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## The functional connectivity of the human caudate: An application of meta-analytic connectivity modeling with behavioral filtering

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### Abstract

Meta-analysis based techniques are emerging as powerful, robust tools for developing models of connectivity in functional neuroimaging. Here, we apply meta-analytic connectivity modeling to the human caudate to 1) develop a model of functional connectivity, 2) determine if meta-analytic methods are sufficiently sensitive to detect behavioral domain specificity within region-specific functional connectivity networks, and 3) compare meta-analytic driven segmentation to structural connectivity parcellation using diffusion tensor imaging. Results demonstrate strong coherence between meta-analytic and data-driven methods. Specifically, we found that behavioral filtering resulted in cognition and emotion related structures and networks primarily localized to the head of the caudate nucleus, while perceptual and action specific regions localized to the body of the caudate, consistent with early models of nonhuman primate histological studies and postmortem

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studies in humans. Diffusion tensor imaging (DTI) revealed support for meta-analytic connectivity modeling's (MACM) utility in identifying both direct and indirect connectivity. Our results provide further validation of meta-analytic connectivity modeling, while also highlighting an additional potential, namely the extraction of behavioral domain specific functional connectivity.

## Keywords

meta-analytic connectivity modeling; functional connectivity; MACM; DTI; caudate

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## 1. Introduction

The human dorsal striatum contains the primary input to the basal ganglia (Haber 2003; Grahn, Parkinson et al. 2008). Comprised of the caudate and putamen, it receives axons from all regions of the cortex with the exception of the primary visual, auditory, and olfactory cortices (Grahn, Parkinson et al. 2008). Anatomical, functional, and/or connectivity abnormalities of the caudate nuclei have been noted in a wide range of disorders including autism (Turner, Frost et al. 2006), Huntington's disease (Bohanna, Georgiou-Karistianis et al.), Parkinson's disease (PD) (Rowe, Hughes et al. 2008), human immunodeficiency virus (HIV) (Melrose, Tinaz et al. 2008), drug addiction (Ma, Liu et al. 2011), depression (Bluhm, Williamson et al. 2009), and attention deficit hyperactivity disorder (ADHD) (Casey, Epstein et al. 2007). Despite its involvement in a range of psychiatric and neurological disorders, few studies have examined the functional connectivity of the human caudate (Postuma and Dagher 2006; Di Martino, Scheres et al. 2008), and no study, to our knowledge, has examined functional connectivity in this structure using advanced meta-analytic techniques. In the present study, we used meta-analytic connectivity modeling (MACM) (Robinson, Laird et al. 2010) to provide an initial model of functional connectivity utilizing decades worth of neuroimaging data collected across various behavioral domains. Describing connectivity models in this manner has the potential to facilitate discovery of specific pathways that are aberrant in populations with known dysfunction of the caudate, which may ultimately lead to the identification of novel interventions.

Early models of the basal ganglia assigned to the caudate a primary role of integrating information from the cortical association and sensorimotor areas of the brain before sending it to distinct ventrolateral thalamic sub-regions, which would then relay the information almost exclusively to the primary motor cortex. These early models have largely been replaced by more complex ones based on evidence of reciprocating but interconnected circuits that link the cortex, basal ganglia, and thalamus (DeLong, Georgopoulos et al. 1983; Alexander, DeLong et al. 1986; Alexander and Crutcher 1990). Five primary circuits have been proposed in the nonhuman primate literature: motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate (Alexander, DeLong et al. 1986). In each of these proposed circuits, the basal ganglia receive input from multiple cortical regions, pass this information to the thalamus where integration operations occur before information is passed to specific cortical regions of one of the segregated functional circuits (Alexander, DeLong et al. 1986). Thus, each cycle within a thalamocortical-basal ganglia circuit concludes with the thalamocortical pathway terminating in specific regions of the cortex, unique to that particular loop. To date, these looping circuits have not been adequately described in human functional neuroimaging studies.

Topographic mapping within the caudate has been demonstrated in animal model. Specifically, segmentation of the caudate nucleus into head and body components has revealed consistent, distinct compartments such that the head of the caudate has been

associated with more cognitive and emotional processing whereas the body/tail of the caudate has been associated with action and perceptual processes. However, similar to the proposed looping circuits, no study to our knowledge has tested this organization in humans.

Here, we test whether the human caudate connectivity patterns support the major circuits identified in the nonhuman primate system, and investigate whether it demonstrates anterior-posterior somatotopic and behavioral topography. Because it is not feasible to investigate this in a single study, we capitalize on the power of meta-analyses and the organization of the BrainMap database (Fox and Lancaster 2002; Fox, Laird et al. 2005; Laird, Lancaster et al. 2005) database to 1) identify behavioral domain-specific networks that we predict will correspond to the circuits described in the primate literature, and 2) determine if the anterior and posterior portions of the caudate demonstrate behavioral domain segmentation as previously described with action and perception networks mapping primarily to the posterior body/tail of the caudate, and cognitive and emotional systems relying on more anterior aspects of the structure. To do so, we use a robust, unbiased meta-analytic approach, coupled with a tractography analysis using diffusion tensor imaging (DTI).

## 2. Methods

Meta-analytic connectivity modeling (MACM) was employed to assess human caudate functional connectivity. Below, we describe methods for region of interest (ROI) selection as well as the implementation of MACM.

### 2.1. ROI Selection

Bilateral caudate ROIs were defined using the Harvard-Oxford Structural Probability Atlas (thresholded at 75% probability) distributed with FSL neuroimaging analysis software (<http://www.fmrib.ox.ac.uk/fsl/fslview/atlas-descriptions.html#ho>) (Smith, Jenkinson et al. 2004). Using anatomically bounded (i.e., irregular) ROIs represents an improvement over methodologies which use regular (i.e., spherical or cuboidal) ROIs (Stein, Wiedholz et al. 2007), ROIs derived from functional activations within a given study (Mohanty, Engels et al. 2007; Gianaros, Sheu et al. 2008), or use atlas-based automatic labeling systems (Tzourio-Mazoyer, Landeau et al. 2002; Williams, Liddell et al. 2006). The mean probability for the left ( $M \pm SD$ :  $87.82\% \pm 6.87\%$ ) and right caudate ( $88.20\% \pm 7.18\%$ ) was over 85%, and the centroid for each had over 95% (left: 96% at Talairach coordinates [x,y,z] -11.2, 6.6, 11.6; right: 98% at Talairach coordinates 13.2, 7.5, 12.0) probability of being part of the caudate. The total volume for the left caudate was 1635 voxels, and the right caudate was 1845 voxels. For additional analyses, we generated a head and body caudate ROI.

**2.1.1. Caudate Head and Body ROIs**—Given that cytoarchitectural, histological, and early neuroimaging studies suggested a behavioral domain segmentation of the caudate, such that the head of the caudate was thought to be involved in more cognition and emotion related processes, while the body/tail was involved primarily with action and perception, we manually divided the caudate ROI into head and body subsections based on previous research (Williams, Warwick et al. 1989; Castellanos, Giedd et al. 1994). Specifically, we designated the boundary between the head and body of the caudate to be the coronal slice containing the interventricular foramina. The bilateral caudate head ROI was 1677 voxels (left, 731 voxels centered at -15, 10, 17; right 946 voxels centered at 15, 9, 19). The bilateral caudate body ROI was 1803 voxels (left, 904 voxels centered at -14, -4, 23; right, 899 voxels centered at 17, -10, 24).

## 2.2. BrainMap Meta-Analysis Methods

To search for all studies that reported activation within each ROI boundary, the left and right caudate ROIs were input into the BrainMap database separately, with restrictions to exclude disease-based studies, and include only activation studies. Whole-brain coordinates of activations from the isolated contrasts were then downloaded (left caudate = 125 papers, 167 experiments, 2466 locations; right caudate = 135 papers, 200 experiments, 2907 locations). The total number of subjects in all studies reporting activation in the left caudate was 2094, and for the right caudate 2136. Papers were drawn from all of the behavioral domains coded in the BrainMap database which includes cognition, emotion, action, interoception, pharmacology, and perception, with cognition representing the majority of studies followed by emotion for both the left and right caudate. For more detailed information regarding the taxonomy and coding strategy of the BrainMap database, please refer to Fox and colleagues (2005), Laird and colleagues (2009; 2011) and the BrainMap lexicon located at <http://www.brainmap.org/BrainMapLex.xls>. Of the final data set, 48% of the papers drawn for the left caudate were coded as cognition, 24% as emotion, 13% as perception, 10% as action, 3% as pharmacology, and 1% as interoception. For the right caudate, 44% were coded as cognition, 25% as emotion, 15% as action, 12% as perception, 2% as interoception, and 2% as pharmacology.

Activation likelihood estimation (ALE) meta-analyses (Turkeltaub, Eden et al. 2002; Laird, Fox et al. 2005; Turkeltaub, Eickhoff et al. 2011) were performed on the sets of coordinates identified as coactivated during left and right caudate activation, to identify regions of convergence. This map served as a 'global' connectivity map, encompassing all behavioral domains. ALE capitalizes on the nature of voxel-wise studies that are commonly reported in a standard stereotactic space ( $x, y, z$ ) by pooling 3D coordinates from like studies, and providing the probability of an event occurring at each brain voxel. Resultant ALE maps from the present study were thresholded conservatively ( $p < 0.001$ , corrected for multiple comparisons via false discovery rate, with minimum cluster volume  $100\text{mm}^3$ ).

**2.2.1. Head Versus Body MACM Functional Connectivity**—The caudate head and body ROIs were input into the BrainMap database and subsequent functional connectivity maps were created based on the resultant ALE analyses, as described above. Ninety-one papers with caudate head activation were drawn from the database (1300 subjects, 109 experiments, 245 conditions, 1709 locations), and 115 papers were drawn for the body/tail of the caudate (1972 subjects, 141 experiments, 304 conditions, 2210 locations).

**2.2.2. Behavioral Domain-Specific MACM Functional Connectivity**—The above BrainMap search results for the left and right caudate ROIs were then restricted to the major behavioral domain categories, and the whole-brain ALE meta-analyses were repeated separately for each ROI, for each domain (e.g., action, cognition, emotion, interoception, pharmacology, and perception). The behavioral domain datasets varied in size (action: 51 papers drawn from the database, representing 777 subjects, 109 experiments, 146 conditions, and 1481 locations; cognition: 151 papers, 2370 subjects, 354 experiments, 501 conditions, 4421 locations; emotion: 72 papers, 1269 subjects, 201 experiments, 290 conditions, 1908 locations; perception: 54 papers, 711 subjects, 95 experiments, 137 conditions, 1606 locations). Interoception and pharmacology were not included in the analysis because they had 6 and 9 papers, respectively. Resultant ALE maps were generated for each behavioral domain with sufficient power. To identify regions of coactivation specific to a given behavioral domain, all other behavioral domain specific connectivity maps except the domain of interest were subtracted from the global functional connectivity map leaving only coactivations that were not involved in any other domains functional connectivity map.

## 2.3. Structural Segmentation Methods

Motivated by prior evidence from nonhuman primates and human neuroimaging studies, we performed a diffusion tensor imaging analysis to probe structural segmentation. Diffusion-weighted data were acquired in forty-nine healthy, Hispanic individuals (age: 40.94 years  $\pm$  8.38; education: 12.47 years  $\pm$  2.69; 16 males, 33 females) who were recruited into an Institution Review Board approved neuroimaging study at the University of Texas Health Science Center at San Antonio, Research Imaging Institute. All individuals included in the analysis were screened for psychiatric illness and neurological conditions, and had never lost consciousness. Data were acquired on a Siemens 3T scanner with a standard 8-channel headcoil. Diffusion weighting was isotropically distributed along 55 directions ( $b$ -value = 0, 700; TR/TE = 7800/88ms, base resolution = 128mm, voxel size = 1.72mm  $\times$  1.72 mm  $\times$  3mm; 50 slices acquired; total scan time = 7min40sec). In each subject, a high-resolution T<sub>1</sub>-weighted scan was obtained for registration purposes (MPRAGE, TR/TE = 2200/3.04ms, tip angle = 13°, voxel size = 0.8mm<sup>3</sup>, 208 slices, base resolution = 320mm, FOV Phase = 70%, FOV Read = 256mm). All images (diffusion-weighted and T<sub>1</sub>-weighted) were skull-stripped using tools provided in FSL (Smith 2002), and manually checked to ensure accuracy.

**2.3.1. Image Analysis**—Probabilistic diffusion tractography was carried out as described previously (Behrens, Woolrich et al. 2003; Behrens, Johansen-Berg et al. 2003; Johansen-Berg, Behrens et al. 2005). In summary, a probability density function was created at each voxel on the principal fiber direction. Connectivity probabilities were estimated between the seed voxels and target voxels by repeatedly sampling connected pathways through the probability distribution function. We used the same anatomically defined bilateral caudate ROIs as described previously as our seed masks, and 11 cortical and subcortical regions covering the whole brain as targets. All targets were generated using the Harvard-Oxford probability atlas and included the following regions: anterior cingulate, paracingulate, prefrontal cortex, precentral gyrus, postcentral gyrus, parietal lobe, temporal lobe, occipital lobe, posterior cingulate, amygdala and hippocampus. All target ROIs were thresholded at 50% probability with the exception of the amygdala and hippocampus, which were more conservatively thresholded (70%). Target ROIs were transformed into each subject's space using registration tools provided in FSL (Jenkinson, Bannister et al. 2002).

From each voxel in the caudate mask, samples were drawn from the connectivity distribution and the proportion of those samples that passed through each of the cortical/subcortical masks was defined as the probability of connection to the target. Segmentation of the caudate was performed by classifying each seed voxel as connecting to the cortical or subcortical mask with the highest connectivity probability. For each target, we thresholded and binarized individual subject results to include only those caudate voxels with a connection probability > 10%. These images were combined to create group probability maps of caudate sub-regions.

Finally, as proof of concept of MACM's potential to identify both direct and indirect connectivity, we manually created ROIs by drawing a 5mm sphere around the centers of each cluster of the resultant whole database ALE maps of the right and left caudate. We chose spheres over anatomical ROIs since we had evidence to support the location of the focus within each cluster, and since those clusters did not encompass the entire anatomical location of the focus. Additionally, we chose to use a spherical ROI because some of the clusters had multiple foci. Therefore, we wanted to capture the independent contribution of each of these foci without getting into shared contribution issues. These were used as targets in a probabilistic tractography analysis with the right and left caudate as seeds, respectively. The same analysis was carried out as with the 11 atlas defined targets described above.



### 3. Results

#### 3.1. Modeling of Functional Connectivity

We observed significant functional connectivity of both the left and right caudate to regions of the left anterior (BA32) and posterior cingulate (BA23), left and right insula (BA13), thalamus (medial dorsal nucleus), and inferior frontal gyrus (BA9), and left middle frontal (BA6) and precentral gyri (Table 1). In addition, we found multiple regions of functional connectivity that were spatially distinct with different Talairach Daemon labels between the right and left caudate maps. Specifically, for the left caudate, we found additional regions of coactivation with the left middle frontal gyrus (BA10), the right middle frontal gyrus, and left inferior frontal gyrus (BA9/46), regions that have been implicated in emotional and cognitive processing. We also found co-activation among the left posterior cingulate gyrus (BA23/31) and anterior cingulate (BA24), as well as the right parahippocampal gyrus (BA27) and hippocampus. Additionally, we found evidence for functional connectivity among the right precentral gyrus, known for its association with motor planning, in addition to the left postcentral gyrus. We found functional connectivity to the left inferior occipital gyrus (BA19), the left fusiform gyrus (BA37), and the left and right parietal lobules. The right caudate showed functional connectivity differences to regions of the left (BA9) and right (BA6) middle frontal gyrus, as well as the left medial frontal gyrus (BA6) and bilateral cingulate (BA32). We found further deviations between functional connectivity between hemispheres with regard to the right thalamus (pulvinar) and right lentiform nucleus (lateral globus pallidus) as well. ALE results are displayed in Figure 1. Differences between hemispheres were based on Talairach Daemon labels as well as proximity of coordinates.

**3.1.1. Behavioral Domain Classification**—One of the advantages to assessing the functional connectivity of a given region using MACM is the opportunity to mine the behavioral domain classification of metadata embedded in the BrainMap database. This additional information allows for the examination of behavioral domains associated with the ALE results to determine if the frequency of domain 'hits' relative to the distribution across the entire database are significantly different (Laird, Eickhoff et al., 2009). We performed a  $\chi^2$  test on the distribution of papers from a search of bilateral caudate ROIs. If the distributions were significantly different from the database, a binomial test was performed to determine which individual domains were over- or under-represented. For the bilateral caudate search, higher than expected frequencies were identified for pharmacology ( $p < 0.0004$ ) and emotion ( $p < 0.0001$ ), and a lower than expected frequency distribution was noted for perception ( $p < 0.0001$ ). Individual caudate analyses (left caudate only and right caudate only) using the same analysis strategy demonstrated higher than expected distributions for emotion ( $p < 0.0001$ ).

Given that we also ran MACM analyses within each behavioral domain to develop domain specific functional connectivity maps (results below), we also performed a post-hoc  $\chi^2$  test on the distribution resulting from bilateral caudate ROIs input into each of the BrainMap behavioral domains to ensure that the ALE results were indeed indicative of that particular behavioral domain. We found that for bilateral caudate results in the domain of action, a higher than expected distribution was found in action ( $p < 0.0001$ ), and lower than expected frequencies were found in cognition ( $p < 0.0001$ ) and emotion ( $p < 0.0001$ ). For cognition, we found lower frequency distributions for action ( $p < 0.0001$ ), interoception ( $p < 0.0003$ ), and perception ( $p < 0.0001$ ), but higher distributions for both cognition ( $p < 0.0001$ ) and emotion ( $p < 0.0001$ ). For emotion, we found lower than expected distributions for action ( $p < 0.0001$ ), cognition ( $p < 0.0009$ ), and perception ( $p < 0.0001$ ), and a higher distribution than expected in emotion ( $p < 0.0001$ ). Finally, for perception, we found lower than expected distributions in cognition ( $p < 0.0001$ ) and emotion ( $p < 0.0000$ ), and higher than

expected in perception ( $p < 0.0001$ ). These data provide evidence for the specificity of the functional connectivity maps generated by behavioral-filtering, with only the cognition-specific based  $\chi^2$  analysis showing significant overlap between two behavioral domains (emotion and cognition).

### 3.2. Behavioral Filtering Analyses

The second analysis strategy was to create behavior domain specific MACM maps. We used identical MACM methods as described above, however, instead of seeding the caudate ROIs into the entire database, we seeded them into each of the behavioral domains to generate a functional connectivity map for each domain. To identify regions of connectivity that were specific to each behavioral domain, we created a binary cumulative mask of all behavioral domain maps, and simply subtracted all but one binary behavioral domain mask from the cumulative map (e.g., to create the action-specific mask, we subtracted emotion, cognition, and perception from the cumulative mask). This eliminated regions that were involved in more than one domain. Results demonstrated behavioral-domain specific regions of coactivation consistent with neurological expectations. For example, there were action-specific clusters noted in the postcentral gyrus and putamen; cognition specific clusters in the posterior cingulate, anterior cingulate, and parahippocampal gyrus; and emotion specific clusters in the amygdala, anterior cingulate, and inferior frontal gyrus (Table 2; Figure 2).

While specificity was demonstrated, we also noted extensive overlap among the behavioral domain networks. For example, the left inferior frontal gyrus (BA47), cingulate gyrus (BA32), and right middle frontal gyrus (BA46) were found to be coactivated with the caudate during cognitive and emotive tasks, while the right precentral gyrus (BA6), right middle frontal gyrus (BA6), right superior parietal lobule (BA7), and left lingual gyrus (BA18) were associated with action and perception tasks (Table 3). Some regions were coactivated across all domains, suggesting a critical connection with the caudate. These regions included bilateral insula (BA13) and the right middle frontal gyrus (BA9) (Figure 3). The foci of the cluster of activation within the caudate for emotion and cognition were found in the head of the caudate, while the foci coordinates for action and perception mapped to the body of the caudate nucleus, further supporting a topographical organization.

### 3.3. Head Versus Body MACM Functional Connectivity

A useful demarcation of the caudate nucleus can be made based on observations that the head of the caudate nucleus is more involved in cognitive and emotional processes compared to the body and tail, which has been associated with more action-based processes. Our initial behavioral domain analysis supports this segmentation with emotion and cognition sharing a cluster of activation within the head of the caudate nucleus, while action and perception share a focus within the body of the caudate nucleus. We ran a complementary analysis using a caudate head ROI and a caudate body ROI to develop a MACM for these regions. We created a cumulative, binary mask, and proceeded to subtract the head or the tail connectivity maps to obtain specificity maps. Results showed consistent patterns of behavioral specificity with the head of the caudate having specific functional connectivity with emotive and cognitive regions including the amygdala and portions of the anterior and posterior cingulate (BA32 and 31, respectively) (Figure 4). The posterior portion of the caudate showed functional connectivity specificity with regions involved in motor control (superior and medial frontal gyri including BA6 and BA8), and perception related processes (occipital clusters were demonstrated as well as regions in the parietal lobe and the posterior cingulate), providing further evidence for a topographic organization. These results should be viewed as preliminary, given that these are not formal statistical comparisons between the head and the tail connectivity maps.

**3.3.1. Anatomical Connectivity: Topographic Organization of the Caudate**—To further delineate the anatomical contributions to the proposed segmentation of the caudate nucleus, we performed a DTI analysis using cortical and selected subcortical targets. We found projections to the precentral gyrus, parietal lobe, and postcentral gyrus to be strongest in the posterior portion of the caudate (Figure 5, Panels B, C, and E respectively). We found strong caudate head projections to the prefrontal cortex (Figure 5, Panel A), but not the amygdala as we hypothesized. Furthermore, many of the target regions appeared to originate from the central portion of the caudate, embracing elements of both the head and body (e.g., paracingulate, anterior cingulate; Figure 5, Panels D and G).

At the individual subject level, we found consistent segmentation such that the prefrontal cortex and regions heavily involved in emotion and cognition (i.e., anterior cingulate) had the strongest connectivity in the head portion of the caudate while more action related regions, such as the pre- and postcentral gyri had stronger connectivity in the posterior regions of the caudate. All 49 subjects showed similar segmentation.

### 3.4. Anatomical Connectivity of MACM: Validation

We took the resultant ALE functional connectivity maps for the left and right caudate, and used the cluster foci as targets in a DTI analysis to determine if MACM is identifying nodes of functional connectivity that account for both direct (anatomical) and indirect relations. 3D-image files containing the output connectivity distribution to the seed masks (left and right caudate independently) were generated for each subject (5000 samples, steplength of 0.5mm, and curvature threshold of 0.2) using FMRIB's diffusion toolbox (FDT) within the FSL software package (Behrens, Johansen-Berg et al. 2003; Behrens, Berg et al. 2007). Each individual's map was thresholded to >20 samples from each seed voxel to eliminate spurious or low connectivity profiles (Leh, Johansen-Berg et al. 2006; Leh, Ptito et al. 2007). The results were binarized and summed across subjects. A cumulative DTI connectivity population map was generated (thresholded to only show reconstructed tracts that were present in over 20% of our subjects) and cluster foci were overlaid to determine which foci had anatomical connections (Figure 6). For the left caudate, we found anatomical support for connections to the ipsilateral superior temporal gyrus (BA22), fusiform gyrus (BA37), inferior occipital gyrus (BA19), lingual gyrus (BA17), the ventral posterior medial and medial nucleus of the thalamus, and the posterior (BA30) and cingulate gyri (BA23/31). We also provide evidence for contralateral connectivity to the right thalamus, superior parietal lobule (BA7), the parahippocampus (BA27) and hippocampus, as well as the superior temporal gyrus (BA22). For the right caudate, we found ipsilateral connectivity to the lentiform nucleus (lateral globus pallidus), the pulvinar, and the insula (BA13). Contralateral connectivity was identified with the inferior temporal gyrus (BA37), medial dorsal nucleus of the thalamus, and the posterior cingulate (BA31). Many of the foci identified by MACM did not appear to have direct connectivity, suggesting that MACM is identifying nodes with both direct and indirect influence from the caudate.

## 4. Discussion

Our results provide strong evidence for a behavior-based topographic organization previously suggested by histological and functional imaging studies, while also demonstrating the utility of using MACM to develop models of functional connectivity that account for both direct and indirect influences. Below, we discuss these differences in the context of their categorical influences.



#### 4.1. Direct Influences on Caudate Functional Connectivity Patterns: Diffusion Tensor Imaging

This is the first study to combine MACM with DTI processing in a large sample of healthy individuals. We interrogated DTI data with two primary purposes. First, we wanted to identify anatomical pathways that would provide support for direct (i.e., monosynaptic) neural influences of the caudate nucleus on other regions of the brain. Second, we wanted to determine if topographical organization of the caudate nucleus is supported in humans. The latter will be discussed in section 4.3.

Using a population tractography approach, we provide monosynaptic connectivity evidence supporting components of previously described circuits that were also identified by MACM. Specifically, we found anatomical connectivity between the caudate and the posterior cingulate and cingulate gyri (BA23/30/31), the parahippocampus, and the hippocampus, which are all regions of the brain considered to be part of the emotion-cognition integrative system (Pessoa 2008) (Figure 6). We also found monosynaptic connectivity to regions of visual processing such as the fusiform gyrus (BA37) and inferior occipital gyrus (BA19). The superior (BA22) and inferior temporal gyri also demonstrated direct connectivity with the caudate. Furthermore, we found anatomical connectivity between the caudate and different nuclei of the thalamus (i.e., pulvinar, medial dorsal nucleus) supporting the longstanding notion that the thalamus provides critical operations that require such architecture for efficiency. This latter connection appears to be the most prominently replicated across studies (Leh, Ptito et al. 2007).

Our results deviate slightly from other research findings regarding anatomical connectivity of the human caudate. For example, Lehericy and colleagues (2004) studied 9 individuals and found corticostriatal connections primarily within the frontal cortex. Their results suggest that fibers associated with the head of the caudate nucleus are directed toward the medial, dorsal (BA9/46) and ventral (BA45/47) prefrontal cortices. Similarly, Leh and colleagues (2007) studied 6 individuals and found caudate projections to the ipsilateral prefrontal cortex, middle and inferior temporal gyrus, frontal eye fields, cerebellum, and thalamus. Though our results parallel some of these connections (inferior temporal gyrus and thalamus), they do not provide the same anatomical support for the prefrontal regions. This difference may be explained by our thresholding, or by the boundaries of our ROIs. We determined monosynaptic connectivity only to the ROIs within these regions that were identified by MACM analyses. Thus, the entire region was not considered for direct influence, rather a 5mm sphere generated around each caudate MACM foci.

DTI studies are often criticized for their inability to provide direct information about functional networks (Di Martino, Scheres et al. 2008). Combining MACM and DTI provides a solution to this issue by elucidating white matter connectivity to ROIs established within functional circuits. Here, we demonstrate how this technique can be used to inform the monosynaptic versus polysynaptic (i.e., indirect) architecture of connectivity models.

#### 4.2. Indirect Influences on Caudate Functional Connectivity: Support from Meta-analytic Connectivity Modeling

Many of the nodes identified by MACM were not supported by our anatomical analyses. These regions were primarily within networks subserving emotion and cognition including the anterior cingulate (BA24/32), prefrontal regions (BA9/46), and insula (BA13). However, portions of the motor (i.e., precentral gyrus [BA6]) and perceptual (i.e., inferior parietal lobule [BA40]) networks were also noted as having polysynaptic influence. These results are supported by other studies noting functional connectivity of the striatum during the resting state (Di Martino, Scheres et al. 2008). Specifically, Di Martino and colleagues (2008)

demonstrated positive coherence between the ventromedial caudate and portions of the orbitofrontal cortex (BA10), dorsolateral prefrontal cortex (BA9), inferior frontal gyrus (BA47), and the anterior cingulate (BA32). Interestingly, they did not find positive coactivations with the parahippocampus or the posterior cingulate as we did. Furthermore, their connectivity analyses revealed negative correlations between the dorsal caudate and the posterior cingulate, portions of the occipital cortex, and the cerebellum. Another resting state study corroborated these negative correlations (Barnes, Cohen et al. 2010), suggesting that some regions identified by MACM, which only identifies regions of coactivation and not deactivations, may be task-dependent hubs, coming online to serve specific processes. Alternatively, it is possible that using different settings for ALE, or using the most refined version may yield these hubs (Eickhoff, Bzdok et al. 2011; Turkeltaub, Eickhoff et al. 2011).

### 4.3 Topographical Organization of the Human Caudate

Nonhuman primate research has suggested a specific organization of the caudate nucleus based on evidence from both anatomical and functional segmentation. For example, Levy and colleagues (1997) proposed a topographic segmentation derived from physiological and lesion studies (Divac, Rosvold et al. 1967; Rolls 1994), and subsequently demonstrated such organization using spatial and nonspatial working memory tasks. They found that a delayed spatial alternation task activated the head of the caudate, which is heavily innervated by dorsolateral prefrontal cortex efferent fibers in the nonhuman primate. Alternatively, a delayed object alternation task activated the body/tail of the caudate, innervated primarily by temporal cortex fibers. This topographic organization has been suggested in human studies (Lehericy, Ducros et al. 2004; Leh, Pfitter et al. 2007; Draganski, Kherif et al. 2008).

Using several predefined cortical targets, we used DTI to project where tracts from specific brain regions terminated within the caudate (Figure 5). We found support for a head/body topographical organization in which emotion and cognitive regions projected mostly to the head of the caudate, and action and perception regions projected close to the posterior portions of the caudate. For example, the prefrontal cortex ROI was largely projecting to the head of the caudate, while the occipital lobe tracts were mostly localized to the ventral body of the caudate.

Researchers have also proposed a slightly different topographical organization of the caudate, with 3 defined functional zones: associative striatum (head of caudate), sensorimotor striatum (dorsolateral rim of the caudate), and the limbic striatum (ventral caudate) (Selemon and Goldman-Rakic 1988; Parent and Hazrati 1995; Nakano, Kayahara et al. 2000; Postuma and Dagher 2006). This has been akin to a dorsal-ventral continuum with a spectrum ranging from cognitive (dorsal) to affective (ventral) control. With regard to these functional zones, we found strong ventral caudate connectivity to the hippocampus and amygdala (Figure 5, Panel H and Panel K, respectively) from our DTI analysis, supporting the concept of a 'limbic striatum'. Additionally, the temporal lobe demonstrated connectivity to the ventral portion of the caudate nucleus (Figure 5, Panel I). We also found some support for the sensorimotor striatum with caudate connectivity to the parietal and postcentral gyrus, both spanning the ventral and dorsal portions (Figure 5, Panel C and E, respectively). Similar connectivity profiles have been suggested. For example, Lehericy and colleagues (2004) found that tracking from 4 large cortical targets (motor, premotor, prefrontal, and orbitofrontal) yielded prefrontal connections projecting to the head of the caudate nucleus. Similarly, Leh and colleagues (2007) found connections with the dorsolateral prefrontal cortex and the dorsal-posterior caudate, as well as ventrolateral prefrontal cortex projections to the ventral-anterior portion of the caudate, while Draganski and colleagues (2008) found that the dorsolateral prefrontal cortex diffusely connected to the rostral and caudal components of the caudate. Our results parallel these findings, but with less specificity (i.e.,

ventral and dorsal prefrontal cortices) in comparison to previous studies because of our chosen cortical targets.

In comparison to the nonhuman primate literature, our results are highly concordant. The associative striatum primarily occupies the head of the caudate nucleus where it receives afferent connections from a variety of cortical areas. Area 46 projects to the head of the caudate nucleus, and Area 9 localizes to the intermediate part of the caudate nucleus, with projections denser ventrally in the nonhuman primate (Nakano 2000; Nakano, Kayahara et al. 2000). This is identical to what we demonstrate in the human (Figure 5, Panel A). The limbic striatum occupies the central portion of the caudate nucleus, much like in our study (Figure 5, Panel G, H, I, K) (Nakano 2000; Nakano, Kayahara et al. 2000).

#### 4.4. BrainMap Database and ALE

The BrainMap database has proven to be an invaluable tool for data mining and developing models of functional connectivity. Here, we have capitalized on the rigorous coding scheme outlined and validated in previous publications (Fox, Laird et al. 2005; Laird, Eickhoff et al. 2009; Laird, Eickhoff et al. 2011), and available at the BrainMap website (<http://www.brainmap.org/BrainMapLex.xls>). Our data support functional segregation of the human caudate. Results strengthen previous studies, which found high concordance of the database coding structure to known intrinsic and task-related networks (Laird, Eickhoff et al. 2009; Smith, Fox et al. 2009; Kurth, Zilles et al. 2010; Eickhoff, Bzdok et al. 2011; Laird, Fox et al. 2011).

We do note that there are limitations to the use of MACM, and ALE, to develop models of functional connectivity. First, results may be influenced by the user-specified criteria within the ALE program (i.e., false discovery rate, minimum cluster size), and by the thresholding of the initial ROIs used for the analysis. This latter point seems to have minimal effects, as noted in Robinson and colleagues (2010) study of the amygdala. There are also minor statistical disadvantages to the ALE algorithm used in the above analyses (i.e., within-group and within-experiment effects on ALE values, a potential underestimation of the right-tail of the null distribution of the random spatial association between experiments, and lack of family-wise error correction) (Eickhoff, Bzdok et al. 2011; Turkeltaub, Eickhoff et al. 2011). Most of these issues have been resolved with a refined ALE algorithm that is now available (Eickhoff, Bzdok et al. 2011). However, the selection and thresholding of target ROIs for inclusion in DTI analyses may have a more pronounced effect on the results, and thus should be rationally considered. To date, there is no guide for these type of analyses, and the selection and thresholding has varied across studies, with the majority using very large target ROIs, despite these targets having documented functional segmentations (Behrens, Johansen-Berg et al. 2003; Johansen-Berg, Behrens et al. 2004; Johansen-Berg, Behrens et al. 2005). We chose to break these large targets into smaller ROIs with probability maps associated to them. As more studies utilize this technique, we'll better understand what the differences that these subjective choices make on results.

#### 4.5. Conclusions

MACM results were consistent with previous studies examining coactivation patterns with the caudate (Blumberg, Stern et al. 2000; Postuma and Dagher 2006; Acheson, Robinson et al. 2009; Bluhm, Williamson et al. 2009). However, our study represents a more robust analysis allowing for the detection of an extensive functional connectivity network that has additional nodes not previously identified by individual studies. We also corroborate evidence supporting connectivity with regions such as the anterior cingulate which, when lesioned, has been shown to reduce the volume of the caudate nucleus (Rauch, Kim et al. 2000). Other MACM studies have consistently shown high coherence with the functional

neuroimaging literature as well (Robinson, Laird et al. 2010; Cauda, Cavanna et al. 2011). Furthermore, our structural and MACM analyses together demonstrate strong support for functional and anatomical segmentation of the caudate nucleus such that the head of the caudate corresponds closely to cognitive and emotional circuits, and the body or posterior portion of the caudate shows a strong link to action and perception related networks.

Finally, nonhuman primate models have dominated the literature for decades, and as such, have also evolved over the years. Alexander and colleagues (1986) proposed the existence of 5 parallel functional looping circuits, while others have proposed that the caudate is composed of 3 functional zones: associative striatum (head of caudate), sensorimotor striatum (dorsolateral rim of the caudate), and the limbic striatum (ventral caudate) (Selemon and Goldman-Rakic 1988; Parent and Hazrati 1995; Nakano, Kayahara et al. 2000; Postuma and Dagher 2006). Our data provide support for 3 of the 5 domain-specific circuits proposed by Alexander and colleagues (Alexander, DeLong et al. 1986). Specifically, the prefrontal, motor, and anterior cingulate circuits were identified in our data. The prefrontal looping circuit is evidenced by the present observations of cognition-specific regions of coactivation with the caudate; the motor loop is represented by identical cortical targets; and the anterior cingulate/limbic loop is similar to our emotion-specific circuit. In addition to support for these circuits, our data allow us to make additional observations. For example, our human-based cognition specific circuit was more expansive and included more medial regions than in the primate models (i.e., cingulate). Our emotion circuit contained distinct caudate coactivations in the amygdala and part of the hippocampus, in addition to the prefrontal region. In summary, MACM results shows strong support for existing primate models, while also providing additional insight into human-specific divergent circuitry.

The human caudate has been implicated in a variety of neurological and psychiatric disorders. Identifying a comprehensive model of functional connectivity may help elucidate the pathophysiological mechanisms underlying these disorders. Furthermore, our data demonstrate that using MACM in combination with DTI methodology may aid in parsing direct from indirect influences, which may ultimately strengthen models of disease. To our knowledge, this is the first study aimed at developing a robust model of the human caudate using MACM, and supplemented with DTI analyses. Future research should examine MACM based functional connectivity models using structural equation modeling (SEM) of healthy and diseased populations with known deficits in the given structure of interest. The use of MACM-derived models should provide improved initial models for SEM and other path analysis techniques. Thus, MACM provides a sturdy foundation for connectivity analyses that may ultimately lead to an improvement in our understanding of healthy cognition and disease pathology. Finally, MACM may be used to compare connectivity patterns that emerge in task-independent functional imaging (i.e., resting state fMRI), during which the default mode network is most robust, and task-dependent connectivity. Combined with the flexibility to identify behavioral domain specific networks, this could advance our understanding of how networks transition as they are recruited for neural processes.

In summary, our study provides additional evidence of the robust utility of MACM. In a recent study, Cauda and colleagues (2011) found high correlations between MACM and resting state fMRI data of the nucleus accumbens. Here, we have demonstrated similar consistency of MACM data with existing fMRI and PET studies of the caudate. Capitalizing on the organizational structure of the BrainMap database (Fox and Lancaster 2002; Fox, Laird et al. 2005; Laird, Lancaster et al. 2005; Laird, Eickhoff et al. 2009), we demonstrate an expanded effectiveness of MACM analyses to elucidate human neural networks specific to behavioral domains. Lastly, we illustrate that when coupled with DTI analysis, MACM can be paired with probabilistic tracking to begin to investigate indirect versus direct influences.

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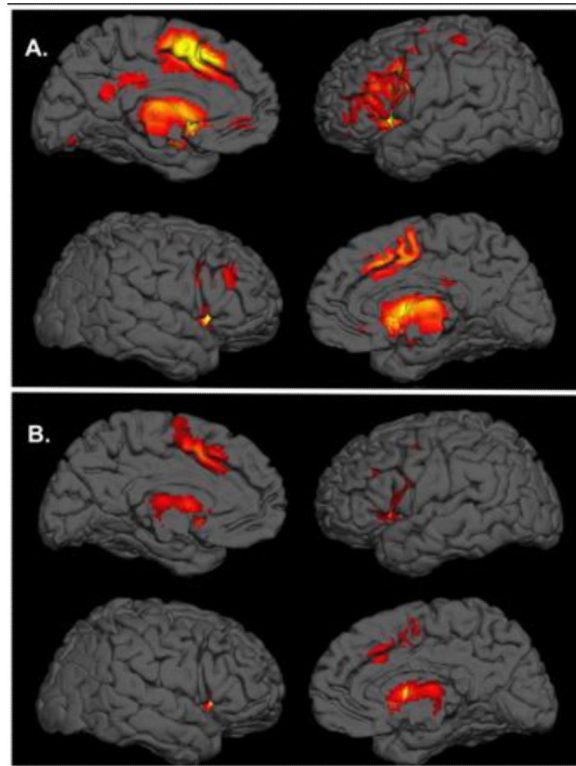
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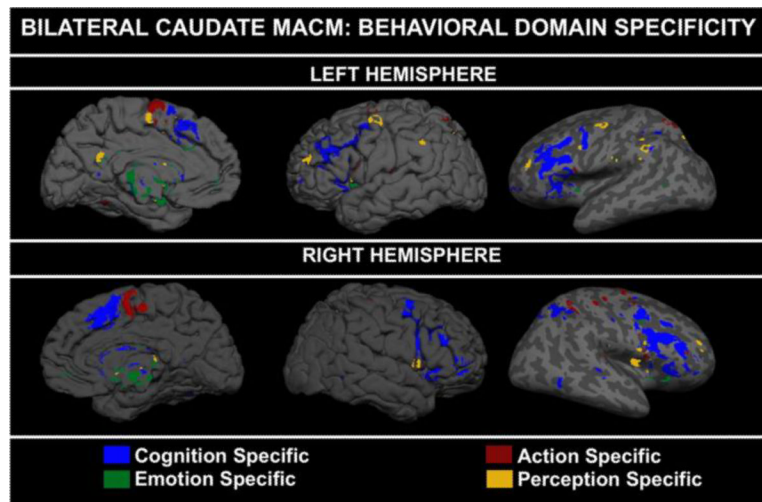


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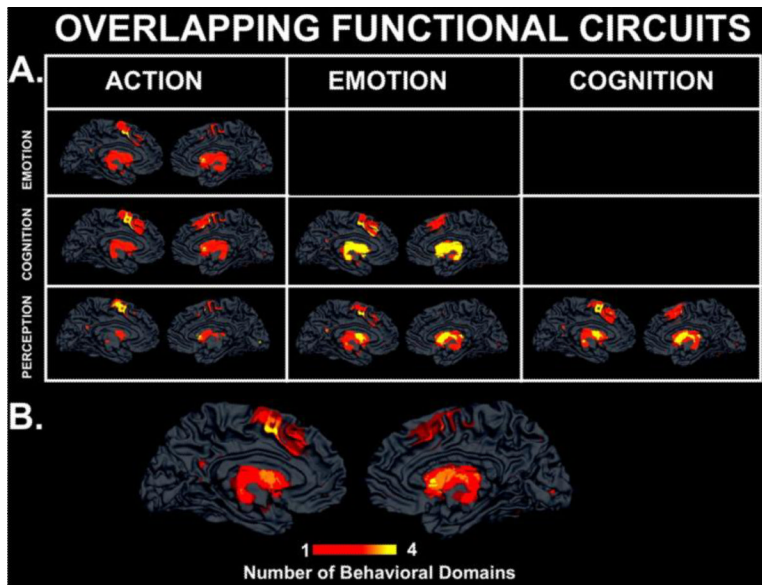
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**Figure 1.** Meta-analytic Connectivity Models of the Human Caudate. Functional connectivity maps of the left (A) and right (B) caudate nucleus.

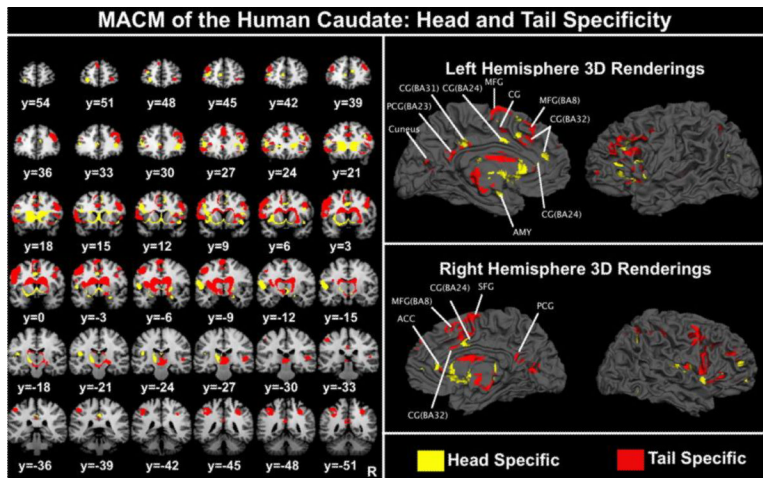


**Figure 2.** Behavioral domain specific functional connectivity. Maps were generated by binarizing a cumulative connectivity map and subtracting each binarized behavioral domain specific map from the cumulative map (with the exception of the behavioral domain of interest). For example, the cognitive-specific map was created by subtracting the emotion-specific, perception-specific, and action-specific maps from a binarized map of the four domains together.

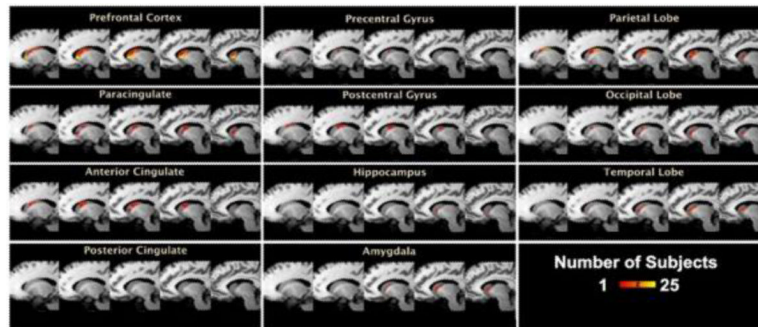


**Figure 3.** Behavioral Domain Connectivity Maps. *A.* MACM behavioral domain results demonstrating overlapping functional circuits across behavioral domains. Yellow indicates overlap, whereas red indicates only one of the two behavioral domains utilizes the region. *B.* Cumulative MACM behavioral domain map demonstrating the number of behavioral domains using each region. Dark red indicates a more specific node (i.e., only one behavioral domain mapped to the region) in the circuit, whereas yellow represents a less domain specific component of the circuit (i.e., all behavioral domain networks access the region). Interoception and pharmacology did not have enough papers entered into the database, and thus lacked power, to be included in these analyses.

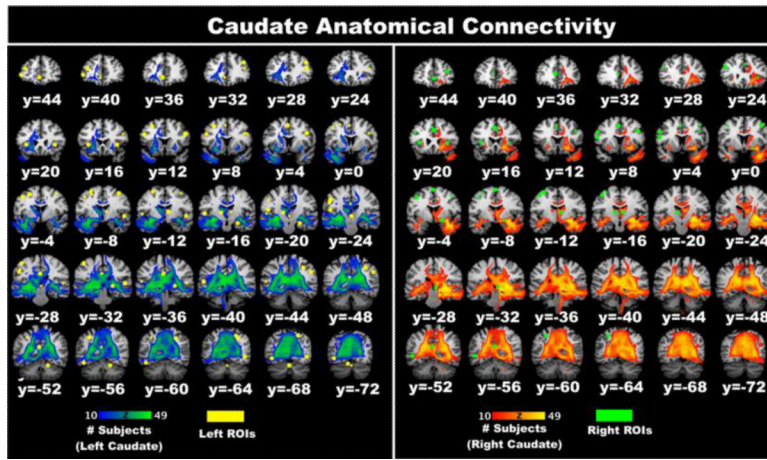




**Figure 4.** Differentiating Topographic Network Organization Using MACM. After manual segmentation based on previous research, functional connectivity differences were noted between the connectivity maps generated for the head (in yellow) and the body (in red) of the caudate.



**Figure 5.** DTI of the Human Caudate. For each cortical and subcortical target, we thresholded and binarized individual subject results to include only those caudate voxels with a connection probability  $> 10\%$ . These images were summed across subjects to generate a population map reflecting anatomical caudate segmentation. Slices shown from left to right are  $x=-15$ ,  $-13$ ,  $-11$ ,  $-9$ , and  $-7$ .



**Figure 6.** MACM and DTI Convergence and Divergence. Cumulative DTI connectivity distributions with right caudate ALE cluster foci in solid green, and tracts red-yellow. Left caudate tracts are in blue-green with solid yellow representing the left caudate MACM foci. Several foci did not have anatomical support as indicated by a lack of tractography to the foci node.

Table 1

ALE meta-analyses on the right and left caudate demonstrated overlapping regions of functional connectivity (top portion of table) as well as spatially distinct differences as determined by a qualitative label and coordinate based review. Results were thresholded at the  $p < 0.001$  level.

Lobe	Region	BA	Clusters Shared for Both Left and Right Caudate Connectivity Analyses							
			Left Caudate Connectivity			Right Caudate Connectivity				
			ALE	x	y	z	ALE	x	y	z
Frontal	Left Middle Frontal Gyrus	6	0.107	-26	-10	56	0.064	-38	-4	44
			0.081	-28	10	46				
			0.106	-40	-4	44	0.045	-30	-12	56
Limbic	Left Precentral Gyrus	9	0.163	-46	10	28	0.065	-50	6	30
	Right Inferior Frontal Gyrus		0.109	42	4	30	0.056	42	8	32
Limbic	Left Posterior Cingulate	23	0.085	-2	-52	20	0.049	-2	-54	20
	Left Anterior Cingulate	32	0.082	-2	46	-2	0.038	-4	36	12
Sub-lobar	Left Insula	13	0.237	-32	18	4	0.151	-32	18	6
			0.077	-46	-22	14				
	Right Insula		0.211	34	18	4	0.160	32	20	4
	Left Caudate	Caudate Head	0.358	-10	8	4	0.197	-12	8	4
	Left Thalamus	Medial Dorsal Nucleus	0.215	-12	-18	8	0.134	-10	-18	10
	Right Thalamus	Medial Dorsal Nucleus	0.168	10	-12	10	0.111	8	-14	10
Hemisphere Specific Clusters Based on Visual Comparison										
Anterior	Right Dentate	Dentate	0.104	18	-54	-22				
Frontal	Left Middle Frontal Gyrus	10	0.087	-34	42	18				
		6	0.100	-24	-4	50				
Limbic	Right Middle Frontal Gyrus	9	0.092	40	30	32				
		46	0.105	42	28	18				
	Left Inferior Frontal Gyrus	46	0.070	-44	42	4				
	Right Inferior Frontal Gyrus	9	0.106	48	12	28				
	Right Precentral Gyrus	6	0.087	38	-8	52				
	Left Superior Frontal Gyrus	6	0.218	-2	4	48				
Limbic	Left Cingulate Gyrus	23	0.090	0	-28	28				
		31	0.086	-2	-36	28				

Clusters Shared for Both Left and Right Caudate Connectivity Analyses												
Lobe	Region	BA	Left Caudate Connectivity			Right Caudate Connectivity			ALE	x	y	z
			ALE	x	y	z	ALE	x				
	Left Anterior Cingulate	24	0.082	-4	36	-2						
	Right Parahippocampal Gyrus	27	0.074	24	-34	0						
		Hippocampus	0.075	26	-18	-16						
Midbrain	Right Midbrain	Red Nucleus	0.106	2	-24	0						
Occipital	Left Lingual Gyrus		0.073	-6	-80	2						
		17	0.078	-18	-86	0						
	Left Inferior Occipital Gyrus	19	0.073	-38	-70	-6						
	Right Inferior Temporal Gyrus	37	0.082	42	-66	-2						
Parietal	Left Postcentral Gyrus	2	0.104	-42	-30	52						
		2	0.074	-48	-26	32						
		2	0.072	-46	-24	38						
	Left Inferior Parietal Lobule	7	0.147	-30	-56	42						
	Right Inferior Parietal Lobule	40	0.114	34	-46	42						
	Right Supramarginal Gyrus	40	0.083	52	-46	32						
	Right Superior Parietal Lobule	7	0.086	22	-66	46						
Posterior	Left Declive	7	0.085	26	-62	40						
		*	0.083	-6	-74	-18						
	Right Declive of Vermis	*	0.072	2	-68	-22						
Sub-lobar	Right Caudate	Caudate Head	0.260	10	8	2						
Temporal	Left Superior Temporal Gyrus	22	0.084	-50	-16	6						
		22	0.095	50	-10	0						
		22	0.092	-52	-40	10						
	Right Superior Temporal Gyrus	22	0.086	52	-32	6						
	Left Fusiform Gyrus	37	0.120	-42	-58	-16						
Frontal	Left Middle Frontal Gyrus	9	0.057	-42	24	28						
	Right Middle Frontal Gyrus	6	0.055	42	0	46						
		10	0.052	32	46	18						
	Left Superior Frontal Gyrus	10	0.039	-26	52	-2						



Lobe	Region	BA	Clusters Shared for Both Left and Right Caudate Connectivity Analyses							
			Left Caudate Connectivity			Right Caudate Connectivity				
			ALE	x	y	z	ALE	x	y	z
	Left Medial Frontal Gyrus	6	0.062	0	-6	62	0.062	0	-6	62
	Left Precentral Gyrus	32	0.113	-2	8	44	0.113	-2	8	44
	Left Inferior Frontal Gyrus	4	0.039	-40	-14	50	0.039	-40	-14	50
	Left Inferior Frontal Gyrus	44	0.081	-50	6	18	0.081	-50	6	18
	Right Cingulate Gyrus	32	0.101	2	20	34	0.101	2	20	34
Limbic	Right Anterior Cingulate	32	0.046	2	46	2	0.046	2	46	2
	Left Cingulate Gyrus	32	0.104	-2	16	40	0.104	-2	16	40
Parietal	Left Superior Parietal Lobule	7	0.066	-26	-62	44	0.066	-26	-62	44
Sub-lobar	Right Caudate	Caudate Body	0.322	12	8	8	0.322	12	8	8
	Right Lentiform Nucleus	Lateral Globus Pallidus	0.041	20	-4	-8	0.041	20	-4	-8
	Right Thalamus	Pulvinar	0.047	6	-30	2	0.047	6	-30	2
Temporal	Left Middle Temporal Gyrus	37	0.046	-48	-54	-2	0.046	-48	-54	-2

Table 2

Regions that demonstrated functional connectivity to the caudate within only one behavioral domain.

Action Specific Clusters					
Lobe	x	y	z	Description	BA
Anterior	4	-58	-18	Right Culmen	
	-16	-58	-20	Left Dentate	
	18	-52	-22	Right Dentate	
Frontal	-52	-14	40	Left Postcentral Gyrus	4
	0	-4	56	Left Medial Frontal Gyrus	6
	-40	26	26	Left Middle Frontal Gyrus	9
	48	6	16	Right Inferior Frontal Gyrus	44
Parietal	-48	-26	28	Left Postcentral Gyrus	2
	-34	-28	50	Left Postcentral Gyrus	3
	-20	-66	46	Left Precuneus	7
	-14	-76	36		7
Temporal	-40	-30	16	Left Superior Temporal Gyrus	41
	48	-26	18	Right Superior Temporal Gyrus	41
	-58	-30	12	Left Superior Temporal Gyrus	42
	60	-20	12	Right Superior Temporal Gyrus	42
Sub-lobar	24	-2	6	Right Putamen	
	10	-14	-2	Right Subthalamic Nucleus	
	-14	-20	6	Left Thalamus (Ventral Posterior Medial Nucleus)	
Cognition Specific Clusters					
Frontal	-48	8	26	Left Inferior Frontal Gyrus	9
	-2	10	46	Left Medial Frontal Gyrus	32
	-44	24	22	Left Middle Frontal Gyrus	46
	-44	42	0	Left Inferior Frontal Gyrus	
Limbic	0	-50	22	Left Posterior Cingulate	30

Action Specific Clusters					
Lobe	x	y	z	Description	BA
	22	-16	-10	Right Parahippocampal Gyrus	35
	0	46	0	Right Anterior Cingulate	
Parietal	-36	-46	36	Left Supramarginal Gyrus	40
Posterior	-38	-58	-16	Left Declive	
	-56	-26	2	Left Superior Temporal Gyrus	22
	50	-28	4	Right Superior Temporal Gyrus	
Temporal	54	-16	2		22
	-50	-54	-6	Left Inferior Temporal Gyrus	37
Sub-lobar	-4	-16	-8	Left Red Nucleus	
Emotion Specific Clusters					
	-44	22	16	Left Inferior Frontal Gyrus	45
Frontal	-44	30	6	Left Inferior Frontal Gyrus	46
	42	28	12	Right Inferior Frontal Gyrus	46
	0	-52	22	Left Posterior Cingulate	23
	0	2	46	Left Cingulate Gyrus	24
	-24	-26	-6	Left Parahippocampal Gyrus	28
Limbic	-2	-36	28	Left Cingulate Gyrus	31
	-2	48	-2	Left Anterior Cingulate	32
	-12	40	-2	Left Anterior Cingulate	
	22	-4	-10	Right Amygdala	
Sub-lobar	-30	20	2	Left Claustrum	
	-2	-14	-6	Left Mammillary Body	
Perception Specific Clusters					
	-4	8	48	Left Superior Frontal Gyrus	6
Frontal	2	-2	58	Right Medial Frontal Gyrus	6
	-56	6	6	Left Precentral Gyrus	44

Action Specific Clusters					
Lobe	x	y	z	Description	BA
	-46	4	18	Left Inferior Frontal Gyrus	44
	10	-74	40	Right Precuneus	7
	-52	-22	16	Left Postcentral Gyrus	40
Parietal	54	-24	22	Right Postcentral Gyrus	40
	-56	-10	16	Left Postcentral Gyrus	43
Posterior	0	-70	-24	Left Tuber of Vermis	
Temporal	-46	-52	4	Left Middle Temporal Gyrus	37
Sub-lobar	-22	-4	-8	Left Lateral Globus Pallidus	
	10	-14	12	Right Thalamus (Medial Dorsal Nucleus)	

**Table 3**

Bilateral caudate ROIs were seeded in each behavioral domain of the BrainMap database to search for regions of coactivation, thus determining behavioral-domain specific functional connectivity. ALE meta-analyses were performed and resultant maps demonstrated overlapping regions of functional connectivity among some brain regions, while others were specific to one behavioral domain (Table 2).

Caudate Functional Connectivity: Shared Clusters Across Behavioral Domains														
Lobe	Action			Cognition			Emotion			Perception			Description	BA
	x	y	z	x	y	z	x	y	z	x	y	z		
Frontal	-36	-4	46	-30	-4	56				-26	-10	56	Left Middle Frontal Gyms	6
	-50	2	30	-42	-2	44								
	-26	-12	56										Left Precentral Gyrus	6
	24	-14	50							38	2	30		
	38	-10	52							38	-10	52	Right Precentral Gyrus	6
	24	-8	62							26	-8	60		
	32	-8	44										Right Middle Frontal Gyrus	6
	38	0	44											
	40	32	32	42	32	32	32	34	28	40	32	32		
	44	8	32	44	8	32							Right Middle Frontal Gyrus	9
Limbic	34	30	30											
	32	54	6										Right Middle Frontal Gyrus	10
	36	46	18							34	46	18		
	42	30	12	46	22	22							Right Middle Frontal Gyrus	10
	-46	20	2	-46	18	2							Left Inferior Frontal Gyrus	46
	-2	20	42	0	22	38							Left Cingulate Gyrus	47
	-30	-60	46	-30	-58	42				-32	-60	46		
										-24	-64	48	Left Superior Parietal Lobule	7
	24	-66	52							24	-66	54	Right Superior Parietal Lobule	7
	-40	-34	42	-56	-42	26								
Parietal	-34	-44	44										Left Inferior Parietal Lobule	40
	34	-42	40	34	-48	38				34	-46	40		
	52	-46	32							52	-46	32	Right Inferior Parietal Lobule	40



Caudate Functional Connectivity: Shared Clusters Across Behavioral Domains																	
Lobe	Action			Cognition			Emotion			Perception			Description	BA			
	x	y	z	x	y	z	x	y	z	x	y	z					
Occipital	-12	-84	-2										-12	-84	-4	Left Lingual Gyrus	18
	-46	10	6			-40	14	16								Left Insula	13
	-30	20	6	-32	20	6	-38	-6	14	-34	14	6					
	48	12	6	32	20	4	38	18	2	34	18	4				Right Insula	13
										46	-24	16					
										48	12	6					
	14	12	8													Left Caudate Body	
	-14	0	14							-14	0	16					
Sub-lobar	12	12	10														
	12	2	10							12	0	16				Right Caudate Body	
	14	-6	18														
				-12	8	4	-10	6	2							Left Caudate Head	
				10	8	4	10	8	2							Right Caudate Head	
				6	-20	-6				2	-22	-4				Right Red Nucleus	
				-8	-18	10	-6	-16	12	-10	-16	8				Left Thalamus (Medial Dorsal Nucleus)	
	12	-12	14	10	-30	0										Right Thalamus	
							2	-28	2	16	-28	6				Right Thalamus (Pulvinar)	