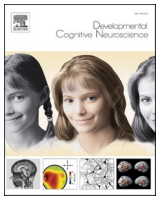
Developmental Cognitive Neuroscience 48 (2021) 100940

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: www.elsevier.com/locate/dcn



Theory of mind performance and prefrontal connectivity in adolescents at clinical high risk for psychosis

Daniel Ilzarbe [a,b,c], Inmaculada Baeza [a,b,c,d], Elena de la Serna [a,d], Adriana Fortea [a,b,c], Isabel Valli [b], Olga Puig [a,d], Mireia Masias [b], Roger Borras [a], Jose C. Pariente [b], Montserrat Dolz [d,e], Josefina Castro-Fornieles [a,b,c,d], Gisela Sugranyes [a,b,c,d,*]

[a] Department of Child and Adolescent Psychiatry and Psychology, 2017SGR881, Institute of Neurosciences, Hospital Clinic de Barcelona, Barcelona, Spain
[b] August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain
[c] Department of Medicine, Universitat de Barcelona, Barcelona, Spain
[d] Centro Investigación Biomédica en Red Salud Mental (CIBERSAM), Madrid, Spain
[e] Department of Child and Adolescent Psychiatry and Psychology, Hospital Sant Joan de Deu, Esplugues de Llobregat, Spain

ARTICLE INFO

Keywords:
Adolescence
High-risk studies
Psychosis
Theory of mind
Functional neuroimaging

ABSTRACT

Theory of mind(ToM) impairment is a key feature of psychotic disorders and has been documented in individuals at clinical high-risk for psychosis (CHR), suggesting that it may predate illness onset. However, no study to date has examined brain functional correlates of ToM in individuals at CHR during adolescence. The "Reading-the-Mind-in-the-Eyes" test was used to measure ToM performance in 50 CHR youth, 15 of whom transitioned to psychosis (CHR-t) at follow-up (12 ± 6 months) and 36 healthy volunteers. Resting-state functional MRI was acquired to evaluate functional connectivity within the default mode network. Group by age interaction revealed an age-positive association in ToM performance in healthy volunteers, which was not present in adolescents at CHR-t. Intrinsic functional connectivity in the medial prefrontal cortex was reduced in adolescents at CHR-t relative to those who did not transition and to healthy volunteers. Survival analyses revealed that participants at CHR with lower medial prefrontal cortex connectivity were at greatest risk of developing psychosis at follow-up. We demonstrate that lack of age-related maturation of ToM and reduced medial prefrontal cortex connectivity both precede the onset of psychosis during adolescence. Medial prefrontal cortex connectivity holds potential as a brain-based marker for the early identification of transition to psychosis.

1. Introduction

Theory of mind (ToM) (Premack and Woodruff, 1978) is the ability to understand that others present independent beliefs, intentions or desires, and to infer their mental states in order to predict their reactions and behaviour. ToM acquisition typically takes place during childhood and adolescence. The earliest signs of ToM have been described in 15-month-old children (Onishi and Baillargeon, 2005), although more evident ToM abilities start to arise around 4 years of age (Barresi and Moore, 1996; Wellman et al., 2001). Cognitive ToM (intentions and beliefs) develops earlier than affective ToM (emotions), which continues to develop during late adolescence and into early adulthood (Sebastian et al., 2012; Vetter et al., 2013). ToM performance improves with age (Wellman et al., 2001) and is considered a key process for successful social development leading into adulthood (Yager and Ehmann, 2006). Impaired ToM performance, which has been traditionally described in autism spectrum disorders (Baron-Cohen et al., 1985; Yirmiya et al., 1998), is also present in schizophrenia (Bora et al., 2009). ToM difficulties in schizophrenia have been associated with general intelligence deficits and with duration of disease (Bora et al., 2009; Thibaudeau et al., 2020). However, the conceptualization of schizophrenia as a neurodevelopmental disorder (Murray and Lewis, 1987) has raised the

Abbreviations: DMN, default mode network; CHR, participants at clinical high risk for psychosis; CHR-nt, participants at clinical high risk who did not transition to psychosis; CHR-t, participants at clinical high risk who transitioned to psychosis; HV, healthy volunteers; RMET, reading-the-mind-in-the-eyes test; fMRI, functional magnetic resonance imaging; gIQ, global intelligence quotient; ToM, theory of mind.

* Corresponding author at: Department of Child and Adolescent Psychiatry and Psychology, Institute of Neurosciences, Hospital Clínic of Barcelona, C/Villarroel 170, 08036, Barcelona, Spain.
E-mail address: gernest@clinic.cat (G. Sugranyes).

https://doi.org/10.1016/j.dcn.2021.100940
Received 21 September 2020; Received in revised form 3 March 2021; Accepted 3 March 2021
Available online 5 March 2021

possibility that ToM impairments may start early on in the developmental pathway, during childhood and adolescence. In fact, an earlier onset of schizophrenia is associated with more pronounced social cognitive deficits in adults (Linke et al., 2015); and impaired ToM performance in adolescents with early-onset-schizophrenia has been described in IQ-matched samples (Li et al., 2017; Tin et al., 2018). We recently examined ToM using the "Reading-the-Mind-in-the-Eyes" test, and documented poorer performance in adolescent patients two years after psychosis onset compared to healthy peers (Ilzarbe et al., 2019). These patients also failed to show the physiological positive association between ToM performance and age. Together, these findings suggested a potential developmental deficit in the acquisition of ToM skills during the early stages of psychosis. In the current study we aimed to examine this issue in a younger, independent sample of participants considered at clinical high risk for psychosis, evaluated before the onset of the disease.

So far, two meta-analyses have described impaired ToM in cohorts at clinical high risk for psychosis (CHR) (Bora and Pantelis, 2013; Van Donkersgoed et al., 2015), suggesting that ToM deficits may predate psychosis onset. Yet when looking at studies individually, ToM findings are mixed; even when examining the same task, for instance the "Reading-the-Mind-in-the-Eyes" test [summarized in Table S1 of supplementary material]. Discrepancies in the literature may be related to differences in the age of participants, with samples usually mixing adolescents and adults, which is an important aspect given potential differences in social cognition specific to developmental stage. Another feature is the availability of longitudinal assessments providing information on outcome. For instance, Davidson et al. (2018) reported a reduced correlation between ToM performance and age in participants at CHR relative to healthy volunteers assessed at cross-section; although in this report there was no information available on transition to psychosis at follow-up in individuals at CHR. Measuring changes over time longitudinally, Shakeel et al. (2019) reported that individuals at CHR who transitioned to psychosis at follow-up (CHR-t) lacked the improvement in ToM performance exhibited by those who did not transition (CHR-nt), but in this case the influence of age was not considered. Similarly, in a 24-month longitudinal study, Healey et al. (2013) reported that poor ToM performance at baseline predicted transition to psychosis, suggesting that the mixed ToM findings in the CHR literature could also be due to differences that are specific to the subsample of individuals who later transition to psychosis (Tor et al., 2017). However, to our knowledge, no study to date has explored whether deficits in ToM performance in CHR individuals who later transition to psychosis are influenced by age.

The medial prefrontal cortex and bilateral temporo-parietal junction are the brain areas most consistently activated during the performance of ToM tasks in functional magnetic resonance imaging (fMRI) studies (Schurz et al., 2014), and they overlap with the Default Mode Network (DMN) (Schilbach et al., 2012). Connectivity between these areas during the resting-state has been correlated with ToM performance (Zemánková et al., 2018) and has been found to be reduced in adult patients with schizophrenia (Schilbach et al., 2016). Our group recently found that adolescents two years after a first psychotic episode presented reduced functional connectivity and a negative association between connectivity in the medial prefrontal cortex and age, suggesting an impact of psychosis on the development of DMN connectivity during adolescence. Furthermore, functional connectivity in the medial prefrontal cortex partially mediated the impairments observed in ToM performance (Ilzarbe et al., 2019).

Evidence concerning connectivity within the DMN during the resting-state in psychotic disorders is inconsistent: a small number of studies have found over-connectivity (Tang et al., 2013), while recent meta-analyses have reported reduced functional connectivity in schizophrenia (Dong et al., 2018; Kühn and Gallinat, 2013). Similar inconsistencies characterise findings in CHR cohorts, with authors reporting either hyperconnectivy (Shim et al., 2010), hypoconnectivity (Pelletier-Baldelli et al., 2018) or both (Du et al., 2018). To our knowledge only two studies have explored resting-state functional connectivity correlates of social cognition in CHR. Vargas et al. (2019) found that in individuals at CHR, better performance in a mentalizing task conducted outside the scanner was associated with greater global efficiency in the medial prefrontal cortex within the mentalizing network. Global efficiency is defined as the average inverse shortest path length between nodes, and serves as an approach to measure integrated processing within a network. Damme et al. (2019) reported reduced functional connectivity during a self-reference task and increased functional connectivity during the resting-state in individuals at CHR between the medial prefrontal cortex and precuneus. Both samples mixed adolescents and young adults without distinguishing those who later transitioned to psychosis. Other ToM task-based fMRI studies found reduced prefrontal cortex activation in individuals at CHR relative to healthy volunteers (Brüne et al., 2011; Marjoram et al., 2006), but also failed to explore the relationship with transition to psychosis. Despite evidence suggesting that changes in brain connectivity associated with ToM in psychosis take place early on and may interact with normal development, no study to date has evaluated the neural correlates of ToM in individuals at CHR according to transition to psychosis and assessed the effects of age on these findings (Cao et al., 2018).

In this context we set out to evaluate ToM performance and its relationship with intrinsic functional connectivity during resting-state fMRI in adolescents at CHR for psychosis, comparing those who transitioned to psychosis (CHR-t) over the follow-up period with those who did not (CHR-nt) and to healthy volunteers, as well as to examine the effect of age on these measures. Our hypotheses were: 1) participants at CHR-t would display worse ToM performance than healthy volunteers and than those at CHR-nt; 2) participants at CHR-t would exhibit less intrinsic functional connectivity in the medial prefrontal cortex within the DMN compared to healthy volunteers and to those at CHR-nt; 3) participants at CHR-t would fail to display the positive association with age in ToM performance and DMN connectivity exhibited by healthy volunteers or CHR-nt; and 4) ToM performance would be associated with intrinsic functional connectivity within the DMN. As a secondary aim, we set out to evaluate the capacity of ToM performance or intrinsic functional connectivity within the DMN to predict transition to psychosis within the CHR group.

2. Materials and methods

2.1. Sample

Participants were recruited as part of the Children and Adolescents Psychosis Risk Syndrome (CAPRIS) study (Dolz et al., 2019): 50 help-seeking adolescents (aged 12–17) meeting criteria for CHR (attenuated positive or negative symptoms or brief limited intermittent psychotic symptoms (Cornblatt et al., 2003) scored using the SOPS (Miller et al., 2003); or with a 1st/2nd degree relative with schizophrenia or a diagnosis of schizotypal disorder, plus a decline in functioning (Klosterkötter et al., 2005) according to SIPS criteria (Miller et al., 2003)); 36 healthy volunteers matched by age and sex, recruited from schools or community settings from the same geographical area. Clinical assessments were carried out at baseline, 6, 12 and 18 months for participants at CHR, and at baseline and 18 months for healthy volunteers. The study was approved by the local Ethical Review Board, and all participants provided written informed assent, and parents or legal guardians gave written informed consent prior to study participation. Further details about the recruitment procedure can be found elsewhere (Dolz et al., 2019). Clinical and neuropsychological assessments and resting state fMRI neuroimaging acquired at baseline were included in the analyses.

2.2. Clinical assessment: baseline

Demographic data, including age, sex and race were collected; socio-

economic status was classified according to the Hollingshead-Redlich scale (Hollingshead and Redlich, 2007), where the highest parental educational and employment status was recorded. All participants were assessed by child and adolescent mental health professionals (psychiatrists and psychologists). CHR criteria were assessed with the Structured Interview for Prodromal Symptoms, scored on the Scale of Prodromal Symptoms (SOPS) (Miller et al., 2003); and global functioning was assessed with the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983). Cannabis use and detailed medication history were recorded for each participant; doses of antipsychotic drugs were transformed into chlorpromazine equivalents (Leucht et al., 2014) and cumulative chlorpromazine equivalents over time were calculated for each individual at the time of scanning. Neurocognitive function was measured using the General Ability Index (referred to as Global Intelligence Quotient; gIQ) (Flanagan and Kaufman, 2008), derived from the Wechsler Intelligence Scale for Children – 4th Edition (WISC-IV) (Wechsler, 2003). The "Reading-the-Mind-in-the-Eyes" Test (Baron--Cohen et al., 2001) was used to evaluate ToM. The task comprises 28 images that reproduce the eyes of different individuals expressing a range of emotions. Participants were asked to identify the gender of the individual (control condition) and the emotion (experimental condition), selected among 4 possible answers.

2.3. Clinical assessment: follow-up

The only information gathered from the longitudinal assessment related to transition to psychosis. This was available for 39 participants at CHR (78 %) and 27 healthy volunteers (75 %), with no differences in age, sex, race, gIQ, socio-economic status, cannabis use or group in relation to the drop-outs. Fifteen adolescents at CHR developed a psychotic episode (30 %) during the follow-up period (mean time to transition: 12.2 (SD = 6.1) months).

Socio-demographic and clinical information are presented in Tables 1 and S2.

2.4. Statistical analyses: socio-demographic and clinical data

Statistical analyses were performed in Stata v.13.1 using *t*-test, ANOVA and chi-square tests for demographic and clinical information. In order to account for both the control and the experimental conditions, performance during the ToM task (% of correct answers) was assessed using a multilevel mixed-effects linear regression model, with group, condition and group by condition interaction as fixed effects, including individual factor as random effect; replicating the methods from our previous article (Ilzarbe et al., 2019). gIQ, sex, age, socio-economic status, cannabis use or baseline clinical severity (total SOPS score, CGAS) were added as covariates to the model when exerting a significant effect ($p \leq .05$). A linear regression model was also used to assess the effect of age on ToM performance, including group, age and group by age interaction. Again, gIQ, sex, socio-economic status, cannabis use or clinical severity (total SOPS score, CGAS) were added as covariates when significant ($p \leq .05$). Bonferroni correction was applied for multiple pairwise comparisons.

2.5. Neuroimaging acquisition and preprocessing

An 8-min eyes-closed resting-state fMRI sequence was acquired in a single session on a 3 T scanner at baseline. Acquisition parameters are detailed in Supplementary material. Resting-state fMRI images were realigned, co-registered to the individual T1-weighted scan, normalized to the Montreal Neurological Institute (MNI) space and smoothed using a 6-mm Gaussian kernel in SPM12. One healthy volunteer (drop-out) and three participants at CHR (one CHR-t, one CHR-nt and one drop-out) were excluded from further neuroimaging analyses due to excessive motion (absolute movement > 3 mm or mean Framewise Displacement >.2 or more than 20 % frames with Framewise Displacement >.3) (Power et al., 2017, 2012; Yan et al., 2013). There were no differences in age, sex, race, gIQ, socio-economic status or cannabis between those excluded due to movement and the rest of the sample. There were no significant differences in the mean Framewise Displacement between CHR and healthy volunteers; or between the three groups (CHR-t, CHR-nt and healthy volunteers).

2.6. Functional connectivity analysis

The component corresponding to the DMN was identified among 20 components estimated by independent component analysis using the GIFT toolbox for SPM12 running in Matlab R2019a. The network was identified by visual inspection and confirmed through the highest correlation with the template (r = .57) [spatial map representation in Fig. S1 of supplementary material]. Replicating the methods from our previous article (Ilzarbe et al., 2019), the spatial maps of the DMN component of each subject were compared in a whole brain analysis in SPM, introducing group, age, group by age interaction, sex and mean framewise displacement as regressors within an inclusive DMN mask created with the mean sample template. Only results surviving family-wise error correction are reported. Next, mean values of intrinsic functional connectivity within each significant cluster were extracted for each individual, and linear regression models were conducted in Stata v.13.1, in which the effects of gIQ, sex, socio-economic status or

Table 1
Baseline socio-demographic and clinical characteristics of the sample subdivided according to transition to psychosis at follow-up.

	CHR-t (n = 15)	CHR-nt (n = 24)	HV (n = 27)	*p* value	*Post-hoc (Bonferroni)*
Socio-demographic					
Age (years) [range]	15.2 (SD = 1.3) [12.6–17.2]	15.7 (SD = 1.7) [12.0–17.9]	15.6 (SD = 1.7) [12.9–18.3]	*.640*	
Sex (% female)	66.7 %	62.5 %	70.4 %	*.838*	
Race (% caucasian)	100.0 %	79.2 %	92.6 %	*.094*	
Socio-economic Status	48.1 (SD = 19.8)	39.2 (SD = 16.2)	50.7 (SD = 14.5)	*.061*	–
Clinical variables					
Global Intelligence Quotient	105.8 (SD = 12.4)	98.6 (SD = 13.7)	107.8 (SD = 12.3)	*.038**	*HV > CHR-nt*
Scale of Prodromal Symptoms (total score)	32.8 (SD = 10.6)	28.9 (SD = 11.0)	1.7 (SD = 2.3)	*<.0001**	*CHR-t = CHR-nt>HV*
- Positive Subscale	9.0 (SD = 4.1)	7.8 (SD = 3.9)	.4 (SD = .8)	*<.0001**	*CHR-t = CHR-nt>HV*
- Negative Subscale	8.5 (SD = 4.7)	10.6 (SD = 5.5)	.4 (SD = .6)	*<.0001**	*CHR-t = CHR-nt>HV*
- Disorganized Subscale	4.4 (SD = 2.8)	3.6 (SD = 2.5)	.3 (SD = .7)	*<.0001**	*CHR-t = CHR-nt>HV*
- General Subscale	10.6 (SD = 3.4)	7.5 (SD = 4.3)	.9 (SD = 2.0)	*<.0001**	*CHR-t > CHR-nt>HV*
Children's Global Assessment Scale	36.0 (SD = 18.2)	50.2 (SD = 16.6)	84.4 (SD = 6.9)	*<.0001**	*HV > CHR-nt > CHR-t*
Reported cannabis use					
- Occasionally - monthly	26.7 %	12.5 %	33.3 %	*.241*	
- Weekly - diary	13.3 %	20.8 %	3.7 %		
Time to transition (months)	12.2 (SD = 6.1)	–	–		

Note: HV = Healthy Volunteers; CHR-t = participants at Clinical High Risk for psychosis who transitioned to psychosis; CHR-nt = participants at Clinical High Risk for psychosis who did not transition to psychosis; SOPS = Scale of Prodromal Symptoms; SD = Standard Deviation; * $p < .05$.

cannabis use were included as covariates in the model when significant ($p \leq .05$). Bonferroni correction was applied for multiple pairwise comparisons. The potential effect of antipsychotic medication on resting-state fMRI measures (cumulative chlorpromazine equivalents (Leucht et al., 2014)) was also evaluated. Correlations between ToM performance and intrinsic functional connectivity were estimated to evaluate their association.

2.7. Survival analysis

In order to account for time to transition in the prediction of psychosis, a survival analysis was performed within the CHR group using Stata v.13.1. Performance in the ToM task and functional connectivity in the clusters showing significant group effects were assessed as predictive variables using Cox proportional hazards models to compute Hazard Ratios. Liu's method (Liu, 2012) for empirical estimation of a diagnostic cut-off point (Area Under the Curve) was used to dichotomize the significant variables, Kaplan-Meier survival curves were then estimated for each group.

3. Results

3.1. Theory of mind task

For the CHR-t, CHR-nt and healthy volunteers contrast, there was no significant group by condition effect ($p = .17$) [Table S3]. However, the linear regression model showed a significant group by age effect between healthy volunteers and CHR-t ($p = .03$; $\omega^2 = .058$); with a positive association between ToM performance and age in healthy volunteers ($\beta = 3.39$; $p = .002$), which was also present at trend-level significance in the CHR-nt group ($\beta = 2.03$; $p = .08$) but not in the CHR-t group ($\beta = -1.37$; $p = .45$) [Fig. 1]. gIQ, sex and socio-economic status were included as covariates in the linear regression model ($ps < .03$) while cannabis use, and ratings in the SOPS and CGAS were excluded, given that they had no significant effect in the model [Table S3].

3.2. Intrinsic functional connectivity

An effect of group was found in the dorsomedial prefrontal cortex within the DMN (cluster 1: [x = -9, y = 47, z = 26]; voxel count = 51; $p^{FWE-corr} = .041$) in the CHR-nt vs CHR-t contrast. Post-hoc analysis with the extracted values showed that CHR-t participants exhibited less connectivity compared to CHR-nt ($p < .001$) and healthy volunteers ($p = .046$) [Figs. 2A and S2A]. A second cluster in the ventromedial prefrontal cortex showed a significant group by age interaction (cluster 2: [x = -12, y = 44, z = -2]; voxel = 50; $p^{FWE-corr} = .044$) in the healthy volunteers vs CHR-nt contrast. Post-hoc analysis with the values extracted from this cluster showed a significant group by age interaction between healthy volunteers and both CHR-t ($p = .001$) and CHR-nt ($p < .001$) groups; where functional connectivity was positively associated with age in healthy volunteers ($\beta = .25$; $p = .001$), while the effect was the opposite in individuals at CHR-nt ($\beta = -.24$; $p = .003$) and CHR-t ($\beta = -.24$; $p = .058$) [Figs. 2B and S2A]. There was no significant effect of socio-economic status, sex, gIQ or cannabis use when included in the models. In individuals at CHR receiving antipsychotic treatment (n = 21), cumulative chlorpromazine equivalents were not correlated with functional connectivity in either of the clusters ($rs \leq |.22|$; $ps \geq .34$).

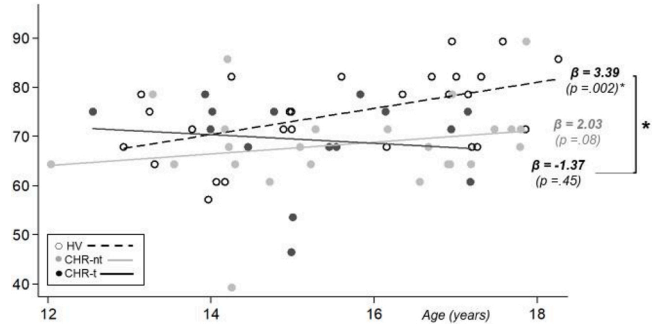


Fig. 1. Scatter-plot representing group by age effects on the experimental condition of the "Reading-the-Mind-in-the-Eyes" Test comparing healthy volunteers vs participants at clinical high risk for psychosis according to transition to psychosis[a].
Note: HV = Healthy Volunteers; CHR = participants at Clinical High Risk for psychosis; CHR-t = participants at Clinical High Risk for psychosis who transitioned to psychosis; CHR-nt = participants at Clinical High Risk for psychosis who did not transition to psychosis; [a]: model also including global intelligence quotient, sex and socio-economic status ($ps < .03$) as covariables; * $p < .05$.

There was a trend-level correlation between ToM performance and functional connectivity in cluster 2 in healthy volunteers (n = 35; r = .32; $p = .058$) [see Fig. S3], not replicated in the other groups.

A secondary Region-of-Interest (ROIs) analysis was performed based on results from our previous study in a sample of patients with early onset psychosis (Ilzarbe et al., 2019). The two ROIs, defined according to regions showing group and group by age effects in the contrast between patients with early onset psychosis relative to healthy volunteers, were located in the dorsal and ventral areas of medial prefrontal cortex within the DMN, respectively [see Fig. S2A]. CHR-t exhibited reduced functional connectivity relative to healthy volunteers at trend-level ($p = .060$) in ROI1 located in the dorsomedial prefrontal cortex; and there was a significant group by age interaction between healthy volunteers and CHR-nt ($p = .028$) in ROI2 in the ventromedial prefrontal cortex [for further information see supplementary material and Fig. S2B].

For the sake of completeness, we conducted contrasts for CHR vs healthy volunteers for both the theory of mind task and resting state fMRI data, which revealed no significant group or group by age effects in either modality. These analyses are presented in Supplementary Material.

3.3. Survival analysis

Out of 50 participants at CHR, 43 were included in the survival analysis (three excluded due to movement and four with no follow-up). Fourteen participants had experienced transition to psychosis during the follow-up period. Only functional connectivity in dorsomedial prefrontal cortex (cluster 1) (HR = .20; $p = .002$) was associated with less probability to transition to psychosis at follow-up. Further analysis allowed to establish a cut-off point in functional connectivity of dorsomedial prefrontal cortex (cluster 1) (cut-off point = 1.52; area under ROC curve = .83; sensitivity = .79; specificity = .79). Participants with low functional connectivity (under the cut-off point) in dorsomedial prefrontal cortex (cluster 1) exhibited a significantly increased risk of transition to psychosis (HR = 6.29; $p = .005$; 95 %CI: 1.75–22.64) [Fig. 3].

4. Discussion

Our study evaluated ToM performance and resting-state fMRI in adolescents at CHR for psychosis and found:

(1) A positive association between ToM performance and age in healthy volunteers, which was absent in participants at CHR-t.
(2) Reduced intrinsic functional connectivity in the dorsomedial prefrontal cortex within the DMN in participants at CHR-t, relative to CHR-nt and to healthy volunteers. Connectivity in the ventromedial prefrontal cortex was positively associated with age in healthy volunteers, while it was negatively associated with age in both CHR-nt and CHR-t.
(3) An association between reduced intrinsic functional connectivity in the dorsomedial prefrontal cortex within the DMN and higher rates of transition to psychosis in individuals at CHR.

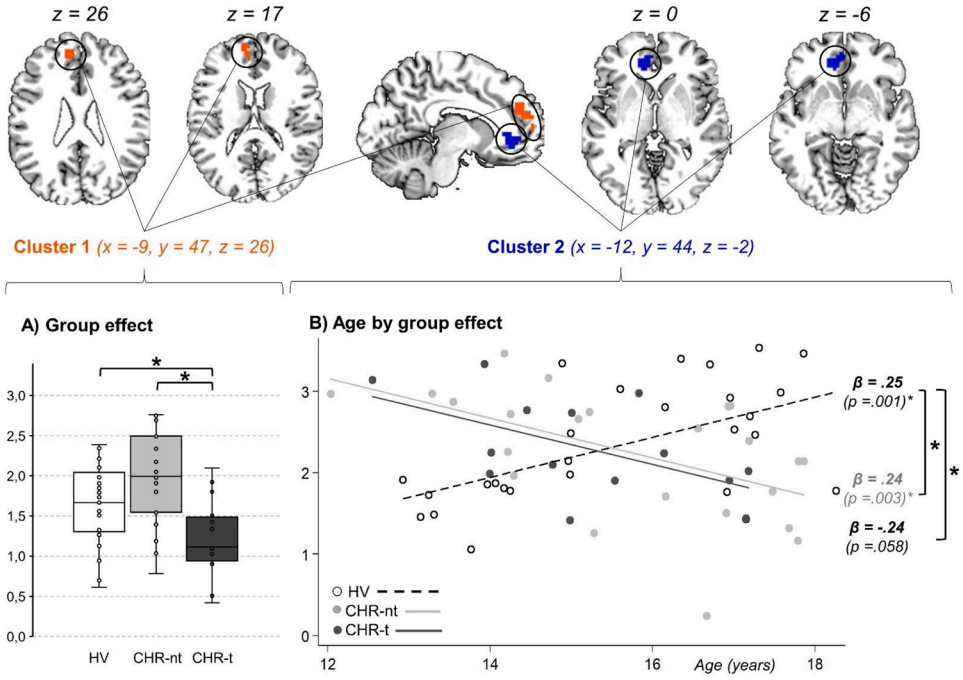


Fig. 2. Clusters within the Default Mode Network showing a significant effect of group (A) and group by age interaction (B) in intrinsic functional connectivity between healthy volunteers and participants at clinical high risk for psychosis divided according to transition to psychosis at follow-up, overlaid on a grayscale brain template.
Note: HV = Healthy Volunteers; CHR-t = participants at Clinical High Risk for psychosis who transitioned to psychosis; CHR-nt = participants at Clinical High Risk for psychosis who did not transition to psychosis; * $p < .05$.

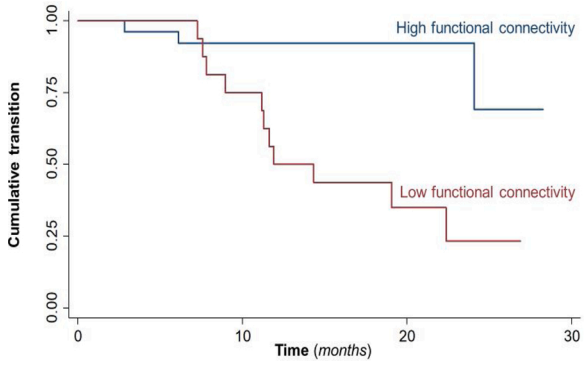


Fig. 3. Kaplan-Meier survival estimates for transition to psychosis within participants at clinical high risk for psychosis divided by functional connectivity ("low" and "high", dichotomized according to the cut-off point of 1.52) in the dorsomedial prefrontal cortex (cluster 1) [x = -9, y = 47, z = 26].

We found no group by condition effects in ToM performance between CHR, CHR-t, CHR-nt and healthy volunteers; contrary to our hypothesis and to findings from the single study examining performance in the same ToM task in individuals at CHR according to transition to psychosis (Healey et al., 2013). Two factors may have contributed to the lack of group effects in ToM performance in our study. First, a potential effect of developmental stage: the sample in the study by Healey et al. (2013) predominantly encompassed adults, while we focused on adolescents. Healthy volunteers in our study exhibited a positive association between ToM performance and age, in line with meta-analytic findings (Peñuelas-Calvo et al., 2019), while participants at CHR who transitioned to psychosis failed to present such association, which coincides with findings by Davidson et al. (2018). This suggests a potential developmental discontinuation of ToM abilities in these individuals, in line with our previous findings in an independent sample of adolescents with early-onset psychosis (Ilzarbe et al., 2019). This would lead to larger ToM impairments in older patients with psychosis, as reflected by the greater effect sizes reported in adult samples with schizophrenia (Bora et al., 2009) than in adolescents with early-onset psychosis (Ilzarbe et al., 2019). Second, effect sizes of ToM impairments in CHR are likely to be smaller in comparison to first-episode psychosis (Bora and Pantelis, 2013) or schizophrenia (Bora et al., 2009; Zhang et al., 2018) given the heterogeneity of CHR samples. Our findings are in line with previous age-related ToM difficulties documented in CHR (Healey et al., 2013; Davidson et al., 2018; Shakeel et al., 2019), and suggest that this lack of age-positive association with ToM performance is due to those individuals at CHR who later transition to psychosis. This is consistent with a recent longitudinal study reporting lack of improvement in ToM performance over time in CHR-t relative to CHR-nt (Shakeel et al., 2019). Our results also expand our previous findings showing a lack of association between age and ToM performance in adolescents with early-onset psychosis (Ilzarbe et al., 2019), suggesting an impaired acquisition in ToM abilities during development, prior to the onset of the psychosis. The emergence of prodromal symptoms and progression to overt psychosis in adolescence, which is a critical period for the maturation of ToM abilities, may explain the greater social cognitive deficits associated with earlier onset of the disease reported in adult samples (Linke et al., 2015).

We observed reduced intrinsic functional connectivity in the dorsomedial prefrontal cortex within the DMN in individuals at CHR who transitioned to psychosis. Similar to our findings, Anticevic et al. (2015) reported hypoconnectivity involving the prefrontal cortex in participants at CHR who transitioned to psychosis relative to healthy volunteers, which is also consistent with the results from two meta-analyses in patients with schizophrenia (Dong et al., 2018; Kühn and Gallinat, 2013). In contrast, Cao et al. (2018) described global hyperconnectivity during the resting-state in participants at CHR who converted to psychosis relative to those who did not. The use of a seed-based-analysis or a ROI-to-ROI analysis, respectively, has been hypothesized to explain the discrepancies between studies (Cao et al., 2018). This group effect is also in line with our previous findings of reduced intrinsic functional connectivity in the medial prefrontal cortex in individuals with early-onset psychosis (Ilzarbe et al., 2019). We have found less connectivity in the CHR-t group compared to healthy volunteers, albeit at trend-level significance (as shown in Fig. S2B), in the same region within the dorsomedial prefrontal cortex as in our earlier article (Ilzarbe et al., 2019). Interestingly, mean values of connectivity were comparable between CHR-t participants and youth with early-onset psychosis, while values in healthy volunteers were higher in our previous study (Ilzarbe et al.,

2019), where participants were overall older. Despite the fact that this is an indirect comparison between two different samples, therefore limiting our capacity to draw conclusions, our findings suggest that youth in the early stages of psychosis may not experience the increase in connectivity in the medial prefrontal cortex typically taking place during adolescence. We indeed found a positive association between connectivity and age in healthy volunteers in the ventromedial prefrontal cortex. In fact, the medial prefrontal cortex is thought to play a key role in the development of the DMN during adolescence, experiencing a sharp increase in connectivity during this period in healthy volunteers (Cai et al., 2018; Dosenbach et al., 2010; Mak et al., 2017; Sato et al., 2014; Truelove-Hill et al., 2020). A meta-analysis reporting greater connectivity within the DMN in adult samples relative to children and adolescents (Mak et al., 2017) suggested that methodological differences between studies could explain discrepant findings in the literature: those using independent component analysis and seed-based analysis tended to find positive correlations with age (Dosenbach et al., 2010; Sato et al., 2014), while those using a ROI-to-ROI approach tended to find negative correlations with age (Marek et al., 2015). In our study, in contrast to the healthy volunteers, both CHR-nt and CHR-t groups showed a negative association between functional connectivity and age. This may suggest a shared neurodevelopmental deficit, as delayed brain maturation has been related with psychopathology (Cropley et al., 2020; Sato et al., 2016). Medial prefrontal cortex disruption has been implicated in several disorders and related with multiple cognitive domains (Hiser and Koenigs, 2018), with regionally specific differences. For instance, ventral areas within the medial prefrontal cortex extending to anterior cingulate cortex (Marusak et al., 2016), as is the case of cluster 2, have been associated with value-based decision-making tasks (Gilbert et al., 2009; Hiser and Koenigs, 2018). On the other hand, dorsal regions of the medial prefrontal cortex, which is where cluster 1 is located, have been related with impaired ToM in schizophrenia (Hiser and Koenigs, 2018). In fact, cluster 1 partially overlaps with significant regions reported by a ToM fMRI-task based meta-analysis in schizophrenia (Sugranyes et al., 2011), and with the prefrontal areas associated with the mentalizing network during resting-state fMRI in schizophrenia (Schilbach et al., 2016) [Fig. S2A]. Besides social cognitive difficulties, disrupted connectivity of the prefrontal cortex in schizophrenia (Zhou et al., 2015) has also been linked with psychotic symptoms (Thoma et al., 2016) and impaired executive functions (Giraldo-Chica et al., 2018); and has been associated with glutamate hypofunction (Limongi et al., 2020). Glutamate levels in the medial prefrontal cortex (overlapping with mentalizing areas) have been associated with resting-state connectivity within the DMN in healthy volunteers (Martens et al., 2020), and positively correlated with better cognitive performance in individuals at high-risk for psychosis (Wenneberg et al., 2020). Our results extend our previous findings of impaired maturation of medial prefrontal cortex connectivity in adolescent-onset psychosis (Ilzarbe et al., 2019), in alignment with the current physiopathological framework for schizophrenia (Howes et al., 2015), and suggest that dysfunction in dorsal and ventral areas of the medial prefrontal cortex is already present in adolescents during the prodromal stage, before the onset of the first episode.

We failed to find an association between ToM performance and functional connectivity in the medial prefrontal cortex, in consonance with a previous study in individuals at CHR (Damme et al., 2019). This dissociation between apparently no impairment in performance in the ToM task and altered functional connectivity of the DMN in participants at CHR who later transition to psychosis, contrasts with our previous finding of a relationship between ToM and functional connectivity within DMN in adolescents with early-onset psychosis (Ilzarbe et al., 2019). An explanation could be that brain disruption may precede ToM deficits in adolescents at CHR who will later develop psychosis. Furthermore, altered connectivity between mentalizing regions may interfere in the acquisition of ToM abilities during development. This could explain why ToM deficits are more pronounced after the onset of psychosis (Ilzarbe et al., 2019), compared to the prodromal stage. If so, functional neuroimaging may be more sensitive towards detecting illness-related changes than behavioural tasks (Ilzarbe et al., 2019; Kim et al., 2009; Malhi et al., 2007), especially during the early stages of the illness. Further, we found that reduced functional connectivity in the dorsomedial prefrontal cortex, overlapping with mentalizing regions in schizophrenia, was a significant marker of transition to psychosis in CHR individuals. Previous studies have also supported the role of functional neuroimaging in detecting risk of transition to psychosis, over the use of clinical variables (Cao et al., 2018); and our findings point to the dorsomedial prefrontal cortex as a potential key region.

The main limitation of our study is the sample size, which may have resulted in lower statistical power, therefore limiting our capacity to detect statistically significant findings, which may have been particularly relevant when assessing ToM performance. Given that earlier age of onset of psychosis has been associated with greater clinical severity (Immonen et al., 2017), differences in clinical severity according to age could have influenced the relationship between age and ToM. Nevertheless, it is worth noting that overall clinical and symptom severity did not exert a significant effect on the estimated statistical models. In contrast, a strength of the study is the fact that our sample is composed exclusively of adolescents (Tor et al., 2017), which allows for the study of CHR individuals during a key period in neurodevelopment (Murray and Lewis, 1987). Furthermore, it also promotes homogeneity of the sample. The evaluation of participants according to their longitudinal outcome is another strength of this study and increases the clinical relevance of our findings. In addition, resting-state fMRI presents advantages in relation to replicability (simpler instructions and less potential confounders), making it more comparable with other studies and easier to translate to clinical daily practice, especially when working with adolescents with mental health disorders, as well as considerations related to cost and equipment requirements (Fox and Greicius, 2010).

4.1. Conclusions

To conclude, our study provides evidence of a lack of an age-positive association in ToM performance and reduced medial prefrontal connectivity in adolescents at CHR who go on to develop a first psychotic episode. Our data increase the understanding of the neural underpinnings of psychosis, suggesting medial prefrontal cortex, within DMN connectivity, as a potential brain-based marker for identifying and monitoring individuals at greatest risk of transition.

Disclosures and acknowledgements

DI has received funding from the Spanish Ministry of Science, Innovation and Universities, Instituto de Salud Carlos III, 'Rio Hortega'contract CM17/00019, with the support of European Social Fund. IB has received funding from the Spanish Ministry of Science, Innovation and Universities, Instituto de Salud Carlos III, contract for intensification INT19/00021, research funding from the Instituto de Salud Carlos III and the Alicia Koplowitz Foundation, and reports honoraria and travel support from Otsuka-Lundbeck and Janssen. ES has received research funding from the Instituto de Salud Carlos III. AF has received educational support from Otsuka-Lundbeck. OP has received research funding from the Alicia Koplowitz Foundation. MD has received research funding from the Instituto de Salud Carlos III and the Alicia Koplowitz Foundation, and reports honoraria and travel support from Shire, Janssen and Osuka-Lundbeck. JC has received research funding from the Instituto de Salud Carlos III, the Government of Catalonia and La Marató TV3. GS has received research funding from the Brain and Behaviour Research Foundation (NARSAD Young Investigator Award), the Instituto de Salud Carlos III, the Government of Catalonia and the Alicia Koplowitz Foundation. The remaining authors declare no conflicts of interest. This work was supported by grants from the Instituto de Salud Carlos III (Fondo de Investigación Sanitaria PI11/1349; PI11/02684;

PI15/0444, PI15/00509 and PI18/00976), ERDF funding, "A way to make Europe", CIBERSAM Network, Alicia Koplowitz Foundation, Ajut a la Recerca Pons Bartran, Fundació Clínic Recerca Biomèdica and NARSAD Young Investigator Award 2017 (26731). This work has been performed thanks to the 3 T Equipment of Magnetic Resonance at IDIBAPS (project IBPS15-EE-3688 cofunded by MCIU and by ERDF). The funding sources had no role in study design, interpretation of results, in the writing of the report or in the decision to submit the article for publication. We would like to thank all the participants and their families for this study.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2021.100940.

References

Anticevic, A., Haut, K., Murray, J.D., Repovs, G., Yang, G.J., Diehl, C., McEwen, S.C., Bearden, C.E., Addington, J., Goodyear, B., Cadenhead, K.S., Mirzakhanian, H., Cornblatt, B.A., Olvet, D., Mathalon, D.H., McGlashan, T.H., Perkins, D.O., Belger, A., Seidman, L.J., Tsuang, M.T., Van Erp, T.G.M., Walker, E.F., Hamann, S., Woods, S.W., Qiu, M., Cannon, T.D., 2015. Association of thalamic dysconnectivity and conversion to psychosis in youth and young adults at elevated clinical risk. JAMA Psychiatry 72, 882–891. https://doi.org/10.1001/jamapsychiatry.2015.0566.

Baron-Cohen, S., Leslie, A.M., Frith, U., 1985. Does the autistic child have a "theory of mind"? Cognition 21, 37–46.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., Plumb, I., 2001. The "Reading the mind in the eyes" test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J. Child Psychol. Psychiat. Assoc. Child Psychol. Psychiatry 42, 241–251. https://doi.org/10.1111/1469-7610.00715.

Barresi, J., Moore, C., 1996. Intentional relations and social understanding. Behav. Brain Sci. 19, 107–154.

Bora, E., Pantelis, C., 2013. Theory of mind impairments in first-episode psychosis, individuals at ultra-high risk for psychosis and in first-degree relatives of schizophrenia: systematic review and meta-analysis. Schizophr. Res. 144, 31–36. https://doi.org/10.1016/j.schres.2012.12.013.

Bora, E., Yucel, M., Pantelis, C., 2009. Theory of mind impairment in schizophrenia: meta-analysis. Schizophr. Res. https://doi.org/10.1016/j.schres.2008.12.020.

Brüne, M., Özgürdal, S., Ansorge, N., von Reventlow, H.G., Peters, S., Nicolas, V., Tegenthoff, M., Juckel, G., Lissek, S., 2011. An fMRI study of "theory of mind" in at-risk states of psychosis: comparison with manifest schizophrenia and healthy controls. NeuroImage 55, 329–337. https://doi.org/10.1016/j.neuroimage.2010.12.018.

Cai, L., Dong, Q., Niu, H., 2018. The development of functional network organization in early childhood and early adolescence: a resting-state fNIRS study. Dev. Cogn. Neurosci. 30, 223–235. https://doi.org/10.1016/j.dcn.2018.03.003.

Cao, H., Chén, O.Y., Chung, Y., Forsyth, J.K., McEwen, S.C., Gee, D.G., Bearden, C.E., Addington, J., Goodyear, B., Cadenhead, K.S., Mirzakhanian, H., Cornblatt, B.A., Carrión, R.E., Mathalon, D.H., McGlashan, T.H., Perkins, D.O., Belger, A., Seidman, L.J., Thermenos, H., Tsuang, M.T., van Erp, T.G.M., Walker, E.F., Hamann, S., Anticevic, A., Woods, S.W., Cannon, T.D., 2018. Cerebello-thalamo-cortical hyperconnectivity as a state-independent functional neural signature for psychosis prediction and characterization. Nat. Commun. 9, 1–9. https://doi.org/10.1038/s41467-018-06350-7.

Cornblatt, B.A., Lencz, T., Smith, C.W., Correll, C.U., Auther, A.M., Nakayama, E., 2003. The schizophrenia prodrome revisited: a neurodevelopmental perspective. Schizophr. Bull. 29, 633–651. https://doi.org/10.1093/oxfordjournals.schbul.a007036.

Cropley, V.L., Tian, Y., Fernando, K., Mansour, S.L., Pantelis, C., Cocchi, L., Zalesky, A., 2020. Brain-predicted age associates with psychopathology dimensions in youths. Biol. Psychiatry Cogn. Neurosci. Neuroimaging. https://doi.org/10.1016/j.bpsc.2020.07.014, 2020.06.13.149658.

Damme, K.S.F., Pelletier-Baldelli, A., Cowan, H.R., Orr, J.M., Mittal, V.A., 2019. Distinct and opposite profiles of connectivity during self-reference task and rest in youth at clinical high risk for psychosis. Hum. Brain Mapp. 40, 3254–3264. https://doi.org/10.1002/hbm.24595.

Davidson, C.A., Piskulic, D., Addington, J., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., McGlashan, T.H., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Walker, E.F., Bearden, C.E., Mathalon, D.H., Woods, S.W., Johannesen, J.K., 2018. Age-related trajectories of social cognition in youth at clinical high risk for psychosis: an exploratory study. Schizophr. Res. 201, 130–136. https://doi.org/10.1016/j.schres.2018.05.001.

Dolz, M., Tor, J., De la Serna, E., Pardo, M., Muñoz-Samons, D., Rodríguez-Pascual, M., Puig, O., Sugranyes, G., Usall, J., Sánchez-Gistau, V., Baeza, I., 2019. Characterization of children and adolescents with psychosis risk syndrome: the Children and Adolescents Psychosis Risk Syndrome (CAPRIS) study. Early Interv. Psychiatry 13, 1062–1072. https://doi.org/10.1111/eip.12728.

Dong, D., Wang, Y., Chang, X., Luo, C., Yao, D., 2018. Dysfunction of large-scale brain networks in schizophrenia: a meta-analysis of resting-state functional connectivity. Schizophr. Bull. 44, 168–181. https://doi.org/10.1093/schbul/sbx034.

Dosenbach, N.U.F., Nardos, B., Cohen, A.L., Fair, D.A., Power, J.D., Church, J.A., Nelson, S.M., Wig, G.S., Vogel, A.C., Lessov-Schlaggar, C.N., Barnes, K.A., Dubis, J.W., Feczko, E., Coalson, R.S., Pruett, J.R., Barch, D.M., Petersen, S.E., Schlaggar, B.L., 2010. Prediction of individual brain maturity using fMRI. Science 329, 1358–1361.

Du, Y., Fryer, S.L., Lin, D., Sui, J., Yu, Q., Chen, J., Stuart, B., Loewy, R.L., Calhoun, V.D., Mathalon, D.H., 2018. Identifying functional network changing patterns in individuals at clinical high-risk for psychosis and patients with early illness schizophrenia: a group ICA study. Neuroimage Clin. 17, 335–346. https://doi.org/10.1016/j.nicl.2017.10.018.

Flanagan, D.P., Kaufman, A.S., 2008. Essentials of WISC-IV Assessment. Wiley.

Fox, M.D., Greicius, M., 2010. Clinical applications of resting state functional connectivity. Front. Syst. Neurosci. 4, 1–13. https://doi.org/10.3389/fnsys.2010.00019.

Gilbert, S.J., Meuwese, J.D.I., Towgood, K.J., Frith, C.D., Burgess, P.W., 2009. Abnormal functional specialization within medial prefrontal cortex in high-functioning autism: a multi-voxel similarity analysis. Brain 132, 869–878. https://doi.org/10.1093/brain/awn365.

Giraldo-Chica, M., Rogers, B.P., Damon, S.M., Landman, B.A., Woodward, N.D., 2018. Prefrontal-thalamic anatomical connectivity and executive cognitive function in schizophrenia. Biol. Psychiatry 83, 509–517. https://doi.org/10.1016/j.biopsych.2017.09.022.

Healey, K.M., Penn, D.L., Perkins, D., Woods, S.W., Addington, J., 2013. Theory of mind and social judgments in people at clinical high risk of psychosis. Schizophr. Res. 150, 498–504. https://doi.org/10.1016/j.schres.2013.08.038.

Hiser, J., Koenigs, M., 2018. The multifaceted role of the ventromedial prefrontal cortex in emotion, decision making, social cognition, and psychopathology. Biol. Psychiatry 83, 638–647. https://doi.org/10.1016/j.biopsych.2017.10.030.

Hollingshead, A.B., Redlich, Frederick C., 2007. Social class and mental illness: a community study, 1958 Am. J. Public Health 97, 1756–1757.

Howes, O., McCutcheon, R., Stone, J., 2015. Glutamate and dopamine in schizophrenia: an update for the 21st century. J. Psychopharmacol. https://doi.org/10.1177/0269881114563634.

Ilzarbe, D., de la Serna, E., Baeza, I., Rosa, M., Puig, O., Calvo, A., Masias, M., Borras, R., Pariente, J.C., Castro-Fornieles, J., Sugranyes, G., 2019. The relationship between performance in a theory of mind task and intrinsic functional connectivity in youth with early onset psychosis. Dev. Cogn. Neurosci. 40 https://doi.org/10.1016/j.dcn.2019.100726.

Immonen, J., Jääskeläinen, E., Korpela, H., Miettunen, J., 2017. Age at onset and the outcomes of schizophrenia: a systematic review and meta-analysis. Early Interv. Psychiatry 11, 453–460. https://doi.org/10.1111/eip.12412.

Kim, E., Jung, Y.C., Ku, J., Kim, J.J., Lee, H., Kim, S.Y., Kim, S.I., Cho, H.S., 2009. Reduced activation in the mirror neuron system during a virtual social cognition task in euthymic bipolar disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 33, 1409–1416. https://doi.org/10.1016/j.pnpbp.2009.07.019.

Klosterkötter, J., Ruhrmann, S., Schultze-Lutter, F., Salokangas, R.K.R., Linszen, D., Birchwood, M., Juckel, G., Morrison, A., Vázquèz-Barquero, J.L., Hambrecht, M., VON Reventlow, H., 2005. The European Prediction of Psychosis Study (EPOS): integrating early recognition and intervention in Europe. World Psychiatry 4, 161–167.

Kühn, S., Gallinat, J., 2013. Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. Schizophr. Bull. 39, 358–365. https://doi.org/10.1093/schbul/sbr151.

Leucht, S., Samara, M., Heres, S., Patel, M.X., Woods, S.W., Davis, J.M., 2014. Dose equivalents for second-generation antipsychotics: the minimum effective dose method. Schizophr. Bull. 40, 314–326. https://doi.org/10.1093/schbul/sbu001.

Li, Dandan, Li, X., Yu, F., Chen, X., Zhang, L., Li, Dan, Wei, Q., Zhang, Q., Zhu, C., Wang, K., 2017. Comparing the ability of cognitive and affective theory of mind in adolescent onset schizophrenia. Neuropsychiatr. Dis. Treat. 13, 937–945. https://doi.org/10.2147/NDT.S128116.

Limongi, R., Jeon, P., Mackinley, M., Das, T., Dempster, K., Théberge, J., Bartha, R., Wong, D., Palaniyappan, L., 2020. Glutamate and dysconnection in the salience network: neurochemical, effective connectivity, and computational evidence in schizophrenia. Biol. Psychiatry 88, 273–281. https://doi.org/10.1016/j.biopsych.2020.01.021.

Linke, M., Jankowski, K.S., Ciołkiewicz, A., Jedrasik-Styła, M., Parnowska, D., Gruszka, A., Denisiuk, M., Jarema, M., Wichniak, A., 2015. Age or age at onset? Which of them really matters for neuro and social cognition in schizophrenia? Psychiatry Res. 225, 197–201. https://doi.org/10.1016/j.psychres.2014.11.024.

Liu, X., 2012. Classification accuracy and cut pointselection. Stat. Med. 31, 2676–2686. https://doi.org/10.1002/sim.4509.

Mak, L.E., Minuzzi, L., MacQueen, G., Hall, G., Kennedy, S.H., Milev, R., 2017. The default mode network in healthy individuals: a systematic review and meta-analysis. Brain Connect. 7, 25–33. https://doi.org/10.1089/brain.2016.0438.

Malhi, G.S., Lagopoulos, J., Owen, A.M., Ivanovski, B., Shnier, R., Sachdev, P., 2007. Reduced activation to implicit affect induction in euthymic bipolar patients: an fMRI study. J. Affect. Disord. 97, 109–122. https://doi.org/10.1016/j.jad.2006.06.005.

Marek, S., Hwang, K., Foran, W., Hallquist, M.N., Luna, B., 2015. The contribution of network organization and integration to the development of cognitive control. PLoS Biol. 13, 1002328 https://doi.org/10.1371/journal.pbio.1002328.

Marjoram, D., Job, D.E., Whalley, H.C., Gountouna, V.E., McIntosh, A.M., Simonotto, E., Cunningham-Owens, D., Johnstone, E.C., Lawrie, S., 2006. A visual joke fMRI investigation into Theory of Mind and enhanced risk of schizophrenia. NeuroImage 31, 1850–1858. https://doi.org/10.1016/j.neuroimage.2006.02.011.

Martens, L., Kroemer, N.B., Teckentrup, V., Colic, L., Palomero-Gallagher, N., Li, M., Walter, M., 2020. Localized Prediction of Glutamate from Whole-brain Functional

Connectivity of the Pregenual Anterior Cingulate Cortex. bioRxiv 2020.02.26.966259. https://doi.org/10.1101/2020.02.26.966259.
Marusak, H.A., Thomason, M.E., Peters, C., Zundel, C., Elrahal, F., Rabinak, C.A., 2016. You say "prefrontal cortex" and I say "anterior cingulate": meta-analysis of spatial overlap in amygdala-to-prefrontal connectivity and internalizing symptomology. Nature Publishing Group 6, 944. https://doi.org/10.1038/tp.2016.218.
Miller, T.J., McGlashan, T.H., Rosen, J.L., Cadenhead, K., Ventura, J., McFarlane, W., Perkins, D.O., Pearlson, G.D., Woods, S.W., 2003. prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophrenia Bulletin, pp. 703–715. https://doi.org/10.1093/oxfordjournals.schbul.a007040.
Murray, R., Lewis, S., 1987. Is schizophrenia a neurodevelopmental disorder? BMJ 295, 681–682. https://doi.org/10.1038/eye.2010.181.
Onishi, K.H., Baillargeon, R., 2005. Do 15-month-old infants understand false beliefs? Science (New York, N.Y.) 308 (5719), 255–258. https://doi.org/10.1126/science.1107621.
Pelletier-Baldelli, A., Andrews-Hanna, J.R., Mittal, V.A., 2018. Resting state connectivity dynamics in individuals at risk for psychosis. J. Abnorm. Psychol. 127, 314–325. https://doi.org/10.1037/abn0000330.
Peñuelas-Calvo, I., Sareen, A., Sevilla-Llewellyn-Jones, J., Fernández-Berrocal, P., 2019. The "Reading the mind in the eyes" test in autism-spectrum disorders comparison with healthy controls: a systematic review and meta-analysis. J. Autism Dev. Disord. 49, 1048–1061. https://doi.org/10.1007/s10803-018-3814-4.
Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage 59, 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018.
Power, J.D., Plitt, M., Laumann, T.O., Martin, A., 2017. Sources and implications of whole-brain fMRI signals in humans. NeuroImage 146, 609–625. https://doi.org/10.1016/j.neuroimage.2016.09.038.
Premack, D., Woodruff, G., 1978. Does the chimpanzee have a theory of mind? Behav. Brain Sci. 4, 515–526.
Sato, J.R., Salum, G.A., Gadelha, A., Picon, F.A., Pan, P.M., Vieira, G., Zugman, A., Hoexter, M.Q., Anés, M., Moura, L.M., Del'Aquilla, M.A.G., Amaro Junior, E., McGuire, P., Crossley, N., Lacerda, A., Rohde, L.A., Miguel, E.C., Bressan, R.A., Jackowski, A.P., 2014. Age effects on the default mode and control networks in typically developing children. J. Psychiatr. Res. 58, 89–95. https://doi.org/10.1016/j.jpsychires.2014.07.004.
Sato, J.R., Salum, G.A., Gadelha, A., Crossley, N., Vieira, G., Manfro, G.G., Zugman, A., Picon, F.A., Pan, P.M., Hoexter, M.Q., Anés, M., Moura, L.M., Del'Aquilla, M.A.G., Edson, A., McGuire, P., Lacerda, A.L.T., Rohde, L.A., Miguel, E.C., Jackowski, A.P., Bressan, R.A., 2016. Default mode network maturation and psychopathology in children and adolescents. J. Child Psychol. Psychiatry 57, 55–64. https://doi.org/10.1111/jcpp.12444.
Schilbach, L., Bzdok, D., Timmermans, B., Fox, P.T., Laird, A.R., Vogeley, K., Eickhoff, S. B., 2012. Introspective Minds: using ALE meta-analyses to study commonalities in the neural correlates of emotional processing, social & unconstrained cognition. PLoS One 7, 30920. https://doi.org/10.1371/journal.pone.0030920.
Schilbach, L., Derntl, B., Aleman, A., Caspers, S., Clos, M., Diederen, K.M.J., Gruber, O., Kogler, L., Liemburg, E.J., Sommer, I.E., Möller, V.I., Cieslik, E.C., Eickhoff, S.B., 2016. Differential patterns of dysconnectivity in mirror neuron and mentalizing networks in schizophrenia. Schizophr. Bull. 42, 1135–1148. https://doi.org/10.1093/schbul/sbw015.
Schurz, M., Radua, J., Aichhorn, M., Richlan, F., Perner, J., 2014. Fractionating theory of mind: a meta-analysis of functional brain imaging studies. Neurosci. Biobehav. Rev. 42, 9–34. https://doi.org/10.1016/j.neubiorev.2014.01.009.
Sebastian, C.L., Fontaine, N.M.G., Bird, G., Blakemore, S.J., De brito, S.A., Mccrory, E.J. P., Viding, E., 2012. Neural processing associated with cognitive and affective theory of mind in adolescents and adults. Soc. Cogn. Affect. Neurosci. 7 (1), 53–63. https://doi.org/10.1093/scan/nsr023.
Shaffer, D., Gould, M.S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., Aluwahlia, S., 1983. A children's global assessment scale (CGAS). Arch. Gen. Psychiatry 40, 1228–1231.
Shakeel, M.K., Lu, L., Cannon, T.D., Cadenhead, K.S., Cornblatt, B.A., McGlashan, T.H., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Woods, S.W., Walker, E.F., Mathalon, D. H., Bearden, C.E., Addington, J., 2019. Longitudinal changes in social cognition in individuals at clinical high risk for psychosis: an outcome based analysis. Schizophr. Res. 204, 334–336. https://doi.org/10.1016/j.schres.2018.08.032.
Shim, G., Oh, J.S., Jung, W., Jang, J., Choi, C.-H., Kim, E., Park, H.-Y., Choi, J.-S., Jung, M., Kwon, J., 2010. Altered resting-state connectivity in subjects at ultra-high risk for psychosis: an fMRI study. Behav. Brain Funct. 6, 58. https://doi.org/10.1186/1744-9081-6-58.
Sugranyes, G., Kyriakopoulos, M., Corrigall, R., Taylor, E., Frangou, S., 2011. Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition. PLoS One 6. https://doi.org/10.1371/journal.pone.0025322.
Tang, J., Liao, Y., Song, M., Gao, J.H., Zhou, B., Tan, C., Liu, T., Tang, Y., Chen, J., Chen, X., 2013. Aberrant default mode functional connectivity in early onset schizophrenia. PLoS One 8, 1–5. https://doi.org/10.1371/journal.pone.0071061.
Thibaudeau, É., Achim, A.M., Parent, C., Turcotte, M., Cellard, C., 2020. A meta-analysis of the associations between theory of mind and neurocognition in schizophrenia. Schizophr. Res. 216, 118–128. https://doi.org/10.1016/j.schres.2019.12.017.
Thoma, R.J., Chaze, C., Lewine, J.D., Calhoun, V.D., Clark, V.P., Bustillo, J., Houck, J., Ford, J., Bigelow, R., Wilhelmi, C., Stephen, J.M., Turner, J.A., 2016. Functional MRI evaluation of multiple neural networks underlying auditory verbal hallucinations in schizophrenia Spectrum disorders. Front. Psychiatry 7, 39. https://doi.org/10.3389/fpsyt.2016.00039.
Tin, L.N.W., Lui, S.S.Y., Ho, K.K.Y., Hung, K.S.Y., Wang, Y., Yeung, H.K.H., Wong, T.Y., Lam, S.M., Chan, R.C.K., Cheung, E.F.C., 2018. High-functioning autism patients share similar but more severe impairments in verbal theory of mind than schizophrenia patients. Psychol. Med. 48, 1264–1273. https://doi.org/10.1017/S0033291717002690.
Tor, J., Dolz, M., Sintes, A., Muñoz, D., Pardo, M., De La Serna, E., Puig, O., Sugranyes, G., Baeza, I., 2017. Clinical high risk for psychosis in children and adolescents: a systematic review. Eur. Child Adolesc. Psychiatry. https://doi.org/10.1007/s00787-017-1046-3.
Truelove-Hill, M., Erus, G., Bashyam, V., Varol, E., Sako, C., Gur, R.C., Gur, R.E., Koutsouleris, N., Zhuo, C., Fan, Y., Wolf, D.H., Satterthwaite, T.D., Davatzikos, C., 2020. A multidimensional neural maturation index reveals reproducible developmental patterns in children and adolescents. J. Neurosci. 40, 1265–1275. https://doi.org/10.1523/JNEUROSCI.2092-19.2019.
Van Donkersgoed, R.J.M., Wunderink, L., Nieboer, R., Aleman, A., Pijnenborg, G.H.M., 2015. Social cognition in individuals at ultra-high risk for psychosis: a meta-analysis. PLoS One 10, 1–16. https://doi.org/10.1371/journal.pone.0141075.
Vargas, T., Damme, K.S.F., Hooker, C.I., Gupta, T., Cowan, H.R., Mittal, V.A., 2019. Differentiating implicit and explicit theory of mind and associated neural networks in youth at Clinical High Risk (CHR) for psychosis. Schizophr. Res. 208, 173–181. https://doi.org/10.1016/j.schres.2019.03.013.
Vetter, N.C., Leipold, K., Kliegel, M., Phillips, L.H., Altgassen, M., 2013. Ongoing development of social cognition in adolescence. Child Neuropsychol. 19 (6), 615–629. https://doi.org/10.1080/09297049.2012.718324.
Wechsler, D., 2003. WISC-IV Escala de Inteligencia Wechsler para Niños. TEA Ediciones, Madrid.
Wellman, H.M., Cross, D., Watson, J., 2001. Meta-analysis of theory-of-mind development: the truth about false belief. Child Dev. 72, 655–684. https://doi.org/10.1021/ol100144t.
Wenneberg, C., Nordentoft, M., Rostrup, E., Glenthøj, L.B., Bojesen, K.B., Fagerlund, B., Hjorthøj, C., Krakauer, K., Kristensen, T.D., Schwartz, C., Edden, R.A.E., Broberg, B. V., Glenthøj, B.Y., 2020. Cerebral glutamate and gamma-aminobutyric acid levels in individuals at ultra-high risk for psychosis and the association with clinical symptoms and cognition. Biol. Psychiatry 5, 569–579. https://doi.org/10.1016/j.bpsc.2019.12.005.
Yager, J.A., Ehmann, T.S., 2006. Untangling social function and social cognition: a review of concepts and measurement. Psychiatry 69, 47–68. https://doi.org/10.1521/psyc.2006.69.1.47.
Yan, C.G., Cheung, B., Kelly, C., Colcombe, S., Craddock, R.C., Di Martino, A., Li, Q., Zuo, X.N., Castellanos, F.X., Milham, M.P., 2013. A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. NeuroImage 76, 183–201. https://doi.org/10.1016/j.neuroimage.2013.03.004.
Yirmiya, N., Erel, O., Shaked, M., Solomonica-levi, D., 1998. Meta-analyses comparing theory of mind abilities of individuals with autism, individuals with mental retardation, and normally developing individuals. Psychol. Bull. 124, 283–307. https://doi.org/10.1037/0033-2909.124.3.283.
Zemánková, P., Lošák, J., Czekóová, K., Lungu, O., Jáni, M., Kašpárek, T., Bareš, M., 2018. Theory of mind skills are related to resting-state frontolimbic connectivity in schizophrenia. Brain Connect. 8, 350–361. https://doi.org/10.1089/brain.2017.0563.
Zhang, T.H., Xu, L.H., Cui, H.R., Tang, Y.Y., Wei, Y.Y., Tang, X.C., Liu, X.H., Cao, X.M., Li, C.B., Wang, J.J., 2018. Changes in correlation characteristics of time consumption and mind-reading performance in pre-onset and post-onset psychosis. Psychiatry Res. 262, 168–174. https://doi.org/10.1016/j.psychres.2018.02.008.
Zhou, Y., Fan, L., Qiu, C., Jiang, T., 2015. Prefrontal cortex and the dysconnectivity hypothesis of schizophrenia. Neurosci. Bull. 31, 207–219. https://doi.org/10.1007/s12264-014-1502-8.