CHOLINERGIC MODULATION OF ATTENTION

by

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

ABSTRACT

Rodent studies indicate that cholinergic inputs to frontoparietal cortex play an important role in signal detection, especially in challenging conditions. fMRI studies have likewise shown frontoparietal activity in humans under task conditions parallel to those used in the rodent studies. While these parallels are suggestive, the degree to which the fMRI activation patterns seen in humans reflect cholinergic activity remains unknown. The studies in this dissertation provide stronger evidence for cholinergic influences on the brain systems supporting attention in humans, and begin to delineate how those influences may differ by brain region and interact with other (e.g. dopaminergic) influences to shape cognition and behavior. First, an electroencephalography study showed that gamma synchronization, which previous studies have linked to cholinergic activity and attentional control, increases in response to a distractor challenge. Furthermore, across participants, greater increases in gamma synchronization in parietal cortex were associated with better distractor resistance, whereas greater increases in gamma dispersion in right prefrontal cortex were associated with greater response time variations thought to reflect difficulty in maintaining consistent control. Another series of experiments leveraged variability in cholinergic integrity (measured using PET) in Parkinson's patients as a natural experiment to determine cholinergic contributions to different aspects of attention and

cognitive control. Thalamic cholinergic integrity made the strongest independent contribution to variation in the ability to detect signals under perceptual challenge, whereas cortical cholinergic integrity was the best independent predictor of the ability to resist content-rich distractors likely to draw attention away from the target signal. Exploratory analyses suggested that parietal cholinergic integrity might play an especially important role in resisting these distractors, consistent with the electroencephalography study results. Finally, a secondary data analysis of a larger sample suggested that in conditions making strong demands on executive control, there may be mutual compensation between cholinergic and dopaminergic systems. To summarize, the present findings provide further evidence for cholinergic contributions to frontoparietal brain systems supporting signal detection, attention, and cognitive control, more precisely define the contributions of thalamic, prefrontal, and parietal inputs, and suggest the possibility of mutual compensation with the dopaminergic system in situations of high executive demand.

Chapter I

INTRODUCTION

"Everybody knows what attention is" (but it might be several things)

What is your experience like as you begin to read this manuscript? Ideally, it is clear and in high contrast on your screen or printed page and you are in a quiet environment with nothing else competing for your attention. Imagine, however, that you are trying to read this on your laptop while traveling on a plane, and your screen is malfunctioning so that the words are in low contrast and the background seems to flicker, or perhaps your computer is fine but the laptop of the person sitting next to you is playing a movie that you've always wanted to see, and you have to resist the temptation to glance over. Alternatively, imagine that the manuscript was in the "flopped" style used by Japanese manga, so that you had to read from back to front, right to left. All of these situations pose challenges to information processing, and terms such as "attention", "cognitive control" and "executive function" are used to describe the processes we use to try to overcome them. In this dissertation, I examine how the brain implements these different aspects of cognitive control, with particular attention to the potential contribution of its cholinergic systems.

The first study (Chapter 2) uses electroencephalogram (EEG) in healthy young adult subjects to examine how gamma-band activity, previously shown to increase with attention and target selection (Fell, Fernández, Klaver, Elger, & Fries, 2003; Fries, Nikolić, & Singer, 2007; Fries, 2009) was related to signal detection and resistance to distraction. Gamma oscillations were of particular interest because the increase of gamma oscillations is associated with cholinergic activities (Metherate, Cox, & Ashe, 1992; Rodriguez, Kallenback, Singer, & Munk, 2004) and the hemodynamic responses (Koch et al. 2009). As described in that chapter, we found evidence for changes in gamma oscillations in response to the distractor that statistically modulated another EEG response (inter-trial coherence) thought to reflect attention to the distractor. Interestingly, these gamma increases were primarily located in left parietal cortex, rather than right prefrontal cortex as we had originally predicted from the previous animal and fMRI studies. However, gamma variability in right prefrontal cortex was related to a potential index of subjective difficulty (response time variability). These findings may thus help better define the role of frontal and parietal components (and indirectly, cholinergic contributions to those components) in cognitive control.

The following three experiments (Chapters 3 – 5) leverage variability in cholinergic denervation among patients with Parkinson's disease as a natural experiment to shed light on how the cholinergic system may contribute to attention and cognitive control in different scenarios: signal detection under perceptual noise; temporal precision, sustaining attention over time, and resisting external distraction, and overcoming conflict. Taken together, the results from these studies support the idea that rather than simply serving as a broad-based, diffuse neuromodular, the cholinergic

system can act in regional (and temporal, although that is not tested here) ways to support specific cognitive functions. In addition, these findings suggest that as the complexity and executive demands of a particular task increase, so do the opportunities for compensation and interactions between different neural systems.

In summary, the experiments in this dissertation suggest that the cholinergic system – or more precisely, systems (basal forebrain/cortical and peduculonpotine/thalamic) - make important and specific contributions to different aspects of attention and cognitive control. Below, I briefly review some of the background literature that provides the motivation for the studies presented here.

Attentional modulation of sensory information

Returning to the above scenarios, what happens when you focus your attention on that malfunctioning screen, or try to ignore the movie from your seatmate's laptop? If you are successful in the first case, what will look to someone walking by like just a bunch of static should for you resolve into words that carry meaning. In the second case, you can clearly hear and follow attention to the movie's dialog if you pay attention to it, but the conversation fades out as you concentrate more and more on your work, and eventually you may even forget that it is there. How does this happen? Did the screen suddenly start behaving, or did your seatmate politely turn the volume down? A more plausible, and scientifically valid explanation would be that we have a capability to process the information coming through the sensory organs in a selective way so that the task-relevant (or, attended) information is weighted more than the task-irrelevant (or,

ignored) information; the cognitive function called as top-down control of attention (Corbetta & Shulman, 2002).

At the moments we experience that task-irrelevant information is fading out as we focus more on the task-relevant information, very similar changes happen in the brain. Selectively attending to certain information over others modulates sensory processing accordingly; the brain activities representing the attended information becomes amplified while the neural representation of the unattended information becomes attenuated. For example, a monkey V4 single cell recording revealed that stimulus in an attended location inside the cell's receptive field increases the cell's response and a stimulus in an unattended location inside the cell's receptive field reduces the cell's response (Moran & Desimone 1985). Moreover, this attentional modulation of sensory processing is particularly strong in the presence of competing information to be ignored (Reynolds, Chelazzi, & Desimone 1999). Human functional magnetic resonance imaging (fMRI) studies showed consistent findings. Multiple items in the visual field create competition and their neural representations are mutually suppressed by one another. Directing attention to one of the items increases the brain activation for the representation of the attended item over the others – counteracting the competition/suppression (Kastner, Weerd, Desimone, & Ungerleider, 1998; Kastner & Ungerleider 2001). Similarly, the hemodynamic responses in the auditory cortex are modulated by selective attention – stronger for the attended vs. ignored stimuli (Jäncke, Mirzazade, & Shah 1999). Of importance, this top-down attentional modulation of sensory processing is mediated by the brain activities in the fronto-parietal network (Corbetta & Shulman, 2002; Hopfinger, Buonocore, & Mangun, 2000; Kastner, Pinsk,

Weerd, Desimone, & Ungerleider, 1999; Kastner & Ungerleider 2000; Kastner & Ungerleider 2001).

Rodent and human studies of cholinergic contributions to attention and cognitive control

Traditionally, the cholinergic inputs to sensory regions are thought to amplify the signal-to-noise ratio of sensory signal – just as attention does as described above. For example, microionophoretic application of ACh to the visual cortex increased the neuronal responses to the inputs from lateral geniculate nucleus (LGN; Sato, Hata, Masui, & Tsumoto, 1987). Importantly, it rarely affected the spontaneous activity, suggesting that ACh specifically amplifies the signal-to-noise ratio of the response of the sensory neurons instead of the general neural activities. In addition, ACh suppress the spread of excitation in visual cortex in vitro (Kimura, Fukuda, and Tsumoto 1999). Stimulation of layer IV mimics inputs from LGN and the application of ACh suppressed the spread of this activation by up to 50%. Moreover, this suppressive effect was cancelled by application of muscarinic cholinergic receptor (mAChR) antagonist. Thus, ACh may weigh the afferent input by suppressing the propagation of excitation in intracortical connections and not suppressing the thalamocortical inputs. Human brain imaging study using a pharmacological manipulation showed findings consistent with these animal study findings. Pharmacologically increasing the availability of ACh using donepezil, cholinesterase inhibitor, decreases the spread of BOLD signal recorded by fMRI in visual cortex (Silver, Shenhav, and D'Esposito, 2008). Again, ACh may switch

the cortical network mode into a state where afferent inputs gain priority over intracortical signals (Kimura, 2000).

Cholinergic inputs to cortex are thought to originate largely from basal forebrain, with another major cholinergic pathway being from the brainstem pedunculopontine nucleus to thalamus (Perry, Walker, Grace, & Perry, 1999 for review). The anatomical characteristics of the basal forebrain allow it to serve as a hub of attentional processing. Basal forebrain (the nucleus basalis of Meynert) cholinergic neurons innervate the neocortical regions including the aforementioned sensory areas and themselves are also innervated by the neocortical and brain stem neurons. This circuitry allows a scenario where arousal signals from the brain stem increases the cholinergic activity of the basal forebrain cholinergic neurons that projects to prefrontal as well as sensory areas (Sarter, Givens & Bruno 2001, Sarter, Gehring, & Kozak 2006). In addition, the basal forebrain cholinergic system has reciprocal direct connections with prefrontal cortex and this provides anatomical grounds to its contribution in the prefrontal and cholinergic modulation of attention (Gaykema, Van Weeghel, Hersh, & Luiten 1991; Zaborszky 2002; Sarter et al., 2001, Sarter et al., 2006 for review). Consistent with this, accumulating evidence supports the idea that the basal forebrain cholinergic inputs comprise a key component for effort-driven, top-down attentional control. Studies showed that global changes of the cholinergic activity modulate the performance in a task with high attentional demand. Specifically, 198lg-G saporin lesion of basal forebrain increases response latency under modality-uncertainty condition (Turchi & Sarter, 1997) and increases animals' vulnerability to cross-modal distractors (Newman

& McGaughy 2008). In contrast, selective nicotinic AChR agonist injection enhanced the performance recovery following the impairment by distraction (Howe et al., 2010).

Importantly, the cholinergic modulation of attention is shown to be based on the basal forebrain-fronto-parietal circuitry rather than a simple input system. Early evidence for this functional circuitry comes from studies that showed the cholinergic inputs to both the medial prefrontal cortex (mPFC) and posterior parietal cortex (PPC) are critical in distractor resistance. A subset of mPFC and posterior parietal cortex (PPC) neurons exhibit increased firing rate when animals perform an attention task in the face of distraction (Gill, Sarter, & Givens 2000; Broussard, Karelina, Sarter, & Givens, 2009). These distractor-related increases of neuronal firing are attenuated by the local cholinergic deafferentation in the mPFC or PPC. More recently, it was shown that rats actually increase mPFC ACh release as they engage in a signal detection task and the magnitude of this increase becomes amplified if there is a distractor challenge (St. Peters, Demeter, Lustig, Bruno, & Sarter, 2011). Moreover, greater distraction-related increases of mPFC ACh release were associated with preserved performance in the face of distraction, and activating PFC cholinergic neurotransmission via NMDA stimulation of NAc enhanced the performance in the distractor condition. Critically, intact cholinergic inputs to both the PCF and PPC were essential for this distractor resistance mechanisms; Local removal of cholinergic inputs to either PFC or PPC removed the performance enhancement by NMDA stimulation. These findings clearly demonstrate that the basal forebrain-fronto-parietal cholinergic circuit functions together to allow resisting distraction.

Recently several human studies, some using the same signal-detection and distraction paradigm used in many of the rodent studies described above (the distractor condition sustained attention task (dSAT), Berry et al. (in press); Demeter, Hernandez-Garcia, Sarter, & Lustig, 2011; Demeter, Sarter, & Lustig, 2008; Howe et al., 2013) have provided at least indirect evidence for conserved and parallel mechanisms in the human brain. For example, when humans are tested using a similar behavioral procedure as St. Peters et al. (2011) did in rats, the right PFC BOLD signal increased in response to distraction (Demeter et al., 2011). Berry et al. (in press) found that individuals with a genetic polymorphism limiting choline transport, a rate-limiting step on cholinergic function, failed to show this right PFC activation in response to distraction. However, they were still able to perform the task (see also Parikh, St. Peters, Blakely, & Sarter, 2013 for evidence from genetically modified mice). These findings suggest that cholinergic innervation/activation in right PFC is involved in overcoming the perceptual noise induced by the distractor in dSAT, but is not essential. Notably, another study with this genetic group showed that they were more vulnerable when faced with a compelling external distractor (Berry et al., 2014), providing additional support for ACh's role in cognitive control.

Additional evidence for the cholinergic system's role in cognition comes from Parkinsons' disease (PD) patients with varying levels of cholinergic function. About 36% of non-demented PD patients exhibit cholinergic denervation in addition to the striatal dopaminergic denervation (Bohnen and Albin, 2011, for review). Degeneration of cholinergic neurons in the nucleus of Meynert has long been understood to be associated with the impaired cognitive functions in PD (Perry et al., 1985), but the

profile of the cholinergic denervation in PD became better illustrated in recent studies. Using in vivo measure of the cortical cholinergic and the striatal dopaminergic functions using positron emission tomography (PET), Bohnen et al. (2012) assessed the profile of cognitive and motor impairments associated with the basal forebrain (cortical) and PPN (thalamic) cholinergic functions. The degeneration in the two cholinergic pathways in PD is heterogeneous with differential consequences. Cortical cholinergic function was correlated with impaired executive, or top-down control, functions independently from the striatal dopaminergic functions. Specifically, lower cortical cholinergic integrity was associated with poorer performance in digit span, trail making, and stroop tasks, but not verbal learning tasks. On the other hand, the thalamic cholinergic function was associated with fall propensity but not with the performance in the cognitive and motor tests. However, thus far most studies of these patients have used relatively broad-based neuropsychological batteries that limit the degree to which specific cognitive processes can be isolated; three of the experiments in this dissertation will attempt to define these deficits more closely.

Neural oscillations in the selective attention

One mechanism by which the cholinergic system may support attention is modulating the temporal structure of neural activity, in particular, gamma-band oscillation (Metherate, Cox, and Ashe, 1992; Buhl, Tamás, and Fisahn 1998; Rodriguez et al., 2004; Kaiser & Lutzenberger, 2003; Kaiser & Lutzenberger, 2005; for review see Deco & Thiele, 2009). The temporal structure of neural responses is suggested to be the building blocks of inter- and intra-cortical communication (Başar, Başar-Eroglu,

Karakaş, & Schürmann, 2001; Buzsáki & Draguhn 2004; Fries 2005; Salinas & Sejnowski 2001; Ward 2003). Selective attention in particular involves both local and long-range neural synchronizations (Engel, Fries, & Singer, 2001, Womelsdorf & Fries, 2007).

Local gamma-band (25-70Hz) synchronizations in the sensory cortices are interpreted as serving to amplify the neural representations of behaviorally relevant information (for a review on gamma see Fell et al., 2003; Fries et al., 2007; Fries, 2009). Specifically, gamma-band synchronization increases in the neurons activated by the attended compared to un-attended stimulus (Fries, Reynolds, Rorie, & Desimone, 2001). Human scalp EEG studies also report local synchronization that may represent signal amplification for the attended information, but with some limitations regarding the precision in source localization. Tiitinen and colleagues (1993) used a dichotic-listening protocol and measured the changes of gamma-band frequency (40Hz) in response to attended inputs. Gamma-band activity increased when subjects paid attention to the target stimuli compared to when they paid attention to a filler task (reading) – in the frontal and central sites. Similarly, local gamma synchronizations increase for attended vs. ignored visual stimulus and in the contralateral hemisphere of the attended visual field (Müller, Gruber & Keil, 2000). Gamma-band oscillation is also shown to increase during visual search in central and occipital components (Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1997).

Gamma-band oscillations and cholinergic activities in attention

Studies using a wide range of methods indicate that gamma-band oscillations are modulated by cholinergic stimulation both at the cellular and functional levels. For example, in vivo stimulation of nucleus basalis in the basal forebrain (a main origin of cortical cholinergic neurons) induces increase of the gamma oscillation in the auditory cortex (Metherate et al., 1992). In vitro cholinergic stimulation of cells also induce gamma burst in the somatosensory cortex and hippocampus. (Buhl et al., 1998; Fisahn, Pike, Buhl, & Paulsen, 1998). Moreover, when rats increase prefrontal ACh release during a signal detection task, there is corresponding increase of gamma oscillation in the prefrontal cortex (Sarter, Howe, & Gritton, 2012). In addition, application of the cholinergic agonist extends the increase of the gamma synchrony induced by light stimuli (Rodriguez et al., 2004).

These previous investigations set the stage for the study presented in the next chapter (Chapter 2), where I use EEG in humans to examine changes in gamma oscillation and their correlations with performance in a modified version of the dSAT.

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Chapter II

LOCAL GAMMA-BAND SYNCHRONIZATIONS AND DISTRACTOR RESISTANCE

Introduction

Imagine walking through an unfamiliar airport, looking for the sign that will lead you to your gate. This task requires you to maintain attention to your goal so that you notice and respond to the sign when it appears in your vision – a task that is much easier if the airport is relatively empty and quiet than if it is busy with hordes of people milling about. The top-down control of attention allows us to stay focused on detecting the sign and to deal with the distraction, and brain imaging studies over the past two decades have consistently shown that the frontoparietal network plays a core role in top-down attentional control (Corbetta, & Shulman 2002; Hopfinger, Buonocore, & Mangun, 2000; Kastner, Weerd, Desimone, & Ungerleider, 1998; Kastner, Pinsk, Weerd, Desimone, & Ungerleider, 1999). The present study examined how oscillatory activity patterns in these regions might be related to signal detection with and without distraction. Specifically, we used scalp electroencephalogram (EEG) to examine how gamma-band (25-70 Hz) synchronizations, thought to reflect attention-related amplification of stimulus information, were related to signal detection and changed in response to the introduction of distraction.

Increases in gamma-band synchrony are influenced by both bottom-up signal salience (e.g., the contrast or brightness of a visual input; Koch, Werner, Steinbrink, Fries, & Obrig, 2009; Niessing et al., 2005) and attentional state (Koch et al., 2009; Müller, Gruber & Keil, 2000; Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1996). These increases are of particular interest because of their potential to connect findings across multiple methods and levels of neuroscientific analysis. Studies of both local field potentials in animal models (Niessing et al., 2005) and EEG in humans (Koch et al. 2009) link increases in gamma synchrony to increases in the hemodynamic response thought to underlie the BOLD signal in fMRI. These increases in gamma-band synchronization are thought to enhance stimulus representations and their integration into information processing, perhaps by synchronizing bursts of action potentials and increasing the chances of neurotransmitter release (e.g., Gray & McCormick, 1996; see discussion by Fries, 2009). They are modulated by acetylcholine (e.g., Metherate, Cox, & Ashe, 1992; Buhl, Tamás, & Fisahn 1998; Rodriguez, Kallenback, Singer, & Munk, 2004), consistent with its role in both bottom-up signal salience and top-down control (e.g., Hasselmo & Sarter, 2011; Sarter, Gehring, & Kozak, 2006).

We therefore examined changes in gamma synchronization during the distractor condition sustained attention task (dSAT), which has been extensively used to study cholinergic contributions to signal detection and top-down control in rodents (e.g., Broussard, Karelina, Sarter, & Givens, 2009; McGaughy & Sarter, 1995; St. Peters, Demeter, Lustig, Bruno, & Sarter, 2011; see reviews by Hasselmo & Sarter, 2011; Sarter, Givens, & Bruno, 2001; Sarter, Lustig, Howe, Gritton, & Berry, 2014; Sarter et al., 2006) and more recently extended to human research (e.g., Demeter, Sarter, & Lustig,

2008; Demeter, Hernandez-Garcia, Sarter, & Lustig, 2011, Demeter, Guthrie, Taylor, Sarter, & Lustig, 2013; Howe et al., 2013; see Lustig, Kozak, Sarter, Young, & Robbins, 2013 for review of the parallels and discrepancies between rodent and human findings). Rodents show increased frontoparietal acetylcholine levels when performing the signal detection task (SAT) without distraction, and further increase these levels in the distractor condition (dSAT; see St. Peters et al., 2011). In humans, fMRI studies show apparently parallel right frontal activations during SAT performance and dSAT-related increases (Demeter et al., 2011; Berry et al., in prep.). Individuals with a genetic polymorphism though to limit cholinergic function show normal SAT-related activation of right prefrontal cortex, but fail to increase this activation in response to the top-down control demands imposed by the distractor condition (Berry et al., in press).

In most previous studies, the distractor condition has been implemented by rapidly changing background illumination: for animal studies, continuously flashing the houselight on and off; for human studies, rapid alternations between dark and light background colors on the computer screen used to present the task. This manipulation increases demands for attention and reduces performance, but there is some ambiguity as to the degree to which it represents “distraction” as that term is usually meant (i.e., by competing for attention) versus making the target signal more difficult to see. In the present study, we used a modified implementation of the distractor that better matched the visual contrast of the SAT and dSAT conditions, and that allowed measurement of an EEG outcome thought to measure attention to the distractor.

Instead of the consistent whole-field grey background used in previous studies, the background used in the present study consisted of a grid with different squares

colored in various shades of grey, so that to the participant it appeared to be a random assortment of squares and rectangles (see Figure 2.1). In the SAT condition, this background remained stable; in the dSAT condition the shades of grey at different locations in the grid changed randomly every 200 ms (5 Hz) so that the squares and rectangles appeared to appear/disappear or move about the screen. Pilot studies verified that these changes in the peripheral visual field impaired performance. Importantly, the distractor flickering at 5Hz was expected to evoke theta-band (5Hz) oscillations in visual areas (Steady-State-Visually-Evoked-Potential (SSVEP)). SSVEP is modulated by selective attention (Morgan, Hansen, & Hillyard, 1996), thus the SSVEP in the present paradigm allows measuring the degree to which attention was misdirected to the distractor.

We therefore tested the following hypotheses: 1) Based on the previous rodent cholinergic and human neuroimaging studies, we expected to find increases in gamma power versus baseline during SAT performance, and 2) that across subjects greater gamma power would be associated with better signal detection. 3) To further test the relationship between gamma and detection-related attention, we also examined how trial-to-trial gamma variability might be related to variability in response time (RT). That is, participants with fluctuations in attention would also be expected to show fluctuations in gamma, and these would be expected to be further reflected in greater variability in response times. 4) Gamma power, particularly in frontoparietal attentional networks, was expected to increase in response to the distractor. 5) Distractor-related increases in gamma were expected to correlate with distractor-related performance declines. Notably, the previous animal and human findings make apparently opposing predictions

here: The rodent data suggest that across subjects, a greater frontoparietal cholinergic response is associated with the ability to resist distractor impairment; that is, subjects with greater distraction-related increases in frontoparietal acetylcholine showed smaller distractor-related performance impairments (St. Peters et al., 2011). In contrast, the human fMRI data indicate that increases in right prefrontal activation are associated with greater distractor vulnerability (Berry et al., in prep.; Demeter et al., 2011). Therefore the present results may be important for helping to resolve this apparent discrepancy. 6) if the distractor induced more attentional fluctuations, we should see an increase in the variability of gamma peak distribution (and RT) 7) the increases between gamma peak variability and RT variability should be correlated 8) 5Hz oscillations (i.e., the SSVEP) will be observed in the distractor condition. 9) 5Hz oscillations in the distractor condition, thought to reflect distractor processing, will be greater in the trials in which target was missed (miss trials) than correctly detected (hit trials) and (10) increases in gamma oscillations in response to the distractor will modulate the magnitude of distractor processing and correlate negatively with the distractor-evoked 5Hz oscillations. Overall, our hypotheses center on the idea that frontoparietal gamma reflects neural processing involved in the attentional processes that support signal detection, and that increases in these processes support preserved detection in the face of distraction.

Methods

Participants

Final analyses included data from 29 healthy young adults (19 females, mean age, 20.1 years, range 18-24 years, 25 right-handed, 1 left-handed, 3 ambidextrous). Participants scored at least 9 on the Extended Range Vocabulary Test (ERVT). Two additional participants were excluded from the analyses, one due to poor performance (below 60% overall accuracy) and the other due to excessive noise in the EEG signal. All participants had corrected to normal vision and no history of attention deficit disorder, seizures, migraines, or psychological disorders such as depression and anxiety.

Modified distractor condition Sustained Attention Task (dSAT)

Stimuli were presented on a 14 inch CRT screen (800×600 screen resolution, 60Hz refresh rate), using Presentation software (Psychology Software tools; http:// http://www.neurobs.com; Version 16.3 Build 12.20.12). Participants were seated at a 50cm distance from the monitor in a sound-attenuating, electromagnetically shielded room with a dim lighting. The task procedure and conditions are illustrated in Figure 2.1. Each trial started with a blue fixation (a '+' sign) presented for 800ms at the center of the screen, followed by a screen divided into 25 by 19 grids, filled with different shades of grey. Each task trial consisted of a variable-duration (1,2, or 3 sec) monitoring period, at the end of which a brief signal - a small grey square, 1x1mm, 34ms - did (signal event) or did not (nonsignal event) appear in the center square. After a short delay (1s), a green '?' sign appeared for 1 second in the center square as a prompt for response.

Participants were given 1 second to respond (they had to respond while the response prompt was presented). The 1s delay between the signal and response cue was inserted in order to separate the signal-related activity and the response cue-evoked activity. Participants indicated whether or not they thought a signal occurred on that trial using left and right index finger responses on a standard keyboard (z and / keys on a standard keyboard respectively, right/left : signal/nonsignal assignment counterbalanced across participants). If a correct response was made within the given 1s, a yellow '$' sign appeared at the center square to notify the participants of the increase in their monetary reward. They were paid 1 cent for percent correct, and penalized 2 cents for percent trials where they missed the signal.

The shades of squares in the background grid were controlled in a way that the net luminance of the whole screen remained constant within and across trials. Seven different shades of grey were used to fill the squares in the grey. The middle darkness grey was assigned to the center square, and the remaining six different shades of grey were equally distributed across the rest of the squares (each shade was assigned to 79 squares) in every grid stimulus.

On standard (SAT) trials, the background remained static throughout the trial, although to reduce predictability, the distribution of shades across the background grid was unique for each such trial. On distractor (dSAT) trials, all the squares in the grid - except for the center square - changed their shades every 200 ms (at 5 Hz) from the beginning of the monitoring period until the onset of the response cue. For both SAT and dSAT trials, the signal was presented on a random half of trials. These SAT and dSAT trials provided the data of primary interest for the present analyses.

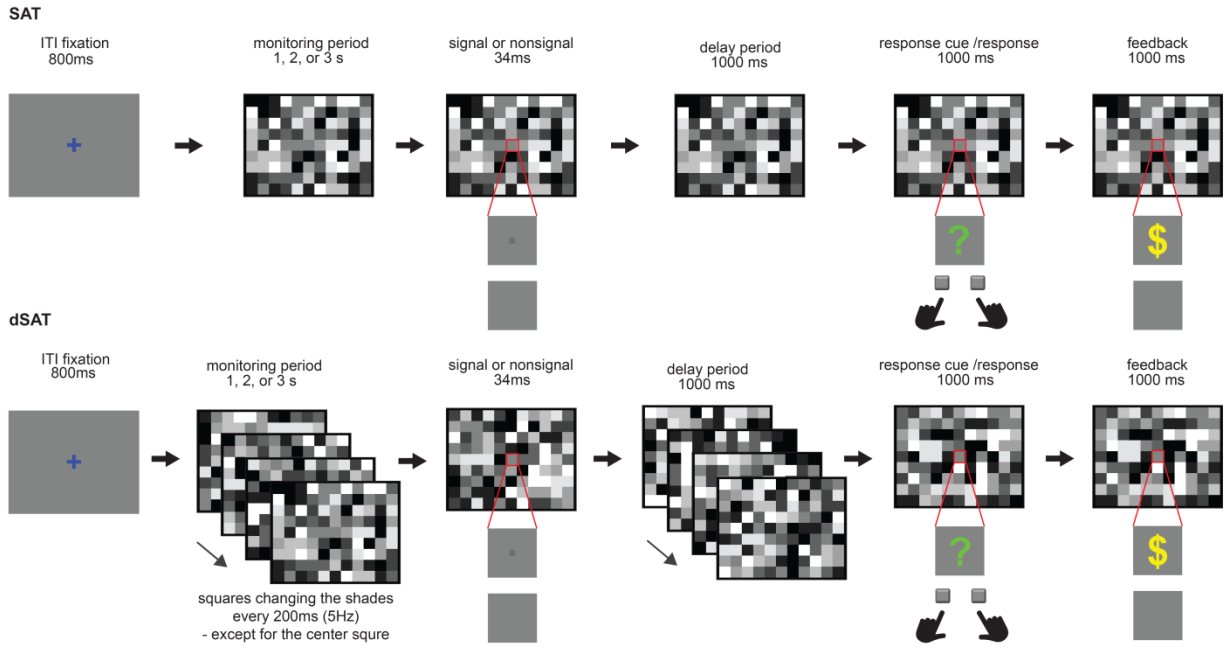

Figure 2.1. Modified Sustained Attention Task (SAT). Each trial started after an inter-trial interval (ITI) of 800ms. Participants monitored the center square to detect the presence or absence of a signal that occurred in the middle of that square on a random 50% of trials after 1-3s of monitoring period. After a short delay (1000 ms) following the signal/nonsignal presentation, a green question mark appeared in the center square for 1 s as a response cue. Participants reported the presence or absence of the signal by buttonpress using their index fingers (e.g., left for yes, right for no). Correct responses made within the 1 s were followed by reward feedback (a yellow $ sign).

To facilitate comparison with event-related fMRI studies from our lab (e.g., Berry et al., in press) using the dSAT, we also included filler trials. These started with a grey fixation (rather than the blue fixation used in SAT and dSAT trials) followed by a display that varied in duration like the SAT and dSAT trials but did not include the possibility of a signal event or any cue to respond. Instead, participants were told that the grey fixation indicated the start of a rest trial, and that they should simply relax while maintaining fixation on the center square. Paralleling the SAT and dSAT trials, the background was static for half of the filler trials and dynamic for the other half.

Participants were asked to complete 7 blocks, and each block included 72 task trials (36 no distractor, 36 distractor) and 36 filler (18 no distractor, 18 distractor) trials; in total, there were 126 signal and 126 nonsignal trials in each condition.

Procedure

All participants first completed informed consent procedures and a health and demographic questionnaire. The EEG cap and electrodes were set up, and the participants filled in a self-rating scale on everyday attention function (Imaginal Processes Inventory (IPI) questionnaire; Singer & Antrobus, 1970). Participants were then given verbal instructions along with a diagram of the stimuli, followed by computerized instructions. The computerized instructions were followed by a practice block in which three mini blocks were embedded: The first mini-block consisted of eight consecutive no distractor (SAT) trials, the second of eight consecutive distractor (dSAT) trials, and the third of 36 trials with all trial types (no distractor (SAT), distractor (dSAT), and filler trials) randomly intermixed. Practice blocks were repeated until the participants reached at least 60% overall accuracy. Participants needed 1-2 practice blocks (1.28 on average). Participants then completed the computerized task, followed by Edinburgh handedness questionnaire (Oldfield, 1972), and an eye-test with low contrast Sloan letters (Precision Vision, www.precision-vision.com).

EEG recording and preprocessing

Electroencephalography (EEG) was recorded from a 64-channel Ag/AgCl scalp electrodes, two mastoid electrodes, and six electrooculorgram (EOG) electrodes, using the BioSemi ActiveTwo system (ActiView version 6.04). The vertical EOG were recorded from electrodes placed above and below each eye and the horizontal EOG were recorded from electrodes placed external to the outer canthus of each eye. Data were recorded at a sampling rate of 1024 Hz and referenced to a ground formed by the common mode sense (CMS) active and driven right leg (DRL) passive electrodes (http://www.biosemi.com/faq/cms&drl.htm). To prevent aliasing effects of high frequency electrode and amplifier noise, low-pass filtering was performed during recording using the ADC's decimation filter, which has a 5th order sinc response with a -3dB point at approximately 205Hz (1/5th of the sampling rate (http://www.biosemi.com/faq/adjust_filter_activeone.htm). All electrode offsets were between ± 20 mV.

Channels identified as noisy during the recording session were replaced using spherical spline interpolation. Data were filtered using an IIR butterworth bandpass filters (high-pass: 0.1Hz, low-pass: 30Hz) and re-referenced by subtracting the average of the two mastoids from the signals of all electrodes. Signals were then visually inspected and screened using the following criteria: blinks at the signal/nonsignal onset, severe noise across the whole channels, unusual sweeps in the mastoid signals, extremely high frequency noise originating from EOG signals. Ocular movement artifacts were corrected using the algorithm from Gratton, Coles, & Donchin (1983). Then EEG epochs were extracted time-locked to the monitoring period onset with [-750

to 1000] ms time window, baselined to the prestimulus period [-750 to 0] ms. Finally, trials in which the absolute voltage range exceeded 100 μV for any electrodes were removed from the analysis. All preprocessing procedures were conducted using EEGLAB (version 9.0.5.6b).

EEG data analyses

Local gamma synchronization

The time-frequency analysis was conducted using short-time discrete Fourier transform as implemented in the newtimef() function of EEGLAB (Delorme & Makeig, 2004). The oscillation power was extracted for 30 linearly spaced frequencies between 3Hz and 60Hz. The DFT uses sinusoidal wavelets with 3 cycles at the lowest frequency incrementing by 0.5 for higher frequency (default in EEGLAB; Delorme & Makeig, 2004). Signals preceeding the monitoring period ([-400 -100] ms from the monitoring period onset) were used as the baseline in the time-frequency analyses. As the final measure of the distractor-induced gamma power increase, the average power of the gamma frequency of interest (25-40Hz; ranges suggested to increase in response to distraction in the pilot data) during the 500 ms following the monitoring onset ([50 500] ms) were extracted from SAT and dSAT condition separately.

Trial-by-trial variations of the gamma synchrony and signal detection performance

In each individual, the power of oscillations at several gamma-band frequencies was extracted from each trial. The oscillation power was extracted for six linearly spaced frequencies from broadly defined low-range gamma-band (25-55Hz) using complex Morlet wavelets with 6 cycles. The frequency with the largest power value in a given trial was identified as the gamma peak of that trial. Then the standard deviation of the gamma peaks was used as an estimation of the dispersion of the gamma peak across trials for each individual.

Inter-trial coherence on the distractor-evoked 5Hz oscillations

The distractor-evoked 5Hz oscillations were evaluated using inter-trial coherence (ITC). Also referred to as “phase-locking factor”, “phase resetting”, “inter-trial phase coherence”, ITC measures the extent to which the phase-angles of the oscillation at a given frequency are consistent across trials (Cohen 2014; Delorme & Makeig, 2004; Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1996) and is commonly used to estimate oscillations evoked by rhythmic stimuli (Bardouille & Ross, 2008; Haenshel & Linden, 2011). The measurement value of ITC ranges from 0 to 1, 0 indicating no coherence and 1 indicating perfect coherence between the EEG data and the time-locking events (Cohen 2014; Delorme & Makeig, 2004). The newtimef function in EEGLAB was used to obtain the ITC at 5Hz from each time point in the epoched signal. The average ITC following the onset of monitoring period ([0 500] ms) were extracted for the hit and miss

trials from each condition. Finally, the significance of distractor-evoked 5Hz oscillations was assessed using the dSAT-SAT contrast in the hit and miss trials.

Statistical Analysis

Paired-sample t-tests were used to analyze the behavioral and neural measures in the SAT vs. dSAT conditions. To evaluate the relationships between the behavioral and neural measures, first-level bivariate correlation analyses were used. Influential cases identified by cook's distance (Cook's distance > 4/n, where n is the sample size, 29 in the present study) were excluded from the correlations. Cook's distance measures the standardized change in the fitted response vector $\hat{y}$ when the given case is deleted (Cook, 1977), and conventionally, cases with Cook's distance greater than 1 or 4/n are considered outliers (Cook & Weisberg, 1982; Bollen & Jackman, 1985). When testing the relationships between the neural and behavioral changes from SAT and dSAT (i.e., distractor effects) residuals were used instead of difference scores. Specifically, linear regression models were conducted on the dSAT measures with SAT measure as the predictor, and the resulting residuals were used as the variables in the correlation analyses. All statistical analyses were conducted using R (version 3.1.1).

Results

Behavioral Results

The distractor condition impaired the correct rejection rate ($t(28) = 7.25$, $p < .0005$, Cohen's $d = 1.35$), but enhanced the hit rate ($t(28) = -5.62$, $p < .0005$, Cohen's $d = 1.04$; Table 2.1). However, response times were slower in dSAT than SAT for both correct rejection and hit trials (correct rejection, $t(28) = -9.57$, $p < .0005$, Cohen's $d = 1.78$; hit, $t(28) = -10.75$, $p < .0005$, Cohen's $d = 2.00$), suggesting the increased hit rate in distractor condition may be driven by a response bias rather than a reduced difficulty of the task. To investigate this possibility, we re-analyzed the data using signal-detection theory methods that allow determination of sensitivity and bias (McMillan & Creeman, 2005). Detection sensitivity (d') was impaired by the distractor ($t(28) = 4.27$, $p < .0005$, Cohen's $d = .79$) and importantly, the response bias (beta) differed significantly between SAT and dSAT ($t(28) = 5.83$, $p < .0005$, Cohen's $d = 1.08$), reflecting that participants were guessing 'yes' more often in dSAT compared to SAT.

Table 2.1. Behavioral results.

	SAT		dSAT	
	m	SD	m	SD
hit rate	0.73	0.12	0.80	0.14
hit response time (ms)	326.01	54.13	374.22	61.20
correct rejection rate	0.96	0.03	0.86	0.09
correct rejection response time (ms)	505.72	61.00	542.53	62.64
d'	2.57	0.70	2.20	0.96
beta	6.00	4.64	1.34	0.95

The shift to a more liberal bias under distraction differs from our previous studies using the dSAT with humans (e.g., Berry et al., in press; Demeter et al., 2008, 2011, 2013). In those prior studies, participants typically became more, rather than less, conservative when the distractor was introduced. The difference between those studies and this one may be related to the difference in the implementation of the distractor condition: In our previous studies, the rapid contrast changes of the entire background may have primarily increased noise and difficulty at the perceptual level; since participants had the experience that the signal became more difficult to see, they may have become more conservative and reluctant to respond "yes". In the distractor used here, although the changing squares/rectangles in the background were distinct from the target signal in both size (much larger) and location (outside the center square), they still constituted sudden-onset visual stimuli, as does the target signal. One possibility is that the bottom-up salience and attentional inputs from these distractors helped push participants towards a more liberal response bias with an increase in false alarms. This explanation is somewhat speculative, but regardless the difference between this and previous studies should be kept in mind when interpreting the results.

EEG Results

Gamma power and variability during SAT performance (Hypotheses 1-3)

Previous rodent (St. Peters et al., 2011) and human (Berry et al., in press; Demeter et al., 2011) studies indicate frontoparietal involvement in the signal-detection task even without distraction. We therefore began by examining gamma synchrony

during the SAT (Figure 2.2) and its correlations with signal sensitivity as indexed by d' (Figure 2.3).

Across subjects, greater gamma power in the left temporoparietal (P7, TP7) and occipital (OZ, IZ) electrodes was significantly associated with better signal detection sensitivity (Figure 2.3). These correlations were unique to SAT condition except for electrode P7 (dSAT *p*s > .1 except for P7; further discussed below). The right prefrontal cortex (PFC) correlation fell short of standard thresholds for statistical significance (r = .36, p = .07), but may still be of conceptual interest because of the previous studies from both rodents and humans indicating right PFC involvement in SAT performance (St. Peters et al., 2011).

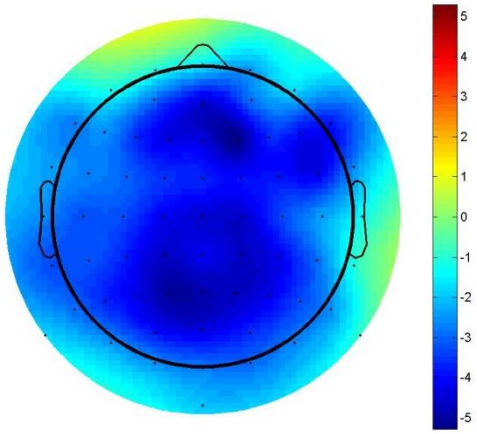

Figure 2.2. Gamma power in SAT. The scalpmap illustrates the t-values resulting from the one-sample t-tests of the average power of the 25-40Hz gamma oscillations following the monitoring onset ([50 500] ms). baseline: [-400 -100] ms.

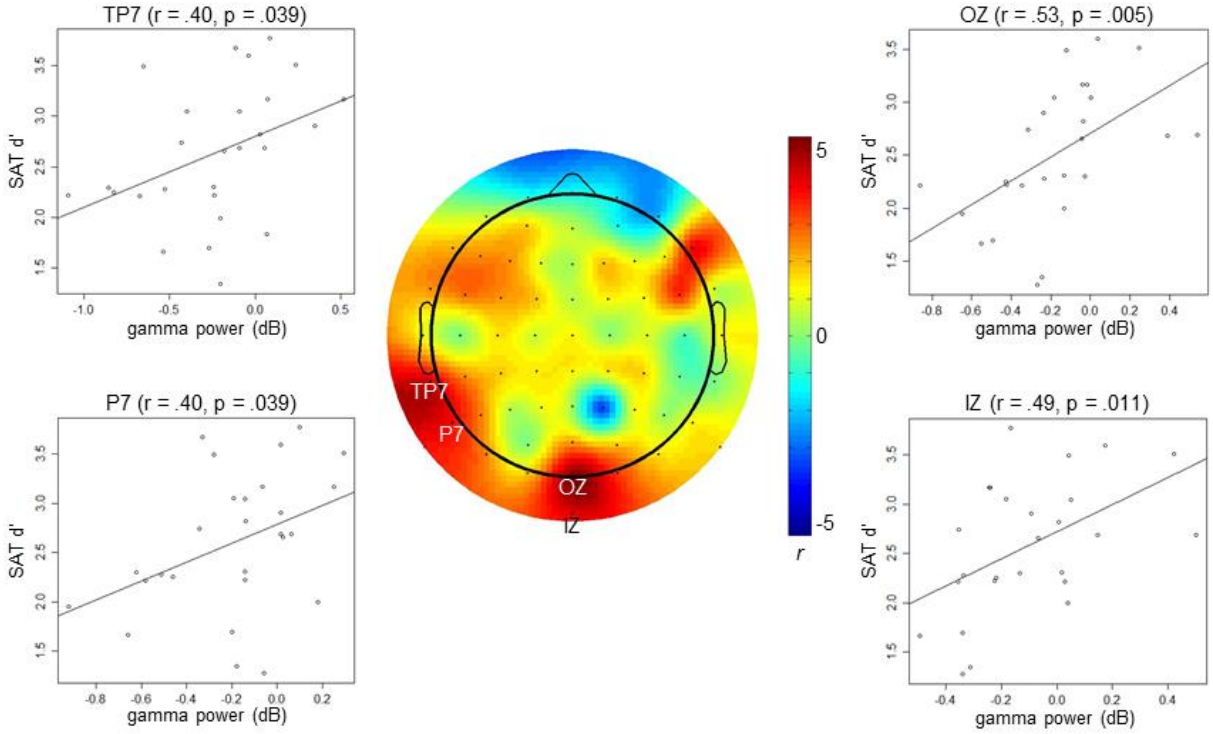

Figure 2.3. Correlations between local gamma synchronization and signal detection sensitivity in the absence of distraction (SAT). The scalpmap illustrates the pearson correlation coefficients at each electrode sites. In two left parietal and two occipital electrode sites, greater local gamma synchronizations were associated with better signal detection sensitivity.

Response time, and especially response time variability, can sometimes be a more sensitive measure to attention fluctuations than accuracy. A participant with good and consistent attentional control would be expected to respond at relatively consistent times across trials, whereas an individual with more attentional fluctuations would have more variability in response times representing a mixture of impulsivity/anticipations, on-task responses, and "just in time" delayed responses. For example, increased response-time variability is associated with and has been suggested as an intermediate endophenotype of attention deficit disorder (see discussion by Vaurio, Simmonds, & Mostofsky, 2009). If gamma on a particular trial reflects attentional control on that trial,

we should then expect to see a relation between the intrasubject variability in gamma peak dispersion and intrasubject variability in response time. This was indeed the case (Figure 2.4). The dispersion of the gamma peaks across trials was significantly correlated with greater RT variance in the midline frontal and left parietal electrodes (Fz, P3, P5, *p*s < .05).

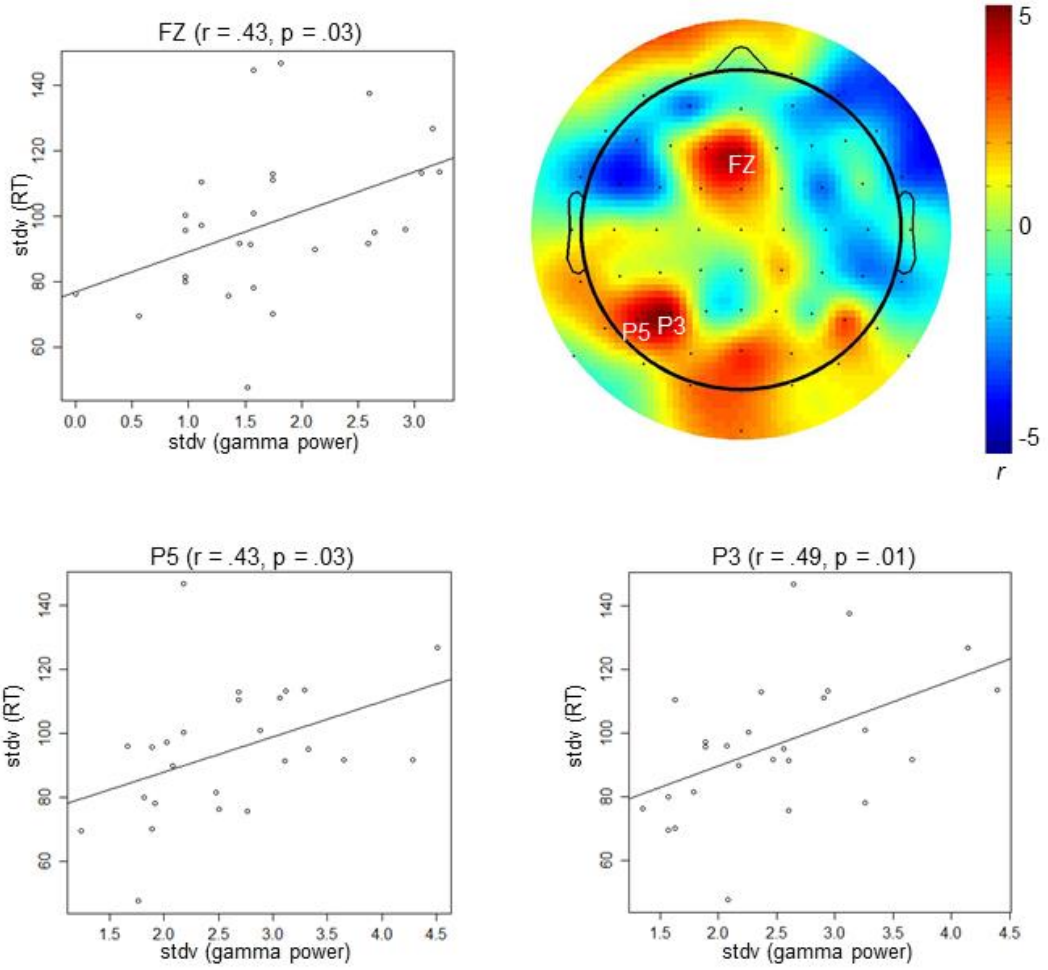

Figure 2.4. Correlations between the trial-by-trial variation of local gamma peak and response time variation. Greater variations of gamma peak across trials in the left parietal and mid-frontal electrode sites were associated with greater fluctuation of response time.

Changes in gamma power and variability related to distraction (Hypotheses 4-6)

Significant increases in gamma power in response to distraction were observed in five left parietal electrodes (Figure 2.5, P3, $t(28)= 2.39$, $p = .02$, Cohen's $d = .44$; P5, $t(28) = 2.05$, $p = .049$; Cohen's $d = .38$; P9, $t(28) = 2.64$, $p = .013$, Cohen's $d = .49$; PZ, $t(28) = 2.13$, $p = .04$, Cohen's $d = .40$; TP7, $t(28) = 3.20$, $p = .003$, Cohen's $d = .59$; $p >= .1$, Cohen's $d < .33$ in all other electrodes).

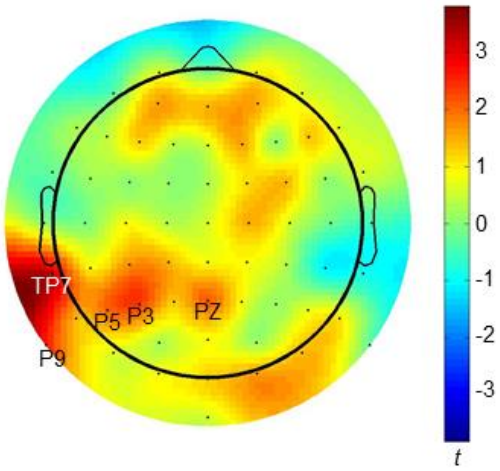

Figure 2.5. Gamma increases in response to distraction. The scalpmap depicts the t-values from the paired-sample t-tests on the gamma oscillation power from dSAT and SAT (dSAT-SAT). The gamma synchronization significantly increased in response to distraction in the left parietal electrode sites.

We next examined the correlations between the neural and behavioral distractor effects in these electrodes. dSAT|SAT residual scores (increase or decrease in dSAT greater than predicted by SAT) were used rather than simple difference scores because the latter are generally less reliable and more subject to baseline differences (e.g., a difference score of 10 is a larger proportional increase for a subject with a baseline measure of 100 than one with a baseline measure of 1000). Among the five electrodes that exhibited significant gamma increases in response to distraction, two left parietal

electrodes (TP7 and P9) showed significant correlations between changes in gamma synchrony and changes in signal detection sensitivity, $|r| > .5$, $p < .01$ in both electrodes (Figure 2.6). Participants who showed a greater increase in gamma had smaller distractor-related performance declines.

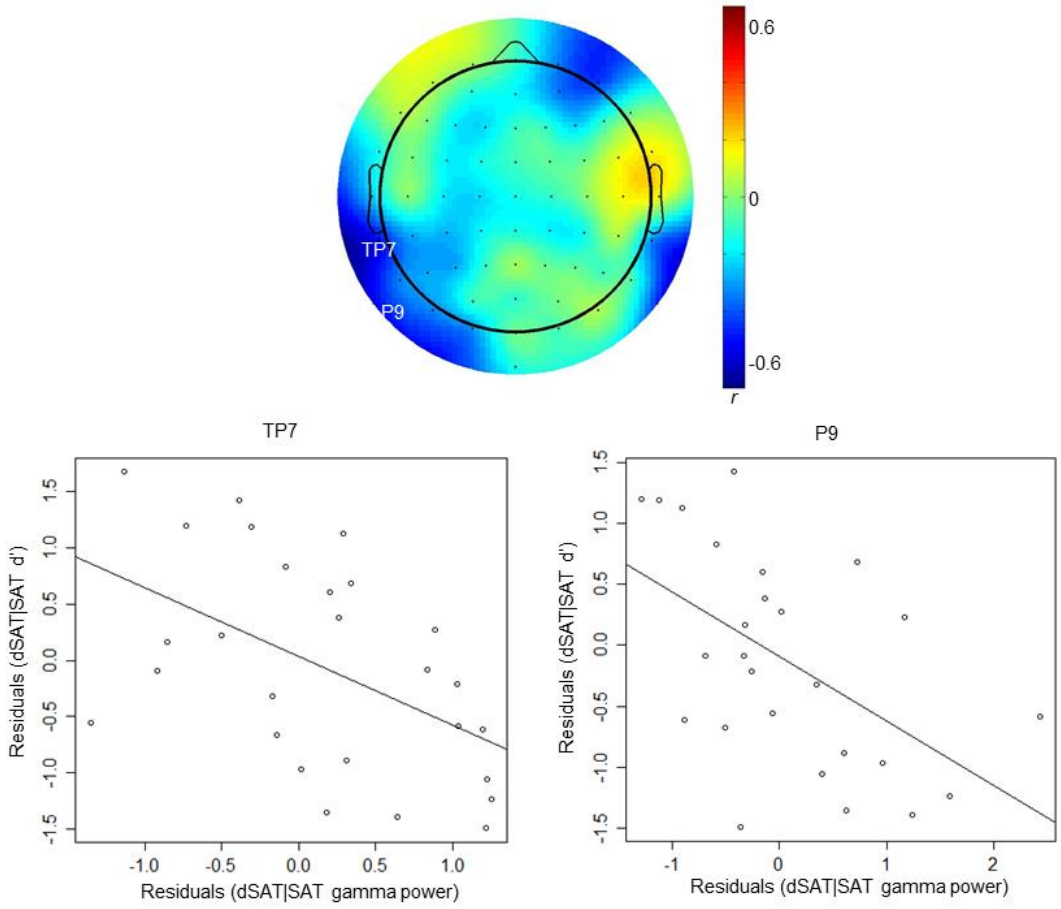

Figure 2.6. Gamma increases in response to distraction and preserved signal detection sensitivity. In the two far lateral electrode sites (TP7, P9) with significant gamma increases in dSAT, greater gamma increases were associated with preserved signal detection sensitivity.

Gamma peak variation increased significantly in response to distraction in the right frontal (FC6, FT8), left parietal (P5), and occipital (Iz) electrodes (Figure 2.7, FC6, $t(28)= 2.36$, $p = .03$, Cohen's $d = .44$; FT8, $t(28) = 3.87$, $p = .0006$; Cohen's $d = .72$; P5, $t(28) = 2.10$, $p = .045$, Cohen's $d = .39$; Iz, $t(28) = 2.23$, $p = .03$, Cohen's $d = .41$).

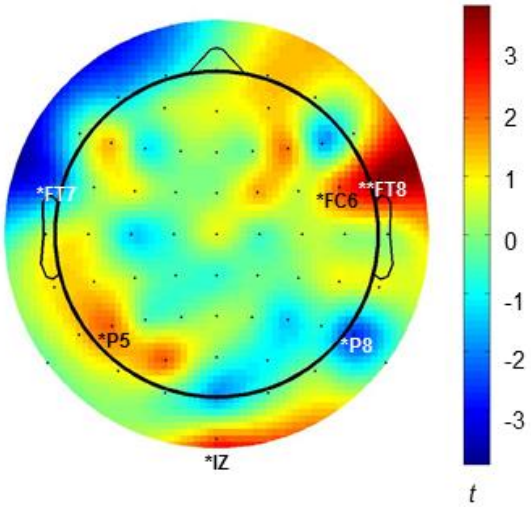

Figure 2.7. Gamma dispersion increases in response to distraction. In the right frontal, left parietal and occipital electrode sites (FT8, FC6, P5, Iz), gamma peaks were significantly more dispersed in dSAT compared in SAT. * p < .05 ** p < .001

Then we examined the correlations between the neural and behavioral distractor effects in these electrodes using dSAT|SAT residual scores. Among the four electrodes that exhibited significant gamma variance increases in response to distraction, one right frontal electrodes (FT8) showed significant correlations between changes in gamma peak dispersion and changes in response time variation, $r = .58$, $p = .001$; Figure 2.8). Participants who showed a greater increase in gamma dispersion in response to distraction had smaller distractor-related response time fluctuation.

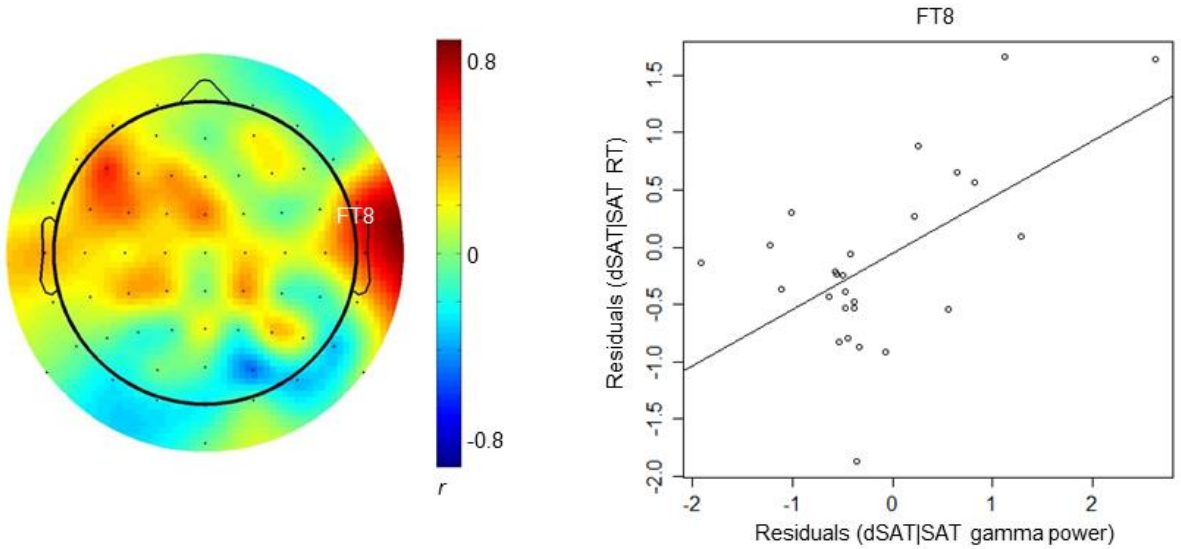

Figure 2.8. Distractor-related gamma dispersion and response time variation. The gamma dispersion increase in response to distraction was associated with greater increase in the response time variation in the right frontal electrode (FT8).

Distractor-entrained oscillation: Inter-trial coherence (ITC)

The scalpmaps in Figure 2.9 depicts the t-values resulting from dSAT vs. SAT paired-sample t-tests on the 5Hz ITC separately for the hit (left) and miss (right) trials. The 5Hz distractor evoked significant 5Hz ITC in parietal and occipital regions in the hit trials (Figure 2.9 scalpmap on the left; $p < .05$ in OZ, O1, O2, POZ, PO4, PO8, P2, P6, P7, P8, P10). Importantly, the distractor-evoked ITC at 5Hz was dramatically more robust and global in miss trials (Figure 2.9, scalpmap on the right; $p < .05$ except for the following 10 electrode sites: FZ, AF4, CP2, CP5, P10 ($.05 <= p <= .06$), FT8, FC6, C4, P9, IZ ($.07 <= p$). This pattern is consistent with our hypothesis that misses may in many cases have resulted because participants' attention was occupied by the distractor.

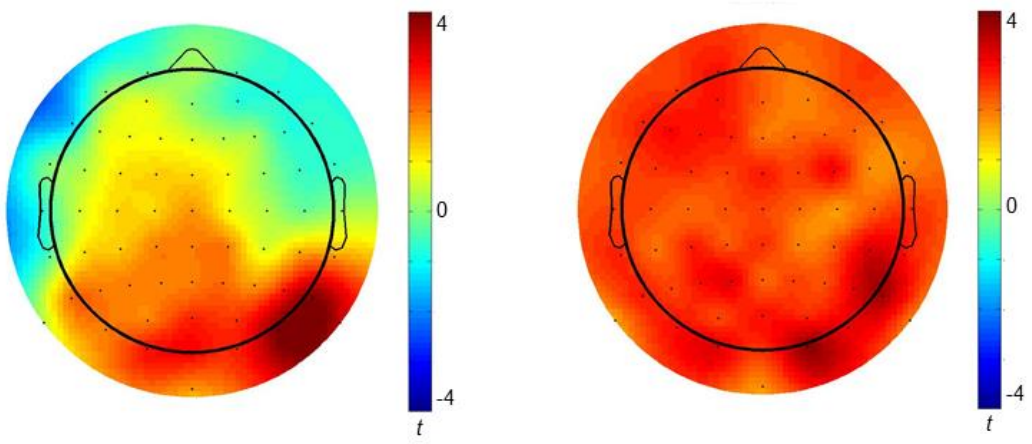

Figure 2.9. Scalpmaps of 5Hz ITC in dSAT. The distractor with periphery visual changes at 5Hz evoked significant 5Hz ITC in the occipital electrode sites for both hit (left) and miss (right) trials. This effect was prominently more robust and global in miss trials.

If the distractor-evoked ITC reflects attention to the distractor, and gamma modulations reflect cognitive control employed to resist the distractor, then distractor-evoked ITC should be modulated by gamma oscillations in the attentional network. For this analysis, we chose electrode sites of interest for the top-down modulatory and bottom-up distractor processing, and tested the dynamics between the two in dSAT hit trials. We selected TP7 and P9 as the electrodes of interest for the top-down modulatory oscillations because their gamma synchronizations significantly increased in response to distraction and these increases were associated with preserved signal detection performance (Figure 2.10, scalpmap on the right; also see section *Gamma increase in response to distraction*). Three occipital electrode sites (O1, OZ, O2) were selected for the bottom-up distractor-evoked 5Hz oscillations because those exhibited the most prominent the distractor-evoked 5Hz ITC in the hit trials (Figure 2.10, scalpmap on the left). We then examined the correlations between gamma power in the top-down modulatory sites and the 5Hz ITC in the bottom-up distractor processing

electrode sites. Greater gamma synchronization in the left parietal electrode site P9 was significantly associated with smaller distractor-evoked 5Hz ITC in the occipital site OZ (Figure2.10, scatterplot in the middle panel, r = -.39, p = .04; other p's > .3).

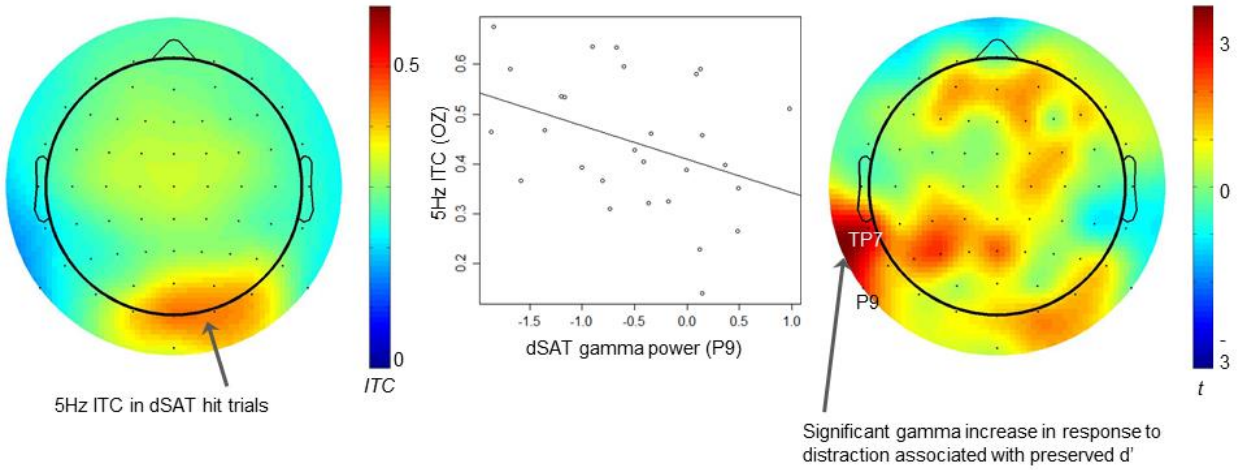

Figure 2.10. Inverse correlation between the left parietal gamma synchronization and the occipital 5Hz ITC in dSAT. Greater local gamma synchronizations in the left parietal electrode site (P9) were associated with smaller distractor-evoked 5Hz oscillations in dSAT.

Discussion

As predicted, the present study found 1) significant midfrontal local gamma synchrony during performance of a signal detection task, 2) correlations between gamma and signal detection sensitivity, and 3) correlations between intrasubject variability in gamma peak and response times. In addition, participants who showed greater increases in local gamma synchrony during the distractor condition had less distractor-related detection sensitivity, and once again gamma variability and response-time variability were related. Finally, 5 Hz ITC thought to reflect attention to the distractor was significantly greater during "miss" trials than during "hit" trials, and was

negatively correlated with parietal gamma synchronization. Together, these findings converge to provide compelling evidence for increases in parietal gamma synchronization as an index of neuronal processing supporting cognitive control, especially resistance to distraction.

In previous studies, enhancement of local gamma synchronization has been most robustly reported during the attentional selection of sensory information (Engel, Fries & Singer, 2001; Womelsdorf & Fries 2007; Jensen, Kaiser, & Lachaux 2007 for reviews). For example, the modality that monkeys are paying attention to determines whether increased gamma-synchronization is located in the somatosensory or visual cortex (Steinmetz et al., 2000). Moreover, human magnetoencephalography (MEG) and intracranial EEG (iEEG) studies repetitively demonstrated that gamma-band oscillation is increased for attended compared to unattended, or ignored stimuli in the visual (Tallon-Baudry, Bertrand, Hénaff, Isnard, & Fischer, 2005), auditory (Debener, Herrmann, Kranczioch, Gembris, & Engel, 2003; Tiitinen et al., 1993) and the somatosensory cortex (Bauer, Oostenveld, Peeters, & Fries, 2006; Brovelli, Lachaux, Kahane, & Boussaoud, 2005). In contrast, local gamma synchronization in the higher association areas such as frontal and parietal regions has not been as extensively studied. Increased parietal gamma has been observed during the pre-saccade period in a delayed saccade task (Medendorp et al., 2007; Van der Werf, Jensen, Fries, & Medendorp, 2008) and interpreted as encoding the motor goals in the visuomotor processing for saccades. To our knowledge, the present study is first to report enhanced local gamma-synchronization as a top-down modulatory mechanism in the higher association areas.

However, there were also some unexpected aspects of the results. Based on our previous rodent and fMRI studies (Demeter et al., 2011; St. Peters et al., 2011), we had initially expected that right prefrontal cortex would be the primary locus of our effects. Instead, it was left parietal. Fully determining the reasons for these differences would likely require a series of experiments, but as a general hypothesis we suspect that the explanation lies in the difference in how the distractor condition was implemented. In those previous studies, the distractor consisted of a whole-field change in background contrast, likely increasing the perceptual difficulty of detection. In the present study, background contrast remained constant across the whole field, but shifted within the field to give the appearance of appearing/disappearing squares and rectangles. These would have the potential to draw attention away from the signal, a suggestion supported by the increase in 5 Hz ITC during the distractor condition, particularly during misses.

Therefore, the critical operations for resisting the distractor in previous studies were most likely those involved in amplifying the representation and detection of the signal, whereas in the present study they would be those involved in keeping attention from being captured by the distractor. This explanation would be consistent with the suggestion by Corbetta and Shulman (2002) that right-lateralized ventral frontoparietal networks are specialized for the detection of relevant stimuli (the process we suggest may have been taxed in the “classic” dSAT), whereas parietal regions are more involved in top-down attention and selection (the processes we suggest may have been taxed by the current distractor), and left parietal cortex being described as particularly important for integrating stimulus representations with the appropriate task set.

The Corbetta and Shulman (2002) framework might help explain the differences in left versus right lateralization; another question is the respective roles of prefrontal versus parietal cortex. As noted earlier, in our previous fMRI studies, greater distraction-related activation of right PFC has been related to larger distractor-related performance impairments; furthermore, participants with a genetic polymorphism thought to reduce cholinergic function did not activate right PFC in response to distraction but did not show performance decrements relative to controls. Both of these findings already suggesting that right PFC does not contribute directly to the control processes needed to maintain performance (Berry et al., in press; in prep.; Demeter et al., 2011). In one of these studies (Berry et al., in prep.) we also found that right PFC – anterior cingulate connectivity was correlated with larger distraction-related performance decrements, whereas those individuals with the strongest right PFC-right parietal connectivity were least affected by the distractor. Therefore, right prefrontal cortex may be involved in sensitivity to increases in demand, a role consistent with observations of its activation when task complexity increases across a number of domains (e.g., switching, working memory, inhibition; see Aron, Robbins, & Poldrack, 2014; Banich & Depue, in press; Chatham et al., 2012; Hampshire et al., 2010 for discussion) and suggestions that it may be involved in something like “attentional effort” in response to such complexity (Sarter et al., 2006). It may then recruit parietal cortex (and/or other relevant regions) to implement the actual control operations.

Further supporting this suggestion, right PFC in the present study was an important locus for relations between neural and behavioral variability. That is, those participants experiencing more subjective difficulty as a result of the distractor would be

expected to show more variance in response times even if they were able to maintain accuracy, and this increase in variance correlated with increases in gamma peak variance in right PFC. Recent animal studies suggest that basal forebrain cholinergic stimulation (electrical or optogenetic) reduces power at low frequencies and increases it at high frequencies, and also increases trial-to-trial neuronal reliability and cortical encoding of visual information (Goard & Dan, 2009; Pinto, Goard et al., 2013; see Ma & Luo, 2012 for related results in the olfactory modality). Although these investigators did not examine right PFC, similar principles may explain the increases in right PFC cholinergic activity (and by extension, right PFC fMRI activity) in previous dSAT studies, and the patterns of gamma variability here. That is, cholinergic innervation of right PFC may be important for sensitivity to the increased load imposed by the distractor, whereas parietal regions (where cholinergic innervation also plays a critical role, e.g., Broussard et al., 2009; St. Peters et al., 2011) may be more important for implementation of top-down control in response to that load.

It was also noted that gamma synchronization increased in response to distraction in a medial posterior electrode (PZ, Figure 2.5). This may reflect the precuneus and/or posterior cingulate cortex activity. The precuneus/posterior cingulate cortex (PCC) region is part of the default mode network, which becomes deactivated as one engages in cognitive tasks (Fransson 2005; Mason et al., 2007; Raichle et al., 2001). The precuneus/PCC region in the default mode network particularly has been identified to serve as a core node as reflected in its prominent functional connectivity with the rest of the default mode network (Fransson & Marrelec, 2008). Moreover, less task-induced deactivation of this region, interpreted as inefficient suppression of task-

irrelevant mental activities, is associated with momentary lapses in attention (Weissman, Roberts, Visscher, & Woldorff, 2006). However, it is unclear at this stage how to interpret the distractor-related increase of the gamma synchronization in the PZ electrode site and whether it reflects the precuneus/PCC activities. Proper source localization analyses will need to be preceded for further interpretation of this result.

To summarize, the present study provides novel findings that the local gamma-band synchronization in the left parietal regions reflect a top-down attentional control mechanism contributing to distractor resistance, whereas variability in right prefrontal cortex is related to variability in performance, especially under distraction. Both previous studies indicating the role of frontoparietal cholinergic innervation in similar tasks (Broussard et al., 2009; Hasselmo & Sarter, 2011; McGaughy & Sarter, 1995; St. Peters et al., 2011; see reviews by Sarter et al., 2001; 2006, 2014;) and those suggesting a strong cholinergic contribution to gamma coherence and stability (Buhl et al., 1998; Metherate et al.,1992; Rodriguez et al., 2004; Kaiser & Lutzenberger, 2003; 2005; for review see Deco & Thiele, 2009) suggest that it plays an important role in the present findings as well, although that connection is admittedly indirect. The present study also focused on signal detection and distraction, and thus cannot speak to whether the neural mechanisms involved here are specific to those operations, or may extend more generally to many situations requiring cognitive control. To address those issues more directly, the studies presented in the following chapters will leverage variation in cholinergic denervation in patients with Parkinson's disease during signal detection with a perceptually-based distractor (the "classic" dSAT), during sustained attention with a distractor designed to draw attention away from the task (more

conceptually similar to that used here), and in a task that taps different aspects of cognitive control (conflict and task-switching).

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Chapter III

CHOLINERGIC DEFICIT IMPAIRS SIGNAL DETECTION AND RESISTANCE TO PERCEPTUAL DISTRACTION: EVIDENCE FROM PATIENTS WITH PARKINSON'S DISEASE

Introduction

The concept of cognitive control is often invoked to explain successful behavior in challenging environments, and deficits in control underlie cognitive and emotional problems in many psychiatric populations. However, control is a complex construct with multiple dimensions (e.g., top-down vs bottom-up, proactive vs. reactive, activation vs. inhibition) subserved by multiple interacting neural systems. Delineating how these systems contribute to different aspects of control is crucial both for basic understanding and for designing appropriate treatments. The present study uses patients with Parkinson's disease (PD) with varying levels of dopaminergic and cholinergic denervation as a natural experiment group to test the connections between these systems and an important first step in control: Detecting relevant cues, especially under challenging conditions.

Although PD is typically considered a dopaminergic disorder, mounting evidence also implicates other systems with at least partially independent timecourses of degeneration and behavioral effects (Müller & Bohnen, 2013). The dual-syndrome hypothesis suggests that dopaminergic denervation primarily leads to executive deficits,

and associates cholinergic declines with visuospatial deficits and dementia (Kehagia, Barker, & Robbins, 2013). However, cortical cholinergic deficits have also been linked to reduced executive, attention, and verbal learning scores in patients without dementia (Bohnen et al., 2012; in press). Patients with primarily thalamic cholinergic denervation, in contrast, show preserved performance on cognitive neuropsychological batteries. Instead, they have an increased incidence of falls and risky driving, possibly reflecting poor integration of sensory cues (Bohnen et al., 2012; Müller et al., 2013; Weathers, Kotagal, Bohnen, & Chou, 2014).

Likewise, behavioral neuroscience studies in rodents have encouraged a shift from traditional descriptions of the cholinergic system as a diffuse neuromodulator of nonspecific functions such as arousal (Lee & Dan, 2012; Perry, Walker, Grace, & Perry, 1999) to a more sophisticated conceptualization acknowledging its operation in spatially-restricted circuits and across different timescales to support different aspects of cognition and behavior (Zaborszky et al., 2013; see reviews by Hasselmo & Sarter, 2010; Sarter, Lustig, Howe, Gritton, & Berry, 2014; but see Moran et al., 2013; Varela, 2014 for current frameworks more in line with the traditional view). For example, maintaining signal-detection performance under challenging conditions depends on increases in right frontoparietal cholinergic efflux measured on the seconds-to-minutes timescale (Gill, Sarter, & Givens, 2000; St. Peters, Demeter, Lustig, Bruno, & Sarter, 2011). In contrast, trial-level shifts from monitoring to initiating signal detection processes depend on transient thalamocortical glutamatergic-cholinergic activity (itself influenced by neuromodulatory cholinergic inputs) on a millisecond-to-seconds timescale (Parikh, Kozak, Martinez, & Sarter, 2007; Howe et al., 2013).

Human neuroimaging results using parallel tasks and/or drug or genetic manipulations of cholinergic function generally support temporally and spatially specific involvement in different functions (see reviews by Klinkenberg, Sambeth, & Blokland, 2011; Newhouse, Potter, Dumas, & Tiel, 2011; Jasinska, Zorick, Brody, & Stien, 2013). However, the specificity of such studies' conclusions is necessarily limited because the effects of drug and genetic manipulations occur throughout the entire brain (and body). In contrast, PD patients' cholinergic denervation occurs along more specific cortical or thalamic pathways. We used this variation as a natural experiment to test the hypothesis of pathway-specific cholinergic contributions to signal detection and increased cognitive control in response to challenge.

Methods

Participants

All experimental procedures were approved by the University of Michigan's Institutional Review Board, and all procedures 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. PD patients were compensated at a rate of $25/hour. HC participants were compensated at a rate of $10-12/hour (the payment rate went up 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 Parkinson's disease. The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) was used to screen for dementia. Our lab also uses the Extended Range Vocabulary Test Version 3 (ERVT; Educational Testing Services, 1976) as a general measure of verbal intelligence and to screen out participants who may 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 number of 19 pairs of participants with PD and healthy age-, gender-, and education-matched controls (healthy controls, HC) completed the study. Age and education matches were with a $\pm$3 year margin of error within a pair. Two patient-control pairs 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, patients had been diagnosed with PD for 5.0 years, and the average severity score was 2.3 (1-5 scale, scores of 4 or more indicate severe disability; Hoehn & Yahr, 1967). Sixteen patients were on dopaminergic treatment (average daily

levodopa equivalent dose (LED; Tomlinson et al., 2010) for those who are on dopaminergic treatment was 615 mg, range 100-1596 mg), and no patient was taking any cholinergic or anti-cholinergic medicines. Three patients were also being 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 as depression and/or anxiety are frequently co-morbid with PD, occurring in 40-50% of patients (Cummings, 1992; Tandberg, Larsen, Aarsland, & Cummings, 1996), and thus can be considered typical of the disorder. One HC reported a previous diagnosis of depression but was not currently under 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 & Brody, 1969), Apathy Evaluation Scale (AES; Glenn, 2005), Beck Depression Inventory II (BDI-II, Beck, Ward, Mendelson, Moch, & Erbaugh,1961), Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), and Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS; copyright: Movement Disorder Society; Goetz et al., 2007)

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., in press; Demeter, Sarter, & Lustig, 2008; Demeter, Hernandez-Garcia, Sarter, & Lustig, 2011; Demeter, Guthrie, Taylor,

Sarter, & Lustig, 2013; Howe et al., 2013; see Lustig, Kozak, Sarter, Young, & Robbins, 2013; Nuechterlein, Luck, Lustig, & Sarter, 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 3.1. 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 (McGaughy & Sarter, 1995; Demeter et al., 2008). On standard, no-distractor (SAT) trials, the background was a static whole-field display of the "silver" color in E-prime. On distractor (dSAT) trials, this silver background alternated with a black background at a 10 Hz rate. Regardless of condition (SAT or dSAT), the signal event was presented against the silver background and consisted of a 3.5 x 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.

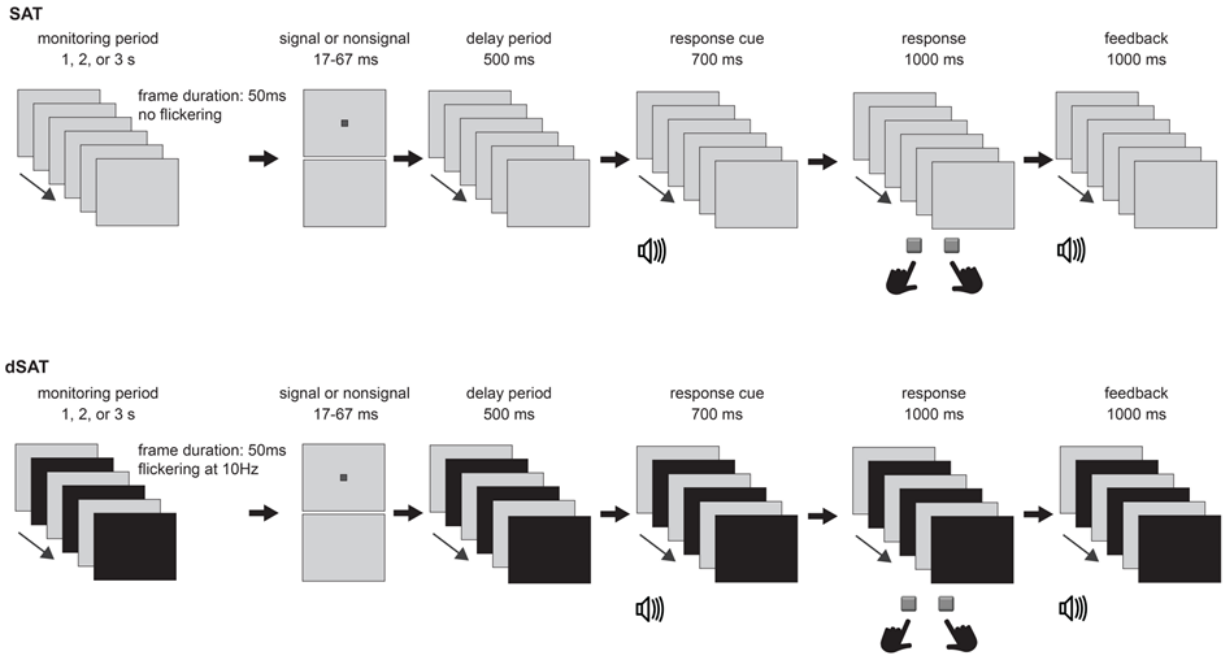

Figure 3.1. Sustained Attention Task (SAT). Each trial starts with a monitoring period with varying intervals (1, 2, or 3ms). A signal may or may not appear after at the end of the monitoring period. Participants must report whether there was a signal or not using the standard keyboard keys when they 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) requires additional attentional control for the task; The whole screen flashes at 10Hz, alternating between gray and black.

Consistent with our recent event-related fMRI and ERP studies (Berry et al., in press; Berry et al., 2012a; Berry et al., 2012b), SAT and dSAT trials were presented intermixed with fixation trials that required no 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. Then 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. Then participants were given 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. On average, the healthy control participants needed 1.6 SAT practice blocks and 1.5 mixed trial practice blocks. PD patients needed slightly more practice for the initial SAT practice to adjust to making speeded responses (1.8 for SAT, 1.4 for mixed block on average). This difference was not statistically significant (SAT t (32) = -.65, p = .52; dSAT t(32) = .28, p = .10).

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 that are the focus of the present paper investigating distraction were mixed (SAT/dSAT) and consisted of 15 trials each of SAT signal, SAT nonsignal, dSAT signal, dSAT nonsignal, and fixation. Trial types were pseudorandomly intermixed within each run so that each trial type followed each trial type an equal number of times.

Positron Emission Tomography (PET)

For the PD patients, Positron Emission Tomography (PET) scan data on dopaminergic and cholinergic function were obtained from previous (Bohnen et al., 2012) or ongoing studies. Participants came in for PET scanning after abstaining from dopaminergic drugs overnight. They first went through dopaminergic PET scanning, and resumed dopaminergic medication during the approximately 30-minute break between dopaminergic and cholinergic PET scanning. The PET scans were obtained within 12 months prior to the behavioral testing session.

The integrity of dopaminergic neurons 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 measures were extracted from caudate and putamen. A factor analysis of the DVR measures from 14 striatal subregions (bilateral ventral, anterior, posterior, and dorsal putamen, and the inferior, middle, and head part of caudate) confirmed this segmentation.

Cholinergic function was estimated using radio-labeled acetylcholine analogue [^{11}C]methyl-4-piperidinyl propionate (PMP) PET, which measures acetylcholinesterase (AChE) activity. 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), with a higher k_3 indicating higher cholinergic integrity. AChE k_3 measures were extracted for the whole cortex and thalamus separately, which reflect cholinergic nerve terminal integrity of the basal forebrain (including Nucleus basalis of Meynert) and the brainstem pedunculopontine nucleus respectively.

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 pooled from the Imaginal Processes Inventory (IPI) questionnaire

(Singer & Antrobus, 1970). The IPI items included the Poor Attentional Control (PAC) scale (Huba, Singer, Aneshenset, & Antrobus, 1982) and its subscales for boredom, mind-wandering, and distractibility.

In a separate session, participants completed the Activities of Daily Living scale (IADL; Lawton & Brody, 1969), Apathy Evaluation Scale (AES; Glenn, 2005), Beck Depression Inventory II (BDI-II, Beck et al., 1961), Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), and Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS; copyright: Movement Disorder Society; Goetz et al., 2007). Participants were tested on their usual dopaminergic medicines in both the sessions.

Statistical Analysis

Statistical analyses were conducted using SPSS and R. In keeping with previous work in both humans and animals, SAT score was used as the primary behavioral measure of signal detection. The advantage of SAT score over other signal-detection indices such as d' is that 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 is calculated using the formula SAT score = (H – FA) / [2×(H – FA) – (H – FA)^2], and ranges from -1.0 to +1.0. 100% correct (hits and correct rejections) performance yields a SAT score of +1.0 and 100% incorrect (misses and false alarms) performance yields a SAT score of -1.0. A SAT score of 0 reflects chance level performance.

To test the potential effects of the distractor condition and/or disease status (healthy vs PD) on signal detection, mixed-design ANOVAs were conducted on the SAT score with the distraction condition (no distractor, distractor) as the within-subject variable and the group (PD, HC) as the between-subject variable. Greenhouse-Geisser sphericity correction was applied if needed, in which case the corrected degrees of freedom (rounded to integers), *F*, and *p* values are reported. Independent-sample t-tests were used for follow-up comparisons on specific measures. 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). As effect sizes, we report Cohen's d for t-tests, and generalized eta squared ($\eta^2_{G,}$ Olejnik & 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 (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, Morris, & Richler, 2012).

Results

Demographic, questionnaire, and neuropsychological data

Table 3.1 provides the demographic information, neuropsychological test results, and overall performance of the PD patients and 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 scale (AES). However, PD patients had significantly higher depression scores (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). [1]

Only low-cholinergic PD patients show significant performance deficits compared to controls

Figure 3.2 (A) depicts SAT scores in the SAT and dSAT conditions for each group. As illustrated there, there was a robust main effect of distraction, $F(1, 32) = 53.88$, $p < .0005$, $\eta^2_G = .29$, but the size of the distractor effect did not differ between the groups, $F < 1$. Follow-up t-tests confirmed that the distractor effect was large and significant within each group (both $p < .0005$, both Cohen's $d > 1.00$). The two groups

[1] Although depression has been associated with various cognitive functions including attentional control (e.g., Ravnkilde et al., 2002; Paelecke-Habermann, Pohl, & Leplow 2005; see Austin, Michell, & Goodwin 2001 for review), we did not controlled for BDI as a covariate as it may confound the results. Depression score and cholinergic cortical activity are correlated positively in our data (r = .53, p = .03; see table 3.2). A potential explanation for this somewhat unexpected positive correlation is that this association may represent compensation for changes in other neural systems associated with depression in Parkinson disease such as norepinephrine, serotonin, etc..

also did not differ in overall performance, $F(1,32) = 1.62$, $p = .21$, $\eta^2_G = .04$, or within either condition tested separately, both $p > .15$, both Cohen's d < .50.

Table 3.1. Comparisons of HC and PD groups. Demographics, general cognitive functions (MoCA), affective states (AES, BDI), motor control (MDS-UPDRS III), overall performance, and PAC scores in PD patients and controls. The t and p values corrected for the violation of equal variances assumption for IADL, Motor UPDRS score, and dSAT non-signal trial omission rate. *d* = Cohen's *d.* ** indicates p < .0005

	HC		PD		group comparisons		
	M	SD	M	SD	*t*	*p*	*d*
Age (years)	64.1	7.9	63.1	8.1	.4	.70	.13
Education (years)	16.5	2.3	16.4	2.4	.0	.97	.04
Extended Range Vocabulary Test	26.3	8.6	25.5	9.0	.3	.78	.09
Montreal Cognitive Assessment	27.2	2.0	26.7	2.3	.7	.48	.24
Instrumental Activities of Daily Living	7.9	0.2	8.0	0.0	-1.0	.33	-.73
Apathy Evaluation Scale	25.0	6.6	27.1	8.3	-.8	.43	-.29
Beck Depression Inventory	3.9	3.9	8.4	5.1	-2.9	.01	-1.02
UPDRS Motor Symptom 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	-.02
SAT signal trial omission rate (%)	3.7	8.0	1.8	1.7	1.0	.35	.34
SAT non-signal trial omission rate (%)	11.3	17.1	6.8	5.8	1.0	.31	.36
dSAT overall accuracy (%)	72.4	19.6	73.3	13.5	-0.1	.88	-.06
dSAT signal trial omission rate (%)	9.9	14.8	3.6	4.6	1.7	.10	.59
dSAT non-signal trial omission rate (%)	15.6	20.6	5.7	5.7	1.9	.06	.68
Overall PAC	12.8	2.5	15.0	2.5	-2.5	.02	-.89
PAC mind wandering	12.9	2.8	15.8	2.9	-2.9	.01	-1.03
PAC boredom	11.7	2.5	13.5	2.8	-1.9	.07	-.68
PAC distractibility	13.9	3.3	15.8	3.8	-1.5	.15	-.53

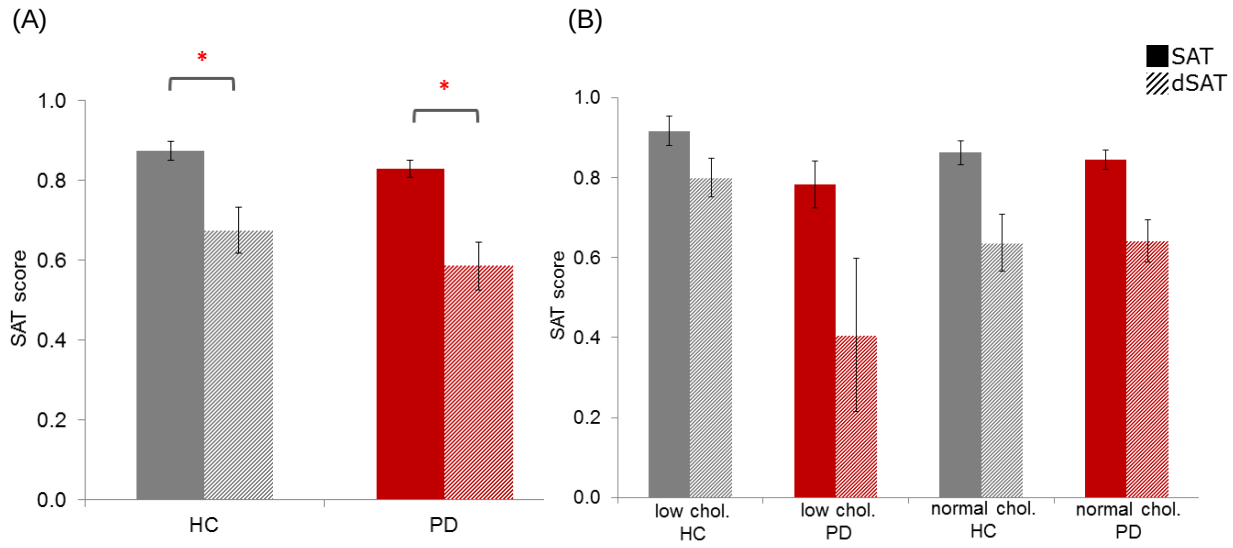

Figure 3.2. Signal detection performance in SAT and dSAT in PD and HC groups. (A) PD (red bars) and HC (gray bars) performed at similar level in the absence of external distraction. Distractor impaired the performance in both the groups, with no significant group difference. (B) In the PD patients with low cortical cholinergic integrity and their healthy counterparts, the distractor impaired performance significantly more in PD than in HC. Such interaction was not observed in PD patients with normal cortical cholinergic integrity and their healthy counterparts.

Although group differences did not approach significance when comparing the HC and PD groups as a whole, the numerical differences illustrated in Figure 3.2 (A) are in the direction of worse overall performance and a greater distraction effect in the PD group. The lack of an overall difference between HC and PD might occur because the majority of our PD patients fell within the "normal" range of cholinergic function as defined by Bohnen et al. (2012). Using the cutoff values from that paper, we re-analyzed the data with patient-control pairs subdivided into "normal-cholinergic" (PD patients with cortical k3 values of 0.022645 or above and their healthy controls, 13 pairs) or "low-cholinergic" (PD patients with cortical k3 values smaller than 0.022645 and their healthy controls, four pairs) groups.

As seen in Figure 3.2 (B), normal cholinergic patients and their healthy controls had equivalent performance, but low-cholinergic patients had worse overall performance and larger distractor effects than their controls. (Interaction between diagnostic group (HC, PD) and cholinergic group (normal, low), $F(1,30) = 4.65$, $p = .03$, , $\eta^2_G = .10$), 3-way interaction with distraction $F(1, 30) = 4.30$, $p = .047$, $\eta^2_G = .03$.

Because of the small size of the cholinergic subgroups, we also carefully examined the individual-subject data. The performance distributions of the HC and PD groups mostly overlapped in the normal-cholinergic pairs but were almost dichotomous in the low-cholinergic pairs. Specifically, for the normal-cholinergic pairs, only one PD patient fell below the range of scores for HC in the No Distractor condition, and there was complete overlap between the PD and HC groups in the Distractor condition. The opposite pattern was observed when comparing the low-cholinergic patients to their healthy controls: In the No Distractor condition, only one PD patient achieved a score high enough to overlap with the HC group and there was no overlap between the groups in the Distractor condition, i.e., all low-cholinergic patients scored worse than all controls.

In summary, these data strongly suggest that for PD patients on dopaminergic medication, signal detection even with the distractor challenge is preserved unless they are also suffering from cholinergic declines. To better understand the relation between cholinergic disruption and attention, we next performed a series of correlation and regression analyses within the PD group.

Self-rated Everyday Attention Scale

PD patients rated themselves more prone to mind wandering ($p < .01$; Table 3.1). For HC, the dSAT distractor effect correlated with the self-report measures of real-world boredom, but this was not the case for the PD patients (See Table 3.2).

Table 3.2. Correlations between the self-report everyday attention measure (PAC scores) and dSAT performance.. ** indicates $p < .0005$

			Self-report Everyday Attention Measure (PAC)				dSAT performance	
			overall score	mind-wandering	boredom	distractibility	baseline	distractor effect
HC	overall score	*r*	1	.92	.81	.82	-.09	-.44
		p		**	**	**	.75	.08
	mind-wandering	*r*	.92	1	.75	.62	-.35	-.32
		p	**		0	.008	.17	.22
	boredom	*r*	.81	.75	1	.38	.05	-.59
		p	**	**		.13	.85	.01
	distractibility	*r*	.82	.62	.38	1	.07	-.25
		p	**	.008	.13		.79	.33
	baseline	*r*	-.09	-.35	.05	.07	1	-.27
		p	.75	.17	.85	.79		.30
	distractor effect	*r*	-.44	-.32	-.59	-.25	-.27	1
		p	.08	.22	.01	.33	.30	
PD	overall score	r	1	.81	.67	.86	-.13	-.11
		p		**	.003	**	.62	.69
	mind-wandering	r	.81	1	.32	.60	-.30	.09
		p	**		.21	.01	.25	.72
	boredom	r	.67	.32	1	.33	.04	-.14
		p	.003	.21		.19	.87	.59
	distractibility	r	.86	.60	.33	1	-.06	-.18
		p	**	.01	.19		.82	.49
	baseline	r	-.13	-.30	.04	-.06	1	-.68
		p	.62	.25	.87	.82		.003
	distractor effect	r	-.11	.09	-.14	-.18	-.68	1
		p	.69	.72	.59	.49	.003	

Thalamic cholinergic measures uniquely predict distractor effects

Table 3.3 shows the simple correlations (Pearson's r) between the performance measures, the PET measures of cholinergic and dopaminergic integrity, and individual difference variables (age and depression score (BDI)) that might contribute to variance on the performance and PET measures. As illustrated there, performance in both conditions as well as the distractor effect (SAT – dSAT) 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. However, there were also significant correlations between age and the PET measures that were related to performance, and so we next conducted a series of hierarchical regression analyses to determine their unique contributions. 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, Miles, & Field 2012).

As our primary question was whether greater cholinergic denervation might increase vulnerability to the distractor, 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 3.4). Critically, in the final model, only age and thalamic k3 remained significant predictors of the distractor effect over and above the other variables. Greater age was associated with a larger distractor effect ($b^* = .64$, $t = 2.65$, $p = .021$)), whereas greater thalamic k3 was associated with a smaller distractor effect ($b^* = -.59$, $t = 2.32$, $p = .039$; See Figure 3.3 (A)). Neither cortical k3 nor caudate DVR approached significance, both $t < 1$.

Table 3.3. Correlations between the behavioral measures, age, depressions score (BDI), and the PET measures. ** indicates p < .0005

		SAT score	dSAT score	distractor effect	age	BDI	thalamic k3	cortical k3	putamen DVR	caudate DVR
SAT score	*r*	1	.85	-.68	-.43	.19	.51	.50	.20	.49
	p		**	.003	.096	.473	.036	.040	.452	.047
dSAT score	*r*	.85	1	-.96	-.55	.21	.54	.47	.08	.42
	p	**		**	.021	.413	.027	.060	.752	.096
distractor effect	*r*	-.68	-.96	1	.56	-.20	-.49	-.39	-.01	-.33
	p	.003	**		.019	.438	.047	.120	.960	.194
age	*r*	-.42	-.55	.56	1	-.34	-.07	-.48	.07	-.38
	p	.096	.021	.019		.185	.794	.051	.803	.131
BDI	*r*	.19	.21	-.20	-.34	1	.14	.53	.13	.30
	p	.473	.413	.438	.185		.595	.029	.613	.266
thalamic k3	*r*	.51	.54	-.49	-.07	.14	1	.57	.22	.32
	p	.036	.027	.047	.794	.595		.017	.405	.216
cortical k3	*r*	.50	.47	-.39	-.48	.53	.57	1	.19	.37
	p	.040	.060	.120	.051	.029	.017		.454	.140
putamen DVR	*r*	.20	.08	-.01	.07	.13	.22	.19	1	.70
	p	.452	.752	.960	.803	.613	.405	.454		.002
caudate DVR	*r*	.49	.42	-.33	-.38	.29	.32	.37	.703	1
	p	.047	.096	.194	.131	.266	.216	.140	.002	

Table 3.4. Hierarchical multiple linear regression model for distractor effects. B, unstandardized coefficient; β, standardized coefficient

	coefficients				model statistics					
	B	β	*t*	*p*	R^2	ΔR^2	Δ F	sig. Δ F	Model Fit *F*	Model Fit *p*
step 1 model					.31	.31	6.88	.02	6.88	.02
constant	-.49		-1.7	.102						
age	.01	.56	2.6	.019						
step 2 model					.55	.23	2.04	.16	3.61	.04
constant	-.10		-.2	.859						
age	.01	.64	2.6	.021						
caudate DVR	.00	.01	.03	.975						
thalamic k3	-15.5	-.59	-2.3	.039						
cortical k3	13.4	.25	.9	.396						

The finding that thalamic (rather than cortical) cholinergic measures predicted distractor effects suggested that their contribution might be related to signal saliency more than top-down control functions. If so, then they should be related to changes in hits, but not changes in correction rejections. This was indeed the case (Table 3.5): When hits were used as the predicted variable, the results for both age and thalamic k3 were even stronger than when SAT score was used as the predicted variable (age: $b^* = .81$, $t = 4.12$, $p = .001$; thalamic k3: $b^* = -.78$, $t = 3.81$, $p = .002$). 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 size of the distractor effect. In contrast, none of the included variables were significant predictors of changes in correct rejections, all $t < 1$. (Figure 3.3 (B-C)). 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.

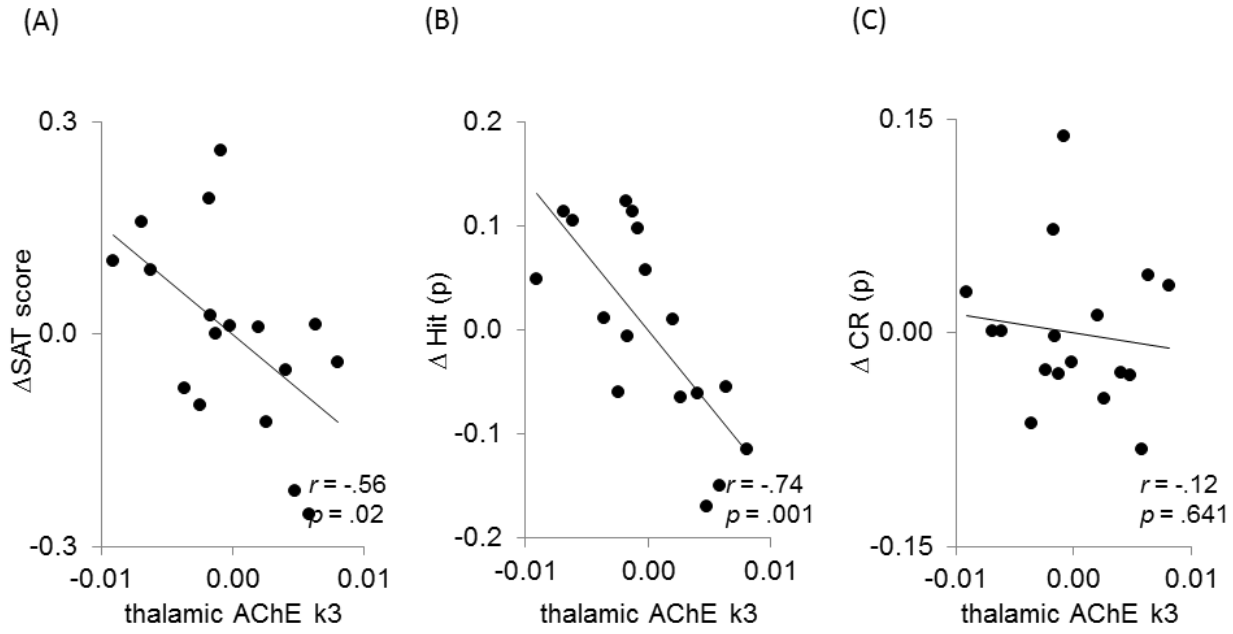

Figure 3.3. Correlations between the distractor vulnerability and thalamic cholinergic function. Residual plots after controlling for age, caudate DVR, and cortical k3. (A) Lower levels of the thalamic k3 was associated with greater vulnerability to distraction. (B-C) Such correlations were mainly driven by the correct detection (hit) rather than correct rejection trials.

Table 3.5. Hierarchical multiple linear regression model for the distractor effect in hit trials. B, unstandardized coefficient; β, standardized coefficient

	coefficients				model statistics					
	B	β	*t*	*p*	R^2	Δ R^2	Δ F	sig. Δ F	Model Fit *F*	Model Fit *p*
step 1 model					.34	.34.	7.6	.02	7.6	.02
constant	-.30		-1.5	.144						
age	.01	.58	2.8	.015						
step 2 model					.71	.37	5.0	.02	7.2	.003
constant	-.25		-.80	.440						
age	.01	.81	4.1	.001						
caudate DVR	.06	.23	1.3	.224						
thalamic k3	-14.5	-.78	-3.8	.002						
cortical k3	15.1	.40	1.8	.105						

Discussion

The present study leveraged PD patients' variation in dopaminergic and cholinergic denervation to assess these systems' contributions to signal detection under both standard and perceptually-challenging conditions. Measures of caudate dopaminergic integrity, cortical cholinergic integrity, and thalamic cholinergic integrity all correlated approximately equally (r values between .42 - .55) with signal detection under both standard and distracting conditions. However, only thalamic cholinergic integrity remained a significant predictor, over and above the other variables in the model, of maintained signal detection under challenge. Furthermore, thalamic cholinergic integrity was specifically related to successful hits under distraction, 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., Morris, Friston, & Dolan, 1997; Kobayashi & Isa, 2002; Langner & Eickhoff, 2013).

To our knowledge, this is the first report linking thalamic cholinergic function to signal detection under noise in humans. As noted earlier, compared to the system-wide effects of genetic comparisons or pharmacologic manipulations, the ability to assess pathway-specific (basal forebrain-cortical vs peduncopontine-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 and from animal studies that allow more detailed examination and experimental manipulation of cholinergic thalamic circuits.

For example, Bohnen et al. (2009) found that patients who reported a history of falls had an approximately 12% reduction in thalamic AChE activity compared to those who did not. Mueller et al. (2013) tied these deficits more specifically to difficulties integrating sensory information into perception and resulting action. They used the sensory organization test of the EquiTest balance platform (NeuroCom), which tests patients' ability to maintain postural stability in a series of conditions that eliminate (e.g., through a blindfold) or distort (by altering visual or proprioceptive input) sensory information. They found that even after controlling for dementia ratings and general motor function (MDS-UPDRS score), thalamic cholinergic integrity was associated with postural integrity scores. Furthermore, this relationship was especially important for those conditions that degraded sensory information, and was specific to thalamic cholinergic integrity; neither cortical cholinergic integrity nor striatal dopaminergic integrity measures showed such correlations.

These patterns extend to other attention-demanding real-world scenarios, and to other patient populations with cholinergic deficits. 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. Again, these deficits were specific: Neither cortical cholinergic nor nigrostriatal dopaminergic denervation differed between safe and risky drivers. Patients with supranuclear palsy, which 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 & LeWitt, 2011). In contrast, although cortical cholinergic loss is a hallmark of Alzheimer's dementia, where cognitive problems are the primary symptom and fall rates are much lower than in PD, these patients show very minor thalamic denervation (less than 1%) relative to age-matched healthy controls (Kotagal, Müller, Kaufer, Koeppe, & Bohnen, 2012). These two patient populations thus provide a double dissociation supporting the specific importance of thalamic cholinergic integrity.

Connecting closely to the patient findings, Grabli et al. (2013) found that in a macaque model of PD, cholinergic PPN lesions showed gait and balance problems resistant to dopaminergic remediation. Critical for an attentional explanation of such findings, in vitro evidence points to acetylcholine's contribution to thalamic and thalamic-cortical interaction processing thought to support stimulus processing and signal detection (see Beierlein, 2014; Runfeldt, Sadovsky, & MacLean, 2014 for recent reviews). For example, using slice preparations, Runfeldt et al. (2014) found that stimulation of cholinergic thalamic inputs re-organized sensory circuits in a way that would be expected to promote accurate signal detection, specifically by reducing spontaneous circuit activity and pruning weak functional connections (both of which would be expected to contribute noise) and prolonging more temporally precise activity that is more likely to represent an incoming signal. (See also Avery, Dutt, & Krichmar, 2014 for related computational modeling work.) Furthermore, Sun et al. (2014) found that cholinergic stimulation of somatosensory thalamic reticular nucleus slices could trigger spike activity and entrain firing to support fast and precise firing of the type likely to support processing of individual stimulus events, rather than just diffuse and long-

lasting neuromodulatory effects, although these may also play a role in changing signal to noise ratios (e.g., Wester & Contrearas, 2013).

The animal studies thus provide a plausible mechanism by which thalamic cholinergic denervation could impair the detection of important sensory signals, while laboratory studies of patients' postural sway under perceptually-challenging conditions and their "real-world" susceptibility to accidents and falls in everyday life provide intuitive clinical outcomes to such impairments. However, falls and accidents are complex, multiply-determined behaviors, making studies like the present one essential for linking the systems neuroscience data to specific cognitive processes that may in turn contribute to these complex outcomes. Indeed, our own studies using animal models suggest that both dual cholinergic/small dopaminergic lesions and large dopaminergic lesions can lead to falls, but for different reasons (Kucinski et al., 2013, under review). Notably, only those animals with cholinergic lesions showed deficits in signal detection and distractor resistance (Kucinski et al., 2013); in animals with large dopaminergic lesions falls were more related to reduced motivation or vigor for movement (Kucinski et al., under review). Bohnen et al. (2014) found that freezing of gait, another risk factor for falls, was related to cortical but not thalamic cholinergic denervation. Together these findings suggest multiple pathways for increased fall risk, and the need for careful neuroscientific and behavioral analysis to determine which pathways may be the most important for individual patients or subgroups.

This points out a limitation of the present study: due to the relative small sample size, we lack the power to make meaningful comparisons between fallers and non-fallers. Instead, the primary contribution is to provide evidence for a specific set of

cognitive processes – those involved in signal detection, especially under perceptual noise – linked to thalamic cholinergic denervation and thus providing a plausible mechanism for increased fall risk. Further substantiation of that mechanism will require further investigation and comparison in large samples of fallers well-characterized for qualitative aspects of their falls as well as attentional function. However, promising results come from studies indicating that PPN stimulation specifically targeting cholinergic regions reduced falls (Thevathasan, et al., 2010).

In summary, the data presented here suggest that thalamic cholinergic denervation makes a unique and important contribution to decreased signal detection, especially under conditions of perceptual noise. The specific decrease in hits, and lack of relationship to false alarms, supports the idea that this decrease in signal detection is due to decreased bottom-up saliency of the stimulus representation, rather than top-down control of attentional selection. The following chapters investigate whether those more top-down functions, such as avoiding the capture of attention by a competing distractor (see also Chapter 2), may be more reliant on cortical cholinergic integrity, and whether the contribution of mutual compensation between cholinergic and dopaminergic systems may become more evident in situations of greater or more complex demands on control.

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Chapter IV

DISTRACTOR VULNERABILITY CORRELATES WITH LOWER CORTICAL CHOLINERGIC INNERVATION IN PARKINSON'S DISEASE

Relevance to dissertation

Using EEG, Chapter 2 found that gamma oscillations thought to reflect cholinergic function (Metherate, Cox, and Ashe, 1992; Buhl, Tamás, and Fisahn 1998; Rodriguez, Kallenbach, Singer, & Munk, 2004; Kaiser & Lutzenberger, 2003; 2005; for review see Deco & Thiele, 2009) and attentional selection (Fell, Fernández, Klaver, Elger, & Fries, 2003; Fries, Nikolić, & Singer, 2007; Fries, 2009; Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1997) increased during presentation of an attention-grabbing distractor, and modulated recurrent oscillatory activity thought to reflect attention to the distractor as well as distractor-induced impairments in signal detection. Chapter 3 tested Parkinson's disease (PD) patients with varying levels and locations of cholinergic denervation, and found that thalamic cholinergic integrity was especially important for signal detection under perceptual noise. We suggested that the difference in localization (left parietal versus thalamic) of effects might have to do with the nature of the distractor.

For both studies, the target signal was a brief, sudden-onset visual stimulus of the sort thought to capture attention reflexively (e.g., Posner & Petersen, 1990). For the task used in Chapter 2, the distractor condition also consisted of sudden-onset visual stimuli appearing in the background. Thus, in this case, resisting the distractor would be expected to rely on attentional selection and integrating stimulus inputs with the appropriate task set (i.e., is a particular visual input a signal to be responded to, or a distractor to be ignored) – functions that Corbetta and Shulman (2002) suggest involve left parietal cortex. In contrast, for the task used in Chapter 3, the "distractor" consisted of rapid whole-field background changes in luminance, which likely reduced the perceptual quality and bottom-up saliency of the target signal. Thus, in this case, successful performance in the distractor condition may rely on the ability to preserve or amplify the saliency of the target signal, consistent with the thalamus's suggested role in regulating the communication of sensory information to cortex (see Sherman & Guillery, 2002; Mitchell et al., 2014 for reviews).

This framework predicts that in the case of a target signal with relatively little bottom-up salience and a distractor that provides a strong competitor to attention, cortical (especially left parietal) regions, rather than thalamus, should be critical for preserving performance during the distractor. The present study tested this hypothesis, again using PD patients with varying levels and locations of cholinergic denervation, but now with a low-salience target (duration differences) and compelling distractor (videos). We also examined potential relations between cholinergic integrity and other attentional functions, including the attentional precision needed for accurate duration processing,

the ability to sustain attention and task performance over time, and self-report measures of attentional function in everyday life.

General Introduction

The hallmark of Parkinson's disease (PD) is motor impairment related to striatal dopaminergic decline. However, a substantial number of patients also show cognitive impairments in a variety of domains (e.g., sustained attention, manipulative/executive functions of working memory, task-set shifting, mental rotation, planning and problem-solivng; for reviews see Lees & Smith, 1983; Dubois & Pillon,1996; Pagonabarraga & Kulisevsky, 2012; Robbins & Cools, 2014) that are not easily explained by striatal dopaminergic denervation. For example, PD (and thus dopaminergic decline) is not necessarily accompanied by cognitive impairment; about 15% of patients do not show any cognitive impairment throughout the disease period (Aarsland, Muniz, & Matthews, 2011). In addition, levodopa has no effects or mixed influence on cognitive function (Morrison, Borod, Brin, Hälbig, & Olanow, 2004; Poewe, Berger, Benke, & Schelosky, 2004; Lewis**,** Slabosz, Robbins, Barker, & Owen, 2005; Molloy et al., 2006; Kehagia, Barker, & Robbins, 2010). This has led to an increasing recognition of PD as a complex disorder to which multiple non-dopaminergic (e.g., cholinergic, serotonergic, noradrenergic) systems also contribute, but currently their contributions remain somewhat ill-defined (see review by Robbins & Cools, 2014). The current study examines how patterns of cholinergic denervation may be related to different specific aspects of controlled attention, both on a laboratory task that allows simultaneous assessment of multiple dimensions of attention (e.g., precision, sustaining, resistance to

distraction) and participants' self-reports of attentional problems in everyday life. In addition to their potential translational relevance, these findings help elucidate the cholinergic system's role in supporting cognitive function.

Mounting evidence suggests that cortical cholinergic denervation may contribute to cognitive dysfunction in PD (see Bohnen & Albin, 2011; Müller & Bohnen, 2013 for reviews). For example, anti-cholinergic medication impairs performance on digit span and the Wisconsin Card sorting task, tests of the storage and executive functions of working memory (Dubois et al., 1987; Dubois, Pillon, Lhermitte, & Agid, 1990). Consistent with these findings, Bohnen et al. (2006) reported that lower cholinergic activity - measured by acetylcholinesterase (AChE) PET - is associated with poor performance on digit span, and significantly but less robustly with tests of executive function such as Stroop and the Trail-Making tasks. Importantly, cortical cholinergic activity did not correlate with disease severity or duration of motor symptoms, suggesting that cholinergic denervation in PD does not simply reflect the degree of PD progress.

Most current studies of potential cholinergic contributions to cognitive deficits in PD have used standardized neuropsychological batteries. These have the advantages of reliability and facilitated comparison across studies, including those with other patient populations. In general, cortical cholinergic declines associated with basal forebrain pathways appear to be more strongly related to cognitive declines, whereas thalamic cholinergic declines associated with pedunculopontine nucleus pathways may be more related to sensory processing and integration (Bohnen et al., 2012). However, the broad nature of many of these tests limits the conclusions that can be made about more

specific cognitive processes, and can lead to confusions when different batteries use the same cognitive-function label for different tests or vice versa. For example, Bohnen et al., (2012) found the largest differences between normal and low cortical cholinergic groups on a global composite score of cognition. When examining the different domain scores contributing to this global composite, the effects for attention, executive function, and verbal learning were similar (verbal learning perhaps slightly smaller than the other two), also suggesting that cholinergic denervation might be associated with general cognitive decline rather than specific functions. There were no differences between the groups on the measure of visuospatial function, which might at first seem to indicate some specificity, but as they note this is somewhat at odds with the conclusions from a previous study (cf., Arsland et al., 2010) perhaps due to the use of different test batteries. Further, other than fall risk, there is limited information about the relation between cholinergic denervation and patients' "real world" cognitive function (see Weathers, Kotagal, Bohnen, & Chou, 2014 for an exception linking thalamic declines to risky driving).

The present study therefore tested patients with varying levels of cholinergic denervation using a paradigm that allows simultaneous assessment of multiple dimensions of attention, and administered a self-report questionnaire that assesses different dimensions of attentional control in everyday life. The laboratory task was the Continuous Temporal Expectancy task (CTET, O'Connell et al., 2009) with video distractor (Berry, Li, Lin, & Lustig, 2014). The CTET requires participants to monitor a stream of stimuli that usually changes at a standard duration; the participant's task is to detect rare target trials that take slightly longer. The target stimulus does not differ in

appearance from the standard, thus providing very little perceptual salience, and instead performance depends on the ability to focus attention on time (see Grondin, 2010; Meck, & Benson, 2002; Zakay & Block, 1997 for reviews). It is quite difficult to sustain this focus over multiple trials, and significant declines can be seen in as little as four minutes. The addition of a laptop to the side of the main task computer (Berry et al., 2014) that is either silent or playing videos allows an additional manipulation of external distraction.

We have previously shown that performance indexes related to these different attentional functions (initial focus or precision, sustaining attention, and resisting distraction) can be dissociated based on factors such as modality, genetics, and age group (Berry et al., 2014a, 2014b; Lin and Lustig, in prep.) Of particular relevance to the present study, Berry et al. (2014b) found that individuals with a polymorphism thought to limit cholinergic function showed a specific deficit in their ability to resist distraction. In addition, the size of the distractor effect measured in the lab correlated with participants' self-reported vulnerability to distraction in everyday life. We therefore expected to find converging evidence here, with those patients who have greater cholinergic declines also showing more vulnerability to distraction.

Methods

Participants

All experimental procedures were approved by the University of Michigan's Institutional Review Board, and all procedures 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. PD patients were compensated at a rate of $25/hour and HC participants were compensated at a rate of $10-12/hour (the payment rate went up during data collection).

Inclusion criteria for the study included the absence of a history of seizures, severe brain injury, and neurological disorders other than Parkinson's disease. The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) was used to screen for dementia. Our lab also uses the Extended Range Vocabulary Test Version 3 (ERVT; Educational Testing Services, 1976) as a general measure of verbal intelligence and to screen out participants who may 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 20 pairs of patients diagnosed with Parkinson's Disease and their age-, genter- and education- matched HC completed the study. Age and education matches were with a $\pm$3 year margin of error within a pair. Out of 20, three patient-control pairs 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, two other patients participants showed pronounced reversed distractor effect, falling outside 1.5 standard deviations from the group average. Thus, 17 PD patients (5 female; mean age

= 65.9; age range 52-85) and their healthy controls (± 3 years; mean age = 67.1; age range 53-84) were included in the final analyses.

The average disease duration of the PD patients was 5.1 years, and the average severity score was 2.3 (1-5 scale, scores of 4 or more indicate severe disability; Hoehn & Yahr, 1967). Thirteen patients were on dopaminergic treatment and the average daily levodopa equivalent dose (LED; Tomlinson et al., 2010) for those who are on dopaminergic treatment was 588 mg (range 100-1596 mg). No patient was taking any cholinergic medicine. Two patients were also being 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 as depression and/or anxiety are frequently co-morbid with PD, occurring in 40-50% of patients (Cummings, 1992; Tandberg, Larsen, Aarsland, & Cummings, 1996), and thus can be considered typical of the disorder. One HC reported a previous diagnosis of depression but was not currently under 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 & Brody, 1969), Apathy Evaluation Scale (AES; Glenn, 2005), Beck Depression Inventory II (BDI-II, Beck, Ward, Mendelson, Moch, & Erbaugh,1961), Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), and Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS; copyright: Movement Disorder Society; Goetz et al., 2007).

Continuous Temporal Expectancy Task (CTET) with video distractor

Both the CTET and the distractor videos were presented on HP laptops (windows7) with a 34.5×19.5 cm LCD screen (1024×768 screen resolution, 60Hz refreshing rate). The laptop used to present the CTET was placed in front of the participants at a 57 cm distance, and the laptop used to present the distractor videos was placed left to it at a 45 degree angle from the task laptop (Figure 4.1 (B)). E-prime software (Psychology Software tools; http://www.pstnet.com/eprime.cfm; version 2.0) was used for CTET stimuli presentation and response recording. Participants wore headphones connected to the laptop presenting the distractor videos, and responded to the CTET using the keyboard on the laptop used to present that task.

On each CTET trial, participants were presented with a black and white 10x10 grid of square tiles (1.27 cm^2 each) divided diagonally into black and white halves. On standard trials, the grid randomly changed orientation (90, 180, or 270°) after 800 ms; on target trials it rotated after 1070 ms. (Figure 3.4 (A)). There was a 20 ms long empty grey screen after each rotation. Participants were instructed to press the spacebar on the laptop keyboard as soon as they detected the target. Responses made during the target display and the following 2480 ms were counted as hits, other responses were counted as false alarms.

Data collection occurred during 10 four-minute long runs, 5 in the No Distractor condition and 5 in the Distractor condition, interleaved. Assignment of distractor condition (No Distractor vs Distractor) to odd vs even runs was counterbalanced across subjects. In the No Distractor condition, the laptop used for video presentation was

silent and displayed a gray screen. In the Distractor condition, the laptop played a series of 30 second video clips from various sources (e.g., cartoons, movies, sports) with sound presented via headphones. Each of the four-minute distractor series consisted of a unique set of video clips; order of clips remained constant within each series and the order of series assignment to Distractor run was counterbalanced across participants. None of the videos contained music or other obviously rhythmic content, or overtly violent or sexual content.

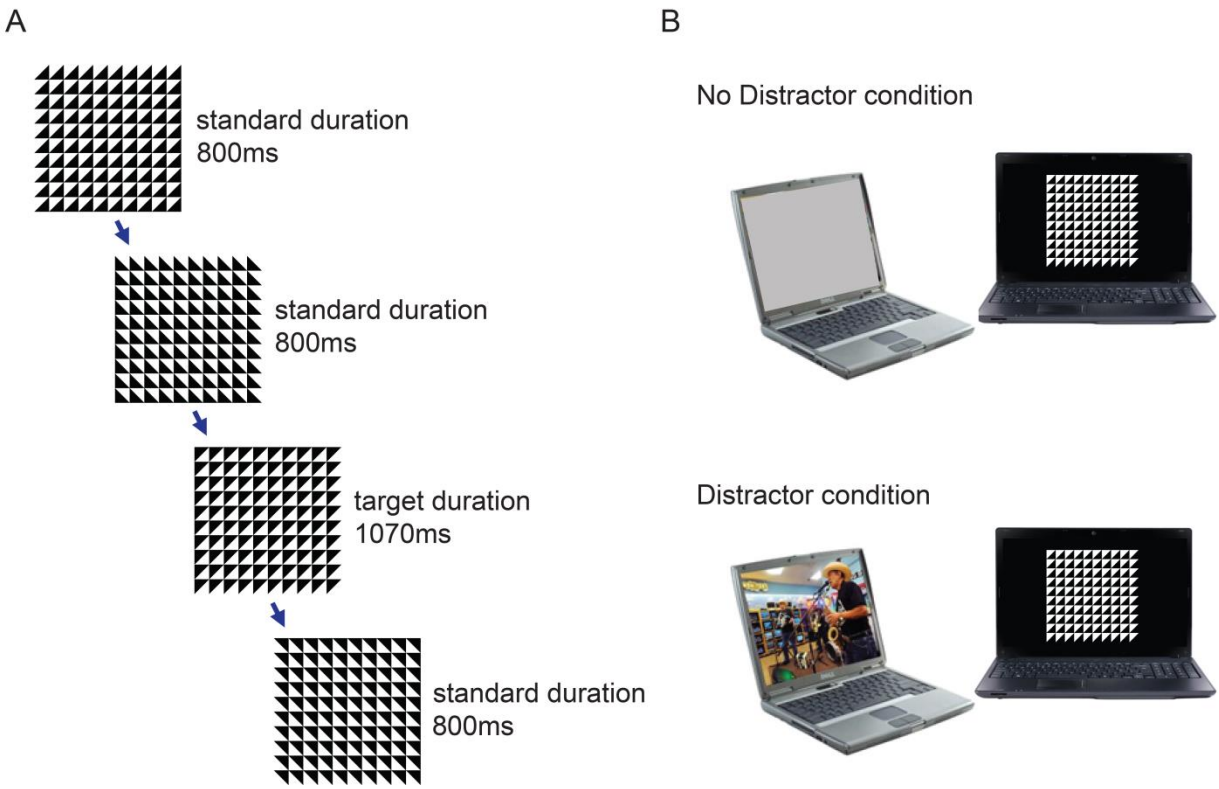

Figure 4.1. CTET with a distractor condition. As shown in (a) each trial consisted of a black and white grid made up of squares divided into triangles. At the end of the trial, the triangles rotated (90,180, or 270 degrees, chosen randomly) to start the next trial. The participant's task was to press the spacebar when they realized that the grid had taken longer than usual (1070 ms rather than the standard 800 ms) to rotate. (b) The distractor manipulation was implemented using a laptop oriented 32° to the left of the main task computer. In the No Distractor condition, the laptop was silent and displayed a gray screen. In the Distractor condition, it played video clips with sound.

Participants first received verbal instruction on the task followed by practice. By default, 6 short blocks of practice were given. A practice block was approximately 30 seconds long, and always contained 3 targets. In the very first practice block, the rotation delay of the targets was exaggerated (1600ms; 800ms longer than non-target trials) in order to make it clear to the participants what they should be looking for. From the second practice block on, the delay was the same as in the experimental blocks (1070ms; 270 ms longer than non-target trials). Participants had to detect all 3 targets in at least one of the five blocks using the 1070 ms target before moving to the experimental trials. All but 15 PD patients and 15 HC control reached this criterion in the first round of practice, those who did not complete another 5 blocks of practice using the 1070 ms target, and all met criterion within this round.

To assess the degree to which the videos captured attention and drew it away from the CTET, we also included a short surprise quiz (15 items, multiple choice) testing memory for the content of the distractor videos. At this end of this questionnaire, participants were asked to answer additional 5 questions to rate their experience during the task. This included five statements and asked to rate the degree to which they identified with each statement on a scale from 1 to 5. Questions 1, 2, and 4 measured mind-wandering, question 3 measured boredom, and question 5 measured distractibility. These questions were based on the Poor Attentional Control (PAC) subscales (See Berry et al., 2014a and *Self-reported attentional function in everyday life* below) but tapped on the state – as opposed to trait – measures.

Self-reported attentional function in everyday life

Participants completed 36 items from the Imaginal Processes Inventory (Singer & Antrobus, 1970). Each item consisted of a statement about cognitive function in everyday life (ex. “I find it difficult to concentrate when the TV or radio is on”), and participants rated the degree to which they identified with each statement on a scale from 1 to 5. Our analyses focus on the 15 items that make up the Poor Attentional Control (PAC) subscale identified in a later factor analysis (Huba et al., 1982).

The PAC has good internal consistency (coefficient alpha = .83) and test-retest reliability (r = .73; see also Tanaka & Huba, 1985-1986). It can be subdivided into subscales (5 questions each) of distractibility, mind-wandering, and boredom. Although Huba et al. (1982) do not provide psychometric data on these subscales, analyses of a large dataset from our lab (N = 510; see Berry et al., 2014a) indicate good internal consistency within subscales (mind-wandering coefficient alpha = .84, distraction coefficient alpha = .79, boredom coefficient alpha = .77). The subscales also have reasonable discriminant validity (average correlation between subscale total and items not in that subscale all r < .49 compared to items in that subscale all r > .72).

PET

The procedures and details of the PET scanning session are described in detail in Chapter 3. The measures used for the dopaminergic and cholinergic functions are identical as in Chapter 3; The [^{11}C]dihydrotetrabenazine (DTBZ) distribution volume ratio (DVR, Bohnen et al., 2009) was extracted from caudate and putamen for the

measures of the striatal dopaminergic functions and the AChE hydrolysis rate (k_3) were extracted from the cortical and thalamic cholinergic regions.

For regional analysis, AChE k3 measures were extracted from 66 grey matter segments of cortex (based on the gray matter segmentation supported by the FreeSurfer image analysis suite, http://surfer.nmr.mgh.harvard.edu/), and thalamus. Then bivariate correlations were conducted with the AChE k3 from each segment and the behavioral distractor effects.

Procedure

At the beginning of the experiment session, participants completed informed consent procedures and a health and demographic information questionnaire. Then they completed the CTET another computerized task as part of a separate study (the dSAT, see Chapter 2), which took approximately 1.5 hours. The order of the two computerized tasks was counterbalanced across subjects. Following the computerized tasks, participants completed ERVT, Edinburgh handedness Inventory (Oldfield, 1971), and 36 items pooled from the Imaginal Processes Inventory (IPI) questionnaire (Singer & 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 Instrumental Activities of Daily Living scale (IADL; Lawton and Brody, 1969), Apathy Evaluation Scale (AES; Marin, 1996; Glenn, 2005), Beck Depression Inventory II (BDI-II, Beck et al., 1961), Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), and Movement Disorder

Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS; copyright: Movement Disorder Society; Goetz et al., 2007). Participants were tested on their usual dopaminergic medicines in both sessions.

For the PD patients, Positron Emission Tomography (PET) scan data on dopaminergic and cholinergic function were obtained from a previous (Bohnen et al., 2012) or ongoing studies.

Statistical Analysis

Statistical analyses were conducted using SPSS (version 21) and R (version 3.1.1). The main dependent variables in CTET were initial performance (hit rate in minute1), performance decline over time (the slope of the hit rate changes over minute 1 to minute 4), and the distractor effect (hit rate difference in no distractor vs. distractor condition). These variables were analyzed using repeated-measures ANOVAs with the within-subject independent variables distraction (no distractor, distractor) and time (minute 1, 2, 3, and 4), and the between-subject variable group (PD, HC). Greenhouse-Geisser sphericity correction was applied if needed, in which case the corrected degrees of freedom (rounded to integers), *F*, and *p* values are reported. Independent-sample t-tests were used to compare the two groups on a specific measure. Bivariate and correlation analyses were used to examine the relationships between variables. Then in order to evaluate how specific neural measures uniquely predicted performance over and above potentially shared variance with other measures, hierarchical multiple regressions were conducted. As effect sizes, we report Cohen's d for t-tests, and generalized eta squared ($\eta^2_{G,}$ Olejnik & Algina, 2003) for repeated measures ANOVAs.

Generalized eta squared typically gives smaller values than partial eta square (η^2_p), but allows comparing effect size across studies (Fitz, Morris, & Richler, 2012).

Results

Participant Groups

The PD and HC groups were equivalent in age, education, and general cognitive functions (Table 4.1). The two groups significantly differed only in the motor control measure (MDS-UPDRS III), depression score (BDI), and Instrumental Activities of Daily Living (IADL). [1] All PD patients were capable of managing daily activities independently whereas some of the HC participants were not due to conditions such as injuries or neuropathy, which explains the higher IADL scores in PD than HC.

[1] Although depression has been associated with various cognitive functions including attentional control (e.g., Ravnkilde et al., 2002; Paelecke-Habermann, Pohl, & Leplow 2005; see Austin, Michell, & Goodwin 2001 for review), we did not controlled for BDI as a covariate it mayconfound the results. Depression score and cholinergic cortical activity are correlated positively in our data ($r = .50$, $p = .04$; see table 4.3). We interpret this somewhat unexpected positive correlation as reflecting potential compensation for changes in other neural systems associated with depression in Parkinson disease such as norepinephrine, serotonin, etc..

Table 4.1. HC and PD groups. Demographics, general cognitive functions (MoCA), affective states (AES, BDI), motor control (MDS-UPDRS III), everyday attention functions, recognition memory test for the video distractors in PD patients and controls (*t* and *p* values for the IADL and MDS_UPDRS scores are corrected for violation of equal variances) . ** indicates p < .0005

	HC		PD		*t*	*p*	Cohen's d
	M	SD	M	SD			
Age (years)	66.5	9.5	65.9	10.2	.2	.863	.06
Education (years)	16.8	2.0	16.7	2.4	.0	.969	.05
Extended Range Vocabulary Test	26.7	8.0	26.5	8.1	.1	.941	.03
Montreal Cognitive Assessment	27.2	1.9	26.7	2.3	.7	.517	.24
Instrumental Activities of Daily Living	7.9	0.3	8.0	0.0	-1.5	.163	N/A
Apathy Evaluation Scale	24.7	6.4	25.9	8.2	-.5	.629	.17
Beck Depression Inventory	4.4	3.6	8.9	4.7	-3.1	.004	1.11
Motor UPDRS (MDS-UPDRS Part III)	5.1	3.6	30.5	13.6	-7.4	**	2.63
Mind Wandering	12.8	2.7	15.5	3.1	-2.7	.011	.96
Boredom	11.5	2.7	13.9	2.7	-2.6	.013	.92
Distractibility	13.4	3.0	15.9	3.6	-2.1	.039	.78
Video Quiz	51.0	25.9	57.2	23.2	-.7	.463	.26

CTET performance comparison between PD and HC

Figure 4.2 depicts the performance change over time in the No Distractor (solid lines) and Distractor (dotted lines) conditions in the PD (black lines) and HC (gray lines) groups. Independent sample t-test on the baseline performance (the No distractor condition minute 1 hit rate) revealed only marginal group difference ($t(32) = 1.81$, $p = .08$, Cohen's $d = .56$) . The effects of distractor, time, and group on the performance (the hit rate) were tested using a 4 × 2 × 2 (time × distractor × group) ANOVA. For comparisons involving the effects of time, the linear contrast was used rather than the standard *F* value, consistent with testing the hypothesis of a decrease in performance over time. Overall, HC showed better performance than PD ($F(1, 32) = 5.37$, $p = .027$, $\eta^2_G = .12$). The hit rate was significantly impaired by distractors ($F(1, 32) = 58.92$, $p < .0005$, $\eta^2_G = .08$) and over time ($F(1, 32) = 56.39$, $p < .0005$, $\eta^2_G = .09$). Importantly,

the distractor effect was significantly greater in PD than HC (distractor by group interaction; F (1, 32) = 13.85, p =.001, η^2_G = .02). In contrast, the performance change over time did not differ in the two groups (no time by group interaction; F (1, 32) = 2.49, p = .125, η^2_G = .004).

PD recognized as much information as HC did from the distractor video clips (Table 4.1, t (32) = -.74, p = .463, Cohen's d =.26). On the exit questionnaire asking the participant's experience in terms of mind wandering, boredom, and distractibility during the task, PD patients scored higher than HC in the first mind-wandering item ("At times of this task, it was hard for me to keep my mind from wandering.") with marginally significant difference (t(32) = -2.0, p = .054, |t| < 1.6, p > .1 in all other items).

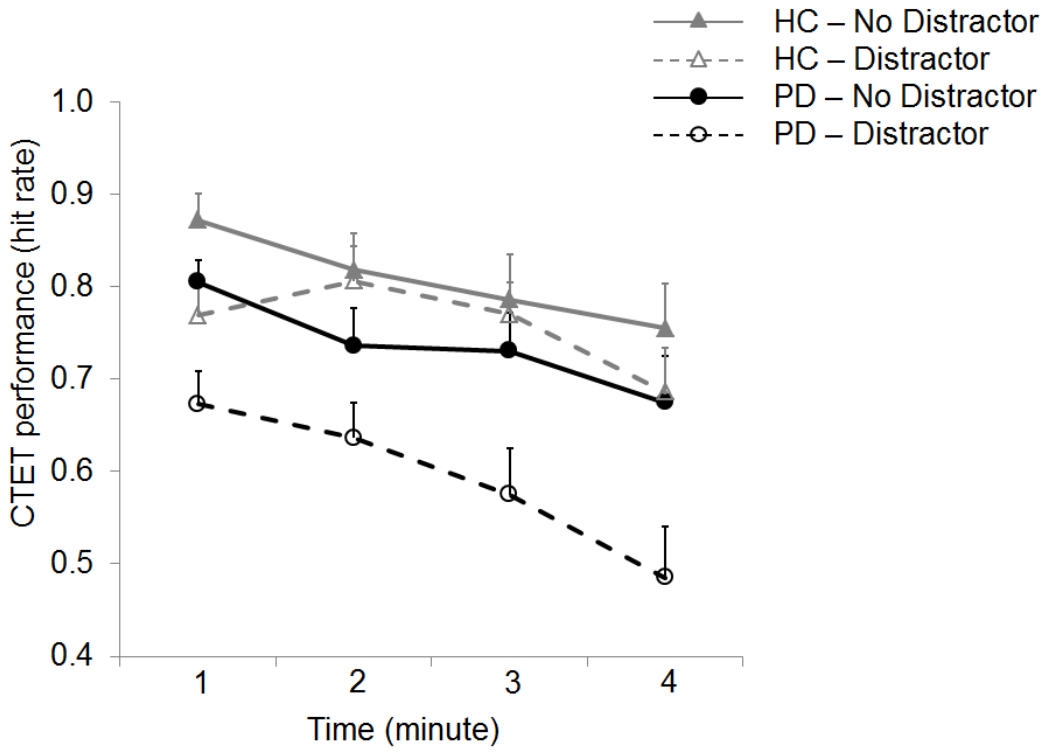

Figure 4.2. CTET performance with and without video distractor. In the absence of external distraction (no distractor condition; filled markers and solid lines), decline of sustained attention did not differ between the groups. However, external distraction (distractor condition; open markers and dotted lines) impaired the performance more in PD than HC. Markers represent the average hit rates for each minute and error bars represent standard error of the mean. .

Self-rated Everyday Attention Scale

PD patients rated themselves more prone to distraction, mind wandering, and boredom than HC did (all *p*s < .05; Table 4.1). For HC, the CTET performance measures correlated with the self-report measures of real-world poor attentional control, consistent with our previous studies (Berry et al., 2014a, 2014b), but this was not the case for the PD patients (See Table 4.2). The patients also did not show any correlations between the self-report measures and the CTET measures, all $r < .23$, $p > .38$.

Table 4.2. Correlations between the self-report everyday attention measure (PAC scores) and CTET performance. Baseline = hit rate in minute1, time on task = hit rate decrease over time, distractor effect = hit rate difference between the no distractor vs. distractor condition in minute 1. ** indicates p < .0005

			Self-report Everyday Attention Measure (PAC)				CTET performance		
			overall score	mind-wandering	boredom	distracti-bility	baseline	time-on-task effect	distractor effect
HC	PAC overall	*r*	1	.96	.82	.92	-.68	-.48	.51
		p		**	**	**	.003	.05	.04
	PAC mind-wandering	*r*	.96	1	.67	.89	-.67	-.40	.49
		p	**		.003	**	.003	.11	.048
	PAC boredom	*r*	.82	.67	1	.55	-.52	-.57	.36
		p	**	.003		.022	.034	.017	.160
	PAC distractibility	*r*	.92	.89	.55	1	-.64	-.34	.51
		p	**	**	.02		.006	.19	.04
	CTET baseline	*r*	-.68	-.67	-.52	-.64	1	.32	-.23
		p	.003	.003	.03	.006		.21	.39
	CTET time-on-task effect	*r*	-.48	-.40	-.57	-.34	.32	1	-.45
		p	.050	.11	.02	.19	.21		.07
	CTET distractor effect	*r*	.51	.49	.36	.51	-.23	-.45	1
		p	.04	.048	.16	.04	.39	.07	
PD	PAC overall	*r*	1	.84	.62	.87	-.02	-.33	-.21
		p		**	.008	**	.94	.19	.41
	PAC mind-wandering	*r*	.84	1	.27	.66	-.20	-.51	-.046
		p	**		.30	.004	.43	.04	.86
	PAC boredom	*r*	.62	.27	1	.29	-.07	.13	-.28
		p	.008	.30		.25	.80	.62	.28
	PAC distractibility	*r*	.87	.66	.29	1	.18	-.34	-.19
		p	**	.004	.25		.48	.18	.46
	CTET baseline	*r*	-.02	-.20	-.07	.18	1	.32	-.06
		p	.94	.43	.80	.48		.21	.82
	CTET time-on-task effect	*r*	-.33	-.51	.13	-.34	.32	1	-.58
		p	.19	.04	.62	.18	.21		.02
	CTET distractor effect	*r*	-.21	-.046	-.28	-.19	-.06	-.58	1
		p	.41	.86	.28	.46	.82	.02	

Cortical cholinergic measures uniquely predict distractor effects

Table 4.3 shows the first-level bivariate correlations (Pearson's *r*) between the performance measures, the PET measures of cholinergic and dopaminergic integrity, and individual difference variables (age and depression score (BDI)) that might contribute to variance on the performance and PET measures. Neither baseline performance nor performance decline over time (slope) correlated with age, BDI score, or any of the PET measures. In contrast, the distractor effect (hit rate difference between the no distractor vs. distractor condition in minute 1) showed moderate to strong correlations (absolute r values between .30 and .58) with age, cortical k3, putamen DVR, and caudate DVR. There were also moderate correlations between age and the cortical k3 and caudate DVR (absolute r values .33-.34). Thus we conducted hierarchical regression analyses to determine the unique contribution of age and the neural measures in the distractor resistance. Although thalamic k3 did not correlate with the distractor effect or age, it was included as a predictor in the hierarchical regression model in order to allow comparisons with the results from Chapter 3. In all of the analyses reported here, the collinearity statistics were within acceptable ranges (tolerance values above .41; values above .10 are typically considered acceptable; all VIF values below 2.4; values below 10 are usually considered acceptable; Field, Miles, and Field 2012).

Table 4.3. Correlations between the behavioral measures, age, depressions score (BDI), and the PET measures. Baseline = hit rate in minute1, time on task = hit rate decrease over time, distractor effect = hit rate difference between the no distractor vs. distractor condition in minute 1.

		baseline	time on task	distractor effect	age	BDI	thalamic k3	cortical k3	putamen DVR	caudate DVR
baseline	*r*	1	.32	-.06	-.20	.20	.10	.13	-.34	-.28
	p		.213	.819	.432	.439	.713	.622	.187	.285
time on task	*r*	.32	1	-.58	-.18	-.29	-.19	.19	.00	.04
	p	.213		.015	.481	.259	.463	.465	.996	.869
distractor effect	*r*	-.60	-.58	1	.46	-.20	-.01	-.52	-.30	-.38
	p	.819	.015		.065	.442	.967	.031	.237	.129
age	*r*	-.20	-.18	.46	1	-.38	-.02	-.34	-.01	-.33
	p	.432	.481	.065		.138	.946	.181	.968	.202
BDI	*r*	.20	-.29	-.20	-.38	1	.24	.50	.08	.34
	p	.439	.259	.442	.138		.360	.040	.751	.185
thalamic k3	*r*	.10	-.19	-.01	-.02	.24	1	.67	.29	.37
	p	.713	.463	.967	.946	.360	.	.003	.256	.149
cortical k3	*r*	.13	.19	-.52	-.34	.50	.67	1	.33	.50
	p	.622	.465	.031	.181	.040	.003		.19	.041
putamen DVR	*r*	-.34	.00	-.30	-.01	.08	.29	.33	1	.75
	p	.187	.996	.237	.968	.751	.256	.191		.001
caudate DVR	*r*	-.28	.04	-.38	-.33	.34	.37	.50	.75	1
	p	.285	.869	.129	.20	.185	.149	.041	.001	

As in Chapter 3, our primary question was whether more severe cholinergic denervation might increase vulnerability to the distractor. Accordingly, we used the distractor effect as the criterion variable. As predictor variables, age was entered in the first step, followed by cortical k3, thalamic k3, and caudate DVR in a single step (See Table 4.4). Critically, in the final model, only cortical k3 was a significant predictor of the distractor effect over and above the other variables with thalamic k3 being a marginally significant predictor in the opposite direction. Greater vulnerability to the distractor was associated with lower cortical k3 (b^* = .77, t = -2.51, p = .027; See Figure 4.3) and

higher thalamic k3 (b^* = .56, t = 2.00, p = .068). Caudate DVR did not approach significance, t < 1.

Table 4.4. Hierarchical multiple linear regression model for distractor effects. B, unstandardized coefficient; β, standardized coefficient

	coefficients				model statistics					
	B	β	*t*	*p*	R^2	Δ R^2	Δ F	sig. Δ F	Model Fit *F*	Model Fit *p*
step 1 model					.21	.21	3.98	.065	3.98	.065
constant	-.15		-1.05	.309						
age	.00	.46	1.99	.065						
step 2 model					.53	.32	2.70	.092	3.36	.046
constant	.20		.833	.421						
age	.00	.15	.681	.509						
caudate DVR	-.03	-.15	-.658	.523						
thalamic k3	8.25	.56	2.00	.068						
cortical k3	-21.73	-.77	-2.51	.027						

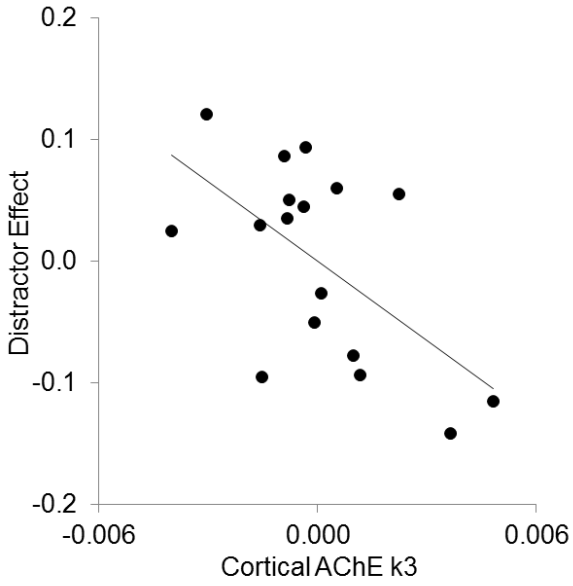

Figure 4.3. Correlation between the cortical k3 and distractor effect with age, thalamic k3, and caudate DVR controlled for. Lower cortical k3 levels were associated with greater distractor effect (r = -.59, p = .013)

Cholinergic functions in subregions of cortex and distractibility

As an exploratory analysis, we evaluated which cortical region provides the best AChE k3 predictor for distractibility. These analyses should be interpreted with caution due to low sample size and lack of correction for multiple comparisons, but provide a preliminary indication that may be useful for constraining hypotheses in future studies with larger sample sizes and more power. Greater distractor vulnerability was associated with low levels of k3 in the left middle frontal gyrus (MFG), broad parietal regions, and ventral temporal regions (Figure 4.4). The strongest correlation was observed in left parietal and bilateral ventral temporal regions. No region showed a positive correlation.

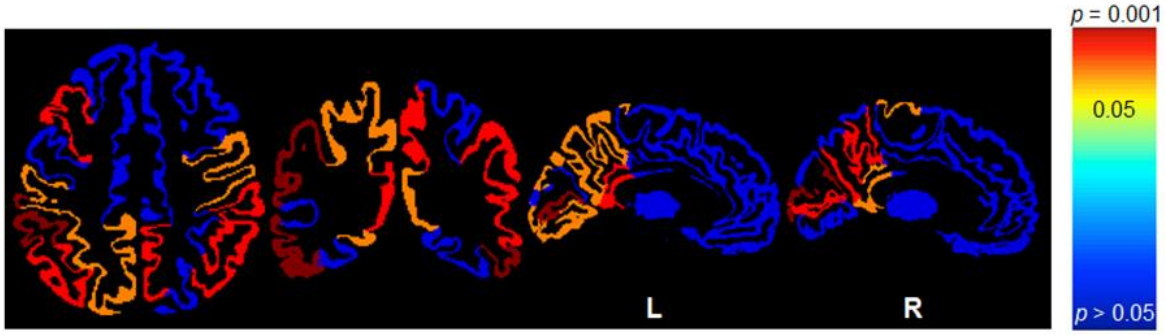

Figure 4.4. Regional-specificity of the correlations between the cholinergic integrity and distractor effect. Greater distractor vulnerability associated with low cholinergic integrity in the left middle frontal gyrus, bilateral posterior cingulate, parietal and temporal regions. p = .01 = r value of -.61; p = .05 = r value of -.48.

Discussion

The results of the present study suggest that cortical cholinergic innervation, perhaps especially in left parietal cortex, plays an important and specific role in the ability to resist distraction from external sources, rather than simply reflecting global

cognitive decline. Compared to HC, PD patients had only marginal impairments on the measure of initial performance thought to reflect attentional precision or performance, and the two groups had similar declines in sustained attention over time. Likewise, when looking within the PD group, cortical cholinergic denervation was significantly correlated with the distractor effect but not with initial performance or declines over time. Regression analyses provided further support by showing that the cortical-cholinergic/distraction relation not only remained, but became even stronger after controlling for age, caudate dopaminergic, and thalamic cholinergic measures[2]. Finally, regional analyses provided preliminary support for the idea that left parietal cholinergic integrity may be of particular importance.

The conclusion that cholinergic innervation of the cortex plays a critical role in the ability to resist external sources of distraction takes on additional interpretative power when the present results are considered in light of other recent findings. In particular, Berry et al. (2014b) tested participants with a genetic polymorphism thought to reduce cholinergic function ((the Ile89Val variant of the choline transporter (CHT) gene SLC5A7 (rs1013940)) in the same paradigm used here, and likewise found a specific vulnerability to distraction, with no deficits in initial performance or in the ability to sustain performance over time. Together these studies thus provide strong converging evidence for a specific role of the cortical cholinergic system in resisting external distraction.

[2] When the same regression model was applied to initial performance and declines in performance over time (slope), none of the included variables was a significant predictor over and above the others. The only relationship in these analysis to approach significance was between initial performance and the caudate dopamine measure ((b* = .53, t = 1.72, p = .11), perhaps consistent with the established role of dopamine in temporal judgments (e.g., Meck, 1996).

In addition, while the regional analyses here should be considered exploratory, it is notable that left parietal cortex – the region in we found gamma oscillations were most strongly associated with the ability to resist distraction (Chapter 2) – was the region most strongly associated with distractor resistance here. Other findings supporting a role for a left parietal involvement in resisting distraction from external sources include animal studies showing that the deafferentation of cholinergic input neurons to posterior parietal cortex reduces the signal-to-noise ratio of cue-evoked responses in rats performing in the face of distractor (Broussard, Karelina, Sarter, & Givens 2009), and that in humans, grey matter density – which may reflect the synaptic density - of left parietal regions is associated with the distractibility in daily life (Kanai, Dong, Bahrami, & Rees, 2011).

The interpretation of some of the other regions correlated with distractor resistance is less clear. Cholinergic integrity of bilateral temporal cortex was also robustly correlated with distractor resistance, possibly due to its involvement in auditory change detection and monitoring acoustic variability (e.g., Watkins, Dalton, Lavie, & Rees, 2007). Since the distractor was presented on separate video screen, out of the direct line of sight if the participant was looking at the task computer, the auditory input from the videos might provide the primary source of distraction. The direction of effects is somewhat counterintuitive, as most studies of cholinergic influences on sensory cortex suggest that it induces an excitatory bias (e.g., Hasselmo & McGaughy, 2004). One important exception is that cholinergic innervation of layer 4 of sensory cortex has been shown to have an inhibitory influence (e.g., Donoghue & Carroll, 1987; Eggermann and Feldmeyer; 2009). An intriguing but admittedly speculative possibility

is that this layer of circuitry drives the effects we see here; testing this hypothesis will likely require experiments in animal models allowing more precise observation and manipulation than is typically feasible in humans. Providing some indirect support, preliminary analysis of the dataset from Chapter 3 (dSAT), which used a visual rather than auditory distractor, and where the distractor likely impaired perception rather than capturing attention, did not find robust correlations between the distractor effect and temporal cortex.

Another question is why the present study found a strong correlation between distractor effects and cholinergic denervation in left prefrontal cortex, especially left middle frontal gyrus (MFG), when previous studies using the dSAT have pointed to right PFC cholinergic contributions in rodents (e.g,. St. Peters, Demeter, Lustig, Bruno, & Sarter, 2011) and specifically right MFG activations in human neuroimaging studies (Berry et al., in prep., in press; Demeter, Hernandez-Garcia, Sarter, & Lustig, 2011). As discussed in Chapters 2, this may be due to the different nature of the signal and distractor in the present paradigm vs. dSAT. Left MFG is associated with executive function and interference control, especially for auditory/verbal stimuli (e.g., Andersson, Ystad, Lundervold, & Lundervold 2009). In contrast, right prefrontal cortex appears to provide an index of attentional effort (Sarter, Gehring, & Kozak, 2006), and at least in humans may be a correlate of dSAT distractor effects rather than an essential part of the network supporting distractor resistance (Chapter 2; see also Demeter et al., 2011; Berry et al., in prep., in press).

When comparing results from the present paradigm with those from the dSAT, it is also interesting to note that in the present study thalamic cholinergic integrity did not

show zero-order correlations with the distractor effect, but began to emerge as a positive predictor of distraction (greater k3 associated with larger distractor effects) in the regression model (p = .07). This trend awaits replication in a larger sample with greater power, but a tempting interpretation is that thalamic cholinergic integrity contributes to bottom-up stimulus salience regardless of whether the stimulus is the target (Chapter 3; dSAT) or the distractor (the videos used as the distractor here).

Another somewhat surprising finding is that while the results from the HC replicated our previous findings of correlations between the CTET performance measures and self-reports of attentional function in everyday life (Berry et al., 2014a, 2014b; Lin & Lustig, in prep.), we did not find those patterns for the PD patients. Nor did PD patients show correlations between the PET measures and the self-report measures, although they did generally give higher ratings in everyday boredom, mind-wandering, and distractibility than did the HC. One possibility is that these more complex, real-world behaviors allow for alternate strategies and mutual compensation between dopaminergic and cholinergic (as well as other, e.g, noradrenergic) systems. While patients on the whole may have reduced functionality in these systems than HC, and thus may be more vulnerable to real-world attentional problems, the balance of the contribution may differ widely across individual patients, so that there is no clear pattern of correlation. Consistent with this idea, rodent lesion data suggest that complex behaviors such as falls are multiply determined, with different types of falls differentially related to combined cholinergic-dopaminergic lesions versus large dopaminergic lesions (Kucinski et al., 2013; in review). Likewise recent human data suggest that interactions between cholinergic and dopaminergic denervation represent compensation on

measures of global cognitive decline (Bohnen et al. in press). In the following chapter we examine the possibility of cholinergic-dopaminergic interactions and mutual compensation in situations with more complexity or executive demand more closely.

To summarize, the present findings identify a specific contribution of cholinergic cortical function, perhaps especially in left parietal cortex, to the resistance of external distraction. Importantly, the significance of the cortical cholinergic contribution was unique to distractor resistance and not found for the baseline performance in the temporal expectancy task or time-one-task effects. Other aspects of the findings open up new questions for further experimentation, including how cholinergic innervation of sensory cortex may contribute to distractor sensitivity versus resistance, and the possibility of interactions and compensation between cholinergic and dopaminergic systems to support attentional control in everyday life. Together with previous animal findings (e.g., Kucinski et al., 2013; in review), the present data suggest that cortical cholinergic integrity leads to an increase in distractibility, which could in turn increase risk for falls, but that other influences also need to be taken into account. The following chapter examines potential cholinergic-dopaminergic interactions in situations of high executive demand.

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Chapter V

EXECUTIVE CONTROLS IN PARKINSON'S DISEASE: COMPENSATORY DOPAMINERGIC-CHOLINERGIC INTERACTIONS

Relevance to dissertation

Chapters 3 and 4 examined specific cholinergic contributions to resistance to different types of distractors. The key characteristic of the dSAT distractor (Chapter 3) was that it increased the perceptual difficulty of the target stimulus, and thalamic cholinergic function was critical in overcoming the distractor. On the other hand, the meaningful, compelling distractor in CTET (Chapter 4) was more likely to capture participants' attention away from the goal-relevant task. Thus overcoming the CTET video distractor required constant re-orienting of attention away from the distractor and toward the goal-relevant task, and cortical cholinergic function played a critical role.

The current chapter examines the significance of cholinergic function when the task requires even stronger executive control than dSAT and CTET. Executive control functions were measured at two different levels of executive demands using a modified version of Stroop task (see below for details). Concepts such as "difficulty" and "executive demand" can be ambiguous, so in the present case we operationalized these as the effect size between the baseline condition and the condition thought to be more demanding, based on performance in healthy controls. The effect size of the distractor

effects was 1.08 for the dSAT, 1.10 for the CTET, and the effect size of the conflict effects were 2.26 for the Stroop conflict, and 2.35 for the dual conflict effects (combined Stroop and task-switching conflict; described further below).

Recent rodent and human studies suggest that the basal forebrain-cortical cholinergic system and caudate dopaminergic circuitry may play compensatory roles in optimizing executive control (Kucinski, Paolone, Bradshaw, Albin, & Sarter, 2013; Bohnen et al., in press). This chapter investigates the possibility that cholinergic and dopaminergic functions may compensate for each other in situations with high executive demand.

General Introduction

Declines in executive function are frequently reported in Parkinson's Disease (PD) (Lee & Smith 1983; Dubois & Pillon 1996; McKinlay, Grace, Dalrymple-Alford, & Roger, 2010; Robbins & Cools, 2014), but the underlying neuropathology is not fully understood. It has been attributed to dopaminergic dysmodulation, in particular disturbed striatal outflow (Dinberger, Frith, & Jahanshahi, 2005; Marie et al., 1999; Taylor, Saint-Cyr, & Lang, 1986), noradrenergic pathology (Bedard et al., 1998; Marsh, Biglan, Gerstenhaber, & Williams 2008), and neuronal loss of the ascending cholinergic (Bohnen et al., 2006; Dubois & Pillon, 1996).

Recently, two competing hypotheses of executive dysfunction in PD have been proposed. The *dual-syndrome hypothesis*, while acknowledging some contribution of other systems, primarily ascribes executive dysfunction in PD to fronto-striatal declines,

whereas declines in the cholinergic (and other) systems are thought to have their primary locus in more posterior regions, and to underlie declines in visuospatial processing and (at later stage) dementia (Kehagia, Barker, & Robbins, 2013). In contrast, the *compensatory hypothesis* (Bohnen et al., in press) links cholinergic deficits more directly to executive dysfunctions. This hypothesis suggests that frontoparietal cholinergic deficits result in the loss of compensatory pathways, thus exacerbating fronto-striatal declines.

Several recent rodent and human studies have reported results that seem more consistent with the compensatory hypothesis. Specifically, cortical cholinergic lesion significantly increases rodents' vulnerability to distraction only in combination with caudate dopaminergic lesions and vice versa – a single cholinergic or dopaminergic lesion does not have much impact on the rats' performance level (Kucinski et al., 2013). In contrast, large dopaminergic lesions (without a cholinergic lesion) led to low vigor for and control over movement, but without apparent effects on attention-motor interactions (Kucinski et al., in review). Similarly, although caudate dopaminergic denervation is frequent in PD patients with minimal or no cognitive changes, Bohnen et al.,(in press) classified patients according to degree of cognitive impairment, and found that the frequency of co-occurrence of cortical cholinergic and caudate dopaminergic deficits increased with the severity of impairment. The frequency of thalamic cholinergic denervation did not show the same pattern, suggesting that the pattern seen for the cortical cholinergic system did not simply represent general declines. Furthermore, the interaction between cortical cholinergic and caudate dopaminergic denervation showed larger differences across the groups when divided by global cognition scores than did

either of the individual measures, Finally, when looking within the cognitive domains that made up the global score, the interaction effect showed a stronger relation to the executive composite score than the scores related to attention, memory, or visuospatial function.

The executive function tests (Delis-Kaplan Executive Function System Sorting Tes; WAIS III Picture Arrangement test) used in Bohnen et al. (in press) primarily tapped planning and sorting aspects of executive function. In the present study, we examine another important aspect of executive function, the ability to flexibly engage the appropriate task set even in the face of conflict. PD patients and healthy controls who had undergone PET assessments of cholinergic ([^{11}C]PMP ligand) and dopaminergic ([^{11}C]DTBZ ligand) function completed a modified version of the Stroop test that includes a rule-switching component (Bohnen, Jolles, & Twijnstra, 1992). This task allows the evaluation of executive control at two levels: the traditional Stroop conflict effect and simultaneous Stroop and rule conflict, which we term 'dual conflict'. The traditional Stroop conflict is created by competition between the automatic response tendency and the rule-based response. Another layer of competition is added to this by implementing a rule-switching component to the Stroop task - the competition between the different response rules. This dual-conflict condition poses a particularly high level of executive demand, as it requires both the ability to overcome the Stroop conflict and cognitive flexibility.

The dual-syndrome hypothesis would predict that caudate dopamine measures would relate to performance on these executive measures, whereas cholinergic innervation might be more related to global performance deficits or reduced

performance at the simpler levels of the task, perhaps reflecting prodromal dementia. In contrast, the compensatory hypothesis suggests that the interaction between measures of caudate dopamine and cortical cholinergic decline should be the strongest predictor of executive impairment. Moreover, as a further test of the hypothesized compensatory relationship between the two systems, we predict that cholinergic variation should explain the variance of the executive control only in a subset of subjects with significant dopaminergic depletion; Similarly, the dopaminergic function should predict the executive control measures only in a subset of subjects with significant cortical cholinergic deficits. Alternatively, the dual-syndrome hypothesis would predict largely independent effects of caudate dopaminergic and cortical cholinergic decline, with a strong correlation between the striatal dopaminergic function and executive control regardless of cholinergic status.

Methods

Participants

140 PD patients and 63 healthy controls (HC) participated in the study. Extreme outliers based on the average response time or error rates were excluded from the analyses (4 PD, 5 HC). Thus, final sample included a total of 136 PD patients (37 female, age range 50-84, mean age = 65.52) and 58 healthy older adults (34 female, age range 40-84, mean age = 64.76). Both DTBZ and PMP PET were obtained for most of the PD patients (except for 1 session during which PMP was aborted for technical reason). All healthy control participants underwent DTBZ PET scanning, but

PMP PET was obtained only from 9 HC. Consequently, when the PMP PET measures were used as a variable, the sample size was down to 135 (PD) and 9 (HC), but in other analyses where PMP measure is not the critical variable, we used the full sample (136 PD and 58 HC) in order to maximize the statistical power. For the 136 PD patients, the average disease duration was 6.1 years (range, 5-19 years) and the average Hoehn and Yahr severity score (Hoehn & Yahr, 1967) was 2.5 (range, 1.0-5.0). No patient was taking any anti-cholinergic or cholinesterase inhibitor drugs.

The data for the present study (PET and Stroop task) were collected in a combined session with other studies. Most of the participants underwent 2 PET imaging sessions, 1 MRI scanning session, and an entire day of motor/neuropsych testing and received monetary compensation ($400) for their participation. All experimental and recruitment procedures were approved by the University of Michigan's Institutional Review Board, and all procedures were fully described to the participants before they consented to take part in the study.

Task and Procedure

All participants completed a modified version of the Stroop task (Bohnen et al., 1992) during laboratory testing (Figure 5.1). The task includes four levels that vary the stimulus presented (word or patch) and the basis on which the participant is to respond (word meaning or ink color). Color-word meaning and ink colors were both drawn from a four-item set: red, yellow, green, and blue, with each used an equal number of times (25) within a level. For each level, the stimuli consisted of 100 items printed as a 10 by

10 array on a white letter size paper. At each level, the experimenter presented the stimulus set to the participants, gave the instruction, and recorded the total time participants took to complete the level and total number of errors in that level.

In level I (word-word), the stimuli were color words printed in black ink against a white background. Participants had to read the color words without stopping in the middle. In level II (patch-ink), the stimuli were color patches randomly intermixed, and participants were to say the ink color of each color patch without stopping. In level III (word-ink level), the stimuli were color words, each printed in a color incongruent with its meaning (i.e., the color word 'red' was never printed in red ink). Participants had to name the ink color and ignore word meaning. In level IV (word-ink-switch level), the stimulus set was similar as in level III, except that 20 items out of the total 100 were outlined with a box (in black ink). The boxes were randomly distributed over the 10 by 10 array. Participants are asked to say the ink color of the color words except that for the ones outlined with a box; they had to read the color words for those outlined.

Participants also completed neuropsychological tests evaluating affective, cognitive, and motor function. The measures included the Beck Depression Inventory II (BDI-II, Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), and the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS; copyright: Movement Disorder Society; Goetz et al., 2007). Participants were cognitively tested on their usual dopaminergic medicines.

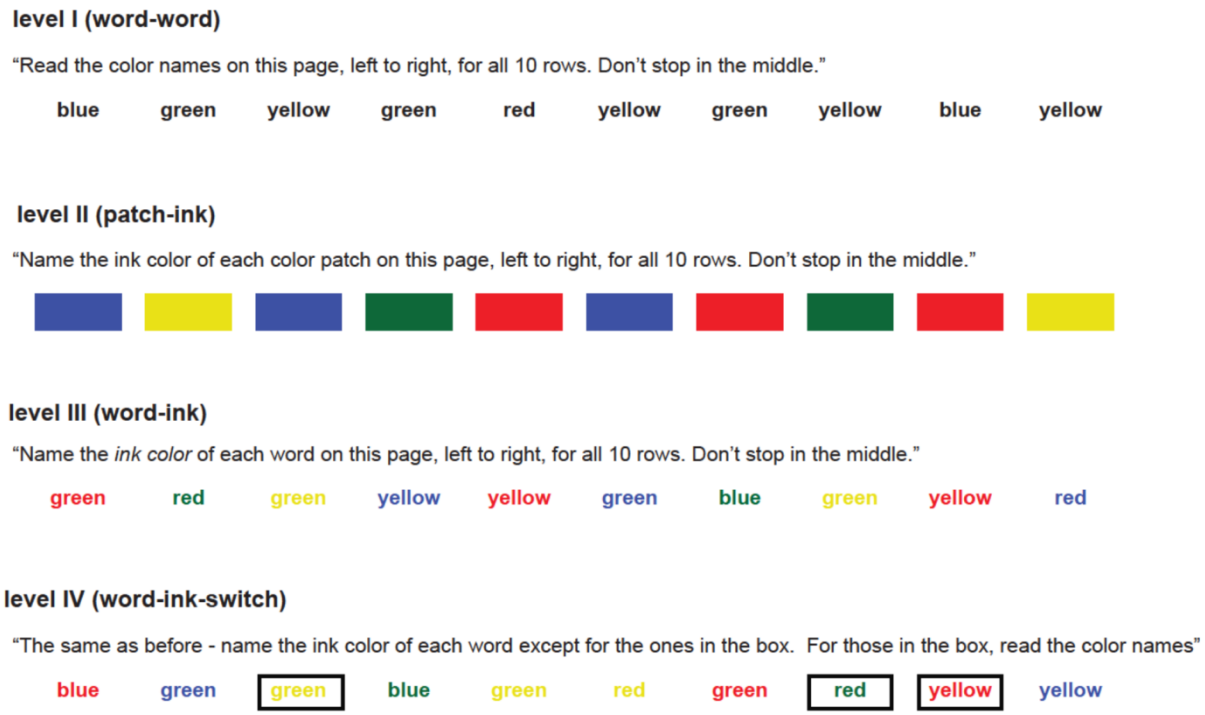

Figure 5.1. Task Procedure: Modified Stroop Task with rule-switching. Participants were presented with 100 items in each level (in a 10 x 10 array), and asked to either read the color names (level I), name the ink color (level II, III), or switch between the rules (level IV). The total response time and accuracy were recorded for each level and converted into Inverse Efficiency Score (IES = RT / accuracy (p)). .

Positron Emission Tomography (PET) scanning

The procedure and preparation of the PET scanning was identical to that described in Chapter 3 and 4. Consistent with Chapter 3 and 4, cholinergic function was estimated using the radio-labeled acetylcholine analogue [11C]methyl-4-piperidinyl propionate (PMP) PET with the primary outcome parameter as AChE hydrolysis rate (k3). Mean AChE k3 measures were extracted from the cortical and thalamic regions separately (the basal forebrain and pedunculopontine nucleus cholinergic target regions, respectively). The dopaminergic neuronal terminal functions were measured with [11C]dihydrotetrabenazine (DTBZ), a vesicular monoamine transporter type 2 (VMAT2)

analogue. DTBZ distribution volume ratio (DVR) was used as the outcome measure (Bohnen et al., 2009), which was extracted from caudate and putamen separately.

Although PD typically affects one side of the striatum more than the other, we did not construct separate predictors from the affected vs. unaffected brain side of the patients for the following reason. Unlike the motor control functions where severe motor symptoms are clearly associated with the severe contralateral striatal denervation, we did not have a concrete ground or hypothesis on how the PD-effected side influences our cognitive measure of interest. To our knowledge, there is no evidence on the lateralization of cognitive flexibility function – particularly in association with PD - , thus we used the bilaterally averaged values. Previous data did not show asymmetry in cholinergic denervation in PD (Bohnen et al., 2009) and additional analyses with the predictors using the measures from the clinically most affected side only yielded similar results as reported above.

Statistical Analysis

The response time (RT) and accuracy were recorded as the performance measure at each task level and then the RT was adjusted for accuracy (Inverse Efficiency Score (IES) = RT / correct (p); Townsend & Ashby, 1978; 1983). The IES difference between levels III and II was used as a measure of the Stroop conflict, and the IES difference between levels IV and level II was used as a measure of dual conflict (i.e., the Stroop and rule conflicts; Bohnen et al., 1992). All statistical analyses were conducted using IBM SPSS Statistics (version 21) or R (3.1.1).

Independent-sample t-tests were used to compare the PD and HC groups, for which we report Cohen's d as effect sizes. Potential relationships between the behavioral and neural measures were first examined using first-level bivariate Pearson correlation analysis. Then, to evaluate the independent as well as possibly compensatory cholinergic and dopaminergic contributions to executive control in PD, hierarchical multiple regressions were conducted in three steps. The first step evaluated age as a predictor for the executive control functions (the Stroop and dual conflict measures separately), then the caudate DVR, and the cortical and thalamic AChE k3 were added as predictors in the second step. In the final step, we tested the model significance changes when the caudate-cortical interaction term was added to the model, as well as the unique contribution of this interaction term and its influence on other variables in the model. This hierarchical regression allows evaluation of whether the caudate-cortical interaction uniquely predicted performance over and above the potentially shared variance with other measures.

Low-dopaminergic group was defined using the 5^{th} percentile of DVR values in the healthy controls (n = 58). Due to the small number of HC with cholinergic PET measures, the low-cholinergic group was defined using the cut-off score defined in a previous study (Bohnen et al., 2012; using the 5^{th} percentile of HC). In each group of patients, bivariate first-level correlation analyses were first used to examine the relationship between the conflict effects and the caudate dopaminergic (in the low- and normal- cortical cholinergic groups) or cortical cholinergic function (in the low- and normal- caudate dopaminergic groups). The initial scatterplot of this first-level correlation suggested potential influential cases, but the cases were not identified as

unusual errors. As it was not extraordinary to have larger variances in the patient data and we had no compelling reason to exclude these cases, we did not remove any case from the analyses. Instead, we additionally used robust regression (with Huber weighting) that weights observations differently depending on their residuals in linear regression (smaller weights for cases with larger residuals) to estimate the amount of variances in the executive functions explained by the cortical cholinergic or caudate dopaminergic function in each group.

Results

Demographic, neuropsychological tests, and overall performance data

Table 5.1 compares the HC (n = 58) and PD (n = 136) on demographic variables, neuropsychological test results, and behavioral performance in the task. PD and HC were comparable in age, education and general cognitive assessment (ps > .1; Cohen's d < .25), but PD patients scored significantly higher in BDI (t = 7.8, p < .0005, Cohen's d = -.97). [1] In all levels of the task, PD patients were slower and made more errors compared to HC (p < .005; Cohen's d < -.40), except for in level I, where effects were marginal (p = .101; Cohen's d = -.17).

[1] Although depression has been associated with various cognitive functions including attentional control (e.g., Ravnkilde et al., 2002; Paelecke-Habermann, Pohl, & Leplow 2005; see Austin, Michell, & Goodwin 2001 for review), we did not controlled for BDI as a covariate there is a possibility that controlling for BDI may confound the results. Depression score and cholinergic cortical activity are correlated positively in our data (r = .50, p = .04; see table 4.3). We interpret this somewhat unexpected positive correlation as reflecting potential compensation for changes in other neural systems associated with depression in Parkinson disease such as norepinephrine, serotonin, etc.. Thus controlling for BDI scores may introduce a confound to the results.

Table 5.1. Demographic and behavioral performance of PD and HC. *t* and *p* corrected for violation of equal variances if applicable. ** $p < .0005$

	HC (N = 58)		PD (N = 136)		*t*	*p*	Cohen's *d*
	M	SD	M	SD			
Age (years)	64.8	12.0	65.5	7.8	-0.5	.66	-0.08
Education (years)	15.8	2.2	15.4	2.8	1.3	.20	0.19
Montreal Cognitive Assessment	26.7	2.2	26.3	2.1	1.4	.17	0.22
Beck Depression Inventory	2.8	3.2	8.1	6.2	-7.8	**	-0.97
STR1 RT (s)	49.1	9.4	54.2	11.6	-3.0	.003	-0.47
STR2 RT (s)	63.5	12.2	72.0	15.5	-3.7	**	-0.59
STR3 RT (s)	112.7	26.6	136.3	42.2	-4.7	**	-0.62
STR4 RT (s)	125.0	29.5	151.3	56.2	-4.3	**	-0.53
STR1 error rate (%)	0.02	0.13	0.13	0.73	-1.7	.101	-0.17
STR2 error rate (%)	0.14	0.44	0.62	1.25	-3.9	**	-0.45
STR3 error rate (%)	0.91	1.16	3.03	4.47	-5.1	**	-0.56
STR4 error rate (%)	1.17	2.16	3.60	5.43	-4.4	**	-0.52

Caudate dopaminergic and cortical cholinergic measures correlate with the Stroop and dual conflict effects in PD

Table 5.2 shows the first-level Pearson correlations between the performance measures, the PET measures of cholinergic and dopaminergic integrity, and individual difference variables (age and depression score (BDI)) that may contribute to variance on the performance and PET measures in 135 PD patients with both the DTBZ and PMP PET measures. Both baseline performance (level I), and both of the conflict effects showed significant correlations with age and caudate DVR ($p < .01$). In addition, cortical k3 showed marginal to significant correlations with age and the behavioral measures. Consistently as in Chapters 3 and 4, age was correlated with the behavioral and the caudate and cortical PET measures ($|r|$ ranges .19~.30, $p < .05$). Thus in the following hierarchical regression analyses, age was entered alone as the predictor in the first model to control for it. In all of the regression models reported here, collinearity

statistics were well within acceptable ranges (all tolerance values above .89; values above .10 are typically considered acceptable; all VIF values below 1.1; values below 10 are usually considered acceptable; Field, Miles, & Field 2012).

Table 5.2. Correlations between the behavioral measures, age, depression score (BDI), and the PET measures in PD. Baseline is the ies measure in level II. ** indicates p < .0005

		baseline	Stroop conflict	dual conflict	age	BDI	thalamic k3	cortical k3	putamen DVR	caudate DVR
baseline	*r*	1	.48	.56	.29	.09	-.16	-.17	-.15	-.34
	p		**	**	.001	.32	.07	.05	.08	**
Stroop conflict	*r*	.48	1	.62	.30	.03	-.11	-.15	-.13	-.24
	p	**		**	**	.75	.21	.08	.12	.005
dual conflict	*r*	.56	.62	1	.24	.03	-.17	-.24	-.14	-.25
	p	**	**		.005	.75	.046	.004	.11	.004
age	*r*	.29	.30	.24	1	-.13	-.25	-.24	.06	-.19
	p	.001	**	.005		.15	.004	.005	.49	.02
BDI	*r*	.09	.03	.03	-.13	1	.15	.25	-.15	-.09
	p	.32	.75	.75	.15		.09	.004	.09	.32
thalamic k3	*r*	-.16	-.11	-.17	-.25	.15	1	.58	.11	.23
	p	.07	.21	.046	.004	.09		**	.19	.006
cortical k3	*r*	-.17	-.15	-.24	-.24	.25	.58	1	.23	.27
	p	.05	.08	.004	.005	.004	**		.008	.002
putamen DVR	*r*	-.15	-.13	-.14	.06	-.15	.11	.23	1	.80
	p	.08	.12	.11	.49	.09	.19	.008		**
caudate DVR	*r*	-.34	-.24	-.25	-.19	-.09	.23	.27	.80	1
	p	**	.005	.004	.02	.32	.006	.002	**	

The caudate dopaminergic-cortical cholinergic interaction uniquely predicts the Stroop and dual conflict effects in PD

To test our compensatory hypothesis, a hierarchical regression model was tested for PD patients data with three steps (n = 135, Table 5.3 for the Stroop conflict effect; Table 5.4 for the dual conflict effect). In the first model, age was entered as the only predictor, followed by the second model age with the caudate DVR, thalamic and

cortical k3 entered as additional predictors. The thalamic measure was not significantly correlated with the behavioral measures, but was included as a predictor in the regression models to allow comparisons with the results in Chapters 3 and 4. In the final model, the caudate DVR-cortical k3 interaction term was added as a predictor. All three models reliably predicted the Stroop (Table 5.3, $p < .005$) and dual conflict effects (Table 5.4, $p < .01$). Importantly, adding the interaction term significantly increased the model fit for both the Stroop ($\Delta F = 4.1$; $p = .046$) and dual conflict effects($\Delta F = 4.7$; $p = .032$).

Table 5.3. Hierarchical multiple linear regression model for the Stroop conflict effect in PD. B, unstandardized coefficient; β, standardized coefficient. ** indicates p < .0005

	coefficients				model statistics					
	B	β	*t*	*p*	R^2	ΔR^2	Δ F	sig. Δ F	Model Fit *F*	Model Fit *p*
step 1 model					.09	.09	13.4	**	13.4	**
constant	0		0	1.0						
age	.30	.30	3.7	**						
step 2 model					.13	.04	1.8	.16	4.7	.001
constant	0		0	1.0						
age	.26	.26	3.0	.003						
caudate DVR	-.18	-.18	-2.1	.04						
thalamic k3	.03	.03	.3	.74						
cortical k3	-.06	-.06	-.6	.55						
step 3 model					.15	.03	4.1	.046	4.7	.001
constant	-.04		-.5	.60						
age	.25	.25	2.9	.005						
caudate DVR	-.24	-.24	-2.6	.009						
thalamic k3	.40	.04	.4	.70						
cortical k3	-.04	-.04	-.4	.67						
caudate DVR * cortical k3	.16	.17	2.0	.046						

Table 5.4. Hierarchical multiple linear regression model for the dual conflict effect in PD. B, unstandardized coefficient; β, standardized coefficient. ** indicates p < .0005

	coefficients				model statistics					
	B	β	*t*	*p*	R^2	Δ R^2	Δ F	sig. Δ F	Model Fit *F*	Model Fit *p*
step 1 model					.06	.06.	8.3	.005	8.3	.005
constant	.14		1.5	.14						
age	.27	.24	2.9	.005						
step 2 model					.12	.06	3.1	.029	4.5	.002
constant	.14		1.5	.14						
age	.19	.17	2.0	.049						
caudate DVR	-.19	-.17	-2.0	.05						
thalamic k3	.00	.00	.0	.99						
cortical k3	-.18	-.16	-1.5	.13						
step 3 model					.15	.03	4.7	.032	4.6	.001
constant	.09		.9	.37						
age	.17	.15	1.8	.07						
caudate DVR	-.27	-.24	-2.6	01						
thalamic k3	.01	.01	.1	.94						
cortical k3	-.16	-.14	-1.3	.18						
caudate DVR * cortical k3	.20	.19	2.2	.03						

To provide clear interpretations of the interaction, we further tested the relationships between the caudate DA, cortical ACh, and cognitive measures of the PD patients in the following ways. First, the cortical cholinergic-executive function relationship was examined in the low and normal dopaminergic groups separately. Then similarly, the caudate dopaminergic-executive control relationships were examined in the low and normal cholinergic groups separately. As described in the methods, the low and normal groups were defined using the 5th percentile value of the healthy control group (Figure 5.2; Table 5.5 shows the sample size of each subgroup).

All the following correlation and robust regression analysis used the sample of 135 PD patients with both the PMP and DTBZ PET measures.

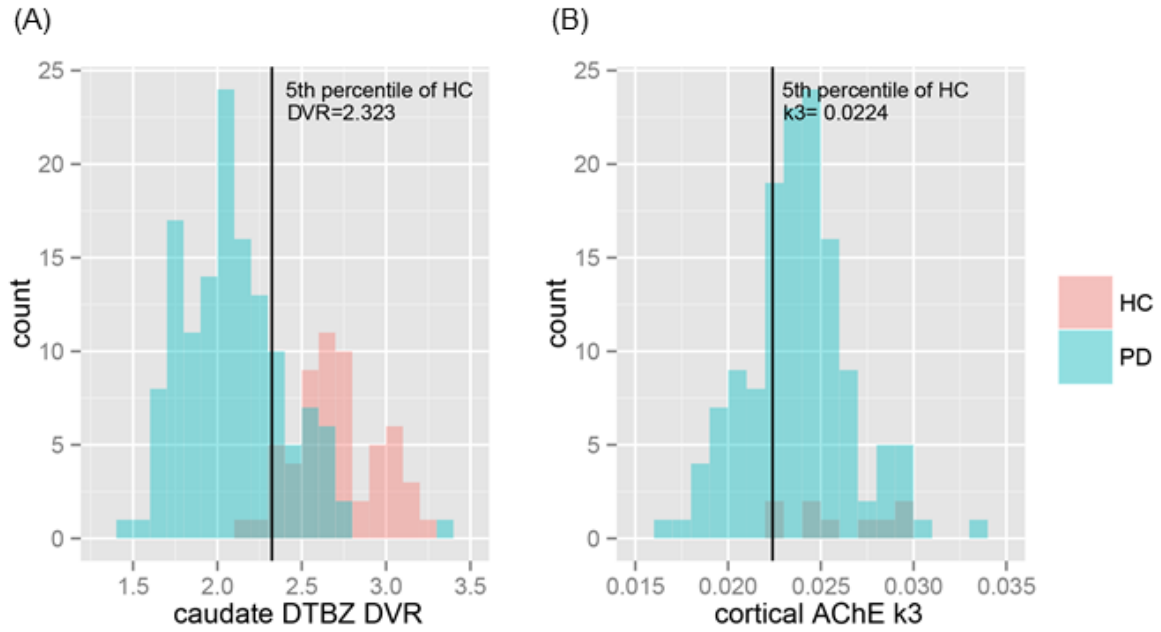

Figure 5.2. Distributions of the caudate VMAT2 DVR and cortical AChE k3 levels. (A) The caudate DTBZ DVR measures of the PD patients are distributed in the lower range of the values obtained from the HC. 81.5% of the PD patients fall into the low caudate dopaminergic function group defined by the 5th percentile of the healthy controls. (B) Compared to the distribution of caudate DTBZ DVR measures, there is substantial overlap between the PD patient and HC distributions of the cortical AChE k3. About 28.1% of the PD patients fell into the low cortical cholinergic group defined by the 5th percentile of the healthy controls.

Table 5.5. Resulting sample size of each PD subgroups (low: 5th percentile of the normal controls)

		cortex k3		
		low	normal	total
caudate DVR	low	37	73	110
	normal	4	21	25
	total	41	94	135

Figure 5.3 illustrate the relationship between the cortical cholinergic function and executive functions in the groups with low (A, C) and normal (B, D) caudate dopaminergic level, with the least square (solid lines) and robust regression (dashed lines) fit lines. Using standard Pearson correlation measures, higher cortical cholinergic functions are marginally to significantly associated with smaller conflict effects in the PD patients with low caudate dopaminergic function (Figure 5.3(A) for Stroop conflict effect, r = -.18, p = .065, Figure 5.3(C) for dual conflict effect, r = -.28, p = .003), but not in PD patients whose caudate dopaminergic functions fall in the normal range (Figure 5.3(B, D), ps ≥ .1). The strength of the cholinergic-conflict correlations did not significantly differ in the Stroop and dual conflicts (Fisher's z = -0.77, p > .1). Robust linear regressions revealed consistent test results only for the dual conflict effect. The variance in the dual conflict effect was reliably predicted by cortical cholinergic measures in the low dopaminergic group (Figure 5.3(C) t(108) = -2.77, p = .007) but not in the normal dopaminergic group (Figure 5.3(D), t(23)=1.65, p > .1).

Similar patterns were found in the low and normal cortical cholinergic groups. Higher caudate dopaminergic function was associated with smaller Stroop conflict effects in PD patients with significant deficits in cortical cholinergic function (Figure 5.4(A), r = -.31, p = .049), but not in PD patients with normal cortical cholinergic function (Figure 5.4(B), r = -.16, p > .1). The correlations between the caudate dopaminergic function and dual-conflict effects were not significant in both the groups (r = -.27, p = .086 in low cholinergic group, r = -.19, p = .067 in normal cholinergic group; no significant difference between these two correlations, Fisher's z = -.44, p > .1). Robust linear regressions did not reveal the caudate dopaminergic function as a significant

predictor for the conflict effects (Figure 5.4(A), t(39) = -1.06, p = .078, Figure 5.4 (B-D), ps > .1)

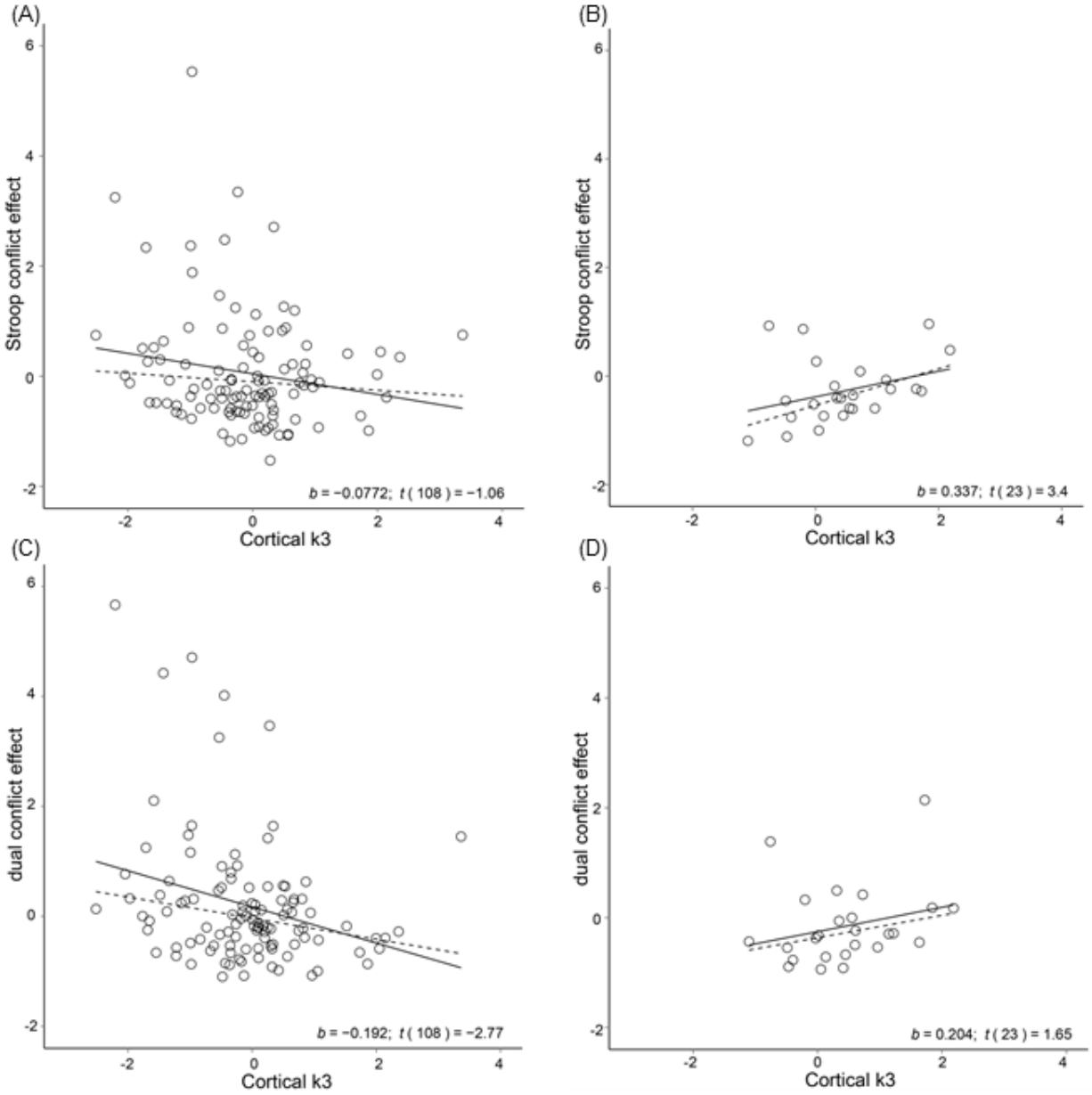

Figure 5.3. Cortical cholinergic function and conflict effects the in low and normal caudate dopaminergic group. (A, C) High levels of cortical cholinergic function were associated with smaller conflict effects in PD patients with low caudate dopaminergic levels. (B, D) The cortical cholinergic-conflict effect correlation is not observed in PD patients with normal caudate dopaminergic levels The fit lines are based on the least squares (solid) and robust regression (dashed) results. The b, t-value, and DF: t-test results for the robust regression coefficients.

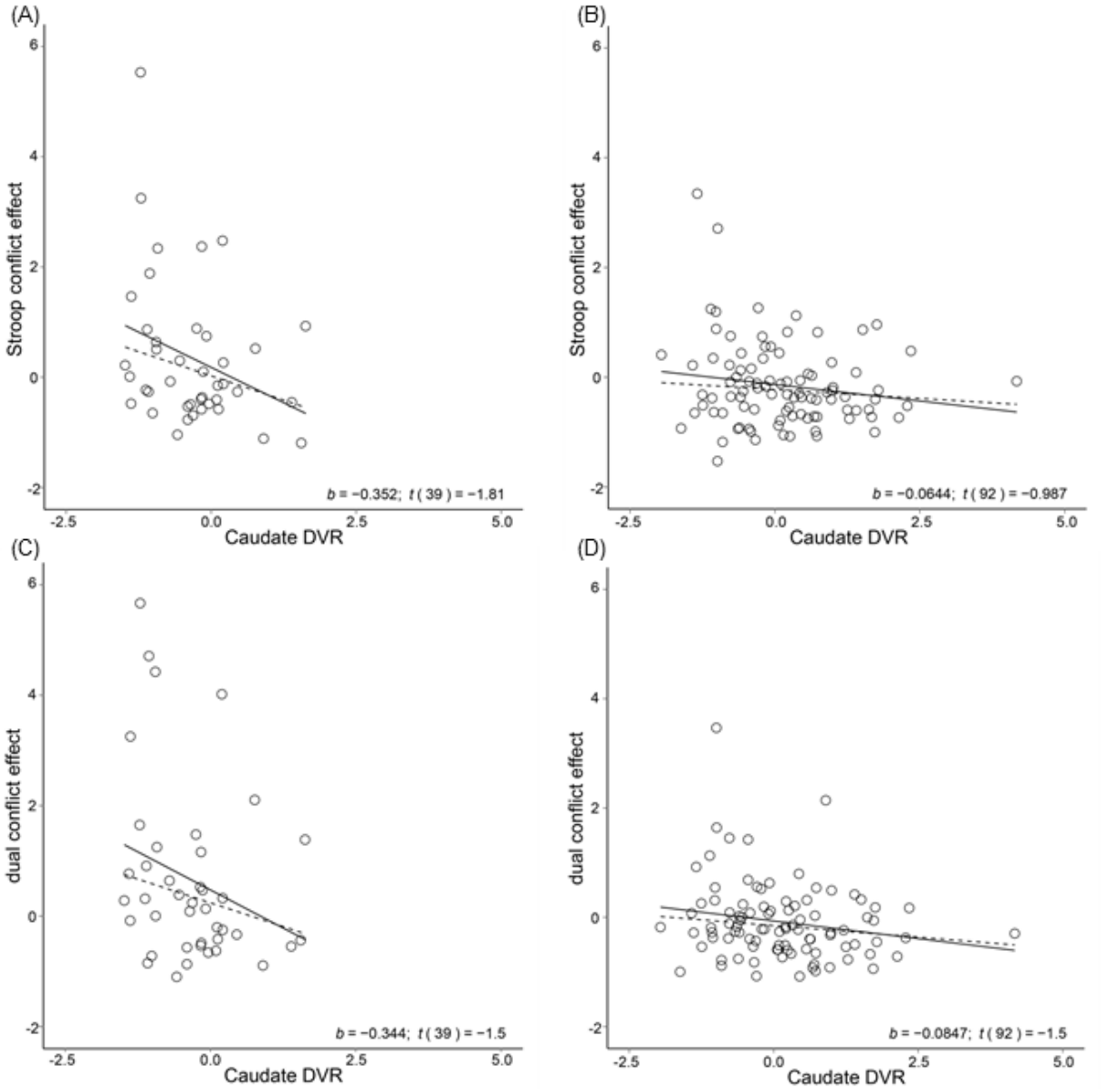

Figure 5.4. Caudate dopaminergic function and conflict effects the in low and normal cortical cholinergic group. (A, C) High levels of caudate dopaminergic function were associated with smaller conflict effects in PD patients with low cortical cholinergic levels. (B, D) The caudate dopaminergic -conflict effect correlation is not observed in PD patients with normal cortical cholinergic levels. The fit lines are based on the least squares (solid) and robust regression (dashed). The b, t-value, and DF: t-test results for the robust regression coefficients.

Discussion

The present study used PET measures of AChE and VMAT2 nerve terminal integrity in PD patients to investigate the independent and/or complementary roles of the cortical cholinergic and caudate dopaminergic functions in executive control function. The results of the hierarchical regression models showed that the cortical cholinergic-caudate dopaminergic interaction explained significant amount of variance in the executive control measures in addition to what can be explained by independent cholinergic and dopaminergic predictors. Further supporting the hypothesis that the cholinergic system may partially compensate for dopaminergic declines, when the interaction term was entered into the model, the strength of the relation (beta value) between the caudate dopaminergic measure and the executive function measures increased, rather than decreased. This indicates that the cholinergic-dopaminergic interaction had a suppressor effect (MacKinnon, Krull, & Lockwood, 2000) on the link between caudate dopamine and executive function.

The compensatory roles of cortical cholinergic and the caudate dopaminergic function were further demonstrated by separate first-level bivariate correlations and robust regression analyses in the 5^{th} percentile groups. Cortical cholinergic modulation of the executive control measures was observed only in PD patients with prominent caudate dopamine impairment (below the 5^{th} percentile of the normal controls). Likewise, the caudate dopaminergic measure modulated executive control only in PD

patients with prominent impairment in cortical cholinergic integrity (below the 5th percentile of the normal controls).[2]

Overall the pattern of results was more consistent with cholinergic compensation for dopaminergic deficits than vice versa (Figure 5.3 versus Figure 5.4). However, this pattern should be interpreted with caution and as possibly representing the specific characteristics of PD rather than as a general principle of cholinergic-dopaminergic interactions supporting executive control. That is, dopaminergic deficits are of course more prevalent in PD patients than are cholinergic deficits. This may influence the relative power to detect dopaminergic compensation for cholinergic deficits both in terms of sample size (the low cholinergic sample was relatively small compared to the low dopaminergic sample, n = 36 vs. n = 108) and restriction of range on the dopaminergic measures, as low dopaminergic function is a hallmark of PD. In particular, there is a floor effect in the DA measures in the low-cholinergic PD group, whereas the

[2] AChE is an enzyme, and as such may be subject to functional regulation, or within-system compensation. For example, DOPA decarboxylase, an enzyme that synthesizes dopamine, is upregulated in PD patients, which is believed to be a compensatory synaptic change (Lee et al., 2000; Wilson et al., 1996). Regulation has also been reported for choline acetyltransferase (ChAT) activity (DeKosky et al., 2002). To our knowledge, there has not been a reported study on AChE regulation, but it is reasonable to assume that AChE is likely to be down-regulated with the functional loss of the presynaptic cholinergic neurons. With down-regulation of AChE going on, it is impossible to dissociate between the variations of AChE coming from the neuronal degeneration and from the down-regulation. This makes it difficult to fairly interpret the AChE variation and pose limitation to using the AChE hydrolysis rates as a continuous variable as in the present study. To address this issue, we conducted an additional analysis parallel to Figure 5.3 but by using AChE as a variable to further dichotomize the low- and normal- DA group instead of using it as a continuous variable (Supplementary Materials). Again, the low- and normal- groups were defined using the 5th percentile of the normal controls. By dichotomizing the groups using the extremely low (5th percentile) criterion, we can assure that the low-cholinergic group represents the cholinergic denervation rather than down-regulation of AChE. The low cortical k3 subgroup exhibited significantly greater conflict effects in the low caudate DA group (normal vs. low AChE t-test: $t(48) = 1.93$, $p = .059$, Cohen's $d = .42$ for Stroop conflict effect , $t(43) = 2.43$, $p < .05$, Cohen's $d = .55$ for dual conflict effect), but not in the normal caudate DA group (ps > .5), confirming our findings from the correlation analyses. However, it needs to be noted that the t-test for the normal caudate DA group was extremely underpowered in this case due to the small sample size of the low-cholinergic subgroup (n = 3, see table2; achieved power = .53 (Stroop) and .75 (dual) for low-DA, but .05 (Stroop), .09 (dual) for normal-DA group).

range of cortical cholinergic measures is quite wide in the low-dopamine group (see Figure 5.4(A) compared to 5.3(A)). This restricted dopamine range might have inherently limited the strength of the DVR-conflict effect correlations (Cohen, Cohen, West, & Aiken, 2003). It is thus possible that a patient population with the opposite pattern of deficits (i.e., more common and/or severe cholinergic deficits than dopaminergic ones) would show the opposite pattern of compensation.

The present results are thus consistent with the hypothesis that declines in the cortical cholinergic system impact executive function in PD, likely by limiting potential pathways of compensation for frontostriatal declines (Bohnen et al., in press), than with the hypothesis that cholinergic deficits in PD lead to largely independent set of deficits evident first in visuospatial declines and later in dementia (Kehagia et al., 2013). The findings extend those of Bohnen et al. to a different aspect of executive function (conflict rather than planning). They also suggest that, at least in PD patients, cholinergic compensation for frontostriatal declines is more pronounced than the reverse. Furthermore, especially when considered together with the results of the previous chapters, they suggest that the importance of cholinergic-dopaminergic interactions increases with demands on executive control. Re-analysis of the dSAT and CTET data presented in Chapters 3 and 4 did not find significant effects of the interaction term, consistent with our assumption that they had lower levels of executive demand than the task used here.[3] Numerically, the relation between the interaction term and the dual-conflict measure was slightly larger than the relation between the interaction term and

[3] It is also a possibility that the interaction analyses with the data in chapter 3 and 4 were underpowered due to the small sample sizes.

Stroop conflict alone, consistent with the slight difference in the conflict effect sizes of these two conditions when compared with the baseline task.

One caveat is that using DTBZ, a type-2 vesicular monoamine transporter (VMAT2) ligand, we were able to reliably assess dopaminergic function in the striatum but not in the prefrontal cortex (or other cortical regions). VMAT2 is expressed by monoamine – serotonergic, noerpinephrinergic, or histaminergic, as well as dopaminergic – neurons (Scherman et al., 1988; Erickson and Eiden, 1993). It is known that most of the VMAT2 bindings in the striatum occur at dopaminergic terminals (Vander Borght et al., 1995; Wilson et al., 1996), but the same does not apply in the cortical regions. Thus the dopaminergic function in the cortical regions cannot be reliably assessed using DTBZ PET measures. Consequently, although the cortical dopamine also plays critical roles in cognitive functions, we were not able to include it as a predictor in the regression models.

In summary, the present study clearly demonstrates compensatory dynamics between the basal forebrain cholinergic and the nigrostriatal dopaminergic systems contributing to impaired executive functions in PD. However, it is important to note that the cholinergic circuitry may not be the only system that is recruited to compensate for the cognitive functional impairment caused by dopaminergic depletion. Recently, a similar compensatory model has been suggested for norepinephrine (E. Vazey, personal communication, November 24th, 2014) in a rodent cognitive flexibility study. They tested the cognitive flexibility (task-switching cost) in rodents with single (striatal dopamine or norepinephrine) and dual lesions (striatal dopamine and norepinephrine). Only the dual-lesioned animals exhibited robustly impaired cognitive flexibility

suggesting that in the dopaminergic single lesion rodents the intact norepinephrine system may be compensating for the functional impairment expected to be induced by the dopaminergic depletion. Future studies are needed for better understanding of the dynamics and compensatory pathways between all three systems – dopaminergic, cholinergic and noradrenergic– in different domains of executive function in PD.

In conclusion, the present study provides novel evidence for compensatory mechanisms between the caudate dopaminergic and cortical cholinergic circuitry supporting executive control function in PD. Rather than a simple "one-to-one" substitution of cholinergic processes for dopaminergic ones, we expect that there will be qualitative differences in performance between an individual whose deficits are caused by moderate denervation of both dopaminergic and cholinergic systems than one whose executive declines are due to more severe frontostriatal dopaminergic decline but only minor cholinergic denervation (cf., Kucinksi et al., 2013; in review) but these may be subtle and require careful experimentation and task analysis to elucidate. Meanwhile, the results from the present study suggest that successful treatment of cognitive deficits in PD will require attention to individual patients' profiles of decline.

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Chapter VI

GENERAL CONCLUSION

Overview

The studies presented here support the idea that rather than being only a diffuse neuromodulator, the cholinergic system – or more properly, systems – act in regionally-defined and process-specific ways to support different components of attention and cognitive control. In signal detection under noise, bottom-up amplification of signal saliency via PPN-thalamic pathways may play a particularly important role (Chapter 3). As cognitive control demand increases, in particular the need to avoid distraction from external competing inputs, basal forebrain-cortical (and especially frontoparietal) pathways play a more important role, and the present studies suggest a differentiation between the roles of right PFC (attentional effort) and left parietal (distractor suppression; Chapter 2 and 4). Finally, as executive demands and especially the need to manage conflict increase, the present data suggest increased interactions between the cortical cholinergic system and other neuromodulatory systems, in particular the fronto-striatal dopamine system (Chapter 5). Below I summarize these findings in more detail, as well as limitations, future directions, and their broader implications.

Summary of findings

Chapter 2 aimed at how gamma-band synchronization thought to reflect the cholinergic activities (Metherate, Cox, and Ashe, 1992; Buhl, Tamás, and Fisahn 1998; Rodriguez, Kallenbach, Singer, & Munk, 2004; Kaiser & Lutzenberger, 2003; Kaiser & Lutzenberger, 2005; for review see Deco & Thiele, 2009) and attentional selection (Fell, Fernández, Klaver, Elger, & Fries, 2003; Fries, Nikolić, & Singer, 2007; Fries, 2009; Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1997) changes to support attentional selection during the signal detection task particularly in a challenging environment with distractors. The study found that local gamma synchronization in the left parietal and occipital regions correlate with signal detection sensitivity and that the intrasubject gamma peak variation correlates with the response time variability in the left parietal regions. Importantly, when there is a distractor challenge, the left parietal gamma synchronization significantly increased, and this increase was associated with preserved performance. On the other hand, the intrasubject gamma distribution became more dispersed in response to distraction in the right prefrontal regions, and the distractor-related increases of the frontal gamma dispersion and response time variability correlated positively with each other. In addition, distractor-entrained 5Hz ITC was significantly greater in miss compared to hit trials reflecting the attention drawn to the distractor. This distractor-entrained ITC was negatively correlated with the left parietal gamma synchronization in the hit trials. In contrast to what was expected based on the previous animal and human studies (St. Peters, Demeter, Lustig, Bruno, & Sarter, 2011; Demeter, Hernandez-Garcia, Sarter, & Lustig, 2011), we did not find gamma increase in the prefrontal cortex. Instead, the distractor-related gamma synchronization

was most prominent in the left parietal regions. This may be due to the discrepancy between the distractor types used in the previous studies (classic dSAT) and Chapter 2. The distractor in the classic dSAT is presented as a flashing houselight (rodent studies) or flashing background (human studies) during the signal detection task, which dramatically increases the perceptual difficulties of the signal. In contrast, the distractor used in Chapter 2 draws attention towards the distractor increasing the probability that the participant fails at sustaining attention to where the signal may appear. Thus, what drives the left parietal involvement in the results in Chapter 2 may be the attentional selection process – as opposed to the attentional effort that the classic dSAT distractor is more likely to recruit. The positive correlations between the distractor-related increases of the right prefrontal gamma dispersion and response time variability further supports this interpretation. However, we can only make indirect interpretations on whether the gamma oscillations and the associated behavioral changes observed in this study reflect the cholinergic activities. In the next three chapters, we used the wide range of the cholinergic integrities in PD patients and the PET measures of the cholinergic functions in order to determine the specific roles that the cholinergic system carries out in the attentional selection, and more generally, in the executive functions.

Chapter 3 and 4 investigated the roles of the cortical and thalamic cholinergic systems in the attentional selection and found that the thalamic and cortical cholinergic systems may support the distractor resistance in different distractor environments. Chapter 3 used the classic dSAT paradigm, in which the distractor makes the signal detection more challenging via presenting strong bottom-up sensory inputs. The accuracy of the signal detection in the absence of distraction correlated with both the

thalamic and cortical cholinergic functions, but critically the distractor resistance was best explained by the thalamic cholinergic function - over and above the effects of the age, cortical cholinergic, and caudate dopaminergic functions. Importantly, this thalamic cholinergic-distractor resistance correlations were driven by the signal trials (as opposed to non-signal trials), further providing evidence that the dSAT distractor impairs signal detection by adding perceptual noise and thus increasing the demand for the selective processing of sensory inputs and that the thalamic cholinergic system support resisting this distractor by maintaining the saliency of bottom-up sensory signals (Morris, Friston, & Dolan, 1997; Kobayashi & Isa, 2002; Langner & Eickhoff, 2013).

Using the same framework as in Chapter 3, Chapter 4 investigated the cholinergic correlates of attentional selection using a sustained attention task with a distractor that would draw attention away from the task instead of increasing the perceptual difficulty of the target selection (CTET; O'Connell et al., 2009; Berry et al., 2014a; 2014b). In this task, the cortical, instead of the thalamic, cholinergic system played a critical role in successfully maintaining attention on the goal-relevant task in the presence of the distractor. This cholinergic-distractor vulnerability correlations were most prominent in the left parietal cortex, left middle frontal gyrus, and bilateral temporal regions. The cholinergic contribution to the distractor resistance in the left parietal lobe was particularly consistent with the findings in Chapter 2. The nature of the distraction in Chapter 2 was more similar to CTET (Chapter 4) rather than dSAT (Chapter3) ; Unlike in dSAT and more like in CTET, the distractor in the modified dSAT (Chapter 2) draws the attention away from the goal-relevant target processing, which was reflected in the increased 5Hz ITC in the miss trials in the distractor condition. The increase of

the left parietal gamma synchrony in response to distraction, which was negatively correlated with the behavioral distractor effects, may reflect the same mechanisms as seen in Chapter 4; Lower levels of the cholinergic functions in the left parietal regions were associated with greater performance disruption by the distractor. Taken together, Chapter 2 and 4 provide converging evidence for the role of the left parietal lobe in the attentional selection. To reiterate, Chapter 3 and 4 demonstrated the differential contributions of the thalamic and cortical cholinergic systems to the attentional selection. In both the studies, the attentional selection was evaluated using signal detection tasks with distractor manipulations.

We next asked whether the cholinergic functions are involved more generally in the executive control when the task poses more complex demands of control. Again using the PET measures of the cholinergic and dopaminergic functions, Chapter 5 investigated the cholinergic and dopaminergic contributions to the executive control functions in a larger sample of PD patients. Importantly, we used modified Stroop task that allowed measuring executive controls at two demand levels; It measured the classic Stroop conflict effect and the dual conflict effect. This chapter critically addressed and investigated the possibility that the cortical cholinergic and striatal dopaminergic systems may make mutually compensatory contributions to the executive control when the task poses more complex demands. The hierarchical regression models revealed that the caudate dopaminergic-cortical cholinergic interaction term explained significant amount of the variances in both the Stroop and dual conflict effects over and above what can be explained by other variables in the model – age, thalamic, cortical cholinergic function, and caudate dopaminergic function. Importantly, additional

analyses supported that the significance of interaction terms means that the cortical cholinergic and the caudate dopaminergic systems compensate for the deficits in the other system. The cortical cholinergic function predicted the conflict effects only in PD patients with low caudate dopaminergic function. Likewise, lower caudate dopaminergic function was associated with greater conflict effects only in PD patients with low cortical cholinergic dopaminergic function.

Limitations and future direction

Findings in Chapter 2 suggest that the local gamma synchronizations in the right frontal and the parietal regions are associated with distractor resistance and may play dissociable roles in the attentional selection – the right prefrontal lobe reflecting the attentional effort and the parietal lobe assisting the attentional selection. These provide coherent interpretation to our previous human fMRI study where the right prefrontal BOLD signal increase in response to distraction was associated with greater behavioral impairment by the distractor challenges (Demeter et al., 2011). However, the study provides no direct evidence for the cholinergic involvement in these frontal and parietal gamma activities. A future study with a pharmaceutical manipulation in combination with the paradigm used in Chapter 2 would allow more clear understanding on the neurochemical mechanisms underlying the present findings, particularly the degree to which we can interpret the gamma activities as the cholinergic signatures.

Another important question that remains unaddressed in the Chapter 2 is the specific mechanisms for the long-range oscillatory modulation suggested in the results.

One of the striking findings in Chapter 2 was that the distractor-entrained oscillation (5Hz ITC) in the occipital regions seemed to be modulated by the local gamma synchronization in the left parietal electrode sites (i.e., the occipital 5Hz ITC and the left parietal gamma power were negatively correlated in the hit trials in the distractor condition). The specific oscillatory dynamics between the modulatory parietal gamma synchronization and the distractor-entrained oscillations need to be further investigated.

Chapter 3~5 used the radio-labeled acetylcholine analogue [^{11}C]methyl-4-piperidinyl propionate (PMP) PET measure to estimate the AChE metabolism (See methods in Chapter 2 for details). The cholinergic regional activity measured by the AChE hydrolysis rate measure maps well with the distribution of choline acetyltransferase (ChAT; Mesulam and Geula, 1992), but it is still an indirect measure of the ACh activities. This measure is also prone to the regulation problems (see chapter 5 for discussion). To address this issue, we have follow-up studies with the [18F]-FEOBV vesicular acetylcholine transporter (VAChT) ligand that traces the α4β2*nicotinic receptor binding, which is the most abundant nicotinic receptor subtype in the human brain.

Conclusions

Despite the remaining questions, the present dissertation work provides several important findings, particularly suggesting potential coherent interpretations for some seemingly inconsistent previous findings. First, it showed that both the thalamic and cortical cholinergic projections support the attentional selection but in differential –

bottom-up vs. top-down - ways. Falling and freezing are both motor symptoms associated with PD, but their underlying neuropathologies seemed different. Fall propensity in PD patients is significantly higher in patients with low thalamic cholinergic functions (Bohnen et al., 2009). On the other hand, freezing is more associated with the cortical but not thalamic cholinergic denervation (Bohnen et al., 2014). These may seem to contradict each other, but the present findings provide a possible interpretation putting the two previous findings together. Both falling and freezing may be triggered by unsuccessful attentional selection but at different levels of selection. Impaired selective processing of the bottom-up, sensory information – caused by thalamic cholinergic denervation – may make one more prone to falls, whereas impaired selective allocation of top-down attention – caused by cortical cholinergic denervation – may make one more prone to freezing.

Second, the present work demonstrated the differential functional relevance of the local gamma synchrony in the prefrontal and parietal regions: the attentional effort and attentional selection, respectively. Our previous animal and human studies using parallel dSAT paradigms showed strikingly converging findings with yet one diverging point. In response to distraction, rats increased the right PFC cholinergic release (St. Peters et al., 2011) and humans increased the right PFC BOLD activities (Demeter et al., 2011). However, greater right PFC cholinergic release in rats were associated with preserved signal detection performance in the face of distraction whereas greater right PFC BOLD signal in humans was associated with greater behavioral impairment in the distractor condition. In Chapter 2, the greater intra-subject gamma peak dispersion was associated with greater behavioral impairment by distractor, which suggests that the

right PFC activities may reflect the attentional effort rather than supporting the selection and the consequent performance. This may explain the seemingly counterintuitive negative correlations between the right PFC BOLD signal and the distractor effect.

Third, the present work showed the compensatory roles of the cortical cholinergic and the caudate dopaminergic systems in the executive control, of which dysfunction is the most prominent cognitive impairment in PD. Recent animal and humans studies suggested that the basal forebrain cholinergic and nigrostriatal dopaminergic circuitries may play complementary roles (See Introduction), and the present study provides strong human study evidence for this model.

To conclude, the present work illustrated the modulatory role of local gamma synchronization in the fronto-parietal attentional network with potentially differential roles in the prefrontal and parietal regions, the distinctive roles carried out by the thalamic and cortical cholinergic systems at different stages of attentional selection, and the interactive roles that the cortical cholinergic and striatal dopaminergic systems play to deal with complex attentional demand. These findings provide potential directions for the treatment for the cognitive impairments not only in PD but also in neuropsychiatric disorders with the cholinergic deficits such as Attentional-deficit-hyperactivity-disorder (ADHD; English et al., 2009).

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Appendix I

Residual scores as measures of distractor effects

In Chapters 3~5, difference scores (cf., ΔSAT scores (dSAT-SAT)) were used to measure the distractor or conflict effects. Residual scores are alternative measures of changes that accounts for the individual differences in the baseline condition (see Cronbach and Furby, 1970 for further discussion). In this appendix, the results from Chapters 3~5 are reported using the residual instead of difference scores as the measure of effects. Consistently as in Chapter 2, linear regression models were conducted on the *distractor* or *conflict* measures with the *baseline condition* measure as the predictor, and the resulting residuals are reported as the distractor or conflict effects.

Chapter III (dSAT)

Distractor effects in HC vs. PD

A. full-sample

group	N	Mean	Std. Deviation	Std. Error Mean
HC	17	0	.18	.04
PD	17	0	.12	.03

Independent sample t-test: t(32) = .0, p = 1.0

B. low-cholinergic group

group	N	Mean	Std. Deviation	Std. Error Mean
HC	4	.0620	.12	.06
PD	4	-.0745	.14	.07

Independent sample t-test: t(6) = 1.5, p = .20

C. normal-cholinergic group

group	N	Mean	Std. Deviation	Std. Error Mean
HC	13	-.0190	0.19	0.05
PD	13	.0229	0.11	0.03

Independent sample t-test: t(24) = -.68, p = .50

Correlations between PAC scores and distractor effect (cf., table 3.2)

** indicates p < .0005

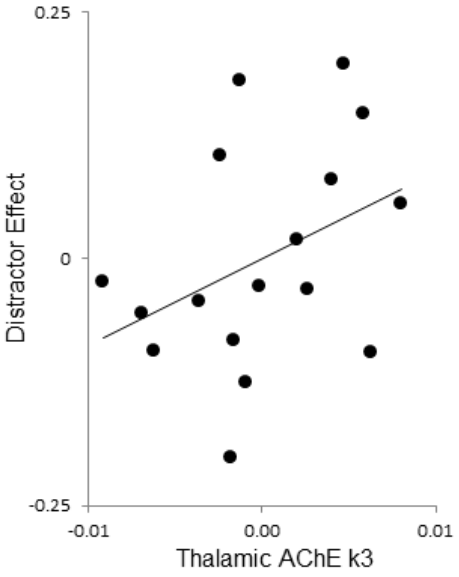
		Self-report Everyday Attention Measure (PAC)			
		overall score	mind-wandering	boredom	distractibility
HC	*r*	.48	.43	.59	.23
	p	.053	.088	.01	.35
PD	*r*	.26	.15	.15	.30
	p	.31	.57	.56	.25

Correlations between distractor effect, age, BDI, and PET measures (cf., table 3.3)

		age	BDI	thalamic k3	cortical k3	putamen DVR	caudate DVR
distractor effect	*r*	-.38	.10	.19	.07	-.16	.00
	p	.13	.70	.46	.79	.53	.99

Hierarchical multiple linear regression model for distractor (cf., table 3.4)

	coefficients				model statistics					
	B	β	*t*	*p*	R^2	Δ R^2	Δ F	sig. Δ F	Model Fit *F*	Model Fit *p*
step 1 model					.14	.14	2.5	.13	2.52	.13
constant	.37		1.57	.14						
age	-.01	-.38	-1.59	.13						
step 2 model					.30	.15	.9	.48	1.27	.34
constant	.68		1.4	.20						
age	-.01	-.63	-2.1	.06						
caudate DVR	-.07	-.23	-.8	.42						
thalamic k3	8.8	.45	1.4	.18						
cortical k3	-16.1	-.40	-1.2	.27						



Correlations between the distractor vulnerability and thalamic cholinergic function (cf., figure 3.3)
Residual plots after controlling for age, caudate DVR, and cortical k3.

r = .38
p = .13

Chapter IV (CTET)

Correlations between the PAC scores and CTET distractor effect (cf., table 4.2).

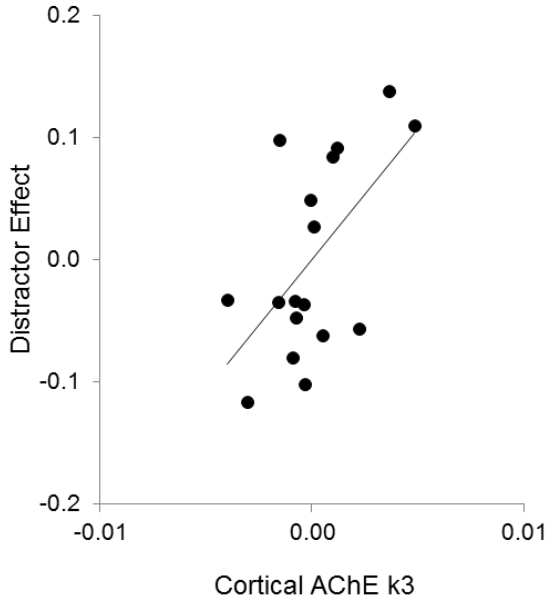
			Self-report Everyday Attention Measure (PAC)			
			overall score	mind-wandering	boredom	distractibility
HC	CTET distractor effect	*r*	-.36	-.34	-.25	-.38
		p	.16	.18	.34	.14
PD	CTET distractor effect	*r*	.22	.06	.28	.18
		p	.41	.83	.28	.48

Correlations between the CTET distractor effect, age, depressions score (BDI), and the PET measures (cf., table 4.3)

		age	BDI	thalamic k3	cortical k3	putamen DVR	caudate DVR
distractor effect	*r*	-.45	.19	.01	.52	.32	.40
	p	.07	.47	.98	.03	.20	.11

Hierarchical multiple linear regression model for distractor effects (cf., table 4.4)

	coefficients				model statistics					
	B	β	*t*	*p*	R^2	ΔR^2	Δ F	sig. Δ F	Model Fit *F*	Model Fit *p*
step 1 model					.20	.20	3.7	.07	3.7	.07
constant	.28		1.9	.08						
age	-.004	-.45	-1.9	.07						
step 2 model					.53	.33	2.8	.09	3.3	.047
constant	-.08		-.33	.75						
age	-.001	-.14	-.60	.56						
caudate DVR	.04	.19	.79	.44						
thalamic k3	-8.4	-.58	-2.04	.06						
cortical k3	21.4	.76	2.48	.03						



Correlation between the cortical k3 and distractor effect with age, thalamic k3, and caudate DVR controlled for (cf., figure 4.3)

r = .58, p = .01

Chapter V (conflict)

Correlations between the conflict effects, age, depression score (BDI), and the PET measures in PD (cf., table 5.2)

		age	BDI	thalamic k3	cortical k3	putamen DVR	caudate DVR
Stroop conflict	r	.19	-.02	-.04	-.08	-.07	-.08
	p	.03	.86	.68	.34	.43	.33
dual conflict	r	.10	-.02	-.10	-.18	-.06	-.06
	p	.25	.78	.25	.04	.47	.46

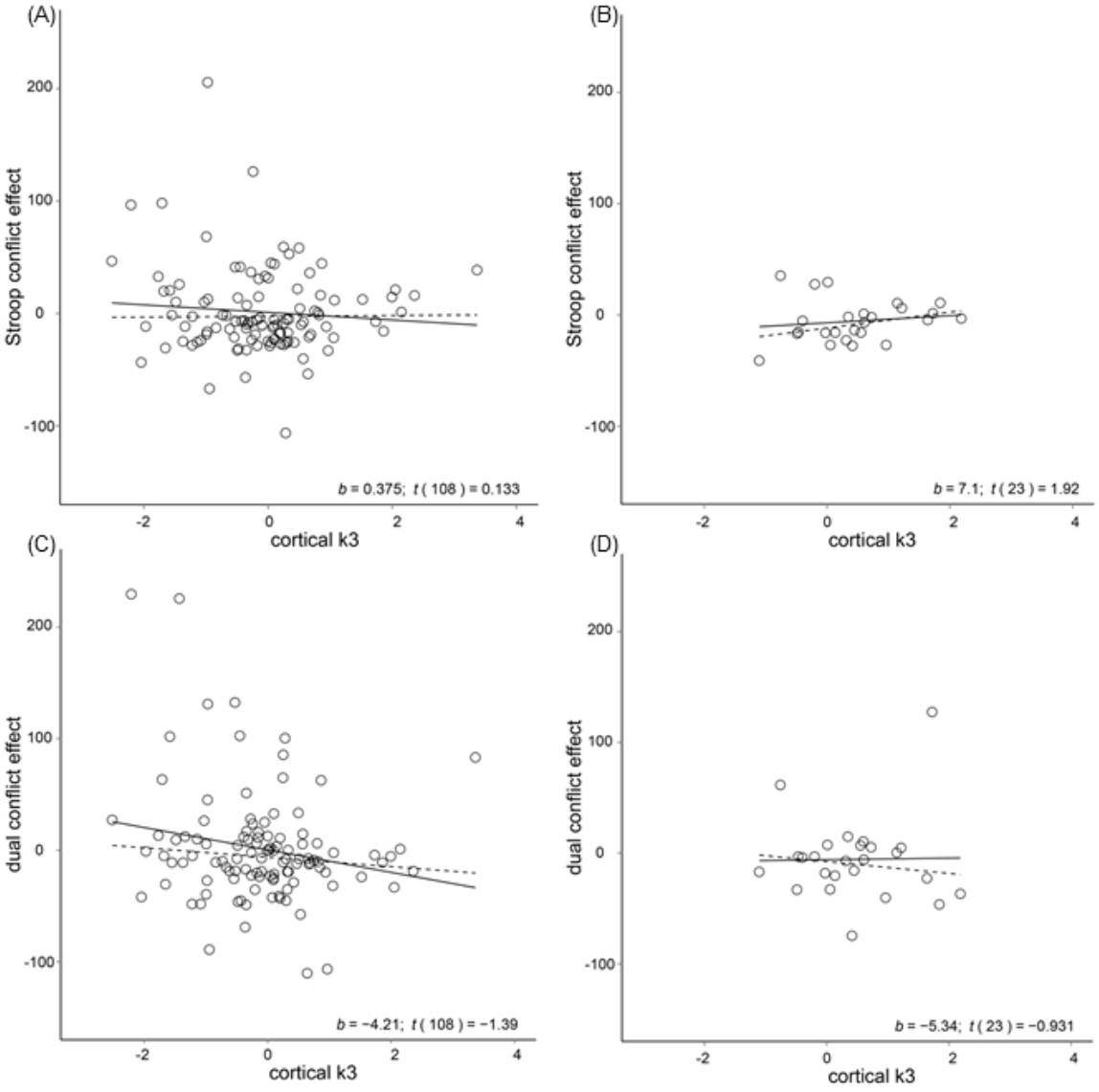
Hierarchical multiple linear regression model for the Stroop conflict effect in PD (cf., table 5.3)

	coefficients				model statistics					
	B	β	*t*	*p*	R^2	Δ R^2	Δ F	sig. Δ F	Model Fit *F*	Model Fit *p*
step 1 model					.04	.04	5.0	.03	5.0	.03
constant	.0		.0	1.0						
age	6.8	.2	2.2	.03						
step 2 model					.04	.01	.2	.89	1.4	.24
constant	.0		.0	1.0						
age	6.4	.2	2.0	.048						
caudate DVR	-1.7	-.1	-.5	.61						
thalamic k3	1.9	.1	.5	.63						
cortical k3	-2.0	-.1	-.5	.60						
step 3 model					.05	.01	.8	.39	1.3	.29
constant	-.7		-.2	.82						
age	6.2	.2	1.9	.059						
caudate DVR	-2.7	-.1	-.8	.44						
thalamic k3	1.9	.1	.5	.61						
cortical k3	-1.7	0	-.4	.66						
caudate DVR * cortical k3	2.7	.1	.9	.39						

Hierarchical multiple linear regression model for the dual conflict effect in PD (cf., table 5.4)

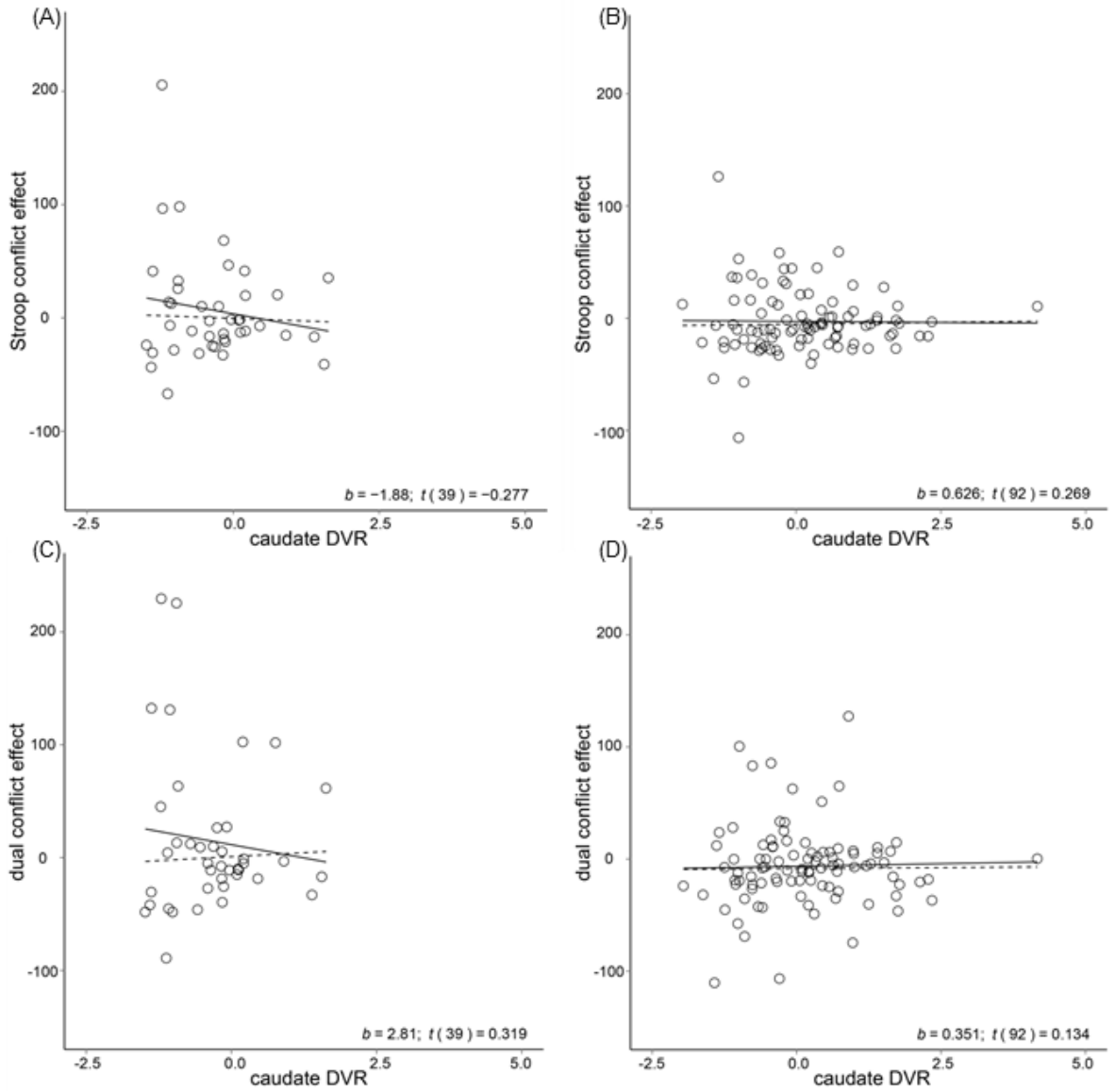
	coefficients				model statistics					
	B	β	*t*	*p*	R^2	Δ R^2	Δ F	sig. Δ F	Model Fit *F*	Model Fit *p*
step 1 model					.01	.01	1.3	.25	1.3	.25
constant	.0		.0	1.0						
age	4.9	.1	1.1	.3						
step 2 model					.04	.03	1.2	.32	1.2	.31
constant	.0		.0	1.0						
age	2.9	.1	.7	.5						
caudate DVR	-.5	-.01	-.1	.9						
thalamic k3	.9	.02	.2	.9						
cortical k3	-8.5	-.2	-1.6	.1						
step 3 model					.04	.01	.7	.39	1.1	.36
constant	-1.0		-.2	.8						
age	2.6	.1	.6	.6						
caudate DVR	-1.8	-.04	-.4	.7						
thalamic k3	1.0	.02	.2	.9						
cortical k3	-8.1	-.2	-1.5	.1						
caudate DVR * cortical k3	3.6	.1	.9	.4						

Cortical cholinergic function and conflict effects the in low and normal caudate dopaminergic group (cf., Figure 5.3).



		cortical k3 – conflict effect	
		Stroop conflict	dual conflict
low caudate DA group (n = 110)	Pearson correlation	r = -.09, p = .4	r = -.20, p = .04
	robust regression	t = .1, p = .9	t = 1.9, p = .2
normal caudate DA group (n = 25)	Pearson correlation	r = .14, p = .5	r = .02, p = .9
	robust regression	t = -1.4, p = .07	t = -.9, p = .4

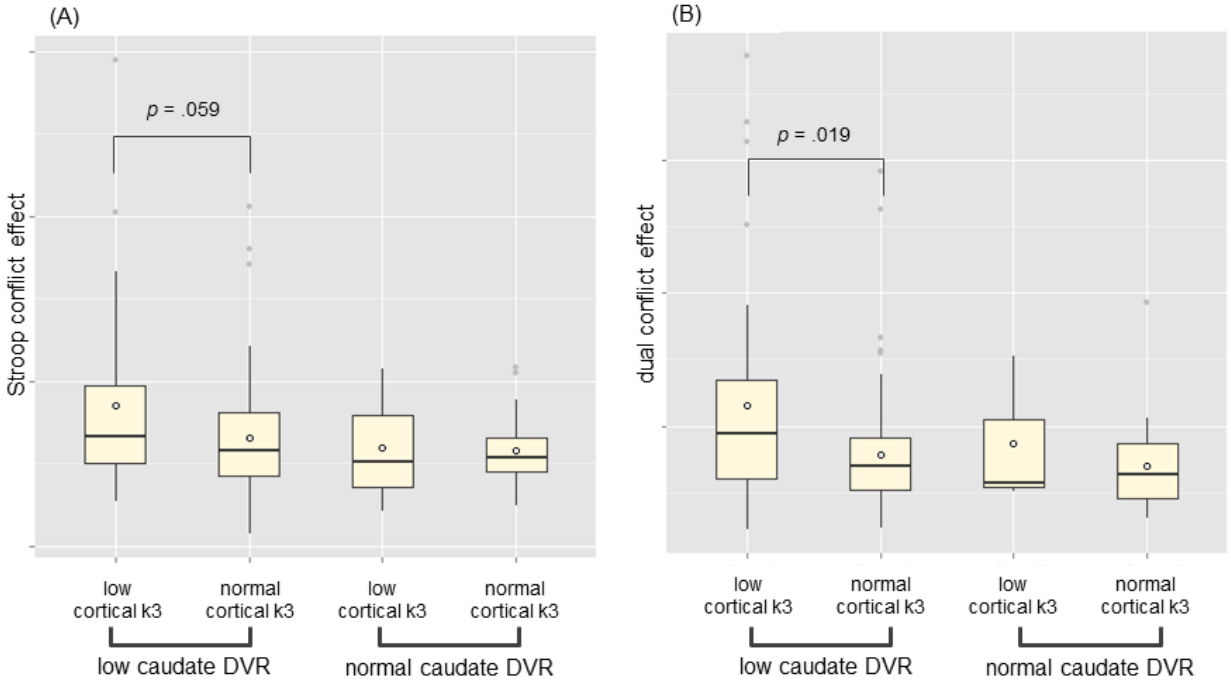
Caudate dopaminergic function and conflict effects the in low and normal cortical cholinergic group. (Cf., Figure 5.4)



		cortical k3 – conflict effect	
		Stroop conflict	dual conflict
low cortical k3 group (n = 41)	Pearson correlation	r = -.16, p = .3	r = -.11, p = .5
	robust regression	t = -.3, p = .8	t = .3, p = .8
normal cortical k3 group (n = 94)	Pearson correlation	r = -.01, p = .9	r = .03, p = .8
	robust regression	t = .3, p = .8	t = .1, p = .9

Appendix II

Supplementary Materials for Chapter V



Conflict effects in the four subgroups. Among the patients with low caudate dopaminergic functions, the subgroup with low cortical cholinergic integrities showed significantly greater Stroop (A) and dual (B) conflict effects compared to the normal cholinergic subgroup (the left two boxes in (A) and (B)). In contrast, conflict effects in the low- and normal- cholinergic group did not differ in PD patients with normal caudate dopaminergic functions (the right two boxes in (A) and (B)). The dots and horizontal lines in the boxes mark the means and medians respectively.