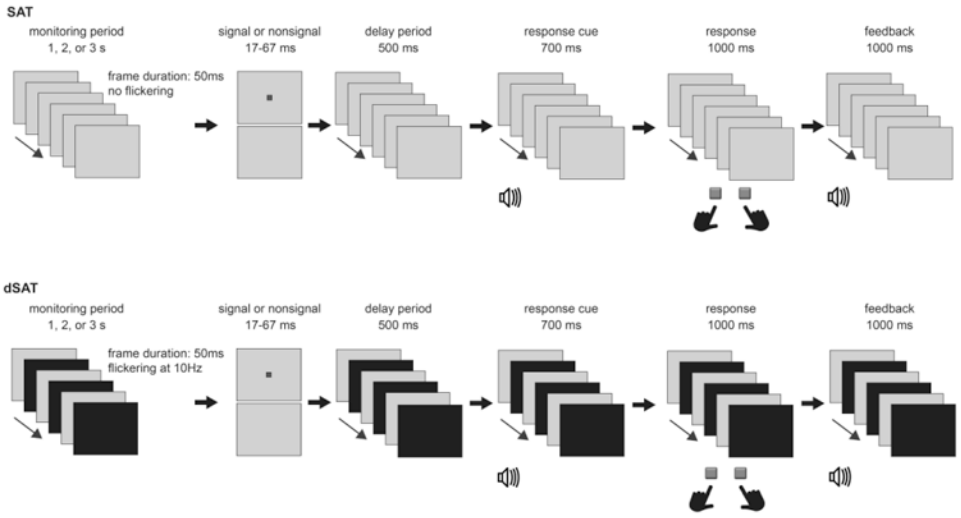

Figure 1. Sustained Attention Task (SAT)

Each trial starts with a monitoring period with varying intervals (1, 2, or 3ms). A signal may or may not appear at the end of the monitoring period. Participants must report whether there was a signal or not using the standard keyboard keys when they hear a response cue following a short delay. Response must be made within one second, and correct responses are followed by a feedback tone. The distractor condition Sustained Attention Task (dSAT) presents an perceptual-attentional challenge: The whole screen flashes at 10Hz, alternating between gray (“silver” in E-prime) and black.

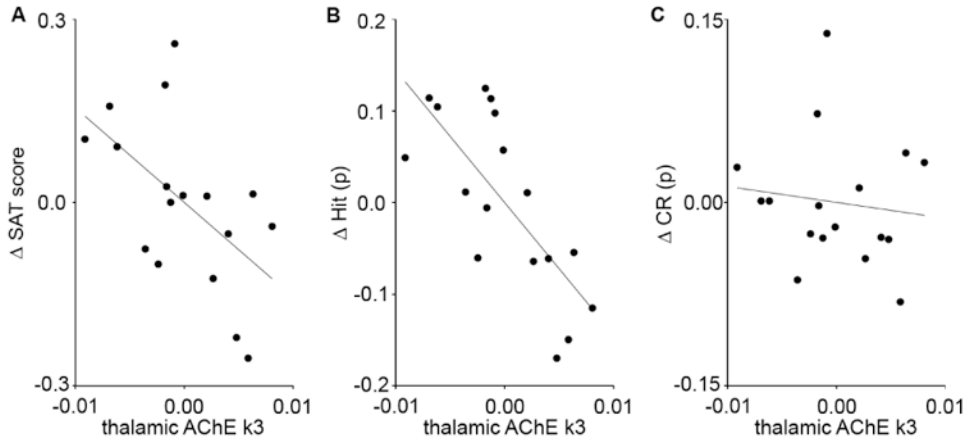

Figure 2. Thalamic cholinergic function uniquely predicts preserved signal detection under challenge

Residual plots after controlling for age, caudate DVR, and cortical k3. (A) Lower levels of the thalamic k3 were associated with greater vulnerability to distraction. (B-C) The link between thalamic cholinergic integrity and signal detection was primarily driven by correct detection (hits) rather than correct rejections.

Table 1

Comparisons of HC and PD groups

Demographics, general cognitive function (MoCA), attention (Poor Attentional Control Scale), affective states (AES, BDI), motor control (MDS-UPDRS III), overall performance, and PAC scores in PD patients and controls. All participants except one healthy control had ceiling IADL scores (little or no impairment; that control had a score of 7). The t and p values were corrected for the violation of equal variances assumption for IADL, Motor UPDRS score, and dSAT non-signal trial omission rate. d = Cohen's d.

	HC		PD		Group comparisons		
	M	**SD**	**M**	**SD**	***t***	***p***	***d***
Age (years)	64.1	7.9	63.1	8.1	0.4	.70	0.13
Education (years)	16.5	2.3	16.4	2.4	0.0	.97	0.04
Extended Range Vocabulary Test	26.3	8.6	25.5	9.0	0.3	.78	0.09
Montreal Cognitive Assessment	27.2	2.0	26.7	2.3	0.7	.48	0.24
Poor Attentional Control Scale (total)	38.5	7.4	45	7.5	-2.5	.02	-0.90
PAC mind wandering	12.9	2.8	15.8	2.9	-2.9	.01	-1.05
PAC boredom	11.7	2.5	13.5	2.8	-1.9	.07	-0.70
PAC distractibility	13.9	3.3	15.8	3.8	-1.5	.15	-0.55
Instrumental Activities of Daily Living	7.9	0.2	8.0	0.0	-1.0	.33	-0.73
Apathy Evaluation Scale	25.0	6.6	27.1	8.3	-0.8	.43	-0.29
Beck Depression Inventory	3.9	3.9	8.4	5.1	-2.9	.01	-1.02
MDS-UPDRS III Score	5.8	5.8	29.4	11.7	-7.5	**	-2.63
SAT overall accuracy (%)	86.4	13.9	86.6	6.3	-0.1	.95	-0.02
SAT score	0.9	0.1	0.8	0.1	1.4	.16	0.49
SAT signal trial omission rate (%)	3.7	8.0	1.8	1.7	1.0	.35	0.34
SAT non-signal trial omission rate (%)	11.3	17.1	6.8	5.8	1.0	.31	0.36
dSAT overall accuracy (%)	72.4	19.6	73.3	13.5	-0.1	.88	-0.06
dSAT score	0.7	0.2	0.6	0.2	1.1	.28	0.38
dSAT signal trial omission rate (%)	9.9	14.8	3.6	4.6	1.7	.11	0.59
dSAT non-signal trial omission rate (%)	15.6	20.6	5.7	5.7	1.9	.07	0.68

** indicates p < .0005

Table 2

Hierarchical multiple linear regression model for distractor effects

B, unstandardized coefficient; β, standardized coefficient

	coefficients				model statistics						power
	B	**β**	***t***	***p***	**R^2**	**Δ R^2**	**Δ *F***	***p* (Δ *F*)**	**Model Fit *F***	**Model Fit *p***	**1- β**
step 1 model					.31	.31	6.88	.02	6.88	.02	0.73
constant	-0.49		-1.7	.102							
age	0.01	.56	2.6	.019							
step 2 model					.55	.23	2.04	.16	3.61	.04	0.87
constant	-0.10		-0.2	.859							
age	0.01	.64	2.6	.021							
caudate DVR	0.00	.01	0.0	.975							
thalamic k3	-15.50	-.59	-2.3	.039							
cortical k3	13.40	.25	0.9	.396							

Table 3

Hierarchical multiple linear regression model for the distractor effect in hit trials

B, unstandardized coefficient; β, standardized coefficient

	coefficients				model statistics						power
	B	**β**	***t***	***p***	**R^2**	**Δ R^2**	**Δ F**	***p*(Δ *F*)**	**Model Fit *F***	**Model Fit *p***	**1- β**
step 1 model					.34	.34.	7.6	.02	7.6	.020	0.79
constant	-0.30		-1.5	.144							
Age	0.01	.58	2.8	.015							
step 2 model					.71	.37	5.0	.02	7.2	.003	0.99
constant	-0.25		-0.80	.440							
Age	0.01	.81	4.1	.001							
caudate DVR	0.06	.23	1.3	.224							
thalamic k3	-14.44	-.78	-3.8	.002							
cortical k3	15.13	.40	1.8	.105							