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Original Article

ORIGINAL ARTICLE

Functional Connectivity of the Dorsal Attention Network Predicts Selective Attention in 4–7 year-old Girls

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Abstract

Early childhood is a period of profound neural development and remodeling during which attention skills undergo rapid maturation. Attention networks have been extensively studied in the adult brain, yet relatively little is known about changes in early childhood, and their relation to cognitive development. We investigated the association between age and functional connectivity (FC) within the dorsal attention network (DAN) and the association between FC and attention skills in early childhood. Functional magnetic resonance imaging data was collected during passive viewing in 44 typically developing female children between 4 and 7 years whose sustained, selective, and executive attention skills were assessed. FC of the intraparietal sulcus (IPS) and the frontal eye fields (FEF) was computed across the entire brain and regressed against age. Age was positively associated with FC between core nodes of the DAN, the IPS and the FEF, and negatively associated with FC between the DAN and regions of the default-mode network. Further, controlling for age, FC between the IPS and FEF was significantly associated with selective attention. These findings add to our understanding of early childhood development of attention networks and suggest that greater FC within the DAN is associated with better selective attention skills.

Key words: attention children, dorsal attention network, early childhood, functional connectivity, fMRI, sustained attention, selective attention

Introduction

Attention is an essential cognitive process that shows profound maturation in early childhood and lays the foundation for the acquisition of more complex skills such as reading (Ferretti et al. 2008; Franceschini et al. 2012). Weak attention skills place children at a disadvantage from the time of school entry, which can have numerous and lifelong consequences on academic attainment, employment, and social skills (Rueda et al. 2010; Stevens and Bavelier 2012). Lifelong attention difficulties are also characteristic of many neurodevelopmental disorders (Atkinson and Braddick 2011), such as autism spectrum disorder (ASD) (Doyle and McDougle 2012; Keehn et al. 2013), attention deficit hyperactivity disorder (ADHD) (Kooistra et al. 2010; Modesto-Lowe et al. 2012), fetal alcohol spectrum disorder (Kooistra et al. 2010), fragile X syndrome (Scerif et al. 2012; Quintero et al. 2014), Williams syndrome (Atkinson and Braddick 2011; Breckenridge et al. 2013a), and Turner syndrome (Quintero et al. 2014).

Attention is deployed by a set of brain networks (Fan et al. 2005), which are believed to modify the way information is processed in sensory regions such as the visual cortex (Desimone and Duncan 1995; Bressler et al. 2008; Noudoost et al. 2010). The dorsal attention network (DAN) is centered on the intraparietal sulcus (IPS) and the frontal eye fields (FEF), and is concerned with orienting one's focus to a particular task. DAN regions are active when focusing attention on an object (Corbetta et al. 2008), and are thought to be responsible for goal-directed top-down processing (Corbetta and Shulman 2002). In adults, functional connectivity (FC) between the IPS and FEF is enhanced during selective attention (Szczepanski et al. 2013), while FC between the IPS and visual regions is increased during sustained visual attention (Lauritzen et al. 2009; Greenberg et al. 2012). DAN regions also show synchronized fluctuations in blood-oxygen level dependent (BOLD) response when adult individuals are resting passively (Beckmann et al. 2005), or engage in passive viewing tasks (Bray et al. 2015).

Top-down attention processes subserved by the DAN show substantial improvements from early childhood to early adolescence. As children develop, attention skills improve, such as searching for an object amongst other similar "distracter" objects ("selective attention"), maintaining attention for longer periods of time ("sustained attention"), and overriding prepotent responses ("executive attention"). These aspects of attention are associated with unique maturation trajectories (Lobaugh et al. 1998; Hommel et al. 2004; Dye and Bavelier 2010; Zhan et al. 2011). Selective attention on simple search accuracy reaches mature levels by age 6 years (Hommel et al. 2004), sustained attention reaches mature accuracy in early adolescence (Zhan et al. 2011), and executive attention shows continued development across adolescence (Zhan et al. 2011).

Despite the abundance of literature on human attention networks (Corbetta et al. 2008; Buschman and Kastner 2015), much less is known about the typical development of FC in the DAN (Konrad et al. 2005). A study using independent component analysis found stronger network FC in the DAN in 11–13 year-old children compared with 19–25 year-old adults (Jolles et al. 2011), and a seed-based FC study showed stronger IPS-FEF FC in 7–12 year-old children compared with 18–31 year-old adults (Farrant and Uddin 2015). These studies suggest a decrease in FC in the DAN between adolescence and adulthood. On the other hand, a more positive association between age and IPS-FEF FC was found in late-childhood/pre-adolescence relative to across-adolescence (Vinette and Bray 2015), which is suggestive of more pronounced maturation in late childhood. Together these findings suggest a non-linear pattern of FC development with a peak in adolescence. We therefore hypothesize that in early childhood an age-related increase in FC will be found between the IPS and FEF. The dorsolateral prefrontal cortex (dlPFC) is sometimes also considered to be part of the DAN, though this is debated (Corbetta and Shulman 2002). Developmental findings regarding dlPFC FC are more suggestive of a linear rather than a nonlinear pattern: a positive age-association in IPS-dlPFC FC was found in pre-adolescence relative to across-adolescence (Vinette and Bray 2015), and increased IPS-dlPFC task-FC in adults relative to children has also been shown (Barber et al. 2013).

FC changes in early childhood and how they relate to early attention development have remained relatively unexplored. Changes in the strength of inter-regional connections are a potential mechanism of improved attention as children mature. Indeed, maturation of fronto-parietal white matter in late childhood has been associated with cognitive development (Mabbott et al. 2006; Dockstader et al. 2012). It has also been suggested that across childhood and adolescence, network development involves parallel processes of segregation (decrease of short-range connections) and integration (increase of long-range connections) to support the maturation of control networks such as the DAN (Fair et al. 2007, 2009), which in turn should support the development of cognitive skills (Power et al. 2010).

Given the ubiquity of attention difficulties in children with neurodevelopmental disorders, and the potential for early childhood therapies to curb atypical developmental trajectories and ultimately improve outcomes (Rueda et al. 2010, 2012), it is important to characterize changes in FC in early childhood and their relation to maturing attention skills. In the present cross-sectional study, we examined the relationship between age and FC of DAN regions in early childhood, and how FC is associated with distinct measures of attention. We assessed FC from functional magnetic resonance imaging (fMRI) data collected during a passive viewing task alongside sustained, selective, and executive attention skills in girls aged 4–7 years. We hypothesized that FC within the core nodes of the DAN, as well as FC between the DAN core nodes and sensory/visual regions would increase with age in early childhood (based on Farrant and Uddin 2015; Vinette and Bray 2015). As children's attention skills improve with age (Lobaugh et al. 1998; Hommel et al. 2004; Dye and Bavelier 2010; Zhan et al. 2011), we further hypothesized that these age-associated FC patterns would positively correlate with children's attention skills.

Methods

Participants

Sixty-three typically developing female children between the ages of 4 and 7 years were recruited to participate in the study. The study was approved by the Conjoint Health Research Ethics Board of the University of Calgary and performed at the Alberta Children's Hospital. Informed consent was obtained from the parents and informed assent from the participants. Potential participants were excluded if they had a history of neurodevelopmental or psychiatric disorders, neurological problems, or other medical problems that prevented participation. Participants' data were evaluated for outliers in behavioral scores (scores >2.5 SD from the mean) and motion on the fMRI scans (<10 min of usable data as described in detail below). A total of 19 participants were excluded: 3 were unable to successfully complete a practice session in an MR simulator, 14 had excessive head motion on their fMRI scan, one was an outlier in the attention measures, and one fell asleep during fMRI acquisition. The final sample consisted of 44 participants (mean age = 5.34 ± 0.8 SD years; mean IQ = 112 ± 10 SD).

Data Acquisition: Procedure

Cognitive assessments and MR imaging were collected over 2 separate 2-hour sessions within 2 weeks. The first session included an IQ assessment using the Wechsler Preschool and Primary Scale of Intelligence - 4th Edition CDN (WPPSI-IV) (Wechsler 2012), and some of the attention measures, as well as training in an MRI simulator in order to acquaint the children with the MR environment. During training in the simulator, children watched the same 18-minute video that was played during the real scan and practiced lying still while the sounds of MR scanning were played to them via headphones. If children were not comfortable in the simulator or not able to hold still, no fMRI data collection was undertaken; 3 children were excluded from the study at this stage. The second session consisted of the actual MR scanning. Children also completed the remainder of the attention tasks. Attention tasks were randomly ordered both across and within sessions and were conducted in a separate testing room adjacent to the MR simulator.

Assessment of Attention Skills

The participants' attentions skills were assessed using 4 tasks adapted from the Early Childhood Attention Battery (Breckenridge et al. 2013b), a measure designed to reflect the structure of the Test of Everyday Attention for Children (Manly et al. 2001) but appropriate for children 3–6 years of age. Children completed 8 subtests. Those included in the analyses reported here were measures of visual sustained attention, auditory sustained attention, selective attention, and executive attention. All of the subtests, except the visual search, were administered via a Dell laptop computer (screen size 31 cm by 17.5 cm), at a 35–50 cm viewing distance; auditory items were played through a set of external speakers. All computerized tasks included an initial practice trial, which was repeated as necessary.

Sustained Attention Tasks

In the visual sustained attention task, a continuous stream of pictures was presented on a computer screen (200 ms presentations with an inter-stimulus interval (ISI) of 1800 ms) and the child was asked to say "yes", "animal", or the name of the animal, when an animal (target) appeared. 30 targets and 120 non-targets (familiar everyday items) were presented and the child received a prompt to pay attention if she missed 4 consecutive targets. The visual sustained attention score was calculated as the number of correct responses minus any false alarms and prompts. The auditory sustained attention task was carried out and scored in the same way as the visual sustained attention task; a continuous stream of words (mono-syllabic animal target words and familiar item non-targets) was presented (average duration 650 ms, ISI 1,350 ms) and the child was also asked to say "yes", "animal", or the name of the animal, when an animal name was presented. The total sustained attention score was then computed as an average of the visual and the auditory sustained attention scores, as we had no specific hypotheses for differences between them with regard to DAN FC.

Selective Attention Task

The selective attention task was a visual search task where children were given 60 s to point to targets (18 red apples) among distracters (162 white apples and red strawberries) on a laminated letter-sized search sheet. The experimenter marked items with an erasable marker as children pointed to them. The score was the total number of correctly identified targets.

Executive Attention Task

The executive attention task was a version of the Wisconsin Card Sorting test (Robinson et al. 1980), adapted for use with young children. Children had to work out which kind of balloon their new teddy bear friend liked. Each trial showed 2 balloons that varied in color and shape. In stage one, the teddy bear liked stickers of a particular color; in stage two it liked stickers of a different color; and in stage 3 it liked stickers of a particular shape. Children received feedback on whether their choice was correct, but no other information was given. A total of 20 possible trials could be given for each stage, with 6 consecutive correct trials required for a pass. If a child failed a stage, the test was discontinued. The task score was the total number of stages (1, 2, 3) that were successfully completed.

Behavioral Analysis

To assess the relationship between age and attention skills, Pearson correlations were computed using SPSS (Chicago, IL).

Functional Connectivity

Data Acquisition

Data were acquired on a 3 T GE MR750w (Waukesha, WI) scanner using a 32-channel head coil. Functional images were acquired in 34 axial slices using a gradient-echo EPI sequence (437 volumes, TR = 2500 ms, TE = 30 ms, FA = 70, matrix size 64 × 64, voxel size 3.5 × 3.5 × 3.5 mm^3; duration: ~18 min). Children watched a series of clips from "Elmo's World" inside the MRI for the duration of the functional scan. Wakefulness was monitored using an SR-Research EyeLink 1000 (Ottawa, ON) infrared camera; only one participant fell asleep during the scan and was excluded from analysis. Anatomical scans were acquired using a T1-weighted 3D BRAVO sequence (TR = 6.764 ms, TE = 2.908 ms, FA = 10, matrix size 300 × 300, voxel size 0.8 × 0.8 × 0.8 mm^3).

Data Preprocessing

Data preprocessing followed a pipeline outlined by Power et al. (2014) and used functions from both AFNI (Analysis of Functional NeuroImages; Cox 1996) and FSL (FMRIB Software Library; Smith et al. 2004). The pipeline included slice-time correction, motion correction, and normalization to the McConnell Brain Imaging Center NIHPD asymmetrical (natural) pediatric template optimized for ages 4.5 to 8.5 years followed by normalization to 2 × 2 × 2 mm MNI152 standard space. Images were denoised by regressing out the 6 motion parameters, as well as signal from white matter, cerebral spinal fluid, and the global signal, and their first-order derivatives. Corrections for time series autocorrelation were not performed, as it has been shown in real data that results of hypothesis testing on FC values remain very similar to those before correction (Arbabshirani et al. 2014). Motion-corrupted volumes were identified by FSL Motion Outliers and censored, specifically, those that exceeded both frame-wise displacement 0.2 mm and 0.3% change in BOLD signal intensity (mean censored volumes = 76.7 ± 54.2 SD; range 2–196). Six scans exhibited a relatively large displacement (>6 mm; mean 3 mm ± 2.9 SD, range 0.5–15 mm) that resulted from one big movement. As these participants contributed enough usable data (>10 min), and they were not outliers in any analysis, their data were not excluded. No significant correlations between age or attention measures and head motion were observed (all $P > 0.1$). Data were spatially smoothed using a 6 mm Gaussian kernel (full-width at half-maximum).

fMRI Analysis

To investigate how age and attention skills are reflected in FC of the 2 core nodes of the DAN, we used regions of interest (ROIs) defined from 4 parcellation units (Wang et al. 2015) along posterior-anterior IPS and in the putative human FEF (IPS0, IPS2, IPS4, and FEF; Fig. 1) as seeds and examined how FC of these seeds across the entire brain varied with age and

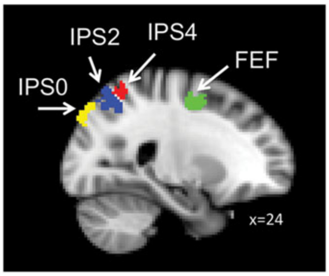

Figure 1. Seeds in DAN regions. We defined seed ROIs using parcellation units from Wang et al. (2015) along the posterior-anterior IPS (0, 2 and 4) and in the putative human FEF.

attention skills. Multiple parcellation units along the IPS were investigated because while the DAN spans the length of the IPS, it has been shown that sub-regions have distinct functional and white matter connectivity (Bray et al. 2013a; Vinette and Bray 2015; Wang et al. 2015). The average time course for each ROI was extracted and entered into a voxel-wise correlation with every other voxel in the brain. Resultant whole-brain correlation maps were normalized using Fisher's r-to-z transform ($z = 0.5[\ln(1 + r) - \ln(1 - r)]$) for comparison across individuals. Group-level statistical testing was conducted using a mixed-effects analysis as implemented in FSL's FEAT. We first examined average group FC across the seeds using a model that contained the group intercept and the z-scored number of censored motion-affected volumes (as covariates of no interest). Voxel-wise thresholding was set at z-score >3.1 and cluster correction was conducted using Gaussian Random Field theory with $P < 0.001$.

Age was then z-scored and entered into a model alongside z-scored Full Scale IQ scores and the z-scored number of censored motion-affected volumes (as covariates of no interest) in order to assess the effects of age on average group FC. Voxel-wise thresholding was set at z-score >2.3, and cluster correction was conducted using Gaussian Random Field theory with $P < 0.05$. The P-value for all results was then Bonferroni-corrected for 4 comparisons (i.e., the number of seeds that were examined; $P < 0.0125$).

We hypothesized that region pairs showing a significant effect of age on FC would also show a relationship with attention skills, after controlling for age. Age-associated FC patterns were similar for IPS2 and IPS4; therefore, subsequent brain-behavior analyses focused on IPS2, a region known to be central in the DAN (Szczepanski et al. 2013), and important for visual-spatial attention (Merriam et al. 2003; Arcaro et al. 2011; Jerde et al. 2012). To test this, sustained and selective attention scores were entered into a partial correlation analysis with FC parameter estimates (β) restricted to a 4 mm radius around each cluster's peak in SPSS. Executive attention only showed a weak correlation with age in our sample and was therefore not followed up on in this analysis. The P-values were Bonferroni-corrected for 9 comparisons (i.e., the number of region pairs that were examined; 1 significant region pair from FEF and IPS0 seeds each, and 7 region pairs from left and right IPS2 seeds; $P < 0.0056$).

The main focus in this study was to examine how age-associated FC patterns related to maturing attention skills; however, we also performed exploratory analyses where z-scored measures of attention were entered into 3 separate models with z-scored age, z-scored Full Scale IQ scores and the z-scored number of censored motion-affected volumes (as covariates of no interest). These analyses assessed the relationship between attention skills and FC independent of age. The findings are presented in the Supplementary Materials: selective attention in Supplementary Figure S1 and Supplementary Table S1; sustained attention in Supplementary Figure S2 and Supplementary Table S2; and executive attention in Supplementary Figure S3 and Supplementary Table S3.

Results

Cognitive Measures

Descriptive analyses of the attention measures revealed the following: sustained attention (mean = 22.68 ± 5.24 SD; range 10.5–30); selective attention (mean = 14 ± 2.59 SD; range 10–18); executive attention (mean = 2.27 ± 0.76 SD; range 1–3). Age was significantly and positively correlated with sustained ($r = 0.59$, $P = 0.0000125$), selective ($r = 0.51$, $P = 0.0002$), and executive attention ($r = 0.26$, $P = 0.044$), though the latter association was weak in our age range (one-tailed P's based on expected gains in attention skills with increasing age: Lobaugh et al. 1998; Hommel et al. 2004; Dye and Bavelier 2010; Zhan et al. 2011).

Average FC Patterns of the DAN Seeds

Average group FC maps of IPS0, IPS2, IPS4, and FEF are shown in Fig. 2. Consistent with previous adult and child studies, we observed positive FC between IPS seeds and other regions of the DAN including putative human FEF, temporo-visual regions (lateral occipital complex, fusiform gyrus, parts of V1-V2 and cuneus), and dlPFC (Farrant and Uddin 2015; Vinette and Bray 2015). Also as expected, we observed negative FC with regions of the default-mode network (DMN) including posterior cingulate (PCC)-precuneus, medial prefrontal cortex (mPFC), and inferior parietal lobule (Farrant and Uddin 2015; Vinette and Bray 2015), as well as insula, caudate, and superior temporal gyrus (STG). IPS2 and IPS4 FC patterns were largely similar, but differed from IPS0 patterns; IPS0 had significant negative FC with dlPFC, and IPS0 exhibited negative FC with a more rostral section of the PCC in the DMN, as well as positive rather than negative FC with precuneus. These observations are consistent with previous work that has shown that IPS subregions are functionally distinct (Bray et al. 2013a; Farrant and Uddin 2015; Vinette and Bray 2015; Wang et al. 2015). We further observed positive FC between putative human FEF and other regions of the DAN, namely IPS as well as mPFC-dlPFC, and negative FC with regions of the DMN including PCC-precuneus, and mPFC and STG, which was again consistent with previous studies (Farrant and Uddin 2015).

FC Associated with Age

Age was significantly correlated with FC from seeds along the IPS and in the FEF (Table 1 and Fig. 3). Specifically, age was negatively correlated with FC between left FEF and ventral temporo-visual areas (Fig. 3A), as well as FC between right IPS0 and a cluster in dlPFC extending to dorsal mPFC (Fig. 3B). The four seeds in left and right IPS2, as well as left and right IPS4 all showed similar effects for age. FC between IPS2/4 and FEF, primary motor cortex (M1), PCC, and putamen was positively correlated with age, whereas FC between IPS2/4 and insula and caudate, V1-V2, as well as DMN regions PCC-precuneus and rostral ACC/rostral mPFC (with lateral extension) was negatively correlated with age (Fig. 3C). Only minor deviations from these patterns were found between seeds (IPS2 and IPS4 in the left and right hemispheres; details in Table 1). For instance,

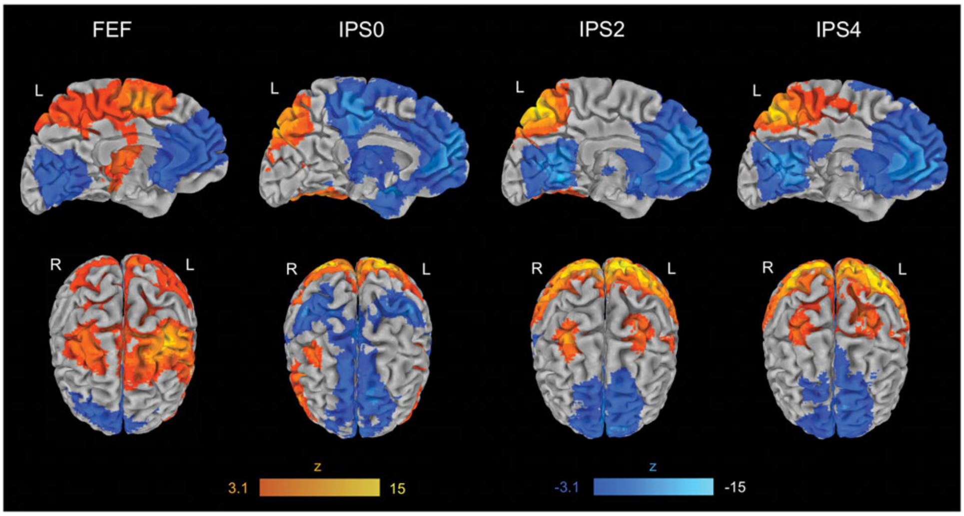

Figure 2. FC with FEF and IPS seeds. Positive and negative average group FC patterns are shown for seeds in the left hemisphere. Warm colors indicate positive FC, while cool colors indicate negative FC. Voxel-wise thresholding was set at z-score >3.1 and cluster correction was conducted using Gaussian Random Field theory with $P < 0.001$.

Table 1 FC is associated with age

Sign of association	Seed lat	Seed	Lat	Connectivity	Voxels	P-value	Z-max	x	y	z
Negative	L	FEF	R	FuG, LOC, ITG, MTG, Caudate	9663	1.55E-06	4.54	15	60	43
Negative	R	IPS0	L	dlPFC, dmPFC	2304	0.000758	4.29	63	70	61
Positive	L	IPS2	L	FEF, M1, PCC, Putamen	3495	0.00153	4.85	56	52	67
			R	FEF, M1	2716	0.00615	4.97	33	55	65
Negative			BIL	rACC, rmPFC, Insula, Caudate	12474	9.16E-09	4.61	55	89	47
			BIL	PCC, Precuneus, V1, V2	4318	0.000391	4.19	41	33	43
Positive	R	IPS2	L	FEF, M1	2647	0.0101	4.27	56	52	67
Negative			BIL	rACC, rmPFC, Insula, Caudate	17016	3.27E-10	5.1	58	86	44
			BIL	PCC, Precuneus, V1, V2	3289	0.00339	4.28	46	25	47
Positive	L	IPS4	BIL	FEF, M1, PCC, Putamen Thalamus, Hippocampus	8936	1.28E-05	4.94	34	55	62
Negative			BIL	rACC, rmPFC, rlPFC Insula, Caudate	14286	1.19E-07	4.68	57	86	44
			BIL	PCC, Precuneus, V1, V2	3963	0.00355	3.78	47	21	47
Positive	R	IPS4	L	FEF, M1	3062	0.00393	4.86	56	52	65
Negative			BIL	rACC, rmPFC, rlPFC Insula, Caudate	14304	2.21E-09	4.63	58	85	56

Note: Parcellation units from Wang et al. (2015) in IPS0, IPS2, IPS4, and FEF were used in the analysis. Average time courses were extracted for each parcellation unit and correlated with every other voxel in the brain. Resultant maps were entered into a regression model with age and showed a relationship between FC and age. (dlPFC, dorsolateral PFC; dmPFC, dorsomedial PFC; FEF, putative human frontal eye fields; FuG, fusiform gyrus; IPS, intraparietal sulcus; ITG, inferior temporal gyrus; Lat, brain laterality; LOC, Lateral occipital cortex; M1, primary motor cortex; MTG, middle temporal gyrus; PFC, prefrontal cortex; PCC, posterior cingulate cortex; rACC, rostral anterior cingulate; rlPFC, rostrolateral PFC; rmPFC, rostromedial PFC; V1, primary visual cortex; V2, secondary visual cortex). Coordinates are in FSL voxel space.

while age was correlated with FC of left IPS2/4 with bilateral FEF-M1, only the right IPS2/4 to left FEF-M1 FC correlation survived multiple comparison correction. However, FC between right IPS2/4 and right FEF-M1 correlated with age at a trend level ($P = 0.021$ and $P = 0.037$, respectively). Similarly, left IPS2/4 FC clusters in FEF-M1 extended to PCC and putamen, whereas right IPS2/4 FC clusters in FEF-M1 did not. Left IPS4 subcortical FC additionally extended to thalamus and hippocampus. Seeds in the right FEF and left IPS0 showed no significant associations between FC patterns and age.

Attention Skills Correlate with Age-associated FC Patterns

Attention measures correlated significantly with age-associated FC patterns after controlling for the effect of age (Table 2 and Fig. 4). Nine region pairs were examined: 1 significant region pair from left FEF and right IPS0 seeds and 7 significant region pairs from left and right IPS2 seeds (see Table 1 for details). Regions pairs from IPS4 seeds were disregarded due to high similarity with IPS2 region pairs and given IPS2's central involvement in the DAN (Szczepanski et al. 2013; see above). Selective attention positively correlated with FC between left IPS2 and cluster peaks in left and right FEF ($r = 0.4$, $P = 0.0039$ and $r = 0.54$, $P = 0.00009$, respectively), as well as with FC between right IPS2 and the cluster peak in left FEF ($r = 0.43$ and $P = 0.002$). Neither selective nor sustained attention correlated with age-associated FC patterns between DAN nodes and DMN regions (all P's one-tailed, based on the assumption of expected gains in attention skills with increasing age (see Lobaugh et al. 1998; Hommel et al. 2004; Dye and Bavelier 2010; Zhan et al. 2011)).

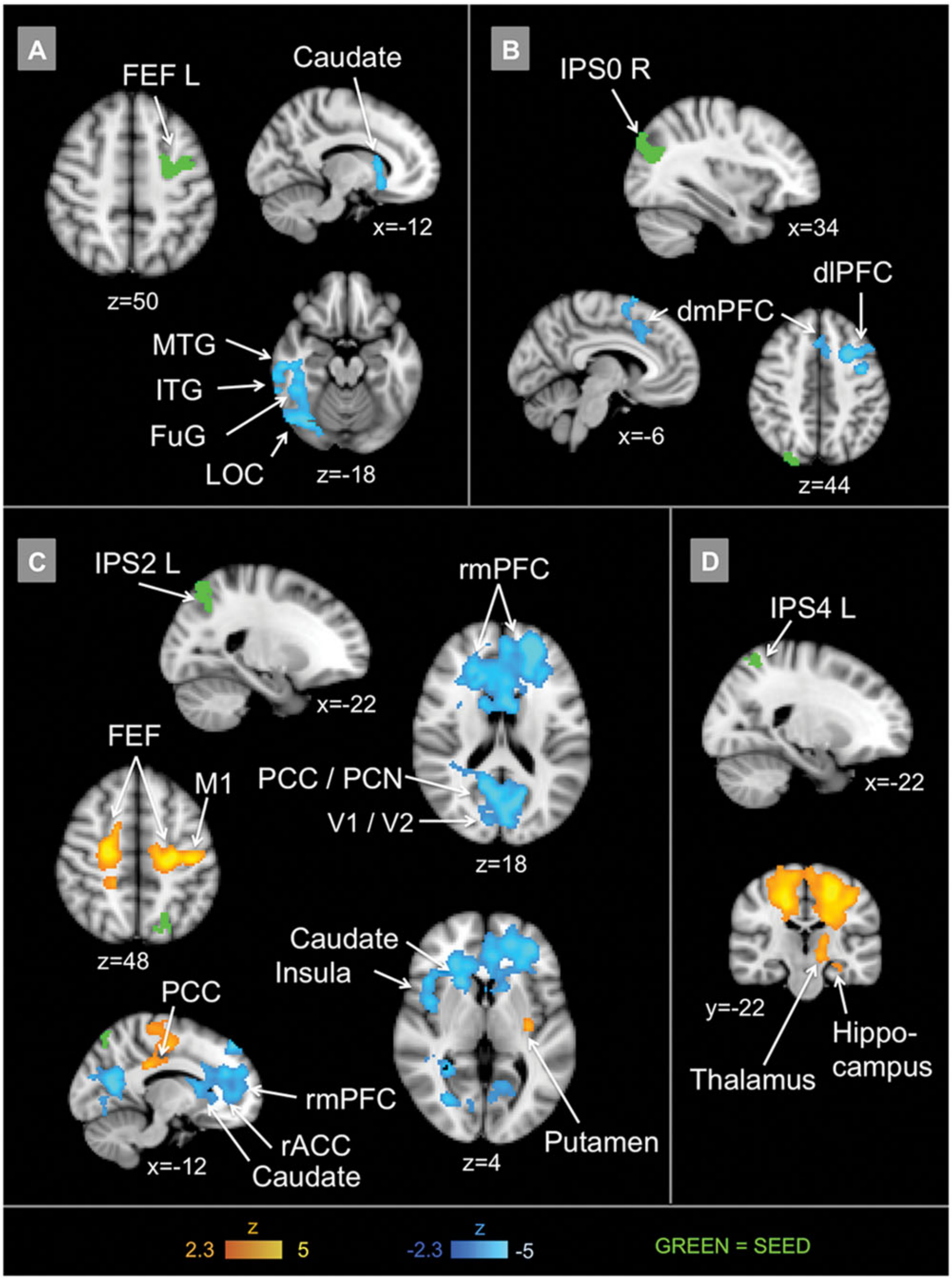

Figure 3. FC associated with age. Linear effects of age are shown for seed ROIs in the left FEF (*A*), the right IPS0 (*B*), and in the left IPS2 (*C*). Seed regions are shown in green, with negative associations in blue and positive associations in orange/yellow. Age-FC correlations are almost identical for the left and right IPS2 and IPS4; a deviation from this pattern in left IPS4 is depicted in (*D*). No significant associations between age and FC of left IPS0 or right FEF were found. dlPFC, dorsolateral PFC; dmPFC, dorsomedial PFC; FEF, frontal eye fields; FuG, fusiform gyrus; IPS 0, 2, 4, intraparietal sulcus 0, 2, 4; ITG, inferior temporal gyrus; L, left; LOC, lateral occipital cortex; M1, primary motor cortex; MTG, middle temporal gyrus; PCC, posterior cingulate cortex; PCN, precuneus; PFC, prefrontal cortex; rACC, rostral anterior cingulate cortex; rmPFC, rostromedial PFC.

Discussion

Early childhood is a period of profound neural development and rapid maturation in attention skills. We investigated the association between age and FC within the DAN, and the association between FC and attention skills in early childhood. We showed that in young girls, age is positively associated with FC between core nodes of the DAN, the IPS and the FEF, while it is negatively associated with FC between the DAN and regions of the DMN. We also found that controlling for age, FC between the IPS and FEF was significantly associated with selective attention scores. These findings add to our understanding of early childhood development of functional networks and suggest that greater FC within the DAN is associated with better selective attention skills in early childhood.

As hypothesized, age was positively correlated with FC between IPS and FEF, meaning that FC between the IPS and FEF was stronger in older children. This finding is in line with models of neural development that suggest increased functional integration of networks as children mature (Fair et al. 2007, 2009; Dosenbach et al. 2010; Power et al. 2010; Menon 2013). As

Table 2 Attention skills correlate with FC patterns after controlling for age

Correlated with	Seed lat	Seed	Lat	Connectivity	Sign of association with age	*r*-value	P-value
Selective attention	L	IPS2	L	FEF	Positive	0.4	0.0039
Selective attention	L	IPS2	R	FEF	Positive	0.54	0.00009
Selective attention	R	IPS2	L	FEF	Positive	0.43	0.002

Note: Selective and sustained attention scores were entered into a partial correlation analysis with the FC parameter estimates (β) restricted to a 4 mm radius around each cluster's peak while controlling for age, in order to assess whether any of the FC patterns associated with age would have a relationship with these attention measures after controlling for age. A total of 9 region pairs were examined: one significant region pair from FEF and IPS0 seeds each, and seven region pairs from left and right IPS2 seeds (see Table 1 for details). Results show that this was the case for selective attention and IPS-FEF connectivity. Executive attention only showed a weak correlation with age in our sample and was therefore not followed up on in this analysis. (IPS, intraparietal sulcus; FEF, putative human frontal eye fields; Lat, brain laterality).

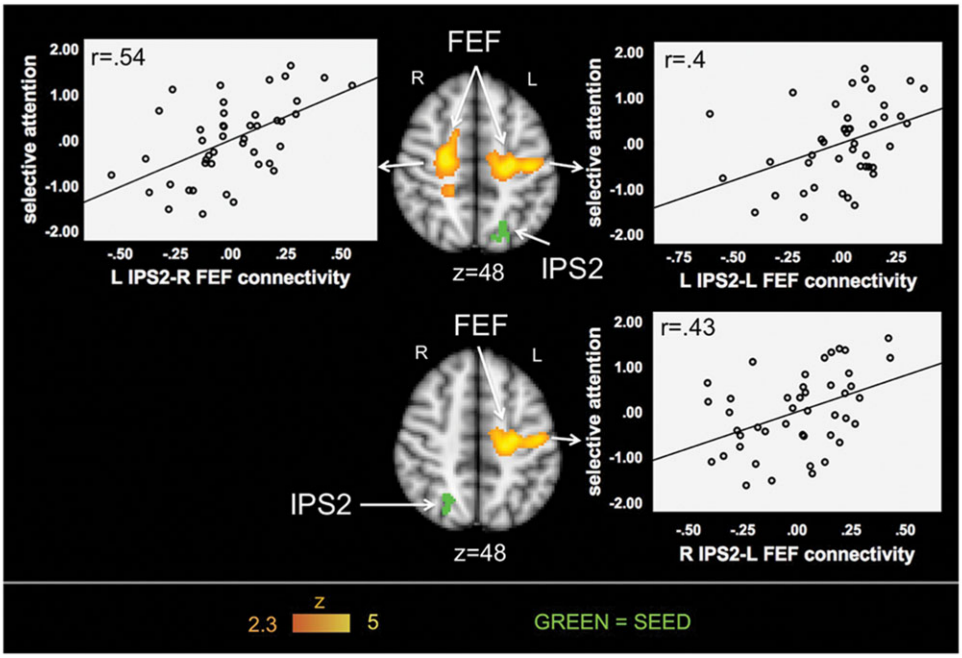

Figure 4. Attention skills positively correlate with age-associated FC patterns after controlling for the effect of age. Selective attention significantly correlated with FC between left IPS 2 and 4 mm radius around cluster peaks in left and right FEF ($r = 0.4$, $P = 0.0039$ and $r = 0.54$, $P = 0.00009$; upper panel), as well as with FC between right IPS2 and a 4 mm radius cluster peak in left FEF ($r = 0.43$ and $P = 0.002$; lower panel). Scatter plots show age-adjusted scores. Central maps illustrate significant effects of age from which ROIs were generated.

FC is significantly associated with underlying white matter structure (Greicius et al. 2009; Honey et al. 2009), these changes with age may be related to maturational processes such as myelination (Yakovlev and Lecours 1967). Properties of fronto-parietal white matter structure along the superior longitudinal fasciculus—a large fiber bundle that links prefrontal to parietal and temporal regions (Thiebaut de Schotten et al. 2011)—have been shown to change with age (Lebel and Beaulieu 2011), and have been linked to improvements in sustained and selective attention in cross-sectional studies in children aged 6–17 years (Mabbott et al. 2006; Dockstader et al. 2012; Klarborg et al. 2013).

Though few studies have assessed the neural correlates of attention developmentally, some have assessed working memory—a related cognitive process that has a protracted maturational trajectory and has been shown to improve up to 22 years of age (Egami et al. 2015). These studies have observed increased activation of fronto-parietal regions with increased working memory capacity (Klingberg et al. 2002; Crone et al. 2006; Scherf et al. 2006). For instance, adolescents showed stronger activation in dlPFC and parietal regions, and better performance on an oculomotor response task in comparison to children 10–13 years of age (Scherf et al. 2006). Similarly, compared to 12 to 17 year-olds and 18 to 25 year-olds, children aged 8 to 12 years failed to recruit the dlPFC and parietal regions when performing an object-working memory task (Crone et al. 2006). This was associated with the younger children performing more poorly on this working memory task, which demanded re-ordering of information. Likewise, in a sample of 9 to 18 year-old children, older children performed better on a visuo-spatial working memory task and showed higher activation in frontal and parietal cortices (Klingberg et al. 2002). Increasing fronto-parietal task-based co-activation with age and working memory ability may reflect increases in underlying FC. While our design precluded examination of task-related activation effects, our findings of greater FC between the IPS and FEF in older children in relation to better attention skills may be consistent with the working-memory literature. Future research should examine the relation between task co-activation, performance, and FC.

Although comprehensive longitudinal studies are lacking, the current literature suggests a steady increase in FC within the DAN with a peak in late childhood/adolescence and attenuation into adulthood (Farrant and Uddin 2015; Vinette and Bray 2015). This pattern has interesting implications for the relationship between FC and cognitive development. Our finding that selective attention was significantly associated with FC between IPS and FEF after controlling for age, suggests that the increase in IPS-FEF FC that occurs with age is in part related to the development of selective attention skills in early childhood. Notably, previous work has shown that selective and sustained attention are mostly developed by mid-childhood (Hommel et al. 2004) and early adolescence (Zhan et al. 2011), respectively. Therefore, increasing IPS-FEF FC in early childhood might reflect network mechanisms that support the acquisition of attention, and other cognitive skills, which become attenuated once these skills are acquired and consolidated. This latter process may be associated with a decline in FC into adulthood.

We also observed that age was negatively correlated with FC between IPS and rostral mPFC, including the anterior cingulate cortex, as well as precuneus and PCC, meaning that negative FC between IPS and these areas was greater in older children. As these areas constitute the DMN (Greicius et al. 2003; Fox et al. 2006), this suggests stronger negative correlations between the DAN and DMN with increasing age, similar to what has been shown in older children 6–20 (Vinette and Bray 2015) and 8–13 years of age (Chai et al. 2014). It has been suggested that the ability to modulate or suppress DMN activity is linked to greater top-down, goal-directed attention (Anticevic et al. 2012; Rubia 2013). In addition, there is evidence that attention is not deployed consistently, but rather fluctuates from moment to moment. In studies where reaction time variability was used as a measure of attention (in)stability, it was positively correlated with activity in the DAN and negatively correlated with activity in the DMN (Esterman et al. 2013, 2014). The authors suggested that there may be 2 attentional states, one that relies on the DMN and is relatively effortless but somewhat prone to error and ideal for sustained attention, and one that relies on the DAN, is effortful and more accurate but less ideal for sustained attention.

While the DAN has been broadly implicated in goal-directed attention (Corbetta and Shulman 2002), each attention component relies on partly dissociable neural substrates. Selective attention relies heavily on the IPS and FEF (Moore et al. 2003) and interactions between them (Szczepanski et al. 2013). As noted above, sustained attention alternately relies on the DAN and DMN, when operating in effortful or relatively effortless modes (Esterman et al. 2014). It has also recently been shown that a distributed network beyond the DAN, referred to as the sustained attention network, mediates inter-individual variability in sustained attention skills (Rosenberg et al. 2016). It is therefore interesting that the only significant association found between FC and attention scores, controlling for age, was for IPS2-FEF FC and selective attention, while effects of DAN or DAN-DMN FC were not significantly predictive of sustained attention. In our hypothesis-driven study, we assessed effects of age on the DAN and the related influences on attention measures. In future work, it would be interesting to take a data-driven approach, similar to Rosenberg et al. (2016), to identifying the most prominent FC patterns predictive of each attention component.

The FC patterns we observed are largely consistent with those observed in older children (Farrant and Uddin 2015; Vinette and Bray 2015) and adults (Farrant and Uddin 2015), despite the fact that children in this study were engaged in passive viewing of video clips during functional data acquisition, rather than at rest (Cantlon and Li 2013; Vanderwal et al. 2015). It has been previously shown that networks are largely similar, though not identical, during free-viewing and rest (Bray et al. 2015; Emerson et al. 2015; Vanderwal et al. 2015). Showing videos increases compliance in young children (Raschle et al. 2009), and may be especially useful for studies in children with neurodevelopmental disorders, many of which include attention difficulties (Atkinson and Braddick 2011; Bray et al. 2011a, 2011b; Keehn et al. 2013; Bray et al. 2013b; von Rhein et al. 2015; Rosenberg et al. 2016).

The approach that we employed in this study is based on the examination of individual differences. Recent studies show that taking individual differences into account can help elucidate the neural underpinnings of the diversity and complexity of cognitive skills, emotions, social competencies and more, and may be useful in the investigation of both typical (Rohr et al. 2013, 2015; Fuentes-Claramonte et al. 2016; Goldfarb et al. 2016; Vossel et al. 2016) and clinical groups (Nebel et al. 2015; van Dongen et al. 2015; von Rhein et al. 2015), particularly as clinical cut-offs may be arbitrary (van Dongen et al. 2015). It has been argued that the traits associated with neurodevelopmental disorders such as ADHD and ASD also exist in the typical population and fall onto a spectrum or continuum (Matthews et al. 2014; van Dongen et al. 2015). The use of dimensional approaches also allows for more statistical power in studies on neurodevelopmental disorders, which are chronically underpowered due to heterogeneity in the populations studied (Sonuga-Barke 2002; Nigg 2005; Sonuga-Barke et al. 2008; Fair et al. 2012) and small sample sizes. Our findings point to neural mechanisms in the brain subserving cognitive mechanisms that control the development of selective attention skills. They highlight possibilities for gleaning insight into how the brain's functional maturation is associated with children's development and may serve as a basis for future studies investigating neurodevelopmental disorders such as ASD and ADHD.

Strengths of this study include the use of multi-component measures of attention, and a sufficiently long scan time to obtain reliable FC estimates. However, there are several limitations. First, this data was collected as part of an ongoing study of genetic disorders affecting girls, and as a result boys were not included in data collection. It has been shown that there are no sex differences in attention skills in this age range (Breckenridge et al. 2013b); therefore, we expect results to generalize, but this should be tested in future work. Second, it is possible that some assessment measures collected at the end of a session may not accurately reflect the children's attentions skills if they were fatigued; this could have introduced additional variability into our data. However, as tests were randomly ordered and spread across two separate sessions, systematic effects were avoided and any residual impact should be minimal. Future studies could shorten sessions, and focus on different aspects of attention or cognitive functions related to attention, to extend our understanding of common underlying mechanisms. Future research could also investigate FC patterns underlying children's attention skills using graph theoretical metrics to identify hubs and characterize network properties. Third, it should also be noted that our findings during a free-viewing paradigm may be different from insights that could be gained during functional attention tasks suitable for a young age range and adapted for MRI. Task-related FC could for instance be modeled using a psychophysiological interaction analysis and may contribute to our understanding of network flexibility. Fourth, we chose to focus this study on an important period of early childhood, but a wider age range may have allowed us to define more pronounced age-related changes in FC. Lastly, while associations with age are suggestive of developmental effects, longitudinal data are necessary to confirm within-subject maturation and the relationship between FC changes and changes in attention measures.

In summary, our findings concur with our hypothesis that FC maturation in the DAN supports the acquisition and development of attention skills, and in particular the development of selective attention, during early childhood. They further support models of development describing increasing network integration (Fair et al. 2007; Fair et al. 2009; Dosenbach et al. 2010; Power et al. 2010; Menon 2013). Our results also corroborate and extend findings of recent studies in older children that have examined the functional development of attention networks in the brain. To our knowledge, this is the first study to investigate relationships between FC and age in early childhood and their association with distinct component processes of attention. Notably, we were able to show significant associations with age across the relatively narrow range of 3 years. This further highlights the profound maturation occurring across this age range, and the enormous potential for early childhood therapies to ameliorate attention difficulties.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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