Differences between the child and adult brain in the local functional structure of the cerebral cortex

Jesus Pujol [a,b,*], Laura Blanco-Hinojo [a,b], Didac Macia [a], Gerard Martínez-Vilavella [a], Joan Deus [a,c], Víctor Pérez-Sola [b,d,e], Narcís Cardoner [b,f,g], Carles Soriano-Mas [b,h,i], Jordi Sunyer [j,k,l]

[a] MRI Research Unit, Department of Radiology, Hospital del Mar, Passeig Marítim 25-29, 08003 Barcelona, Spain
[b] Centro Investigación Biomédica en Red de Salud Mental, CIBERSAM, Barcelona, Spain
[c] Department of Clinical and Health Psychology, Autonomous University of Barcelona, Spain
[d] Institute of Neuropsychiatry and Addictions, Hospital del Mar-IMIM, Spain
[e] Department of Psychiatry, Autonomous University of Barcelona, Barcelona, Spain
[f] Mental Health Department, Parc Taulí Sabadell University Hospital, Spain
[g] Department of Psychiatry and Forensic Medicine, Autonomous University of Barcelona, Spain
[h] Department of Psychiatry, Bellvitge University Hospital, Bellvitge Biomedical Research Institute (IDIBELL), Spain
[i] Department of Psychobiology and Methodology in Health Sciences, Autonomous University of Barcelona, Spain
[j] ISGlobal, Barcelona, Spain
[k] Pompeu Fabra University, Barcelona, Catalonia, Spain
[l] Ciber on Epidemiology and Public Health (CIBERESP), Madrid, Spain

ARTICLE INFO

ABSTRACT

Imaging studies on neuronal network formation provide relevant information as to how the brain matures during adolescence. We used a novel imaging approach combining well-established MRI measures of local functional connectivity that jointly provide qualitatively different information relating to the functional structure of the cerebral cortex. To investigate the adolescent transition into adulthood, we comparatively assessed 169 preadolescents aged 8–12 years and 121 healthy adults. Whole-brain functional connectivity maps were generated using multi-distance measures of intracortical neural activity coupling defined within iso-distant local areas. Such Iso-Distant Average Correlation (IDAC) measures therefore represent the average temporal correlation of a given brain unit, or voxel, with other units situated at increasingly separated iso-distant intervals. The results indicated that between-group differences in the functional structure of the cerebral cortex are extensive and implicate part of the lateral prefrontal cortex, a medial frontal/anterior cingulate region, the superior parietal lobe extending to the somatosensory strip and posterior cingulate cortex, and local connections within the visual cortex, hippocampus, amygdala and insula. We thus provided detail of the cerebral cortex functional structure maturation during the transition to adulthood, which may serve to establish more accurate links between adolescent performance gains and cerebral cortex maturation. Remarkably, our study provides new information as to the cortical maturation processes in prefrontal areas relevant to executive functioning and rational learning, medial frontal areas playing an active role in the cognitive appraisal of emotion and anxiety, and superior parietal cortices strongly associated with bodily self-consciousness in the context of body image formation.

1. Introduction

Developmental changes in brain structure and function implicate the progressive sculpting of a multi-scale pattern of neural connections. Neuroimaging research increasingly contributes to characterizing neuronal network maturation. Previous studies focusing on identifying developmental changes based on functional connectivity metrics or functional anatomy mapping do indeed coincide in indicating that brain maturation evolves with a combination of network integration and segregation (e.g., see reviews Cao et al., 2017; Menon, 2013; Khundrakpam et al., 2016; Oldham and Fornito, 2019).

Moving beyond the identification of anatomical change location, we used a novel approach designed to map the spatial *structure* of local cortical functional connections using a composite measure. Essentially, we expanded well-established MRI measures of local functional connectivity (Sepulcre et al., 2010; Tomasi and Volkow, 2010; Zang et al., 2004) by combining the connectivity measures of varying distances.

Our Iso-Distant Average Correlation (IDAC) measures represent the average functional MRI temporal correlation of a given brain unit, or voxel, with other units situated at increasingly separated iso-distant intervals (Macia et al., 2018). Three IDAC measures are combined to generate color-coded RGB maps that inform not only of the location of changes (functional anatomy), but also the functional structure of local cortical connections (a kind of "*functional histology*" by using analogies).

We comparatively analyzed the functional structure of the cerebral cortex in preadolescence and adulthood. The child brain transforms into an adult brain during adolescence through a sensitive period of rapid maturation and adaptation, which makes the individual cognitively more capable, albeit emotionally vulnerable (Davey et al., 2008; Paus et al., 2008; Dahl et al., 2018). Differences in the functional structure of the cerebral cortex between adults and preadolescents may thus provide us with useful information as to the maturational changes evolving during the developmental period of adolescence.

During development, the cerebral cortex specializes in functionally distinct areas largely according to the pattern of neural connections (Cao et al., 2017; Khundrakpam et al., 2016; Long et al., 2017). The progression of local connections is based on morphological and neurochemical changes known to be highly active during adolescence. Synaptic pruning, myelination of intra-cortical axons and the increase in axonal caliber are all indeed accelerated during adolescence (Paus et al., 2008; Larsen and Luna, 2018). The synaptic architecture is lastly stabilized by the "perineuronal nets", a component of the extracellular matrix that ensheaths cell bodies and proximal dendrites (Larsen and Luna, 2018; Takesian and Hensch, 2013). Gamma-aminobutyric acid (GABA) neurotransmission also matures during adolescence (Larsen and Luna, 2018; Silveri et al., 2013). Interestingly, GABA signaling promotes synapse elimination and axon pruning in developing cortical inhibitory interneurons (Wu et al., 2012). Such developmental changes in the structure of connections may affect both local and distant functional connectivity between regions.

Our composite local functional connectivity measure may uniquely inform the connectivity-related specialization of the cerebral cortex. The combination of three measures provides a more complete functional characterization of local connections than previous approaches, as local connectivity is distance-specific to a large extent. Indeed, the connectivity mapping based on combining three distance effects proved to discriminate well between major classical anatomo-functional cortical areas (Macia et al., 2018). An illustration of the capability of IDAC measures to capture local distance-specific differences was observed in obsessive-compulsive disorder patients in orbitofrontal and sensory cortices (Pujol et al., 2019a). Multi-distance local measures may thus provide a more complete characterization of the local spatial structure than measures based on a single distance and, in turn, may serve to identify differences between the child and adult brain in cortical area specialization.

The most notable performance gains in adolescence include the refinement of executive functioning skills, learning to reason about abstract concepts and creating a mature understanding of self (Dahl et al., 2018; Paus, 2005; Blakemore and Choudhury, 2006; Davey et al., 2019). Accordingly, we hypothesized that the largest differences in the functional structure of the cortex between adults and preadolescents would be identified in brain areas integrating different information sources such as the prefrontal cortex and posterior multimodal areas. Thus, we tested whether IDAC measures may capture developmental functional specialization in these areas. Existing developmental data are indeed consistent with the notion that the associative, higher-order cortex maturates later than primary areas in childhood (Menon, 2013; Khundrakpam et al., 2016; Oldham and Fornito, 2019; Chomiak and Hu, 2017; Pujol et al., 1993). Interestingly, some studies have indicated that adolescence may be critical for developing sexual dimorphism in functional connectivity between associative areas (Ernst et al., 2019; Shaw et al., 2011; Wu et al., 2013; Satterthwaite et al., 2015). Our study may contribute to previous research by providing a detailed depiction of cerebral cortex functional structure maturation and thus enable a better understanding of the adolescent transition to adulthood.

2. Methods

2.1. Participants

The children sample was selected from participants of a large-scale project designed to assess the effects of environmental factors on brain development (BREATHE, The European Commission: FP7-ERC-2010-AdG, ID 268479) (Pujol et al., 2016). The comparative sample involved healthy participants from a previously reported study characterizing the functional structure of the cerebral cortex with IDAC measures in adults (Pujol et al., 2019a). Both children and adults were volunteers selected from the same healthy general population of the metropolitan area of Barcelona.

A total of 169 typically developing children with a mean age of 9.8 years, SD of 0.9, range 8.0 to 12.0 and male/female: 80/89 were selected from a primary sample of 263 participants (Pujol et al., 2016) on the basis of strict imaging quality (see below). The adult sample included 121 participants with a mean age of 34.6 years, SD of 10.2, range 16 to 61, male/female: 66/55 and the level of education was primary in 9 participants (7%), secondary in 52 (43%) and university level in 60 (50%). Sex distribution did not differ between children and adult groups ($\chi^2 = 0.15$, $p = 0.236$).

For the child sample, all parents or tutors signed the informed consent form approved by the Research Ethical Committee (No. 2010/41221/I) of the IMIM-Parc de Salut Mar, Barcelona, Spain and the FP7-ERC-2010-AdG Ethics Review Committee (268479-22022011). For the adult sample, the study protocol was approved by the Institutional Review Board of the University Hospital of Bellvitge (Barcelona). Written informed consent was obtained from each participant. The whole study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Data will be available via a request to the Authors with no particular restrictions, although a formal data sharing agreement will be considered.

2.2. MRI acquisition

All study participants were uniformly assessed with a single MRI scanner. We used a 1.5-T Signa Excite system (General Electric, Milwaukee, Wisconsin) equipped with an eight-channel phased-array head coil and single-shot echo-planar imaging software. The functional sequence consisted of gradient recalled acquisition in the steady state (repetition time, 2000 ms; echo time, 50 ms; and pulse angle, 90°) in a 24-cm field of view, with a 64×64 pixel matrix and a slice thickness of 4 mm (interslice gap, 1.5 mm). Twenty-two interleaved sections, parallel to the anterior-posterior commissure line, were acquired to generate 120 whole-brain volumes (total duration of 4 min), excluding 4 initial additional dummy volumes. In the child sample, the functional sequence lasted 6 min, but only the first 4-min acquisition was used to make both samples comparable. All participants were instructed to relax, stay awake, and to lie still without moving, while keeping their eyes closed throughout the procedure.

In both children and adults, high-resolution 3D anatomical images were also obtained using an axial T1-weighted three-dimensional fast spoiled gradient inversion recovery-prepared sequence (repetition time 11.9 ms; echo time 4.2 ms; flip angle 15°; field of view 30 cm; 256×256-pixel matrix; slice thickness 1.2 mm), which served to assist functional connectivity image preprocessing.

2.3. Image processing

Imaging data were processed using MATLAB version 2014b (The MathWorks Inc, Natick, Mass) and Statistical Parametric Mapping soft-

ware (SPM8; The Wellcome Department of Imaging Neuroscience, London).

Anatomical and functional images were visually inspected to detect possible acquisition artifacts. Functional MRI images were slice-time corrected, realigned and then smoothed by convolving the image with a $4 \times 4 \times 4$ mm^3 full width at half maximum (FWHM) Gaussian kernel.

The resulting realignment parameters were used for scrubbing, namely, discarding motion-affected volumes (Power et al., 2014). For each subject, mean inter-frame motion measurements (Pujol et al., 2014) served as an index of data quality to flag volumes of suspect quality across the run. At time points with mean inter-frame motion > 0.2 mm, the corresponding volume, the immediately preceding and the succeeding two volumes were all discarded. Using this procedure, a mean of 3.66 (SD, 5.2; range, 0–19) volumes from the total of 120 volumes included in the functional MRI sequence were removed in the child sample, and 3.02 (SD, 8.9; range 0–53) volumes in the adult sample ($p = 0.441$, ns).

Image volumes were then co-registered to their anatomical images with an affine transformation. A warping matrix was also estimated for every subject to match a group template created from the 3D anatomical individual acquisitions and then to the Montreal Neurological Institute (MNI) space using DARTEL normalization (Ashburner, 2007). Image volumes were re-sliced to $3 \times 3 \times 3$ mm. Estimated DARTEL normalizations to the MNI space were applied to the IDAC results to enable group inferences.

Analyses were conducted in a gray matter mask split into left and right hemispheres, so that no adjacent voxels from the medial regions of one hemisphere would be locally associated with those from the other hemisphere. The two hemispheres were brought back together once the IDAC values had been calculated. The left and right hemisphere gray matter masks were obtained by setting a threshold of $p > 0.4$ on the gray matter probability maps obtained from the DARTEL group template. As IDAC value estimations were carried out in every subject's native space, the template masks were back-transformed with the inverse estimated normalization.

All time series were regressed on the 6 rigid body realignment parameters and their first-order derivatives, and on the average white matter, CSF and global brain signals extracted from the native tissue masks. Finally, all functional MRI time series were band-passed with a Discrete Cosine Transform (DCT) filter letting through frequencies in the 0.01–0.1 Hz interval.

In the child sample, 94 participants were excluded from an initial sample of 263 subjects on the grounds of imaging quality and the strict mean inter-frame motion (Pujol et al., 2014) criterion of > 0.1 mm, in addition to sub-optimal 3D anatomical image quality. The excluded children were slightly younger (9.5 ± 0.9 years *vs* 9.8 ± 0.9 years, $t=$ 2.2 and = 0.027) and showed a marginal difference in sex distribution (male/female: 55/39 *vs* 80/89, $\chi^2 = 3.0$ and $p=0.095$). In the adult sample, three participants (2 women) were also excluded from an initial sample of 124 subjects due to head motion during MRI acquisition. Supplementary Fig. 1 shows frequency distribution histograms of mean inter-frame motion for included children and adults.

2.4. Iso-Distant Average Correlation (IDAC) maps

The study aimed at describing local connectivity in the cortex and tightly integrated structures such as the hippocampus and amygdala. Data from the basal ganglia, brainstem and cerebellum were not included in the analysis. Whole-cortex IDAC maps were generated by estimating the average temporal correlation of each voxel with all its neighboring voxels placed at increasingly separated Euclidean iso-distant intervals. IDAC was computed in native space separately for each hemisphere after realignment and smoothing. Three IDAC maps were obtained at distance intervals 5–10 mm, 15–20 mm and 25–30 mm. The definition and mathematical formulation of IDAC measures are exten-
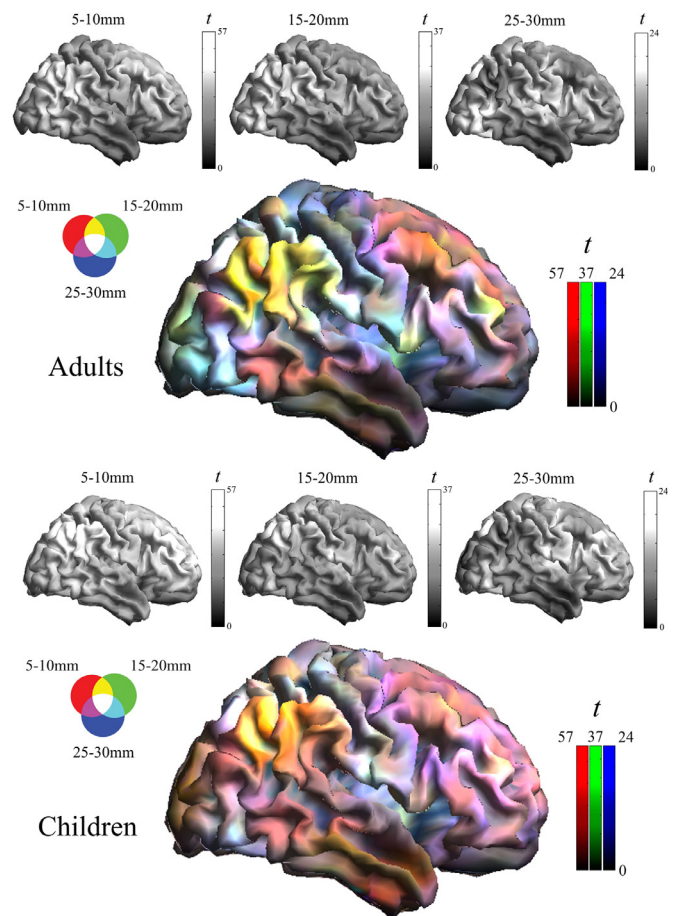

Fig. 1. One-sample Iso-Distant Average Correlation (IDAC) brain maps. The gray images correspond to individual distance IDAC maps. The color images show the result of superimposing the three IDAC maps using RGB (red, green and blue). The composite images are thus made up of primary RGB colors and their secondary combinations. Note that such a multi-distance map is able to discriminate between various cortical areas.

sively described in our early report (Macia et al., 2018) and in the Supplementary material.

Multi-distance IDAC color maps were generated from the overlay of the three IDAC maps using an RGB color codification (e.g., Fig. 1). RGB color channels enabled the display of three values simultaneously. RED corresponding to the results from 5 to 10 mm IDAC map analyses, GREEN from 15 to 20 mm and BLUE from 25 to 30 mm. The overlapping of these primary colors produces a full range of secondary colors, which illustrate the variations in the functional structure of the cerebral cortex and group differences.

To establish a color-coding, each gray image corresponding to the three individual IDAC maps (5–10 mm, 15–20 mm and 25–30 mm) was separately scaled to its maximal t value using conventional, automated SPM tools (see Fig. 1). Composite RGB maps were generated from individual (three distances) one-sample IDAC maps and individual between-group comparison t-maps.

2.5. Statistical analysis

IDAC connectivity maps were included in SPM group-wise random-effects analyses adopting a 2×3 mixed design ANOVA (ANCOVA) model (group [children, adults] by distance [5–10 mm, 15–20 mm and 25–30 mm]). A motion summary measure (mean inter-frame motion) for each participant was included as a covariate. To provide a complete depiction of the differences between the child and adult cerebral cortex,
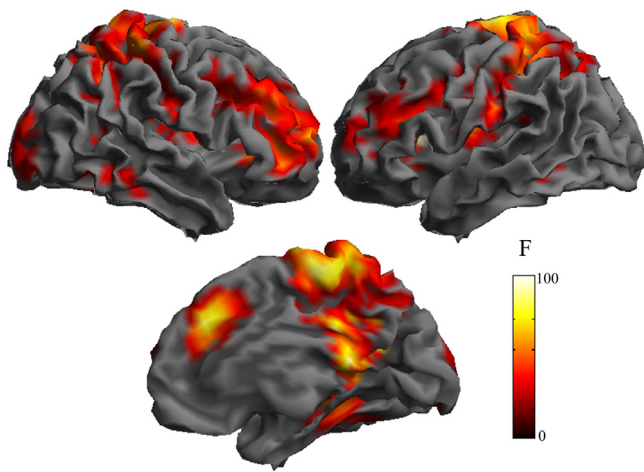
Fig. 2. Main effect of group illustrating the differences between children and adults in IDAC measures across the three distance maps (ANOVA). Height threshold $F= 23$ {$p<0.05$ – FWE}.

we tested for main group effects, post-hoc between-group differences in connectivity for each IDAC map and group-by-distance interactions. An ANOVA model was also used to assess differences in IDAC measures between males and females within age groups, and group by sex interactions to identify potential differential development effects.

In all the analyses, results were considered significant when clusters formed at a threshold of $p< 0.005$ survived whole-brain family-wise error (FWE) correction ($p< 0.05$), calculated using SPM, which was further adjusted at $p< 0.006$ using Bonferroni correction for multiple comparisons (6 simple effects, 2 main effects and the interaction). The overall differences between both study samples were displayed at higher thresholds (equivalent to single-voxel FWE-correction) to emphasize brain areas showing the most robust developmental effects.

3. Results

Whole-brain maps of the local functional structure of the cerebral cortex were generated from combined IDAC functional connectivity measures in both adults and preadolescents. The RGB composition of short (5–10 mm), middle (15–20 mm) and long-distance (25–30 mm) maps is illustrated in Fig. 1. The maps were able to parcellate the cerebral cortex into regions arguably resembling the parcellations we can find in traditional brain atlases (e.g., Brodmann, 2006). For example, in the adult sample, the angular and supramarginal gyri of the inferior parietal lobule are both mostly connected at short and medium local distances (typically yellow in the maps), whereas in the lateral occipital cortex the dominant pattern involves high connectivity at the longer local distance ranges.

The analysis of the main effect of group comparing IDAC functional connectivity measures across the three distances did demonstrate significant differences in a number of regions. The differences were robust in the lateral and medial prefrontal cortex extending to the anterior cingulate cortex, the posterior/superior parietal cortex extending to the paracentral lobule, somatosensory strip and posterior cingulate cortex, the occipital visual cortex, hippocampus, amygdala, and insula (Fig. 2 and Supplementary Table 1).

A map of between-group differences in local functional connectivity was then generated for each of the three IDAC distances reporting simple effects (Fig. 3). Overall, this set of analyses showed that differences between both age groups were not homogeneous across the three distances. For instance, parietal cortices showed stronger functional connectivity in children than adults predominantly at short distances, whereas the occipital cortex showed weaker functional connectivity in children at long local distances. Statistical testing of group-
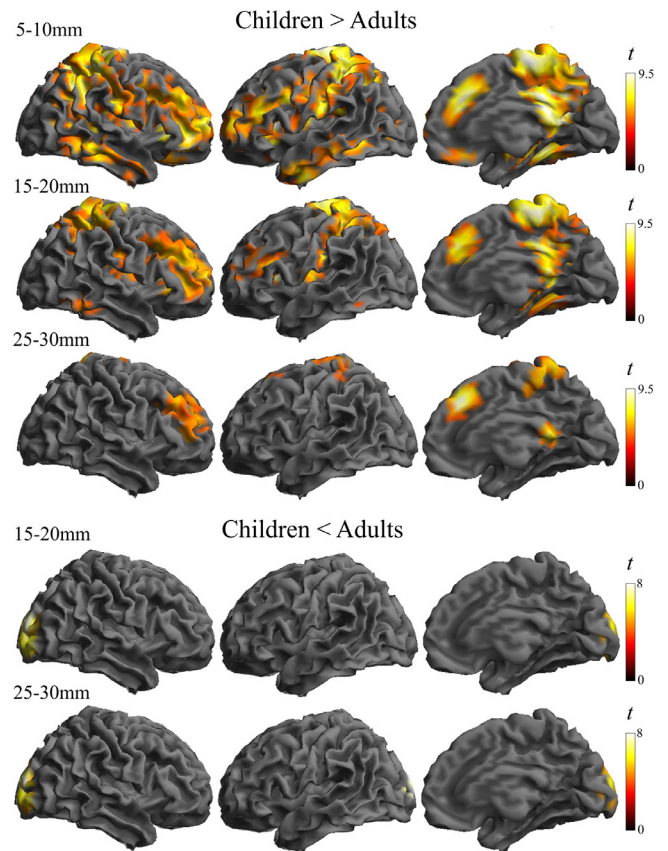

Fig. 3. Single effects illustrating differences between children and adults in IDAC measures at three functional connectivity distances. Height threshold $T= 4.7$ {$p<0.05$ – FWE}.
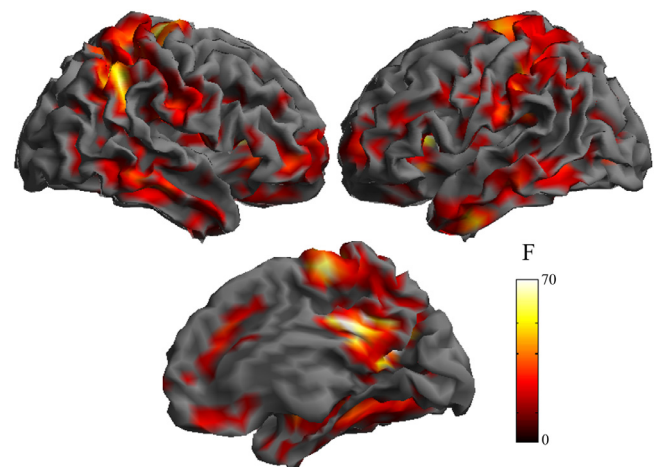

Fig. 4. ANOVA group (children vs adults) by distance (5–10 mm, 15–20 mm and 25–30 mm) interactions as to local functional connectivity IDAC measures. Height threshold $F= 13.6$ {$p<0.05$ – FWE}.

by-distance interactions confirmed such distance effects for most of the identified areas. We would mention, however, that the significant interaction effect was partial in frontal lobe areas and marginal in the visual cortex, in terms of anatomical extension (Fig. 4, Supplementary Table 2).

The details of distance effects may be jointly appreciated in Fig. 5 showing differences across the three distances in integrated RGB maps of IDAC differences. These results would indicate that preadolescents
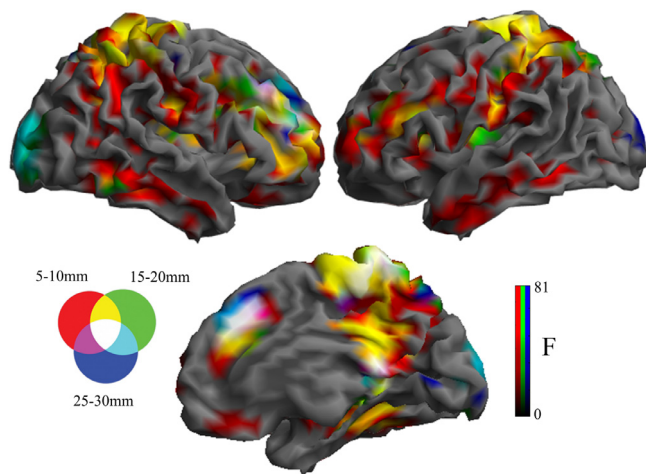
Fig. 5. RGB (red, green and blue) display of the differences between Children and Adults in IDAC measures. The color map corresponds to the superimposition of between-group differences in IDAC measures at functional connectivity distances 5–10 mm (red), 15–20 mm (green) and 25–30 mm (blue). The composite images are made up of primary RGB colors and their secondary combinations. Height threshold $F= 23$ {$p<0.05$ – FWE}.

and adults differ in the functional structure of the cerebral cortex, as opposed to expressing a non-specific effect that globally affects all local functional connectivity.

3.1. Sex analysis

We found no differences in the functional structure of the cerebral cortex between preadolescent girls and boys. By contrast, we did find significant differences between adult women and men, primarily involving somatosensory and visual areas. Specifically, men showed stronger functional connectivity at long local distances in these regions (Fig. 6 and Supplementary Table 3). Group-by-sex interaction showed a relatively specific developmental effect involving the visual cortex (Fig. 7 and Supplementary Table 4). Post-hoc analysis indicated that such an interaction effect corresponded to stronger connectivity in men than in boys (Supplementary Table 4). No significant results were obtained in the contrast women > girls.

4. Discussion

Relevant previous research has characterized developmental changes in the overall functional organization of the brain using a variety of functional connectivity metrics and mapped the functional anatomy of maturing brain areas. We have explored a new dimension of the developmental process by using a multivariate functional connectivity measure that shed light upon the changes occurring in the *spatial structure* of local functional connections of the cerebral cortex during the adolescent transition from childhood to adulthood. Differences in the functional structure of the cerebral cortex between less mature preadolescents and adults were extensive, particularly in the prefrontal cortex, posterior parietal lobe extending to the posterior cingulate cortex and occipital visual areas.

The prefrontal cortex is an anatomically and functionally complex late-maturing structure implicated in complex behavior. In accordance with our expectations, we found age-group differences in the functional structure of the prefrontal cortex involving both dorsolateral and medial areas. Previous research has reported a predominant increase in connectivity between the lateral prefrontal cortex and other regions of the fronto-parietal network during late development (e.g., Sherman et al., 2014; Wendelken et al., 2016; Solé-Padullés et al., 2016), which may interestingly combine with connectivity reductions (Wendelken et al., 2016; Sherman et al., 2014). These studies have characterized the assembling of the prefrontal cortex with other areas at a network scale. By
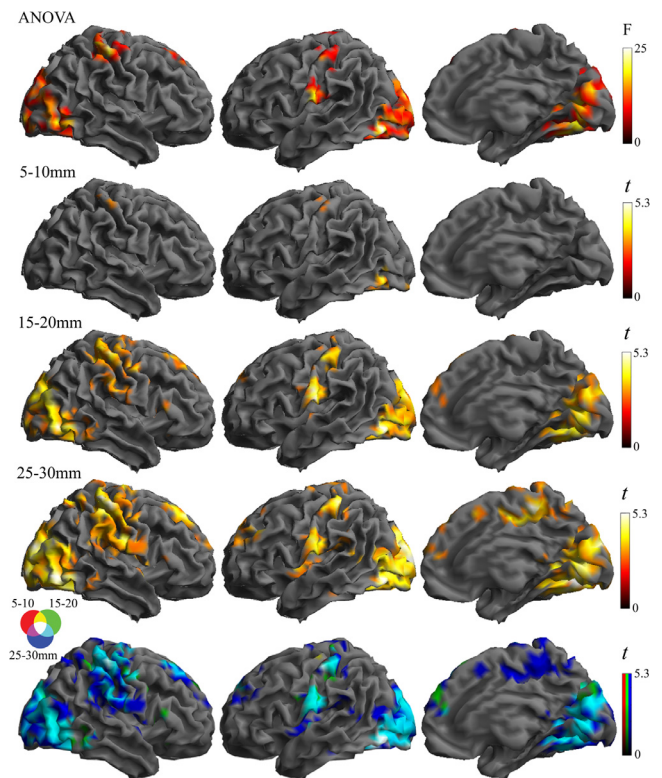

Fig. 6. Differences between men and women in IDAC measures (adult sample). Differences across the three distance maps in ANOVA are shown, together with separate distance analysis results and RGB (red, green and blue) display of their combination. All results are displayed at cluster level $p_{FWE-corrected} < 0.05$).

contrast, the dominant pattern in our study involved local IDAC reductions. Such different effects in the frontal lobe are compatible with a general trend in network configuration during development implicating integration of distant elements and local area segregation (Cao et al., 2017; Menon, 2013; Khundrakpam et al., 2016; Oldham and Fornito, 2019).

To further illustrate how integration and segregation may combine during developmental frontal network shaping, we performed a conventional functional connectivity analysis using the region-of-interest approach adopted by Sherman et al. (2014) and Wendelken et al. (2016). The results showed both higher and lower functional coupling between the elements of the network in older subjects (see Supplementary Region-of-Interest Analysis). Specifically, the selected lateral prefrontal regions showed weaker connectivity in adults with a part of the network including areas showing lower IDAC (i.e., lateral and medial areas of the frontal lobe), which did, however, concur with stronger connectivity with other frontal regions, the inferior parietal cortex and ventral striatum.

Our IDAC mapping shows, in detail, the differences between the child and adult brain at a regional scale and reveal a complex local pattern with diverse effects at different distances and locations across the cerebral cortex, which may unprecedentedly inform cortical area specialization in terms of connectivity. We recently illustrated the non-uniform role of the prefrontal cortex in learning, with dorsal areas being more closely associated with executive functioning and ventral areas with verbal memory while learning educational material (Pujol et al., 2019b). Interestingly, reasoning ability was related to functional connectivity between the left prefrontal cortex and inferior parietal lobule in 12-to-18-year-old participants in a developmental study (Wendelken et al., 2016).

Between-group differences were also robust in the medial aspect of the prefrontal cortex and the posterior cingulate cortex. At first sight, both findings may be interpreted as a single effect on the default mode
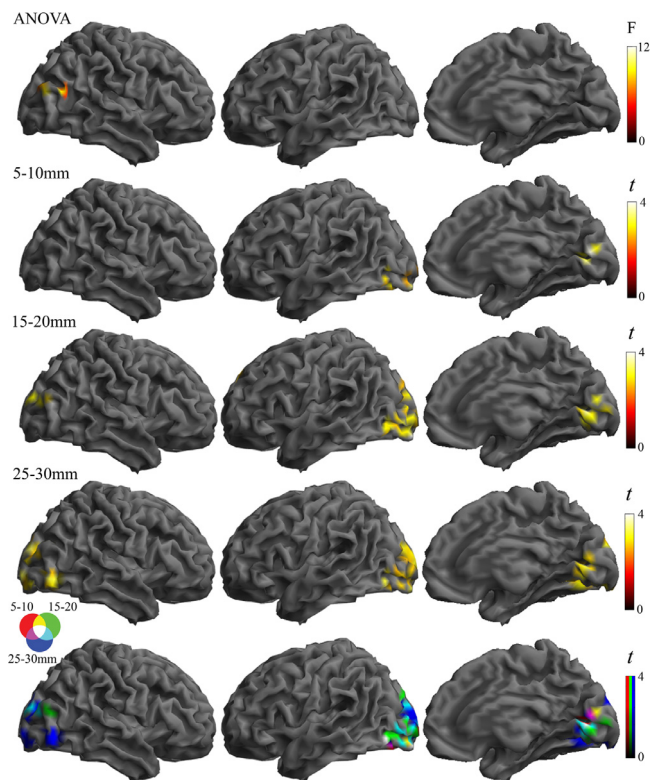
Fig. 7. Group (children vs adults) by sex (males vs females) interactions in Iso-Distance Average Correlations (IDAC) functional connectivity measures. Interaction effects across the three distance maps are shown, together with separate distance analysis results and RGB (red, green and blue) display of their combination. All results are displayed at cluster level $p_{\text{FWE-corrected}} < 0.05$.

network. However, a closer inspection would suggest that the involved medial frontal area is not the core element of the default mode network (Harrison et al., 2008) and implicates the adjacent anterior cingulate cortex. Supplementary Fig. 2 confirms that the area showing a developmental effect in the current study is posteriorly located. Among other roles, this medial frontal region is implicated in the cognitive appraisal of emotion and anxiety (Somerville et al., 2013; Pujol et al., 2013; Harrison et al., 2015). These results are therefore consistent with the late maturation of self-appraisal processes (Davey et al., 2019). Interestingly, this medial frontal region showed reduced cortical functional connectivity differentiation in individuals with psychopathy (Contreras-Rodríguez et al., 2015), for whom a developmental origin has been proposed (Pujol et al., 2019c).

The posterior cingulate cortex is the posterior core element of the default mode network. In contrast with the anterior medial frontal aspect of the default mode network, we found robust group differences in the posterior cingulate cortex during the transition to adulthood, which are consistent with other developmental studies (Sherman et al., 2014; Ernst et al., 2019; Fair et al., 2008). However, the anterior and posterior elements of the default mode network may not be completely coupled at rest until late adolescence (Fair et al., 2008), particularly during challenging tasks (Pujol et al., 2008).

In addition to the perhaps more predictable prefrontal and posterior cingulate cortex changes, we found highly robust differences in the parietal lobe involving virtually all its posterior (and superior) aspect and extending to the somatosensory strip. All these areas have been strongly linked to body image formation or bodily self-consciousness, which is the most somatic facet of self-consciousness (Blanke et al., 2015; Ronchi et al., 2018). Bodily self-consciousness refers to body-centered perception based on the multimodal integration of proprioceptive, vestibular, visual and interoceptive bodily inputs (Blanke et al.,

2015; Ronchi et al., 2018). Previous functional connectivity research has also shown that adolescence is an active period in the formation of parietal lobe networks (Marcos-Vidal et al., 2018; O'Rawe et al., 2019; Shaw et al., 2011; Vinette and Bray, 2015). Interestingly, other studies have indicated that a functional breakdown in the parietal connections may be a risk for developing psychiatric and neurological disorders associated with distorted body perception (Ronchi et al., 2018; Via et al., 2018).

The visual cortex was also sensitive to age effects. In this case, we found an inverse pattern showing an increase in adults, as opposed to reduction, in local functional connectivity involving the longest local connections (15–30 mm). Coherent visual perception combines reciprocal interactions between striate and extrastriate visual areas (Prasad and Galetta, 2011). The bulk of vision maturation takes place at early ages, and mostly under the age of 5 years (Saygin et al., 2016; Kiorpes, 2015). However, our data are consistent with other studies indicating that some aspects of the visual function may mature later (e.g., Gomez et al., 2018; Kiorpes, 2016; Kovács et al., 1999).

Developmental imaging studies indicate that visual cortex connectivity between occipital visual areas and other distant (extra-occipital) elements of the visual system indeed progresses until and during adolescence (Shaw et al., 2011; Vinette and Bray, 2015). What is perhaps more surprising, in our study, is the connectivity progress observed within the occipital lobe (i.e., strengthening the coupling between extrastriate and striate visual areas). It remains to be established, however, whether late visual striate and extrastriate cortex functional connectivity maturation parallels the relatively slow performance refinement of vision, in terms of, for instance, stereopsis—our ability to appreciate distance and depth—or two-dimensional motion perception (Kiorpes, 2015).

Previous studies have shown that differentiation in functional connectivity between boys and girls is active during adolescence in parietal lobe connections related to complex visual function (Shaw et al., 2011), default mode network (Ernst et al., 2019) and for some global network properties (Wu et al., 2013). Other studies demonstrated strong sex differences in global brain connectivity measures in a large 9-to-22 year-old sample (Satterthwaite et al., 2015), but weak differences in 6-to-10 year old children (Langen et al., 2018). We tested for sex differences and did observe their presence in the adult sample involving visual and somatosensory cortices. In addition, our analysis captured developmental differences between males and females in the visual cortex. Significant interaction was not observed in the somatosensory cortex at the study's threshold, perhaps indicating a more subtle effect. It has been contemplated that the sensory and perceptual processes differ between men and women (Hamilton, 2008), with male or female advantages depending on the specific operation tested (e.g., Satterthwaite et al., 2015; Spies and Sevincer, 2018; Goyette et al., 2012). It may be of interest in future study to test whether sex differences in the functional structure of sensory areas are related to differences in sensory processing performance.

Finally, differences between children and adults were also observed in the hippocampus, amygdala and insula. These structures are part of the limbic (and paralimbic) system, which includes a series of primitive formations surrounding the boundary (or *limbus*) of the neocortex (Morgane et al, 2005). Therefore, our results suggest that the shaping of connections may similarly be active during late development in basic systems regulating emotional and motivational processes. However, we would like to point out that although the hippocampus and amygdala are closely integrated to the cerebral cortex, they have a markedly distinct architecture and pattern of connections (Morgane et al, 2005), which arguably could be captured only in part by our IDAC approach in its current form (i.e., limited to three measures within a 30-mm radius).

A limitation of our study may be the absence of a longitudinal assessment in the same cohort. Although cross-sectional designs are not ideal for the study of developmental changes, such a limitation may be mitigated by the large sample size. A similarly important limitation is the use of only four minutes of resting-state data to compute our con-

nectivity measures. Although prior studies have shown that acquisitions of three to five minutes result in stable estimates of functional connectivity measures (Braun et al., 2012; Van Dijk et al, 2010), the reliability of measuring individual differences in the strength of connectivity can be greatly improved by increasing the scan lengths from five minutes up to 13 min (Birn et al., 2013). Interestingly, by using exceptionally large acquisitions (e.g., 5 h), functional connectomes become reliable to the level of individual humans (Gordon et al., 2017). Therefore, recommendations for future work should include the use of both longitudinal designs and longer acquisitions. Our study was also limited in that a complete demographic characterization and a comprehensive behavioral assessment covering general brain functioning were not obtained. Moreover, the study design, based on assessing children and adult samples, renders the control for potential confounders less optimal in the absence of similar behavioral testing.

4.1. Conclusions

We have provided some detail relating to the cerebral cortex functional structure during the transition to adulthood, which may serve to establish more accurate links between adolescent performance gains and cerebral cortex maturation. Remarkably, our study provides new information as to the cortical maturation processes in lateral prefrontal areas relevant to executive functioning and rational learning, the medial frontal/anterior cingulate area playing an active role in the cognitive appraisal of emotion and anxiety, and the superior parietal lobe extending to the somatosensory strip and posterior cingulate cortex strongly associated with bodily self-consciousness in the context of body image formation.

Funding

Data and code availability statement

Data will be available via a request to the authors with no particular restrictions, although a formal data sharing agreement will be considered.

Declaration of Competing Interest

The authors report no financial interests or potential conflicts of interest.

Credit authorship contribution statement

Jesus Pujol: Conceptualization, Data curation, Writing - review & editing. **Laura Blanco-Hinojo:** Formal analysis, Writing - review & editing. **Didac Macia:** Software, Writing - review & editing. **Gerard Martínez-Vilavella:** Formal analysis, Writing - review & editing. **Joan Deus:** Data curation, Writing - review & editing. **Víctor Pérez-Sola:** Conceptualization, Writing - review & editing. **Narcís Cardoner:** Conceptualization, Investigation, Writing - review & editing. **Carles Soriano-Mas:** Conceptualization, Investigation, Writing - review & editing. **Jordi Sunyer:** Conceptualization, Supervision, Writing - review & editing.

Acknowledgments

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118150.

References

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. NeuroImage 38 (1), 95–113 Oct 15.

Birn, R.M., Molloy, E.K., Patriat, R., Parker, T., Meier, T.B., Kirk, G.R., Nair, V.A., Meyerand, M.E., Prabhakaran, V., 2013. The effect of scan length on the reliability of resting-state fMRI connectivity estimates. NeuroImage 83, 550–558 Dec.

Blakemore, S.J., Choudhury, S., 2006. Development of the adolescent brain: implications for executive function and social cognition. J Child Psychol Psychiatry 47 (3-4), 296–312 Mar-Apr.

Blanke, O., Slater, M., Serino, A., 2015. Behavioral, neural, and computational principles of bodily self-consciousness. Neuron 88 (1), 145–166 Oct 7.

Braun, U., Plichta, M.M., Esslinger, C., Sauer, C., Haddad, L., Grimm, O., Mier, D., Mohnke, S., Heinz, A., Erk, S., Walter, H., Seiferth, N., Kirsch, P., Meyer-Lindenberg, A., 2012. Test-retest reliability of resting-state connectivity network characteristics using fMRI and graph theoretical measures. NeuroImage 59 (2), 1404–1412 Jan 16.

Brodmann, K., 2006. Brodmann's Localisation in the Cerebral Cortex. Springer US, New York.

Cao, M., Huang, H., He, Y., 2017. Developmental connectomics from infancy through early childhood. Trends Neurosci. 40 (8), 494–506 Aug.

Chomiak, T., Hu, B., 2017. Mechanisms of hierarchical cortical maturation. Front. Cell Neurosci. 11, 272 Sep 11.

Contreras-Rodríguez, O., Pujol, J., Batalla, I., Harrison, B.J., Soriano-Mas, C., Deus, J., López-Solà, M., Macià, D., Pera, V., Hernández-Ribas, R., Pifarré, J., Menchón, J.M., Cardoner, N., 2015. Functional connectivity bias in the prefrontal cortex of psychopaths. Biol. Psychiatry 78 (9), 647–655 Nov 1.

Dahl, R.E., Allen, N.B., Wilbrecht, L., Suleiman, A.B., 2018. Importance of investing in adolescence from a developmental science perspective. Nature 554 (7693), 441–450 Feb 21.

Davey, C.G., Fornito, A., Pujol, J., Breakspear, M., Schmaal, L., Harrison, B.J., 2019. Neurodevelopmental correlates of the emerging adult self. Dev. Cogn. Neurosci. 36, 100626 Apr.

Davey, C.G., Yücel, M., Allen, N.B., 2008. The emergence of depression in adolescence: development of the prefrontal cortex and the representation of reward. Neurosci. Biobehav. Rev. 32 (1), 1–19.

Ernst, M., Benson, B., Artiges, E., Gorka, A.X., Lemaitre, H., Lago, T., et al., 2019. and IMAGEN Consortium. Pubertal maturation and sex effects on the default-mode network connectivity implicated in mood dysregulation. Transl. Psychiatry 9 (1), 103 Feb 25.

Fair, D.A., Cohen, A.L., Dosenbach, N.U., Church, J.A., Miezin, F.M., Barch, D.M., Raichle, M.E., Petersen, S.E., Schlaggar, B.L., 2008. The maturing architecture of the brain's default network. Proc. Natl. Acad. Sci. U.S.A. 105 (10), 4028–4032 Mar 11.

Gomez, J., Natu, V., Jeska, B., Barnett, M., Grill-Spector, K., 2018. Development differentially sculpts receptive fields across early and high-level human visual cortex. Nat. Commun. 9 (1), 788 Feb 23.

Gordon, E.M., Laumann, T.O., Gilmore, A.W., Newbold, D.J., Greene, D.J., Berg, J.J., Ortega, M., Hoyt-Drazen, C., Gratton, C., Sun, H., Hampton, J.M., Coalson, R.S., Nguyen, A.L., McDermott, K.B., Shimony, J.S., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., Nelson, S.M., Dosenbach, N.U.F., 2017. Precision functional mapping of individual human brains. Neuron 95 (4), 791–807 Aug 16.e7.

Goyette, S.R., McCoy, J.G., Kennedy, A., Sullivan, M., 2012. Sex differences on the judgment of line orientation task: a function of landmark presence and hormonal status. Physiol. Behav. 105 (4), 1045–1051 Feb 28.

Hamilton, C., 2008. Cognition and Sex Differences. Palgrave MacMillan, New York.

Harrison, B.J., Fullana, M.A., Soriano-Mas, C., Via, E., Pujol, J., Martínez-Zalacaín, I., Tinoco-Gonzalez, D., Davey, C.G., López-Solà, M., Pérez Sola, V., Menchón, J.M., Cardoner, N., 2015. A neural mediator of human anxiety sensitivity. Hum. Brain Mapp. 36 (10), 3950–3958 Oct.

Harrison, B.J., Pujol, J., López-Solà, M., Hernández-Ribas, R., Deus, J., Ortiz, H., Soriano-Mas, C., Yücel, M., Pantelis, C., Cardoner, N., 2008. Consistency and functional specialization in the default mode brain network. Proc. Natl. Acad. Sci. U. S. A. 105 (28), 9781–9786 Jul 15.

Khundrakpam, B.S., Lewis, J.D., Zhao, L., Chouinard-Decorte, F., Evans, A.C., 2016. Brain connectivity in normally developing children and adolescents. NeuroImage 134, 192–203 Jul 1.

Kiorpes, L., 2015. Visual development in primates: neural mechanisms and critical periods. Dev. Neurobiol. 75 (10), 1080–1090 Oct.

Kiorpes, L., 2016. The puzzle of visual development: behavior and neural limits. J. Neurosci. 36 (45), 11384–11393 Nov 9.

Kovács, I., Kozma, P., Fehér, A., Benedek, G., 1999. Late maturation of visual spatial integration in humans. Proc. Natl. Acad. Sci. U. S. A. 96 (21), 12204–12209 Oct 12.

Langen, C.D., Muetzel, R., Blanken, L., van der Lugt, A., Tiemeier, H., Verhulst, F., Niessen, W.J., White, T., 2018. Differential patterns of age-related cortical and subcortical functional connectivity in 6-to-10 year old children: a connectome-wide association study. Brain Behav. 8 (8), e01031 Aug.

Larsen, B., Luna, B., 2018. Adolescence as a neurobiological critical period for the development of higher-order cognition. Neurosci. Biobehav. Rev. 94, 179–195 Nov.

Long, X., Benischek, A., Dewey, D., Lebel, C., 2017. Age-related functional brain changes in young children. NeuroImage 155, 322–330 Jul 15.

Macia, D., Pujol, J., Blanco-Hinojo, L., Martínez-Vilavella, G., Martín-Santos, R., Deus, J., 2018. Characterization of the spatial structure of local functional connectivity using multi-distance average correlation measures. Brain Connect. 8 (5), 276–287 Jun.

Marcos-Vidal, L., Martínez-García, M., Pretus, C., Garcia-Garcia, D., Martínez, K., Janssen, J., Vilarroya, O., Castellanos, F.X., Desco, M., Sepulcre, J., Carmona, S., 2018. Local functional connectivity suggests functional immaturity in children with attention-deficit/hyperactivity disorder. Hum. Brain Mapp. 39 (6), 2442–2454 Jun.

Menon, V., 2013. Developmental pathways to functional brain networks: emerging principles. Trends Cogn. Sci. 17 (12), 627–640 Dec.

Morgane, P.J., Galler, J.R., Mokler, D.J., 2005. A review of systems and networks of the limbic forebrain/limbic midbrain. Prog. Neurobiol. 75 (2), 143–160 Feb.

Oldham, S., Fornito, A., 2019. The development of brain network hubs. Dev. Cogn. Neurosci. 36, 100607 Apr.

O'Rawe, J.F., Huang, A.S., Klein, D.N., Leung, H.C., 2019. Posterior parietal influences on visual network specialization during development: an fMRI study of functional connectivity in children ages 9 to 12. Neuropsychologia 127, 158–170 Apr.

Paus, T., Keshavan, M., Giedd, J.N., 2008. Why do many psychiatric disorders emerge during adolescence? Nat. Rev. Neurosci. 9 (12), 947–957 Dec.

Paus, T., 2005. Mapping brain maturation and cognitive development during adolescence. Trends Cogn. Sci. 9 (2), 60–68 Feb.

Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. NeuroImage 84, 320–341 Jan 1.

Prasad, S., Galetta, S.L., 2011. Anatomy and physiology of the afferent visual system. Handb. Clin. Neurol. 102, 3–19.

Pujol, J., Blanco-Hinojo, L., Maciá, D., Alonso, P., Harrison, B.J., Martínez-Vilavella, G., Deus, J., Menchón, J.M., Cardoner, N., Soriano-Mas, C., 2019a. Mapping alterations of the functional structure of the cerebral cortex in obsessive-compulsive disorder. Cereb. Cortex 29 (11), 4753–4762 Dec 17.

Pujol, J., Blanco-Hinojo, L., Martínez-Vilavella, G., Canu-Martín, L., Pujol, A., Pérez–Sola, V., Deus, J., 2019b. Brain activity during traditional textbook and audiovisual-3D learning. Brain Behav. 9 (10), e01427 Oct.

Pujol, J., Giménez, M., Ortiz, H., Soriano-Mas, C., López-Solà, M., Farré, M., Deus, J., Merlo-Pich, E., Harrison, B.J., Cardoner, N., Navinés, R., Martín-Santos, R., 2013. Neural response to the observable self in social anxiety disorder. Psychol. Med. 43 (4), 721–731 Apr.

Pujol, J., Harrison, B.J., Contreras-Rodriguez, O., Cardoner, N., 2019c. The contribution of brain imaging to the understanding of psychopathy. Psychol. Med. 49 (1), 20–23 Jan.

Pujol, J., Macià, D., Blanco-Hinojo, L., Martínez-Vilavella, G., Sunyer, J., de la Torre, R., Caixàs, A., Martín-Santos, R., Deus, J., Harrison, B.J., 2014. Does motion-related brain functional connectivity reflect both artifacts and genuine neural activity? NeuroImage 101, 87–95 Nov 1.

Pujol, J., Martínez-Vilavella, G., Macià, D., Fenoll, R., Alvarez-Pedrerol, M., Rivas, I., Forns, J., Blanco-Hinojo, L., Capellades, J., Querol, X., Deus, J., Sunyer, J., 2016. Traffic pollution exposure is associated with altered brain connectivity in school children. NeuroImage 129, 175–184 Apr 1.

Pujol, J., Reixach, J., Harrison, B.J., Timoneda-Gallart, C., Vilanova, J.C., Pérez-Alvarez, F., 2008. Posterior cingulate activation during moral dilemma in adolescents. Hum. Brain Mapp. 29 (8), 910–921 Aug.

Pujol, J., Vendrell, P., Junqué, C., Martí-Vilalta, J.L., Capdevila, A., 1993. When does human brain development end? Evidence of corpus callosum growth up to adulthood. Ann. Neurol. 34 (1), 71–75 Jul.

Ronchi, R., Park, H.D., Blanke, O., 2018. Bodily self-consciousness and its disorders. Handb. Clin. Neurol. 151, 313–330.

Satterthwaite, T.D., Wolf, D.H., Roalf, D.R., Ruparel, K., Erus, G., Vandekar, S., Gennatas, E.D., Elliott, M.A., Smith, A., Hakonarson, H., Verma, R., Davatzikos, C., Gur, R.E., Gur, R.C., 2015. Linked sex differences in cognition and functional connectivity in youth. Cereb. Cortex 25 (9), 2383–2394 Sep.

Saygin, Z.M., Osher, D.E., Norton, E.S., Youssoufian, D.A., Beach, S.D., Feather, J., Gaab, N., Gabrieli, J.D., Kanwisher, N., 2016. Connectivity precedes function in the development of the visual word form area. Nat. Neurosci. 19 (9), 1250–1255 Sep.

Sepulcre, J., Liu, H., Talukdar, T., Martincorena, I., Yeo, B.T., Buckner, R.L., 2010. The organization of local and distant functional connectivity in the human brain. PLoS Comput. Biol. 6 (6), e1000808.

Shaw, D.J., Grosbras, M.H., Leonard, G., Pike, G.B., Paus, T., 2011. Development of functional connectivity during adolescence: a longitudinal study using an action-observation paradigm. J. Cogn. Neurosci. 23 (12), 3713–3724 Dec.

Sherman, L.E., Rudie, J.D., Pfeifer, J.H., Masten, C.L., McNealy, K., Dapretto, M., 2014. Development of the default mode and central executive networks across early adolescence: a longitudinal study. Dev. Cogn. Neurosci. 10, 148–159 Oct.

Silveri, M.M., Sneider, J.T., Crowley, D.J., Covell, M.J., Acharya, D., Rosso, I.M., Jensen, J.E., 2013. Frontal lobe γ-aminobutyric acid levels during adolescence: associations with impulsivity and response inhibition. Biol. Psychiatry 74 (4), 296–304 Aug 15.

Solé-Padullés, C., Castro-Fornieles, J., de la Serna, E., Calvo, R., Baeza, I., Moya, J., Lázaro, L., Rosa, M., Bargalló, N., Sugranyes, G., 2016. Intrinsic connectivity networks from childhood to late adolescence: effects of age and sex. Dev. Cogn. Neurosci. 17, 35–44 Feb.

Somerville, L.H., Jones, R.M., Ruberry, E.J., Dyke, J.P., Glover, G., Casey, B.J., 2013. The medial prefrontal cortex and the emergence of self-conscious emotion in adolescence. Psychol. Sci. 24 (8), 1554–1562 Aug.

Spies, M., Sevincer, A.T., 2018. Women outperform men in distinguishing between authentic and nonauthentic smiles. J. Soc. Psychol. 158 (5), 574–579.

Takesian, A.E., Hensch, T.K., 2013. Balancing plasticity/stability across brain development. Prog. Brain Res. 207, 3–34.

Tomasi, D., Volkow, N.D., 2010. Functional connectivity density mapping. Proc. Natl. Acad. Sci. U. S. A. 107 (21), 9885–9890.

Van Dijk, K.R., Hedden, T., Venkataraman, A., Evans, K.C., Lazar, S.W., Buckner, R.L., 2010. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. J. Neurophysiol. 103 (1), 297–321 Jan.

Via, E., Goldberg, X., Sánchez, I., Forcano, L., Harrison, B.J., Davey, C.G., Pujol, J., Martínez-Zalacaín, I., Fernández-Aranda, F., Soriano-Mas, C., Cardoner, N., Menchón, J.M., 2018. Self and other body perception in anorexia nervosa: the role of posterior DMN nodes. World J. Biol. Psychiatry 19 (3), 210–224 Apr.

Vinette, S., Bray, S., 2015. Variation in functional connectivity along anterior-to-posterior intraparietal sulcus, and relationship with age across late childhood and adolescence. Dev. Cogn. Neurosci. 13, 32–42 Jun.

Wendelken, C., Ferrer, E., Whitaker, K.J., Bunge, S.A., 2016. Fronto-parietal network reconfiguration supports the development of reasoning ability. Cereb. Cortex 26 (5), 2178–2190 May.

Wu, K., Taki, Y., Sato, K., Hashizume, H., Sassa, Y., Takeuchi, H., Thyreau, B., He, Y., Evans, A.C., Li, X., Kawashima, R., Fukuda, H., 2013. Topological organization of functional brain networks in healthy children: differences in relation to age, sex, and intelligence. PLoS One 8 (2), e55347.

Wu, X., Fu, Y., Knott, G., Lu, J., Di Cristo, G., Huang, Z.J., 2012. GABA signaling promotes synapse elimination and axon pruning in developing cortical inhibitory interneurons. J. Neurosci. 32 (1), 331–343 Jan 4.

Zang, Y., Jiang, T., Lu, Y., He, Y., Tian, L., 2004. Regional homogeneity approach to fMRI data analysis. NeuroImage 22 (1), 394–400.