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 Masías b, Roger Borras a, Jose C. Pariente b, Montserrat Dolz d, e, Josefin Castro-Fornieles a,b,c,d,e, Gisela Sugranyes a, b, c, d, e

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

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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; Thibaudau 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 Clinic of Barcelona, C/Villarroel 170, 08036, Barcelona, Spain.
E-mail address: germest@clinic.cat (G. Sugranyes).

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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 hyperconnectivity (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 (Brune 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 (Correll et al., 2003) scored using the SAPS (Miller et al., 2003); or with a 1st/2nd degree relative with schizophrenia or a diagnosis of schizotypal disorder, plus a decline in functioning (Köster 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 assessed with the Children’s Global Assessment Scale (CGAS) (Wechsler, 2003). 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), the spatial maps of the DMN component corresponding to the DMN was identified among 20 significant clusters. The component of each subject were compared in a whole brain analysis in SPM12 running in Matlab R2019a. The network was 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, cannabis use or baseline clinical severity (total SOPS score, CGAS) were added as covariates to the model when exerting a significant effect (p ≤ .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 ≤ .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
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 \( \text{Leucht et al., 2014} \)) 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 \( \text{Liu, 2012} \) 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 \( p = .03 \); \( \beta = .058 \); 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; \( p^{\text{FWECorr}} = .041 \)) 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; \( p^{\text{FWECorr}} = .044 \)) 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 \( rs < .22; ps \geq .34 \).

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 \( \text{Izarbe et al., 2019} \). 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) \( \text{HR} = .20; p = .002 \) 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) \( \text{cut-off point} = 1.52 \); 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 \( \text{HR} = 6.29; p = .005; 95 \% \text{CI}: 1.75–22.64 \) [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.
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 age and ToM performance, in line with meta-analytic findings (Pe & others, 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 of 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).
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.

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