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Brain Activation and Aberrant Effective Connectivity in the Mentalizing Network of Preadolescent Children at Familial High Risk of Schizophrenia or Bipolar Disorder

Lotte Veddum, Vibeke Bliksted, Yuan Zhou, Anna Krogh Andreassen, Christina Bruun Knudsen, Aja Neergaard Greve, Nanna Lawaetz Steffensen, Merete Birk, Nicoline Hemager, Julie Marie Brandt, Maja Gregersen, Line Korsgaard Johnsen, Kit Melissa Larsen, William Frans Christiaan Baaré, Kathrine Skak Madsen, Hartwig Roman Siebner, Kerstin Jessica Plessen, Anne Amalie Elgaard Thorup, Leif Østergaard, Merete Nordentoft, Ole Mors, Torben Ellegaard Lund, and Martin Dietz

ABSTRACT

BACKGROUND: Schizophrenia and bipolar disorder are characterized by social cognitive impairments, and recent research has identified alterations of the social brain. However, it is unknown whether familial high risk (FHR) of these disorders is associated with neurobiological alterations already present in childhood.

METHODS: As part of the Danish High Risk and Resilience Study–VIA 11, we examined children at FHR of schizophrenia (n = 121, 50% female) or bipolar disorder (n = 75, 47% female) and population-based control children (PBCs) (n = 128, 48% female). Using functional magnetic resonance imaging and dynamic causal modeling, we investigated brain activation and effective connectivity during the social cognition paradigm from the Human Connectome Project.

RESULTS: We found similar activation of the mentalizing network across groups, including visual area V5, the dorsomedial prefrontal cortex, and the posterior superior temporal sulcus (pSTS). Nonetheless, both FHR groups showed aberrant brain connectivity in the form of increased feedforward connectivity from left V5 to pSTS compared with PBCs. Children at FHR of schizophrenia had reduced intrinsic connectivity in bilateral V5 compared with PBCs, whereas children at FHR of bipolar disorder showed increased reciprocal connectivity between the left dorsomedial prefrontal cortex and the pSTS, increased intrinsic connectivity in the right pSTS, and reduced feedforward connectivity from the right pSTS to the dorsomedial prefrontal cortex compared with PBCs.

CONCLUSIONS: Our results provide first-time evidence of aberrant brain connectivity in the mentalizing network of children at FHR of schizophrenia or FHR of bipolar disorder. Longitudinal research is warranted to clarify whether aberrant brain connectivity during mentalizing constitutes an endophenotype associated with the development of a mental disorder later in life.

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Social cognitive impairments, in particular theory of mind (ToM) deficits, have been suggested as an endophenotype for schizophrenia and bipolar disorder (1–4). ToM is the ability to infer and predict other peoples' mental states, knowing that these may differ from one's own (5,6). The simplest aspects of ToM develop during infancy and the preschool years, whereas more complex mentalizing abilities develop in middle childhood and adolescence (7,8). Functional neuroimaging studies of adults have identified a network of brain regions activated when reasoning about mental states, including the medial prefrontal cortex (mPFC) and the posterior superior temporal sulcus (pSTS) at the temporoparietal junction (9–13). The same regions have been identified in middle childhood (14–17), with stronger functional network integration with age (18–20). Hence, the social brain undergoes continuous development from infancy to adulthood, with adolescence being a critical developmental period of synaptic reorganization and changes in functional integration within the mentalizing network (21–23).

Recent meta-analyses have confirmed the presence of abnormalities in the mentalizing network of individuals with schizophrenia, with results showing both decreased and increased activation compared with control children (24–28). Similarly, abnormal activation of the mentalizing network has also been identified in bipolar disorder (29–33). Schizophrenia, and to some extent bipolar disorder, are conceptualized as neurodevelopmental disorders, which suggests that

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neurobiological abnormalities emerge before illness onset due to abnormal brain development (34–37). Consistent with this, a developmental dysfunction of synaptic efficacy has been proposed as a likely disorder mechanism in schizophrenia (38,39). Studies of brain connectivity in schizophrenia and bipolar disorder suggest that abnormalities in the mentalizing network do not merely result from abnormal activation of particular brain regions but rather from synaptic dysfunction across the brain. This abnormality in synaptic integration may underlie social cognitive deficits (33,40–42) and may contribute to the emergence and maintenance of psychotic and mood symptoms, due to abnormal perception and interpretation of social stimuli. Computational theories that describe brain connectivity as a process of predictive coding are becoming increasingly useful for understanding psychotic symptoms and false beliefs (43). Predictive coding offers a natural framework for understanding ToM as inferring the hidden states of another agent's intentions. This inference rests on an internal model of the mental states that causes an observed social behavior. In psychopathology, this social inference can go awry and generate false beliefs and delusions (40,44).

Schizophrenia and bipolar disorder have high heritability estimates, and offspring of parents diagnosed with either disorder have a significantly increased risk of developing a mental disorder themselves (45–47). We have previously shown that children at familial high risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) exhibit intact ToM abilities (48,49). Nonetheless, typical behavioral performance does not preclude neurobiological abnormalities (50). Using functional magnetic resonance imaging (fMRI) and dynamic causal modeling (DCM), a recent study found aberrant brain connectivity within the mentalizing network in individuals with first-episode schizophrenia compared with control children, even though the groups did not differ behaviorally (40). Additionally, previous fMRI studies of adult first-degree relatives of individuals with schizophrenia found decreased activation in the mPFC and abnormal activation of right hemisphere regions of the mentalizing network (51,52), whereas another study did not identify any differences (53). Similarly, abnormal activation and functional connectivity within the mentalizing network have been identified in adult first-degree relatives of individuals with bipolar disorder (33). This suggests that abnormalities in the mentalizing network could constitute an endophenotype. However, it is unknown whether abnormal brain activation or brain connectivity is already present during childhood, years before illness onset.

To answer these questions, we used fMRI and DCM of brain connectivity to identify differences within the mentalizing network of preadolescent children at FHR-SZ or FHR-BP compared with population-based control children (PBCs). We hypothesized that children at FHR-SZ or FHR-BP would show deviant brain activation and aberrant effective connectivity in the mentalizing network compared with PBCs.

METHODS AND MATERIALS

This fMRI study is part of the first follow-up of The Danish High Risk and Resilience Study–VIA, a population-based, representative cohort study examining 522 children, including those born to parents diagnosed with schizophrenia (n = 202) or bipolar disorder (n = 120) and PBCs (n = 200). To date, the children have been examined twice: at age 7 (54) and at age 11, at which time brain imaging was added to the assessment (55). Of the initial cohort, a total of 453 children participated at follow-up (FHR-SZ, n = 179; FHR-BP, n = 105; PBC, n = 181), equaling a retention rate of 89%. Data acquisition for the follow-up study was conducted from March 1, 2017, to June 30, 2020. The study was approved by the Danish Data Protection Agency and the National Committee on Health Research Ethics (Study No. H16043682). All children received written and verbal information about the study, and written informed consent was obtained from the children's legal guardians.

Participants

Participants were identified through the Danish Civil Registration System and the Danish Psychiatric Central Research Register (56,57). The PBC children were matched on a one-to-one basis to the FHR-SZ children based on age, sex, and municipality. The FHR-BP children were a nonmatched sample but were comparable to the 2 other groups on age and sex.

Descriptive and Clinical Measures

Level of functioning was measured with the Children's Global Assessment Scale (58). Emotional and behavioral problems were assessed with the Child Behavior Checklist, School-age version, which was completed by the primary caregiver (59). IQ was estimated using the Reynolds Intellectual Screening Test (60). Handedness was assessed using The Edinburgh Handedness Inventory 10-item version (61). Dropout analyses were performed on descriptive and clinical measures for children who participated versus children who did not participate in this fMRI study. Analyses of descriptive and clinical measures were conducted using Stata IC software, version 16.1 (62). We ascertained one-way analysis of variance or χ^2 tests followed by pairwise comparisons in case of a significant main effect of group. The alpha level was set to $p < .05$.

fMRI Acquisition

We used the social cognition paradigm from the Human Connectome Project (HCP) (50), which is a well-validated fMRI task that has previously been shown to generate robust activation in the mentalizing network (50,63). Additionally, it was recently used to investigate brain connectivity in healthy individuals (13) and people with first-episode schizophrenia (40). The HCP social cognition paradigm was presented using E-prime 2.0 (Psychology Software Tools, Inc.) (see the Supplement and Figure S2 for a detailed description). fMRI data were acquired at 2 distinct sites in Denmark using a multiband, gradient echo, echo-planar imaging (EPI) sequence obtained via a C2P agreement with the Center for Magnetic Resonance Research in Minneapolis, Minnesota (64). At the Center of Functionally Integrative Neuroscience at Aarhus University Hospital, we used a Siemens MAGNETOM Skyra 3T scanner with a 32-channel head coil to acquire EPI with an in-plane acceleration factor of 2, a multiband factor of 3, and a total readout time per slice of 21 ms, volume repetition time of 1081 ms, echo time of 30 ms, flip angle of 65°, field of view of 192 × 187 mm, and in-plane resolution of 78 × 76.

We acquired 472 whole-brain volumes consisting of 54 transverse slices with voxel size of 2.46 × 2.46 × 2.5 mm. At the Danish Research Center for Magnetic Resonance at Copenhagen University Hospital Hvidovre, we used a Siemens MAGNETOM Prisma 3T scanner with a 64-channel head coil to acquire EPI with an in-plane acceleration factor of 2, a multiband factor of 3, and a total readout time per slice of 21 ms, repetition time of 1052 ms, echo time of 30 ms, flip angle of 65°, field of view of 192 × 187 mm, and in-plane resolution of 78 × 76. We acquired 520 whole-brain volumes consisting of 54 transverse slices with voxel size of 2.46 × 2.46 × 2.5 mm.

Analysis of Behavioral Measures From the HCP Social Cognition Paradigm

We tested for differences in task accuracy, task sensitivity, and response time within each group between social and nonsocial conditions using paired *t* tests and differences between groups within each condition using two-sample *t* tests. Task sensitivity was analyzed with *d*-prime (65), which is a measure from signal detection theory of how well participants discriminate between stimulus conditions by penalizing hits by false alarms. All between-group analyses were corrected for age, sex, and test site. All tests were thresholded at $p < .05$ and corrected for multiple comparisons using the Benjamini-Hochberg procedure with the false discovery rate set to 5% (66).

fMRI Analysis

fMRI data were analyzed using SPM12 (revision 7771). The images were realigned within participants using rigid-body transformation, resampled to 2-mm^3 voxels, and spatially normalized to Montreal Neurological Institute space using the ICBM template of European brains (SPM EPI template). The time-series were high-pass filtered at 1/128 seconds, and temporal correlations were modeled with a first-order autoregressive model. Social and nonsocial conditions were modeled as a block design convolved with a canonical hemodynamic response function and fitted to the time series using a general linear model. To account for effects of head movement, we included a 24-parameter set consisting of immediate head movement and movement during the previous volume (67). For quality control, we calculated the framewise displacement (68). We excluded participants with head movement above 2 mm (voxel size) in more than 10% of the volumes. In the final sample, movement did not differ across groups ($F_{2,321}$ = 0.1753, p = .8303). We created contrast images to test for visual stimulation and the difference in activation between social and nonsocial conditions. Contrast images were smoothed with an 8-mm full width at half maximum Gaussian kernel. Using a one-sample *t* test, we first tested for brain activation in PBCs to identify regions involved in mentalizing. Then, we tested between-group differences in brain activation using analysis of variance and adjusted for age, sex, and test site. All tests were thresholded at $p < .05$ and familywise error whole-brain corrected for multiple comparisons using Gaussian random field theory (69).

DCM of Effective Brain Connectivity

We used a two-state DCM for fMRI (DCM12; revision 7479) to estimate the effective (synaptic) connectivity within and between brain areas. This DCM models extrinsic connections between brain areas as excitatory feedforward and feedback connections and the intrinsic connectivity within an area in terms of the synaptic influence of inhibitory interneurons on excitatory cells. This allows modeling of each cortical area as an increase or decrease in cortical inhibition (70). DCM uses a biophysical model of brain connections that cause neuronal dynamics, as opposed to metrics of functional connectivity that operate at the (phenomenological) level of the observed fMRI signal (see the Supplement for further description of DCM for fMRI). We analyzed the connectivity within the mentalizing network under 2 alternative hypotheses. The first hypothesis was formulated as a full DCM in which both extrinsic (excitatory) connections and intrinsic (inhibitory) connections encode social stimuli compared with nonsocial stimuli. The second hypothesis was a reduced model in which only extrinsic connections encode social stimuli. Finally, we included a null DCM to test the belief that no connections encode any differences between experimental conditions (Figure S3).

We estimated the full DCM using variational Bayesian inference (71). This provides both the posterior distribution of the connection strengths and the free-energy approximation to the marginal likelihood of the model itself, known as the model evidence. A reduced model and a null model were then estimated using Bayesian model reduction (72). We then compared alternative hypotheses using both random-effects Bayesian model selection (73,74) of DCMs at the single-participant level and fixed-effects Bayesian model comparison of parametrical empirical Bayes (PEB)–DCMs at the group level. Finally, we used PEB to identify increases or decreases in connection strengths at the group level and test for group differences using Bayesian inference. All group effects were adjusted for age, sex, and test site. All DCM results were thresholded at a posterior probability >0.95.

RESULTS

Sample Characteristics

We included data from 324 children (FHR-SZ, n = 121; FHR-BP, n = 75; PBC, n = 128) (Figure S1). The number of children who participated at each test site was balanced, and the groups did not differ in age, sex, IQ, or handedness. Children at FHR-SZ or FHR-BP had lower levels of functioning and exhibited more emotional and behavioral problems than PBCs (Table 1). Comparisons of the participating children (n = 324) and nonparticipating children (n = 121) revealed no differences in sex (p = .163), emotional and behavioral problems (p = .187), or distribution across FHR groups (p = .737). However, the participating children had higher levels of functioning (p = .012) and a higher IQ (p = .017) (Table S1A). Dropout analyses based on FHR status revealed that these differences were driven by differences between the participating versus nonparticipating children at FHR-SZ (Table S1B).

Behavioral Measures

We found no differences between groups in task accuracy or task sensitivity. However, we observed a difference in response time between groups, both for social conditions and for nonsocial conditions. Children at FHR-SZ were slower at

Table 1. Demographic and Clinical Characteristics of the Participating Preadolescent Children

					Pairwise Comparisons (*p* Value)		
	FHR-SZ, *n* = 121	FHR-BP, *n* = 75	PBCs, *n* = 128	*p* Value	FHR-SZ vs. PBCs	FHR-BP vs. PBCs	FHR-SZ vs. FHR-BP
Sex, Female	60 (49.59%)	35 (46.67%)	61 (47.66%)	.915[a]	–	–	–
Age, Years	12.10 (0.30)	12.08 (0.29)	12.12 (0.27)	.592[b]	–	–	–
C-GAS[c]	67.34 (15.03)	69.05 (15.03)	74.85 (14.08)	<.001[b,d]	<.001[d]	.007[d]	.439
CBCL[e]	22.23 (20.13)	20.59 (20.55)	12.95 (12.96)	<.001[b,d]	<.001[d]	.002[d]	.587
IQ[f]	96.12 (10.82)	97.72 (9.90)	98.47 (10.29)	.200[b]	–	–	–
Handedness[g]							
Left-handed	10 (8.26%)	9 (12.00%)	9 (7.03%)	.263[a]	–	–	–
Right-handed	99 (81.82%)	63 (84.00%)	113 (88.28%)				
Ambidextrous	12 (9.92%)	3 (4.00%)	6 (4.69%)				
Test Site							
CFIN	60 (35.50%)	35 (20.71%)	74 (43.79%)	.238[a]	–	–	–
DRCMR	61 (39.35%)	40 (25.81%)	54 (34.84%)				

Values are presented as mean (SD) or *n* (%).

CBCL, Child Behavior Checklist, School-age version; CFIN, Center of Functionally Integrative Neuroscience, Aarhus University Hospital; C-GAS, Children's Global Assessment Scale; DRCMR, Danish Research Center for Magnetic Resonance, Hvidovre Hospital; FHR-BP, familial high risk of bipolar disorder; FHR-SZ, familial high risk of schizophrenia; PBCs, population-based control children.

[a]χ^2 test.

[b]One-way analysis of variance.

[c]Ranging from 0 to 100, where a lower score reflects poorer global functioning. C-GAS scores in this sample range from 34 to 98 (FHRSZ, *n* = 121; FHR-BP, *n* = 75; PBC, *n* = 126).

[d]Statistically significant result at significance level $p < .05$.

[e]Ranging from 0 to 266, with higher scores reflecting more problem behavior. CBCL scores in this sample range from 0 to 126 (FHR-SZ, *n* = 114; FHR-BP, *n* = 75; PBC, *n* = 124).

[f]Estimated using the Reynolds Intellectual Screening Test (55), where a higher score reflects a higher level of general intelligence. Reynolds Intellectual Screening Test index scores in this sample range from 24 to 126.

[g]Handedness was assessed with the Edinburgh Handedness Inventory (54), and data are presented according to the laterality quotient score.

responding than PBCs both in social conditions (t_{244} = 2.3, p = .02, Cohen's d = 0.30) and in nonsocial conditions (t_{244} = 2.5, p = .01, Cohen's d = 0.40). Children at FHR-BP were also slower at responding than PBCs both in the social conditions (t_{198} = 2.8, p = .006, Cohen's d = 0.40) and in the nonsocial conditions (t_{198} = 3.5, p = .0006, Cohen's d = 0.50). Children at FHR-SZ or FHR-BP did not differ in response time in either condition (Table S2).

We found no differences in task accuracy within each group between social and nonsocial conditions. However, we observed a difference in task sensitivity between social and nonsocial conditions in children at FHR-SZ (t_{120} = 7.3, $p < .000001$, Cohen's d = 0.67), children at FHR-BP (t_{74} = 5.9, $p < .000001$, Cohen's d = 0.68), and PBCs (t_{127} = 8.4, $p < .000001$, Cohen's d = 0.75). This shows that the children were more sensitive overall to social than nonsocial conditions. We also found a difference in response time between social and nonsocial conditions in PBCs (t_{127} = 2.8, p = .006, Cohen's d = 0.32) but not in children at FHR-SZ or FHR-BP, indicating that PBCs were slower at responding to social than nonsocial conditions (Figure 1A–C and Table S2).

Brain Activation

When the PBC children perceived visual stimuli (both social and nonsocial conditions), we observed increased bilateral activation of extrastriate area V5. When the PBCs perceived social compared to nonsocial conditions, we observed increased activation in visual area V4, the fusiform gyrus, bilateral pSTS, bilateral inferior frontal gyrus, bilateral precuneus, cerebellum, and right thalamus (Table 2 and Figure 2). We found no differences in regional brain activation between groups during social compared to nonsocial conditions.

Effective Brain Connectivity

We analyzed the effective connectivity within a cortical network comprising bilateral visual area V5, bilateral pSTS, and the dorsomedial prefrontal cortex (dmPFC) in the right hemisphere. This cortical network was based on the peak activations in PBCs (Table 2) and results from previous studies that showed activation in these regions during the same (13,40,75) or similar mentalizing tasks (12,22,63).

Bayesian model comparison of the PEB-DCMs at the group level revealed that a cortical network with changes in both between-area (excitatory) and within-area (inhibitory) connections had the highest Bayesian model evidence in PBCs (posterior model probability >0.99). This was confirmed by a random-effects Bayesian model comparison (posterior model probability > 0.95 and protected exceedance probability > 0.99) (Figure 3A). PBCs had a bilateral increase in feedforward connectivity from V5 to the pSTS and an increase in feedforward connectivity from the right pSTS to the dmPFC. In the right hemisphere, there was an increase in feedback connectivity from the pSTS to V5. Simultaneously, there was a decrease in intrinsic connections within the left and right pSTS and the left V5 (Figure 3B, C).

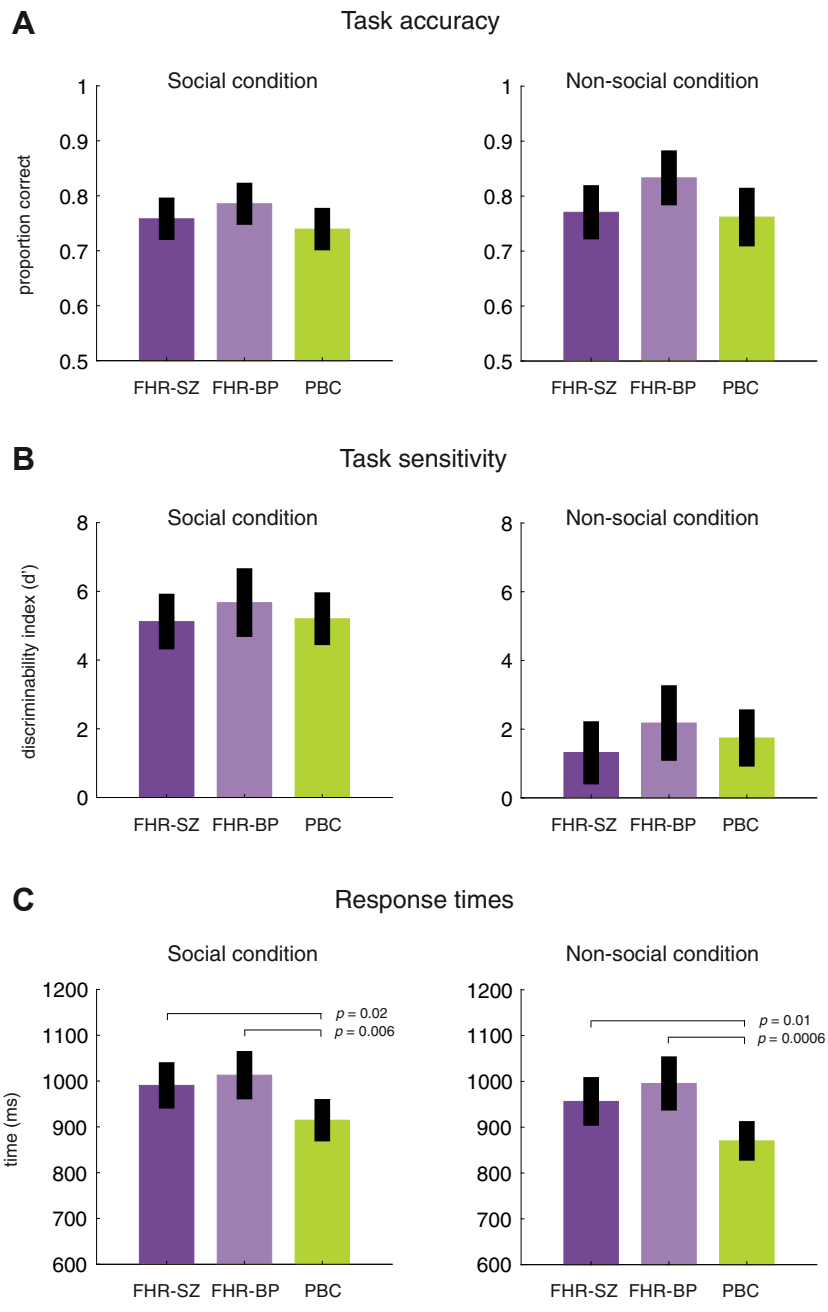

Figure 1. **(A–C)** Behavioral results from the social cognition task from the Human Connectome Project. Results are presented with mean and 95% confidence intervals. FHR-BP, familial high risk of bipolar disorder; FHR-SZ, familial high risk of schizophrenia; PBC, population-based control children.

Aberrant Brain Connectivity in Children at FHR-SZ

When comparing children at FHR-SZ with PBCs, Bayesian model comparison of the PEB-DCMs at the group level revealed that a cortical network with changes in both between-area and within-area connections had the highest Bayesian model evidence (posterior model probability > 0.96). This was confirmed by a random-effects Bayesian model comparison (posterior model probability > 0.96 and protected exceedance probability > 0.99) (Figure 4A). Children at FHR-SZ had stronger feedforward connectivity from V5 to the pSTS in the left hemisphere and decreased intrinsic coupling within the left and right V5 compared with PBCs (Figure 4B, C).

Aberrant Brain Connectivity in Children at FHR-BP

When comparing children at FHR-BP with PBCs, Bayesian model comparison of the PEB-DCMs at the group level revealed that a cortical network with changes in both between-area and within-area connections had the highest Bayesian

Table 2. Peak-Level Brain Activations in Preadolescent Population-Based Control Children

MNI Coordinates					
x	y	z	*t* Statistic (*df*)	Anatomical Region	Probabilistic Atlas[a]
46	−66	−4	9.92 (127)	Right middle temporal gyrus	hOc5 (V5)
−42	−68	6	9.20 (127)	Left middle temporal gyrus	hOc5 (V5)
26	−94	−4	16.82 (127)	Lateral occipital cortex	hOc4lp (V4)
−42	−48	−16	13.99 (127)	Fusiform gyrus	Area FG4
52	−44	10	13.50 (127)	Right pSTS	Supramarginal
−56	−50	10	9.61 (127)	Left pSTS	Supramarginal
12	12	66	8.11 (127)	Dorsomedial prefrontal cortex	Superior frontal gyrus
52	28	12	11.87 (127)	Right inferior frontal gyrus	Area 45
−38	10	24	6.96 (127)	Left inferior frontal gyrus	Area 44
18	−52	20	10.33 (127)	Right precuneus	Precuneus
−16	−58	20	9.35 (127)	Left precuneus	Precuneus
−22	−80	−32	8.87 (127)	Left cerebellum	Crus I
10	−12	8	7.57 (127)	Right thalamus	Thalamus

MNI, Montreal Neurological Institute; pSTS, posterior superior temporal sulcus.
[a]Anatomical classification using the SPM anatomy toolbox (5,6).

model evidence (posterior model probability > 0.99). This was confirmed by a random-effects Bayesian model comparison (posterior model probability > 0.97 and protected exceedance probability > 0.99) (Figure 5A). Children at FHR-BP had stronger feedforward and feedback connectivity between V5 and the pSTS in the left hemisphere than PBCs. In the right hemisphere, children at FHR-BP had reduced feedforward connectivity from the pSTS to the dmPFC compared with PBCs. Simultaneously, children at FHR-BP had increased intrinsic coupling within the right pSTS (Figure 5B, C).

Differences in Effective Brain Connectivity Between the FHR-SZ and FHR-BP Groups

When comparing the 2 FHR groups, Bayesian model comparison of the PEB-DCMs at the group level revealed that a cortical network with changes in both between-area and within-area connections had the highest Bayesian model evidence (posterior model probability > 0.99). This was confirmed by a random-effects Bayesian model comparison (posterior model probability > 0.98 and protected exceedance probability > 0.99) (Figure 6A). Children at FHR-SZ had reduced feedforward connectivity from V5 to the pSTS in the left hemisphere compared with children at FHR-BP. In contrast, children at FHR-SZ had stronger feedforward connectivity from the pSTS to the dmPFC in the right hemisphere than children at FHR-BP. Finally, children at FHR-SZ exhibited reduced levels of intrinsic connectivity in bilateral V5 and the right pSTS (Figure 6B, C).

DISCUSSION

We identified no differences between groups in brain activation in the mentalizing network. However, using DCM, we found that children at FHR-SZ or FHR-BP exhibited aberrant brain connectivity within the mentalizing network compared with PBCs. Behaviorally, children at FHR-SZ or FHR-BP were slower at responding than PBCs, and all groups were more sensitive to social than nonsocial stimuli.

We did not observe any group differences in task accuracy or task sensitivity, indicating that the groups did not differ in categorizing social and nonsocial conditions. This corresponds to the results from our behavioral study of the same cohort where the groups displayed comparable ToM abilities

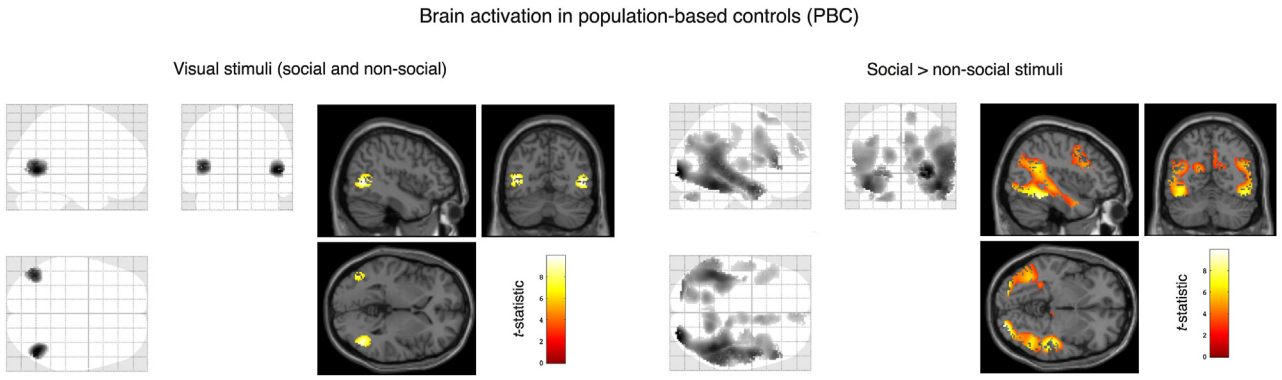

Figure 2. Brain activation during the social cognition task from the Human Connectome Project.

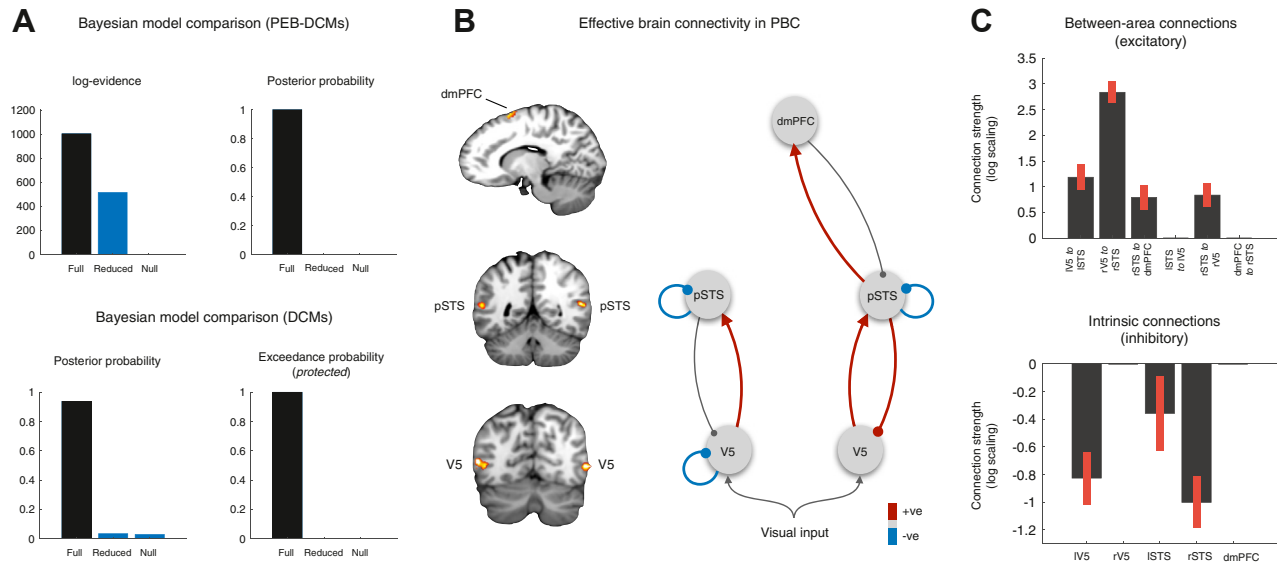

Figure 3. **(A–C)** Dynamic causal modeling (DCM) of effective brain connectivity in population-based control children (PBCs). +ve indicates positive (an increase); −ve indiates negative (a decrease). dmPFC, dorsomedial prefrontal cortex; l, left; PEB, parametric empirical Bayes; pSTS, posterior superior temporal sulcus; r, right.

(49). Furthermore, our results revealed that the FHR groups were slower at responding to both types of conditions than PBCs, indicating that children at FHR-SZ or FHR-BP may be more uncertain before reaching a decision. Another possible explanation relates to the widespread neurocognitive impairments that have been identified within the same cohort, including deficits in processing speed and visuospatial memory (76). All children were more sensitive to social than nonsocial stimuli, which suggests an overattribution of mental states (hypermentalizing) (77–79). Speculatively, this tendency may indicate that their ToM abilities are not yet fully developed (7,8,49).

Our fMRI results replicate previous findings of brain activation during mentalizing tasks (9–12), and the HCP social cognition paradigm in particular (13,40,50,75), with consistent activation of the dmPFC and pSTS. Moreover, the pathway from motion-sensitive area V5 to the pSTS has been proposed

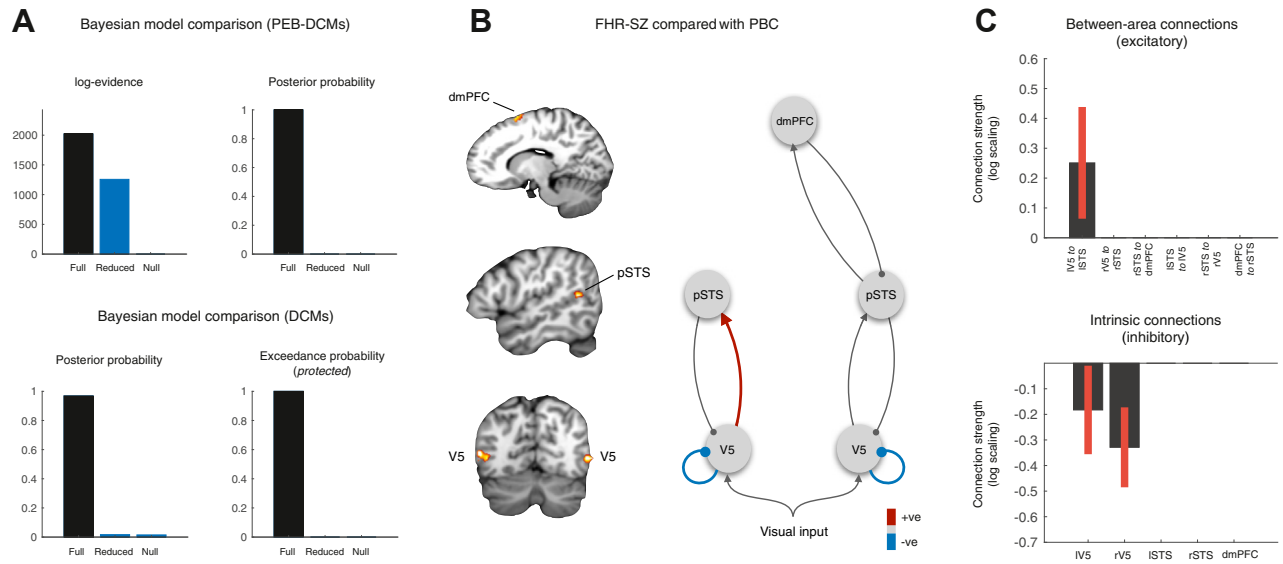

Figure 4. **(A–C)** Dynamic causal modeling (DCM) of effective brain connectivity in preadolescent children at familial high risk of schizophrenia (FHR-SZ) compared with population-based control children (PBCs). +ve indicates positive (an increase); −ve indiates negative (a decrease). dmPFC, dorsomedial prefrontal cortex; l, left; PEB, parametric empirical Bayes; pSTS, posterior superior temporal sulcus; r, right.

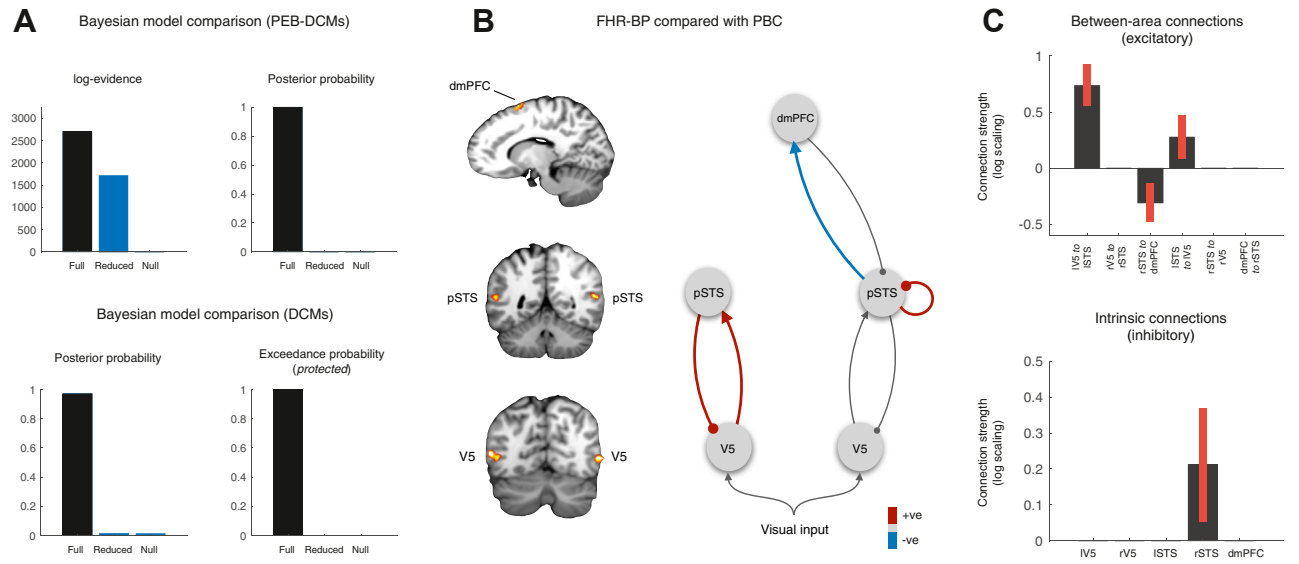

Figure 5. **(A–C)** Dynamic causal modeling (DCM) of effective brain connectivity in preadolescent children at familial high risk of bipolar disorder (FHR-BP) compared with population-based control children (PBCs). +ve indicates positive (an increase); −ve indiates negative (a decrease). dmPFC, dorsomedial prefrontal cortex; l, left; PEB, parametric empirical Bayes; pSTS, posterior superior temporal sulcus; r, right.

as a third visual stream that is functionally specialized for social representations (80). This visual pathway has feedforward and feedback projections to the dorsal PFC via the superior longitudinal fasciculus, which supports our findings of feedforward and feedback connections between the pSTS and the dmPFC (81). However, consistent with our behavioral results, we found no differences in brain activation between groups. This is in contrast to studies of adult first-degree relatives of individuals with schizophrenia or bipolar disorder (33,51,52). However, a key difference is that the children in our study were at a developmental stage at which the brain circuitry underlying mentalizing is still not fully developed (7,8,22,23,49), which could make detection of groupwise differences challenging. Additionally, results from our dropout analyses revealed that the participating children at FHR-SZ were higher functioning than the nonparticipating children at FHR-SZ.

We identified both shared and unique profiles of aberrant brain connectivity in the mentalizing network in children at FHR-SZ or FHR-BP compared with PBCs. We found a shared profile of abnormally high levels of feedforward connectivity

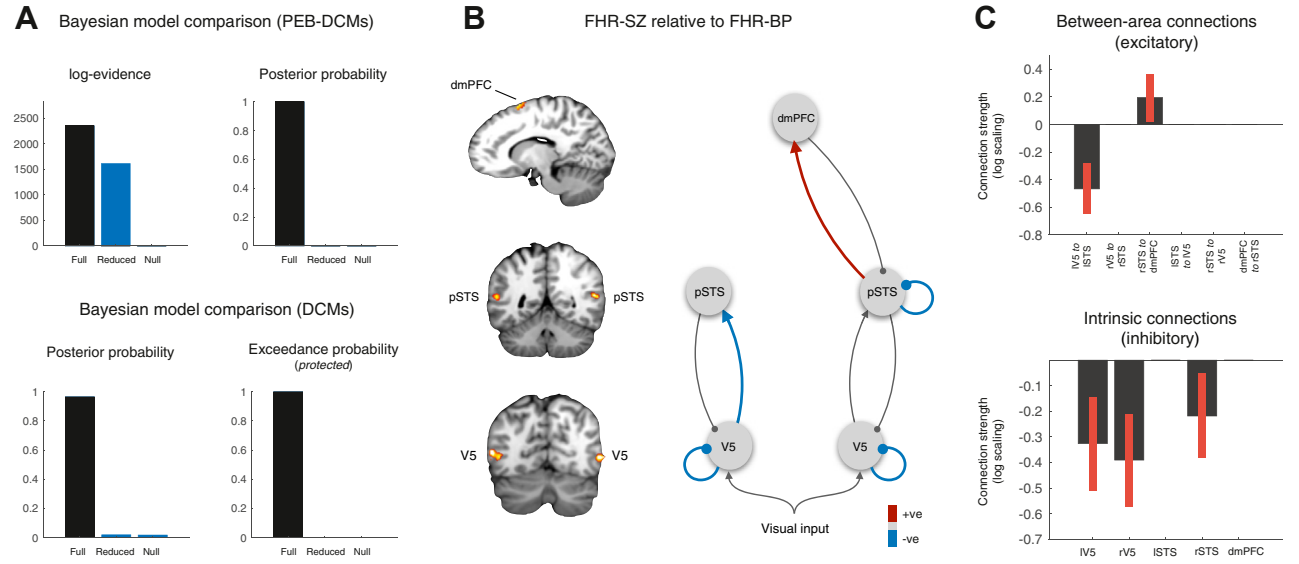

Figure 6. **(A–C)** Dynamic causal modeling (DCM) of effective brain connectivity in preadolescent children at familial high risk of schizophrenia (FHR-SZ) compared with children at familial high risk of bipolar disorder (FHR-BP). +ve indicates positive (an increase); −ve indiates negative (a decrease). dmPFC, dorsomedial prefrontal cortex; l, left; PEB, parametric empirical Bayes; pSTS, posterior superior temporal sulcus; r, right.

from V5 to the pSTS in both FHR groups, which is consistent with previous findings in first-episode schizophrenia (40). We found a unique profile of reduced connectivity between the pSTS and the dmPFC in children at FHR-BP. We also identified unique profiles of within-area coupling in different areas of the mentalizing network, with disinhibition in bilateral V5 in children at FHR-SZ and increased inhibition of the right pSTS in children at FHR-BP.

In predictive coding, feedback connections from higher to lower regions of the cortical hierarchy are thought to encode the brain's internal predictions about the external world, such as one's belief about other agents' mental states (82). In contrast, feedforward connections from lower to higher regions mediate the ensuing prediction errors inconsistent with the brain's prior predictions. When exposed to social stimuli, the influence of prediction errors on posterior beliefs is controlled by their precision or certainty, which is presumably encoded by cortical gain mechanisms via inhibition of excitatory principal cells. The role of prediction errors is then to resolve the uncertainty with which the brain represents the external world. Children at FHR-SZ had increased feedforward connectivity from V5 to the pSTS, which may reflect a state where prediction errors are weighted by an abnormally high level of precision during social stimuli. This replicates previous findings in first-episode schizophrenia (40), where this was interpreted as a failure to integrate information carried by prediction errors into the patient's model of another agent's mental states. Children at FHR-BP also exhibited stronger feedforward connectivity from V5 to the pSTS, accompanied by feedback connectivity. This shared profile of stronger feedforward connectivity may reflect a state in which children at FHR-SZ or FHR-BP are more uncertain about visual information before they reach a decision and must resolve this uncertainty via an increase in prediction errors. Behaviorally, this is reflected in their slower response times. In FHR-BP, the increase in recurrent connectivity may be interpreted as a failure of both prediction errors and the subsequent updating of visual representations via feedback connections. At higher levels of the mentalizing network, children at FHR-BP showed reduced feedforward connectivity from the pSTS to the mPFC accompanied by increased intrinsic coupling within the pSTS. This may reflect a decoupling of prediction errors from the temporal cortex to the PFC via increased inhibition in the pSTS and a subsequent reduction in feedforward connections to the dmPFC. Similarly, studies have identified abnormal activation in the pSTS and reduced functional connectivity with the PFC in schizophrenia (42,83–86). However, we did not observe any alterations in the circuit between the temporal cortex and the PFC in children at FHR-SZ.

The current study has several strengths. To our knowledge, it is the first to investigate brain activation and brain connectivity in young offspring of parents with schizophrenia or bipolar disorder. We included a large sample of same-aged children, thereby diminishing the effect of age-related differences, and we used a well-validated fMRI paradigm. However, our study also has limitations. The cross-sectional design does not allow interferences about neurodevelopmental alterations. Currently, our follow-up study of the same cohort at age 15 is ongoing (87), which will allow investigation of developmental changes. Moreover, in this study, the effects of other relevant factors such as psychopathology, environmental factors, and genetics have not been taken into account. However, we have planned a series of studies to examine the putative effect of these factors on pathophysiology in the same cohort. Finally, there are limitations to the specificity of brain connections in DCM for fMRI. While DCM for electroencephalography and magnetoencephalography allows for a richer neurophysiological complexity by virtue of the electrophysiological signal, DCM for fMRI is limited to a simple model of putative excitatory and inhibitory connections to explain the observed fMRI signal.

Conclusions

While impairments are not evident on a behavioral level or in brain activation, we identified both shared and unique profiles of aberrant brain connectivity within the mentalizing network in preadolescent children at FHR-SZ or FHR-BP. This may reflect a shared neurobiological endophenotype as well as unique biomarkers related to schizophrenia and bipolar disorder.

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ARTICLE INFORMATION

From the Department of Clinical Medicine, Faculty of Health and Medical Sciences, Aarhus University, Aarhus, Denmark (LV, VB, AKA, CBK, ANG); Psychosis Research Unit, Aarhus University Hospital Skejby–Psychiatry, Aarhus, Denmark (LV, VB, AKA, CBK, ANG, NLS, MB, OM); iPSYCH–The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Copenhagen, Denmark (LV, VB, AKA, CBK, ANG, NLS, MB, NH, JMB, MG, KJP, AAET, MN, OM); CAS Key Laboratory of Behavioral Science, Institute of Psychology, Beijing, PR China (YZ); Department of Psychology, University of Chinese Academy of Sciences, Beijing, PR China (YZ); CORE - Copenhagen Research Center for Mental Health, Mental Health Center, Copenhagen University Hospital, Copenhagen, Denmark (NH, JMB, MG, MN); Child and Adolescent Mental Health Center, Copenhagen University Hospital, Mental Health Services, Copenhagen, Denmark (NH, LKJ, KML, AAET); Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark (JMB, MG, LKJ, HRS, KJP, AAET, MN); Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Amager and Hvidovre, Copenhagen, Denmark (LKJ, KML, WFCB, KSM, HRS); Department of Neurology, Copenhagen University Hospital Bispebjerg and Frederiksberg, Copenhagen, Denmark (HRS); Division of Child and Adolescent Psychiatry, Department of Psychiatry, the University Hospital of Lausanne, Lausanne, Switzerland (KJP); Center of Functionally Integrative Neuroscience, Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark (LØ, TEL, MD); and Department of Neuroradiology, Aarhus University Hospital, Aarhus, Denmark (LØ).

Address correspondence to Lotte Veddum, Ph.D., at lotved@rm.dk, or Martin Dietz, Ph.D., at martin@cfin.au.dk.

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