A comprehensive study of whole-brain functional connectivity and grey matter volume in children and young adults

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Introduction Neuroimaging studies of human brain development show maturation of brain structure (*e.g. 1*), as well as brain function (*e.g. 2*). However, the relation between development of brain structure and function is still not well understood. Examination of the developing brain from a network perspective, studying functional brain connectivity 'at rest', is expected to give further insights into human brain development. Recently, a few studies have shown that functional connectivity undergoes important changes throughout childhood and adolescence (*e.g. 3, 4*). Yet, most of these studies focused on specific regions or networks, and did not take the well-known grey matter differences into account as a potential explanation for changing functional connectivity. In the present study 1) we investigated voxel-wise whole-brain functional connectivity in children and adults, without a priori restriction to specific seed regions or networks, and 2) we examined to what extent observed changes in functional brain connectivity can be explained by changes in local grey matter.

Methods Nineteen children (11-13 years) and twenty-nine adults (19-25 years) underwent a resting-state fMRI scan and a high-resolution structural scan at 3T. Resting-state functional connectivity was analyzed by means of a group Independent Component Analysis (ICA) on the complete dataset (i.e. adults and children), in combination with a dual regression technique that allows whole-brain voxel-wise comparisons of connectivity between groups for each of the networks (*5*). Whole brain structural analyses were performed using voxel-based morphometry (VBM). Finally, to study the direct influence of grey matter volume on functional connectivity findings, the connectivity analysis was repeated, now including grey matter volume information as a voxel-dependent covariate. All analyses were performed using FSL (www.fmrib.ox.ac.uk/fsl), thresholding at $p < 0.05$, corrected.

Results Resting-state data from the complete dataset were decomposed into 25 separate functional networks, of which 13 were decided to be functionally relevant. Double regression results indicated that all 13 networks were present both in adults and in children (Figure 1). However, networks in children were more widespread than adult networks. Eight networks showed regions with increased connectivity for children compared to adults (i.e. network 2, and 7-13), including regions in frontal and parietal association cortices. In addition, three networks showed regions with decreased connectivity for children compared to adults (i.e. network 1, 5 and 6), including occipital pole, parahippocampal gyrus and postcentral gyrus. VBM analysis of structural images revealed grey matter differences in many regions across the whole brain. Yet, our analyses show that the majority of the observed changes in functional connectivity cannot be explained by changes in grey matter volume.

Conclusion With these results we provide new insights in the development of functional brain connectivity and its relation with structural brain maturation. First, visual inspection shows that throughout the entire brain, functional networks appear to extend over larger regions in children. These findings may be explained by increasing segregation and specialization of neural networks over the course of development (*3, 4*). The majority of networks showed regions with increased connectivity for children compared to adults. However, some networks (the visual network, the sensory-motor network and a network that could be characterized as the ventral stream) showed the opposite effect: less connectivity in children. In general, these results suggest that most networks that are associated with higher order cognitive functions show areas of increased connectivity for children compared to adults, whereas networks associated with more basic sensory and motor functions showed decreased connectivity. Most of the observed differences in functional connectivity could not be explained by local cortical grey matter volume.

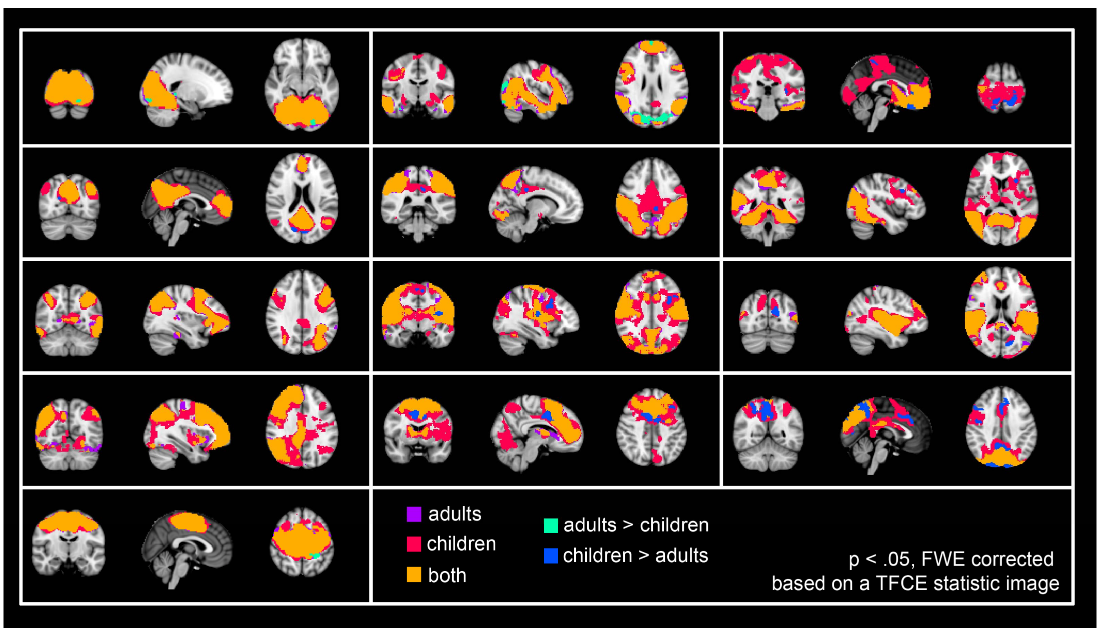

Figure 1. Double regression results for each of the thirteen components of interest; spatial maps for children, adults, and children versus adults, overlaid on coronal, sagittal and axial slices of a MNI standard brain.

References (1) J. N. Giedd, Journal of Adolescent Health 42, 335 (2008); (2) B. Luna, A. Padmanabhan, K. O'Hearn, Brain Cogn (2009); (3) D. A. Fair et al., Proceedings of the National Academy of Sciences of the United States of America 104, 13507 (2007); (4) A. M. C. Kelly et al., Cerebral Cortex 19, 640 (2009); (5) N. Filippini et al., Proc. Natl. Acad. Sci. U. S. A 106, 7209 (2009)