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Research article

Religious and spiritual importance moderate relation between default mode network connectivity and familial risk for depression

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HIGHLIGHTS

- High risk status for depression has been associated with increased default mode network (DMN) connectivity in this sample. Belief in the importance of religion/spirituality, however, was associated with lower DMN connectivity in the same sample.
- Adopting religion/spirituality as personally important may represent adaptive neural effects in the default mode network, and may be associated with resilience endophenotypes in persons at high risk for depression.
- The potentially protective effect of religious/spiritual importance on risk for depression was restricted to connectivity within the default mode network (DMN) and was not observed within central executive network (CEN) circuitry. This has implications for meditation-based therapies of depression that appear to rely on inverse DMN-CEN connectivity, as well.

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ABSTRACT

Individuals at high risk for depression have increased default mode network (DMN) connectivity, as well as reduced inverse connectivity between the DMN and the central executive network (CEN) [8]. Other studies have indicated that the belief in the importance of religion/spirituality (R/S) is protective against depression in high risk individuals [5]. Given these findings, we hypothesized that R/S importance would moderate DMN connectivity, potentially reducing DMN connectivity or increasing DMN-CEN inverse connectivity in individuals at high risk for depression. Using resting-state functional connectivity MRI (rs-fcMRI) in a sample of 104 individuals (aged 11–60) at high and low risk for familial depression, we previously reported increased DMN connectivity and reduced DMN-CEN inverse connectivity in high risk individuals. Here, we found that this effect was moderated by self-report measures of R/S importance. Greater R/S importance in the high risk group was associated with decreased DMN connectivity. These results may represent a protective neural adaptation in the DMN of individuals at high risk for depression, and may have implications for other meditation-based therapies for depression.

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1. Religious and spiritual importance moderate relation between default mode network connectivity and familial risk for depression

Increased functional connectivity within the default mode network (DMN), as well as reduced inverse connectivity between the DMN and the central executive network (CEN), has been associated with major depressive disorder (MDD). Recent studies suggest that contemplative practices (e.g., mindfulness meditation) may counter these effects by reducing DMN connectivity and increasing DMN-CEN inverse connectivity [1–3]. Similar effects have been reported with antidepressant medication [4]. Unknown, however, is whether connectivity changes emerge from contemplative practices themselves, or are also demonstrable in individuals who place high importance on religion/spirituality (R/S), irrespective of their contemplative practice(s). The influence of R/S has scarcely been examined on biological markers thought to index risk for MDD.

Employing resting-state functional connectivity MRI (rs-fcMRI), we recently reported that individuals at high familial risk for depression have increased DMN connectivity and reduced inverse DMN-CEN connectivity. This suggests that this pattern of altered

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connectivity may represent a risk marker for the development of MDD. Moreover, we have previously shown that belief in the high importance of R/S is protective against MDD recurrence [5] and is associated with biological markers of resilience, including thicker cortices [6] and greater EEG alpha [7]. Using the same cohort, we now examined the influence of self-report ratings of R/S importance on DMN connectivity. Given our previous findings, we hypothesized that R/S importance would moderate the relation between (i) DMN connectivity and (ii) familial risk for depression.

2. Material and methods

Following procedures detailed in Posner et al. [8], participants (N = 104) aged 11–60 years were drawn from Weissman et al.'s [9,10] 3-generation, longitudinal study comprising families at high and low risk for MDD. Risk status was defined by MDD status in the probands from Generation 1 (G1). That is, the offspring and grandchildren in Generations 2 and 3 (G2 and G3) were considered high risk if G1 was diagnosed with MDD, otherwise they were considered low risk. The present study collected data from G2 and G3. Diagnostic interviews were conducted using the Schedule for Affective Disorders and Schizophrenia-Lifetime (SAD-L) [11]. Participants also completed the Parental Bonding Instrument (PBI) [26], which assesses care, overprotection, and affectionless control in parental behavior.

Details on image processing are described in Posner et al. [8]. Briefly, we obtained MRI scans from 111 descendants of G1 families, ages 11–60. MRI scans from 7 individuals were excluded because of excessive head motion and/or imaging artifacts, leaving 104 individuals available for group comparisons. Of these, 57 participants comprised the high-risk group, and 47 the low-risk group. Participants were group-matched on sex and age. Images were acquired on a GE Signa 3.0T whole body scanner using an 8-channel head coil. During resting state acquisition, participants were instructed to remain still with their eyes closed and to let their minds wander freely. Two 9-min resting state scans were obtained for each participant (http://www.fil.ion.ucl.ac.uk/spm/). Functional images were slice time and motion corrected, coregistered with a high-resolution anatomical scan, normalized to Montreal Neurological Institute (MNI) space, resampled at 3 mm^3, and smoothed with a Gaussian kernel of 8 mm^3 FWHM [12]. Connectivity processing consisted of independent component analysis (ICA) and a hierarchical partner matching algorithm [13] to isolate a network of regions corresponding to the DMN. Partner matching is a clustering algorithm that identifies ICA-derived independent components that share spatial properties across subjects [14]. Head motion during scanning was quantified by root mean square (RMS) and peak/average (across volumes) framewise displacement (FD) [15]. Head motion was minimal in both groups (mean FD in high-risk group = 0.10 ± 0.05 mm; mean FD in low-risk group = 0.08 ± 0.03 mm; RMS in high-risk group = 0.54 ± 0.54 mm; RMS in low-risk group = 0.51 ± 0.20 mm) and there were no group differences in the head motion parameters (p's > 0.1). Head motion parameters were included as covariates in group-level analyses.

Brain regions in which DMN connectivity differed significantly between the high relative to low familial risk groups were identified in Posner et al. [8]. Specifically, increased DMN connectivity was observed in the left lateral parietal lobe and the precuneus in the high relative to low risk group. Further, compared with the low risk group, the high risk group showed decreased DMN-CEN inverse connectivity in the anterior portion of the dorsolateral prefrontal cortex (DLPFC) bilaterally. We examined associations between these four regions and participants' ratings on an item from the SAD-L: *How important to you is religion or spirituality?* This self-report rating was obtained at the same time as the MRI data and was treated as a binary variable [5,16].

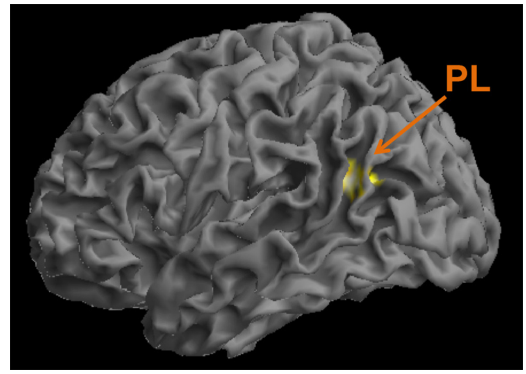

Fig. 1. As previously shown Posner et al. [8], individuals at high familial risk for depression had increased default mode network (DMN) connectivity within the inferior portion of the left parietal lobe (PL). This same region showed decreased DMN connectivity in high-risk individuals who reported religious/spiritual (R/S) as personally important.

For each region, we extracted the connection strength (z-score) using the SPM eigenvariate function with a 5 mm radius sphere centered at the peak voxel. Planned comparisons using linear regression models with generalized estimation equations (GEE) [17] were then run to adjust for possible non-independence of observations due to potential correlation of sibling outcomes. The dependent variable was connection strength in previously implicated brain regions – precuneus, left lateral parietal lobe, and the DLPFC bilaterally; the independent variables were family history of MDD, R/S importance, and the interaction of family history and R/S. Effects controlled for age, gender, history of depression, anxiety, or substance abuse, present depressive or anxiety symptoms, in-scanner head motion, frequency of religious attendance.

3. Results

We found a significant association between greater R/S importance and decreased DMN connectivity in the left lateral parietal lobe (Wald $\chi^2(1) = 5.16$, $p = 0.02$; Fig. 1). This effect was mostly driven by an interaction between R/S importance and familial MDD risk status (Wald $\chi^2(1) = 7.80$, $p = 0.005$). That is, high R/S ratings were associated with decreased DMN connectivity in the group at high familial risk for MDD, but not in the low-risk group (see Fig. 2). No moderating effects were observed in the other DMN region, the precuneus (R/S importance: Wald $\chi^2(1) = .14\,0.14$, $p = 0.71$; familial risk: Wald $\chi^2(1) = 0.33$, $p = 0.56$; R/S importance*familial risk: Wald $\chi^2(1) = 0.72$, $p = 0.40$).

Further, no association between R/S importance and familial risk for MDD was observed in the CEN regions: Right DLPFC (R/S importance: Wald $\chi^2(1) = 0.75$, $p = 0.39$; familial risk: Wald $\chi^2(1) = 0.10$, $p = 0.75$; R/S importance*familial risk: Wald $\chi^2(1) = 0.30$, $p = 0.59$) and Left DLPFC (R/S importance: Wald $\chi^2(1) = 0.07$, $p = 0.80$; familial risk: Wald $\chi^2(1) = 0.09$, $p = 0.77$; R/S importance*familial risk: Wald $\chi^2(1) = 0.10$, $p = 0.75$), respectively.

4. Supplemental analyses

We ran additional analyses to explore potential confounds including developmental stage, parental behavior, and R/S importance as a continuous rather than a binary variable. These did not meaningfully affect our results. For more details, please see the Supplemental Materials.