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Compensatory dopaminergic-cholinergic interactions in conflict processing: Evidence from patients with Parkinson's Disease

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Abstract

Executive functions are complex both in the cognitive operations involved and in the neural structures and functions that support those operations. This complexity makes executive function highly vulnerable to the detrimental effects of aging, brain injury, and disease, but may also open paths to compensation. Neural compensation is often used to explain findings of additional or altered patterns of brain activations by older adults or patient populations compared to young adults or healthy controls, especially when associated with relatively preserved performance. Here we test the hypothesis of an alternative form of compensation, between different neuromodulator systems. 135 patients with Parkinson's Disease (PD) completed a vesicular monoamine transporter type2 (VMAT2) and acetylcholinesterase PET scanning to assess the integrity of nigrostriatal dopaminergic, thalamic cholinergic, and cortical cholinergic pathways and a behavioral test (Stroop + task-switching) that put high demands on conflict processing, an important aspect of executive control. Supporting the compensatory hypothesis, regression models controlling for age and other covariates revealed an interaction between caudate dopamine and cortical cholinergic integrity: Cortical cholinergic integrity was a stronger predictor of conflict processing in patients with relatively low caudate dopaminergic function. These results suggest that although frontostriatal dopaminergic function plays a central role in executive control, cholinergic systems may also make an important contribution. The present results suggest potential pathways for remediation, and suggest that the appropriate interventions for each patient may depend on their

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Conflict of interest

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particular profile of decline. Furthermore, they help to elucidate the brain systems that underlie executive control, which may be important for understanding other disorders as well as executive function in healthy adults.

Introduction

Brain injuries and neurodegenerative disorders can serve as “natural experiments” that provide insights into brain structure-function relations that would otherwise not be possible for technical or ethical reasons. Classic cases include patients with dramatic lesions, such as H.M. or Phineas Gage (Corkin and Scoville, 1984; Scoville and Milnder 1957; Harlow, 1868; Damasio et al., 1994). Neurodegenerative diseases provide another such opportunity, and cross-sectional or longitudinal analyses at different stages of severity fit especially well with the RDoC (Research Domain Criteria) mandate of understanding brain-behavior relationships throughout the entire range of function. The heterogeneity of neuromodulator system decline in Parkinson’s disease (PD) may make it particularly instructive. In addition to the dopaminergic declines that define the disorder, Parkinson’s patients often have degeneration along other neural pathways (cholinergic, noradrenergic, serotonergic, etc.; Dunois et al., 1983; Gaspar et al., 1991; Halliday et al., 1990; Kuhls et al., 1996; Rommelfanger and Weishenker 2007; Scatton et al., 1983; Stern et al., 1984). There are large individual differences in the degree of degeneration in these other pathways, and those differences can be relatively independent of each other and of the degree of dopaminergic decline (e.g., Bohnen and Albin, 2011; Dunois et al., 1983; Hall et al., 2014; Monchi et al., 2016; Müller and Bohnen, 2013; Perry et al., 1985; Pillon et al., 1989). These individual differences and their behavioral consequences can be leveraged to help illuminate the role that different neuromodulator pathways play in different aspects of cognition (see Calabresi et al., 2007; 2014; Frey, 2017 for reviews; see also Lopes et al., 2017 for functional connectivity measures).

We recently used this approach – using a PD patient sample with a particular neural degeneration as an natural experimental group – to demonstrate that thalamic cholinergic pathways play an important role in supporting the detection of targets that have strong “bottom-up” perceptual salience, whereas cortical cholinergic pathways support the ability to resist salient distractors (Kim et al., 2017; in press). Here we take a similar approach to examine how cholinergic and dopaminergic pathways contribute to executive functions, specifically the ability to overcome conflict from both long-term (Stroop) and short-term (task switching) response habits.

Executive function impairments are common in PD (Lees & Smith 1983; Dubois & Pillon 1996; McKinlay et al., 2010; Robbins & Cools, 2014), but the underlying neuropathology is not fully understood. The dual syndrome hypothesis (Kehagia et al., 2013), and the compensatory hypothesis (Bohnen et al., 2015; see also Bezard et al., 2003) take somewhat different views on the role of the cholinergic system. While the dual-syndrome hypothesis acknowledges some degree of overlap, it generally considers frontal-striatal dopaminergic declines as primarily responsible for executive control deficits in PD, and cholinergic degeneration as leading to memory, visuospatial, and psychiatric symptoms associated with

PD dementia. In contrast, the compensatory hypothesis posits a more direct role for the cholinergic system. It proposes that frontostriatal dopamine declines may lead to compensatory reliance on (and possibly increased activity in) cortical cholinergic circuits.

By this view, patients who also have cortical cholinergic declines have reduced efficiency of cholinergically-mediated frontal-executive processes that might otherwise compensate for frontal-striatal dopaminergic losses. The compensatory hypothesis thus predicts that patients with both cholinergic and dopaminergic declines should have exacerbated executive function impairments, rather than the more global cognitive and psychiatric declines and prodromal dementia predicted to accompany cholinergic denervation by the dual-syndrome hypothesis.

The compensatory hypothesis is based in part on findings that a substantial proportion of patients with no apparent cognitive deficits, including on executive tasks, nonetheless had substantial denervation of caudate dopaminergic pathways (Bohnen et al., 2015). In contrast, cognitive impairment had a linear relationship with cortical cholinergic denervation. That is, even among nondemented patients, those with more severe cognitive deficits were more likely to have cholinergic denervation, usually accompanied by caudate dopaminergic denervation. Regression analyses indicated the caudate-dopaminergic and cortical-cholinergic pathways had both independent and interactive effects on cognitive outcomes. Furthermore, both the independent and interactive effects were stronger for executive-function tests than for verbal learning, psychomotor speed, or visuospatial measures.

The executive function measures examined in Bohnen et al. (2015) primarily tapped executive-control processes involved in planning and sequencing (Delis-Kaplan Executive Function System Sorting Test; WAIS III Picture Arrangement test). However, as noted earlier, executive control is a complex construct that incorporates a number of cognitive processes (see, e.g., Banich, 2009; Miyake et al., 2000), making it important to test whether the findings of Bohnen et al. are specific to planning and sequencing, or generalize to other aspects of executive control. Therefore, in the present study, we examine conflict processing, another important aspect of executive control.

Nondemented PD patients 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 et al., 1992). This task therefore places particularly high demands on executive-control processes, as on most trials participants must resist word-reading responses in order to name the ink color, but on occasional “switch” trials, they need to temporarily abandon the color-reading task set, return to word reading, and then immediately switch back to color-reading. In addition to the *per se* switching demands, this also makes it more difficult to maintain the “read the color” task set on the Stroop trials, increasing conflict (see discussions by Bugg et al., 2008; Kane & Engle, 2003, and others). The straightforward prediction from the dual-syndrome hypothesis is that measures of dopaminergic integrity should be the primary predictors of performance on both of these measures. In contrast, the compensatory hypothesis predicts an interaction between dopaminergic and cholinergic integrity, such that cortical-cholinergic integrity should be an especially important contributor to performance in patients with relatively low dopaminergic integrity.

Methods

Participants

All experimental procedures were approved by the University of Michigan's Institutional Review Board, and were fully described to the participants before they consented to take part in the study. The data for the present study (PET and Stroop task) were collected in a combined session with other studies (Bohnen et al., 2015; Shah et al., 2016). Since the Stroop paradigm requires color discrimination, participation for the current study was limited to patients without color blindness. Thus, the patient sample of the current study was a subset of the Bohnen et al., 2015 study sample. Most of the participants underwent 2 PET imaging sessions, 1 MRI scanning session, and an entire day of motor/neuropsychological testing and received monetary compensation ($400) for their participation.

140 PD patients and 63 healthy controls (HC) participated in the study. Outliers whose overall behavioral performance (average Inverse Efficiency Score (IES) over 4 levels in the task, see Statistical Analysis) fell outside 3 standard deviations from the group means were excluded from the analyses (4 PD, 1 HC). One PD patient completed the dopaminergic and not the cholinergic scans due to technical problems. In order to keep a consistent dataset across analyses for the PD group, we omitted this person from the reported analyses. (Including this participant did not change any conclusions.) Thus, the final sample included a total of 135 PD patients (37 female, age range 50–84, mean age = 65.43) and 62 healthy older adults (37 female, age range 40–84, mean age = 65.17).

On average, motor symptom duration of the PD patients was 6.1 years (range, 5–19 years, standard deviation (SD) = 4.27) and the median Hoehn and Yahr severity score, assessed in the dopaminergic "off" state, was 2.5 (range, 1.0–5.0, SD = .58; Hoehn and Yahr, 1967). 128 patients were on dopaminergic treatment (average levodopa equivalent daily dose (LEDD; Tomlinson et al., 2010) was 744 mg, range 30–3180 mg). No patient was taking any cholinergic or anti-cholinergic medications.

Participants also completed neuropsychological tests evaluating affective, cognitive, and motor function. The measures included the Beck Depression Inventory II (BDI-II, Beck et al., 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). All participants had a minimum MoCA score of 19; as seen in Table 1 there were no differences between the HC and PD groups.

Modified Stroop Task

All participants completed a modified version of the Stroop task (Bohnen et al., 1992) during laboratory testing (Figure 1). The task includes four levels that vary the stimulus presented (word or color 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 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 were asked to say the ink color of the color words on most trials, but for the items outlined with the box they were to read the word. The difference score between levels III and II in this task indexes Stroop conflict effect, and the difference score between levels IV and II measures dual-conflict effect (Bohnen et al., 1992).

Positron Emission Tomography (PET)

PET data were collected using the same protocol as our previous studies (Kim et al., 2017; in press). To avoid potential confusion that might be introduced by different methodological descriptions across these papers, with permission of the editors we largely reproduce the text describing the PET data collection. Further details on the PET methodology can also be found in the Supplemental Methods and in Bohnen et al. (2012).

PD patients and HC underwent PET scanning that traces dopaminergic and cholinergic nerve terminal integrity. Patients came in for dopaminergic PET scanning in the dopaminergic off-state, i.e., after abstaining from dopaminergic drugs overnight. They resumed the dopaminergic medications immediately after the dopaminergic PET scanning before the 30-minute break before the cholinergic PET scanning. The PET scans were obtained close to the behavioral testing session (median 1 day; SD = 36.29; range 0 – 367 days; within 30 days for 184 out of 197 participants).

Although PD typically affects one side of the striatum more than the other, we report the values averaged over both hemispheres, rather than using separate predictors from the affected vs. unaffected brain side of the patients for the following reason: Unlike motor control functions, where the laterality of motor symptom severity is clearly associated with the (contra)lateral severity of striatal denervation, we did not have any concrete grounds on which to hypothesize on how the PD-effected side might influence the cognitive measures used here. To our knowledge, there is no evidence on the lateralization of striatal support of conflict or cognitive flexibility – particularly in association with PD - and our previous data did not show asymmetry in cholinergic denervation in PD (Bohnen et al., 2009). As a precaution, we did repeat our analyses using the measures from the clinically most affected side, and the conclusions were largely the same. Therefore, because averaged estimates typically provide more stable estimates than individual measures, we report the averaged measures for better quantification of our effects.

The integrity of dopaminergic nigrostriatal nerve terminals was measured with [^{11}C]dihydrotetrabenazine (DTBZ), a vesicular mono- amine transporter type 2 analogue (VMAT2; see Bohnen et al., 2012 for details on DTBZ preparation, injection, and scanning parameters). The primary outcome parameter is DTBZ distribution volume ratio (DVR, Bohnen et al., 2009). Greater DVR indicates better dopaminergic terminal function. DTBZ DVR was measured for caudate and putamen. DTBZ PET scans were obtained for all PD and HC participants.

Cholinergic function was estimated using radio-labeled acetylcholine analogue [^{11}C]methyl-4-piperidinyl propionate (PMP) PET, which measures acetylcholinesterase (AChE) activity. PMP PET scans were performed in the dopaminergic medication 'on' state. Details on PMP preparation, injection, and scanning parameters have been described previously (Bohnen et al., 2012). The primary outcome parameter is AChE hydrolysis rate (k3; min-1), with a higher k3 indicating higher cholinergic nerve terminal integrity. Although PMP PET is an indirect measure of cholinergic activity, it has been validated in both rodent and primate models (e.g, Kilbourn et al., 1996; Selden et al., 1998) as well as in humans (e.g., Kuhl et al., 1996; 1999). We are not aware of any evidence suggesting that dopaminergic therapy affects brain AChE hydrolysis rates. To the extent that dopaminergic therapy may affect cholinergic activity, its effects may be more likely to be on the availability of nicotinic or muscarinic receptors rather than AChE, given its long half-life of approximately 2.8 days (Wenthold et al., 1974).

AChE k3 was measured for cortex and thalamus, the target regions of two major cholinergic pathways, separately. Cortical measures are used to index cholinergic nerve terminal integrity of the basal forebrain (including the nucleus basalis of Meynert), whereas thalamic measures primarily (though not exclusively) reflect integrity of the brainstem pedunculopontine nucleus (Bohnen and Albin, 2011; Bohnen et al., 2012; see review by Varela, 2014).

Statistical Analysis

Response time (RT) and accuracy were recorded as the performance measures 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 task-switching conflicts; Bohnen et al., 1992). Note that the inclusion of “switch” trials in the dual-conflict condition likely increases conflict on the Stroop trials (similar to manipulations of congruency; e.g., Bugg et al., 2008; Gonthier et al., 2016; Kane & Engle, 2003), so that the increase in demand from III to IV is nonlinear.

Independent-sample t-tests were used to compare the PD and HC groups on demographic measures and performance. First-level bivariate correlations were then used to characterize the relationships between the different measures, especially the neural predictors of the Stroop and dual-conflict effects. As described below, results for HC replicated previous effects of dopaminergic system status being negatively associated with age and positively associated with measures of executive function (e.g., Berry et al., 2016). A follow-up

analysis controlled for age to test the assumption that age accounted for the dopamine-executive function correlation.

Our main hypotheses concerned the ability of cortical cholinergic integrity, caudate dopaminergic integrity, and their interaction, to predict the executive function measures. For ease of comparison with our prior studies examining the role of the thalamic cholinergic pathway in supporting bottom-up attention to salient signals and the cortical cholinergic pathway in supporting the ability to resist distraction from salient but irrelevant stimuli (Kim et al., 2017; in press) we first report analyses following the same series of hierarchical regression models used in those prior studies: The first step evaluated age as a predictor for the executive control functions (the Stroop and dual conflict measures separately). The second step added caudate DVR, cortical k3, and thalamic k3. The final step tested the critical interaction term (caudate-dopaminergic × cortical cholinergic). This final step in the hierarchical regression allows evaluation of whether the caudate-cortical interaction uniquely predicted performance over and above the shared variance with the other measures.

As an additional way to test and illustrate the hypothesized caudate-cortical interaction, we examined the correlation (and robust regression, see below) between each executive function measure and one of the PET measures (e.g., cortical AChE k3) in patient subgroups defined by the level of the other PET measure (e.g., low-, and normal- caudate DTBZ DVR). First, we tested the cortical cholinergic-executive function relationship in the low- and normal-dopaminergic groups. Next, we tested the caudate dopaminergic-executive function relationship in low- and normal- cortical cholinergic groups. The low-dopaminergic group was defined using the 5^{th} percentile of DVR values in the healthy controls (n = 62). Due to the small number of HC with cholinergic PET measures in the present study (n = 10), the low-cholinergic group was defined using the cut-off score defined in a previous study from a larger HC sample (n = 29; Bohnen et al., 2012; using the 5^{th} percentile of HC). Figure 2(B–C) shows the distribution of the DVR and k3 values in PD and HC overlaid with each other along with the cut-off values used to group patients into low- / normal- groups.

In each group of patients, bivariate first-level correlation analyses were first used to examine the relationship between the conflict effects and caudate dopaminergic function (in the low- and normal- cortical cholinergic groups) or cortical cholinergic function (in the low- and normal- caudate dopaminergic groups). Visual inspection of the initial scatterplot of this first-level correlation suggested potential influential cases, but formal outlier analyses did not identify these cases as unusual errors. As it is not extraordinary to have relatively large variance in 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 variance in the executive functions explained by cortical cholinergic or caudate dopaminergic measures in each group. Age and thalamic k3 levels were controlled for in these correlation/robust regression analyses.

As effect sizes, we report Cohen's d for t-tests, Pearson's r for bivariate correlations, and standardized beta coefficient for multiple regression. G*power software (v 3.1., Faul et al., 2007; 2009) was used to estimate power for the critical multiple regression analyses.

Results

Demographic, neuropsychological tests, and overall performance data

Table 1 compares the HC (n = 62) and PD (n = 135) on demographic variables, neuropsychological test results, and behavioral performance in the task. PD and HC were comparable in age, education and general cognitive assessment (p > .1; absolute Cohen's d < .20), but PD patients scored significantly higher in BDI ($t = -8.1$, $p < .0005$, Cohen's $d = -1.00$). The higher BDI scores in PD are expected, as mild to moderate depressive symptoms occur in 40–50% of PD patients (Cummings, 1992; Tandberg et al., 1996). We therefore did not exclude participants on that basis. In all levels of the task, PD patients were slower and made more errors compared to HC ($p < .01$; Cohen's $d < -.33$), except for the error rate in level I, where effects were marginal ($p = .096$; Cohen's $d = -.18$).

Overall PET measures

Mean VMAT2 DTBZ DVR values for PD patients (n = 135) in the present study were mean (M) = 2.0710, SD = 0.3466 for caudate, M= 1.7743, SD = 0.2813 for putamen; M = 1.8732, SD=0.2881 for striatum (caudate and putamen together). For HC (n = 62), DVR values were M = 2.8188, SD = 0.3056 for caudate, M = 3.5763, SD = 0.3351 for putamen; M = 3.3238, SD = 0.3135 for striatum. For comparison, Bohnen et al. (2012) previously reported striatal DTBZ DVR values of M = 1.93, SD = 0.27 for PD (n=101) and M = 3.03, SD = 0.31 for HC (n = 29).

PMP PET was obtained from 135 PD and 10 HC. Mean PMP k3 values (min^{-1}) in the present study were PD: cortical M = 0.0238, SD = 0.0028; thalamic M = 0.0546, SD = 0.0055; HC: cortical M = 0.0257, SD = 0.0031, thalamic M = 0.0608, SD = 0.0066. For comparison, the values reported from a larger sample in Bohnen et al. (2012) were PD (n = 101): cortical M=.0236, SD=.0027; thalamic M=.0542, SD=.0056); HC (n = 29): cortical M=.0263, SD=.0027; thalamic M=.0599, SD=.0074.

Stroop and dual-conflict effects correlate with caudate dopaminergic measures in both groups, and with cortical cholinergic measures in PD

Table 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 the 62 HC (except for cholinergic PET measures, HC N = 10) and 135 PD patients with both the DTBZ and PMP PET measures. For the HC, correlations with the cholinergic PET measures represent data from only those 10 participants who completed the cholinergic scans. We report these for completeness, but do not interpret them given the small sample size.

For the HC, neither caudate nor putamen dopamine measures predicted the speed of color naming used as a baseline measure for the executive-control tasks (p > .50), and the correlation between color-naming speed and age was only marginal (p = .07). Consistent with other findings linking increased age, reduced dopaminergic function, and executive control, the age, dopaminergic, and executive control (Stroop effect, dual-conflict effect) measures were moderately intercorrelated in the HC group. Controlling for age eliminated the ability of either dopaminergic measure to predict the performance measures (all r < .15, p > .25).

For the PD, color naming as well as the conflict effects showed significant correlations with age and caudate DVR ($p < .01$). Thalamic k3 showed significant correlations with age (p = .004) and dual conflict effects (p = .046). In addition, cortical k3 showed marginal to significant correlations with age (p = .005) and the behavioral measures (r = −.15 – −.24, p .08 – .004). Consistent with our previous findings (Kim et al., 2017, in press), age was correlated with the behavioral and the caudate and cortical PET measures ($|r|$ ranges .19~.30, $p < .05$). Controlling for age reduced the correlation value by a small amount (approximately |r| .03–.06) for all measures (new values for caudate-DVR: color naming r = −.31, p < .0005, Stroop r = −.19, p = .32, dual-conflict r = −.21, p = .016; new values for corftical k3: color-naming r = −.09, p = .215, = .026, Stroop r = −.09, p = .32, dual conflict r = −.20, p = .023; compare to values in Table 2).

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

A hierarchical regression model with three steps was used to test the compensatory hypothesis in the PD group. (Table 3 for the Stroop conflict effect; Table 4 for the dual conflict effect). In all of the regression models reported here, collinearity statistics were well within acceptable ranges (all tolerance values above .88; values above .10 are typically considered acceptable; all VIF values below 1.2; values below 10 are usually considered acceptable; Field, Miles, & Field 2012).

In the first model, age was entered as the only predictor, followed by the second model with caudate DVR, thalamic k3, and cortical k3 entered as additional predictors. In the final model, the caudate DVR-cortical k3 interaction term was added as a predictor. All three models reliably predicted the Stroop (Table 3, Model Fit $p < .005$) and dual conflict effects (Table 4, Model Fit $p < .01$). Importantly, adding the interaction term significantly increased the model fit for both the Stroop ($\Delta F = 4.06$; $p = .046$) and dual conflict effects ($\Delta F = 4.69$; $p = .032$), and the interaction term was a significant predictor over and above the effects of age or the individual PET measures (significant beta values for both Stroop and dual-conflict conditions; see Table 3).

Controlling for BDI and MoCA indices increased the model fit, suggesting that these variables accounted for additional variance in the conflict effects. Importantly, however, it made only miniscule changes to the b* values of the caudate-cortical interaction predictor (See Supplemental Materials). There was a slight change in significance associated with the interaction term due to the loss in degree of freedom that comes with adding additional variables in the model. We also conducted additional control analyses to confirm that our

results were not confounded by the gap between PET and behavioral data collection or dopaminergic medication dosage (LEDD; See Supplemental Materials for details).

We next explored the interaction by dividing the patients into groups based on one measure (caudate DVR or cortical cholinergic) and then testing the effects of the other variable within each subgroup. That is, 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 5^{th} percentile value of the healthy control group (Figure 2 (B–C); Table 5 shows the sample size of each subgroup).

Figure 3 illustrates the relationship between cortical cholinergic function and the executive measures 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. Robust linear regression revealed cortical k3 as a stronger predictor of conflict effects in the low caudate dopaminergic group compared to the normal dopaminergic group ($b^* = -.52$ as opposed to $b^* = -.32$ for Stroop conflict, $b^* = -.77$ as opposed to $b^* = -.62$ for dual conflict). In contrast, caudate DVR was a strong predictor of conflict effects regardless of the cortical cholinergic groups (Figure 4, all $| b^* | > .75$).

Discussion

Executive functions are complex, both in terms of the cognitive operations involved and in the brain structure and functions that support them. They are therefore among the last cognitive functions to fully develop, and often the first and most impaired by aging, brain injury, and disease (see, e.g., Casey et al., 2005; Cepeda & Kramer, 2001; Craik & Bialystock, 2006; Craik et al., 2006; Glisky, 2007; Luszxz, 2011; Paus 2005). These impairments often impact real-life functions including the management of finances and medication, job performance, and even the ability to participate in social interactions and understand jokes (e.g., Uekermann et al., 2007). However, a potential silver lining to this complexity is that it opens paths to compensation at both the behavioral and neural level. At the behavioral level, this often includes the increased use of environmental support, and modifying activities so that they do not exceed one's level of ability (Craik & Byrd, 1982; Baltes, 1997). At the neural level, increased or altered patterns of activation, such as those measured by fMRI, are often associated with better performance and thus interpreted as compensation in many populations, including both patients and healthy adults (e.g., Cabeza et al., 2002; Eberling et al., 1997; Helmich et al., 2007; see reviews by Appel-Cresswell et al., 2010l Barulli & Stern, 2013; Bezard et al., 2003; Grady, 2008; Navntoft & Dreyer, 2016; Rajah & D'Esposito, 2005; Reuter-Lorenz & Lustig, 2005;). Here we used data from patients with PD to examine the potential for a different form of compensation, between the cholinergic and dopaminergic neuromodulator systems.

Our results are consistent with the hypothesis that the cholinergic and dopaminergic systems both play a role in executive function, and that each may compensate to some degree for declines in the other. Both the cortical-cholinergic and caudate-dopamine measures

predicted conflict effects at the level of zero-order correlations, although only the caudate-dopamine term remained a significant independent predictor in the regression model. However, the cortical-cholinergic × caudate-dopaminergic interaction term explained a significant amount of variance in both Stroop and dual-conflict measures, beyond the effects of the individual predictors.

Furthermore, 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 – that is, only after controlling for this interaction was the extent of impairment associated with caudate dopamine denervation revealed.

We cannot fully rule out the possibility of prodromal dementia in either the HC or PD, but our results generally do not support the idea that the effects found here are related to nonspecific neurocognitive decline. Neither the putamen-dopaminergic nor thalamic-cholinergic measures were related to either conflict measure. Furthermore, PD patients and HC had equivalent scores on the dementia screen(MoCA), and controlling for scores on this measure did not impact the conclusions.[1]

It is also important to note that other neuromodulator systems that were not measured here (e.g., serotonergic, noradrenergic) likely also make a contribution to executive control. However, studies in rodents, where specific neuromodulator systems can be targeted, provide supporting evidence for specifically cholinergic-dopaminergic interactions. For example, in a dual-lesion (cortical-cholinergic and striatal-dopaminergic) model of PD, the cholinergic lesion significantly affected rodents' vulnerability to distraction and falls only in combination with caudate dopaminergic lesions and vice versa – neither cholinergic nor dopaminergic lesions had much impact on these measures by themselves (Kucinski et al., 2013). Pharmacologic enhancement of cholinergic function (donepezil and idalopirdine) improved the ability to recover from distractor effects, especially the ability to re-instate correct performance after a short disruption (Kucinski et al., 2017). 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., 2015).

This leads to the next obvious question about the current results: What does "compensation" between the dopaminergic and cortical cholinergic systems – and perhaps others - entail? Do they make equivalent contributions to executive control quantitatively (in terms of their relative importance and degree of variance accounted for), and/or qualitatively (do they support the same cognitive operations, or different ones)? Our ability to answer these

[1]As an additional check, we also examined the correlations between MoCA score and the PET measures for the PD patients. Both before and after controlling for age, the caudate DVR measure was if anything the strongest predictor of MoCA (before controlling for age: $r = .17$, $p = .049$; after controlling for age: $r = .17$, $p = .057$; the slight change in p value is most likely due to the loss of degrees of freedom entailed by the partial correlation). There was no relationship between MoCA and the cholinergic measures (thalamic or cortical) either before or after controlling for age, all $r < .15$, $p > .20$. Although the MoCA is an imperfect instrument, these results do not provide evidence for the hypothesis of prodromal dementia linked to cholinergic declines in this sample.

questions is limited by the particulars of this study (including the use of a paper-and-pencil behavioral measure rather than a computerized one that might have allowed more fine-grained analyses of different trial types and of within-subject response-time variation). It is also important to note that we measured the striatal dopaminergic and cortical (and thalamic) cholinergic status of participants at a relatively broad level, not online activity of these systems during the tasks within specific (e.g., frontal-parietal) circuits.[2] However, our results offer some promising clues, especially when considered in combination with other findings.

First, our results do support a primary role for caudate dopaminergic function in executive function. This of course comes with the caveat that dopaminergic denervation is a major feature of PD, but similar zero-order correlations between the caudate dopamine measure and the executive-control measures were also found for the healthy controls. Second, decomposition of the interaction (Figures 3 and 4) suggests that at least in the conditions tested here, cortical-cholinergic compensation for dopaminergic deficits is more prominent than the reverse. That is, especially for Stroop conflict, the relationship between cortical k3 and performance was stronger for the low-caudate group than for the normal-caudate group (Figure 3), whereas the relationship between caudate dopamine and performance was quite high for both low and normal cortical cholinergic groups (Figure 4).

Third, the cholinergic contribution was generally larger for the dual-conflict condition than for the Stroop conflict condition (Figure 4 A&B vs C&D), whereas the difference in the size of the cholinergic contribution for the low versus normal caudate-dopamine groups (i.e., the compensatory effect) was more prominent for the Stroop conflict measure than for the dual-conflict measure (Figure 4 A&C vs B&D). On the one hand, this might simply reflect the higher demands associated with dual conflict (Stroop + task-switching) than for Stroop alone. However, another possibility is that this reflects qualitative differences in the demands made by these conditions and the operations supported by striatal dopaminergic and cortical cholinergic function, respectively.

Caudate dopaminergic function has been linked to cognitive flexibility via updating and reinforcing stimulus-response associations with this function further modulated by reward (e.g., Cools et al., 2001; O'Doherty et al., 2004). This can also lead to attentional biasing towards previously-reinforced stimulus-response associations even when they are not appropriate (Anderson et al., in press). It has also been suggested that dopaminergic function may be involved in representations of task context (e.g., Braver & Barch, 2002), but it is not clear whether these context effects are caudate-specific. Some animal data suggest that dopaminergic modulation of top-down control depends at least in part in cooperation with cortical cholinergic circuits (St. Peters et al., 2011).

[2]At a reviewer's suggestion, we examined the possibility of differential effects across subregions. However, the subregion results were highly intercorrelated and co-linear, and factor analysis also returned them as a single factor, arguing against such separation. Despite this, to address the reviewer's query we conducted separate models for each subregion (see Supplementary Materials). In general the results for the different subregions were in a similar direction to, but weaker than, the results found for the whole-cortical measure, and typically did not meet standard criteria for statistical significance. One exception was that the occipital cortex k3 × caudate DVR interaction for the dual-conflict condition was approximately as strong as the whole-cortex measure, possibly reflecting differential cholinergic declines in this region in PD (see, e.g., Shimada et al., 2009). However, given the relatively large number of comparisons when one considers each region separately, and the lack of an a priori reason to predict a particular relationship to the dual-conflict condition, we do not interpret this strongly but only report it for completeness.

On the basis of this and other findings, we have suggested that cortical cholinergic function, particularly in fronto-parietal circuits, may operate at multiple timescales to support top-down control: a sustained (on the order of seconds to minutes) neuromodulatory effect helping to support the maintenance of relevant task sets when challenged by distractors (e.g., Berry et al., 2015; 2017), and a transient (millisecond scale) response involved in breaking out of the ongoing task and reactivating dormant task sets in response to an external cue (e.g., Howe et al., 2013; Parikh et al., 2007; Gritton et al., 2016; see Sarter, Parikh, & Howe, 2009 and Lustig & Sarter, 2015 for reviews of the human and animal literature; Sarter, Albin, Kucinski, & Lustig, 2014 for relevance to PD). Although in most cases they would work together to support goal-driven behavior, the hypothesized cholinergic contribution may be distinguished from the dopaminergic one in that the emphasis is on the more abstract level of task-set representations, rather than specific stimulus-response associations. (See also Kehagia et al., 2010, 2014 for rodent and patient evidence on the role of different frontal circuits and neuromodulators at different levels of task representation and implementation).

The PET data in the present study do not allow us to assess the temporal features of cholinergic activity, but the demands of each task suggest that the longer-term neuromodulatory component may be especially important for the Stroop task, whereas the dual-conflict task may also require the transient component's involvement. The Stroop task requires overcoming habitual stimulus-response (i.e., word-reading) associations, and updating them to reflect the current task context and new stimulus-response association of color-reading. This stimulus-response updating function is consistent with ideas of dopaminergically-mediated processes.

However, Stroop performance can also be supported by (potentially cholinergically-modulated) top-down maintenance of the goal of focusing on the color information and preventing the currently-irrelevant word-information dimensions of the stimulus from entering the focus of attention (e.g., Bugg et al., 2008; Kane & Engle, 2003; Gonthier et al., 2016). For low-caudate dopamine patients, who may have particular difficulty in updating to the color-reading rather than word-reading response, the ability to maintain the task set of filtering out currently-irrelevant word information may be especially important. We previously showed that cortical cholinergic integrity, but not caudate dopaminergic integrity, predicted the ability to resist distraction from salient but irrelevant external stimuli (Kim et al., in press). Notably, the performance of low-cholinergic PD patients was similar to that of healthy individuals with a genetic polymorphism that reduces the ability to sustain cholinergic activity (Berry et al., 2014).

In contrast, the dual-conflict condition requires not only sustaining the task set of responding to the color information on most trials, but also the occasional re-activation of the dormant word-reading task set. The reactivation of dormant (after relatively long periods of disuse) task sets has been linked to transient basal forebrain-right prefrontal cholinergic activity in rodents (Parikh et al., 2007), and a series of cross-species experiments suggests that a similar transient right prefrontal activation observed using fMRI in humans during the re-activation of dormant task sets is cholinergically-mediated (Howe et al., 2013). Notably, optogenetic stimulation of these cholinergic transients can trigger responses associated with the

previously-dormant response set even in the absence of the relevant stimulus (Gritton et al., 2016).

A potentially important difference between the current study and many studies of task-switching is that most task-switching studies use frequent switches, with both tasks active about 50% of the time; whereas in the current study the alternative word naming task was rare and occurred on only 20% of trials. The transient cholinergic response associated with re-activation of dormant task sets appears to be primarily active in the case of rare switches to the alternate rule, and to not be as critical when task-switching involves dynamically switching between rules that are both in a relatively active state due to recent use (Parikh et al., 2007; Howe et al., 2013).

The differences between (re)activating a relatively dormant task rule in response to rare switch demands versus dynamic switching between recently-used, and presumably highly-activated, conflicting stimulus-response associations may also explain why some aspects of our results differ from those observed by Beste et al. (2012). They tested healthy subjects and individuals with pre-symptomatic Huntington's disease ("pre-HDs") in a paradigm that has some similarities to our dual-conflict condition, but with both congruent and incongruent trials, and frequent (50% of trials) task switches. Pre-HDs had equivalent performance to controls on all trials except incongruent (e.g., BLUE printed in green ink) trials that required a task switch (word vs color reading, or vice versa), consistent with a specific role of dopaminergic modulation of frontal-striatal circuits in flexibly alternating between conflicting stimulus-response associations. Further, caudate volume correlated with electrocorticography (EEG) measures (N2 event-related potential amplitude and power in the delta band) associated with the selecting the correct response and inhibiting the incorrect one.

At a reviewer's suggestion, we examined whether caudate volume was related to our PET measures or behavioral effects, but did not find any evidence for such. The different patterns between the two studies are likely due to both the differences in the physiological measures used (caudate volume and N2 are both likely to reflect the combined effects of several factors, whereas the PET measures assess more restricted aspects of functional activity that may precede measurable volume declines), and the tasks. In particular, the more frequent rule-switching used in the Beste et al. study is more consistent with the hypothesized contribution of caudate dopamine function to dynamic stimulus-response updating, as opposed to the relatively infrequent rule re-activation required in our study.

Compensation for reduced dopaminergic function may also rely more heavily on different systems in these more dynamic updating situations. Vazey et al. (2014, personal communication) found evidence for a compensatory role of norepinephrine in these cases: They tested task-switching (with equivalent rule-use) in a dual-lesion model similar to that used by Kucinsinki and colleagues, but in this case adding norepinephrine rather than cholinergic lesions to the striatal dopamine lesions. Only the dual-lesioned animals exhibited robustly impaired cognitive flexibility. This suggests that in the dopaminergic single lesion rodents, the intact norepinephrine system may have compensated for the functional impairment that would otherwise be induced by dopaminergic depletion (See also Berry et

al., 2017 and Kehagia et al., 2010 for discussion of the potentially complementary and interacting roles of different neuromodulator systems in supporting cognitive control).

Together these findings suggest a heuristic framework in which frontostriatal dopaminergic function supports executive function through the reinforcement and updating of the appropriate stimulus-response associations for the current task context, cortical cholinergic modulation supports the (re)activation of more abstract task-goal representations after disuse or in the face of challenge, and norepinephrine helps support switching between task rules that are in relatively activated states. This conceptualization is considerably more complex than those that focus almost exclusively on the role of dopamine in executive function, but in the end will itself most likely prove to be overly simplistic. However, it may provide a useful guide for manipulating parameters (e.g., the level of abstraction and frequency of switches in task-switching) in both healthy and clinical populations to establish the relative contributions, and interactions, of these systems. Meanwhile, the present results, support the hypothesis that cortical cholinergic function can help compensate for dopaminergic declines to support executive function. Although the multi-system, interactive nature of executive function may make things more difficult for us as scientists, it may also provide avenues for compensation and remediation in patient populations and even healthy adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Task Procedure: Modified Stroop Task with rule-switching

Participants were presented with 100 items in each level (in a 10 × 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).

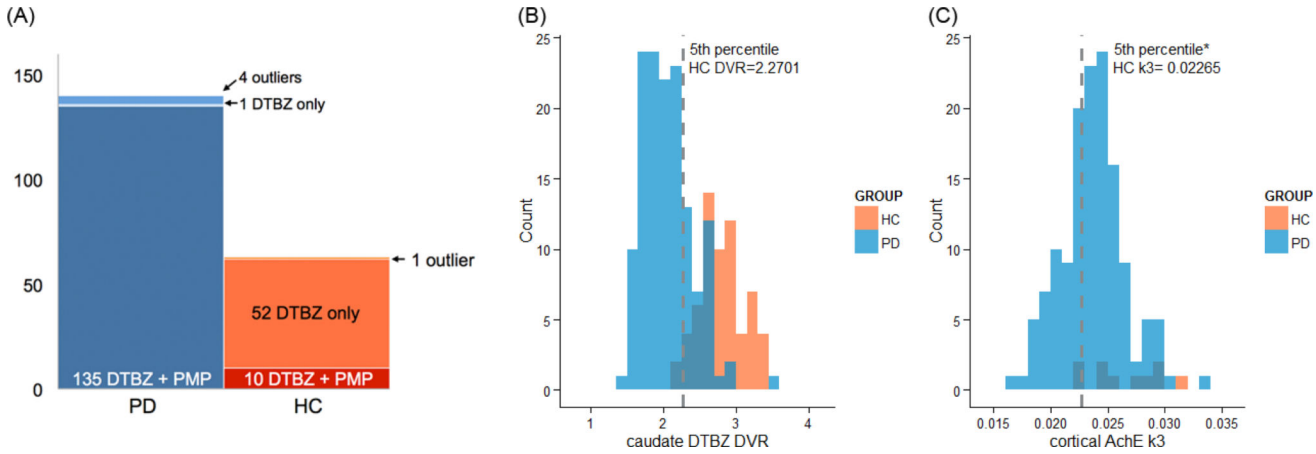

Figure 2. Sample size of the PET data and distributions of the caudate DVR and cortical k3 levels

(A) Both types of PET scans were obtained for 135 out of total number of 140 PD patients. Dopaminergic PET was obtained for 62 HC, but cholinergic PET was limited to 10 HC. (B) The caudate DTBZ DVR measures of the PD patients are distributed in the lower range of the values obtained from the HC. 74.1% of the PD patients fall into the low caudate dopaminergic function group defined by the 5th percentile of the healthy controls. (C) 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 30.4% of the PD patients fell into the low cortical cholinergic group defined by the 5th percentile of the healthy controls.

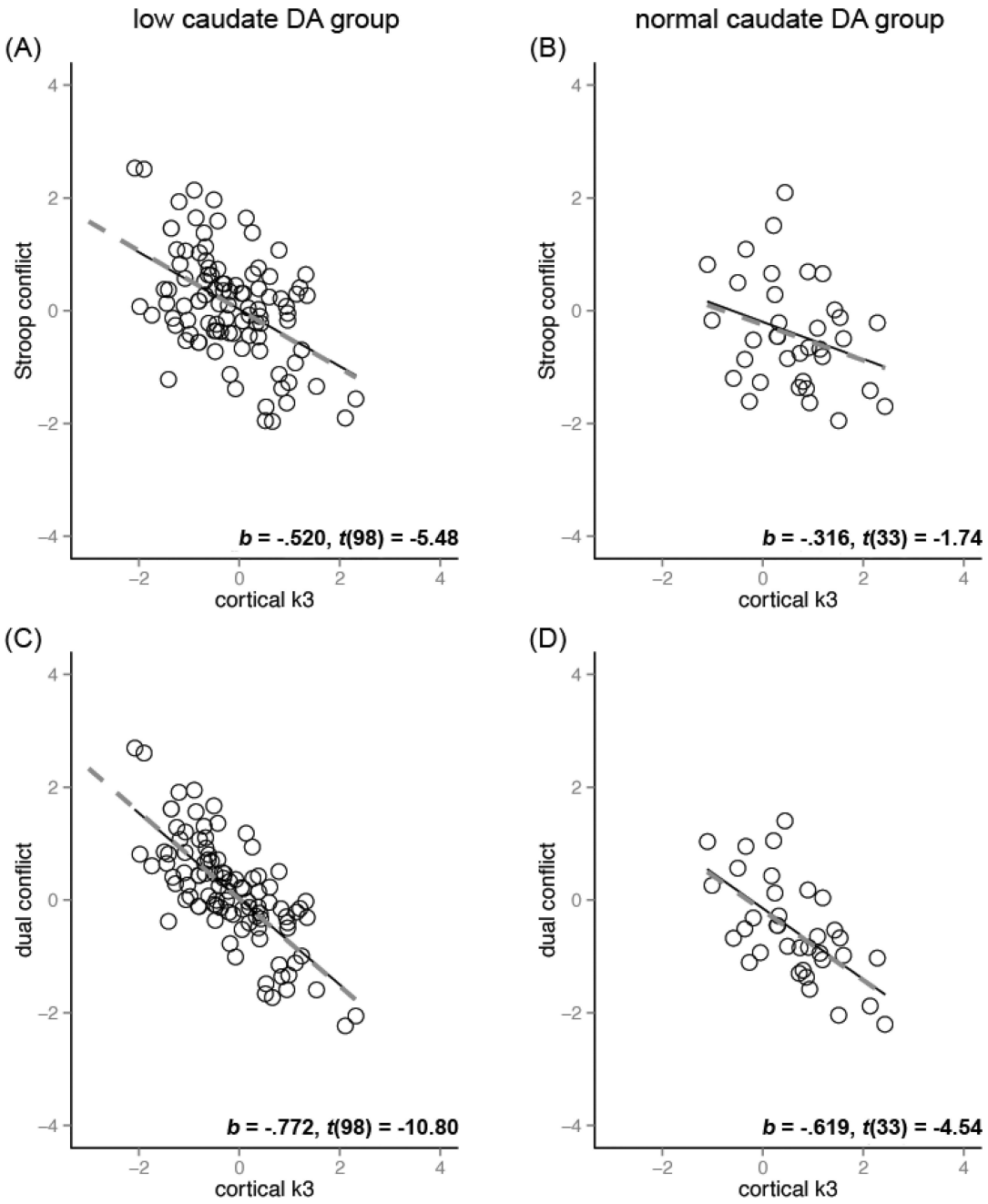

Figure 3. Cortical cholinergic function and conflict effects the in low and normal caudate dopaminergic group after controlling for age and thalamic k3

Data shown are for the conflict effects residualized on age and thalamic k3). Left column: low caudate DA group. Right column: normal caudate DA group. (A, C) Cortical k3 was a significant predictor of conflict effects in all cases except for the Stroop conflict effect in the normal caudate DVR group ($p = .06$, other p's $< .0001$). This association between cortical k3 and conflict effects were stronger in low caudate DVR group (A, C) than normal caudate DVR (B, D) group. The fit lines are based on the least squares (solid) and robust regression (dashed) results. The b*, t-value, and DF: t-test results are for the robust regression coefficients.

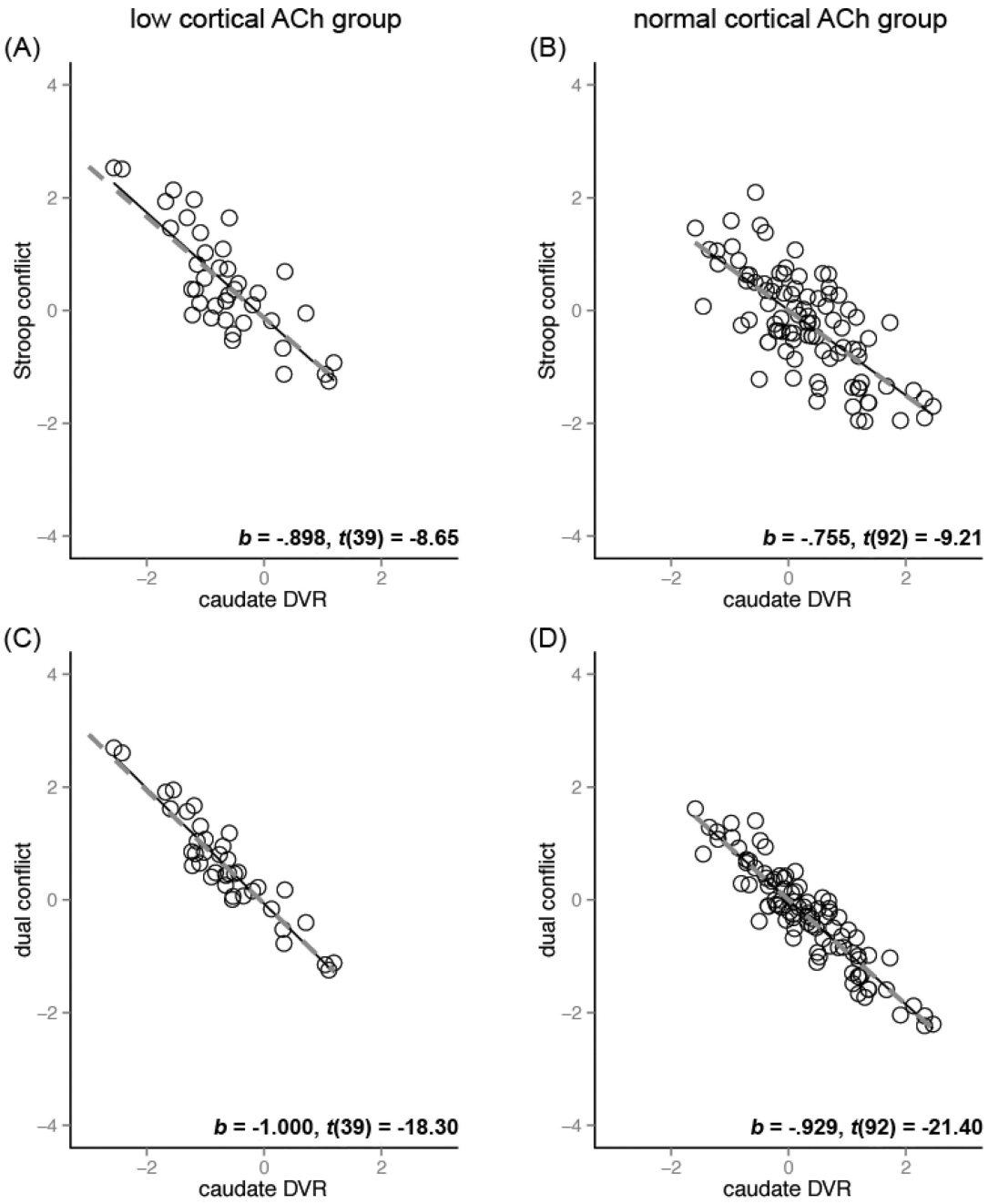

Figure 4. Caudate dopaminergic function and conflict effects the in low and normal cortical cholinergic group after controlling for age and thalamic k3

Data shown are for the conflict effects residualized on age and thalamic k3. Left column: low cortical ACh group. Right column: normal cortical ACh group. High levels of caudate dopaminergic function were associated with smaller conflict effects in both low and normal cortical cholinergic groups (all $p < .0001$). The fit lines are based on the least squares (solid) and robust regression (dashed). The b*, t-value, and DF: t-test results are for the robust regression coefficients.

Table 1

Demographic and behavioral performance of PD and HC. t & p corrected for violation of equal variances if applicable.

	HC (N = 62)		PD (N = 135)		*t*	*p*	Cohen's d
	M	SD	M	SD			
Age (years)	65.2	11.9	65.4	7.7	−.2	.879	−.02
Education (years)	15.9	2.3	15.4	2.8	1.3	.198	.19
Montreal Cognitive Assessment (MoCA)	26.6	2.4	26.3	2.1	.9	.357	.14
Beck Depression Inventory (BDI)	2.7	3.2	8.1	6.2	−8.1	**	−1.00
STR1 RT (s)	49.2	9.4	54.2	11.6	−3.0	.003	−.46
STR2 RT (s)	63.7	12.6	72.0	15.6	−3.7	**	−.57
STR3 RT (s)	113.8	26.6	136.3	42.4	−4.5	**	−.59
STR4 RT (s)	126.6	31.0	151.4	56.4	−4.0	**	−.50
STR1 error rate (%)	.02	.13	.13	.74	−1.7	.096	−.18
STR2 error rate (%)	.23	.66	.61	1.26	−2.9	.005	−.34
STR3 error rate (%)	1.47	2.62	3.02	4.49	−3.1	.003	−.39
STR4 error rate (%)	1.82	3.28	3.60	5.45	−2.8	.005	−.37
STR1 IES	49.23	9.45	54.34	11.84	3.0	.003	−.46
STR2 IES	63.86	12.63	72.51	16.04	3.8	**	−.58
STR3 IES	115.61	27.31	142.02	50.48	4.8	**	−.60
STR4 IES	129.43	33.61	159.70	69.60	4.1	**	−.50

M = mean, SD = standard deviation

** indicates p < .0005.

Table 2

Correlations between the behavioral measures, age, depression score (BDI), and the PET measures in HC (n=62, except for correlations with cholinergic PET measures, n =10) and PD (n = 135).

				Individual Characteristics		Task Performance			Cholinergic PET		Dopaminergic PET	
				age	**BDI**	**color naming**	**Stroop conflict**	**dual conflict**	**thalamic k3**	**cortical k3**	**putamen DVR**	**caudate DVR**
HC	Individual Characteristics	age	r	1.00	−.09	.23	.53	.40	.00	.12	−.28	−.46
			p		.510	.068	**	.001	.999	.746	.030	**
		BDI	r	−.09	1.00	−.01	−.01	−.04	.23	.28	−.02	.02
			p	.510		.957	.913	.739	.524	.427	.881	.872
	Task Performance	color naming	r	.23	−.01	1.00	.15	.20	−.20	.05	.03	−.04
			p	.068	.957		.233	.114	.583	.894	.798	.784
		Stroop conflict	r	.53	−.01	.15	1.00	.72	−.37	−.23	−.26	−.32
			p	**	.913	.233		**	.290	.529	.039	.011
		dual conflict	r	.40	−.04	.20	.72	1.00	−.55	−.47	−.23	−.30
			p	.001	.739	.114	**		.097	.176	.068	.017
	Cholinergic PET	thalamic k3	r	.00	.23	−.20	−.37	−.55	1.00	.82	.10	.09
			p	.999	.524	.583	.290	.097		.004	.791	.807
		cortical k3	r	.12	.28	.05	−.23	−.47	.82	1.00	.04	.01
			p	.746	.427	.894	.529	.176	.004		.923	.976
	Dopaminergic PET	putamen DVR	r	−.28	−.02	.03	−.26	−.23	.10	.04	1.00	.83
			p	.030	.881	.798	.039	.068	.791	.923		**
		caudate DVR	r	−.46	.02	−.04	−.32	−.30	.09	.01	.83	1.00
			p	**	.872	.784	.011	.017	.807	.976	**	
PD	Individual Characteristics	age	r	1.00	−.13	.29	.30	.24	−.25	−.24	.06	−.19
			p		.148	.001	**	.005	.004	.005	.492	.024
		BDI	r	−.13	1.00	.09	.03	.03	.15	.25	−.15	−.09
			p	.148		.322	.753	.746	.088	.004	.090	.320
	Task Performance	color naming	r	.29	.09	1.00	.48	.56	−.16	−.17	−.15	−.34
			p	.001	.322		**	**	.065	.050	.078	**

			Individual Characteristics		Task Performance			Cholinergic PET		Dopaminergic PET	
			age	**BDI**	**color naming**	**Stroop conflict**	**dual conflict**	**thalamic k3**	**cortical k3**	**putamen DVR**	**caudate DVR**
	Stroop conflict	r	.30	.03	.48	1.00	.62	−.11	−.15	−.13	−.24
		p	**	.753	**		**	.212	.076	.124	.005
	dual conflict	r	.24	.03	.56	.62	1.00	−.17	−.24	−.14	−.25
		p	.005	.746	**	**		.046	.004	.113	.004
Cholinergic PET	thalamic k3	r	−.25	.15	−.16	−.11	−.17	1.00	.58	.11	.23
		p	.004	.088	.065	.212	.046		**	.194	.006
	cortical k3	r	−.24	.25	−.17	−.15	−.24	.58	1.00	.23	.27
		p	.005	.004	.050	.076	.004	**		.008	.002
Dopaminergic PET	putamen DVR	r	.06	−.15	−.15	−.13	−.14	.11	.23	1.00	.80
		p	.492	.090	.078	.124	.113	.194	.008		**
	caudate DVR	r	−.19	−.09	−.34	−.24	−.25	.23	.27	.80	1.00
		p	.024	.320	**	.005	.004	.006	.002	**	

** indicates $p < .0005$

Table 3

Hierarchical multiple linear regression model for the Stroop conflict effect in PD.

	coefficients				model statistics						power
	B	**β**	***T***	***p***	**R^2**	**Δ R^2**	**Δ F**	**sig. Δ F**	**Model Fit *F***	**Model Fit *p***	**1−β**
step 1 model					.09	.09	13.42	**	13.42	**	.95
constant	.00		.00	1.000							
age	.30	.30	3.66	**							
step 2 model					.13	.04	1.78	.155	4.7	.001	.96
constant	.00		.00	1.000							
age	.26	.26	3.05	.003							
caudate DVR	18	−.18	−2.07	.040							
thalamic k3	.03	.03	.33	.739							
cortical k3	06	−.06	−.60	.550							
step 3 model					.15	.03	4.06	.046	4.7	.001	.97
constant	04		−.53	.601							
age	.25	.25	2.88	.005							
caudate DVR	24	−.24	−2.65	.009							
thalamic k3	.04	.04	.39	.696							
cortical k3	−.04	−.04	−.43	.670							
caudate DVR * cortical k3	.16	.17	2.01	.046							

All variables standardized before being entered in the model. B, unstandardized coefficient; β, standardized coefficient.

** indicates p < .0005

Table 4

Hierarchical multiple linear regression model for the dual conflict effect in PD.

	coefficients				model statistics						power
	B	**β**	***t***	***p***	**R^2**	**Δ R^2**	**Δ F**	**sig. Δ F**	**Model Fit *F***	**Model Fit *p***	**1−β**
step 1 model					.06	.06.	8.28	.005	8.28	.005	.83
constant	.00		.00	1.000							
age	.24	.24	2.88	.005							
step 2 model					.12	.06	3.09	.029	4.49	.002	.94
constant	.00		.00	1.000							
age	.17	.17	1.99	.049							
caudate DVR	−.17	−.17	−1.97	.051							
thalamic k3	.00	.00	.01	.989							
cortical k3	−.16	−.16	−1.52	.131							
step 3 model					.15	.03	4.69	.032	4.63	.001	.97
constant	−.05		−.56	.574							
age	.15	.15	1.81	.073							
caudate DVR	−.24	−.24	−2.60	.010							
thalamic k3	.01	.01	.07	.943							
cortical k3	−.14	−.14	−1.35	.180							
caudate DVR * cortical k3	.18	.19	2.17	.032							

(N = 135, all PD patients with both the DTBZ and PMP PET measures). All variables standardized before being entered in the model. B, unstandardized coefficient; β, standardized coefficient.

** indicates p < .0005

Table 5

Resulting sample size of each PD subgroups

		cortical k3		
		low	**normal**	**total**
caudate DVR	Low	36	64	100
	normal	5	30	35
	total	41	94	135

(low: 5th percentile of the normal controls)