



HAL
open science

Evolution of spatial patterns of brain activity over development: a role in the functional specialization of brain networks

Kuzma Strelnikov, Malik Berdier, Pierre Payoux, Pascal Barone, Chloe Farrer

► To cite this version:

Kuzma Strelnikov, Malik Berdier, Pierre Payoux, Pascal Barone, Chloe Farrer. Evolution of spatial patterns of brain activity over development: a role in the functional specialization of brain networks. 2023. hal-04246153

HAL Id: hal-04246153

<https://hal.science/hal-04246153>

Preprint submitted on 17 Oct 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Public Domain

Evolution of spatial patterns of brain activity over development: a role in the functional specialization of brain networks

Strelnikov, Kuzma^{1,2}, Berdier, Malik^{3,4}, Payoux, Pierre^{5,6}, Barone, Pascal^{3,4}, Farrer, Chloe^{3,4}

¹ Clinical Research Direction, Purpan University Hospital, Toulouse, France

² Centre for Cognitive and Brain Sciences, University of Macau, Taipa, Macau SAR, China

³UMR 5549, Faculté de Médecine Purpan, Centre National de la Recherche Scientifique, Toulouse, France

⁴ Centre de Recherche Cerveau et Cognition, Université de Toulouse, Université Paul Sabatier, Toulouse, France

⁵ Nuclear Medicine Department, Purpan University Hospital, Toulouse, France

⁶ ToNIC, Toulouse NeuroImaging Center, Université de Toulouse, Inserm, UPS, France

Abstract

The development of functionally specialized brain networks allows the emergence and improvement of cognitive abilities. This specialization partly emerges from the interactions between brain regions through changes in the temporal correlations of their brain activity. Nevertheless, it is now well assumed that the functioning of brain networks also depends on the spatial organization of their brain activity. However, how this spatial organization is formed during development remains unknown as to whether it contributes to the functional specialization of brain networks. This study attempts to answer these questions by examining age-related changes in the spatial correlations of brain activity within the theory of mind network. The results show, for the first time, an age-related increase in the spatial correlations of brain activity within this network, reflecting an increase in the similarity of spatial patterns across the network. Furthermore, this increase was associated with improved children's performance in a theory of mind task. We propose that the increasing similarity of spatial patterns during development has important implications for understanding the functional specialization of brain networks.

Keywords: functional specialization, theory of mind, brain development, spatial cross-correlation

Introduction

The development of cognitive skills results from a combination of changes in the brain structure and functioning of brain networks (Gogtay et al., 2004; Menon, 2013). These changes enable these networks to become more functionally specialized by refining their brain areas' response and function properties (Johnson, 2011; Menon, 2013). It is now well assumed that functional specialization depends on intrinsic changes in the individual brain areas and in their dynamic interactions (Brown et al., 2005; Johnson, 2000; Schlaggar and McCandliss, 2007). Changes in the functional connectivity of brain networks, with a decrease in the temporal correlations of local brain areas and an increase of the temporal correlations between its more distant brain areas, have consistently been reported across various functional brain networks, making it a general principle of development of functional connectivity (Fair et al., 2009; Supekar et al., 2009; Vogel et al., 2010). Yet, it is also known that the functioning of mature brain networks also depends on the spatial organization of their brain activity (Haxby et al., 2001; Kanwisher et al., 1997). Distributed patterns of brain activity have been reported for various cognitive systems, revealing that information is also encoded in the spatial distribution of neural activity across brain networks. Recently, Sadoun et al. (2020) have further expanded our understanding of how spatial patterns contribute to the functioning of brain networks by showing that the local spatial pattern of brain activity within one brain region is preserved in other brain regions of the same brain network. They found that brain regions present some spatial correlations of their brain activity with other brain regions of the same network. These spatial correlations have been reported for brain networks involved in face and word processing (Sadoun et al., 2020). For example, spatial patterns of brain activity in the fusiform face area were robustly correlated to brain regions involved in face-specific representations. These findings, therefore, show a similarity in the spatial patterns of brain activity across brain areas and that this similarity could contribute to the processing and transfer of information within the network.

However, despite increasing and refined evidence that spatial organization of brain activity contributes to network functioning, it remains unknown how this spatial organization emerges through development and whether and how the formation of spatially distributed patterns of brain activations contributes to the specialization of brain networks. To answer this question, we analyzed the developmental changes in spatial correlations between brain areas of a functional brain network using the analysis methodology developed by Sadoun et al. (2020).

We have taken the fMRI data from the cross-sectional study of Richardson et al. (2018), in which they studied changes in the activity of the network supporting theory of mind (the capacity to understand others' mental states (Premack and Woodruff, 1978) in different groups of children aged 3 to 12 and in a group of adults during a theory of mind task. Richardson et al. (2018) have analyzed brain regions of the ToM network: the TPJ, the precuneus, and the medial prefrontal cortex in the left and right hemispheres. Their study shows that this network is already functional by the age of three years and then undergoes a significant increase in the temporal correlation of its brain activity, increasing its functional specialization over development.

In this study, we examined whether the spatial correlation of brain activity also changes with age, therefore testing for an increase in the similarity of spatial patterns across the ToM network. An increase in similarity would mean higher resemblance in spatial coding between the areas and suggest the holistic treatment of information in each area of the network. We also examined whether developmental changes in the spatial correlations of the network were associated with improvements in children's theory of mind performance.

Materials and methods

fMRI data

The data used in this study were taken from the study of (Richardson et al., 2018) and extracted from the OpenfMRI database, access number ds000228. Richardson and colleagues worked on the development of the network associated with the theory of mind with a cross-sectional paradigm. Their study included 122 children aged 3 to 12 years and 33 adults with an average age of 30 years, divided into different age groups. The sample included 17 3-year-olds, 14 4-year-olds, 34 5-year-olds, 23 7-year-olds, and 34 8-12-year-olds, as well as a control group of 33 adults.

Subjects were subjected to an fMRI scan and viewed a silent version of the animated cartoon whose events allowed the children to infer mental states to the characters, thus mobilizing regions of the theory of mind. Richardson et al. (2018) analyzed ToM-specific regions of interest, such as the right temporo-parietal junction (RTPJ) and the left temporo-parietal junction (LTPJ), the precuneus (PC), the left dorsomedial prefrontal cortex (DMPFC), the medial median prefrontal cortex (MMPFC), and the ventro-medial prefrontal cortex (VMPFC). They established the evolution of temporal correlations between regions within this network during development. Furthermore, an increase in the average signal correlation in the ToM network was associated with success in the theory of mind task. Therefore, these results suggest an increase in the functional specialization of the ToM network during development. In other words, these regions become increasingly specialized in theory of mind. Using the same dataset, we asked whether the development of functional specialization is also based on the spatial organization of activity, which may become more similar in ToM regions.

Spatial correlation of theory of mind regions

Spatial organization of the activity

We used the spatial cross-correlation method developed by Sadoun et al. (2020), which allowed us to examine similarities in spatial organization between different regions. Brain activation maps obtained using contrasts corresponding to ToM-specific regions (ToM vs. Pain) were used to examine changes associated with this network during development. We used one ToM region as a "seed" (which consisted of 1000

voxels) and assessed the degree of similarity in the spatial organization of activity between the seed and other ToM regions. To study this similarity, we used a cross-correlation technique with all possible 3D rotations of a seed. The cross-correlation technique provides a unique correlation value for each voxel, highlighting similarities in the spatial organization of activity between the selected seed and other regions throughout the brain. In this way, we looked for the existence of similar spatially encoded information between the seed and other brain areas.

Whole brain spatial correlation

Therefore, in this study, we took all regions of interest from the Richardson et al. (2018) ToM network as "seed" and evaluated their spatial correlation across the brain. As a reminder, these regions are the right temporoparietal junction (RTPJ) and left temporoparietal junction (LTPJ), precuneus (PC), dorsomedial prefrontal cortex (DMPFC), medial prefrontal cortex (MMPFC), and ventromedial prefrontal cortex (VMPFC). We also used control regions not involved in ToM, namely the sensory-motor and auditory cortices.

For our analysis, we have chosen a cubic seed of 1000 voxels with a diagonal of 10 voxels. Due to the rotation, the seed, which is a cube, covers the volume of a sphere with a radius of 5 voxels. The 3D pattern of the "seed", located at a site in the brain, is rotated in steps of 10 degrees around the z, y and x axes, and for each rotation step, the the rotated seed is correlated with every possible location in brain activity. Only the "seed" is rotated by 10 degrees. The rest of the brain remains in its original position.

A rotation of 10 degrees corresponds to a maximum displacement of less than 1 voxel, which means that no voxel is ignored by the rotation. With rotation steps of 10 degrees, 18 rotation steps around an axis were performed. The total number of rotations is $18 \times 18 \times 18 = 5832$. The maximum correlation values obtained among all possible rotations are recorded per voxel. Higher correlations indicate a greater similarity in spatial organization between the seed and the target regions. The maximum correlation value that the "seed" can obtain during the rotations equals 1, and the value at the "seed" coordinates must be 1 or 0.9999.

Following this step, correlations per voxel were replaced with the Fisher z-transformed values to approximate the normal distribution, which is necessary for the SPM analysis. We also created random images from the z-transformed images to compare our correlation maps to this random map using unpaired Student's t-tests. These maps were obtained by randomly permuting the coordinates in the z-transformed images. The null hypothesis is that the correlations (represented by the z-values) are randomly distributed in the brain for each subject (Sadoun et al., 2020). Ultimately, these random images were used for statistical analysis, as to be considered statistically significant, the data must be significantly different from a random distribution of the same type of data.

Changes in correlation within the theory of mind network during development

Analysis of the evolution of spatial correlation during development in the whole brain

Statistical analysis was applied to the maximum values of the cross-correlations of each seed with the other brain regions after the z-transform. This analysis allowed us to highlight the location of significant correlations in the brain for each age group. We compared the obtained z-values to random ones using the unpaired t-test with a statistical threshold of $p = 0.001$ (cluster formation threshold) and a minimum spatial extent threshold equal to 10 voxels. Therefore, a location was considered significant if the corrected p-value (FWE: Family-Wise Error corrected p-value) was less than $p = 0.05$.

Then, in a second step, an unpaired t-test was performed to compare the correlations between children aged 8-12 years and children aged 3 years, then between adults and children aged 3 years, and finally, adults and children aged 8-12 years. We then compared the z-values between these age groups using an unpaired t-test, with a statistical threshold of $p = 0.001$ (threshold for cluster formation) and a minimum spatial extent threshold equal to 10 voxels. A location was considered significant if the corrected p-value was less than $p = 0.05$.

In sum, these analyses measure changes in spatial correlation during development across the brain to identify brain areas associated with the theory of mind.

Analysis of spatial correlation evolution in regions of interest

Following the whole-brain approach, we also wanted to study the evolution of spatial correlations during development in the regions of interest. For each seed, we used the linear mixed effect models to evaluate the coordinate-level z-correlation coefficient associated with the ToM network as defined by Richardson et al. (2018). Using a linear mixed effects model (R lme4 and mutcomp libraries), we tested the within-subject factor Region and the between-subject Age factor, Subject being the random effect. We then performed post hoc tests to investigate significant differences between age groups in all ToM regions (the glht (General Linear Hypotheses Test) post-hoc test).

Relationship between the spatial organization of the theory of mind network and behavioral performance

Performance tasks

Before the fMRI examination, Richardson et al. (2018) administered a series of ToM-related tests to all children, including listening to an experimenter tell a story and answering prediction and interpretation questions that required reasoning about the characters' mental states. In other words, the easiest questions involved reasoning about similar and different desires, true beliefs, and emotion prediction. In contrast, the more difficult questions dealt with reasoning about false beliefs, moral blame, and second-order false beliefs. Two analogous booklets were used; children aged 3 to 4 and 10 to 12 listened to a story in which students searched for snacks, and 5-year-olds listened to a story involving helping students find their books; 7- to 9-year-olds

were divided between these two groups. Each child's performance on the ToM task was summarized by the proportion of questions answered correctly among 24 matched items (14 prediction items and 10 explanation items). Two additional control questions were asked to ensure that the children were paying attention after checking that all children had answered these questions correctly.

Their performance was also ranked according to a composite false belief score based on 6 explicit false belief questions (4 predictive and 2 explanatory questions). These six questions were chosen because they are false belief questions describing unexpected changes in position or content. Thus, children were classified as "pass" for explicit false beliefs if they answered five or six of the six false belief questions correctly, "inconsistent" if they answered three or four questions correctly, and "fail" if they answered zero or two questions correctly.

Therefore, based on data from Richardson et al. (2018), and using bootstrapping, we tested for a significant correlation between the average ToM network (z-score) and scores between successful and unsuccessful children on the false belief tasks.

For children aged 3 to 9 years and all child subjects, we tested the correlation between their false belief performance scores and the average spatial correlation of the ToM network (z-score). This process was also applied for the different "seeds" of this network.

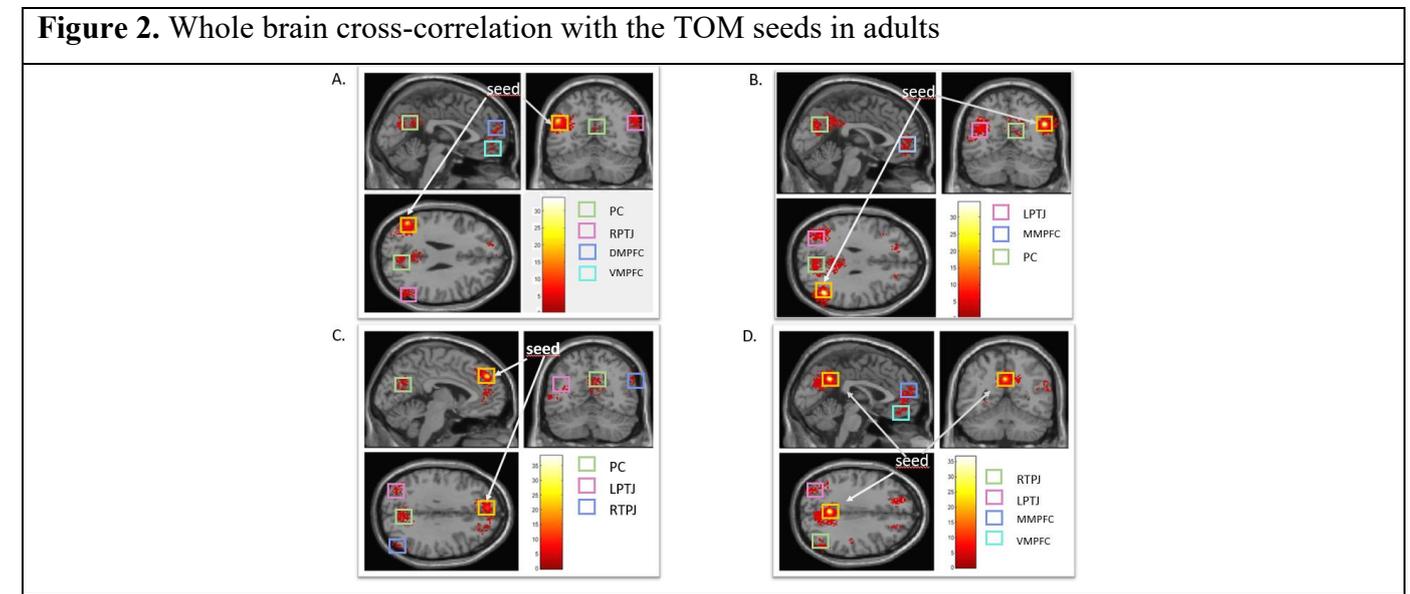
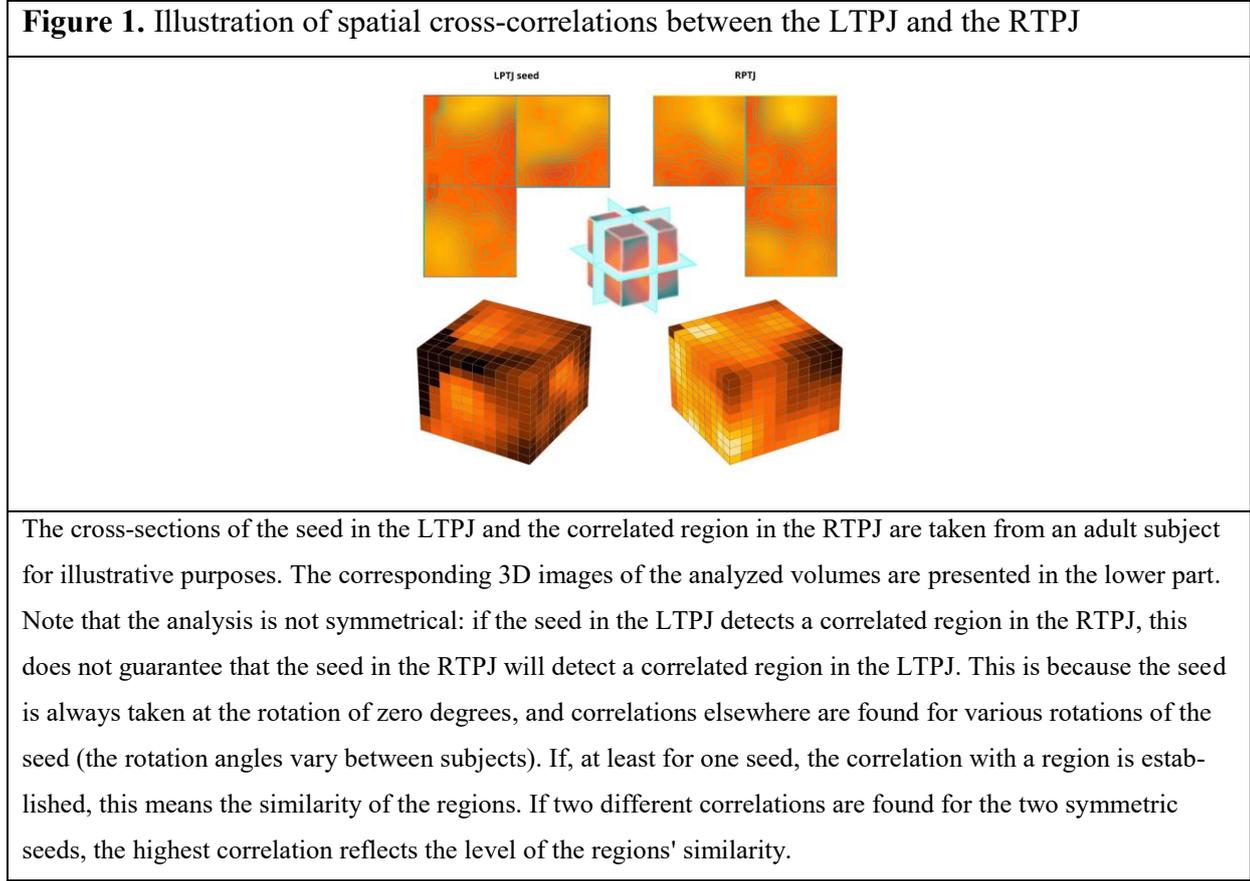
In summary, this set of analyses shows how changes in the spatial organization of brain activity during development explain changes in children's theory of mind performance. This association would indicate that these changes in the spatial organization of the ToM network contribute to the specialization of the network during development.

Results

Spatial correlations within the ToM network in adults

To examine whether brain areas of the ToM network were spatially correlated in adults, we analyzed the spatial cross-correlations of all ToM brain areas identified by Richardson et al. (2018) over the whole brain. This whole brain approach allowed us to assess these spatial correlations without a priori about the regions that could be spatially correlated with these ToM areas. The brain areas identified by Richardson et al. (2018) were used as seeds and included the right and left temporo-parietal junction (RTPJ and LTPJ), the precuneus (PC), the dorsomedial prefrontal cortex (DMPFC), the mesial medial prefrontal cortex (MMPFC), and the ventromedial prefrontal cortex (VMPFC). For each of these seeds, we obtained significant spatial cross-correlations with other brain areas of the ToM network identified by Richardson et al. (2018) and additional close brain areas (see Table 1 in Supplementary Materials). Significant spatial cross-correlations were consistently obtained between the posterior brain areas of the ToM networks (left and right TPJ, and precuneus, $r=0.48\pm 0.03$ (bias-corrected bootstrap, $p<0.05$), see Figure 1) as well as between posterior and prefrontal

brain regions ($r=0.49\pm0.05$, $p<0.05$). For prefrontal brain areas, significant correlations were obtained with posterior brain regions ($r=0.50\pm0.02$, $p<0.05$) and some other prefrontal areas of the network (MMPFC and DMPFC, $r=0.46\pm0.02$, $p<0.05$), (see Figure 2). These results show that some brain areas within the ToM network are spatially correlated, revealing that brain activity within the adults' ToM network shows similar spatial patterns.



A. The seed is in the LTPJ. B. The seed is in the RTPJ C. The seed is in the DMPF D. The seed is in the PC.
 In each case, areas from the ToM network are identified, meaning that spatial cross-correlations with each seed reveal spatial similarity between the ToM regions in adults.

Age-related changes in the spatial correlations of the ToM network

Age-related changes for the ToM ROIs

We evaluated the age-related changes in spatial correlations between the areas of the ToM network identified by Richardson et al. (2018). Consistently with Richardson et al. (2018), who showed age-related increases in temporal correlations within the ToM network, we also obtained significant age-related changes in the spatial correlations within this network, although not for all the ToM areas. A significant effect of age was obtained for the LTPJ ($\chi^2=12.86$, $p=0.025$) and the PC ($\chi^2=19.55$, $p=0.002$), and it was close to significance for RTPJ ($\chi^2=10.42$, $p=0.06$). For prefrontal regions, an effect of age was obtained for the VMPFC ($\chi^2=13.64$, $p=0.02$), and we observed a tendency for the MMPFC ($\chi^2=10.04$, $p=0.07$). We also obtained a significant effect of the region for all ToM brain areas ($\chi^2>11.46$, $p<0.022$), showing that the spatial cross-correlations differed between ToM areas. Comparing the spatial correlations between age groups using post hoc analyses, we showed that the spatial correlations between the ToM brain areas followed different developmental trajectories as they occurred at distinct ages for distinct ToM brain areas. (see Table 1) Changes in spatial correlations between posterior regions occurred very early (from three years old) and remained stable at an early age. Spatial correlations between the LTJ and the RTPJ increased between 3 and 5 years old ($t=3.61$, $p\text{-value} = 0.0042$) and then remained stable until adulthood, as shown by non-significant differences in these spatial correlations between all other older age groups (Figure 3A). The spatial correlations between PC and RTPJ (Figure 3B) increased between three and twelve years ($t=3.27$, $p = 0.0137$) and did not show any changes until adulthood. Regarding the spatial correlations between posterior and prefrontal regions, an increase in spatial correlations between RTPJ and VMPFC was observed between twelve years and adulthood (all $t=3.35$, $p=0.02$). For the PC, we found a significant increase in the spatial correlations with VMPFC between four-year-olds and seven-year-olds ($t=2.87$, $p<0.046$) but a significant decrease between seven and twelve years old ($t=-2.79$, $p=0.058$) (see Table 1). Finally, an increase in the spatial correlations between prefrontal areas was observed between the MMPFC and the VMPFC between 5 years old and adulthood ($t=3.19$, $p=0.018$) and between VMPFC and DMPFC between the ages of three and seven years old ($t=2.89$, $p=0.044$) (see figures 3C and 3D).

Table 1. Post hoc comparisons for the effect of age

Age difference	Correlation pair	t-value	p-value
<i>Comparisons for adults</i>			
adults - 12yo	VMPFC-RTPJ	3.347	0.0109
adults-5yo	MMPFC-VMPFC	3.190	0.0182

adults - 5yo	RTPJ-VMPFC	3.025	0.0301
adults - 5yo	VMPFC-RTPJ	2.878	0.0461
adults - 3yo	LTPJ-RTPJ	3.731	0.00281
adults - 3yo	PC -RTPJ	2.665	<i>0.0817</i>
adults - 3yo	RTPJ-VMPFC	2.852	0.0495
adults - 3yo	VMPFC-RTPJ	3.249	0.0150
<i>Comparisons for 8-12yo</i>			
12yo - 7yo	PC-VMPFC	neg 2.798	<i>0.0575</i>
12yo - 5yo	MMPFC-VMPFC	2.752	<i>0.0651</i>
12yo - 4yo	PC -RTPJ	3.081	0.0253
12yo - 3yo	LTPJ-RTPJ	3.587	0.00470
12yo - 3yo	PC -RTPJ	3.277	0.0137
<i>Comparisons for 7yo</i>			
7yo - 5yo	PC-VMPFC	2.777	<i>0.0609</i>
7yo - 4yo	PC-VMPFC	2.874	0.0467
7yo - 3yo	LTPJ-RTPJ	3.044	0.02844
7yo - 3yo	PC -RTPJ	2.666	<i>0.0815</i>
7yo - 3yo	VMPFC-DMPFC	2.893	0.0442
<i>Comparisons for 5yo</i>			
5yo - 3yo	LTPJ-RTPJ	3.611	0.0042
5yo - 3yo	MMPFC-VMPFC	neg 2.782	<i>0.0601</i>
<i>Comparisons for 4yo</i>			
4yo - 3yo	DMPFC-PC	neg 2.21	<i>0.0708</i>

Significant changes in correlation between the age groups within the pairs of the ToM areas are presented as well as tendencies (in italics). The first area in the pair is the seed. The 12yo group indicates children of 8-12 years old.

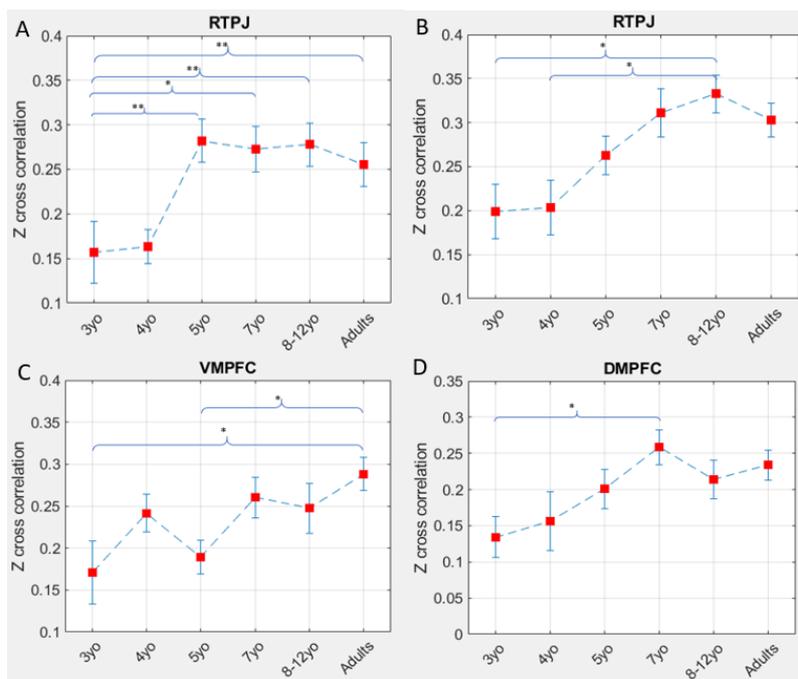


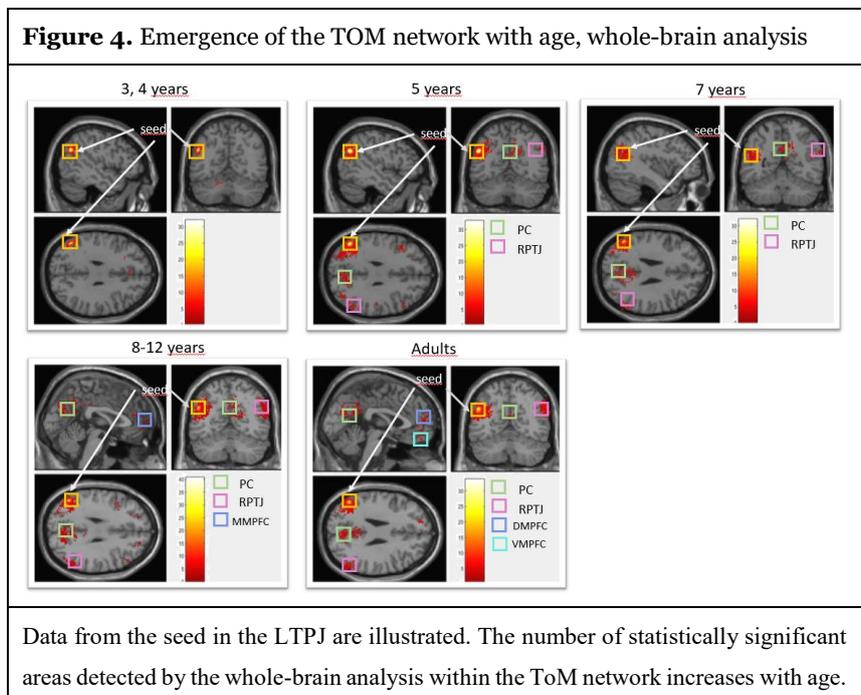
Figure 3. Examples of age-related changes in spatial correlations within the ToM network. A. Spatial cross-

correlations between the LTPJ (seed) and the RTPJ. B. Spatial cross-correlations between the PC (seed) and RTPJ C. Spatial cross-correlations between the RTPJ (seed) and VMPFC. D. Spatial cross-correlations between the VMPFC (seed) with DMPFC. * = 0.05, ** = 0.01.

Age-related changes over the whole brain

Assessing the spatial correlations of all ToM brain area across the whole brain for each age group, we observed additional spatial correlations with ToM areas other than the ones of Richardson et al. (2018). We first observed an increase in the number of ToM areas with significant spatial correlations through development (see Figure 4 for an example in the RTPJ). While only one significant spatial correlation was obtained at three years old, the number of spatial correlations rises to eight at five years old, to sixteen between eight and twelve years old, and twenty in adults (see Table 1 in Supplementary materials for all significant spatial correlations for each age group). This analysis also confirmed the differences in the developmental trajectories of spatial correlations within the ToM network. An increase in spatial correlations between ToM areas occurred along a posterior-anterior axis with an early increase of spatial correlations between posterior regions and posterior-prefrontal areas (between three years old and eight-twelve years old) and a later increase of spatial correlations between prefrontal areas (after twelve years old) (see Figure 3 for an example with four ToM brain areas).

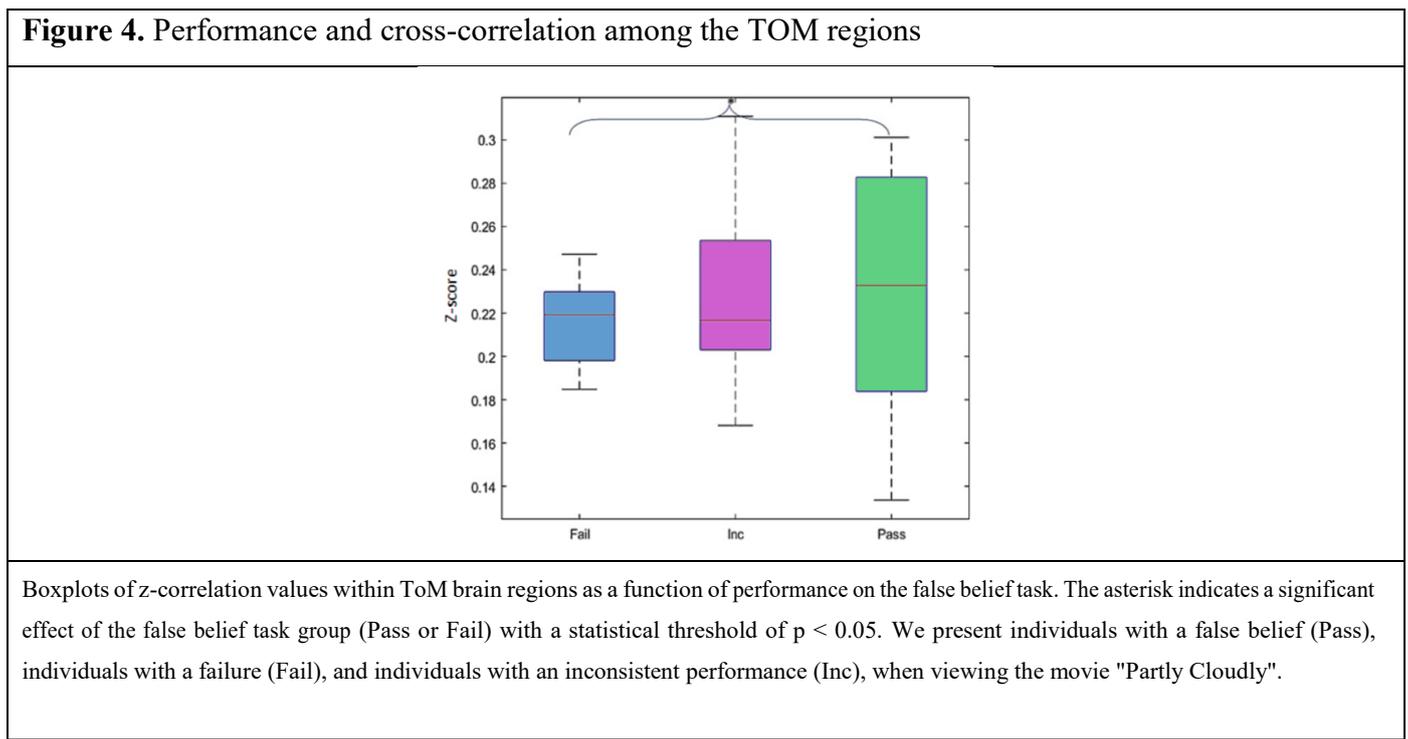
All these results show an increase in the similarity of the spatial patterns of brain activity between ToM areas through development, with this similarity occurring at different ages for distinct ToM brain areas.



Age-related changes in spatial cross-correlations and theory of mind performance

To assess whether the age-related changes in the spatial correlations of the ToM network explain children's improvement in the theory of mind performance over development, we conducted a correlational analysis between the mean spatial correlations of the ToM network, calculated for each child's overall spatial correlations between ToM brain areas, and children's false belief performance on the ToM task by taking all children from three to twelve years old. We obtained a significant correlation between the mean spatial correlation of the ToM network and children's ToM performance ($r= 0,24$; $p= 0.01$). However, conducting an additional partial correlation analysis by adding the age factor as a covariate, this correlation was no longer significant, showing that age explained both the increase in the mean spatial correlation of the network and the improvement in ToM performance.

We then conducted another analysis using performance in another ToM task where children were administered a 6-question test on false beliefs and were classified into three categories according to their performance: "pass," "fail," and "inconsistent" categories (Richardson et al., 2018). We used a bootstrap analysis to compare the z-scores of the mean spatial correlations of the ToM network between children who pass the task, those who fail, and those with inconsistent results. This analysis was only conducted in children aged between three and five years old to obtain a sufficient number of children in each category. We found a significant increase in the mean spatial correlation of the ToM network in children who passed the false belief task compared to those who failed ($p<0.05$, bootstrap) (see Figure 4). We also compared the z-scores of the spatial correlations between the LTPG and the RTPJ in those children, as only these correlations increased during the preschool ages. Spatial correlations between the LTPJ and the RTPJ were increased for children who passed the test compared to those who failed (bias-corrected bootstrap, $p<0.05$).



Controlling for an effect of brain growth

We finally assessed whether the age-related increases in the spatial cross-correlations between ToM brain areas were not explained by a general increase in brain growth through development. We assessed the spatial correlations over the whole brain of two brain areas outside the ToM network as well as their age-related changes: the sensorimotor cortex (x,y, and z; -34, -32, 44) and the primary auditory cortex (x, y, and z; -46, -24, 12). No significant spatial correlations and no age effects were observed for these two brain areas showing that a general increase in brain growth cannot explain the age-related changes in the spatial correlations between ToM brain areas.

Discussion

The functional specialization of brain networks allows information to be more efficiently processed and transferred and is partly explained by changes in their functional connectivity. Yet, it has recently been shown that information processing and transfer within mature functional brain networks also depend on the spatial correlations of their brain activity (Sadoun et al., 2020). We tested for the first time whether the spatial correlations also evolve across development by evaluating the age-related changes of spatial correlations within the ToM brain network. We show some developmental changes in the spatial correlations between ToM brain areas, suggesting that these changes might contribute to the functional specialization of the ToM brain network.

We analyzed the fMRI data obtained by Richardson et al. (2018) where they examined the developmental changes in the ToM network (Left and right TPJ, PC, VMPFC, MMPFC, and DMPFC) in participants of different age groups while they were reasoning about others' mental states. Spatial correlations were observed between some brain areas of the ToM network in adults, showing a similarity in the spatial patterns of brain activity within this network and that a large amount of spatial information in brain activity is shared between ToM areas. Similarity in the spatial patterns of brain activity has been observed in functional brain networks involved in face and word processing (Sadoun et al., 2020). The present findings are the first to show that this similarity is also present in the ToM network, suggesting that this spatial organization is not limited to the perceptual system but applies to various cognitive systems. Furthermore, spatial correlations were well limited to brain areas of the ToM network, as we did not observe any correlations with two brain areas outside this network, the sensorimotor and auditory cortices, revealing that similarity in the spatial patterns of brain activity is limited to brain areas sharing common functional properties.

Interestingly, these correlations were observed for close and distant brain areas of the ToM network, further showing that this spatial similarity can be considered a general network property. Spatial patterns of activation distributed across voxels have already been observed for various domains of social perception, including theory of mind (Brooks et al., 2021) for review), with the technique of the multivoxel pattern analysis (Haxby

et al., 2001; Kanwisher et al., 1997). Yet the present study is the first to show that the local spatial patterns of brain activity are preserved across several brain regions of the ToM network, revealing the importance of the similarity in the spatial patterns of brain activity for processing and representing social information.

The ToM network is functionally distinct very early as its brain areas are activated by tasks engaging the theory of mind in children as young as three (Richardson et al., 2018). It then undergoes significant neuro-anatomical and neurofunctional changes across development, explaining its improved efficiency and functional specialization. Neurofunctional changes concern the individual brain areas and the interaction between those brain areas, with an age-related increase in the temporal correlations between ToM brain areas (Richardson et al., 2018). The present study further shows that the spatial correlations between regions of the ToM network also evolve over development. We first observed that the number of brain areas with spatial correlations increased across development; from eight brain areas during preschool, there were twenty spatial correlations in early adulthood. We also observed that most of these spatial correlations increased with age, showing that for many brain areas of the network, the spatial patterns of their brain activity were more and more similar between preschool ages and adulthood.

A noticeable finding is that there were important differences in the age-related changes between ToM regions. Distinct developmental trajectories of spatial correlations were observed between the posterior and the prefrontal areas of the ToM network. Spatial correlations between the posterior regions, between the left and right TPJ and the precuneus, appeared early and showed an early increase during preschool. They also stabilized early, as they did not change from preschool until adulthood, except for the RTPJ and the precuneus. An early increase and stabilization of the spatial correlations between the left and right TPJ is consistent with the observation that early temporal correlations were also stronger between these homologous pairs (Richardson et al., 2018).

Regarding the correlations between the posterior and the prefrontal regions of the ToM network, even though their number increased from the preschool ages to early adulthood, their developmental trajectories were more complex. There were some differences in their age of appearance; while some occurred early, in the preschool ages, others appeared during adolescence. Furthermore, not all these correlations remained stable; some disappeared in adolescence and reappeared in adulthood. Finally, contrary to Richardson et al. (2018), we show that not all these correlations increased in strength with age, as a few decreased with age. Finally, the developmental trajectories of the spatial correlations between the prefrontal regions were also more complex, with some increasing and decreasing correlations at distinct periods and one very late occurrence of one spatial correlation, in early adulthood, between the DMPFC and the MMPFC.

The age-related increase in the spatial correlations of brain activity within the ToM network echoes well-reported developmental changes in the individual brain areas and in the interactions between these areas. For example, the complex developmental trajectories of the spatial correlations involving prefrontal areas during childhood (with some spatial correlations disappearing and reappearing and others increasing and decreasing) are in line with the consistent evidence that the recruitment of the prefrontal regions during ToM task is not

yet stabilized in childhood (Blakemore et al., 2007; Goddings et al., 2012; Wang et al., 2006). Similarly, the late occurrence of the DMPFC-MMPFC spatial correlation in early adulthood could also be explained by the increasing recruitment of the medial PFC between adolescence and adulthood. These findings suggest that the increasing similarity in the spatial patterns of brain activity within the ToM network might depend on the increasing recruitment of its brain areas during ToM tasks. We, therefore, speculate that the early increase we observed during the preschool ages in the spatial correlations between the parietal regions might be explained by increasing recruitment of these areas during these ages. However, while there is evidence that the ToM network is functionally distinct at these ages (Richardson et al., 2018), it is unknown whether the recruitment of the parietal areas of the Tom network increases in the preschool ages as fMRI studies of theory of mind have focused on children older than five years old (Decety et al., 2008; Kobayashi et al., 2007; Ohnishi, 2004; Saxe et al., 2009). More research is needed to test whether this is indeed the case.

Differences in the developmental trajectories of spatial correlations between the parietal and prefrontal areas of the ToM network also echo other differences in the development of some structural brain measures between these brain areas. For example, differences in the developmental trajectories of cortical thickness have been reported between the medial prefrontal cortex and the lateral parietal cortex, with respective increasing and decreasing cortical thickness across late childhood (Giedd et al., 1999; Sowell et al., 2004). Likewise, the later increase of spatial correlations in the prefrontal areas of the ToM network between adolescence and adulthood is also consistent with the well-reported finding of a late maturation pattern of the prefrontal areas, not limited to the ToM network, with a loss of grey matter in these regions occurring later, during adolescence and reaching an adult-like level at the beginning of adulthood (Gogtay et al., 2004).

The present findings are also consistent with the well-reported developmental changes in the interactions between functionally related brain areas. An increase in the functional connectivity between the distant brain areas of a network has consistently been shown to occur later in the development and has been observed for multiple brain networks, suggesting that this late integration of distant areas is a general principle of the development of functional connectivity (Fair et al., 2009; Vogel et al., 2010). Even though this trend has not been specifically reported for the ToM network, given its generalization across multiple brain networks we can reasonably expect that the same trend is at work for the development of ToM brain network. Consistent with this general principle, we observed that the number of spatial correlations between the more distant brain areas of the ToM network, between the parietal and the prefrontal areas, increased during middle childhood and adolescence, suggesting that the development of similar spatial patterns across the ToM network can be related to the changes in the functional connectivity of the network.

Another objective was to evaluate whether changes in the spatial correlations of the ToM network related to theory of mind improvements over development. Analyzing preschoolers' performance in the false belief task in the study by Richardson et al. (2018), we observed that the mean spatial correlation within the network

was more significant in preschool children who passed the false belief task than those who failed. We further show that changes in the spatial patterns of brain activity across areas also contribute to cognitive changes over development. Interestingly, this result also holds when considering only the changes in the spatial correlations that were the most pronounced during the preschool ages, between the left and the right TPJ, further suggesting that ToM improvements changes during preschool might mainly be attributed to the changes in the interactions between these two brain areas.

It has been theorized that the development of functional brain networks depends on their regions interacting in increasingly organized patterns over development (Fair et al., 2009; Johnson, 2000; Vogel et al., 2010). The interactive specialization framework indeed proposes that refined information processing of brain regions over development depends on changes in the activity patterns of other brain regions (Johnson, 2000). These changes were mainly documented in the temporal domain, with variations in the temporal correlations of brain activity between regions of the same network. The present findings showing an increase in the spatial correlations within the ToM network that echo several pieces of evidence of brain maturation and explain improvements in ToM performance suggest that the increasing similarity in the spatial patterns of brain activity within the ToM network can also contribute to its functional specialization. Functional specialization allows brain networks to refine their field in some cognitive processing. It depends on intrinsic changes in the individual brain areas and changes in the functional connectivity of the network, with an increase in the temporal correlations between ToM brain areas (Richardson et al., 2018).

Using fMRI in children with prosopagnosia, Zhang et al. (Zhang et al., 2015) decoded the presented faces from the occipital cortex, but not successfully from the right fusiform face area (FFA), whereas, in the controls, decoding faces was successful both in the occipital cortex and in the right FFA. Thus, spatial coding must be present both in the occipital cortex and the right FFA to perceive faces correctly. This is an example of holistic processing where the whole face is coded in each implicated area. By analogy, our results on the similar spatial structure in the areas of the ToM network suggest that similar information is spatially coded. Therefore, one can suggest that instead of the different aspects of the ToM processed in different areas, there is holistic ToM information in each area of the network. The transmission of spatial coding between the areas could be electrophysiologically explained by the cortical traveling waves, described as spatially extended patterns in which aligned activity peaks move sequentially across the cortical surface (Bhattacharya et al., 2022).

The present findings show that the increasing similarity in the spatial patterns of brain activity might also contribute to improving the functioning of the brain network, perhaps because more and more similar spatial patterns of brain activity benefit the processing and transfer of information within the network, subsequently contributing to its functional specialization over development. Finally, although the present study is limited to the development of the ToM network, the fact that the developmental changes in the spatial correlations observed between ToM brain areas are consistent with the general principle of brain development, we speculate that the increasing spatial similarity of brain activity is not specific to the ToM network but might

contribute to the functional specialization of various brain networks.

Conclusions

By analyzing the fMRI data of the Richardson et al. (2018) study, where participants of different age groups performed a ToM task, we show that the spatial correlations of brain activity between brain regions of the ToM network increase with age, both in terms of the number of brain areas showing spatial correlations with other brain areas of the network and in terms of the strength of these correlations, except for a few correlations that decrease over time. We also show that the increase in the spatial similarity of brain activity explains the improvement in preschoolers' theory of mind performance. These results suggest that the increasing spatial similarity of brain activity over development might contribute to the functional specialization of brain networks. Besides, similar spatial coding suggests that instead of the different aspects of the ToM processed in the explored ToM areas, holistic ToM-related information is present in each area of the network.

References

- Bhattacharya, S., Brincat, S.L., Lundqvist, M., Miller, E.K., 2022. Traveling waves in the prefrontal cortex during working memory. *PLoS Comput Biol* 18, e1009827. <https://doi.org/10.1371/journal.pcbi.1009827>
- Blakemore, S.J., Ouden, H., Choudhury, S., Frith, C., 2007. Adolescent development of the neural circuitry for thinking about intentions. *Social Cognitive and Affective Neuroscience* 2, 130–9.
- Brooks, J.A., Stoler, R.M., Freeman, J.B., 2021. Computational approaches to the neuroscience of social perception. *Soc Cogn Affect Neurosci* 5;16(8):827-837. <https://doi.org/10.1093/scan/nsaa127>.
- Brown, T.T., Lugar, H.M., Coalson, R.S., Miezin, F.M., Petersen, S.E., Schlaggar, B.L., 2005. Developmental changes in human cerebral functional organization for word generation. *Cerebral Cortex* 15, 275–290.
- Decety, J., Michalska, K.J., Akitsuki, Y., 2008. Who caused the pain? An fMRI investigation of empathy and intentionality in children. *Neuropsychologia* 46, 2607–2614.
- Fair, D.A., Cohen, A.L., Power, J.D., Dosenbach, N.U., Church, J.A., Miezin, F.M., Schlaggar, B.L., et al., 2009. Functional Brain Networks Develop from a “Local to Distributed” Organization. *PLoS Comput Biol*. <https://doi.org/10.1371/journal.pcbi.1000381>.
- Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., Paus, T., Evans, A.C., Rapoport, J.L., 1999. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci* 2, 861–863. <https://doi.org/10.1038/13158>
- Goddings, A.L., Burnett Heyes, S., Bird, G., Viner, R.M., Blakemore, S.J., 2012. The relationship between puberty and social emotion processing. *Developmental Science*.
- Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., Nugent, T.F., Herman, D.H., Clasen, L.S., Toga, A.W., Rapoport, J.L., Thompson, P.M., 2004. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc. Natl. Acad. Sci. U.S.A.* 101, 8174–8179. <https://doi.org/10.1073/pnas.0402680101>
- Haxby, J.V., Gobbini, M.I., Furey, M.L., Ishai, A., Schouten, J.L., Pietrini, P., 2001. Distributed and Overlapping Representations of Faces and Objects in Ventral Temporal Cortex. *Science* 293, 2425–2430. <https://doi.org/10.1126/science.1063736>
- Johnson, M.H., 2011. Interactive specialization: a domain-general framework for human functional brain development? *Dev. Cogn. Neurosci* 1, 7–21.
- Johnson, M.H., 2000. Functional brain development in infants: elements of an interactive specialization framework. *Child. Dev* 71, 75–81.
- Kanwisher, N., McDermott, J., Chun, M.M., 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J Neurosci* 17, 4302–11.
- Kobayashi, C., Glover, G.H., Temple, E., 2007. Children’s and adults’ neural bases of verbal and nonverbal “theory of mind.” *Neuropsychologia* 45, 1522–1532.
- Menon, V., 2013. Developmental pathways to functional brain networks: emerging principles. *Trends Cogn. Sci* 17, 627–640.
- Ohnishi, T., 2004. The neural network for the mirror system and mentalizing in normally developed children: an fMRI study. *Neuroreport* 15, 1483–1487.
- Premack, D., Woodruff, G., 1978. Does the chimpanzee have a theory of mind? *Behavioral and Brain Sciences* 1, 515–526.
- Richardson, H., Lisandrelli, G., Riobueno-Naylor, A., Saxe, R., 2018. Development of the social brain from age three to twelve years. *Nat Commun.* Mar 12;9(1):1027. <https://doi.org/10.1038/s41467-018-03399-2>.
- Sadoun, A., Chauhan, T., Mameri, S., Zhang, Y.F., Barone, P., Deguine, O., Strelnikov, K., 2020. Stimulus-specific information is represented as local activity patterns across the brain. *NeuroImage* 223, 117326. <https://doi.org/10.1016/j.neuroimage.2020.117326>
- Saxe, R.R., Whitfield-Gabrieli, S., Scholz, J., Pelphrey, K.A., 2009. Brain regions for perceiving and reasoning about other people in school-aged children. *Child. Dev* 80, 1197–1209.
- Schlaggar, B.L., McCandliss, B.D., 2007. Development of neural systems for reading. *Annual Review of Neuroscience* 30, 475–503.
- Sowell, E.R., Thompson, P.M., Leonard, C.M., Welcome, S.E., Kan, E., Toga, A.W., 2004. Longitudinal

- mapping of cortical thickness and brain growth in normal children. *Journal of Neuroscience* 24, 8223–31.
- Supekar, K., Musen, M., Menon, V., 2009. Development of Large-Scale Functional Brain Networks in Children. *PLoS Biol* 7, e1000157. <https://doi.org/10.1371/journal.pbio.1000157>
- Vogel, A.C., Power, J.D., Petersen, S.E., Schlaggar, B.L., 2010. Development of the brain's functional network architecture. *Neuropsychol Rev.* <https://doi.org/10.1007/s11065-010-9145->
- Wang, A.T., Lee, S.S., Sigman, M., Dapretto, M., 2006. Developmental changes in the neural basis of interpreting communicative intent. *Social Cognitive Affective Neuroscience* 1, 107–21.
- Zhang, J., Liu, J., Xu, Y., 2015. Neural Decoding Reveals Impaired Face Configural Processing in the Right Fusiform Face Area of Individuals with Developmental Prosopagnosia. *J. Neurosci.* 35, 1539–1548. <https://doi.org/10.1523/JNEUROSCI.2646-14.2015>

Supplementary materials

Supplementary Table 1. Coordinates of significant whole-brain correlations and their anatomical locations in adults

Seed	Re-gions	p-va-lue(cluster)	Clus-ter size	z value	x(mm)	y(mm)	z(mm)
LTPJ	RTPJ	<0.001	495	6.93	58	58	34
	Precu-neus	<0.001	530	5.26	-4	-46	26
	MMPFC	<0.001	244	4.64	4	48	-12
RTPJ	LTPJ	<0.001	1129	6.56	-36	-64	30
	Precu-neus	<0.001	1259	6.26	2	-44	32
	MMPFC	<0.001	596	5.05	0	50	8
PC	LTPJ	<0.001	907	5.84	-34	-60	28
	MMPFC	<0.001	782	5.64	8	52	10
	DMPFC	<0.001	366	5.61	-14	36	34
	RTPJ	<0.001	582	5.18	48	-72	40
DMPFC	Precu-neus	<0.001	809	5.95	10	-68	32
	LTPJ	<0.001	692	5.81	-36	-74	32
	RTPJ	<0.001	210	4.80	54	-62	24
MMPFC	DMPFC	<0.001	470	6.51	-18	46	28
	RTPJ	<0.001	530	6.23	54	-72	34
	Precu-neus	<0.001	1577	6.15	8	-54	28
	LTPJ	<0.001	1256	6.07	-38	-62	24
VMPPFC	RTPJ	<0.001	729	6.18	54	-72	30
	LTPJ	<0.001	719	6.03	-46	-62	12
	Precu-neus	<0.001	946	5.96	2	-72	28