Correlated Activation between Striatal and Cortical Regions during a Movement-Related Signal Detection Task: A Re-Analysis of Two fMRI Datasets

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Cue-directed shifts from ongoing behavior to initiating new (cue-directed) behavior are critical for many tasks, including changing direction and avoiding falls. Rodent studies have shown that transient activations of the cholinergic system are necessary and sufficient for producing cue-directed shifts of attention and response in the Sustained Attention Task (SAT). Other rodent studies suggest that cue-triggered shifts from an ongoing motor task (e.g. walking) to a new motor task (e.g. turning) are also cholinergically mediated. These findings have potential implications for patients with Parkinson's disease: falls in such patients often occur in turning situations and are more related to cholinergic declines than to the dopaminergic declines that are the hallmark of the disease. We first re-analyzed a human fMRI SAT dataset using psychophysiological interaction (PPI) and found increased interactions between specific cortical and striatal regions during shifts from ongoing to cue-directed behavior. To test the hypothesis that these would generalize to a shift in motor behavior, we next reanalyzed Stop Signal Task (SST) fMRI data from a public dataset, asking whether the functional co-activation correlations showed similar patterns as the PPI-identified striatal and cortical connections in the SAT. Linear regression analysis of the SST fMRI data found that the striatal 'seed' region's activation for the Correct Stop vs Correct Go contrast predicts a significant amount of the variance in the a priori target regions identified from the SAT dataset for the same contrast. This indicates that there is correlation in the activity between the two regions during the trials where a cue-triggered change in movement occurs. This finding provides converging evidence that interactions between these striatal regions and higher processing cortical regions are important for cue-guided shifts in task sets, including motor-based task sets.

Abbreviations: PD – Parkinson's Disease; SAT – Sustained Attention Task; SST – Stop Signal Task; ABCD – Adolescent Brain Cognitive Development; DEAP – Data Exploration and Analysis Portal

Keywords: Parkinson's Disease; fMRI; cholinergic system; cue-guided shifts

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Introduction

Parkinson's disease (PD) is a major neurodegenerative disorder that substantially impacts not only the individual patient's life but also the public health and economics of society. Research predicts that by 2020 nearly 1 million people in the US alone will be diagnosed with the disorder (Marras et al., 2018). As of 2010, the national economic burden of Parkinson's disease was $14 billion (Kowal et al., 2013), with that number expected to increase dramatically over the years. The disease itself is best known for its motor symptoms: bradykinesia (slowness of movement), muscular rigidity, tremor at rest, and impairments in posture and gait (Kalia & Lang, 2015). This symptomatology is related to the degeneration of the dopaminergic system in the basal ganglia, specifically the substantia nigra, and treated by dopaminergic medications and/or

deep brain stimulation. However, many symptoms - including problems in cognition, mood, and sleep as well as gait, balance, and increased vulnerability to falls - are not alleviated by dopaminergic treatments and may even be exacerbated by them (Smulders et al., 2016). Furthermore, these symptoms often precede the motor symptoms and cause more serious deterioration to patients' quality of life (Kalia & Lang, 2015). Even when on dopaminergic medications, for example, up to 68% of PD patients experience at least one fall per year (King et al., 2012; Yang et al., 2016).

This vulnerability to falls in patients with PD is more strongly related to cholinergic declines than to the dopaminergic degradation that is the hallmark of the disease (Bohnen et al., 2009; Bohnen & Albin, 2011; Bohnen et al., 2013). More recently, degeneration of specific subcomponents of the cholinergic system has been linked to impairments in specific aspects of attention (Kim et al., 2017; Kim et al., 2019a; Kim et al., 2019b). Of particular relevance to falls, impairments in signal detection (Kim et al., 2017) and sensory integration related to balance (Müller et al., 2013; Bohnen et al., 2012) have been linked to cholinergic system degeneration in Parkinson's patients.

Falls are especially likely to occur in situations that require stopping an ongoing behavior (walking) and initiating a new behavior (turning) in response to an external cue, such as an upcoming obstacle or intersection, or the sound of an upcoming car beeping its horn. As we will describe further below, signal-induced stopping of an ongoing behavior and initiating a new one has been linked to a specific pattern of cholinergic activation in rodents, and to a specific pattern of fMRI activation in humans (Howe et al., 2013). In this study, we present a basic-science re-analysis of two existing fMRI datasets, both from healthy populations, focusing on contrasts that emphasize stopping an ongoing behavior and initiating a new one.

The first dataset was originally used to elucidate the brain regions and networks involved in changing from the 'monitoring' to 'detection' states in the human Sustained Attention Task (SAT; Demeter et al., 2008; see e.g., St Peters et al., 2011; Paolone et al., 2012 for the rodent version). The human SAT is a signal detection task which closely parallels a task used in rodents to demonstrate the critical role of fast-acting cholinergic transients in making the switch from ongoing behaviors associated with monitoring for the signal to new behaviors associated with indicating its detection (Howe et al., 2013). The second dataset uses the stop-signal task, which more explicitly requires a change in motor behavior: participants must stop an ongoing motor movement in response to a cue. If strong parallels are found between these two datasets, that would encourage further investigation into the possibility that cholinergic degeneration, rather than or perhaps in combination with dopaminergic degeneration, contributes to PD-related impairments in this operation and fall vulnerability, and potentially provide opportunities for new treatments.

Traditional views of the cholinergic system emphasize a slow, diffuse neuro-modulatory component, but there is increasing evidence for a fast, temporally- and spatially-specific component (Parikh et al., 2007; Sarter, Parikh, & Howe, 2009; Sarter et al, 2014; Sarter et al., 2016; Sarter & Lustig, 2020). More recently, it has even been suggested that this transient component can account for the effects previously ascribed to the more diffuse system (Sarter & Lustig, 2019). Cholinergic transients seem to be especially important for breaking out of an existing task set and engaging a new one in response to environmental cues. For example, in a cued appetitive response task with very long delays between trials, cholinergic transients in the prefrontal cortex were recorded and shown to precede the onset of cue-evoked shifts in the rats' attention (Parikh & Sarter, 2008).

Results from parallel studies in rats and humans using the SAT also support the idea that cholinergic transients are the mechanism behind cue-evoked shifts in behavior. Specifically, cholinergic transients are involved when there is a shift from monitoring for cues to cue-guided performance (Howe et al., 2013). In this study, both humans and rats underwent SAT testing. In both experiments, the most interesting finding occurred when there was an incongruent hit (i.e. a hit response preceded by either a correct rejection or a miss). These trials require a shift from the no-signal, monitoring state (which comprises the vast majority of task time; signals

only occur on 50% of trials and are very brief), to the signal detection and response state. When this shift from monitoring for a cue to detecting a cue and performing the related behavior happens, cholinergic transients occur in the rats and the right rostral prefrontal cortex is selectively active in humans. Notably, transients are not observed for "congruent hit" trials – those preceded by another hit – presumably because the signal detection state has already been activated by the previous trial. By this interpretation, cholinergic transients occur only when breaking out of an ongoing task (i.e. monitoring for cues) to a new task (cue directed behavior).

In addition, a study by Gritton et al. (2016) showed that cholinergic transients are, in fact, causally related to this phenomenon, and can induce the shift in task set and behavior. This study found that inducing cholinergic transients in the basal forebrain and medial prefrontal cortex of mice during cued trials of SAT enhances the rate of cue detection. More importantly, it found that inducing transients during uncued (i.e. nonsignal) trials of SAT (where they are normally not seen) increases the number of false alarms (i.e. incorrectly perceiving the cue when the cue is not actually present). In other words, the induced cholinergic transient forced a transition to the "detection" task and response set even without a signal to be detected.

Taken together these studies show that cholinergic transients are not only present specifically during cue-evoked shifts in attention in behavior but are also sufficient to induce that shift. However, although the attentional tasks described above require a change in the motor program to register the change in response (e.g. initiate pressing the correct response key or lever during the cued trials; in SAT, no response is required on uncued trials), the motor change is relatively minor. Do similar mechanisms underlie more dramatic changes in motor programs?

Although preliminary, some data from rodent experiments suggests that transient activity in striatal cholinergic interneurons could play a similar role in 'resetting' motor behaviors (Avila, Kucinski, & Sarter, 2017; Avila, Kucinski, & Sarter, 2018; Kucinski & Sarter, 2018). These experiments determined if cholinergic transients were necessary and sufficient to cause the shift in motor behavior, and whether inducing cholinergic transients could recover motor ability. Two distinct types of motor tasks were used. Kucinski & Sarter (2018) used the Michigan Complex Motor Control Task (MCMCT), in which rats traversed a series of stationary and rotating rods, at inclines or horizontally. The frequency of falls was measured in this task. Avila et al. (2018) used the Cued Turning Treadmill Task (CTTT), in which rats walked on a treadmill until the onset of a 'stop' or 'turn' cue, after which they must perform the corresponding motor action. The accuracy of responses to the cues was measured with a focus on turn cue accuracy. The CTTT in particular utilizes the idea of a cue-based shift from an existing motor task (walking) to a new motor task (turning), which closely resembles the focus of Howe et al. (2013).

In both studies, three experimental groups of rodents performed the tasks. One group of rats had dual cholinergic-dopaminergic lesions, which impaired both systems, mimicking the degeneration seen in PD patients prone to falls. In the other two groups, cholinergic function was manipulated via Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) selectively expressed in the cholinergic striatal interneurons. In one group, the DREADDs selectively inhibited the striatal cholinergic neurons. In the other group, which also received dual lesions, excitatory DREADDs were used to selectively activate just the striatal cholinergic neurons, while the dopaminergic system remained inactivated.

For both motor tasks, dual lesions resulted in poorer performance, reflected by a higher fall rate in MCMCT and a lower cue-triggered turning accuracy in CTTT. This could suggest that either the cholinergic system or the dopaminergic system, or a combination of the two, underlies this mechanism. However, in both tasks, selectively inhibiting just the cholinergic system through DREADDS also impaired performance in the same way, and selectively activating the cholinergic system through DREADDS rescued behavioral performance (fall rate and turning accuracy equivalent to control group). This shows that the cholinergic system is both necessary and sufficient for complex motor movements and cue-directed shifts in motor

behavior. These motor task studies point to the same conclusion as the attentional tasks previously described: the cholinergic system is a sufficient and necessary mechanism behind cue-evoked shifts in behavior.

While there is strong evidence from animal studies for cholinergic transients being the basis for cue-evoked shifts in motor behavior, little analogous research has been done in humans. We are working to develop a fMRI-compatible human version of the CTTT. However, a number of technical difficulties, including response collection and head movement issue, remain to be solved. To begin to assess the likelihood that we will find a transient striatal component related to resetting motor programs, the present analysis investigates potential changes in striatal connectivity related to resetting attentional and motor task sets.

Specifically, we first re-analyzed the human data from the Howe et al. (2013) study using psychophysiological interactions analysis (PPI) to examine the changes in striatal activity associated with "incongruent hits", i.e. those that required breaking out of the ongoing monitoring task set and initiating the "respond to the signal" task set. PPI allows us to analyze the interactions between brain regions during different psychological contexts. (O'Reilly et al., 2012). PPI analyses start with a seed region chosen by the researcher for analysis, and then identifies target regions that have higher correlation with the seed region in one psychological context compared to another. For this analysis, we chose basal ganglia seed regions known to be involved in the selection of appropriate motor programs (Groenewegen, 2003). These included the left dorsal caudate, the right dorsal caudate, the bilateral dorsal putamen, and the left ventral striatum. The basal ganglia also house the substantia nigra, where degradation of dopaminergic neurons occurs in PD (Kalia & Lang, 2015). For this study, these regions are particularly important because, as Avila et al. (2018) demonstrated, selectively inhibiting striatal cholinergic neurons is enough to impair cue-triggered motor behavior.

The connectivity patterns identified in the re-analysis of the Howe et al. (2013) data were then the a priori connections tested in a re-analysis of the Stop-Signal Task (SST) fMRI data from the large (4500 participants) Adolescent Brain and Cognitive Development study ("ABCD Data Repository", 2017). The SST is a task that involves changes in movement in response to a cue (Casey et al., 2018). On most trials in the SST, the participant presses one of two buttons in response to a cue (in this case a left- or right-pointing arrow). However, on some trials a 'stop signal' (an upwards pointing arrow in this case) is presented after the cue, signaling to the participant to not press the button. Since the signal occurs after the cue, the participant has most likely already began the motions to press the button before they receive the stop signal telling them otherwise. The signal acts as a cue for the participant to change their motor plan (from 'Go' to 'Stop'). Because SST is designed so that the participants receive stop signals on a minority of trials, their existing pattern of movement is set to 'Go' and they have to change it when they detect the stop signal.

If the signal detection and subsequent change in the motor task set (SST), operates in the same way as in an attentional task (SAT), we would expect to see similar connectivity patterns or correlated activity. The functional connectivity patterns identified in the re-analysis of the Howe et al. (2013) dataset identified increased striatal connectivity to a number of regions, especially prefrontal and parietal regions involved in cognitive control, for incongruent hits vs congruent hits (i.e., those that did vs did not require a change in task set). We hypothesize that there will be similar patterns of increased functional co-activation for the 'Correct Stop' SST trials vs 'Correct Go' SST trials.

Of course, it is important to note that the psychophysiological interactions (PPI) connectivity methods used in the re-analysis of the Howe et al. (2013) data are not the same as the co-activation measures used in the present analysis. See, e.g. Eickhoff et al. (2011) as well as Rogers et al. (2007) and Rubinov & Sporns (2010) for discussion of different connectivity measures and how they may be related. However, the different measures often, though not always, provide converging evidence (Laird et al., 2009; Eickhoff et al., 2011). Furthermore, if there are strong similarities across these two analyses despite the differences in the tasks, population, and methodology, that might be interpreted as

Table 1: Brain Regions Determined from PPI and the Rationale for the Analogous DEAP Regions

PPI Connectivity Regions			
Seed Region	***Notes for DEAP Region***	**Target Region**	***Notes for DEAP Region***
Bilateral Dorsal Caudate	*bilateral regions were split into respective hemispheres for DEAP analysis; DEAP did not identify 'dorsal caudate' so 'caudate' was used in place*	Right Supramarginal precentral gyrus	*two separate regions in DEAP; analyzed separately as 'supramarginal' and 'precentral'*
		Right Superior occipital gyrus	*superior occipital' not identified by DEAP, but other regions part of BA19 used instead ('lingual', 'cuneus', 'lateraloccipital')*
Left Dorsal Caudate	*DEAP did not identify 'dorsal caudate' so 'caudate' was used in place*	Left pallidum	*identified as a region in DEAP*
		Right Superior occipital gyrus	*superior occipital' not identified by DEAP, but other regions part of BA19 used instead ('lingual', 'cuneus', 'lateraloccipital')*
		Right superior frontal	*identified as a region in DEAP*
		Right Inferior parietal lobule/supramarginal	*two separate regions in DEAP; analyzed separately as 'inferior parietal' and 'supramarginal'*
Right Dorsal Caudate	*DEAP did not identify 'dorsal caudate' so 'caudate' was used in place*	Right Supramarginal/precentral	*two separate regions in DEAP; analyzed separately as 'supramarginal' and 'precentral'*
		Right Fusiform gyrus	*identified as a region in DEAP*
Bilateral Dorsal Putamen	*bilateral regions were split into respective hemispheres for DEAP analysis; DEAP did not identify 'dorsal putamen' so 'putamen' was used in place*	Right Dorsal ACC	*dorsal ACC' not identified by DEAP; 'caudal anterior cingulate' and 'rostral anterior cingulate' used instead*
		Right Superior occipital gyrus (BA19)	*superior occipital' not identified by DEAP, but other regions part of BA19 used instead ('lingual', 'cuneus', 'lateraloccipital')*
		Right Supramarginal/postcentral	*two separate regions in DEAP; analyzed separately as 'supramarginal' and 'postcentral'*
Left Ventral Striatum	*DEAP did not identify 'ventral striatum' but did identify 'accumbens area', a part of the ventral striatum*	Right Inferior parietal lobule	*inferior parietal lobule' not identified by DEAP; analyzed as 'inferior parietal' and 'supramarginal'*
Right Ventral Striatum	*DEAP did not identify 'ventral striatum' but did identify 'accumbens area', a part of the ventral striatum*	Vermis 4/5/ culmen	*DEAP did not identify 'vermis 4/5 culmen' and did not divide the cerebellum into smaller regions, so this was excluded from the study*

evidence that these links are especially robust and generalizable. Thus, while not providing definitive evidence on its own, such a finding would strongly encourage a smaller sample but more targeted human imaging study using methods that more closely parallel those used in the animal studies described above.

Material and Methods

Establishing striatal connectivity patterns in the Howe et al. (2013) dataset

The Howe et al. (2013) study used 15 human participants, all ranged 18-27 years in age (8 female, mean age = 22.1 years). Participants performed the SAT in the fMRI scanner as described by Demeter et al. (2008). SAT trials consisted of both signal and nonsignal trials, where the signal was a small, dark gray square centrally presented. After a monitoring period (1-3 s), the signal either did occur (signal event) or did not occur (nonsignal event). Participants were cued to report the presence or absence of the signal 500 ms after the signal or nonsignal offset. There were four possible results for each trial: a 'hit' (signal event, signal reported), a 'miss' (signal event, no signal reported), a 'correct rejection' (nonsignal event, no signal reported), or a 'false alarm' (nonsignal event, signal reported). There was a total of 75 trials in each experimental run.

The trial sequence of interest for this analysis was the 'incongruent hit' sequence where a hit response followed either a correct

rejection or miss response, because in this sequence, the participants shift from monitoring for the signal to detecting the signal and performing the associated behavior (reporting the signal).

Psychophysiological interactions analysis (PPI) was done on the fMRI data from this SAT trial sequence. The seed regions were the left dorsal caudate, the right dorsal caudate, the bilateral dorsal putamen, and the left ventral striatum. A full list of the target regions determined by the PPI analysis of the Howe et al. (2013) data can be found in Table 1. Briefly, many of the identified target regions are prefrontal and parietal regions involved in cognitive control.

Testing functional co-activation patterns in the ABCD dataset

Having used the Howe et al. (2013) dataset to establish the striatal connectivity patterns of interest, we then conducted functional co-activation analyses of the first curated published data release from the Adolescent Brain Cognitive Development (ABCD) study ("ABCD Data Repository", 2017). A full and detailed description of the study and its methods can be found in the August 2018 issue of the journal Developmental Cognitive Neuroscience (Feldstein & Luciana, 2018); a summary is also available at the ABCD study website (ABCD Protocols, https://abcdstudy.org/scientists/protocols/).

Briefly, the first data release includes data from approximately 4500 children, ages 9-11, sampled from 21 sites around the country. The subjects complete a wide battery of tasks; the one of importance here is the fMRI Stop Signal Task. Casey et al. (2018) has the complete description of the fMRI machine protocols, the running procedures, and the data gathering methods. fMRI analysis methods are described in Hagler et al. (2019). We summarize the aspects relevant to our analyses below.

The Stop Signal Task was administered to the subjects in the scanner according to Logan (1994). Participants were asked to indicate the direction of an arrow cue (either right-pointing or left-pointing) by pressing one of two buttons as quickly as possible with their dominant hand. In 16.67% of the trials, a 'stop signal' (an up-right arrow) was presented after the cue and participants were tasked to inhibit their button pressing. Because the majority of the trials were 'Go' (i.e. did not contain a stop signal), there was a strong prepotent 'Go' response (Casey et al., 2018). This would have to be switched away from for the Stop trials. The primary contrast of interest for the present analysis was therefore Correct Stop vs Correct Go.

DEAP Dataset Analysis

The Data Exploration and Analysis Portal (DEAP) contains the published data of the ABCD study as well as statistical analysis functions tailored to work with the study (DEAP, RRID:SCR_016158). The brain-activation measures reported in DEAP and used for the present analysis are the beta weights for the Correct Stop vs Correct Go trails in the SST, as determined using the general linear model implemented in AFNI (see Hagler et al., 2019 for details).

Our first step was to determine the brain regions in the DEAP database analogous to the brain regions in the PPI analysis. See Table 1 for a list of the original PPI regions from the Howe et al. (2013) re-analysis dataset, the ABCD/DEAP regions chosen to parallel those, and the reasoning behind the decisions made. We then examined the ABCD/DEAP functional co-activation patterns corresponding to the striatal functional connectivity patterns identified in the re-analysis of the Howe et al. (2013) dataset, using the regression model function available in DEAP (implemented using the GAMM4 function in R). Recommended data censoring procedures (Hagler et al., 2019) were used to remove outliers by excluding the upper and lower 0.05% of the data from the analysis.

For each striatal seed region, a generalized mixed-effect model was used to examine the degree to which the seed region predicts the target region. Standard covariates (fixed: race/ethnicity, sex, education, income, marital status of parents, age; random: site) were included to control for potential influences of those effects. The regression was run using the seed regions' beta weights to predict the target region beta weights. Subjects were nested within family (sibs) and families nested within site.

Table 2: GAMM4 Analysis of Paired Brain Regions

PPI Connectivity				*Censored Beta Weight Correlation*			
Seed Region		**Target Region**					
Region Name	**DEAP Region Name**	**Region Name**	**DEAP Region Name**	**SST DEAP R^2 Value**	**ANOVA p-value**	**Significance**	
Left Dorsal Caudate	*caudate.lh*	Right Supramarginal Precentral Gyrus	supramarginal.rh	0.40746	<1e-6	***	★
			precentral.rh	0.40799	<1e-6	***	
		Right Superior Occipital Gyrus	lingual.rh	0.33798	<1e-6	***	
			cuneus.rh	0.23043	<1e-6	***	
			lateraloccipital.rh	0.19178	<1e-6	***	
		Left Pallidum	pallidum.lh	0.23597	<1e-6	***	
		Right Superior Frontal	superiorfrontal.rh	0.40103	<1e-6	***	
		Right Inferior Parietal Lobule/ Supramarginal	inferiorparietal.rh	0.4192	<1e-6	***	
			supramarginal.rh	0.40746	<1e-6	***	★
Right Dorsal Caudate	*caudate.rh*	Right Supramarginal Precentral Gyrus	supramarginal.rh	0.44958	<1e-6	***	
			precentral.rh	0.43312	<1e-6	***	
		Right Superior Occipital Gyrus	lingual.rh	0.33902	<1e-6	***	
			cuneus.rh	0.23341	<1e-6	***	
			lateraloccipital.rh	0.21291	<1e-6	***	
		Right Fusiform Gyrus	fusiform.rh	0.34043	<1e-6	***	
Bilateral Dorsal Putamen	*putamen.lh*	Right Dorsal ACC	caudalanteriorcingulate.rh	0.48428	<1e-6	***	
			rostralanteriorcingulate.rh	0.24025	<1e-6	***	
		Right Superior Occipital Gyrus (BA19)	lingual.rh	0.32951	<1e-6	***	
			cuneus.rh	0.2164	<1e-6	***	
			lateraloccipital.rh	0.16029	<1e-6	***	
		Right Supramarginal/Postcentral	supramarginal.rh	0.45835	<1e-6	***	
			postcentral.rh	0.29505	<1e-6	***	
	putamen.rh	Right Dorsal ACC	caudalanteriorcingulate.rh	0.50108	<1e-6	***	
			rostralanteriorcingulate.rh	0.23916	<1e-6	***	
		Right Superior Occipital Gyrus (BA19)	lingual.rh	0.32305	<1e-6	***	
			cuneus.rh	0.21919	<1e-6	***	
			lateraloccipital.rh	0.15066	<1e-6	***	
		Right Supramarginal/Postcentral	supramarginal.rh	0.49044	<1e-6	***	
			postcentral.rh	0.33622	<1e-6	***	
Left Ventral Striatum	accumbens.area.lh	Right Inferior Parietal Lobule	inferiorparietal.rh	0.1411	<1e-6	***	
			supramarginal.rh	0.13707	<1e-6	***	

★ same seed region-target region pair Target DEAP Regions with SST DEAP R^2 Value > 0.35

This was implemented using GAMM4 function in R. GAMM4 output both R^2 values for the model and an ANOVA analysis, which were used to determine the degree to which the seed region predicts the target region.

Results

The primary outcome measure of interest was the R^2 value indicating the amount of variance in the target region for the Correct Stop vs Correct Go contrast that was predicted by the striatal 'seed' region's activation for that same contrast, over and above the other variables in the model. Table 2 summarizes the results. It should be noted that while Table 2 lists 31 seed-target pairs, there are only 30 unique pairings; the left caudate-right supramarginal pair, denoted by the star in Table 2, was duplicated due to the differing regional divisions between the PPI and DEAP analyses. Because of the large number of participants in the ABCD dataset, even relatively small effect sizes may reach traditional levels of statistical significance. We therefore focus on and identify those that meet the heuristic criterion for 'large' effect sizes (Cohen, 1988: .02 small, .15 moderate, .35 and above large); these are marked in blue. Figures 1 and 2 show the plots of the linear regression models for the seed region-target region pairs with R^2 values over 0.35. Each dot corresponds to a data point, while the histograms along the axis show the distribution of beta weights for the seed and target regions. The calculated model is displayed as a line with 95% confidence intervals. Visually, the regression lines seem to be a good fit for the data (the data is clustered along the regression line), which is in line with the large R^2 values for these pairings.

All R^2 values of the linear regressions generated are greater than 0.14. Of the 30 unique pairs analyzed, 16 have an R^2 value above 0.25, and 10 have R^2 values over 0.40 (including, for example, the right putamen-right supramarginal pair and the right putamen-right caudal anterior cingulate pair). In other words, for a third of the

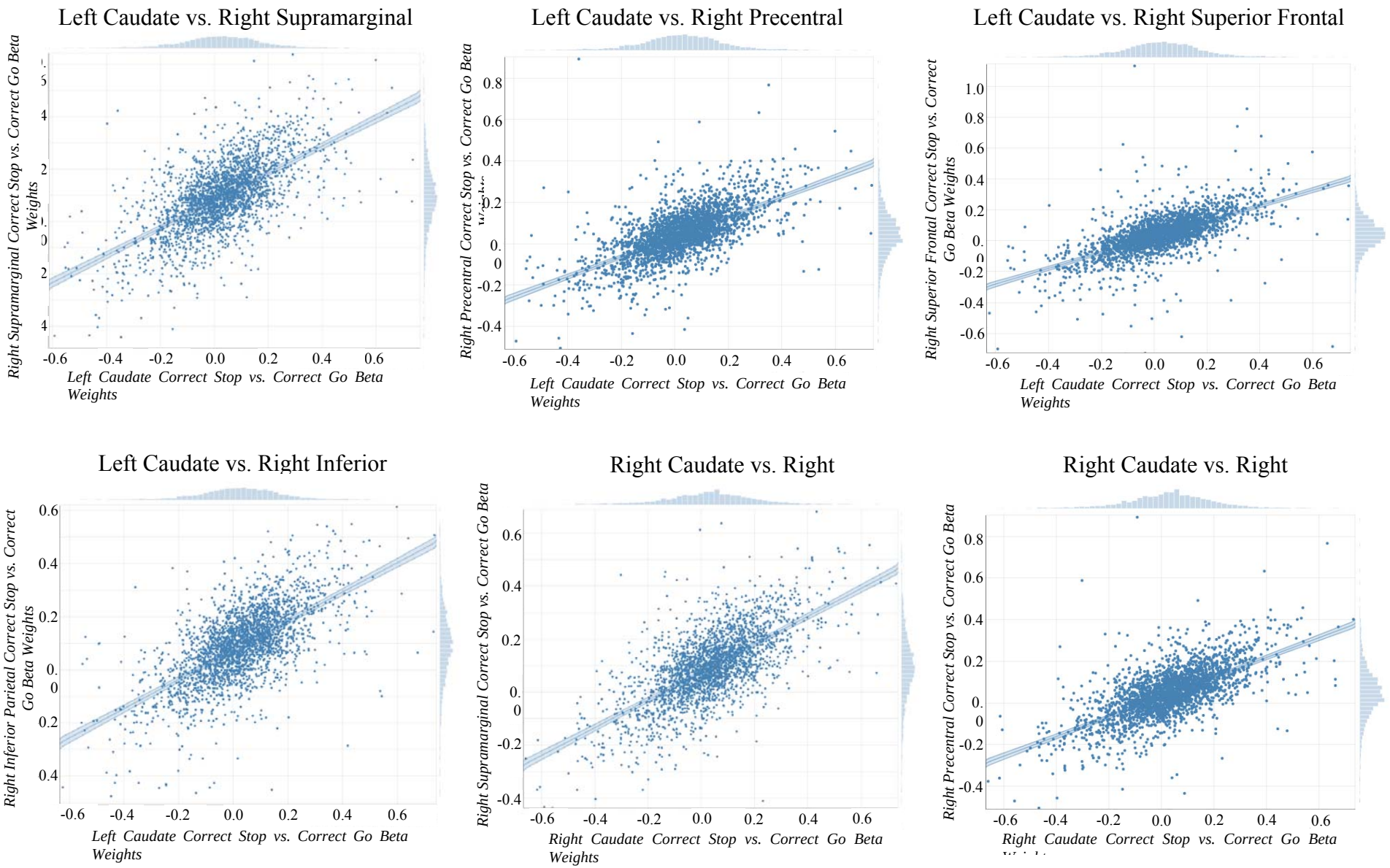

Figure 1: GAMM4 Linear Regressions for Caudate Seed Region-Target Region Pairs with $R^2 > 0.35$. Seed regions' Correct Stop vs. Correct Go beta weights were used to predict the target region beta weights of the same contrast in this generalized mixed-effect model. Each dot corresponds to a data point, while the histograms at the top and right show the distribution of beta weights for the seed and target regions respectively. All plots have an R^2 value greater than 0.35, meaning that at least 35% of the variance in activity in the target region can be predicted by the activity in the seed region for this contrast.

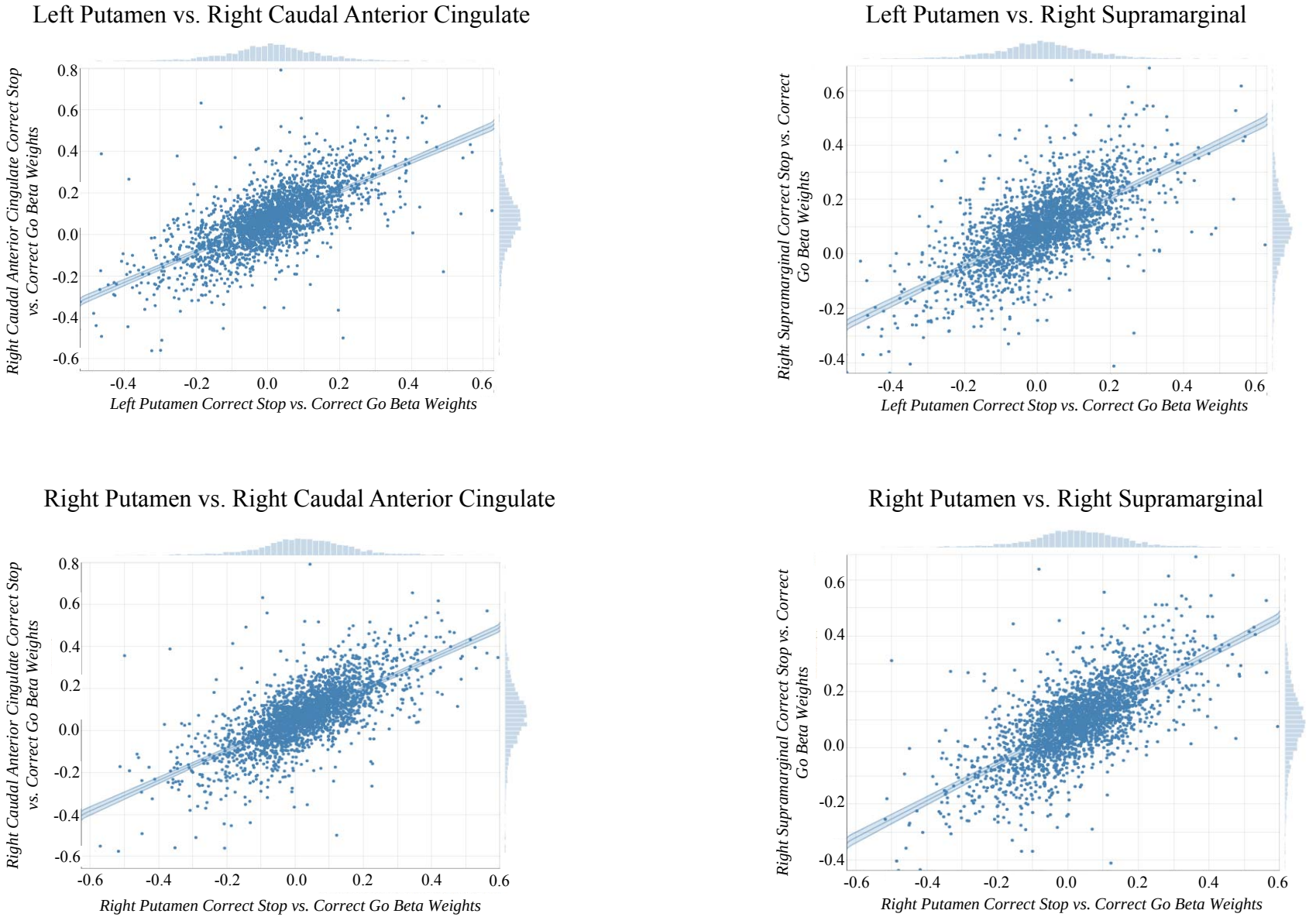

Figure 2: GAMM4 Linear Regressions for Putamen Seed Region-Target Region Pairs with $R^2 > 0.35$.

Table 3: Rank Comparison between PPI Strength and DEAP Correlation

Seed Region	Target Region	Coordinates*	Rank of PPI Strength*	Rank of DEAP Correlation
Left Dorsal Caudate	Right Supramarginal Precentral Gyrus**			
	Right Superior Occipital Gyrus	36 -88 30	1	4
	Left Pallidum	-20 4 -2	3	3
	Right Superior Frontal	22 26 32	2	2
	Right Inferior Parietal Lobule/ Supramarginal	-24 8 4	4	1
Right Dorsal Caudate	Right Supramarginal Precentral Gyrus	60 -22 40	1	1
	Right Superior Occipital Gyrus**			
	Right Fusiform Gyrus	30 -38 -18	2	2
Bilateral Dorsal Putamen	Right Dorsal ACC	12 32 28	1	2
	Right Superior Occipital Gyrus (BA19)	38 -86 30	2	3
	Right Supramarginal/Postcentral	52 -32 36	3	1
Left Ventral Striatum	Right Inferior Parietal Lobule	60 -40 28	1	1

* data from Howe et al. 2013 re-analysis

** regions derived from Bilateral Dorsal Caudate PPI analysis, excluded from Rank Comparison

pairs analyzed, at least 40% of the variance in beta weights is accounted for by the linear regression model between the seed region and the target region.

Of the 10 regions with a large effect size (R^2>0.35), only 4 seed-target region pairs have R^2 values above 0.45: right dorsal putamen- right caudal anterior cingulate (R^2 = 0.50108), left dorsal putamen- right caudal anterior cingulate (R^2 = 0.48428), right dorsal putamen- right supramarginal (R^2 = 0.49044), and left dorsal putamen- right supramarginal (R^2 = 0.45835). These pairs were derived from the bilateral dorsal putamen- right dorsal ACC and the bilateral dorsal putamen- right supra-marginal/postcentral pairings in the original PPI analysis. Notably, the putamen is a major site of degeneration in Parkinson's disease, and these findings - and others (Li et al., 2008; Hu & Li, 2011) - support that it interacts with fronto-parietal regions in situations requiring a shift in cognitive-motor behavior.

To get a better view of the correspondence between the Howe et al. (2013) re-analysis results and the present analysis, Table 3 compares the ranking of PPI strength to DEAP correlation for each seed region. Target regions that only occurred in the bilateral region PPI analysis were excluded from the rankings of the left and right components of that region (this was only applicable to the left and right dorsal caudate). As shown, the ranking of DEAP correlation for each seed regions remains generally consistent to the PPI strength ranking for each region, although there are exceptions. These exceptions all involve the occipital gyrus region, which tends to vary between being first and being last in importance for the rankings.

Discussion

Although all 31 seed-target region pairs proved to have significant relationships in the DEAP analysis, the focus will be on the 11 pairings that had a 'large' effect size, according to the heuristic criterion described by Cohen (1980). For these pairings, there was a large effect of the seed region's beta weights for Correct Stop versus Correct Go in explaining the variance in the target region's same measure. This means that there is a stronger correlation in activity between the seed-target regions during the Correct Stop trials of SST (where participants had to shift their ongoing movement to a different movement in response to a cue) compared to during Correct Go trials of SST (where no cue-triggered change in movement occur).

This aligns with the conclusions drawn from the PPI reanalysis of the Howe et al. (2013) study. The PPI reanalysis determined that, for these seed-target pairs, there is more correlated activity during SAT trials where detecting a signal is used to break out of an existing attentional-motor task to engage in a new taskset (incongruent hits) compared to when no such signal-based change in motor task happens (consecutive hits). Both the PPI analysis and the DEAP analysis show that there is correlated

activity between subcortical striatal regions and higher processing frontal cortical regions during this type of task, although they use somewhat different definitions of "correlational activity". Again, see Eickhoff et al. (2011) for analyses indicating that these often give converging evidence.

The seed-target pairs with a large effect size mostly involve the right supramarginal gyrus in some form and the right caudal anterior cingulate regions as targets (with both the left and right caudate and the bilateral putamen as seed regions). The caudate and the putamen are part of the striatum, which is involved in motor plan selection, and has been the focus of many of the papers on cue-triggered shifts in movement (Groenewegan, 2003; Avila, Kucinski, & Sarter, 2017; Avila, Kuinski, & Sarter, 2018; Kucinski & Sarter, 2018). The right supramarginal gyrus is typically associated with functions in empathy, emotion, memory, and language processing (Russ et al., 2003; Hartwigsen et al., 2010; Silani et al., 2013), but has shown to be involved in proprioception, which is essential for motor control (Ben-Shabat et al., 2015). It is possible that, in order to successfully execute the change in motor plan in SST, brain regions associated with proprioception must increase their activity. Additionally, the caudal anterior cingulate has been shown to modulate the supplementary motor area when task-related motor control is needed (Asemi, 2015) and possibly influences motor preparation activity before movement even starts (Lee & Grafton, 2015). Given that SST requires task-related motor control, especially when stopping movement in response to a cue, it comes as no surprise that this region is preferentially active.

The DEAP analysis also converges with the conclusions of Avila (2018). In the Avila paper, DREADD manipulation of the striatum to activate and inhibit cholinergic neurons showed that cholinergic activity is necessary and sufficient for producing cue-triggered shifts in motor task sets. This aligns with the strong effect size of the caudate and putamen (both part of the striatum) in the DEAP analysis. Although the DEAP analysis study also suggests that the striatal region is involved specifically in these cue-triggered shifts from an existing motor plan to a new one, we cannot definitively say that the results from this study were solely cholinergically mediated; other neurotransmitter systems, like dopaminergic systems, exist in this area.

The rank ordering of each target region to their seed region is roughly the same between the DEAP correlation analysis and the PPI connectivity analysis. The differences between the rankings that are seen involve the occipital region. This region tends to be very prominent in the PPI rankings, but very low in the DEAP rankings. This is mostly likely due to differences between the visual stimuli in the SAT and SST. SAT uses a small, short duration dot as a signal while SST uses a big upwards arrow as a signal. Therefore, there may be an increased burden on the visual system to detect the signal in the SAT compared to the SST, which would explain why there is more prominence of occipital lobe in the PPI rankings, since they are based off of the SAT.

Limitations of this study include, as discussed, the fact that we cannot be sure that the results are due to cholinergic transients. Directly measuring cholinergic transients in humans is not currently possible, as it requires implantation of probes directly into the brain tissue. However, as the previous work by Howe et al. (2013) shows, a cross species comparison can be made between parallel measurements of rodent cholinergic transients and human fMRI activation transients. Furthermore, the demonstration that transient cholinergic stimulation in rodents can also induce fMRI-like transient increases in brain tissue oxidation changes strongly suggests a relationship between the two measures. Another limitation is that there is no method to tell the 'direction' of connectivity from the DEAP analysis; that is, from these results, we are unable to tell in which direction information flows. Is it from the striatum to the cortex or vice versa? As previously mentioned, future studies will attempt to design a motor-specific paradigm to be run in the fMRI, where participants have an even more explicit change in movement in response to a cue. Unlike the DEAP database which uses pre-processed data, future experiments using the fMRI motor paradigm will allow for direction of connectivity analysis (Rogers et al., 2007). If the results of this re-analysis hold, we would expect to see similar functional connectivity and correlated brain areas, perhaps with stronger

relationships. In addition, after initial testing with healthy participants, PD patients can be tested with the motor fMRI paradigm to see how their behavioral performance and fMRI activity compares.

Nevertheless, the significant correlation of fMRI activity between the striatal seed regions and the cortical target regions for the 'Correct Stop' SST trials compared to that of the 'Correct Go' SST trials converges on existing evidence that interactions between these striatal regions and higher processing cortical regions are important for cue-guided shifts in task sets, particularly motor-based task sets. The focus here on a specific cognitive-motor control operation (shifting task and response sets) that in turn is linked to specific hypotheses about its functional neuroanatomy - including relevant neuro-transmitter activity - may help advance research into treatment options beyond the general notion that striatal-cortical interactions are involved in motor control.

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