



## Structure-function coupling within the reward network in preschool children predicts executive functioning in later childhood

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### ABSTRACT

Early differences in reward behavior have been linked to executive functioning development. The nucleus accumbens (NAc) and orbitofrontal cortex (OFC) are activated by reward-related tasks and identified as key nodes of the brain circuit that underlie reward processing. We aimed to investigate the relation between NAc-OFC structural and functional connectivity in preschool children, as well as associations with future reward sensitivity and executive function. We showed that NAc-OFC structural and functional connectivity were not significantly associated in preschool children, but both independently predicted sensitivity to reward in males in a left-lateralized manner. Moreover, significant NAc-OFC structure-function coupling was only found in individuals who performed poorly on executive function tasks in later childhood, but not in the middle- and high-performing groups. As structure-function coupling is proposed to measure functional specialization, this finding suggests premature functional specialization within the reward network, which may impede dynamic communication with other regions, affects executive function development. Our study also highlights the utility of multimodal imaging data integration when studying the effects of reward network functional flexibility in the preschool age, a critical period in brain and executive function development.

### 1. Introduction

Reward processing depicts how individuals use reinforcement-related perceptions to guide goal-directed behaviors (Halachakoon et al., 2020) and it includes reward anticipation, response, and learning from reward information (Hélie et al., 2017; Novick et al., 2018). Reward processing is closely linked to executive functioning (Kohls et al., 2009; Lertladaluck et al., 2020; Qu et al., 2013; Tarullo et al., 2018) and is thought to be a core component of cognition with inputs to

other cognitive functions (Hélie et al., 2017). For instance, Walsh et al. (2019) found that reward sensitivity helps to attenuate the effects of irrelevant distracting information and facilitate attentional engagement, a crucial element of executive function. Variations in reward behavior may also predict future outcomes for neurodevelopment and psychopathologies featuring executive dysfunction (Belden et al., 2016; Kamkar et al., 2017; van Hulst et al., 2017). Dysregulation of the reward and executive control networks have been reported to underlie psychopathologies such as substance abuse (Weissman et al., 2015), internet

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gaming disorders (Dong et al., 2015) and depression (Zhang et al., 2021). Despite the converging evidence demonstrating the close link between reward processing and executive functioning, the effect of reward network connectivity on the future development of executive function skills is not well understood. While some studies suggested that reward-related networks mature before executive networks and that reward processing affects future executive function (Karlsgodt et al., 2015), other studies have shown that executive function moderates reward processing (Kryza-Lacombe et al., 2021).

Several brain regions are consistently activated during reward-related tasks and are collectively termed the ‘reward network’. This network is a complex system integrating limbic and cortical signaling (Corlett et al., 2004; Elliott et al., 2003; Knutson et al., 2001; Schultz et al., 2000; Tanaka et al., 2004) with two key nodes - the nucleus accumbens (NAc) and the orbitofrontal cortex (OFC; Brodmann areas 10, 11, 47) (Kringelbach, 2005). The NAc mediates goal-directed behavior by integrating hippocampus-dependent contextual information and amygdala-dependent affective information with PFC-dependent executive control (Grace, 2000; Mogenson et al., 1980). Dopaminergic innervation from the ventral tegmental area (VTA) of the midbrain selectively shifts the balance between limbic and PFC synaptic inputs in the NAc and mediates executive functions required for goal-directed behavior (Goto and Grace, 2005). Thus, the NAc is linked to multiple dimensions of reward behavior and is involved in global reward processing. The accumbens tract, a white matter pathway that connects the NAc and OFC, is linked to reward processing and observed to influence risky decision-making under stress (Chahal et al., 2021; Karlsgodt et al., 2015; Kringelbach, 2005; Park et al., 2021; Uy and Galván, 2020). In addition, abnormalities in NAc-OFC functional connectivity have been associated with reward and motivation-related dysfunction in addiction and depression literature (Bracht et al., 2021; Höfflich et al., 2019).

Recent literature focuses on structure-function (SC-FC) coupling as a method of incorporating information from both structural (microstructure) and functional connectivity (macro level function). Functional connectivity is postulated to require the presence of structural connectivity, where the white matter architecture of the brain imparts a distinct signature on neuronal coactivation patterns. SC-FC coupling is derived from correlating structural connectivity and functional connectivity measures, and occurs when inter-regional white matter connectivity predicts the strength of inter-regional functional connectivity. Thus, a higher degree of SC-FC coupling has been interpreted as a higher degree of functional specialization, while a lower degree of SC-FC coupling has been interpreted as a higher degree of functional flexibility (Baum et al., 2020). For example, functional networks that mature early (e.g., motor network) have high structure-function coupling; networks with protracted development (e.g., salience network, default mode network) have been shown to have lower structure-function coupling (Vázquez-Rodríguez et al., 2019). There is strong literature support for protracted maturation of the reward network (Achterberg et al., 2016; Barnea-Goraly et al., 2005; Lebel et al., 2012; Simmonds et al., 2014), where shifting functional dynamics (e.g., heightened striatal functional activation in adolescents compared to children and adults, reconfiguration of subcortical-cortical connections) (Betzel et al., 2014; Fareri et al., 2015; Gee et al., 2013; Menon, 2013; Swartz et al., 2014; Van Leijenhorst et al., 2010) and pronounced structural connectivity changes (e.g., accumbens tract fractional anisotropy peaks in mid-adolescence before decreasing rapidly) (Karlsgodt et al., 2015) are observed into adulthood (Casey et al., 2019; Murty et al., 2016). In addition, several studies have reported associations between SC-FC coupling and performance in executive function tasks, especially in transmodal cognitive networks (Baum et al., 2020; Reijmer et al., 2015). A higher degree of SC-FC decoupling was also observed in elderly patients with cognitive impairment compared to healthy controls (Wang et al., 2018).

A better understanding of the relations between reward network

variations in preschool years and future reward behavior as well as executive functioning is crucial as this will open windows of opportunity for effective preventive intervention within this critical window of heightened neuroplasticity. Our current study addressed this knowledge gap using MRI-derived reward network measures collected during preschool age and measures of reward sensitivity and executive function collected between ages 6–8.5 years. Three MRI-derived reward network measures used in our study include NAc-OFC structural connectivity (SC = accumbens tract streamline density), NAc-OFC functional connectivity (FC = NAc-OFC BOLD time-series correlation), and SC-FC coupling (correlation between NAc-OFC structural and functional connectivity). We first investigated whether (1) NAc-OFC structural connectivity was associated with functional connectivity at preschool age in each hemisphere, i.e. whether functional connectivity is tethered to structural connectivity within the reward network in preschool children. Next, we explored (2) the relation between NAc-OFC connectivity measures and future reward sensitivity. One key question was whether structural and functional connectivity both independently contributed to reward sensitivity or had overlapping effects. While sex differences in reward processing are well documented (Rand et al., 2016; Soutschek et al., 2017), most studies have focused on adolescents and adults (Braams et al., 2015; Cardoos et al., 2017; Forbes et al., 2010; Laube et al., 2017; Op de Macks et al., 2011). Therefore, we also explored if sex differences in reward processing were observed in children. Finally, we investigated (3) the relation between NAc-OFC connectivity measures and future executive function. We were particularly interested in studying whether SC-FC coupling, a proxy for functional network specialization, affects the development of executive function. Thus, we looked at executive function task performance in later childhood (age 7 and 8.5 years).

We hypothesized that: (1) NAc-OFC structural connectivity would not be significantly associated with NAc-OFC functional connectivity in preschool years, as functional flexibility and neuroplasticity are expected in this age group, (2) NAc-OFC structural and functional connectivity measures would be significantly associated with sensitivity to reward and (3) lower degree of functional specialization within the reward network (low SC-FC coupling) will facilitate functional flexibility, resulting in high performance in executive functioning tasks at later time points.

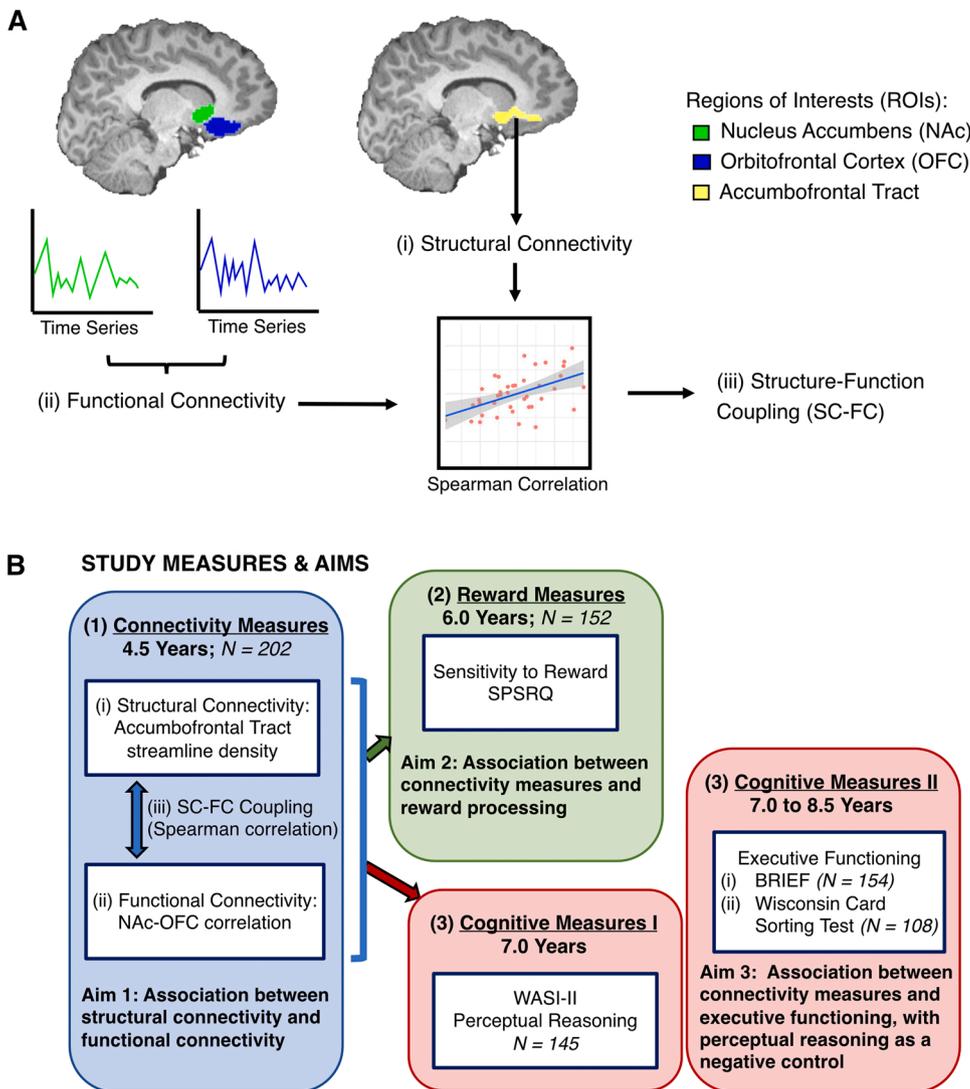
## 2. Methodology

### 2.1. Participants

Participants were recruited from Growing Up in Singapore Towards Healthy Outcomes (GUSTO), a large longitudinal, Singaporean birth cohort study. The GUSTO study was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB) and the Singapore Health Centralized Institutional Review Board (CIRB). Structural and functional neuroimaging data (Fig. 1A) was collected from 202 individuals of both sexes at age 4.5 years. Written consent was obtained from all guardians on behalf of the children enrolled in this study. Baseline characteristics of study participants are delineated in Table 1 (‘Neuroimaging Dataset’). Demographics were compared with all individuals with complete data for reward processing and executive functioning measures (Table 1, ‘Behavioral Dataset’), and no significant demographic differences were observed between the two datasets. Sample size for each analysis is summarized in Fig. 1B.

### 2.2. MRI acquisition

Subjects at age 4.5 years underwent magnetic resonance imaging (MRI) of the brain utilizing a 3-Tesla scanner (Magnetom Skyra; Siemens, Germany). Diffusion-weighted images (DTI) were acquired using a single-shot echo planar imaging (EPI) sequence with sensitivity encoding parallel imaging scheme; SENSE reduction factor = 3, matrix



**Fig. 1.** Study design. (A) Structural (i) and functional connectivity (ii) ROIs, specifically the nucleus accumbens (green), orbito-frontal cortex (blue), and accumbofrontal tract (yellow). Structure-function coupling (iii) was derived from correlating structural and functional connectivity. (B) Study data was collected at different time points (age 4.5 years to 8.5 years). Three connectivity measures (blue) were collected – structural connectivity, functional connectivity, and structure-function coupling. Subject numbers (N) represent the number of subjects who have complete data for both neuroimaging measures and the specified task/questionnaire. BRIEF, Behavior Rating Inventory for Executive Function; SPSRQ, Sensitivity to Punishment and Sensitivity to Reward Questionnaire; WASI-II, Wechsler Abbreviated Scale of Intelligence – Second Edition; SC-FC Coupling, Spearman correlation between structural connectivity and functional connectivity.

size =  $96 \times 96$ , field of view =  $192 \times 192 \text{ mm}^2$ , slice thickness = 2 mm, repetition time = 8200 ms, echo time = 85 ms, flip angle =  $90^\circ$ , 30 non-collinear directions, b value =  $1000 \text{ s/mm}^2$ . 3D T1-weighted MPRAGE images were acquired with the following imaging parameters: repetition time = 2000 ms, echo time = 2.08 ms, field of view =  $192 \times 192 \text{ mm}^2$ , matrix size =  $192 \times 192$ , slice thickness = 1 mm. Resting-state functional MRI (rsfMRI) images were acquired with a gradient-echo planar imaging sequence sensitive to blood oxygenation level-dependent (BOLD) contrast. One run of rsfMRI was collected: 5.32 min (120 time points), repetition time = 2660 ms, echo time = 27 ms, flip angle =  $90^\circ$ , 3 mm isotropic voxels, matrix =  $64 \times 64$ , field of view = 64, 48 interleaved axial slices with no gap.

### 2.3. Construction of NAc-OFC structural connectivity

DTI datasets were analyzed using tools implemented in FMRIB's Software Library (FSL, v6.0) (Smith et al., 2004). To prepare for eddy processing, b0-images were skull stripped using the brain extraction tool to generate a mask that excludes non-brain tissues. Each subject's diffusion-weighted images were registered to their respective non-diffusion-weighted (b=0) image to correct for spatial distortion due to eddy currents and subject motion (Andersson and Sotiropoulos, 2016), with outlier replacement. The outlier correction utilized a

Gaussian process to replace the outlier slice using predictions based on undistorted data (Andersson et al., 2016) and a threshold of 3 standard deviations was set to detect outlier slices.

Within-voxel probability density functions of the principal diffusion direction were estimated using Markov Chain Monte Carlo sampling in FSL's BEDPOSTX tool (Behrens et al., 2007). A spatial probability density function was then estimated across voxels based on these local probability density functions using FSL's PROBTRACKX tool (Behrens et al., 2003), in which 5000 samples were taken for each input voxel with a 0.2 curvature threshold, 0.5-mm step length, and 2000 steps per sample. Seed masks, waypoints, termination and exclusion masks were defined on the MNI152 T1 1 mm template. For the accumbofrontal tract (Fig. 1A), exclusion masks were defined as the Harvard-Oxford superior frontal gyrus, midline bisecting the hemispheres and regions posterior to the ventral striatum, and the seed masks were predefined ROIs of the bilateral accumbens areas and orbitofrontal cortex, similar to the methodology described by Karlsgodt et al. (Karlsgodt et al., 2015). Masks were normalized to each subjects' diffusion space using FSL's Linear and Non-Linear Image Registration Tool (Jenkinson and Smith, 2001) applying the affine parameters obtained by coregistering the first b0 volume to the MNI152 T1 1 mm template. The resulting tracts were thresholded at 0.5% and visually inspected to confirm successful tracing in each individual subject. The relative streamline probabilities between the NAc and OFC were calculated for each subject.

**Table 1**  
Summary of demographic characteristics of the neuroimaging dataset compared to the behavioral dataset.

Characteristic	GUSTO participants				
	Neuroimaging dataset (n = 202)		Behavioral dataset (n = 452)		Group comparison p (test stat)
	Mean	SD	Mean	SD	
Age at scan (years)	4.59	0.09	–	–	–
Gender (% male)	46.5	–	51.1	–	0.611(0.259)
<b>Ethnicity:</b>					
Chinese (%)	46.5	–	56.4	–	0.364(2.019)
Malay (%)	36.1	–	30.1	–	
Indian (%)	17.3	–	13.3	–	
Gestational Age (weeks)	38.7	1.3	38.7	1.6	0.767(0.297)
Maternal age at birth (years)	30.8	5.2	31.2	5.1	0.283(1.073)
<b>Highest maternal education:</b>					
Primary (%)	7	–	4.2	–	0.290(2.476)
Secondary/Technical (%)	45.5	–	37.7	–	
GCE 'A' Levels/University (%)	47.5	–	58.0	–	
<b>Household monthly income, SGD:</b>					
< 2000 (%)	23.4	–	13.8	–	0.0562(5.76)
2000–5999 (%)	58.5	–	55.6	–	
≥ 6000 (%)	18.1	–	30.6	–	
fMRI excluded outliers (count)	17.5	16.3	–	–	–
fMRI mean motion (mm)	0.15	0.088	–	–	–
DTI motion (mm)	1.7	1.6	–	–	–

Maternal education and household income information were obtained at birth of subject. Two-sample t-tests were used to assess group differences for continuous variables;  $\chi^2$  test was used to assess group differences for categorical variables.

#### 2.4. Construction of NAC-OFC functional connectivity

Pre-processing was performed using the CONN toolbox version 20b with the default pre-processing pipeline (Whitfield-Gabrieli and Nieto-Castanon, 2012). Briefly, scans underwent realignment with SPM12 realign & unwarp procedure (Andersson et al., 2001), where all scans were coregistered and resampled to the first scan using b-spline interpolation. Temporal misalignment between different slices of the functional data were corrected using SPM12 slice-timing correction (STC) procedure (Henson et al., 1999), where the functional data is time-shifted and resampled using sinc-interpolation to match the time in the middle of each acquisition time. Scan volumes with framewise displacement above 0.9 mm or global BOLD signal changes above 5 standard deviations were identified as potential outliers. Framewise displacement was computed at each timepoint by estimating the largest displacement among six control points placed at the center of a defined bounding box. Global BOLD signal change was calculated as the change in average BOLD signal within SPM's global-mean mask scaled to standard deviation units at each timepoint. Functional and anatomical data were normalized into standard MNI space and segmented into grey matter, white matter, and CSF tissue classes using SPM12 unified segmentation and normalization procedure (Ashburner and Friston, 2005). Both functional and anatomical data were resampled using 4<sup>th</sup> order spline interpolation. Functional data was smoothed using spatial convolution with a Gaussian kernel of 6 mm full width half maximum (FWHM), and the first four scans excluded to allow for magnetic field saturation. For denoising, BOLD signal variance over time explained by nuisance variables was removed from the data using Ordinary Least Squares regression. Noise components include identified outliers, motion parameters, and mean white matter and CSF signal (Power et al., 2012). Next, BOLD time series were band-pass filtered to preserve only frequencies between 0.008 and 0.09 Hz (Biswal et al., 1995; Fox and Raichle, 2007). Finally, an ROI-to-ROI analysis was performed, using subject-specific masks for NAC and OFC (derived from Harvard-Oxford

atlas, Fig. 1A). NAC-OFC functional connectivity was computed by measuring the Fisher-transformed bivariate correlation coefficients of the BOLD time series between the NAC and OFC through a hemodynamic response factor-weighted general linear model. To maximize power in our analysis, subjects were not excluded from further analysis based on motion parameters. Instead, motion parameters were controlled for in statistical analysis (Section 2.6), and a sensitivity analysis was conducted in subsets of participants who passed motion criteria for both functional and/or structural connectivity to determine if motion changed the main findings (Supplement S6 and S7).

#### 2.5. Cognitive and behavioral measures

##### 2.5.1. Sensitivity to reward (SPSRQ-C)

Sensitivity to reward was assessed at age 6 years with the Sensitivity to Punishment and Sensitivity to Reward Questionnaire for children (SPSRQ-C) (O'Connor et al., 2004). The questionnaire was rated by parents and contained 33 items divided into a Punishment Sensitivity scale (15 items), and a Reward Sensitivity scale (18 items) (see Supplement S2). Each item is scored on a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree) (Luman et al., 2012). Scores from the Reward Sensitivity subscale were used for subsequent analysis.

##### 2.5.2. Executive function (BRIEF-2)

Executive functioning was assessed at age 7 years using the Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2) Parent Form. The BRIEF-2 consists of 10 clinical scales; (1) Inhibit, (2) Self-Monitor, (3) Shift, (4) Emotional Control, (5) Initiate, (6) Task Completion, (7) Working Memory, (8) Plan/Organize, (9) Task-Monitor and (10) Organization of Materials. Higher scores on BRIEF-2 are associated with poorer executive functioning (Sherman and Brooks, 2010; Skogan et al., 2016). The BRIEF-2 Global Executive Composite (GEC) scores were used for subsequent analysis.

##### 2.5.3. Perceptual reasoning (WASI-II)

The Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II) was administered at age 7 years. WASI-II is a lab-based measure of intelligence quotient (IQ) with test items parallel to the corresponding subtests in the comprehensive Wechsler scale providing a measure of performance IQ. Block design and matrix reasoning subtests from the Perceptual Reasoning Index (PRI) Scale were used in our current study. Composite scores for perceptual reasoning were computed and used for analysis (Oswald et al., 2016; Wechsler, 2011). The PRI is a measure of fluid reasoning, spatial processing, attentiveness to detail and visual-motor integration. The block design subtest is designed to measure the ability to analyze and synthesize abstract visual stimuli. It also involves non-verbal concept formation and reasoning, broad visual intelligence, fluid intelligence, visual perception and organization, simultaneous processing, visual-motor coordination, learning and the ability to separate figure-ground in visual stimuli. The matrix reasoning subtest taps fluid intelligence, broad visual intelligence, classification and spatial ability, knowledge of part-whole relationships, simultaneous processing, and perceptual organization.

##### 2.5.4. Cognitive flexibility (WCST)

The Wisconsin Card Sorting Test (WCST) is a lab-based measure of set-shifting/cognitive flexibility administered at age 8.5 years. The task involves participants matching a response card to one of four stimulus cards according to one of three rules – number, color, shape. The task consists of 64 trials, and the rule changes after 10 correct responses without informing the participants. For the current study, the outcome variable was completed categories (number of times 10 correct responses in a row were made, reflecting overall success) (Heaton et al., 1993; Landry and Mitchell, 2021).

## 2.6. Statistical analysis

All statistical analyses were performed in R (v4.04).

### 2.6.1. Linear regression

Linear regression was used to model the relation between (i) functional (outcome) and structural connectivity (predictor) of the NAc-OFC; (ii) reward sensitivity (outcome) and NAc-OFC structural and functional connectivity (predictors); (iii) composite executive functioning (outcome) and NAc-OFC structural and functional connectivity (predictors). Sex was included as a covariate for all models, and regression analyses were repeated in males and females if sex had a significant effect on outcome. For models with connectivity measures, each hemisphere was assessed independently, and fMRI motion parameters (number of outliers, mean max motion, mean motion), and DTI parameters (DTI motion, NAc and OFC volumes) were included as covariates of no interest.

### 2.6.2. Correlation analysis deriving SC-FC coupling

Partial correlation between NAc-OFC structural and functional connectivity was calculated as a proxy for group-level SC-FC coupling using the spearman method (Baum et al., 2020) with the Ppcor package (Kim, 2015). Sex, fMRI motion parameters (number of outliers, mean max motion, mean motion), DTI motion parameters, volume of NAc and OFC were included as covariates of no interest. To investigate the potential role of NAc-OFC SC-FC coupling at 4.5 years of age on reward behavior (age 6 years) and cognitive outcomes at later time points (age 7–8.5 years), scores from both questionnaire-based (BRIEF-2, SPSRQ-C) and lab-based (WCST, WASI-II) assessments were divided into three groups – low (1st quartile), average (2nd and 3rd quartiles), and high (4th quartile) (Supplement S3). SC-FC coupling at 4.5 years of age was compared across the 3 groups for SPSRQ-C, BRIEF-2, WCST and WASI-II. WASI-II was included as a measure of general intelligence, to assess if our findings were specific to executive function. A significant positive correlation between NAc-OFC structural and functional connectivity is indicative of strong coupling, an index of poor functional flexibility.

## 3. Results

### 3.1. Association between NAc-OFC structural and functional connectivity

NAc-OFC structural connectivity (indexed by streamline density) was not significantly associated with NAc-OFC functional connectivity (indexed by Pearson correlation of BOLD signal between the two nodes) at 4.5 years of age for either cerebral hemisphere (Right:  $\beta = -0.0118$ , SE = 0.0208,  $t = -0.567$ ,  $p = 0.5714$ ; Left:  $\beta = 0.0122$ , SE = 0.0188,  $t = 0.653$ ,  $p = 0.515$ ; Supplement S4A).

### 3.2. Relation between NAc-OFC connectivity and sensitivity to reward

The relation between NAc-OFC connectivity and reward sensitivity was assessed in two ways: (i) regression models with structural (accumbosfrontal tract streamline density) and functional connectivity (NAc-OFC BOLD time-series correlation) measures; (ii) group-level comparison of SC-FC coupling.

Linear regression analyses revealed that sex was a significant predictor of sensitivity to reward ( $\beta = -3.171$ ,  $p = 0.009$ ; Table 2), where reward sensitivity was lower in males. We then conducted follow-up analyses where regression analyses were repeated separately for males and females. Left NAc-OFC structural and functional connectivity had a significant association with sensitivity to reward at age 6 years in males but not in females (Table 2). The full regression models are specified in Supplement S4B.

SC-FC coupling was not significant for sensitivity to reward (Fig. 2;  $p > 0.2$ ; Supplement S3 for group scores).

**Table 2**

Summary of structural and functional connectivity estimates from regression models predicting sensitivity to reward.

Reward	Predictor	Estimate	Std. Error	t value	Pr (>  t )
Full dataset N = 152	rOFCxrNAc	-0.0498	3.0300	-0.0164	0.9869
	lOFCxlNAc	-4.3190	3.0775	-1.4034	0.1627
	sc_NAcOFC_r	0.4888	0.8797	0.5557	0.5793
	sc_NAcOFC_l	0.5141	0.8049	0.6388	0.5240
	sexMale	<b>-3.1715</b>	<b>1.2042</b>	<b>-2.6337</b>	<b>0.0094</b>
Males only N = 67	rOFCxrNAc	-2.5230	4.4837	-0.5627	0.5759
	lOFCxlNAc	<b>-10.2887</b>	<b>4.3034</b>	<b>-2.3908</b>	<b>0.0203</b>
	sc_NAcOFC_r	-1.6722	1.5113	-1.1064	0.2734
	sc_NAcOFC_l	<b>2.9631</b>	<b>1.2479</b>	<b>2.3746</b>	<b>0.0211</b>
	rOFCxrNAc	2.1157	4.1286	0.5125	0.6099
Females only N = 85	lOFCxlNAc	0.6100	4.5029	0.1355	0.8926
	sc_NAcOFC_r	1.8232	1.0860	1.6788	0.0975
	sc_NAcOFC_l	-0.8940	1.1096	-0.8056	0.4231

### 3.3. Relation between NAc-OFC connectivity and later executive function

The relation between NAc-OFC connectivity and executive function was assessed in two ways: (i) regression models with connectivity measures; (ii) group-level comparison of SC-FC coupling.

There was no association between structural and functional connectivity measures in either hemisphere and executive functioning (BRIEF-2 GEC scores;  $p > 0.5$ ; Supplement S4C). Sex was not a significant covariate ( $p = 0.646$ ). The BRIEF-2 was chosen as an outcome as it measures general executive functioning.

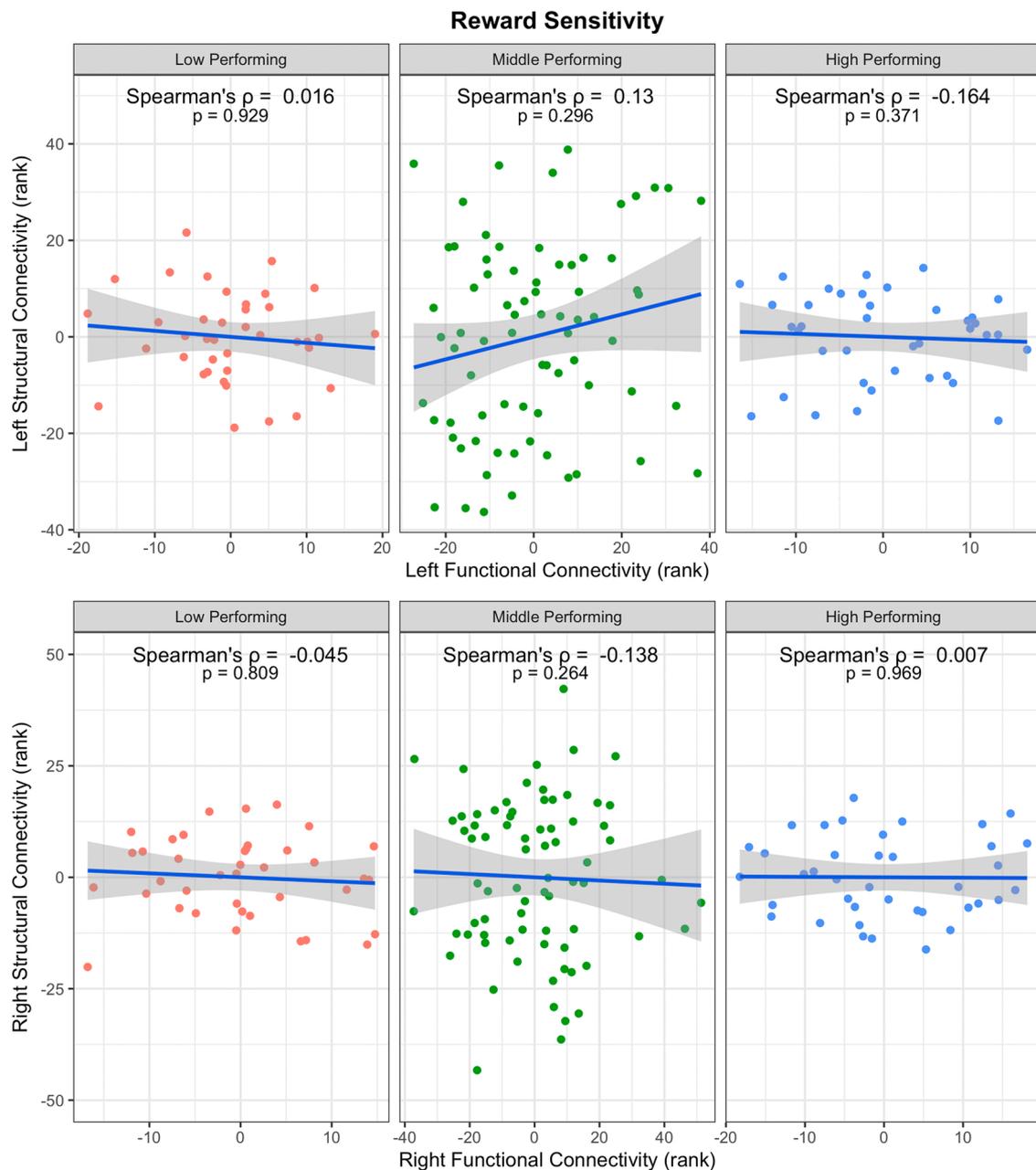
Left SC-FC coupling was significant in the lowest performing group for executive function in both the questionnaire-based (BRIEF-2 GEC scores) and the lab-based WCST (completed categories) assessments (Fig. 3). However, left SC-FC coupling was low and not significant in all three performance groups for general cognition measured using the WASI-II perceptual reasoning. Also, differences in right SC-FC coupling were not observed between the three performance groups for measures of executive function and general cognition (Supplement S5). These findings suggest that there is a left-lateralized association between NAc-OFC network functional flexibility at age 4.5 years and executive function at age 7 and 8.5 years (see Supplement S3 for group scores).

## 4. Discussion

To our knowledge, our study is the first to explore the relations between NAc-OFC structural and functional connectivity, reward sensitivity, and executive functioning in a prospective manner. Highlights of the current study include the integration of multimodal imaging data in a large cohort of children within the critical period of brain development. We also employed a unique joint analysis method that incorporates measures of structural and functional connectivity (SC-FC coupling), producing a measure of functional flexibility within the brain reward circuit. Further, data collection that spanned several time points enabled us to examine reward sensitivity and executive functioning outcomes in later childhood.

### 4.1. NAc-OFC structural and functional connectivity

Our study provides evidence that NAc-OFC functional connectivity is not tethered to its structural connectivity at 4.5 years of age. Although prior evidence highlighted the strong correlation between measures of structural and functional connectivity (Goñi et al., 2014; Honey et al., 2009; Mišić et al., 2016; Saygin et al., 2011; Shen et al., 2012), this may not hold true in transmodal association cortices, especially in young children at a peak age for neuroplasticity. The OFC receives inputs from all sensory modalities and is a typical example of a polymodal association cortex (Barbas, 1988). The NAc-OFC structure-function connectivity divergence demonstrated in our study likely recapitulates the



**Fig. 2.** Residual plots showing NAc-OFC structural connectivity ranks (Y-axis) and functional connectivity ranks (X-axis), where subjects are divided into groups based on reward sensitivity scores and ranked within each group. Each plot represents connectivity in a hemisphere – left and right. Residuals are calculated after taking the effects of sex, fMRI motion parameters (outliers removed, mean motion, max motion) and DTI parameters (motion, volume of NAc and OFC) into account. The spearman correlation ( $\rho$ ) and significance ( $p$ ) are displayed.

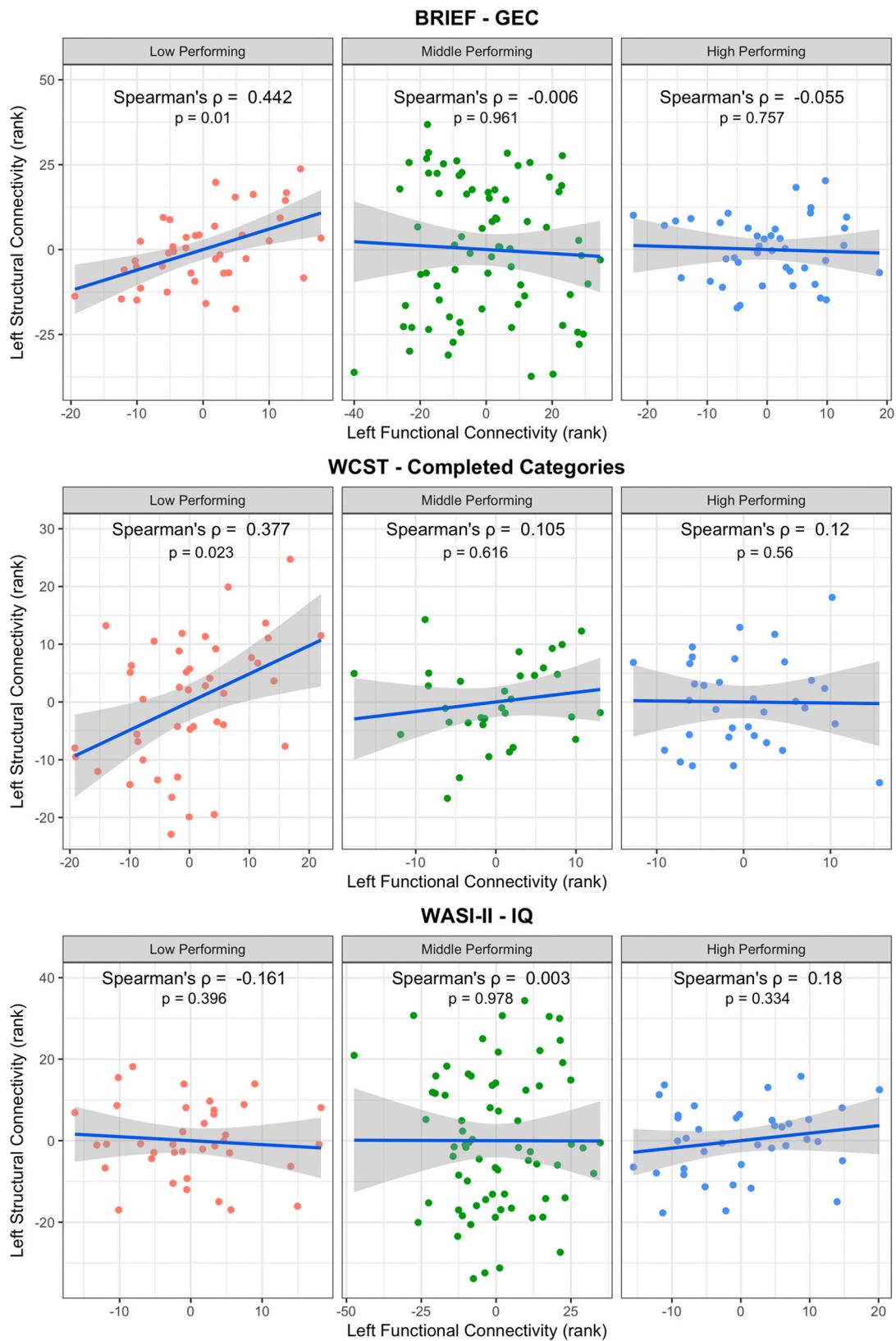
unimodal-transmodal brain region hierarchy. The protracted development of the transmodal association cortex in humans provides an extended window for neuroplasticity that involves activity-dependent myelination (Miller et al., 2012) and synaptic pruning (Petanjek et al., 2011). This period of neuroplasticity sculpts functional specialization in transmodal association cortices and may be critical for developing higher-order executive functions such as working memory, mental flexibility, and inhibitory control (Larsen and Luna, 2018).

#### 4.2. NAc-OFC connectivity and reward processing

Our study builds on the current reward network literature by revealing that NAc-OFC structural and functional connectivity at the preschool age, but not SC-FC coupling, are significantly associated with

later sensitivity to reward, but only in males. In addition, we showed that structural and functional connectivity both independently contributed to reward sensitivity at a later age. Kamkar et al. showed that the association between early experience and reward-related behaviors in later childhood was partially mediated by ventral striatal/NAc reward activation (Kamkar et al., 2017). Our findings support this finding by showing that variance in connectivity measures, perhaps reflecting differences in early experience affecting brain development, is a significant predictor of later reward sensitivity.

We observed that gender differences in sensitivity to reward were present as early as preschool age. Surprisingly, sensitivity to reward was lower in males than females. Research in the area of reward behavior involving adolescents and adults have consistently demonstrated greater reward sensitivity in males (Li et al., 2007; Zhang et al., 2020) that is



**Fig. 3.** Residual plots showing left NAc-OFC structural connectivity ranks (Y-axis) and functional connectivity ranks (X-axis), where subjects are divided into groups based on task/questionnaire performance and ranked within each group. Residuals are calculated after taking the effects of sex, fMRI motion parameters (outliers removed, mean motion, max motion) and DTI parameters (motion, volume of NAc and OFC) into account. The spearman correlation ( $\rho$ ) and significance ( $p$ ) are displayed. Note: BRIEF-GEC, Behavior Rating Inventory for Executive Function Global Executive Composite; WASI-II, Wechsler Abbreviated Scale of Intelligence – Second Edition Perceptual Reasoning; WCST, Wisconsin Card Sorting Test.

attributed to the modulating role of pubertal hormones. The gender dimorphism of reward sensitivity observed in our cohort of preschool children, in the opposite direction compared to adolescents and adults, suggests that reward sensitivity in preschool children is driven by a different neural mechanism. This conclusion is supported by a previous study by Wang et al. that demonstrates mechanistic differences in reward processing between children, adolescents, and adults (Wang et al., 2020). Electroencephalography studies in children have also suggested separate neural mechanisms for reward processing in males and females (Crowley et al., 2013; Ding et al., 2017). Cultural expectations and learning experiences (Heilman and Chen, 2005) in early childhood may play a crucial role in the shaping of the sensitivity of the dopaminergic reward system and hence affect reward behavior (Pessiglione et al., 2006; Schultz, 2015). Our findings provide further evidence that a different neural mechanism underlies reward behavior in young children and highlight the risks of extrapolating findings in adolescents and adults to children.

We also found that the association between NAc-OFC connectivity and reward sensitivity in males is lateralized to the left hemisphere. Lateralization of functions in the brain has been demonstrated in many different cognitive domains, with the intent to reduce bilateral redundancy and to increase efficiency (Vallortigara et al., 1999). Previous studies suggested that hemispheric lateralization exists in the reward network, mediated via a right-left push-pull system (Sacré et al., 2019). The predominant location of effects to the left hemisphere demonstrated in our study is consistent with previous studies that demonstrated left-lateralized reward-system effects (Balconi et al., 2014; Benningfield et al., 2014). A recent study by Lopez-Persem et al. also suggested functional lateralization of reward response specifically in the lateral OFC, though they found the default mode network more connected to the right than the left hemisphere (Lopez-Persem et al., 2020). It is, however, worthwhile to note that some studies report the absence of significant hemispheric difference in relation to reward behaviors (Gottfried et al., 2003; Ouerchefani et al., 2017; Palminteri et al., 2009). While our results suggest hemispheric differences, we cannot rule out that low statistical power rather than a true laterality effect is responsible for the lack of significant effects in the right hemisphere. Future studies are needed to address this in a more precise manner.

#### 4.3. NAc-OFC SC-FC coupling and executive functioning

We found that NAc-OFC structural and functional connectivity were not significantly associated with future executive functioning. Conversely, SC-FC coupling at the group-level was linked to later performance in executive functioning measures. Specifically, significant/higher degree of SC-FC coupling between the NAc and the OFC was only present in preschool children with low executive function performance in later childhood. Our study findings differ from the current literature where higher SC-FC coupling/less decoupling was associated with better performance in executive function tasks (Baum et al., 2020; Reijmer et al., 2015). However, there are key differences between our studies. For one, SC-FC coupling does not align uniformly across the whole brain and we specifically studied the reward network. We posit that higher NAc-OFC SC-FC coupling reflects a lower degree of functional flexibility within the reward network, where functional connectivity is largely tethered to local white matter tracts. On the other hand, higher functional flexibility suggests functional communication at the circuit level involving diverse and indirect structural pathways (Baum et al., 2020). Executive function and decision-making are influenced by two distinct brain networks (McClure et al., 2007; Montague and Berns, 2002); (1) the executive control network (includes the lateral prefrontal and parietal cortices) (McClure et al., 2007) that is related to delayed rewards and (2) the reward network (includes the NAc and OFC) (McClure et al., 2007; Monterosso et al., 2012) that is related to immediate rewards. Dopamine projections to NAc can organize corticothalamic circuits (Haber, 2003), providing a mechanism by which reward sensitivity can

guide higher-order learning and decision-making (Balleine and O'Doherty, 2010; Botvinick, 2012). Given the diversity of subcortical structures and cortical networks that the reward network engages and disengages with to influence executive functions, functional flexibility is hypothesized to be important for executive function development. High SC-FC coupling is proposed to reflect limited dynamic recruitment to meet diverse demands, which may explain why significant SC-FC coupling was only observed for the low performance group.

Second, we collected neuroimaging data at preschool age, while other studies largely collected data in aging populations (Reijmer et al., 2015; Wang et al., 2018). At preschool, the brain is highly plastic and has yet to undergo the structural and functional reorganization (e.g., synaptic pruning, myelination) that occurs throughout adolescence where brain networks become increasingly segregated and specialized (Menon, 2013). From a developmental perspective, a prolonged period for activity-dependent remodeling of neural circuits is suggested to be crucial for healthy maturation of cognitive functions (Baum et al., 2020). Therefore, premature functional specialization in transmodal regions at a young age may impede these developmental processes. Studies on early life stress also support that premature/accelerated development in children are linked to increased probability of mental health disorders and low performance in cognitive tasks (Callaghan and Tottenham, 2016). Our study suggested that altered structural and functional connectivity within the reward network could confer risk for executive dysfunction.

Our findings showed that relating the organization of structural connectivity to patterns of functional connectivity through joint analysis (SC-FC coupling) could allow the characterization of network dynamics that underlie reward behaviors and executive functioning. This is not surprising as brain functional connectivity is intricately linked to its structural connectivity patterns (Greicius et al., 2009; Honey et al., 2009). Therefore, multimodal approaches may improve the estimation of brain connectivity by combining the strengths of each individual modality - diffusion MRI and resting-state functional MRI in our current context. Recently, an increasing number of multimodal explorations have been conducted to improve our understanding of brain mechanisms and interactions between functional and structural networks (Abdelnour et al., 2014; Greicius et al., 2009; Hagmann et al., 2008; van den Heuvel et al., 2009; Honey et al., 2009; Park and Friston, 2013; Pineda-Pardo et al., 2014; Wang et al., 2015). SC-FC coupling reflects organization of functional networks and may provide an early marker of clinically relevant network alterations.

#### 4.4. Study limitations

Despite the strengths of this study (e.g. multimodal neuroimaging data; data collected over multiple time points), potential limitations should be noted. First, accurately reconstructing the complexity of human white matter pathways from diffusion MRI and tractography remains challenging (Zalesky et al., 2016). Second, motion artifacts remain an important confound for all neuroimaging-based studies of brain development. In addition to rigorous quality assurance protocols, we address this issue by quantifying and controlling for the influence of in-scanner head motion in our analyses. We also performed a sensitivity analysis where subjects who failed motion criteria for functional and structural connectivity were excluded. As the main findings remained unchanged (Supplement S6 and S7), we are confident that our results were not significantly confounded by motion. Third, scanning protocols were designed for feasible data collection in young children. However, our study could have benefited from a longer rs-fMRI scan, as the test-retest reliability of functional connectivity from 120 volumes is low given the dynamic functional connectivity changes occurring throughout development (Di Martino et al., 2014; Hutchison and Morton, 2015; López-Vicente et al., 2021). Finally, given that the data collection time points in the current study spanned several years, we only have complete data for a subset of participants. It is possible that

participants excluded due to missing data may not be completely at random, and this should be taken into consideration when generalizing findings. However, sampling bias is a potential source of error for all cohort studies, and our sample size is one of the largest with neuroimaging data at the preschool age. These limitations notwithstanding, our findings highlight that SC-FC coupling within the reward network in preschool children may be a critical neurobiological factor that contributes to executive functioning in later childhood.

## 5. Conclusion

By quantifying SC-FC coupling within the reward network during early childhood and their effect on executive functioning, our results offer critical insights into the basis of many neurodevelopmental and neuropsychiatric disorders which are unambiguously associated with executive dysfunction. Clearly, more work will be necessary to fully understand the role of reward network SC-FC coupling in executive functioning and its related psychopathologies. Future studies should aim at whole brain analysis which will be useful to capture the interactions between different networks and brain regions crucial for cognitive and behavioral functions as well as the developmental trajectory of SC-FC coupling. The latter is crucial for future studies examining SC-FC coupling in disease states at different stages of brain development.

## Data statement

The data that support the findings of this study are not publicly available. Restrictions apply to the availability of these data, which were used under license for the current study. Data is, however, available from the corresponding author upon reasonable request and with the permission of the Singapore Institute for Clinical Sciences (SICS), A\*STAR Research Entities (ARES).

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yap-Seng Chong is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec, and Danone. All other authors report no financial relationships with commercial interests.

## Data availability

Data may be made available from the corresponding author upon reasonable request and with the permission of the Singapore Institute for Clinical Sciences (SICS), A\*STAR Research Entities (ARES).

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.dcn.2022.101107](https://doi.org/10.1016/j.dcn.2022.101107).

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