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Convergence of prefrontal and parietal anatomical projections in a connectional hub in the striatum

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ABSTRACT

Visual attentional bias forms for rewarding and punishing stimuli in the environment. While this attentional bias is adaptive in healthy situations, it is maladaptive in disorders such as drug addiction or PTSD. In both these disorders, the ability to exert control over this attentional bias is associated with drug abstinence rates or reduced PTSD symptoms, indicating the interaction of visual attention, cognitive control, and stimulus association. The inferior parietal lobule (IPL) is central to attention, while the prefrontal cortex (PFC) is critical for reward, cognitive control, and attention. Importantly, regions of the IPL and PFC commonly project to the rostral dorsal caudate (rdCaud) of the striatum. We propose an anatomical network architecture in which IPL projections converge with PFC projections in a connectional hub in the rdCaud, providing an anatomical substrate for the interaction of these projections and their competitive influence on striatal processing. To investigate this, we mapped the dense projections from the caudal IPL and prefrontal (dlPFC, vlPFC, OFC, dACC, and dmPFC) regions that project to the medial rdCaud with anatomical tract-tracing tracer injections in monkeys. These inputs converge in a precise site in the medial rdCaud, rostral to the anterior commissure. Small retrograde tracer injections confirmed these inputs to the medial rdCaud and showed that a proximal ventral striatal location has a very different pattern of cortical inputs. We next used human resting-state functional connectivity MRI (fcMRI) to examine whether a striatal hub exists in the human medial rdCaud. Seed regions in the human medial rdCaud revealed cortical correlation maps similar to the monkey retrograde injection results. A subsequent analysis of these correlated cortical regions showed that their peak correlation within the striatum is in the medial rdCaud, indicating that this is a connectional hub. In contrast, this peak striatal correlation was not found in the ventral striatal location, suggesting that this site is not a connectional hub of cortical regions. Taken together, this work uses the precision of monkey anatomy to identify a connectional hub of IPL and PFC projections in the medial rdCaud. It also translates this anatomical precision to humans, demonstrating that, guided by anatomy, connectional hubs can be identified in humans with fcMRI. These connectional hubs provide more specific treatment targets for drug addiction, PTSD, and other neurological and psychiatric disorders involving the striatum.

1. Introduction

Visual attentional bias develops during incentive-based learning in response to positively or negatively reinforced stimuli (Anderson et al., 2011a, 2011b; Hickey et al., 2010; Koster et al., 2005; Schmidt et al., 2015). This attentional bias is adaptive in healthy situations; it allows us to quickly procure rewards or avoid punishments in the environment. However, attentional bias can also be maladaptive and strengthen stimulus-outcome associations, leading to the formation of harmful habits such as drug addiction (Field and Cox, 2008; Franken, 2003; Robinson and Berridge, 1993) or nonproductive responses as in post-traumatic stress disorder (PTSD) (Block and Liberzon, 2016; Hayes et al., 2012). In these situations, cognitive control is limited in its ability to mediate between attentional bias and action. Indeed, addiction studies have shown that the degree to which control can be exerted over attentional drug bias correlates with improved abstinence rates (Fadardi and Cox, 2009; Ziaee et al., 2016). Similarly in PTSD, training in keeping one's attention away from threatening stimuli leads to reduced PTSD symptoms (Badura-Brack et al., 2015; Kuckertz et al., 2014; Schoorl et al., 2013). Together, these observations indicate an interaction of visual attention, cognitive control, and stimulus-outcome associations leading to habit development.

Abbreviations: rdCaud, rostral dorsal caudate; vCaud, ventral caudate; fcMRI, resting-state functional connectivity MRI

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The striatum has a well-established, central role in the development of stimuli salience, reinforcement conditioning, and the habitualization of behavior (Everitt et al., 2008; Everitt and Robbins, 2005; Robinson and Berridge, 2001; Yin and Knowlton, 2006). Prior anatomical tract-tracing and human neuroimaging studies have shown that cortical regions processing visual attention, stimulus association, and cognitive control connect with the dorsal caudate of the striatum. Monkey tract-tracing cases show that the orbitofrontal cortex (OFC), ventrolateral prefrontal cortex (vlPFC), dorsolateral prefrontal cortex (dlPFC), dorsomedial prefrontal cortex (dmPFC), and dorsal anterior cingulate cortex (dACC) all project to the dorsal caudate. Interestingly, the inferior parietal lobule (IPL), which is central to visual attention, also projects to the dorsal caudate (Cavada and Goldman-Rakic, 1991; Yeterian and Pandya, 1993). The IPL is involved specifically in attention spontaneously drawn towards behaviorally relevant stimuli (bottom-up or ventral attention) (Corbetta et al., 2008; Corbetta and Shulman, 2002; Steinmetz and Constantinidis, 1995), such as drugs of abuse. Indeed, the IPL, as well as parts of the PFC, shows increased activity during the presentation of drug-related visual stimuli in addiction (e.g., drug paraphernalia) (Garavan et al., 2000; Grant et al., 1996; Kilts et al., 2014; Kühn and Gallinat, 2011; Maas et al., 1998) or viewing emotional stimuli in PTSD (Mazza et al., 2013; Mueller-Pfeiffer et al., 2013).

Human resting-state functional connectivity MRI (fcMRI) and diffusion MRI (dMRI) have indicated the convergence of parietal and PFC connections in the human dorsal caudate. fcMRI has revealed that there is a longitudinal zone involving the rdCaud that is functionally linked with distributed caudal IPL and prefrontal regions in the dlPFC, vlPFC, and dACC (Barnes et al., 2010; Choi et al., 2012; Di Martino et al., 2008). Importantly, Jarbo and Verstynen (2015) linked these fcMRI findings to dMRI structural connectivity. This study clearly demonstrated that structural connections of the parietal, OFC, and dlPFC converge in a longitudinal zone encompassing the rdCaud. Together, neuroimaging studies reveal an overlap of parietal and PFC connections in the dorsal caudate. However, the specific prefrontal and parietal areas that converge in the dorsal caudate, nor the precise extent and location of this convergence, are not well defined.

Here, using the precision of monkey anatomical tract-tracing, we build upon the prior monkey and human studies by examining whether there is anatomic convergence within the dorsal caudate of the terminal fields of projections from the caudal IPL and the vlPFC, dlPFC, dmPFC, dACC, and OFC, regions involved in visual attention, stimulus-outcome association, and cognitive control (Bush et al., 2000; Fuster, 2008; Levy and Wagner, 2011; Rolls, 2002; Venkatraman and Huettel, 2012). In particular, based on our prior demonstration of a connectional hub of prefrontal projections in the medial caudate (Averbeck et al., 2014), we hypothesized that caudal IPL projections converge with vlPFC, dlPFC, dmPFC, dACC, and OFC projections in a specific connectional hub within the rostral dorsal caudate (rdCaud). This connectional hub would be a unique region within the longitudinal zone identified from fcMRI and dMRI studies that receives the greatest convergence of inputs from multiple regions of parietal cortex, OFC, and dlPFC, as well as of vlPFC, dmPFC, and dACC, which are important for switching behaviors and context-dependent action selection (Bunge, 2004; Rushworth et al., 2002; Toni et al., 1999; Woodward et al., 2006).

To investigate this, we first identified the precise site of convergence in the rdCaud by charting the projections from caudal IPL with those from the vlPFC, dlPFC, dmPFC, dACC, and OFC. To confirm this convergence, we placed retrograde tracer injections in the area of convergence in the medial rdCaud and, using unbiased stereology, identified and quantified the inputs from the caudal IPL and PFC. We also charted the cortical inputs to a proximal ventral caudate location (vCaud) with retrograde tracer injections, which resulted in a very different pattern of cortical inputs. We next used fcMRI in healthy human subjects to examine whether a similar striatal hub architecture of convergent PFC and IPL connections exists in the human rdCaud. The results show that a site in the human medial rdCaud contains converging inputs from the caudal IPL, vlPFC, dlPFC, dmPFC, dACC, and OFC. In contrast, a different set of cortical areas input to the human vCaud. These results provide anatomical evidence for the convergence and interaction of caudal IPL and five prefrontal areas within a connectional hub in the medial rdCaud. Moreover, there is a homologous region or hub within the human caudate with a similar set of convergent inputs. As such, this striatal hub is likely to be central for the influence of visual attention and control on striatal processing.

2. Materials and methods

2.1. Overview

The present study consists of three levels of analyses. First, we identified the location of convergence of caudal IPL and PFC projections in the striatum of monkeys. We placed anterograde tracer injections in input regions to the rdCaud in the caudal IPL, vlPFC, dlPFC, dmPFC, dACC, and caudal OFC, and traced dense terminal projections in the striatum. To compare the labeled anatomy between cases from different monkeys, each case was merged onto a standard monkey brain model. Convergence of projections was assessed and quantified with a heatmap of overlapping projections from each case.

Having identified the medial rdCaud as a connectional hub of the caudal IPL and the above PFC projections, we confirmed and characterized this convergence using small retrograde tracer injections in the medial rdCaud. The pattern of labeled cells in 2 rdCaud cases was compared to those from 2 cases with injections in a proximal ventral caudate location, the vCaud. One case each of the rdCaud and vCaud cases was charted and the density of labeled cells in each cortical area was quantified to determine the strengths of those inputs.

Finally, we examined human fcMRI for evidence of a similar connectional hub in the human rdCaud. The position of the center of the convergence in the monkey rdCaud was determined, and the corresponding human location was identified with the proportionally same spatial location in the human striatum. Using a single 2 mm^3 voxel seed region at this human rdCaud site, a whole brain fcMRI map (N=500) was generated to identify functionally connected cortical regions to the rdCaud and then compared with the monkey anatomy. To confirm that the human medial rdCaud is the major striatal hub of connectivity with these cortical regions, a striatal fcMRI map was created using a seed region of cortical regions with correlations of 1.5 standard deviations or greater above the mean with the medial rdCaud seed region. These results were compared with those of the vCaud, which were obtained with the same process using a single 2 mm^3 voxel seed region at the human vCaud location corresponding to the monkey vCaud injection site.

2.2. Injection sites

6 anterograde cortical injections were placed in prefrontal and parietal regions previously shown to project to the dorsal caudate (Haber et al., 2006; Künzle, 1978; Selemon and Goldman-Rakic, 1985; Yeterian and Van Hoesen, 1978). These were 5 functionally diverse regions of the dlPFC in the dorsal bank of the principal sulcus (area 46), dmPFC (area 9), vlPFC in the ventral limb of the arcuate sulcus (area 45), dACC (area 24), and OFC in the lateral bank of the medial orbital sulcus (area 13). The caudal IPL injection was in the ventral lip of the caudal intraparietal sulcus (areas 7a/PG and 7a/Opt). 4 retrograde striatal injections were placed in the medial rdCaud or vCaud. All injection cases had labeling throughout the cortex and no contamination (tracer leakage into an adjacent cortical area, structure, or white matter).