The changing brain : neurocognitive development and training of working memory

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Chapter 3

Functional connectivity of spontaneous brain activation in children and young adults

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Abstract

Over the past decade, examination of functional connectivity using functional magnetic resonance imaging (fMRI) has become an important tool to investigate functional changes in patient populations, healthy aging and recently also child development. Most prior developmental studies focused on functional connectivity between brain regions important for cognitive or emotional control and the so-called *default mode network*. In the present study we investigated whole brain functional connectivity in children (11-13 years; n = 19) and young adults (19-25 years; n = 29), without a priori restrictions to specific regions. We found similar patterns of functionally connected regions in children and young adults, but there were differences in the size of functionally connected regions (i.e., the number of voxels), as well as in the strength of functional connectivity (i.e., the correlation value) between brain regions. This indicates that functional connectivity continues to change during adolescence. Developmental differences were found across the whole brain, but the effects differed for functional connectivity patterns associated with higher cognitive and emotional functions and functional connectivity patterns associated with basic visual and sensory-motor functions. Finally, we showed that the majority of functional connectivity differences could not be explained on the basis of grey matter density alone.

3.1 Introduction

The development of cognitive, social, and emotional functioning is accompanied by changes in the magnitude and the extent of activation in the neural systems underlying these functions (e.g., Blakemore, 2008; Casey et al., 2008; Luna et al., 2009). Recently, some studies have shown that also the *functional connectivity* between brain regions changes throughout childhood and adolescence (Fair et al., 2009; Kelly et al., 2009; Supekar et al., 2009; Thomason et al., 2008). Functional connectivity is defined as the "temporal correlation of a neurophysiological index measured in different brain areas" (Friston et al., 1993) and can be studied by analyzing correlations of spontaneous blood oxygen level dependent (BOLD) signal fluctuations between brain regions obtained from functional magnetic resonance imaging (fMRI; for a review, see Fox and Raichle, 2007). The correlation patterns of these spontaneous fluctuations show close correspondence to task-related activation patterns, even in a task-free setting (Biswal et al., 2010; Smith et al., 2009). Although functional connectivity patterns are broadly consistent with anatomical connectivity (e.g., Bullmore and Sporns, 2009), strong BOLD correlations have also been found between regions with no direct anatomical connections (Honey et al., 2009; Koch et al., 2002; Vincent et al., 2007; Zhang et al., 2008).

One of the most used methods to investigate functional connectivity is to calculate the correlation of the BOLD time course from a specific seed region of interest with the time courses from all other voxels in the brain (Fox and Raichle, 2007). With this method, Kelly et al. (2009) investigated developmental changes in functional connectivity with the anterior cingulate cortex. They demonstrated that children showed more diffuse functional connectivity patterns and increased functional connectivity with regions close to the seed region, as compared with adults, who showed more focal functional connectivity patterns and increased functional connectivity with regions at long distances from the seed region. These findings indicate that functional brain development is characterized by a transition from large, undifferentiated systems to specialized neural networks (e.g., Fair et al., 2009) and they are in agreement with developmental differences in functional connectivity between other brain regions (Fair et al., 2008; Fair et al., 2009; Fair et al., 2007). However, prior studies focused mainly on functional connectivity between brain regions important for cognitive or emotional control and the so-called *default mode network* (Raichle et al., 2001). It is currently not clear whether these functional connectivity differences can be found for other functional domains. Furthermore, it is unknown to what extent observed developmental differences in functional brain connectivity could be explained by local differences in grey matter density.

In the present study 1) we investigated voxelwise whole brain functional connectivity in children (11-13 years) and young adults (19-25 years), without a priori restriction to specific seed regions, and 2) we corrected the results for differences in grey matter density. We used an independent component analysis (ICA)-

based approach, in which the entire BOLD dataset is decomposed into distinct *functional networks* (defined as brain regions with strong interregional functional connectivity), based on their different temporal characteristics (Fox and Raichle, 2007). This approach makes it possible to study the full repertoire of functional networks including visual, auditory and sensory-motor networks, the default-mode network, and networks associated with higher cognitive functions (Smith et al., 2009). In general, we expected to find more diffuse patterns of functional connectivity in children, although we hypothesized that developmental effects might differ across functional networks depending on their functional domain.

3.2 Method

Participants

Twenty-nine young adults (age 19.3-25.3, M = 22.2, SD = 1.67, 16 female) and twenty children participated in the study. Data from one child were excluded due to scanner artifacts, resulting in a group of nineteen children (age 11.5-13.3, M = 12.5, SD = .51, 10 female). Sex distributions did not differ between the age-groups, χ^2 (1, n = 48) = .30, p = .863. The participants were right-handed according to self-report. They were screened for MRI using a comprehensive medical questionnaire to exclude participants with contraindications for MRI and to ensure that participants did not have a history of psychiatric or neurologic illness. All participants gave written informed consent for participation in the study. Parents of children that participated in the study gave written informed consent as well. Young adults received financial compensation for participation. Children received a gift and their parents received a monetary compensation for travel costs. The experiment was approved by the Central Committee on Research involving Human Subjects in the Netherlands.

Image acquisition

Scanning was performed with a standard whole-head coil on a 3-Tesla Philips Achieva MRI system (Best, Netherlands) in the Leiden University Medical Center. First, a resting-state scan was acquired. During this scan, all participants were instructed to lie still with their eyes closed and not to fall asleep. A total of 160 T2*-weighted whole brain Echo Planar Images (EPI) were acquired, including two dummy scans preceding the scan to allow for equilibration of T1 saturation effects (TR = 2.2 s; TE = 30 ms, flip angle = 80°, 38 transverse slices, 2.75 × 2.75 × 2.72 mm + 10% interslice gap). In addition, a high-resolution EPI scan was obtained (for registration purposes) as well as a T1-weighted anatomical scan (EPI scan: TR = 2.2 ms; TE = 30 ms, flip angle = 80°, 84 transverse slices, 1.964 × 1.964 × 2 mm;

3D T1-weighted scan: TR = 9.717 ms; TE = 4.59 ms, flip angle = 8°, 140 slices, .875 × .875 × 1.2 mm, FOV = 224.000 × 168.000 × 177.333). In accordance with Leiden University Medical Center policy, all anatomical scans were reviewed and cleared by a radiologist. No anomalous findings were reported.

Functional connectivity data analysis

For the functional connectivity analyses, we used an independent component analysis (ICA)-based approach (using MELODIC; Multivariate Exploratory Linear Decomposition into Independent Components), in combination with a *dual regression technique* (see also Biswal et al., 2010; Filippini et al., 2009). This technique allows voxelwise comparisons of functional connectivity between groups, using Randomise implemented in FSL (FMRIB's Software Library, www.FMRIb.ox.ac.uk/fsl; Smith et al., 2004).

The following prestatistics processing was applied: motion correction (Jenkinson et al., 2002); non-brain removal (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 4.0 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50.0s). To register EPI scans to standard space, functional scans of an individual were registered to the corresponding high resolution EPI images, which were registered to the T1 images, which were registered to standard MNI space (Jenkinson et al., 2002; Jenkinson and Smith, 2001).

The dual regression approach included three stages (see also Biswal et al., 2010; Filippini et al., 2009). The first stage involved the decomposition of all data in separate functional networks. For that purpose, time series of all young adults and children were temporally concatenated into a single 4D time series. This 4D time series was separated in 25 components using Independent Component Analysis (ICA) in MELODIC, with automatic dimensionality estimation (i.e., the number of components to extract was determined by MELODIC). One advantage of the ICA technique is that it automatically isolates noise-related signal fluctuations such as head motion (Damoiseaux et al., 2006; Fox and Raichle, 2007). This can be especially relevant in children. We selected nine components based on spatial similarity to functional networks described before (Damoiseaux et al., 2006; Supplementary figure S3.1: A-I): network A: visual system; network B: sensory-motor system; network C: default-mode network; network D: auditory system; network E: ventral stream; network F: executive control system; network G: dorsal attention system; network H: frontoparietal network (left hemisphere); network I: frontoparietal network (right hemisphere). In addition, we selected four other components that were potentially relevant functional networks (Supplementary figure S3.1: J-M): network J: anterior default mode network; network K: occipitoparietal network; network: L insula/operculum - cingulate network; network M: superior parietal network. The

assemblies of brain areas that constituted these functional networks are described in the Supplementary material (Supplementary figure S3.1). The other 12 components were related to white matter, CSF, head-movement, and other (non-neuronal) noise.

The second stage involved the identification of subject-specific component maps. First, individual time series were extracted for each component, using the 25 component maps in a (spatial) regression against the individual data. The resulting time series matrices were then entered in a second (temporal) regression against the associated data to estimate 25 spatial component maps for each individual.

In the final stage of the analysis, we used one-sample nonparametric t-tests to obtain group averages and two-sample t-tests to obtain group differences for each of the 13 selected functional networks. Voxelwise nonparametric permutation testing was performed using Randomise in FSL (with 5000 permutations; Nichols and Holmes, 2002). All statistical maps were thresholded at $p < 0.05$, FWE corrected for multiple comparisons using the Threshold-Free Cluster Enhancement (TFCE) technique (Smith and Nichols, 2009). Group comparisons were masked by group main effects (i.e., voxels that fell within the group map of the children and/or the group map of the young adults, thresholded at $p < 0.05$, FWE corrected for multiple comparisons using the TFCE technique).

We studied developmental differences in the size of functional networks, as well as in the strength of functional connectivity in all regions within these networks. Changes in the size of functional networks were examined by calculating the average number of voxels with a $z > 3.1$ (corresponding to a $p < .001$, uncorrected) for each network in each group. When a group showed a significantly larger number of voxels in a particular functional network, this was referred to as "more widespread functional connectivity". Changes in the strength of functional connectivity were examined by using a voxelwise comparison of correlation values between children and young adults. Higher correlation values in a specific area correspond to stronger involvement of that area in the functional network. When a group showed higher correlation values within a particular functional network, this was referred to as "increased functional connectivity". In contrast to seed-based analyses, the present method is not well suited to calculate developmental changes in the distance of functional connections.

Correction for grey matter differences

Some additional analyses were carried out to determine whether the observed differences in functional connectivity were influenced by underlying differences in grey matter density or registration error (Oakes et al., 2007). First, a voxel-based morphometry (VBM) analysis was performed to highlight regions with differences in grey matter density between children and young adults, using FSL-VBM with

default settings (Ashburner and Friston, 2000; Good et al., 2001). The following prestatistics processing was applied: non-brain removal (Smith, 2002); tissue-type segmentation (Zhang et al., 2001), nonlinear registration to MNI152 standard space (Andersson et al., 2007a; Andersson et al., 2007b). A study-specific template was created by averaging structural images from 19 children and 19 (randomly selected) young adults. Then, the native grey matter images were nonlinearly re-registered to this template map. The registered partial volume images were then modulated to correct for local expansion or contraction. The resulting images were spatially smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Finally, group maps for children and young adults were compared by voxelwise nonparametric permutation testing (with 5000 permutations; Nichols and Holmes, 2002), correcting for multiple comparisons across space (thresholded at $p < 0.05$) using the TFCE technique (Smith and Nichols, 2009).

Second, the fMRI data were reanalyzed using grey matter density information of each participant as a voxel-dependent covariate (see also Filippini et al., 2009). By including structural information into the functional connectivity analysis, the results are corrected for differences in grey matter density and the effects of possible misregistrations are accounted for (Oakes et al., 2007). One- and two sample nonparametric t-tests were performed to obtain group averages as well as group differences for all functional networks. Voxelwise nonparametric permutation testing was performed using Randomise in FSL (with 1000 permutations due to computational burden; Nichols and Holmes, 2002). The statistical maps were thresholded at $p < 0.05$, FWE corrected for multiple comparisons using the TFCE technique (Smith and Nichols, 2009). Group comparisons were masked by group main effects (thresholded at $p < 0.05$, FWE corrected for multiple comparisons using the TFCE technique).

3.3 Results

Functional connectivity

During the first stage of the analysis, resting-state fMRI data from the whole group were decomposed into 25 separate patterns of functionally connected regions, defined as functional networks. Hence, a functional network is characterized by strong functional connectivity between regions within the network. Nine of these networks were selected based on spatial similarity to functional networks described before (Damoiseaux et al., 2006; Supplementary figure S3.1: A-I). In addition, we selected four other functional networks that seemed functionally relevant (Supplementary figure S3.1: J-M). Inspection of the spatial patterns of group main effects revealed overlapping functional networks in children and young adults (Figure 3.1A). Core

Table 3.1 Overview of functional connectivity differences for the 13 networks of interest

Network	Regions showing increased/reduced activation in children
Children > Young adults	
C Default mode network	Bilateral Cuneus*
D Auditory system	Left Middle Frontal Gyrus*, Left Operculum/Insula and Bilateral Supplementary Motor Cortex
F Executive control system	Bilateral Anterior Cingulate Gyrus/Supplementary Motor Cortex*, Bilateral Superior Frontal Gyrus/Precentral Gyrus*, and Left Middle Frontal Gyrus
G Dorsal attention system	Left Posterior Cingulate Gyrus*
J Anterior default mode network	Bilateral Superior Parietal Lobule/Precuneus/Postcentral Gyrus/Lateral Occipital Cortex*, Bilateral Medial Frontal Cortex/Subcallosal Cortex*, Bilateral Anterior Cingulate Gyrus, Left Insula, and Right Superior Temporal Gyrus/Planum Temporale
K Occipitoparietal network	Left Middle Frontal Gyrus* and Left Insula
L Insula/Operculum - Cingulate network	Left Cuneus*, Right Temporal Pole, and Right Insula
M Superior Parietal network	Bilateral Precuneus*, Bilateral Lateral Occipital Cortex, Bilateral Occipital Pole*, Intracalcarine Cortex, Bilateral Paracingulate Gyrus/Anterior Cingulate Cortex*, Posterior Cingulate Cortex, Right Middle Frontal Gyrus*, and Right Precentral Gyrus
No difference	
H Frontoparietal network (left)	-
I Frontoparietal network (right)	-
Children < Young adults	
A Visual system	Bilateral Posterior Hippocampus* and Bilateral Occipital Pole/Occipital Fusiform Gyrus
B Sensory-motor system	Left Postcentral Gyrus/Superior Parietal Lobule*
E Ventral stream	Bilateral Occipital Fusiform Gyrus*, Lateral Occipital Cortex*, Cuneus*, Left Supramarginal Gyrus*, Right Frontal Pole, Right Frontal Orbital Cortex, and Right Anterior Hippocampus

All differences are FWE corrected using $p < 0.05$, based on the TFCE statistic image, and masked by group main effects.
Only clusters > 10 voxels are reported in the table.
* Group differences that survived when grey matter was added as a covariate.

regions of all 13 functional networks were found in both groups (all $p < 0.05$, FWE corrected, based on the TFCE statistic image). To examine whether functional networks were more widespread in children, we calculated for both groups the average number of voxels with a $z > 3.1$ (corresponding to a $p < .001$, uncorrected; Figure 3.1B). A Mann-Whitney test showed that network D, F, J, L, and M were significantly larger in children than in young adults (network D: $U = 174$, $p = .032$, $r = .31$; network F: $U = 184$, $p = .054$, $r = .28$ network J: $U = 129$, $p = .002$, $r = .45$; network L: $U = 142$, $p = .005$, $r = .41$ and network M: $U = 86$, $p < .001$, $r = .58$). None of the functional networks was larger in adults.

Voxelwise group-comparisons revealed increased functional connectivity in children compared to young adults in 8 of the 13 networks (i.e., network C, D, F, G, J, K, L, and M; all $p < 0.05$, FWE corrected, based on the TFCE statistic image). Regions showing increased functional connectivity included frontal areas, mainly in middle frontal gyrus and in regions along the midline (i.e., anterior cingulate gyrus, supplementary motor cortex, and ventromedial prefrontal cortex). Further, increased functional connectivity was found in a few temporal regions and in frontal operculum/anterior insula. Many functional networks also showed increased functional connectivity in posterior regions such as cuneus, precuneus, posterior cingulate gyrus, and superior parietal lobule. (Table 3.1; Figure 3.1A). Three functional networks showed reduced functional connectivity in children compared to young adults (i.e., network A, B, and E; all $p < 0.05$, FWE corrected, based on the TFCE statistic image). Reduced functional connectivity was found in several occipital regions, frontal pole, left postcentral gyrus/superior parietal lobule and in the hippocampus (Table 3.1; Figure 3.1A). Two networks did not show any significant differences between groups: the left and right frontoparietal network (i.e., network H and I).

Grey matter

VBM analyses yielded significant group differences in grey matter in several regions across the whole brain (Supplementary figure S3.2, $p < 0.05$, FWE corrected, based on the TFCE statistic image). Most cortical regions exhibited increased grey matter density for children compared to young adults. Reduced grey matter density was found in bilateral hippocampus/amygdala, bilateral cerebellum, and right occipital pole.

Given the extensive grey matter differences, we aimed to study whether the observed functional connectivity differences were influenced by grey matter density (or registration error). To this end, grey matter information was added as a voxel-dependent covariate in the functional connectivity analysis (Filippini et al., 2009; Oakes et al., 2007). Despite the grey matter correction, we still found significant functional connectivity differences in all 11 functional networks that initially showed group differences (Table 3.1; Supplementary figure S3.3, and S3.4; all $p <$

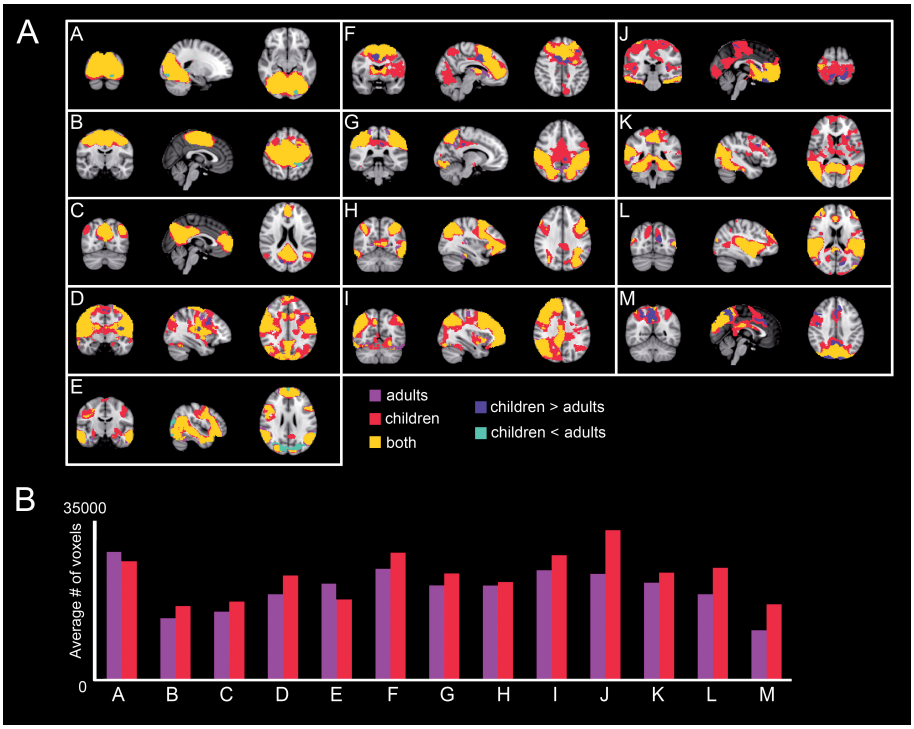

Figure 3.1 (A) Spatial group maps representing young adults (purple), children (red), and the overlap between children and young adults (orange) for the 13 networks of interest. Regions that showed increased functional connectivity for children compared to young adults are presented in blue; regions that showed reduced connectivity are presented in green. Images are overlaid on coronal, sagittal, and axial slices of an MNI standard brain and thresholded using $p < 0.05$, FWE corrected, based on the TFCE statistic image. The left side of the image corresponds to the right side of the brain. (B) The average number of voxels with a $z > 3.1$ in each of the 13 functional networks of interest for young adults (purple) and children (red). Network D, F, J, L, and M were significantly larger in children than in young adults.

0.05, FWE corrected, based on the TFCE statistic image). However, some effects were reduced and a few regions were no longer significantly different. In other words, in these regions it was not possible to distinguish functional connectivity differences from grey matter density effects or registration error.

3.4 Discussion

Functional connectivity is defined as the temporal correlation of BOLD fluctuations from different parts of the brain (Fox and Raichle, 2007; Friston et al., 1993), and can be organized in the brain in a number of functional networks (defined

as brain regions with strong interregional functional connectivity). In the present study we examined whole brain functional connectivity in children and young adults. We found similar functional networks in children and young adults. That is, core regions of all functional networks were present in both groups. This is in agreement with developmental task fMRI studies that demonstrated that core task-related regions can already be detected early in development (Casey et al., 1997; Gaillard et al., 2000; Holland et al., 2001; Passarotti et al., 2003). However, we found differences in the size of functional networks (i.e., the number of voxels in a functional network), as well as in the strength of functional connectivity in specific areas within these networks (i.e., the correlation value). These findings suggest that while the basic configuration of functional networks in the brain has been established by the age of 12, the fine-tuning or specialization of functional networks may continue during adolescence. This is consistent with the hypothesis that large-scale anatomical networks are prespecified, while activity dependent processes might be crucial for functional specialization of these networks (Johnson, 2005; Raichle, 2006; Rakic et al., 2009).

Functional connectivity differences

The majority of functional networks (i.e., 8 out of 13) showed regional increases of functional connectivity in children and for these functional networks functional connectivity was often more widespread. This is in agreement with prior studies of functional connectivity (Kelly et al., 2009) and task activation in children (Casey et al., 2002; Durston et al., 2006; Holland et al., 2001; Konrad et al., 2005; Moses et al., 2002; Tamm et al., 2002). In addition, it has been demonstrated that children show more functional connectivity between functional networks (Stevens et al., 2009) and lower levels of hierarchical functional organization (Supekar et al., 2009). Taken together, these developmental differences indicate that functional networks in children are less specialized or efficient (Durston et al., 2006; Fair et al., 2009; Fair et al., 2007; Johnson and Munakata, 2005).

We specifically found increased functional connectivity in functional networks associated with complex cognitive or emotional functions, such as the executive control system, the dorsal attention system, and the default mode network. Increased functional connectivity was also found in the auditory network. Although this network is associated with auditory perception, it is probably also involved in higher cognitive functions related to language (Smith et al., 2009). Surprisingly, functional networks associated with basic visual or sensory-motor functions (i.e., the sensory-motor system, the visual system, and the ventral stream) showed the opposite effect. These networks involved regions with reduced functional connectivity in children compared to young adults. Although most prior studies did not specifically focus on functional connectivity in basic visual and sensory-motor networks, one study demonstrated reduced functional connectivity in a motor control network in children and adolescents (8-12 and 13-17 years) compared to young

adults (Kelly et al., 2009). Thus, the present results suggest qualitatively different developmental trajectories for functional connectivity between regions associated with complex cognitive or emotional functions and between regions associated with basic visual or sensory-motor functions.

Correction for grey matter density

In agreement with prior studies, we found extensive grey matter differences between children and adults. The majority of cortical areas showed increased grey matter density in children (Giedd, 2004; Gogtay et al., 2004; Sowell et al., 2003; Sowell et al., 2001b), whereas reduced grey matter density was found in anterior hippocampus and amygdala (Giedd et al., 1996; Guo et al., 2007; Ostby et al., 2009), cerebellum (Konrad et al., 2005; Sowell et al., 2002b) and occipital cortex (Giedd et al., 1999). Despite the extensive grey matter differences, a functional connectivity analysis using grey matter density as a voxel-dependent covariate still revealed significant functional connectivity differences in all 11 networks that initially showed group differences. These results suggest that the majority of functional connectivity differences are not simply explained by grey matter density effects or registration error.

The underlying anatomy and physiology of developing functional connectivity

One remaining question is how to relate changes of functional connectivity to anatomical and physiological changes in the developing brain. Structural brain maturation involves a multitude of complex and overlapping processes (Johnson, 2005; Stiles, 2008; Uylings, 2006), and from the present data we cannot conclude directly which underlying mechanisms contribute to changes of functional connectivity across development. However, some parallels exist between the development of functional connectivity and anatomical, histological and neurochemical processes described elsewhere. For example, we found similar connectivity patterns in children and young adults, which seems consistent with the fact that major pathways are in position by the age of 12 and the peak of dendritic development has been reached (LaMantia and Rakic, 1990; Mrzljak et al., 1990; Petanjek et al., 2008). At the same time, the majority of these functional networks showed regional increases of functional connectivity in children. This might be related to the increased number of synaptic contacts in children (Bourgeois et al., 1994; Bourgeois and Rakic, 1993; Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997) and/or the high levels glucose metabolism and cerebral blood flow (Chiron et al., 1992; Chugani, 1998; Chugani et al., 2002).

It could be hypothesized that development of functional connectivity is guided by selective elimination (or "reorganization" Kostovic, 1990) of synapses, which enhance the specificity and efficiency of information processing (Changeux and Danchin, 1976; Chechik et al., 1998; Goldman-Rakic, 1987). In addition, myelination and/or increases in axon diameter (Benes et al., 1994; LaMantia and Ra-

kic, 1990; Paus et al., 1999; Yakovlev and Lecours, 1967) may increase the speed of neuronal signal transmission and modulate the synchrony of neuronal firing across functional networks (Fields, 2008; Paus, 2010). Finally, the efficiency of communication across functional networks might be further modulated by the protracted development of neurotransmitter systems (Benes, 2001; Kostovic, 1990). Taken together, the functional connectivity differences that were found in the present study may reflect a combination of factors, including myelination, synaptic reorganization, changing levels of neurotransmitters, and decreasing glucose metabolism and cerebral blood flow, all of which should be investigated further in future research. To this end, investigations into the development of functional connectivity could be combined with MRI measures of anatomical connectivity, electrical measures of brain activity (e.g., EEG or local field potential recordings), and/or postmortem histological data (Fox and Raichle, 2007).

Conclusion

The results of the present study indicate that although the basic configuration of functional networks in the brain has been established by the age of 12, functional networks continue to change during adolescence (or young adulthood) depending on the functional domain. In addition, we showed that the majority of functional connectivity differences could not be explained on the basis of grey matter density alone. In future studies, it is important to replicate the present results across a wider age range and to identify the underlying anatomical and neurophysiological mechanisms that cause these functional connectivity differences. Finally, the age period between 12 and 25 is characterized by important changes in neurocognitive skills, and psychosocial functioning. These changes are dependent upon the rapid accumulation of experiences and are accompanied by a changing (social) environment in which significant others (e.g., peers, parents, teachers) play an important role. Development of functional connectivity in the brain may be a prerequisite for the proper development of psychological functions. On the other hand, functional connectivity might also be shaped by experience and develop in relation to the environmental demands (Raichle, 2006; Sporns et al., 2004). The interplay between the development of functional connectivity and cognitive, social, and emotional maturation is therefore an important direction for future research.

3.5 Supplementary material

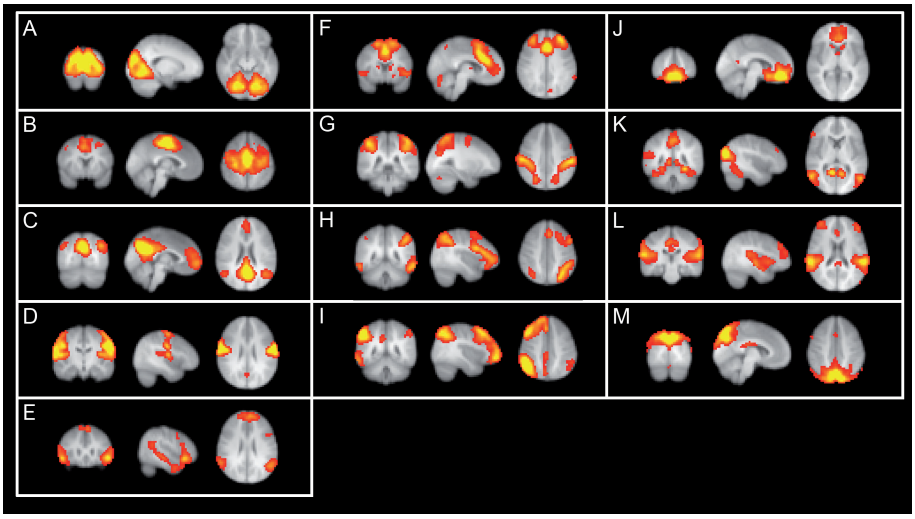

Figure S3.1 ICA maps of the 13 networks of interest estimated from the complete dataset (i.e., concatenated time series of all adults and children). Images are *z* statistics overlaid on coronal, sagittal, and axial slices of an MNI standard brain. Yellow to red are *z* values, ranging from 3.0 to 10.0. The left side of the image corresponds to the right side of the brain.

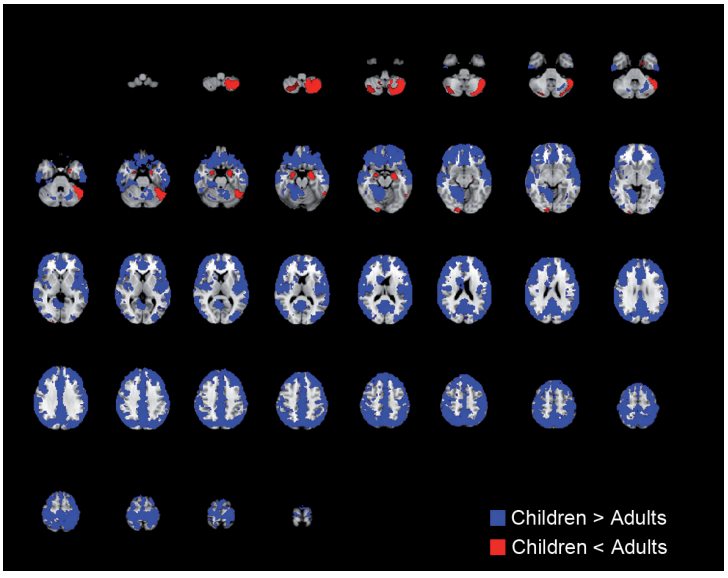

Figure S3.2 VBM results showing regions with increased (blue) and reduced (red) grey matter volume in children compared to adults. Images are overlaid on axial slices of an MNI standard brain and thresholded using $p < 0.05$, FWE corrected, based on the Threshold-Free Cluster Enhancement (TFCE) statistic image. The left side of the image corresponds to the right side of the brain.

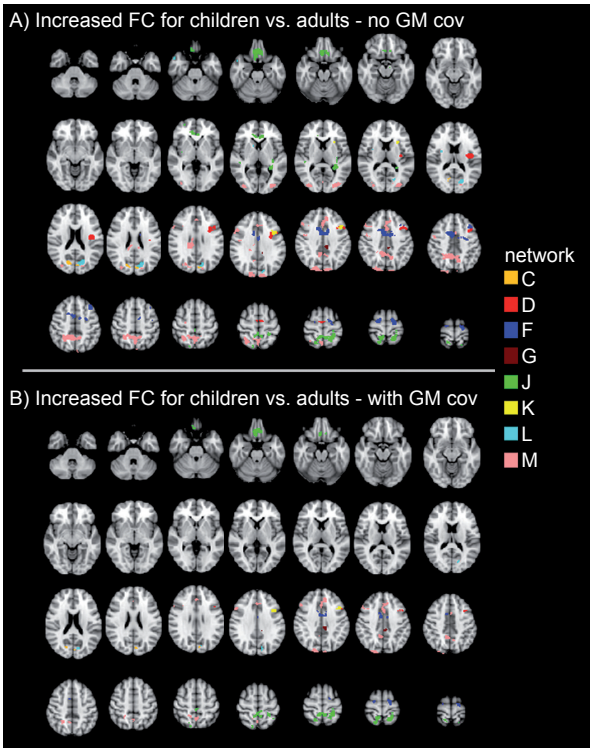

Figure S3.3 Regions showing increased functional connectivity in children compared to adults for network C, D, F, G, J, K, L, and M. Images are overlaid on axial slices of an MNI standard brain and thresholded using $p < 0.05$, FWE corrected, based on the TFCE statistic image. The left side of the image corresponds to the right side of the brain. (A) Functional connectivity differences when grey matter differences were not taken into account. (B) Functional connectivity differences when grey matter differences were included as a covariate in the analysis. FC = functional connectivity; GM cov = grey matter covariate.

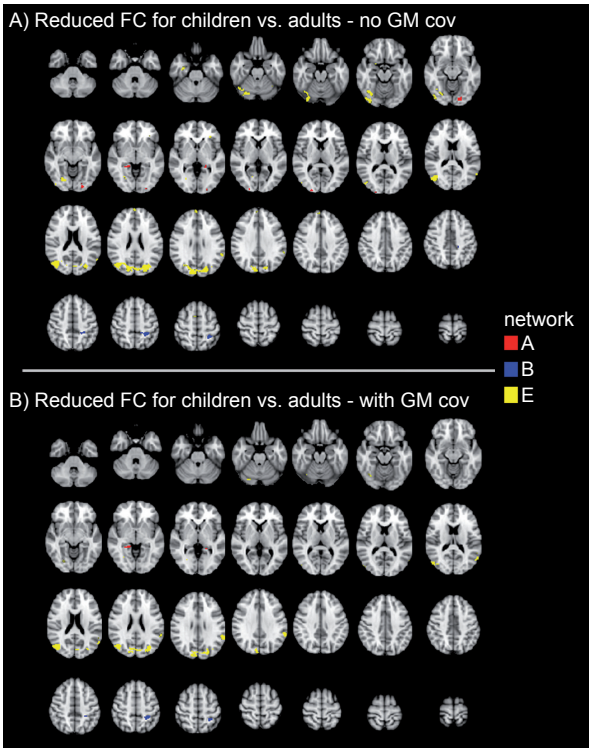

Figure S3.4 Regions showing reduced functional connectivity in children compared to adults for network A, B, and E. Images are overlaid on axial slices of an MNI standard brain and thresholded using $p < 0.05$, FWE corrected, based on the TFCE statistic image. The left side of the image corresponds to the right side of the brain. (A) Functional connectivity differences when grey matter differences were not taken into account. (B) Functional connectivity differences when grey matter differences were included as a covariate in the analysis. FC = functional connectivity; GM cov = grey matter covariate.