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Individual Differences in Impulsivity and Mesocorticolimbic Connectivity Strength in Pre-adolescence

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Abstract

Individual differences in pre-adolescent impulsivity, or the preference for smaller immediate rewards over larger delayed rewards, has been related to a multitude of outcomes measured later in life, such as physical and psychological health, substance dependence, financial well-being, academic achievement, social adjustment, and criminal behaviour. The mesocorticolimbic dopamine pathway (MCLP), a neural circuitry involved in reward motivated behaviours and decision-making, has been extensively linked to the delay discounting task, an effective tool for quantifying trait impulsivity. While previous research has demonstrated a negative correlation between the structural connectivity strength of the right dorsolateral prefrontal tract and the functional activity of striatum throughout development, the differences in tract strength within the MCLP and the relation to interindividual differences in impulsive behaviour in pre-adolescence has been understudied. The current study hypothesized that MCLP white fiber tract strength is related to interindividual differences of trait impulsivity in participants aged 9 to 12 years old. A probabilistic tractography approach, where every seed region voxel is sampled 1000 times for streamlines to the target of interest, was used to assess tract connectivity in a 58 X 58 whole-brain matrix. After correcting for multiple comparisons, the results demonstrated no significant correlations between white matter connectivity and individual differences in the delay discounting task. Given the small sample size and univariate approach, this large scale analysis was not sufficiently powered to detect any relationship between white matter and impulsivity. Future studies should apply further steps, such as correction for susceptibility induced distortions, to the constructed pipeline and investigate white matter differences with a variety of tensor metrics, such as fractional anisotropy and mean diffusivity.

Keywords: impulsivity, structural connectivity, DTI, pre-adolescence

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Impulsivity is a multidimensional construct that includes three components: acting without thinking, impatience, and sensation/novelty seeking (Wheelan et al., 2012). Importantly, each of these components have been shown to influence one's ability to make decisions and are independently associated with self-reported risky behaviour, such as substance use and gambling (Reynolds & Fields, 2012; Reynolds, 2006). Using the delay discounting task, an effective behavioural tool for quantifying impatience, previous research has linked the preference for small immediate rewards over larger delayed rewards to decreased academic success, substance abuse, and attention deficit hyperactivity disorder (ADHD) (Duckworth & Seligman, 2005; Madden, Petry, Badger & Bickel, 1997; Barkely, Edwards, Laneri, Fletcher & Metevia, 2001).

The ability to exhibit impulse control, or select for actions that lead to larger delayed rewards over smaller immediate rewards, is variable throughout development and between individuals (Steinberg et al., 2009; Peters & Büchel, 2011). As demonstrated by the seminal Stanford Marshmallow Experiment, where children aged 3-6 were offered a choice between one immediate marshmallow or two delayed marshmallows, individual differences in the ability to delay gratification take root early in life (Mischel, Ebbesen & Zeiss, 1972). Interestingly, studies have shown that these early life differences in impulsivity predict a number of outcomes later in life (Schlam, Wilson, Shoda, Mischel & Ayduk, 2013; Shoda et al., 1990). For example, one longitudinal study done by Moffit et al. (2011) followed 1000 children for 32 years after birth and discovered that impulse control measured in childhood predicted physical and psychological health, substance dependence, financial well-being, academic achievement, social adjustment, and criminal behaviour measured later in life. Thus, individual differences in impulsivity have a

predictive value; the ability to withhold from taking a small immediate reward is related to a multitude of positive outcomes later in life.

Similar to the delay discounting task, decisions that are arise throughout life, such as attending post-secondary education, exercising, starting a retirement savings account or investing your money, often require the evaluation of options that are associated with varying outcomes at different points in the future. The mesocorticolimbic dopamine pathway (MCLP), a neural circuitry involved in decision making and reward-motivated behaviours, has been consistently shown to be recruited during delay discounting (Peters & Büchel, 2011). Specifically, neuroimaging studies have demonstrated the role of two networks within the circuitry: a ventral valuation network and dorsal control network. The valuation network, which is involved in placing a subjective incentive value on the different options, includes ventral striatum (VS), amygdala, and ventromedial prefrontal cortex. The control network, which plays a role in cognitive control and inhibiting prepotent responses, includes the dorsal striatum, dorsal anterior cingulate cortex (dACC), dorsal and ventral lateral prefrontal cortex (dlPFC/vlPFC), and the posterior parietal cortex (van den Bos & McClure, 2013; Figner et al., 2010; Peters & Büchel, 2011).

Using functional magnetic resonance imaging (fMRI), a study by McClure et al. (2004) reported that VS activity was significantly higher when subjects chose a smaller, immediate reward when compared to a larger, delayed reward. Additionally, another study by Hariri et al. (2006) demonstrated that adults who exhibited the strongest preference for immediate over delayed rewards, also showed the largest magnitude of VS activation. Collectively, these two studies provided evidence that VS activity is tightly coupled with immediate reward preferences, and that the magnitude of VS activity also covaries with individual differences. Recently, a study

by van den Bos et al. (2015) used diffusion tensor imaging (DTI) to establish changes in MCLP structural connectivity throughout development. The researchers identified that greater medial striatum-right dlPFC tract strength from adolescence to adulthood was associated with less impulsive behaviour on the delay discounting task. Using fMRI, the same study showed an increase in negative functional coupling between activity in the right dlPFC and medial striatum when delaying gratification. Overall, these results suggest that the dlPFC tract strength is involved in dampening the striatum's response to immediate rewards throughout development, and that structural integrity within the MCLP can be used to predict one's ability to display impulse control.

However, an important distinction should be made between factors that drive developmental changes and those that influence interindividual differences, as they may not be equivalent. Although the current literature has demonstrated an association between MCLP functional/structural connectivity and impulsive behaviour from adolescence to adulthood, what makes individuals unique in terms of preference for rewards has been understudied. Specifically, individual differences in MCLP tract strength during pre-adolescence, an age where differences in the ability to delay gratification holds strong predictive value over outcomes later in life, requires further research. The current study will attempt to identify interindividual differences in impulse control that pre-adolescence exhibit through a delay discounting task, and the relationship with white matter fiber tract strength in the MCLP.

Based on recent findings that showed frontostriatal tracts predict decreased delay discounting whereas subcorcticostriatal tracts predict increased delay discounting in adults (van den Bos, Rodriguez, Schweitzer & McClure, 2014), the current study hypothesizes that individual differences in impulsivity are associated with MCLP structural connectivity strength

in pre-adolescence. Specifically, we predict that increased structural connectivity between the dlPFC and ventral striatum is negatively correlated with impulsive behaviour, or steeper discounting rates. To address these questions, we employed the delay discounting task in children aged 9-12, and acquired DTI scans to determine the MCLP's white matter integrity. By using a probabilistic tractography analysis, a procedure where each seed region voxel is repeatedly labeled according to the target structure of interest, a probability measure can be computed to assess tract connectivity between the regions of interest.

Methods

Participants

Twenty-eight healthy and typically-developing children between the ages of 9 and 12 years (mean age ± SD = 10.2 ± 1.1 years, 14 females) were recruited from a London research database. All participants were right handed and reported no developmental, neurological or psychiatric disorder at the time of the study. Informed written consent and verbal assent was obtained from the children and guardians before behavioural and MRI data collection. The study consisted of two separate sessions, and participants were compensated with a $25 CAD gift card following each session. All aspects of the study were conducted in accordance with the Declaration of Helinski and approved by the ethics committee at Western University.

Delay Discounting

In the first session, the Delay Discounting task (DD) was used to measure impulsivity through the construct of impatience (Fishburn & Rubinstein, 1982). Across 88 separate trials, participants were asked to choose between a small immediate reward or a larger delayed reward. The value of the immediate reward varied between $0 and $20 in increments of $1, and the delayed award was fixed at $20 with the delay period set to either 7, 30, 90, or 180 days. Every

unique combination of immediate reward value and delay period was presented in a randomized order. Indifference points, where the participant transitions from choosing the immediate reward to choosing the delayed reward, were estimated using a logistic regression method and used to model participant choices. By fitting these points to a hyperbolic discounting function, we were then able to determine how steeply participants discounted the value of future rewards:

$$V = A/(1+kD),$$

where V is the indifference point, A is the amount in dollars of the delayed reward, and D is the delay period in days. Impulsive behaviours, or preference for immediate over delayed rewards, are modeled by larger values of the discounting parameter (-log k).

MRI Data Acquisition

In session one, the children were also exposed to a mock scanner that simulated an MRI environment to minimize fear and discomfort during the actual neuroimaging procedure. In session two, images were obtained using a 3-Tesla Siemens Magnetom Prisma Fit scanner and a Siemens Prisma 32-channel head coil. For every participant, two scans of whole-brain diffusion-weighted images (55 slices of 2mm thickness; TR= 6300 ms; TE= 75 ms; FOV=179 x 140 x 110 mm; voxel size = 2.1 x 2.1 x 2.0 mm; 96 x 96 in-plane matrix) were acquired in an interleaved order using an echo-planar imaging (EPI) pulse sequence. Both scans were phase encoded from anterior to posterior. Images were acquired using 64 diffusion directions with a b-value of 700s/mm^2. A reference image with no diffusion weighting (b= 0 s/mm^2) was also acquired. The DTI acquisition time was approximately 7 min for each scan. We also collected a high-resolution T1-weighted anatomical image using a 3D MPRAGE pulse sequence (176 slices; voxel size = 1 mm^3; 256 × 256 matrix). The entire MRI procedure took approximately 1 hour to complete.

DTI Preprocessing

Visual inspection of every participant's two DTI scans was completed in FSLview and 4 participants that had 8 or more volumes of uncorrectable artifacts were excluded from the study. For every participant, the DTI scan with the least amount of noise was included for analysis. Eddy current correction from the FMRIB diffusion toolbox (FDT v3.0, www.fmrib.ox.ac.uk/fsl/fdt) in FSL was used to correct the DTI data for head motion and eddy currents (Smith et al., 2004; Woolrich et al., 2009). The brain extraction tool (BET) was used to strip and exclude the skull from the analysis (Behrens et al., 2003).

DTI Analysis: Probabilistic Tractography

BEDPOSTX (FDT v3.0) processing on the diffusion-weighted images of every participant was completed in order to obtain an estimation of diffusion parameters and model crossing fibres within each voxel of the brain (Behrens, Berg, Jbabdi, Rushworth & Woolrich, 2007). The output from BEDPOSTX was used to run PROBTRACKX, a function that samples 1000 iterations from every voxel within the seed region, each time computing a streamline through these local samples to generate a probabilistic streamline to the target. The resulting number of successful streamlines to the target was averaged across every seed mask voxel to provide a single streamline value. This averaged count was then divided by the total number of iterations to determine a probabilistic value that was used to assess tract connectivity between the two regions:

$$C = SS/I$$

where C is the tract connectivity, SS is the number of successful streamlines averaged across all seed voxels, and I is the total number of streamline iterations.

Regions of Interest (ROI)

For the hypothesis driven portion of the study, two striatal seed masks including the executive and limbic labelled sub-regions were obtained from the Oxford-Imanova Striatal Connectivity Atlas (7 sub-regions). The executive labelled sub-region includes both the dorsal and ventral striatum, whereas the limbic labelled sub-region includes only the ventral striatum. Seventeen MCLP target masks including areas encoding the right and left dlPFC and vmPFC were obtained from Yeo et al.'s (2011) functional connectivity parcellations.

To examine whole-brain structural connectivity, all 51 parcellations from Yeo et al. (2011) and all 7 striatal masks were used to create a 58 X 58 connectivity matrix. Every region was both treated as a seed to initiate streamlines, and as a target for whole-brain analysis. All ROIs were obtained in MNI space and transformed to each participant's native diffusion-weighted space before probabilistic tractography analysis using FLIRT, a linear registration tool in FSL (Jenkinson et al., 2002).

Structural Connectivity and Behavioural Analysis

A total of 34 Pearson correlations were calculated between structural connectivity values of the MCLP and delay discounting scores. For the whole brain approach, a total of 3364 Pearson correlations were computed between the 58 X 58 connectivity matrix and delay discounting scores to investigate possible unidentified regions involved in impulsive behaviour. Since a higher delay discounting score (–log(k)) reflects less impulsive behaviour, positive correlations between DD scores and structural connectivity values indicates an inverse relationship. A False Discovery Rate (FDR) analysis was computed on all p-values to correct for multiple comparisons.

Results

Initially, results demonstrated that connectivity from the ventral striatum to the right cingulate cortex is negatively correlated with delay discounting scores ($r(28) = -0.433$, $p < 0.05$; Figure 1). However, after correction for multiple comparisons using FDR, the results revealed that structural connectivity within the MCLP is not significantly correlated with delay discounting scores across individuals ($q > 0.05$). Tract connectivity measures from executive and limbic striatal regions to 17 cortical targets, including the dorsolateral PFC, ventral PFC, orbitofrontal cortex (OFC), and cingulate cortex (CC), was not able to predict impulsive behaviour.

Our exploratory analysis on whole-brain structural connectivity profiles and delay discounting behaviour revealed a pattern of positive correlations (Figure 2). Interestingly, connectivity from various striatal seeds to frontal regions in the left hemisphere was shown to positively correlate with delay discounting scores ($r(28) = 0.422$, $p < 0.05$), indicating an inverse relationship with impulsivity. However, after correction for multiple comparisons using FDR, not a single correlation from 58 X 58 matrix was significant ($q > 0.05$).

Discussion

Despite our hypothesis that individual differences in impulsivity would be associated with MCLP structural connectivity in pre-adolescence, we did not find any significant results (Figure 1). Variability in ventral and dorsal striatal connections to 17 unique MCLP targets (including the dlPFC, vPFC, OFC, CC) was not significantly related to delay discounting scores after a False Discovery Rate analysis. Before this correction, there was a negative correlation between the ventral striatum's connection with the cingulate cortex and delay discounting scores ($r(28) = -0.433$, $p < 0.05$), suggesting that increased connection predicts increased impulsivity.

However, this result is not in line with previous studies which have implicated the dACC as a part of a cognitive control network that inhibits prepotent responses (van den Bos & McClure, 2013; Figner et al., 2010; Peters & Büchel, 2011). Given the current model, increased structural connectivity between the ventral striatum and cingulate cortex should predict strengthened impulse control rather than more impulsive behaviour. Nonetheless, our opposing results did not survive correction for multiple testing ($q > 0.05$), which was necessary to assess for false positives given the high number of comparisons (34 tests).

The exploratory approach to assess for differences in whole-brain connectivity and delay discounting scores also did not yield any significant results after correcting for multiple comparisons (3364 tests; $q > 0.05$). Before the correction, the 58 X 58 whole-brain connectivity matrix displayed patterns of positive correlations between frontostriatal tracts and the delay discounting task. This aligns with the current framework that the PFC is somehow involved in dampening the ventral striatum's activation during reward-related decision making (van den Bos et al., 2015). Although an individual with increased structural integrity between these two regions may display greater impulse control, our results cannot be fully interpreted beyond chance alone.

With every comparison we computed between MCLP structural connectivity and delay discounting, the risk of finding false positives increased, and our sample size was not large enough to power the analysis. Due to this loss of power, any relationship between structural connectivity and impulsivity was not able to be detected. Initially, our study recruited and scanned 44 participants, however uncorrectable imaging artifacts, registration distortions and uninterpretable behavioural data, resulted in the exclusion of 18 participants (N= 28).

Uncorrectable imaging artifacts resulting from excessive head motion while in the scanner is a common problem to overcome when working with a pediatric sample. Even small amplitude micro-movements of the head from one data frame to the next lead to systematic distortions in quantitative MRI analyses, including functional and structural approaches (Power et al., 2011; Van Dijk, Sabuncu & Buckner, 2012; Yendiki, Koldewyn, Kakunoori, Kanwishe & Fischl, 2013). During our MR imaging procedure, the children watched a film, which has been shown to decrease head motion (Vanderwal, Kelly, Eilbott, Mayes, & Castellanos, 2015), and we corrected for head motion within our pre-processing pipeline, however not all distortions could be resolved. A recent study by Greene et al. (2018) described behavioural interventions that could be used to reduce head motion in pediatric populations. The researchers reported that real-time head motion feedback decreases motion during MRI scans in young children. They also demonstrated that movies, but not feedback, significantly alters functional connectivity MRI data. Given the diminished sample size after excluding participants for excessive imaging artifacts, future research on various behavioural interventions to reduce head motion in a pediatric sample could be beneficial.

Additionally, the two scans taken for every participant were phase encoded in the same direction, meaning that we were unable to estimate and correct for susceptibility induced distortions. These distortions are caused by off-zero resonance fields and only effect the diffusion image, causing a geometric mismatch with the anatomical image which cannot be corrected with FLIRT registration (Andersson, Skare & Ashburner, 2003). Regions that are adjacent to bone-air interfaces, including the frontal lobes, temporal poles and brain stem, are most likely to become warped due to differing magnetic susceptibility (Treiber et al., 2016). Given the importance to correct for these distortions when assessing white matter changes in the

frontal cortex, our inability to apply topup in FSL could have negatively impacted our assessment of structural connectivity in the MCLP.

Pediatric brains are different in size and shape from adult brains and continue to develop throughout childhood. Previous studies on pediatric populations have identified several advantages of using age-matched standardized templates over adult templates during pre-processing of MR images (Wilke, Holland, Altaye & Gaser, 2008; Carmen, Sanchez, Richards & Almli, 2013; Wilke, Schmithorst, & Holland, 2003). A study by Wilke, Schmithorst, and Holland (2002) assessed 148 healthy children aged 5-18 years with both a standard adult and custom pediatric template and reported a strong age-effect of lateral deformation in all dimensions. The researchers also reported that non-linear deformations show localized correlations with age, and are most pronounced in parietal and frontal areas. On the other hand, registration of MR images to custom pediatric templates significantly decreased the total amount of volume change. In the current study, our pediatric population was not matched with age-specific templates, increasing the amount of distortions created during registration. As these distortions have been shown to localize to the frontal areas, the strength of our analysis on MCLP connectivity could have been effected.

Furthermore, the current study only assessed white matter changes via probabilistic tractography. Although this fiber tracking algorithm is more sensitive to uncertainty and can more reliably reconstruct crossing fibers than deterministic tractography (Behrans et al., 2003; Behrens, Berg, Jbabdi, Rushworth & Woolrich, 2003), it still only provides a single measure of white matter integrity. This univariate approach further underpowered our analysis, and made it difficult to detect whether impulsivity is related to other structural changes in the MCLP. Previous white matter studies have employed multi-variate approaches for assessing structural

changes in the brain, including measures such as fractional anisotropy, and radial, axial and mean diffusivity (Alexander, Lee, Lazar & Field, 2007; Cortez-Conradis et al., 2013).

Future directions should focus on methods to better power the thousands of tests which we ran, including increasing the sample size and testing a multi-variate approach. As discussed, future DTI studies on a pediatric population could implement behavioural interventions for reducing head movement, topup to correct for susceptibility induced distortions, and age-matched templates for better registration. Additionally, a multi-variate approach could assess white matter differences using a number of different tensor metrics to investigate how impulsivity relates with other parameters of connectivity. Although the current study did not find any significant results in terms of MCLP connectivity strength and individual differences in impulsive behaviour, the work done to construct and implement a pre-processing and analysis pipeline will be very beneficial for future studies in the lab.

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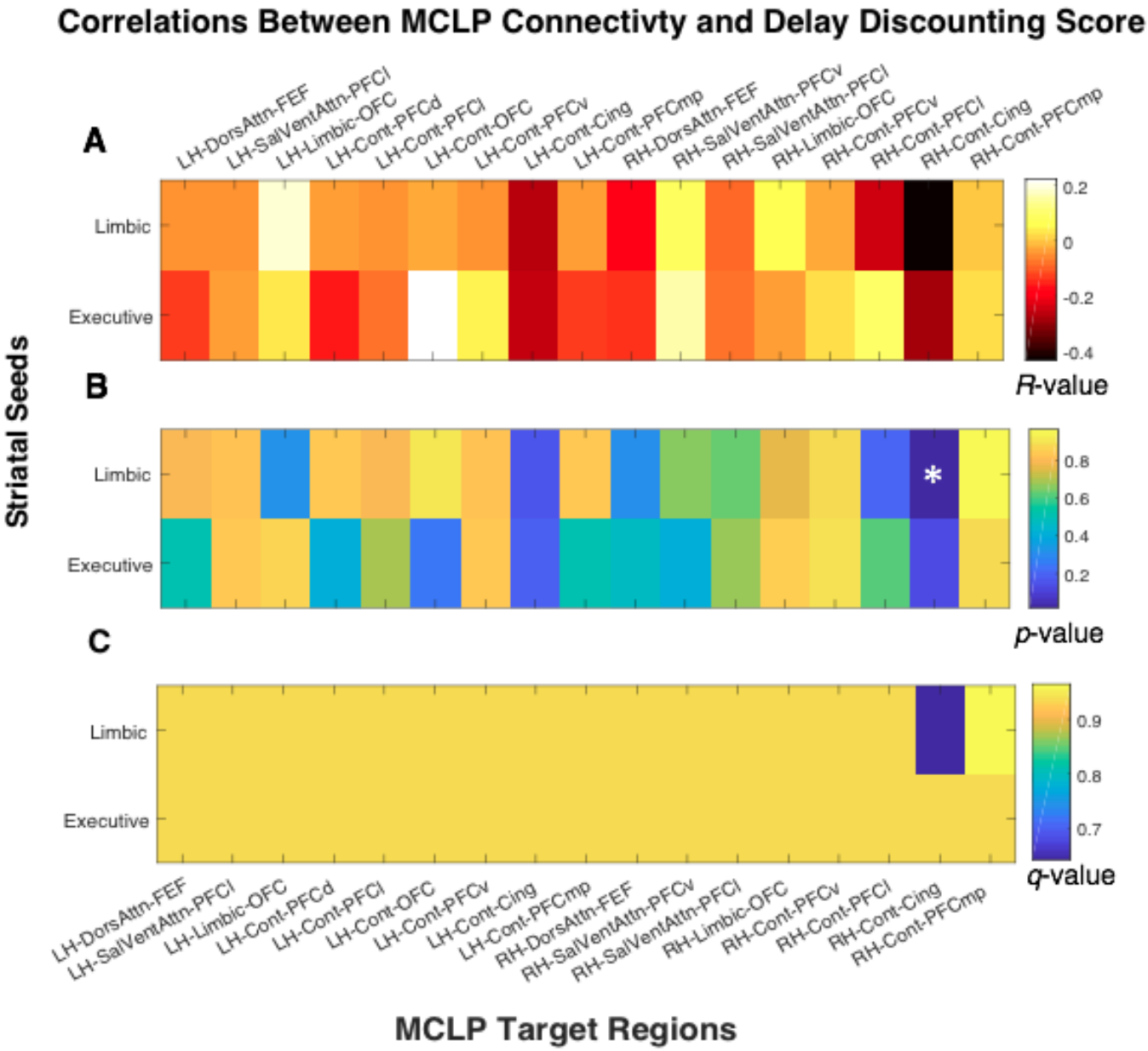

Figure 1. Pearson correlations between frontostriatal white matter connectivity and delay discounting scores (-log *k*) in pre-adolescent individuals. Limbic seed regions correspond to ventral portions of the striatum and executive seed regions correspond to ventral and dorsal portions of the striatum. A) Negative *R*-values reflect a positive relationship between connectivity strength and impulsivity, whereas positive values reflect a negative relationship. B) Analysis of *p*-values demonstrated a significant negative correlation between structural connectivity from the ventral striatum to the right cingulate cortex and delay discounting ($r(28) = -0.433$, $*p < 0.05$). C) However, after an FDR analysis to correct for multiple comparisons, the

adjusted *q*-values revealed that the identified correlation was not significant ($q > 0.05$). LH= left hemisphere; RH= right hemisphere; DorsAttn= dorsal attention system; SalVentAttn= ventral attention; Cont= frontoparietal control; FEF= frontal eye fields; PFCl= lateral prefrontal cortex; OFC= orbital frontal cortex; Cing= cingulate cortex; PFC= prefrontal cortex; p, posterior; l, lateral; m, medial; d, dorsal; v, ventral.

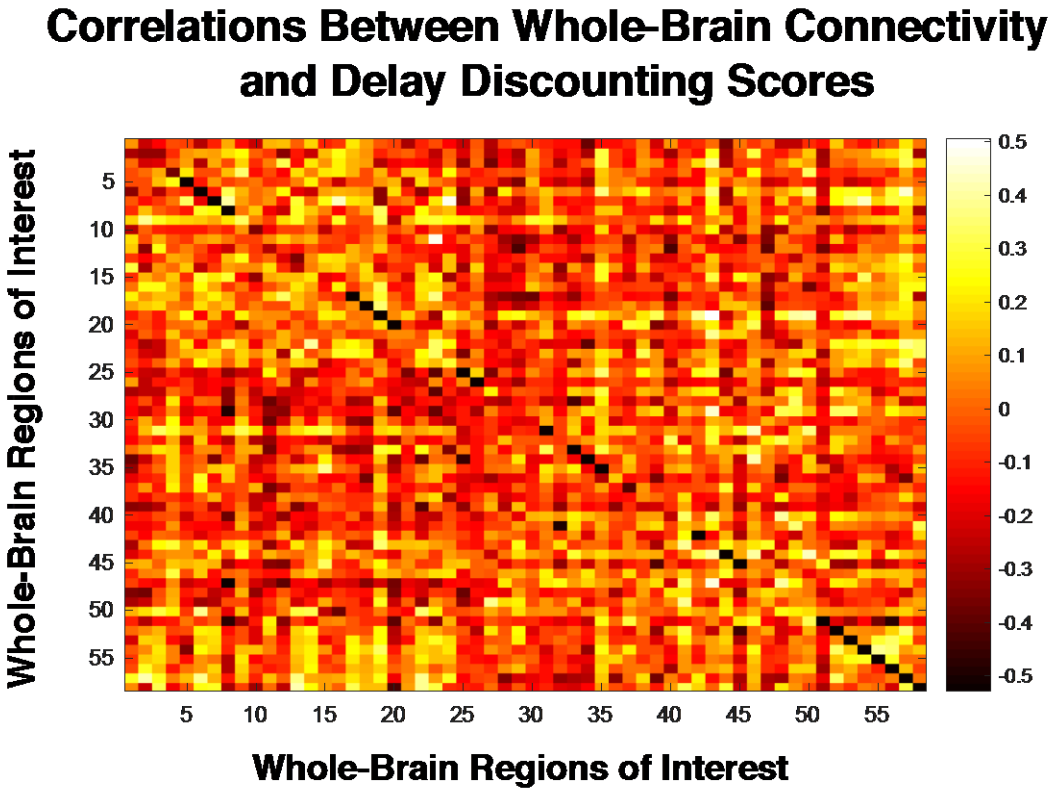

Figure 2. Pearson correlations between a whole-brain cross-connectivity matrix and delay discounting scores (-log *k*) in pre-adolescent individuals. Regions of interest (ROIs) labelled from 1 to 51 are 7-network functional parcellations from Yeo et al. (2011). ROIs labelled from 52 to 58 include striatal regions from the Oxford-Imanova Striatal Connectivity Atlas. Negative *R*-values reflect a positive relationship between connectivity strength and impulsivity, whereas positive values reflect a negative relationship. After an FDR analysis to correct for multiple comparisons, the adjusted *q*-values revealed that the identified correlations were not significant ($q > 0.05$).