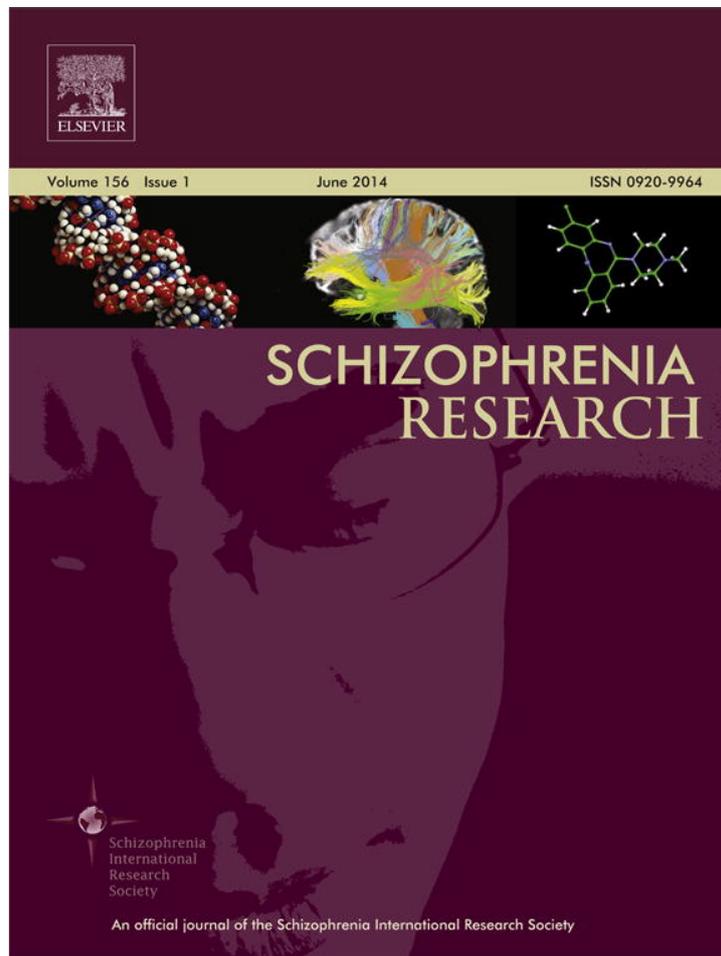


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The relationship between default mode network connectivity and social functioning in individuals at familial high-risk for schizophrenia

David Dodell-Feder ^{a,*}, Lynn E. DeLisi ^{b,c}, Christine I. Hooker ^a^a Department of Psychology, Harvard University, Cambridge, MA 02138 USA^b Boston VA Medical Center, Brockton, MA 02301 USA^c Department of Psychiatry, Harvard Medical School, Boston, MA 02215 USA

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ABSTRACT

Unaffected first-degree relatives of individuals with schizophrenia (i.e., those at familial high-risk [FHR]), demonstrate social dysfunction qualitatively similar though less severe than that of their affected relatives. These social difficulties may be the consequence of genetically conferred disruption to aspects of the default mode network (DMN), such as the dMPFC subsystem, which overlaps with the network of brain regions recruited during social cognitive processes. In the present study, we investigate this possibility, testing DMN connectivity and its relationship to social functioning in FHR using resting-state fMRI. Twenty FHR individuals and 17 controls underwent fMRI during a resting-state scan. Hypothesis-driven functional connectivity analyses examined ROI-to-ROI correlations between the DMN's hubs, and regions of the dMPFC subsystem and MTL subsystem. Connectivity values were examined in relationship to a measure of social functioning and empathy/perspective-taking. Results demonstrate that FHR exhibit reduced connectivity specifically within the dMPFC subsystem of the DMN. Certain ROI-to-ROI correlations predicted aspects of social functioning and empathy/perspective-taking across all participants. Together, the data indicate that disruption to the dMPFC subsystem of the DMN may be associated with familial risk for schizophrenia, and that these intrinsic connections may carry measurable consequences for social functioning.

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1. Introduction

Deficits in social functioning represent one of the most disabling aspects of schizophrenia. Increasing evidence suggests that social deficits are associated with familial risk for the illness. More specifically, compared to individuals without an affected first-degree relative, individuals at familial high-risk (FHR; i.e., those with a first-degree relative with schizophrenia) demonstrate greater social withdrawal and isolation (Hodges et al., 1999; Miller et al., 2002), worse social competence (Dworkin et al., 1991; Cornblatt et al., 1992), less social involvement, and greater social problems with peers (Dworkin et al., 1993, 1994; Hans et al., 2000; Glatt et al., 2006). Importantly, these early emerging social deficits in FHR prospectively predict schizophrenia-spectrum diagnoses later in life (Tarbox and Pogue-Geile, 2008; Matheson et al., 2013; Tsuji et al., 2013). Taken together, the data indicate that in FHR, who are already at increased risk for schizophrenia due to genetic factors (Gottesman, 1991; Keshavan et al., 2004), social deficits may play a contributing causal role in the development of the disorder.

Consequently, social dysfunction may represent a putative risk marker, and a target for preventative intervention.

However, using social dysfunction itself as a marker for illness risk in FHR or targeting social dysfunction itself for preventative intervention in at-risk groups, may prove challenging. For one, social dysfunction is likely a distal product of myriad factors (e.g., biological, environmental, epigenetic) that dynamically interact over the course of development (Tarbox and Pogue-Geile, 2008; Matheson et al., 2013), making it difficult to identify specific pathophysiological mechanisms. Furthermore, by the time social dysfunction becomes apparent, the contributing pathophysiological mechanisms may have long been at work, making its remedy all the more difficult. Perhaps for these reasons, social skills training programs for individuals with schizophrenia have demonstrated only moderate efficacy in treating social dysfunction (Pfammatter et al., 2006; Kurtz and Mueser, 2008), and the effects of pharmacological intervention on social dysfunction are negligible (Swartz et al., 2007). These issues have prompted a search for determinants of social functioning that may better reflect more proximal pathophysiological mechanisms conferring risk (e.g., neural systems and associated cognitive processes), and that may be more amenable to identification and early intervention.

In line with findings demonstrating that normal cognitive functioning relies on the functional integration of distributed brain regions (Bressler

* Corresponding author at: Department of Psychology, Harvard University, 1008 William James Hall, 33 Kirkland St. Cambridge, MA 02138, USA.
 E-mail address: feder@fas.harvard.edu (D. Dodell-Feder).

and Menon, 2010), researchers have proposed that widespread “dysconnectivity,” or aberrant patterns of functional co-activation between brain regions, may give rise to the clinical and cognitive phenomena that characterize schizophrenia (Friston and Frith, 1995; Stephan et al., 2006, 2009). Indeed, much research has demonstrated that functional connectivity within and between several different functionally relevant cortical networks is altered in schizophrenia (Calhoun et al., 2009; Rotarska-Jagiela et al., 2010; Pettersson-Yeo et al., 2011; Repovs et al., 2011; Woodward et al., 2011; Baker et al., 2014). This seems to be especially true of the “default mode network” (DMN) — a set of regions including medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), medial temporal lobes (MTL), and lateral temporoparietal areas (temporo-parietal junction [TPJ], posterior inferior parietal lobule [pIPL]), that are preferentially engaged during passive, spontaneous, stimulus-independent states, such as mind-wandering and self-reflection (Raichle et al., 2001; Buckner et al., 2008; Andrews-Hanna et al., 2010a,b; Andrews-Hanna, 2012). As revealed during resting-state scans, individuals with schizophrenia exhibit abnormal patterns of connectivity in the form of both decreased and increased temporal correlations between regions within this network (Bluhm et al., 2007; Zhou et al., 2007; Whitfield-Gabrieli et al., 2009; Mannell et al., 2010; Ongur et al., 2010; Rotarska-Jagiela et al., 2010; Skudlarski et al., 2010; Camchong et al., 2011; Chai et al., 2011; Woodward et al., 2011; Alonso-Solis et al., 2012; Liemburg et al., 2012; Liu et al., 2012; Meda et al., 2012; Mingoia et al., 2012; Baker et al., 2014). Functional connectivity in the DMN is moderately heritable (Glahn et al., 2010), and many studies have found FHR to exhibit similar patterns of abnormal connectivity as their affected relatives (Whitfield-Gabrieli et al., 2009; Jang et al., 2011; Liu et al., 2012; Meda et al., 2012; van Buuren et al., 2012; Unschuld et al., 2013), suggesting that DMN connectivity may constitute a risk marker for the disorder (Pettersson-Yeo et al., 2011; Whitfield-Gabrieli and Ford, 2012).

Though several studies have demonstrated links between DMN connectivity and symptoms (Bluhm et al., 2007; Whitfield-Gabrieli et al., 2009; Rotarska-Jagiela et al., 2010; Camchong et al., 2011; Woodward et al., 2011; Liemburg et al., 2012; Meda et al., 2012; Mingoia et al., 2012) as well as non-social aspects of cognition (Whitfield-Gabrieli et al., 2009; Camchong et al., 2011; Unschuld et al., 2013) in both individuals with schizophrenia and their first-degree relatives, few studies have investigated the relationship between DMN connectivity and social behavior. The lack of research in this area is surprising since certain components of the DMN may support social cognitive processes relevant for social functioning. More specifically, using graph-analytic and hierarchical clustering methods, Andrews-Hanna et al. (2010b) found that the functional architecture of the DMN could be parsed into a core set of hubs (PCC, anterior MPFC [aMPFC]) and two subsystems: the dMPFC subsystem, comprising dorsal MPFC (dMPFC), ITPJ, LTC, and temporal pole (TempP), and MTL subsystem, comprising ventral MPFC (vMPFC), pIPL, retrosplenial cortex (Rsp), parahippocampal cortex (PHC), and hippocampal formation (HF). In the same study, functional MRI revealed that the dMPFC subsystem was preferentially engaged when participants were directed to think about their present mental states, while the MTL subsystem was preferentially engaged when participants were directed to think about their future. Indeed, the dMPFC subsystem exhibits substantial overlap with the network of regions recruited during theory-of-mind (ToM) (Mitchell, 2006; Buckner and Carroll, 2007; Schilbach et al., 2008, 2012; Spreng et al., 2009; Spreng and Grady, 2010; Mars et al., 2012) — the ability to attribute and reason about mental states — and additional work has shown that the function and structure of the network supporting ToM predicts aspects of social functioning in schizophrenia (Hooker et al., 2011; Dodell-Feder et al., 2014) and in FHR (Dodell-Feder et al., in press). Interestingly, individuals with first-episode psychosis, who demonstrate marked impairment in ToM (Bora and Pantelis, 2013), have been shown to exhibit DMN abnormalities specifically within the dMPFC, and not MTL subsystem (Alonso-Solis et al., 2012). Thus, it

stands to reason that in FHR, genetically conferred aberrant patterns of connectivity within the dMPFC subsystem may result in difficulty reasoning about the mental states of others, which contributes to impaired social functioning.

Here, we investigate this possibility in a group of FHR individuals with resting-state fMRI and functional connectivity analysis. We used a hypothesis-driven approach analyzing ROI-to-ROI connectivity between the DMN hubs, and within the dMPFC subsystem and MTL subsystem. Furthermore, to investigate whether functional connectivity within the DMN predicted aspects of social functioning, we examined the relationship between dMPFC subsystem connectivity and social functioning using a widely used measure of social behavior and empathy/perspective-taking. Given the relevance of the dMPFC subsystem for social cognition, the well-replicated findings of social difficulties in FHR, and decreased dMPFC connectivity in first-episode psychosis, we predicted that compared to controls, FHR would exhibit reduced connectivity in the dMPFC subsystem. Furthermore, we hypothesized that connectivity within the dMPFC subsystem would be associated with our measures of social functioning and empathy/perspective-taking. Because the neural bases of social cognition appear to be relevant for social functioning regardless of diagnosis or risk-status (Dodell-Feder et al., 2014, in press), we predicted that these relationships would exist across all participants.

2. Materials and methods

2.1. Participants

Twenty FHR and 17 non-FHR control individuals participated in the study.¹ FHR status was defined as having at least two affected relatives: one first-degree relative with schizophrenia or schizoaffective disorder, and a second relative (1st, 2nd, or 3rd degree) with a history of psychosis. FHR participants were recruited from the New England area through brochures, community and online advertisements, and with the help of the National Alliance on Mental Illness (NAMI) (Francis et al., 2012; Thermenos et al., 2013). Control participants had no familial history of psychosis, psychiatric hospitalization, or suicide, and were matched to the FHR group on age, gender, and education (Table 1). These individuals were recruited through online advertisements. Exclusion criteria for all participants were as follows: past/current DSM-IV psychotic disorder, neurological disorder, past/current use of antipsychotic/mood stabilizing medications, IQ < 70, non-native English speaking, and MRI contraindicators. Personal and family history of psychopathology was assessed with the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) and Family Interview for Genetic Studies (Maxwell, 1996), respectively. Given that there exists shared variance between familial risk-status and psychopathology (Erlenmeyer-Kimling et al., 1997; Kendler and Gardner, 1997; Chang et al., 2002; Keshavan et al., 2004), we did not exclude FHR (or controls) for psychopathology other than the disorders listed above in order to maintain external validity. Diagnoses in the FHR and control group are listed in Table 1. IQ was estimated using the matrix and vocabulary subscales of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Harvard University's Internal Review Board approved this study. Participants gave written informed consent and were monetarily compensated for their time.

2.2. Social variables

2.2.1. Social Adjustment Scale — Self-Report

The Social Adjustment Scale — Self-Report (SAS) (Weissman et al., 1978) consists of 54-items designed to measure social functioning in the following six areas over the past two weeks: work (as a paid worker,

¹ Data from a subset of these participants are reported in Dodell-Feder et al. (in press).

Table 1
Participant characteristics.

	FHR	Controls	Between-group difference
<i>n</i>	20	17	
Gender (male/female)	6/14	3/14	$\chi^2(1, N = 37) = .76, p = .38$
Age	27.0 (4.0) [20–33]	26.1 (4.1) [21–35]	$t(35) = .71, p = .48$
Education (years)	16.1 (1.5) [13–19]	16.3 (0.8) [15–18]	$t(35) = .62, p = .54$
Lifetime DSM-IV diagnosis (<i>n</i>)			
MDD	5		
ADHD	1		
Substance abuse		2 ^a	
Comorbid diagnoses ^b	4		
Lifetime Medication Use (<i>n</i>) ^c			
Stimulant	4		
Anti-Depressant	5	1	
IQ ^d	118.1 (9.6) [95–136]	118.4 (11.8) [97–135]	$t(34) = .07, p = .95$
SAS ^e	55.4 (6.6) [47–67]	49.7 (8.9) [38–73]	$t(33) = 2.17, p = .04, d = .73$
IRI-PT ^f	21.8 (4.1) [15–28]	21.3 (3.8) [16–28]	$t(33) = .40, p = .69, d = .14$
IRI-EC	19.0 (4.7) [12–27]	21.9 (4.6) [12–26]	$t(33) = 1.84, p = .07, d = .63$
IRI-FS	14.2 (5.1) [5–25]	18.6 (4.1) [10–26]	$t(33) = 2.84, p = .008, d = .96$
IRI-PD	7.7 (4.7) [0–16]	11.1 (5.8) [1–21]	$t(33) = 1.93, p = .06, d = .65$

Note. Values represent the mean, standard deviation in parentheses, and range in brackets, where applicable. MDD = Major Depressive Disorder, ADHD = Attention Deficit Hyperactivity Disorder, SAS = Social Adjustment Scale – Self-Report, IRI-PT = Perspective-Taking, IRI-EC = Empathic Concern, IRI-FS = Fantasy Scale, IRI-PD = Personal Distress.

^a Neither participant had used the substance (marijuana, cocaine) in at least 1 year prior to the experiment.

^b Two individuals met criteria for MDD and ADHD, 1 individual met criteria for MDD and an anxiety disorder, and 1 individual meet criteria for MDD, an anxiety disorder, ADHD, and substance abuse.

^c Two FHR individuals reported lifetime use of both a stimulant and anti-depressant medication.

^d Data not available for 1 FHR.

^e Data not available for 2 FHR.

^f IRI data not available for 1 FHR and 1 control.

homemaker, or student), social and leisure activities, relationship with extended family, role as a marital partner, parent, and functioning within the family unit. Within each area, questions assess performance, relationship quality, and subjective interest and satisfaction. Questions are answered on a 5-point scale with higher scores indicating greater social impairment. Final scores reflect the average across all areas. The SAS exhibits adequate psychometric properties (Weissman et al., 1978), discriminates schizophrenia-spectrum conditions from non-patient populations (Blanchard et al., 1998; Kwapil, 1998), and correlates with behavioral and neural measures of social cognition (Eack et al., 2010; Dodell-Feder et al., 2014).

2.2.2. Interpersonal Reactivity Index

The Interpersonal Reactivity Index (IRI) (Davis, 1980) is a 28-item self-report questionnaire consisting of four subscales designed to measure different dimensions of empathy: perspective-taking (IRI-PT; e.g., “I sometimes try to understand my friends better by imagining how things look from their perspective.”), empathic concern (IRI-EC; e.g., “I am often quite touched by things that I see happen.”), fantasy (IRI-FS; e.g., “I really get involved with the feelings of the characters in a novel.”), and personal distress (IRI-PD; e.g., “Being in a tense emotional situation scares me.”). Each subscale consists of seven items that are rated on a 5-point scale (0 = *does not describe me well* to 4 = *describes me very well*). We chose to measure empathy/perspective-taking with the IRI for several reasons. First, the IRI has been demonstrated to exhibit adequate psychometric properties and correlates with other measures of empathy (Davis, 1983). Second, non-clinical populations exhibit substantial variability on this measure unlike many of the most commonly used behavioral measures of ToM such as the False-Belief Task (e.g., Pickup and Frith, 2001), Faux Pas Task (e.g., Stone et al., 1998), and Hinting Task (e.g., Corcoran et al., 1995) (see Dodell-Feder et al., 2013 for a discussion). Lastly, the IRI measures empathy/perspective-taking in the context of the participant’s daily interpersonal relationships and interactions, which is closer to the interpersonal processes we were interested in for the current study than what is typically assessed by laboratory-based ToM tasks.

2.3. MRI data acquisition

Participants were scanned with a 3 T Siemens scanner at Harvard University’s Center for Brain Sciences. A T1-weighted multi-echo MPRAGE structural scan (176 sagittal slices, $1 \times 1 \times 1$ mm voxels), and 6.2-minute resting-state functional scan (47 axial slices, TR/TE/flip angle = 3000 ms/30 ms/85°, $3 \times 3 \times 3$ mm voxels) were acquired as part of a battery of other scans unrelated to the current study. The first four images of the resting-state scan were not analyzed to allow for steady state equilibrium. Prior to the resting-state scan, participants were instructed to keep their eyes open, let their mind wander, and keep their head still.

2.4. fMRI data preprocessing

Data were preprocessed in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) in the following steps: corrected for temporal differences in slice acquisition, realigned to the mean functional image, coregistered to the anatomical image, normalized using the SPM template image, and smoothed with an 8 mm FWHM Gaussian kernel.

The Artifact Detection Toolbox (ART; http://www.nitrc.org/projects/artifact_detect/) was used to identify outlier scans in global signal ($>3SD$ mean signal) and movement (>1 mm of composite motion from the previous volume). Because measures of functional connectivity may be spuriously influenced by head motion (Power et al., 2012; Van Dijk et al., 2012), we evaluated group differences in the percentage of outlier scans and head motion. Overall, the mean percentage of outliers identified per group was small ($M \pm SD$ FHR = 1.1 ± 1.6 , Controls = 0.3 ± 0.7) and did not differ between groups, $t(35) = 1.80, p = .081$. Mean translation and rotation also did not differ between groups, translation: $t(35) = .24, p = .813$, rotation: $t(35) = .44, p = .661$.

2.5. Functional connectivity analyses

Functional connectivity analyses were conducted using the CONN Functional Connectivity Toolbox v.13 (<http://www.nitrc.org/projects/conn/>; Whitfield-Gabrieli and Nieto-Castanon, 2012). This toolbox

implements a component-based noise reduction method (CompCor) that estimates BOLD signal from subject-specific white matter and CSF masks (Behzadi et al., 2007). These sources of noise, along with the outlier scans identified with ART, the six motion parameters estimated during realignment, and their temporal derivatives, were regressed from the BOLD time-series at each voxel. The residual BOLD time-series was then band-pass filtered ($.008 < f < .09$).

Following Andrews-Hanna et al. (2010b), we defined ROIs (8 mm spheres) comprising the DMN hubs (PCC, aMPFC), dMPFC subsystem (dMPFC, TPJ, LTC, TempP), and MTL subsystem (vMPFC, pIPL, Rsp, PHC, HF) (see Fig. 1 for a depiction of these regions and coordinates). For each participant, we extracted the ROI-to-ROI BOLD time-series correlations, which were converted using Fisher's r -to- z transform to allow for parametric testing. Two-sample t -tests (two-tailed) were used to investigate between-group differences in the average ROI-to-ROI correlation between the DMN hubs (i.e., PCC-aMPFC) and all ROI-to-ROI pairs comprising the dMPFC subsystem and MTL subsystem. Follow-up analyses investigated group differences in the ROI-to-ROI correlations between individual regions within each subsystem (e.g., dMPFC-ITPJ, vMPFC-pIPL). To reduce the probability of Type I error, we controlled the false-discovery rate ($q < .05$) for comparisons within each subsystem. Cohen's d is reported as the measure of effect size. As an estimate of plausible population effect sizes and the precision of these estimates, all effect sizes are accompanied by 95% confidence intervals (CIs; bias-corrected-and-accelerated) derived from 2000 bootstrap samples using the BootES function (Gerlanc and Kirby, 2012; Kirby and Gerlanc, 2013) in R (R Core Team, 2013). The bootstrap method,

which generates an empirical sampling distribution to approximate the population distribution, is well suited for situations in which the data may be non-normally distributed, as is often the case with smaller samples, or when the population distribution is unknown (Kirby and Gerlanc, 2013).

2.6. Analysis of functional connectivity and behavioral data

Linear regression was used to test the hypothesis that ROI-to-ROI connectivity within the dMPFC subsystem would be associated with the social variables. In models demonstrating a significant relationship between connectivity and SAS or IRI scores, we ran an additional model testing whether the association was different between groups by including a group*connectivity interaction term in the regression model. R^2 and b values are provided with 95% CIs derived from 2000 bootstrap samples using the boot function (Davison and Hinkley, 1997; Canty and Ripley, 2013) in R. The statistical threshold was set to $p < .05$.

3. Results

3.1. Functional connectivity

We first investigated group differences in average functional connectivity between the DMN hubs and all ROI-to-ROI pairs within the dMPFC and MTL subsystem. Compared to controls, FHR exhibited significantly less average functional connectivity within the dMPFC

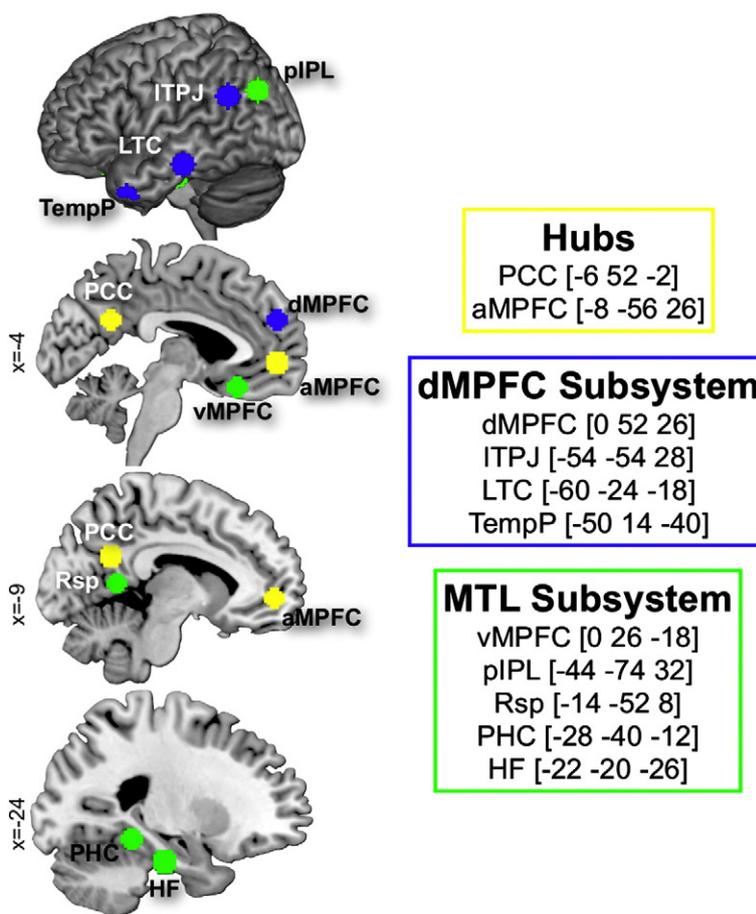


Fig. 1. Depiction of the default mode network's hubs (yellow), dMPFC subsystem (blue), and MTL subsystem (green), and accompanying MNI coordinates. PCC = posterior cingulate cortex, aMPFC = anterior medial prefrontal cortex, dMPFC = dorsal medial prefrontal cortex, ITPJ = left temporo-parietal junction, LTC = lateral temporal cortex, TempP = temporal pole, MTL = medial temporal lobe, vMPFC = ventral medial prefrontal cortex, pIPL = posterior inferior parietal lobule, Rsp = retrosplenial cortex, PHC = parahippocampal cortex, HF = hippocampal formation. Figure adapted from Andrews-Hanna et al. (2010b).

Table 2
Group differences in ROI-to-ROI connectivity.

	Regions	Direction	t^a	p	q	d [95% CI]
Hubs	aMPFC-PCC	–	.24	.81		.08 [–.66, .73]
	dMPFC					
	M^b	Controls > FHR	3.83	<.001		1.26 [.57, 1.91]
	dMPFC-ITPJ	Controls > FHR	2.38	.02	.03	.79 [.02, 1.50]
	dMPFC-LTC	Controls > FHR	3.32	.002	.01	1.09 [.34, 1.84]
	dMPFC-TempP	–	1.19	.24	.24	.39 [–.34, 1.10]
	ITPJ-LTC	Controls > FHR	2.84	.007	.02	.94 [.14, 1.75]
	ITPJ-TempP	–	1.49	.14	.17	.49 [–.21, 1.13]
MTL	LTC-TempP	Controls > FHR	2.54	.02	.03	.84 [.16, 1.52]
	M^b	–	.75	.46		.25 [–.50, .95]
	vMPFC-pIPL	–	.44	.66	.74	.14 [–.52, .76]
	vMPFC-Rsp	–	1.10	.28	.40	.36 [–.39, 1.08]
	vMPFC-PHC	–	1.58	.12	.40	.52 [–.25, 1.24]
	vMPFC-HF	–	1.17	.25	.40	.39 [–.30, 1.09]
	pIPL-Rsp	–	1.51	.14	.40	.50 [–.25, 1.24]
	pIPL-PHC	–	1.44	.16	.40	.48 [–.18, 1.18]
	pIPL-HF	–	1.36	.18	.40	.45 [–.25, 1.04]
	Rsp-PHC	–	.58	.56	.71	.19 [–.51, .84]
	Rsp-HF	–	.19	.85	.85	.06 [–.67, .76]
	PHC-HF	–	1.26	.22	.40	.41 [–.24, 1.12]

Note. aMPFC = anterior medial prefrontal cortex, PCC = posterior cingulate cortex, dMPFC = dorsal medial prefrontal cortex, ITPJ = left temporo-parietal junction, LTC = lateral temporal cortex, TempP = temporal pole, vMPFC = ventral medial prefrontal cortex, pIPL = posterior inferior parietal lobule, Rsp = retrosplenial cortex, PHC = parahippocampal cortex, HF = hippocampal formation.

^a $df = 35$.

^b Mean correlation between all ROI-to-ROI pairs within the respective subsystem.

subsystem, which was a very large effect (Table 2, Fig. 2). No group differences were observed in average functional connectivity between the DMN hubs or within the MTL subsystem.

Next, we investigated whether particular regions drove the subsystem-level effects described above. To address this question, we examined ROI-to-ROI correlations between individual regions within each subsystem. In the dMPFC subsystem, compared to controls, FHR exhibited significantly reduced connectivity in the following ROI pairs: dMPFC-ITPJ, dMPFC-LTC, ITPJ-LTC, and LTC-TempP (Table 2, Fig. 2). These effects were large, ranging from .79 to 1.09. No group differences emerged between any ROI-to-ROI correlation in the MTL subsystem.

Nine individuals in the FHR group had a lifetime diagnosis of major depressive disorder (MDD). In order to rule out the possibility that group differences were being driven by mood pathology in the FHR group, we conducted follow-up analyses excluding these individuals. Between-group differences in functional connectivity were largely unchanged (Supplementary Table 1). However, greater connectivity between dMPFC-ITPJ and ITPJ-LTC in controls versus FHR were reduced to trend levels of statistical significance ($q = .06$). Notably, the effect sizes for these differences remained large ($d > .8$).

We additionally examined whether lifetime psychoactive medication use contributed to the group differences by re-running these analyses excluding participants from both groups with such history. None of the findings were changed (Supplementary Table 2).

3.2. Relationship between functional connectivity and the social variables

We hypothesized that connectivity between regions of the dMPFC subsystem would be related to the social variables across all participants. Consistent with this hypothesis, ITPJ-LTC connectivity was negatively associated with SAS score, such that greater connectivity predicted less social impairment (Table 3, Fig. 3). Additionally, dMPFC-TempP connectivity positively predicted IRI-PT and IRI-FS, and LTC-TempP connectivity positively predicted IRI-PD. These relationships were not different between FHR and controls (Supplementary Table 3). Supplementary Table 4 depicts the results from all models.

To evaluate whether the presence of lifetime MDD in the FHR group contributed to these relationships, we conducted follow-up analyses excluding FHR individuals with a lifetime MDD diagnosis from the regression models. All models remained statistically significant except for the relationship between dMPFC-TempP connectivity and IRI-PT, which was reduced to a trend level of significance ($p = .096$) (Supplementary Table 5).

To evaluate the possibility that greater connectivity between regions of the dMPFC subsystem positively predicted any cognitive outcome, and not just social variables, we evaluated the relationship between ROI-to-ROI connectivity and IQ. No associations reached statistical significance ($ps > .15$).

4. Discussion

In the current study, we find that functional connectivity within the dMPFC subsystem of the DMN may be associated with familial risk for schizophrenia. Furthermore, connectivity between certain regions of the dMPFC subsystem may be associated with social functioning and aspects of empathy/perspective-taking. These data add to an increasing body of literature demonstrating aberrant patterns of DMN connectivity in schizophrenia and unaffected first-degree relatives, and provides novel evidence that connectivity between certain regions of the DMN may carry consequences for social behavior in FHR and non-FHR individuals.

Our finding of reduced dMPFC, but not MTL subsystem connectivity replicates findings with first-episode psychosis patients (Alonso-Solis et al., 2012), suggesting specificity in the DMN regions affected by psychosis and familial risk status. This subsystem-level effect, which was large in magnitude, was driven by reduced FHR connectivity between dMPFC-ITPJ, dMPFC-LTC, ITPJ-LTC, and LTC-TempP. These

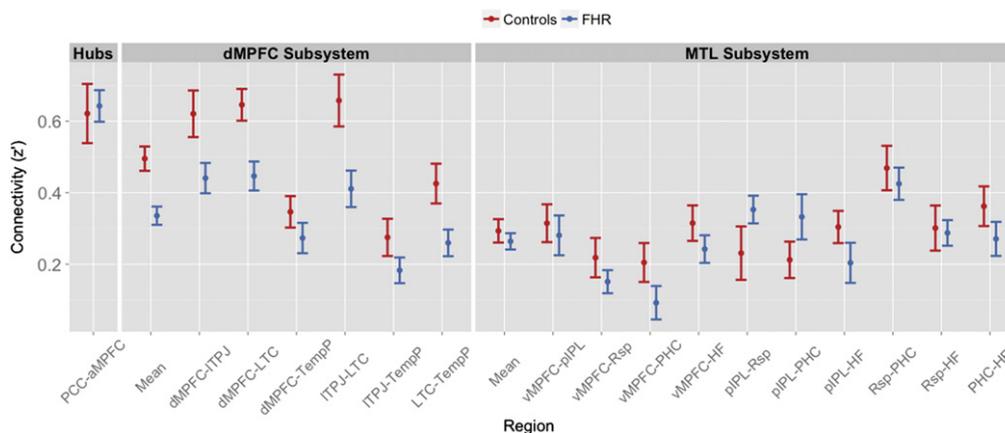


Fig. 2. Functional connectivity (Fisher's r -to- z transformed values) between the DMN hubs, and regions of the dMPFC and MTL subsystem. Error bars depict standard error of the mean. Between-group difference statistics are displayed in Table 2.

Table 3
Functional connectivity in regions of the dMPFC subsystem predicts social functioning and empathy/perspective-taking.

ROI-to-ROI correlation predicting (→) Social variable	R ² [95% CI]	b [95% CI]	t	p
ITPJ-LTC → SAS	.159 [.021, .364]	−11.44 [−20.21, −4.46]	2.50	.018
dMPFC-TempP → IRI-PT	.126 [.004, .390]	7.86 [.09, 13.36]	2.18	.036
dMPFC-TempP → IRI-FS	.152 [.002, .451]	11.15 [.34, 21.53]	2.43	.021
LTC-TempP → IRI-PD	.150 [.007, .366]	9.72 [2.66, 17.68]	2.41	.022

Note. ITPJ = left temporo-parietal junction, LTC = lateral temporal cortex, dMPFC = dorsal medial prefrontal cortex, TempP = temporal pole, SAS = Social Adjustment Scale – Self-Report, IRI-PT = Perspective-Taking, IRI-FS = Fantasy Scale, IRI-PD = Personal Distress.

specific ROI-to-ROI findings are also consistent with functional and structural connectivity studies demonstrating reduced frontal-temporal connections across schizophrenia patients, FHR, and individuals at clinical high-risk for the illness (Pettersson-Yeo et al., 2011). When excluding FHR individuals with a lifetime diagnosis of MDD, the difference between FHR and controls in dMPFC-ITPJ and ITPJ-LTC connectivity was reduced to a trend level of significance ($q = .06$); however, all other differences were unchanged, and the effect sizes remained large. This suggests that reduced dMPFC subsystem connectivity in the FHR group is largely independent of mood pathology. Follow-up analyses also demonstrated that the group differences in functional connectivity could not be attributed to lifetime psychoactive medication use.

The dMPFC subsystem exhibits substantial overlap with the network of brain regions recruited when attributing and reasoning about the mental states of oneself and others (Mitchell, 2006; Schilbach et al., 2008, 2012; Andrews-Hanna, 2012; Mars et al., 2012). This suggests an important role for the dMPFC subsystem in social cognitive processes

and associated social behavior. Consistent with this idea, we found that across all participants, the extent of ITPJ-LTC connectivity predicted scores on our measure of social functioning, such that greater connectivity was associated with less social impairment. Greater dMPFC-TempP connectivity was associated with more empathic concern and the tendency to be transported into the mental life of fictional characters. Lastly, greater LTC-TempP connectivity predicted greater experience of discomfort in highly emotional situations. None of these relationships were different between FHR and control individuals. Furthermore, except for the relationship between IRI-PT and dMPFC-TempP connectivity, which was reduced to a trend level of significance, all other relationships were unchanged when excluding FHR individuals with a lifetime MDD diagnosis. This suggests that the brain-behavior relationships observed here were not driven by mood pathology in the FHR group. Regarding the function of the dMPFC subsystem, one possibility is that increased connectivity is related to positive cognitive outcomes in general. However, connectivity within this subsystem only predicted the social variables, and not IQ suggesting that this subsystem may specifically

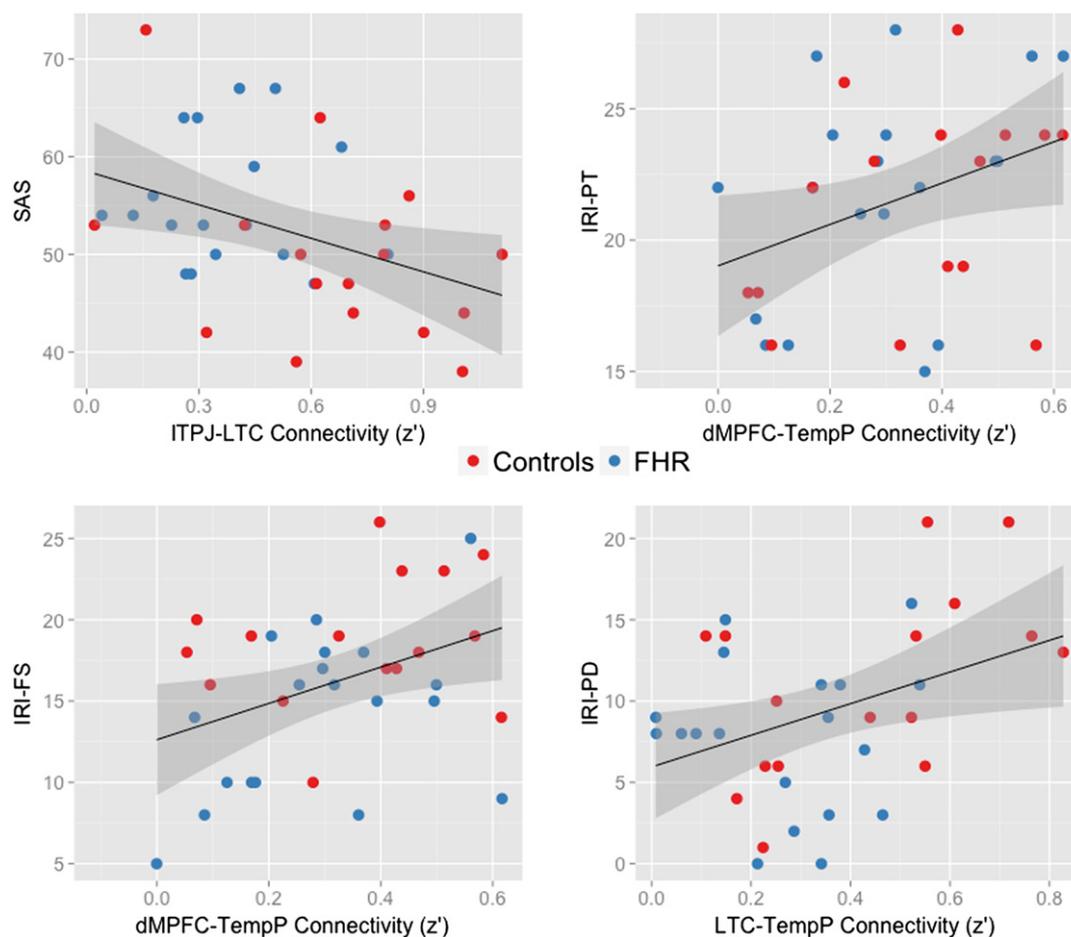


Fig. 3. Functional connectivity predicts social functioning (SAS = Social Adjustment Scale – Self-Report; higher scores denote greater social impairment) and aspects of empathy/perspective-taking (IRI-PT = Perspective-Taking, IRI-FS = Fantasy Scale, IRI-PD = Personal Distress). Shaded area represents 95% CI.

support social cognitive processes and behavior. Collectively, these findings suggest that the functional coherence of the dMPFC subsystem carries important, measurable consequences for self-reported social functioning and empathy/perspective-taking in at-risk states and in health.

These findings are of particular interest when considered alongside the large body of work demonstrating a relationship between behavioral and neural measures of ToM and social impairment in schizophrenia and FHR (Couture et al., 2006; Fett et al., 2011; Hooker et al., 2011; Dodell-Feder et al., 2014, in press). Taken with our findings, it is possible that in FHR, genetically conferred disruption to the connections within the dMPFC subsystem contributes to ToM impairment, which results in difficulty inferring the beliefs and emotions of others. This in turn may lead to misattribution of intentions, increased interpersonal conflict and stress, social withdrawal and isolation, compromised social networks and support, and other social difficulties that are characteristic of FHR, predictive of later schizophrenia diagnoses (Tarbox and Pogue-Geile, 2008; Matheson et al., 2013), and precipitate and exacerbate psychotic symptoms (Horan et al., 2006; Hooley, 2007; Velthorst and Meijer, 2012). In FHR, such a pathway could be interpreted within a “double-vulnerability” or “two-hit” (Tsuji et al., 2013) framework of illness risk and progression. Genetically conferred social impairment, via disruption to the neural mechanisms and neurocognitive processes supporting social behavior may indicate an initial vulnerability. Social impairment itself may represent a second vulnerability in the sense that it fosters an environment amenable to illness progression characterized by increased stress and depleted social support. Given findings of aberrant DMN connectivity and social impairment in multiple disorders (Lynch et al., 2013; Redcay et al., 2013), it is likely that such a pathway would not be specific to FHR and schizophrenia, and may represent a transdiagnostic mechanism connecting genetic risk to social impairment and illness progression. Of course, given that the data here are cross-sectional and cannot speak to a causal mechanism, this account is highly speculative. A direct test of such a mechanism would be very informative for neurodevelopmental models of psychopathology.

Central to this account is uncovering precisely what hypoconnectivity within the DMN means for social cognitive processes. For example, if social cognition best characterizes the default state of the human brain (Mitchell, 2006), does less connectivity mean that individuals are somehow less primed and ready for or attuned to social inference and interaction? (Mitchell, 2006; Schilbach et al., 2008) Addressing this question with additional research will provide vital information regarding the nature of social difficulties in psychopathology and their pathophysiological mechanisms.

Several limitations are noteworthy. FHR differed from controls on many of the brain and social variables, which may have led to a clustering of data points by group, and inflated regression estimates of the brain-behavior relationships. With that said, we found at least one relationship – dMPFC–TempP connectivity predicting IRI-PT – in which neither variable differed between groups. Additionally, while we show here that connectivity captures a significant portion of the variance in our social measures (between 12.6 and 15.9%), much of the variance in social behavior remains unexplained. A more thorough account of social functioning in schizophrenia and FHR would need to incorporate additional factors. Furthermore, our measures of social behavior were all self-report making them subject to self-perception biases. Future work should test these relationships with more objective measures that better assess day-to-day social behavior. Regarding our sample, a large percentage of FHR individuals met criteria for MDD. Although this may be expected given that FHR individuals carry greater risk for psychiatric morbidity (Erlenmeyer-Kimling et al., 1997; Kendler and Gardner, 1997; Chang et al., 2002; Keshavan et al., 2004), mood pathology may confound group differences in connectivity or the connectivity–social variable relationships. With that said, exclusion of these individuals from follow-up analyses left the main findings largely unchanged. Lastly, a relatively small number of participants were tested

in the current study. Although *n*'s of 15 or greater should be adequate to detect group differences when there exist strong a priori hypotheses and large effect sizes (Carter et al., 2008), as in the current study, these findings should be treated as preliminary and replicated with larger samples and additional measures of social functioning of the type described above.

In summary, we find that reduced connectivity within the dMPFC subsystem of the DMN may be associated with familial risk for schizophrenia and aspects of social behavior. Together, these data point towards aberrant connectivity within the DMN as a marker of risk for schizophrenia, a contributing factor related to social impairment, and a potential target for early intervention.

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Contributors

D. Dodell-Feder designed the study, collected and analyzed the data, and wrote the first draft of the manuscript. C. I. Hooker designed the study, supervised collection and analysis of the data, and assisted in manuscript composition. L. E. DeLisi created the recruitment infrastructure and provided feedback on the design, analyses, and manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.schres.2014.03.031>.

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