Theory of Mind network activity is altered in subjects with familial liability for schizophrenia

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Running title: Theory of Mind in schizophrenia relatives

Word counts: Abstract: 183; Main text: 4.186; Figures: 3; Tables: 2
Supplements: 4 figures, 6 tables, methodological information

ABSTRACT

As evidenced by a multitude of studies, abnormalities in Theory of Mind (ToM) and its neural processing might constitute an intermediate phenotype of schizophrenia. If so, neural alterations during ToM should be observable in unaffected relatives of patients as well, since they share a considerable amount of genetic risk. While behaviorally, impaired ToM function is confirmed meta-analytically in relatives, evidence on aberrant function of the neural ToM network is sparse and inconclusive. The present study therefore aimed to further explore the neural correlates of ToM in relatives of schizophrenia. 297 controls and 63 unaffected first-degree relatives of patients with schizophrenia performed a ToM task during functional magnetic resonance imaging. Consistent with the literature relatives exhibited decreased activity of the medial prefrontal cortex. Additionally, increased recruitment of the right middle temporal gyrus and posterior cingulate cortex was found, which was related to subclinical paranoid symptoms in relatives. These results further support decreased medial prefrontal activation during ToM as an intermediate phenotype of genetic risk for schizophrenia. Enhanced recruitment of posterior ToM areas in relatives might indicate inefficiency mechanisms in the presence of genetic risk.

KEYWORDS

mentalizing; intermediate phenotype; psychosis; imaging genetics; medial prefrontal cortex

INTRODUCTION

Theory of Mind (ToM) or mentalizing, the cognitive capability to infer and represent one's own and other people's mental states (Premack & Woodruff, 1978), is fundamental for social interaction, because it enables us to understand and predict the behavior of our conspecifics and forms the basis for empathy and prosocial behavior. Frith (1992) hypothesized that deficits in ToM underlie typical symptoms of schizophrenia, such as disorganization and delusional ideas. In line with this, multiple meta-analyses congruently showed large effect sizes for ToM deficiencies in patients with schizophrenia (Bora, Yücel, & Pantelis, 2009; Chung, Barch, & Strube, 2014; Savla, Vella, Armstrong, Penn, & Twamley, 2013; Sprong, Schothorst, Vos, Hox, & van Engeland, 2007) that were a strong predictor for poor functional outcome, compromised social competence, and lower quality of life (Brüne, Abdel-Hamid, Lehmkämper, & Sonntag, 2007; Fett et al., 2011; Maat, Fett, & Derks, 2012). Also, functional magnetic resonance imaging (fMRI) studies demonstrated that patients exhibit abnormal brain activity in regions essential for mentalizing (Carrington & Bailey, 2009; Van Overwalle, 2009), specifically reduced recruitment of the medial prefrontal cortex (MPFC), temporoparietal junction (TPJ), posterior cingulate cortex, and precuneus (PCC/Pcu) (Brunet, Sarfati, Hardy-Baylé, & Decety, 2003; Lee et al., 2006; Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011; Walter et al., 2009).

In light of heritability estimates of up to 80% for schizophrenia (Sullivan, Daly, & O'Donovan, 2012; Wray & Gottesman, 2012), the strong evidence for ToM impairments led to the hypothesis that these might be genetically influenced and constitute an intermediate phenotype of the disease (Gottesman & Gould, 2003; Martin, Robinson, Dzafic, Reutens, & Mowry, 2014; Meyer-Lindenberg & Weinberger, 2006). Congruently, various candidate risk genes for schizophrenia were associated with behavioral ToM performance (Bosia et al., 2011; Lackner, Sabbagh, Hallinan, Liu, & Holden, 2012; Rodrigues, Saslow, Garcia, John, & Keltner, 2009; Xia, Wu, & Su, 2012) and two recent imaging genetics studies showed that the genome-wide supported schizophrenia risk variant rs1344706 within ZNF804A

(O'Donovan et al., 2008; Riley et al., 2010; Williams et al., 2011; Zhu et al., 2014; in the yet largest genome-wide association study on schizophrenia investigating 36.989 patients and 113.075 controls another single nucleotide polymorphism within ZNF804A, rs11693094, in high LD with rs1344706 (R^2=.84) reached genome-wide significance; Ripke et al., 2014) was associated with altered brain activity during mentalizing in core ToM areas in the same directionality as observed in patients: In 109 healthy controls (HC) without familial liability for schizophrenia brain activity within the MPFC, TPJ and PCC/Pcu decreased with increasing number of risk alleles (Walter et al., 2011). Importantly, these findings were recently replicated in an independent sample of 188 HC (Mohnke et al., 2014).

If intermediate phenotypes really constituted an intermediate step from genetic risk to disorder, they should be observable in subjects at familial, i.e. genetic high risk (FHR) for a disorder, although to a lower degree (Gottesman & Gould, 2003; Meyer-Lindenberg & Weinberger, 2006). There is meta-analytic support for moderate behavioral ToM impairments in FHR (Bora & Pantelis, 2013; Lavoie et al., 2013) and indeed performance is intermediate between HC and patients with schizophrenia (Janssen, Krabbendam, Jolles, & van Os, 2003; Mazza, Di Michele, Pollice, Casacchia, & Roncone, 2008; Versmissen et al., 2008). However, it has been suggested that differences between groups might at least partially be explained by the presence of some psychotic symptoms or schizotypal traits rather than familial risk status (Irani et al., 2006; Kelemen, Kéri, Must, Benedek, & Janka, 2004; Marjoram et al., 2006b).

Studying ToM deficits in FHR has a number of advantages over studying patients with manifest disease, e.g. results are free from or less impaired by confounding factors such as medication, socioeconomic consequences, and psychological stressors. In addition, it is important to investigate ToM deficits in FHR because they are a major predictor of diminished psychosocial functioning (Brüne et al., 2007; Caletti et al., 2013; Fett et al., 2011; Ventura et al., 2015) that has repeatedly been shown to be compromised in FHR (Glatt, Stone, Faraone, Seidman, & Tsuang, 1996; Tarbox & Pogue-Geile, 2011). This can lead to

social withdrawal and thereby less social support, which, in the presence of subclinical symptoms, can foster the conversion to manifest illness. Congruently, reduced psychosocial functioning was shown to precede the diagnosis of schizophrenia (Tarbox & Pogue-Geile, 2008). Hence, in face of its possible predictive value for developing schizophrenia, the study of ToM alterations and its genetic influences might elucidate important mechanisms in the interplay of biological and psychosocial etiological factors. Neural mechanisms of ToM dysfunction in FHR have received little attention so far with data from only three independent samples published to date. While one investigation reported effects of psychotic symptoms but not familial risk (Marjoram et al., 2006a), two others found group differences within the ToM network that were unrelated to symptomatology but predictive of psychosocial functioning (de Achával et al., 2012; Dodell-Feder, Delisi, & Hooker, 2014; Villarreal et al., 2014). However, comparability between studies is limited by inconsistent directions of group effects, the employment of tasks that tapped differing social-cognitive processes (emotion recognition, social reasoning) and small sample sizes (including 14-24 FHR).

Therefore, we aimed to shed further light on aberrant ToM processing in FHR investigating the largest sample of this population with regard to this topic so far. Based on the existing literature and our own previous work, our main hypothesis was that first-degree relatives of patients with schizophrenia would exhibit diminished activity within brain areas central to mentalizing: the MPFC, TPJ, and PCC/Pcu. As a secondary aim we were interested in investigating associations of neural ToM network function and subclinical psychotic symptomatology.

METHODS

Subjects

All subjects were enrolled in the NFGN[+] MooDS multicenter imaging genetics study and were aged between 18 and 60 years. A total of 63 (n=24 male) unaffected first-degree relatives of patients with schizophrenia, recruited via psychiatric hospitals, mental health support groups, media advertisements, and practitioners in Berlin, Bonn, and Mannheim were included. General exclusion criteria for both groups comprised a lifetime history of significant general medical, psychiatric (including alcohol and drug dependence), or neurological illness, current or past psychotropic pharmacological treatment, and head trauma (see Supplementary Figure S1 for exclusions). Index patients were diagnosed by an experienced clinician using the structured clinical interview for DSM-IV (SCID-I) (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) or provided a medical report of a licensed psychiatrist confirming the diagnosis of schizophrenia. Affected patients did not suffer from any other psychotic or affective disorder. FHR had no family history of multiple different psychiatric diagnoses (e.g. cases of both, affective and psychotic disorders in the kinship).

FHR were compared with a sample of 297 HC described previously (Mohnke et al., 2014). FHR and HC did not differ in demographic variables (table 1). Control participants were recruited from the same study sites as FHR using media advertisements and mailing lists. HC did not report any cases of current or past history of psychotic or affective disorders in first-degree relatives. All participants gave written informed consent before participation. The study was approved by local ethics committees of the Universities of Bonn, Heidelberg and Charité-Universitätsmedizin Berlin.

fMRI task

The ToM cartoon task was previously shown to robustly activate the mentalizing network and to possess excellent test-retest-reliability (intra class correlation coefficients range from 0.76 to 0.82 for key ToM areas) (Mohnke et al., 2014; Schnell, Bluschke, Konradt, & Walter, 2011; Walter et al., 2011). Trials of a ToM and a control condition were presented in alternation. In the ToM condition subjects had to take the perspective of the protagonist in short cartoon

stories and judge changes in his/her affective states (better, worse, equal compared to the preceding picture). In the control condition, subjects were asked to detect changes in the number of depicted living beings (more, less, equal than in the preceding pictures; see Supplementary Material for details).

Imaging Parameters

Data acquisition was performed on Siemens Trio 3T MR scanners at the Charité - Universitätsmedizin Berlin, the Life and Brain Center of the University of Bonn, and the Central Institute of Mental Health Mannheim using identical sequence protocols. fMRI data were acquired using echoplanar imaging (EPI) with the following parameters: 240 volumes, 28 slices of 4mm + 25% gap, TR 2s, TE 30ms, flip angle 80°, FOV 192mm, descending slice order. Quality control measurements were conducted on every day of data collection according to a multicenter quality assurance protocol (Friedman & Glover, 2006), revealing stable signals over time and comparable quality between sites. In order to account for any remaining differences in hardware parameters (e.g. mean signal, drift, signal to noise ratio, spatial noise), site was used as covariate for all analyses.

Neuropsychological testing and psychopathological questionnaires

Following MRI assessment, subjects completed neuropsychological tests and psychopathological questionnaires on a second day. Neuropsychological tests assessed verbal intelligence (Multiple choice vocabulary test, MWT-B) (Lehrl, 2005) and inductive reasoning (WAIS matrix reasoning subtest) (Von Aster, Neubauer, & Horn, 2006). Self-report measures included scales for psychotic symptoms taken from the Symptom checklist-90-Revised (SCL-90-R, subscales 'Paranoid ideation' and 'Psychoticism') (Franke, 2002), depression (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Hautzinger, Bailer,

Worall, & Keller, 1995), and trait anxiety (STAI-T) (Laux, Glanzmann, Schaffner, & Spielberger, 1981). German versions of all measures were applied.

Functional imaging processing

A total of 239 volumes were included in the analyses for each subject. Image processing and statistical analyses were conducted using statistical parametric mapping methods with SPM8 (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) implemented in Matlab 8.3 (Mathworks, Natick, Massachusetts, USA). Functional image preprocessing included correction for acquisition delay, followed by 4th degree B-spline realignment to a mean image (data were excluded if movement parameters exceeded >3mm translation and/or >3° rotation). The images were then spatially normalized to a standard EPI template (created by the Montreal Neurological Institute (MNI)) with volume units (voxels) of 3x3x3mm. Spatial smoothing was carried out using a 9mm full width at half maximum (FWHM) Gaussian filter to increase sensitivity for effects in cortical target regions in group inferences. Individual first level models included five epoch regressors (1. ToM and 2. control stories (one block encompassing the time span of an entire story, i.e. all 3 pictures), instructions for 3. ToM and 4. control stories, and 5. button presses) that were convolved with the standard canonical hemodynamic response function. In addition, six regressors modeling head motion were included as covariates of no interest.

Statistical analyses

Group differences in brain activation during mentalizing were analyzed using second-level random-effects analyses. Specifically, a 2-sample t-test was employed to investigate differences between HC and FHR including the individual ToM>control contrasts modeled at the first level. Site, age, sex, and reaction time as well as response accuracy differences

between task conditions were included as regressors of no interest. Task performance parameters were included to account for different attentional demands of task conditions (Schnell et al., 2011) (see results).

Statistical analyses were carried out within four regions of interest (ROIs) for which we had specific a priori hypotheses (see above) using the Wake Forest University PickAtlas (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003; Tzourio-Mazoyer et al., 2002; www.fmri.wfubmc.edu). Functional ROIs of comparable size (545-692 voxels) were generated for the MPFC, bilateral TPJ and PCC/Pcu. These regions were shown to exhibit altered activity in patients with schizophrenia (Brüne et al., 2011; Brunet et al., 2003; Das, Lagopoulos, Coulston, Henderson, & Malhi, 2012; Lee et al., 2006; Sugranyes et al., 2011; Walter et al., 2009) and to be modulated by a genetic risk variant for schizophrenia (Mohnke et al., 2014; Walter et al., 2011). The ROIs were created literature-based on coordinates reported by a meta-analysis on brain areas involved in ToM (Van Overwalle, 2009) using the toolbox TWURoi (see Supplementary Material for details).

Demographic, task performance, and psychological measures were analyzed using IBM SPSS Statistics Version 22.0 (IBM Corp., 2013). Group differences in categorical variables were examined using χ^2-tests, whereas effects on continuous variables were analyzed employing (M)ANCOVAs and t-tests for independent samples. Similar to neuroimaging analyses, age and sex were included as covariates in analyses of task performance parameters. Associations between brain activity and psychopathology were assessed by extracting individual beta weights from the peak voxels of group differences during mentalizing (see below) and correlating these with questionnaire scores externally within SPSS. If not reported otherwise, the significance threshold for all analyses was set to $p<.05$. Multiple comparisons were accounted for by applying Bonferroni correction for behavioral analyses. All neuroimaging analyses were corrected using familywise error (FWE) correction within the aforementioned ROIs or across the whole brain.

RESULTS

Neuropsychological and psychopathological parameters

FHR reported higher psychoticism, depression, and trait anxiety, and exhibited lower verbal intelligence than HC (table 1). Effects on psychopathological variables, but not intelligence, were robust to Bonferroni-correction for multiple testing (critical p=.016).

ToM task performance

Repeated measures ANCOVAs revealed longer reaction times in the ToM compared to the control condition (see Supplementary Table S1). An effect of condition was not observable for response accuracy. Reaction times varied differently across conditions for FHR and HC. Post hoc t-tests showed that FHR had longer response latencies than HC during mentalizing (t=-2.39, p=.02), but not during the control condition (t=-1.08, p=.28; figure 1).

There were significant effects of age on task performance. Response latencies increased with age in both conditions (ToM: r=.30, p=.00; control: r=.36, p=.00). The age effect was modulated by task condition for accuracy of responses. Correlational analyses revealed that this was due to a stronger inverse relationship in the ToM (r=-.34, p=.00) than the control condition (r=-.21, p=.00).

In order to assess whether differences in performance between task conditions were related to more general cognitive abilities, we performed correlations with neuropsychological parameters. Only in FHR there was a negative association between verbal intelligence and reaction time differences between the ToM and the control condition. We did not observe any further significant correlations (Supplementary table S2).

Functional neuroimaging

Similar to HC FHR activated typical ToM areas during mentalizing including frontal, temporal, parietal, and dorsal midline structures (see Supplementary Table S3).

HC exhibited significantly stronger activity than FHR in the MPFC (x=-6, y=44, z=33; Z=4.06, $p_{FWE-ROI}$=.003; figure 2). In the reverse contrast, FHR showed significantly stronger activity than HC within the right middle temporal gyrus (MTG; x=48, y=-52, z=6; Z=3.63; $p_{FWE-ROI}$=.018) and the PCC (x=-3, y=-46, z=27; Z=3.44; $p_{FWE-ROI}$=.032; figure 3).

Since we observed effects of age and sex on neighboring brain regions (see Supplementary Tables S4 and S5), we, besides covarying for these variables, masked their effects out in an additional analyses (see Supplementary Material for details). This was done in order to rule out that effects of demographic variables were confounded with group differences. However, this approach did not change the results described above. Supplementary Figure S4 illustrates that the effects showed little overlap. There were no interaction effects between group and demographic variables located within target areas or withstanding correction for multiple comparisons (Supplementary Table S6).

Correlations between brain activity, psychopathology, and task performance

Specifically in FHR, the magnitude of right MTG and PCC activation positively correlated with the degree of self-reported paranoid ideation in the SCL-90-R (table 2), although these results would not withstand correction for multiple testing (critical p=.002). Group effects in brain activity only marginally changed when 'paranoid ideation' scores were included as further covariate (HC>FHR: MPFC: Z=3.99, $p_{FWE-ROI}$=.005; FHR>HC: MTG: Z=3.50, $p_{FWE-ROI}$=.027; PCC: Z=3.37, $p_{FWE-ROI}$=.041). We did not observe any further associations between brain activity and psychopathological or neuropsychological variables (table 2).

DISCUSSION

We investigated the yet largest sample of unaffected first-degree relatives of patients with schizophrenia performing a ToM task while undergoing fMRI. Behaviorally, we found further evidence for impaired ToM processing in FHR, which showed longer reaction times specifically in the ToM condition. On the neural level, there was decreased MPFC activation in FHR compared to HC, mirroring findings in patients with schizophrenia (Sugranyes et al., 2011; Walter et al., 2009) and HC carrying a risk variant for schizophrenia (Mohnke et al., 2014; Walter et al., 2011). In addition, we observed increased activation in FHR compared to HC in the MTG and PCC. These effects were opposite in directionality to findings in patients (Sugranyes et al., 2011). In FHR, activation of the MTG and PCC correlated with attenuated paranoid ideation.

Behavioral findings

In task performance parameters, FHR showed increased reaction times while mentalizing. This is largely consistent with meta-analytical findings in FHR (Anselmetti et al., 2009; de Achával et al., 2012). It should be noted however, that our task was optimized for neuroimaging and not behavioral readouts and this finding could in principle also be due to the difficulty of the ToM compared to the control condition, as we did not study a high level control condition of similar difficulty without mentalizing. In line with this idea, in FHR decreasing verbal intelligence was associated with increasing reaction time differences between task conditions. This suggests that lower intelligence was associated with more effort to complete the ToM condition in this group. Since FHR had reduced verbal intelligence compared to HC, this indicates, although the correlation was weak and would not withstand Bonferroni correction, that part of the variance in group differences in reaction times might be attributable to more general cognitive factors. This is consistent with the literature showing that differences between patients with schizophrenia or FHR and HC in mentalizing abilities are in some part due to other neuropsychological parameters. However, in most studies group effects remained significant after accounting for more general cognitive factors,

suggesting that ToM effects were not completely dependent on basal neuropsychological functioning (de Achával et al., 2010; Janssen et al., 2003; Mazza et al., 2008; Montag et al., 2012; Pickup, 2008).

MPFC findings

In accordance with our a priori hypothesis we found reduced activation in the MPFC in FHR. The MPFC is a key mentalizing area, involved in the representation of intentions, beliefs, and preferences of others, as well as forming social judgments, and extracting social scripts (Bzdok et al., 2012; Carrington & Bailey, 2009; den Ouden, Frith, Frith, & Blakemore, 2005; Freeman, Schiller, Rule, & Ambady, 2010; Kang, Lee, Sul, & Kim, 2013; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014; Van Overwalle & Baetens, 2009; Van Overwalle, 2009). Diminished MPFC activity during ToM has been reported in patients with schizophrenia repeatedly and confirmed meta-analytically (Sugranyes et al., 2011). Assuming that an intermediate phenotype is similar in subjects with familial risk, our findings are consistent with patient findings. However, in the studies published until now results were equivocal. Similar to our findings, Dodell-Feder et al. (2014) observed reduced ventral MPFC recruitment in FHR compared to HC while reasoning about emotions. Furthermore, these authors found that reduced MPFC activation was predictive of self-reported social functioning over the month following scanning. Two other fMRI studies did not report MPFC abnormalities in FHR (de Achával et al., 2012; Marjoram et al., 2006a). However, in the study by Marjoram and colleagues (2006a) reduced MPFC activation was apparent in FHR subjects with psychotic symptoms compared to those without. In our data we could not confirm an association between MPFC recruitment and self-reported psychotic symptoms. These inconsistencies can be explained by various factors. Power and sensitivity of studies are influenced by task differences and crucially, sample size. As our study includes the yet largest sample of FHR and may thus provide the greatest statistical power so far, we tentatively conclude that our results show evidence for reduced MPFC activation as an intermediate phenotype for

schizophrenia. This is also in line with the fact that risk allele dosage of a well-established genome wide risk variant for schizophrenia, rs1344706 within ZNF804A, was also associated with reduced MPFC activation in two independent cohorts (Mohnke et al., 2014; Walter et al., 2011).

MTG and PCC findings

In the right MTG and PCC, we observed *increased* activation in FHR compared to HC. Both regions were consistently observed to be activated in mentalizing studies (Bzdok et al., 2012; Schurz et al., 2014; Van Overwalle & Baetens, 2009). Temporoparietal areas are also associated with the attribution of beliefs and inference of action goals and thereby ultimately action understanding. The Pcu/PCC is assumed to contribute to mental state understanding by mental imagery (Schurz et al., 2014). However, this region is involved in a variety of further cognitive processes, such as autobiographical memory, reward, and emotional stimulus processing and there is also evidence that its role might be to distinguish between these cognitive states (Utevsky, Smith, & Huettel, 2014). Hypothesizing another more coordinative role, Young and Saxe (2008) postulated that the TPJ and Pcu/PCC might integrate beliefs with other relevant features.

In patients, both hypo- and hyperactivation of the PCC was reported during mentalizing, however, middle temporal recruitment was reduced in most studies (Sugranyes et al., 2011). In studies on FHR, results are not that straightforward. Partly consistent with our results, de Achával et al. (2012) observed heightened temporal activity in patients and relatives compared to controls during emotion recognition but reduced Pcu/PCC activation. Although Marjoram et al. (2006a) did not find significant differences between FHR and HC in brain activation, they reported less temporoparietal activity in relatives experiencing current psychotic symptoms compared to those who never experienced any. Dodell-Feder et al. (2014) observed reduced bilateral TPJ activity in FHR while subjects were engaged in social reasoning. Again, we would like to point out differences in power and task design between

studies. Whether our results are reliable however, has to await results from future studies with sufficient sample sizes.

We want to suggest two potential mechanisms that may underlie increased posterior ToM network activity. Posterior ToM regions might be inefficiently hyperactivated in FHR, similar to effects previously observed in working memory in this population (Callicott et al., 2003). In case of such inefficiency, we would expect functional activation to be positively related to increased symptomatology. Indeed, we found positive correlations between self-reported paranoid ideation and right MTG as well as PCC activation. This notion would be further supported by a relation between activation of these regions and differing task demands. Future studies might use a parametric design to further explore this idea. Alternatively, increased recruitment could also represent inappropriately increased mentalizing. It has been assumed earlier that hyperactivation of the ToM network could underlie psychotic symptoms, since patients with schizophrenia tend to over-attribute intentions to agents, even in situations in which no mentalizing is required ("hyper-intentionality"-hypothesis) (Ciaramidaro et al., 2015; Walter et al., 2009). This explanation is congruent to theoretical considerations according to which inadequate mental state attribution could entail delusional ideation and thus, also fits the correlational findings (Frith, 1992). ToM tasks evoking possible delusional interpretations might be used in future studies to pursue this possibility. We would like to point out further that, inconsistent to results by Marjoram et al. (2006a), group differences between HC and FHR remained significant after accounting for paranoid ideas and thus, are not better explained by differences in subclinical symptomatology rather than familial risk status for schizophrenia.

Limitations

Our results are limited by the fact that our behavioral measure of ToM performance is not highly sensitive to differences between groups, but was primarily developed to yield strong and consistent ToM network activation. This could be the reason why we found a significant

group x condition interaction for reaction times but not for response accuracy. Second, although effects of familial risk status were located within core ToM regions, it is not yet clear whether they are generalizable to other ToM and social cognitive processes, since our task specifically demanded affective perspective taking. Some of the inconsistencies to other studies on neural ToM abnormalities in FHR are likely explained by differences in task demands challenging varying psychological subprocesses and employing differing types of stimuli. While, probably most similar to our paradigm, the task employed by Marjoram et al. (2006a) required the understanding of cartoons depicting jokes, Dodell-Feder et al. (2014) tapped into social-cognitive reasoning beyond understanding of mental states, requiring conclusions about behavior likely following affective as well as cognitive states after reading text stimuli. In contrast, the paradigm used by De Achaval et al. (2012) required more basal facial emotion recognition. Hence, for better comparable results there is a need to disentangle these subprocesses. Furthermore, the correlations between brain activity and questionnaire data did not survive correction for multiple testing. Hence, replication with sufficiently powered samples is essential here. Third, our study lacks direct comparison with patients with manifest illness, which would provide valuable data on the importance and potential interplay of familial genetic risk and psychotic symptomatology.

Summary and conclusions

Investigating the yet largest sample of FHR, we found further evidence that reduced MPFC activation during mentalizing might qualify as an intermediate phenotype of schizophrenia. Furthermore, we identified potentially inefficiently increased posterior ToM network activation in FHR, which was at least nominally correlated with subclinical paranoid symptoms. There is additional independent evidence that ToM network function was predictive of psychotic symptoms (Marjoram et al., 2006a) and social functioning (Dodell-Feder et al., 2014; Villarreal et al., 2014) in FHR. Thus, in line with a biopsychosocial etiological model, genetically mediated aberrant ToM function might entail both subclinical symptomatology as

well as impaired social functioning that could act together in the development of manifest schizophrenia.

FUNDING

ACKNOWLEDGEMENTS

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FIGURES

Figure 1.   Task performance

There were significant effects of task condition for response accuracy (number of correct responses) and reaction times. FHR had higher response latencies specifically during the ToM condition.

Annotations: ToM Theory of Mind condition; control control condition; FHR Familial high risk (first-degree relatives), n=63; HC healthy controls, n=297; response accuracy is number of correct responses in respective task condition; n sub-sample size.

Figure 2.   Group differences in MPFC activity during mentalizing

HC exhibited higher activity in the MPFC during ToM than FHR.

Annotations: ToM Theory of Mind; FHR Familial high risk (first-degree relatives), n=63; HC healthy controls, n=297; n sub-sample size; MPFC medial prefrontal cortex; ROI region of interest; FWE familywise error correction.

The ToM main effect is depicted at p<.01 FWE correction for the whole brain (green). The group effect is shown at an FWE ROI-corrected level of p<.05 (red).

Figure 3.   Effects of familial risk status in FHR within posterior ToM areas

FHR exhibit stronger right MTG and PCC activity than HC during ToM.

Annotations: ToM Theory of Mind; FHR Familial high risk (first-degree relatives), n=63; HC healthy controls, n=297; n sub-sample size; MTG middle temporal gyrus; PCC posterior cingulate cortex; ROI region of interest; L left; R right; FWE familywise error correction.

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TABLES

Table 1.　　Demographic and psychological variables

	FHR (n=63)	HC (n=297)	Test statistics
Demographics			
Sex (male/female)	24/39	142/155	χ^2=1.98 (.16)
Age	31.79±11.38	33.58±9.92	t=1.26 (.21)
Years of education	15.33±2.51	15.47±2.55	t=0.37 (.71)
Handedness (left/right/both)	53/6/3*	268/22/6*	χ^2=2.09 (.35)
Site (Berlin/Bonn/Mannheim)	19/22/22	131/88/78	χ^2=4.31 (.12)
Neuropsychology			
MWT-B	29.38±3.49	30.37±3.26	**F=4.40 (.04)**
WAIS Matrix reasoning	21.13±3.70	20.58±3.83	F=1.06 (.30)
Psychopathology			
SCL-90-R			
Paranoid ideation	0.24±0.43	0.21±0.34	F=0.43 (.52)
Psychoticism	0.14±0.25	0.06±0.14	**F=11.82 (.00)**
BDI	4.60±4.95	2.90±3.42	**F=9.99 (.00)**
STAI-T	39.05±11.34	35.23±9.07	**F=7.85 (.01)**

Annotations:　　FHR Familial high risk (first-degree relatives); HC healthy controls; n sub-sample size; *data missing from 1 participant; ± standard deviation; significance values are indicated in brackets; MWT-B Mehrfachwahl-Wortschatz-Intelligenztest Version B; WAIS Wechsler adult intelligence scale; SCL-90-R Symptom checklist 90 – Revised; BDI Beck depression inventory; State-Trait-Anxiety-Inventory, Trait Version.

Table 2.   Correlations between psychopathology, neuropsychology and regional brain activity

	FHR						HC					
	SCL-PI	SCL-Ps	BDI	STAI-T	MWT-B	WAIS MR	SCL-PI	SCL-Ps	BDI	STAI-T	MWT-B	WAIS MR
MPFC	.21 (.10)	.24 (.06)	.18 (.17)	.25 (.06)	-.04 (.77)	-.10 (.42)	.08 (.19)	.10 (.10)	-.02 (.71)	-.03 (.57)	.04 (.50)	.11 (.07)
MTG R	**.32 (.01)**	.12 (.37)	.05 (.72)	.08 (.56)	.04 (.78)	.20 (.13)	.06 (.31)	.08 (.20)	-.05 (.42)	.00 (.97)	-.06 (.32)	-.10 (.11)
PCC	**.27 (.03)**	.05 (.70)	.08 (.56)	.01 (.94)	-.23 (.07)	.07 (.61)	.05 (.40)	.06 (.33)	-.01 (.92)	.03 (.62)	.03 (.64)	-.03 (.66)

Annotations: Spearman correlations (significance values in brackets) between individual beta weights extracted from the peak voxels of significant group differences between FHR and HC (MPFC: x=-6, y=44, z=33; MTG R: x=48, y=-52, z=6; PCC: x=-3, y=-46, z=27), psychopathology, and neuropsychology measures.

FHR familial high risk (first-degree relatives); HC healthy controls; MPFC medial prefrontal cortex; MTG R right middle temporal gyrus; PCC posterior cingulate cortex; SCL-PI/SCL-Ps Symptom checklist 90 – Revised subscales 'Paranoid ideation' and 'Psychoticism'; BDI Beck depression inventory; STAI-T State-Trait-Anxiety-Inventory, Trait Version; MWT-B Mehrfachwahl-Wortschatz-Intelligenztest Version B; WAIS MR Wechsler adult intelligence scale, subtest Matrix Reasoning.
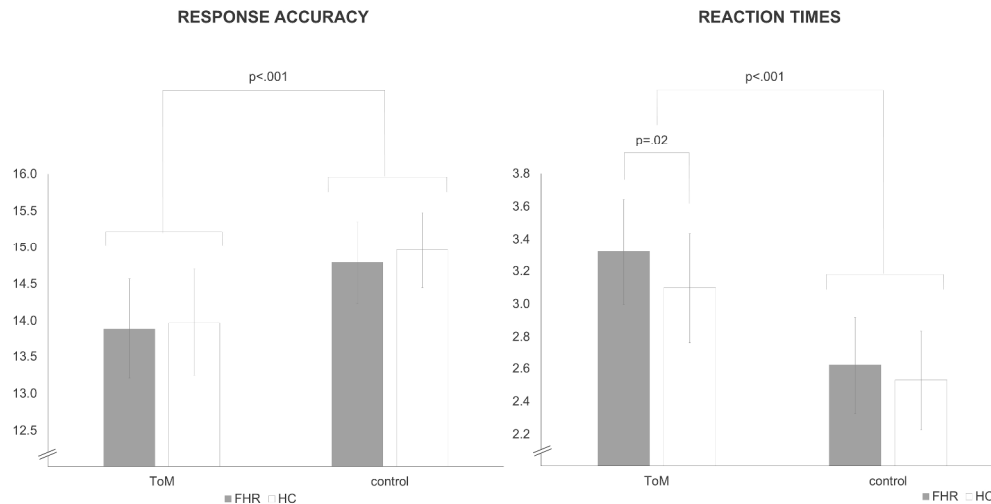
Figure 1. Task performance

There were significant effects of task condition for response accuracy (number of correct responses) and reaction times. FHR had higher response latencies specifically during the ToM condition.

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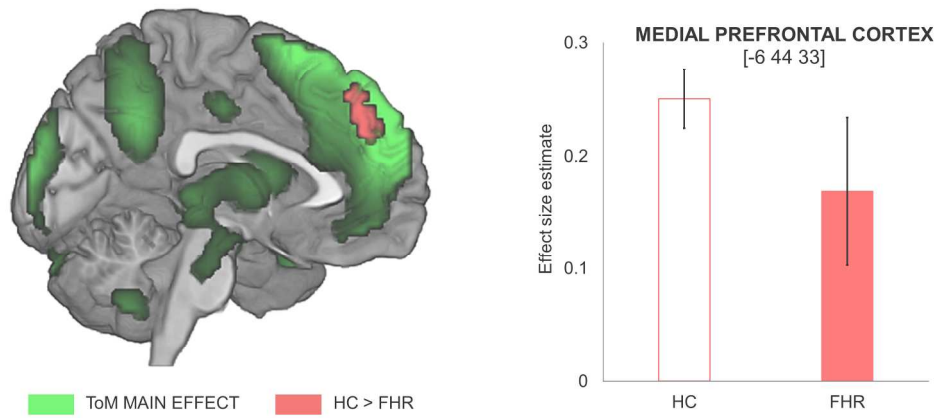1000x600mm (96 x 96 DPI)

Figure 2. Group differences in MPFC activity during mentalizing

HC exhibited higher activity in the MPFC during ToM than FHR.

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The ToM main effect is depicted at p<.01 FWE correction for the whole brain (green). The group effect is shown at an FWE ROI-corrected level of p<.05 (red).
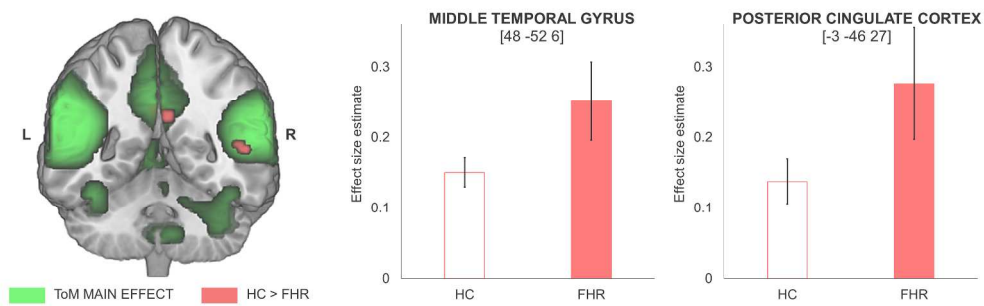651x300mm (96 x 96 DPI)

Figure 3. Effects of familial risk status in FHR within posterior ToM areas

FHR exhibit stronger right MTG and PCC activity than HC during ToM.

Annotations: ToM Theory of Mind; FHR Familial high risk (first-degree relatives), n=63; HC healthy controls, n=297; n sub-sample size; MTG middle temporal gyrus; PCC posterior cingulate cortex; ROI region of interest; L left; R right; FWE familywise error correction.
The ToM main effect is depicted at p<.01 FWE correction for the whole brain (green). Group effects are shown at an FWE ROI-corrected level of p<.05 (red).
837x268mm (96 x 96 DPI)