



Medial temporal lobe default mode functioning and hippocampal structure as vulnerability indicators for schizophrenia: A MRI study of non-psychotic adolescent first-degree relatives ☆☆☆



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ABSTRACT

Background: Clues to the etiology and pathophysiology of schizophrenia can be examined in their first-degree relatives because they are genetically related to an ill family member, and have few confounds like medications. Brain abnormalities observed in young relatives are neurobiological indicators of vulnerability to illness. We examined the hypothesis that the hippocampus and parahippocampus are structurally abnormal and are related to default mode network (DMN) function and cognitive abnormalities in relatives of probands.

Methods: Subjects were 27 non-psychotic, first-degree relatives of individuals diagnosed with schizophrenia, and 48 normal controls, ages 13 to 28, undergoing high-resolution magnetic resonance imaging (MRI) at 1.5 T. After structural scan acquisition a subset of subjects performed 2-back working memory (WM) and 0-back tasks during functional MRI (fMRI) alternating with rest. fMRI data were analyzed using SPM-8. Volumes of total cerebrum, hippocampus, and parahippocampal gyrus were measured using semi-automated morphometry.

Results: Compared to controls, relatives had significantly smaller left hippocampi, without volumetric reduction in the parahippocampus. Relatives showed significantly less suppression of DMN activity in the left parahippocampal gyrus. Left hippocampal and posterior parahippocampal volumes were inversely and significantly associated with DMN processing (smaller volumes, less suppression) in relatives. Task suppression in parahippocampal gyrus significantly correlated with WM performance within the relatives.

Conclusion: Results support the hypothesis that the vulnerability to schizophrenia includes smaller hippocampi and DMN suppression deficits, and these are associated with poorer WM. Findings suggest a primary structural, neurodevelopmental, medial temporal lobe abnormality associated with altered DMN function independent of psychosis.

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1. Introduction

Kraepelin (1919) and Bleuler (1911) originally hypothesized schizophrenia to be a brain disorder, with substantial evidence confirming this now widely accepted idea (Shenton et al., 2001; Harrison, 2004). Within the context of widespread brain abnormalities, structural alterations of the medial temporal lobe (MTL), especially the hippocampus, are among the most robust findings in schizophrenia (Tamminga et al., 2010). In neurodevelopmental models of schizophrenia, structural alterations of the MTL have been prominent. For example, in an animal model of perinatal excitotoxic damage to the ventral hippocampus applied early in life, rats behave essentially normally until puberty when they develop hyperdopaminergic behaviors (Lipska and Weinberger, 1993). Murray et al. (2004) hypothesized that “on a background of shared genetic predisposition to psychosis, schizophrenia, but not bipolar disorder, is subject to additional genes or early insults, which impair neurodevelopment, especially of the medial temporal lobe” (p. 405) (Fig. 1).

The MTL consists of the amygdala, hippocampus, including the cornu ammonis 1–4 (CA1–4), dentate gyrus, fimbria and subiculum, and the surrounding perirhinal, entorhinal and parahippocampal cortices. Our focus is on the hippocampus proper and the parahippocampal gyrus, with the hypothesis that these regions are affected early in development in individuals who develop schizophrenia and that abnormalities can be observed in close relatives because they are genetically related to an ill family member (Seidman et al., 1997, 2002).

The hippocampus and parahippocampus play a central role in declarative memory (Squire and Zola-Morgan, 1991), and more recently have been shown to be involved in working memory (WM) (Ranganath and D'Esposito, 2001; Nichols et al., 2006). Interestingly, this region also is one of the core regions of the default mode network (DMN) in healthy subjects (Vincent et al., 2006; Buckner et al., 2008; Kahn et al., 2008; Greicius et al., 2009) and patients with schizophrenia (Kumari et al., 2010). The DMN comprises regions more active during rest than during various cognitive tasks (Buckner et al., 2009). The MTL is involved in the DMN for both task-induced deactivation analyses as well as functional connectivity analyses (Vincent et al., 2006; Kahn et al., 2008; Buckner et al., 2008, 2009). Moreover, multiple DMN regions are functionally correlated with the hippocampus, further supporting the premise that the MTL is included in the network.

Many investigators have pursued the hypothesis that the hippocampus is abnormal in the first degree relatives of individuals with schizophrenia, expressed in declarative memory deficits (Faraone et al., 1995; Cirillo and Seidman, 2003), smaller brain volumes (Seidman et al., 1997, 1999, 2002, 2003) and functional brain dysfunction (Thermenos et al.,

2007). In meta-analyses of relatives of individuals with schizophrenia, verbal declarative memory (Cirillo and Seidman, 2003; Trandafir et al., 2006; Agnew-Blais and Seidman, 2013) and hippocampal volume (Boos et al., 2007) are among the most robust deficits, supporting the hypothesis. While most of these studies focused on adult relatives who had passed through the age of risk for schizophrenia (Boos et al., 2007), recent studies of younger relatives under the age of 30 have shown similar findings (Agnew-Blais and Seidman, 2013; Thermenos et al., 2013) suggesting the alterations are present in childhood.

The neuroimaging studies of younger relatives under the age of 30 consistently identify MTL alterations compared to controls (cf. review by Thermenos et al., 2013) with few negative findings (Karnik-Henry et al., 2012). Early studies demonstrated a smaller “amygdala–hippocampal complex” in youth at familial high-risk (FHR), in which the amygdala and hippocampus were not separated due to existing limitations of anatomical resolution and segmentation procedures (Keshavan et al., 1997, 2002; Schreiber et al., 1999; Lawrie et al., 2001). More recent studies have demonstrated smaller hippocampal volumes (Ho and Magnotta, 2010; Sismanlar et al., 2010; Francis et al., 2013) alterations in hippocampal white matter (Hao et al., 2009), right-left asymmetry (Qiu et al., 2009), and shape (Ho and Magnotta, 2010) in nonpsychotic relatives under the age of 30. Thus, the hippocampus proper is abnormal in young individuals at FHR, consistent with results observed in older relatives. The parahippocampal gyrus (PHG) has been studied less frequently and the only published study of PHG in young relatives has shown thinner cortex in nonpsychotic relatives than in controls (Karnik-Henry et al., 2012). We had found smaller PHG volume in older relatives (Seidman et al., 2003).

An important question regarding the risk for schizophrenia as expressed in nonpsychotic young relatives is whether DMN functioning is altered in the MTL, and whether this abnormality is associated with MTL volume abnormalities. In our previous work (Whitfield-Gabrieli et al., 2009), we observed that patients with schizophrenia in their first psychotic episode and young nonpsychotic relatives exhibited significantly reduced task-related suppression in medial prefrontal cortex (MPFC) in relation to a two-back WM task. Increased task-related MPFC suppression correlated with better WM performance in patients and relatives and with less psychopathology. During WM task performance, patients and relatives had greater activation in right dorsolateral prefrontal cortex (DLPFC) than controls. During rest and task, patients and relatives exhibited abnormally high functional connectivity within the DMN that correlated with psychopathology. Further, during both rest and task, patients exhibited reduced anticorrelations between MPFC and DLPFC, a region that was hyperactivated by patients and relatives during WM performance. Among patients, the magnitude of MPFC task suppression negatively correlated with default connectivity, suggesting an association between the hyperactivation and hyperconnectivity in schizophrenia. However, in that paper we did not address the role of the MTL in DMN.

Surprisingly, there is very limited published research on the relationship between brain structure and DMN function, and even less in schizophrenia. Harms et al. (2013) studied patients with schizophrenia and their relatives and examined relationships between brain volumes and brain activity during a 2-back task, finding that reduced hippocampal volume was associated with reduced activity in regions subserving WM (the dorsal anterior cingulate cortex and left inferior frontal gyrus). However, they did not examine DMN function in relation to structure in that study. To our knowledge, there are no studies of MTL gray matter volume abnormalities and DMN functioning, no studies of DMN function in MTL in relatives of persons with schizophrenia, and no studies examining the relationship of MTL structural and DMN functional alterations in nonpsychotic relatives of persons with schizophrenia.

We tested four hypotheses: 1) Hippocampal and parahippocampal volumes are smaller in non-psychotic young adult relatives than in controls; 2) DMN alterations in relatives will be observed in MTL; 3) reduced MTL volumes will be correlated with less DMN suppression in MTL in

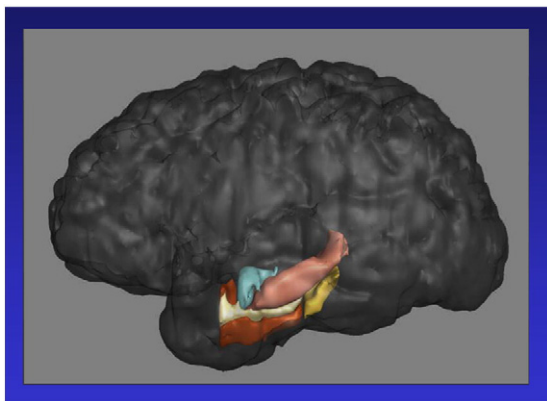


Fig. 1. Visualization of the anatomy of the medial temporal lobe of the left hemisphere: This depicts a segmented medial temporal lobe (in which the lateral surface of the left temporal lobe is stripped away) including the amygdala (blue), hippocampus (brown), anterior parahippocampus (dark brown), posterior parahippocampus (gold), and white matter/performant path (white).

relatives; and 4) failure to suppress DMN processing in MTL will be associated with worse WM performance.

2. Methods

2.1. Subjects

Subjects were 27 FHR offspring and siblings of persons with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, depressed type, and 48 children of healthy adults with no family history of psychosis, selected to be comparable on age, sex, parental socio-economic status (SES), ethnicity and handedness, recruited as part of the Harvard Adolescent Family Risk Study (Seidman et al., 2006a). In previous papers, we reported on results related to prefrontal volumes in these same subject samples (Rosso et al., 2010) and WM in a subset of these subjects with fMRI (Seidman et al., 2006b; Whitfield-Gabrieli et al., 2009; Seidman et al., 2012). Hippocampal and parahippocampal structural and DMN data in those regions have not been previously reported from this study. Here we also report fMRI DMN data in a subset of those who had structural data ($n = 17$ FHR, 19 controls).

Participants were excluded if they had any lifetime history of psychotic illness, substance dependence, neurological disease, head injury or medical illness with demonstrated cognitive sequelae, sensory impairments, or a full-scale IQ estimate less than 70. Control subjects had an additional exclusion criterion of any first-degree biological relative with lifetime history of psychotic disorder. Participants were not receiving psychotropic medications at the time of assessments.

After probands gave consent, their children and siblings (ages 13–25) were contacted to participate as study subjects. The study was approved by human research committees at the Massachusetts Mental Health Center, Massachusetts General Hospital (MGH), and Harvard University. Subjects 18 years and older gave written informed consent. For subjects younger than 18, legal guardians gave informed consent and the child gave assent. Subjects received payment for their participation.

2.1.1. Psychiatric assessment

Patient and control probands were administered the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) and the Family Interview for Genetic Studies (Maxwell, 1996). Relatives of probands were screened for symptoms of psychosis, substance use, and mood disturbance using the Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (Geller et al., 1994). Other selection criteria were assessed using our Neurodevelopmental Questionnaire (Faraone et al., 1995).

2.1.2. Neuropsychological testing

General intellectual ability (IQ) was prorated using eight subtests from the Wechsler Intelligence Scale for Children (Wechsler, 1991) or the Wechsler Adult Intelligence Scale (Wechsler, 1997). Handedness was measured by questionnaire (Annett, 1970).

2.2. MRI acquisition and image analysis

Whole brain MR images were collected on a Siemens 1.5 T scanner at the MGH Martinos Center (Charlestown, Massachusetts). A sagittal localizer scan was followed by a coronal T2-weighted sequence to rule out clinical neuropathology. Two sagittal 3D magnetization prepared rapid acquisition gradient echo (MP-RAGE; T1-weighted, non-selective inversion-prepared spoiled gradient echo pulse) sequences were used for morphometric analyses (TR/TE/T1/flip = 2.73 s/3.39 ms/1.0 s/7, bandwidth = 190 Hz/pixel, sampling matrix = 256×192 pixels, FOV = 256×256 mm, effective slice thickness = 1.33 mm on a 170 mm slab of 128 partitions). Whole-brain gradient echo EPI had the following parameters: 21 contiguous axial slices parallel to the anterior commissure–posterior commissure line; 5 mm, 1 mm skip, TR/TE/flip = 2000/40/90; voxel size $3.1 \times 3.1 \times 5$ mm; FOV = 200 mm.

2.2.1. fMRI: working memory and control vigilance tasks

Subjects performed two runs of a sequential letter, block-designed visual N-back WM task with blocks of rest, 0-back and 2-back trials, as previously described (Seidman et al., 2006b). In each run, three 32-second blocks of the 0-back task alternated with three 32-second blocks of the 2-back task (sixteen 200 ms trials per block, with an 1800 ms inter-stimulus interval). Each task block was preceded by a 20-second block of fixation. Hit rate and reaction times were dependent variables.

2.2.2. Approach to measurement of brain anatomy

Volumetric morphometry was undertaken by semi-automated, anatomically-guided methods identical to those employed previously for segmentation of the hippocampus (Seidman et al., 2002) and parcellation of the parahippocampal gyrus (Seidman et al., 2003) in an older, independent sample of relatives (see Fig. 2). All measurements were performed blind to group status and sociodemographic information.

2.2.3. Gray and whole brain segmentation

Structural scans were transferred to the MGH Center for Morphometric Analysis (CMA) and coded for image analysis, using Cardviews software (Filipek et al., 1989; Kennedy et al., 1989). Brain images were positionally normalized to overcome variations in head position by using a standard 3-dimensional coordinate system on each scan. This 'self-referential' system is based directly on the individual brain, and is not warped to a template. The datasets were then segmented into gray, white, and cerebrospinal fluid tissue classes using a semi-automated intensity contour algorithm for external border definition and signal intensity histogram distributions for delineation of gray-white borders (Filipek et al., 1994).

2.2.4. Cortical parcellation of the parahippocampal gyrus

The neocortex was divided into 48 parcellation units (PUs) per hemisphere (Caviness et al., 1996). The PHGs are medial, inferior, cortical structures that compose a considerable portion of the limbic system (Fig. 2 contains a schematic representation). Parcellation was performed by the second author (IMR) for 60 of the 75 subjects, after she had demonstrated excellent ($\geq .80$) interrater reliabilities with a previously trained technician who had parcellated the other 15 brains. Volumes (in ml) were calculated by multiplying the area of each PU by slice thickness, and then summing over all slices in which the PU appeared.

2.2.5. Reliability

In 16 blindly segmented brains, intraclass correlation coefficients (ICCs) were 0.93 for total cerebral volume, 0.91 for left hippocampus and 0.92 for the right hippocampus. As previously reported (Seidman et al., 2003), interrater reliability for PHa was good (0.92), as was intrarater reliability (ICC = 0.88). ICCs for PHp = 0.81. Intrarater reliability was also good for PHp (0.93).

2.2.6. Volumetric analysis

The volume of each structure was calculated by multiplying the number of voxels assigned to that structure on each slice by the slice thickness and summing across all slices in which the structure appeared. To control Type 1 error, we combined PHa and PHp for structural analyses.

2.3. Data analysis

2.3.1. Brain structure

Analyses of structural volumes used relative volumes of hippocampal and parahippocampal ROIs (absolute volume / total cerebral volume * 100) to control for scaling effects of brain size. Repeated measures analysis of covariance (ANCOVA) examined group differences in regional MTL volumes. Hippocampus and the PHG were the dependent variables using hemisphere (left, right) as a within subject repeated measure. Group (FHR, controls) and sex were entered as independent

variables and age was an a priori covariate. Significant main or interaction effects of group ($p \leq .025$, Bonferroni corrected for total hippocampus and parahippocampal volumes, and $p \leq .0125$ when including both

hemispheres separately) were followed by least square mean contrasts. If the interaction of group \times sex was not significant it was excluded from the final model. For MTL ROIs found to differ significantly between

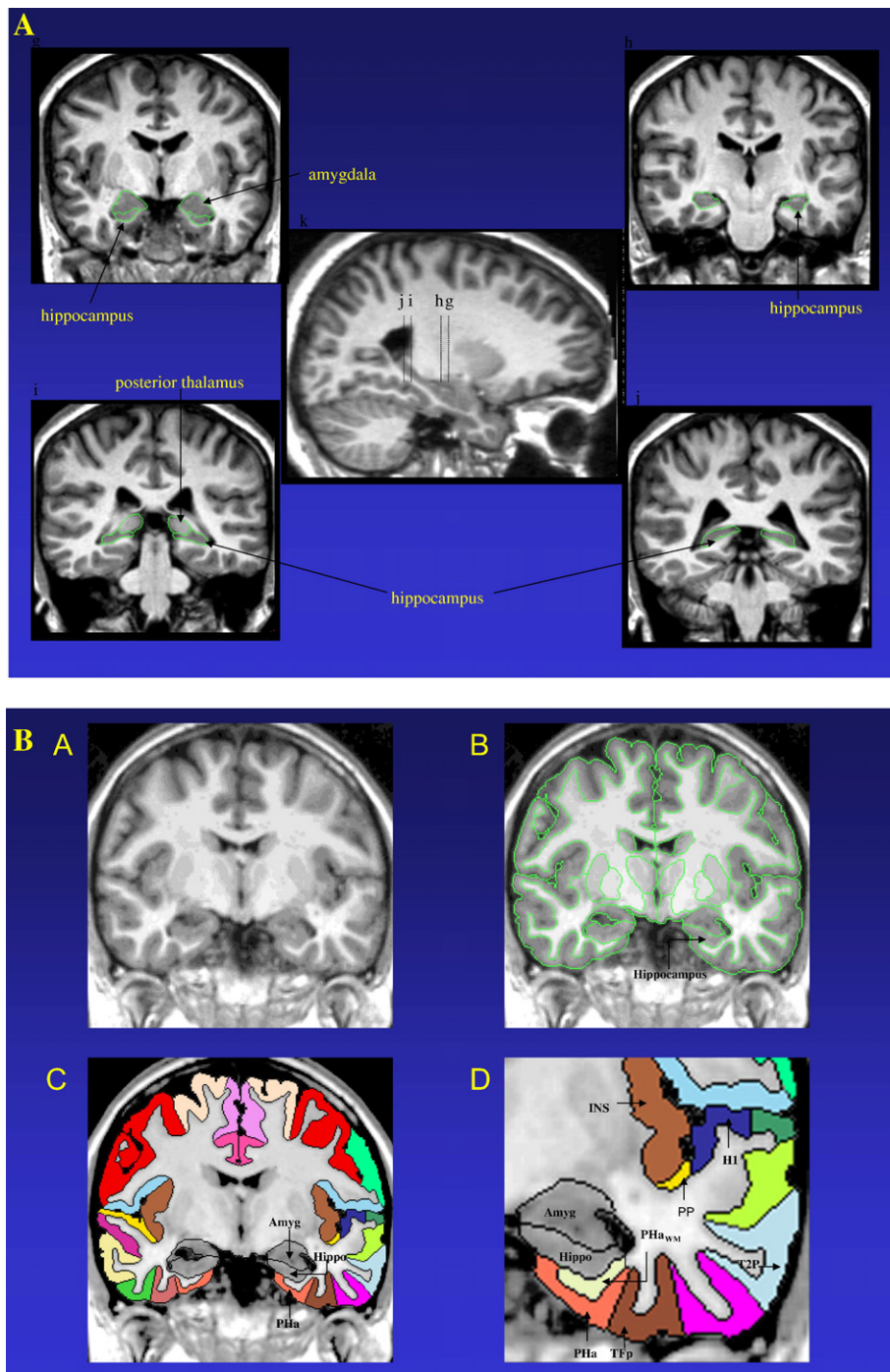


Fig. 2. A–C: A. This figure explains the method of *segmentation* of the hippocampus (observed in radiological convention), as performed in our study under the supervision of NM (fourth author). The amygdala and hippocampus are first defined as a continuous gray matter mass in the primary segmentation. Then they are manually partitioned from each other at the rostral coronal plane where hippocampus appears (see panel A for details). This includes clearly defined segments of hippocampus in ventromedial relation to the anterior tip of the ventral horn of the lateral ventricle. The caudal pole of the amygdala is present in medial and superior relation to the hippocampus in the coronal plane *Rosene and van Hoesen (1987)*. The anterior tip of hippocampus is separated from the ventral and posterior border of the amygdala. Using lateral and sagittal views, one can distinguish and trace this border of the amygdala that is usually enhanced by the anterior end of the temporal horn of the inferior lateral ventricle. In cross-reference, corresponding axial views help identify this border. In the coronal view, the sawtooth pattern of hippocampus is identified and traced. B and C. Parcellation of the parahippocampal gyrus: (52). Parts A and B show the coronal plane of an unsegmented and segmented brain, prior to carrying out cortical parcellation (C and D). The PHG comprises the PHa (anterior portion) and the PHp (posterior portion). The anterior border of the PHa is the plane that approximates the posterior end of the temporal pole. Its posterior border is the coronal plane at the level of the lateral geniculate nucleus. Its lateral border is the collateral sulcus, while medially it borders the hippocampus. The entorhinal cortex is a part of the PHa parcellation unit. The anterior border of the PHp is immediately posterior to the coronal plane that passes through the lateral geniculate nucleus (i.e., the posterior border of the PHa). Its posterior border is the coronal plane *n* at the level of the anterior-most tip of the calcarine fissure in the retrosplenial area, which approximates the zone of transition between the PHG and the lingual gyri (C). Its lateral and medial borders are the same as the PHa's. Surrounding areas of the temporal cortex parcellation units are shown in figure (D) and schematically in panel C. (see next page)

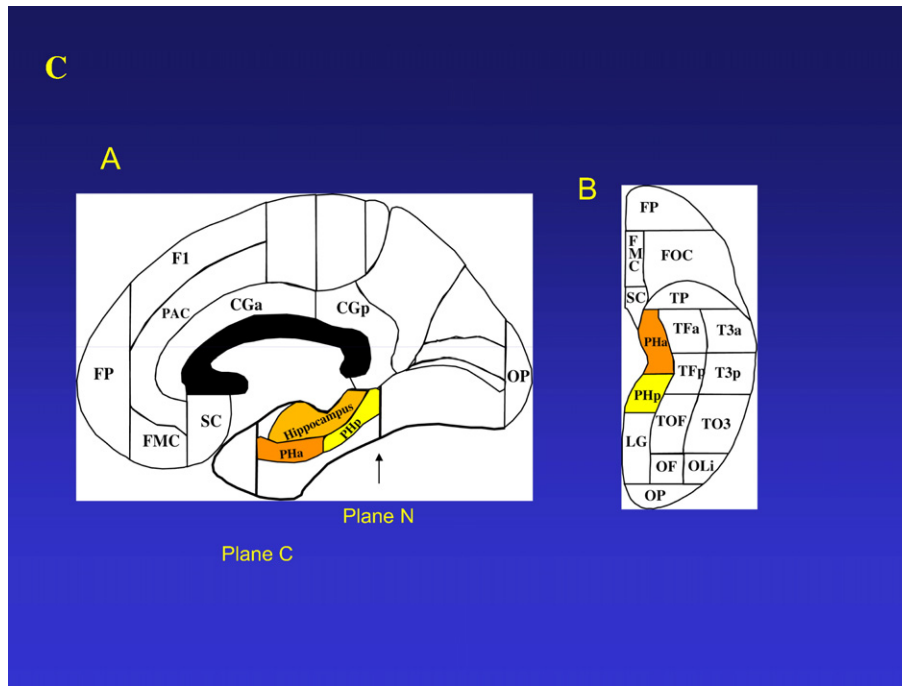


Fig. 2 (continued).

groups, mixed effect ANCOVAs evaluated the effect of adjusting the error term for familiarity; since these mixed models did not alter any findings, their results are not detailed.

2.3.2. Default mode functioning

For each participant, functional images from fMRI were realigned, normalized to the Montreal Neurological Institute template supplied with SPM-8, and smoothed with an 8-mm Gaussian kernel. Within-subject analyses used a block-based general linear model. Each block (2-back, 0-back, and rest) was modeled using a boxcar function convolved with a canonical hemodynamic response function. Estimated motion correction parameters were included as additional covariates. In order to investigate the degree of DMN task-related suppression in the MTL, we extracted the mean contrast parameter (i.e., weighted linear combinations of the parameter estimates) for the rest >2-back WM conditions in the anatomically defined MTL regions. Between-group analyses on the degree of task suppression within the MTL were performed between the controls and relatives. MTL volumes were correlated with DMN suppression within the MTL, and with WM task performance. Effect sizes were calculated by d (Cohen, 1988).

3. Results

3.1. Demographic and cognitive characteristics

Groups were comparable except for a significantly lower parental SES in the FHR group (Table 1). There were no significant differences between groups in 0 back or 2 back WM performance.

3.2. MTL volumes

Total cerebral exterior did not differ significantly by group ($p = 0.12$). In the repeated measures ANCOVA predicting hippocampus volumes, there was a significant main effect of group ($F = 6.23$, $df = 1/71$, $p = .02$) and a significant group X hemisphere interaction ($F = 6.62$, $df = 1/71$, $p = .01$), after accounting for nonsignificant contributions of sex ($F = 0.17$, $df = 1/71$, $p = .68$) and age ($F = 1.39$, $df = 1/71$, $p = .24$). When parental SES was added to the model ($F = .01$,

$df = 1$, $p < .97$), the left hippocampus remained significantly smaller in FHR participants ($F = 8.53$, $df = 1$, $p < .0047$). (See Table 2.)

In the repeated measures ANCOVA predicting PHG volumes, the main effect of group was not significant ($F = 0.26$, $df = 1/71$, $p = .61$) nor were the effects of sex ($F = 0.33$, $df = 1/71$, $p = .56$) or age ($F = 1.46$, $df = 1/71$, $p = .23$). There were no significant two-way interactions with hemisphere.

3.3. Motion in fMRI analyses

Motion related outliers in the blood oxygenation level-dependent (BOLD) intensity time series were identified using a threshold of 3 standard deviations from the mean. On average, only 1% of the trials were identified as outliers for each subject, and there was no significant difference among groups in the number of identified outliers ($p = .26$). Moreover, there were no significant between-group differences in motion parameters (p -values for all six motion parameters – XYZ translation and pitch roll and yaw rotation- were $p > .19$ or larger).

Table 1

Demographic characteristics [Mean \pm SD or N (%)] of youth at familial high-risk (FHR) for schizophrenia and control subjects.

	FHR n = 27	Controls n = 48	p
Age (years)	19.0 \pm 4.2	17.7 \pm 3.7	.15
Female	12 (44%)	28 (58%)	.25
Caucasian	14 (52%)	29 (60%)	.15
Right-handed	25 (93%)	42 (89%)	.64
Education (years)	10.7 \pm 2.7	11.1 \pm 3.3	.67
Parental SES ^a	38 \pm 26	47 \pm 15	.01
Full-scale IQ ^{b,d}	97.4 \pm 11.3	103.2 \pm 15.4	.10
2-Back accuracy (% hit rate) ^{c,d}	88.4 \pm 8.6	89.4 \pm 8.2	.70

^a SES: Socioeconomic status, assessed with the Four Factor Index (Hollingshead, 1975).

^b Full-scale IQ: Prorated from 8 subtests of the Wechsler Intelligence Scale for Children—Third Edition (WISC-III) or the Wechsler Adult Intelligence Scale—Third Edition (WAIS-III).

^c For the 2-back working memory task, n = 17 FHR, 19 controls.

^d Effect sizes, using Cohen's d was 0.42 for IQ and 0.12 for 2-back accuracy (Cohen, 1988).

3.4. DMN functioning

We found between group differences in task suppression within the MTL after covarying movement (Fig. 3A). The results for hippocampus showed a non-significant trend for reduced DMN suppression in relatives (left, $p < .06$, right, $p = .08$). Relatives had significantly less task suppression than controls in the left PHG during the 2-back WM task ($p = .03$) and a non-significant trend in the right PHG ($p < .07$). See Table 3 for effect sizes.

3.5. Brain structure–DMN relationships

Within the relatives, left hippocampal volumes significantly correlated with DMN task suppression in left hippocampus in the direction of smaller volumes, less suppression ($r = .496$, $p = .04$) (see Fig. 3B), and showed a similar trend in the right hippocampus ($r = .435$, $p = .08$). A comparable relationship was noted between left PHG volume and DMN task suppression in left PHG posterior area in the direction of smaller volumes, less suppression ($r = .493$, $p = .044$). There was a similar but non-significant trend for the right PHG ($r = .425$, $p = .089$).

3.6. Brain structure, DMN and relationship to cognition

Task suppression in the left PHG significantly correlated with 2-back WM performance within the relatives ($r = .66$, $p = .004$) (see Fig. 3C), as did the right PHG ($r = .61$, $p = .009$). The left and right PHG volume were not significantly correlated with WM accuracy (left, $r = .34$, $p = .17$; right, $r = .35$, $p = .17$).

4. Discussion

In this study, we observed a number of associations that contribute to a growing picture of altered neural substrates in nonpsychotic, unmedicated youth at FHR for schizophrenia. First, non-psychotic relatives had significantly smaller left hippocampal volumes than controls, replicating a body of research showing smaller hippocampal volumes in relatives, including our own prior study using similar morphometric analytic procedures on an older, independent sample of relatives (Seidman et al., 1997, 1999, 2002, 2003). Second, DMN alterations in relatives of individuals with schizophrenia were observed in the MTL, in the left PHG. Third, in relatives, less DMN suppression in the left

hippocampus was significantly correlated with smaller left hippocampal and left PHG volumes, for the first time demonstrating this structure–function relationship in schizophrenia risk. Fourth, reduced suppression of DMN processing in PHG was associated with significantly worse WM performance, highlighting an aspect of the functional importance of DMN activity.

These results provide support for the view that smaller hippocampal volume is among the most robust indicators (along with PFC) of brain vulnerability in those at FHR for schizophrenia, and that smaller hippocampal volumes are independent of psychosis in FHR. The association of hippocampal volume and hippocampal DMN activity indicates that the structural impairment is functionally significant (Schobel et al., 2009). The direction of the association appears to be meaningful – less gray matter volume is associated with less capacity to suppress activity in DMN functioning. However, many questions remain to be answered. For example, is the abnormality associated with life experience such as psychosocial stress (McEwen and Magarinos, 1997) or intrinsic biological factors (either genetic or acquired through pre-perinatal complications/PPCs)? In people with schizophrenia, smaller hippocampal volumes have been shown to be associated with PPCs (McNeil, 1995; Stefanis et al., 1999), and hippocampal function has been associated with genetic variations (Hall et al., 2008; Freedman and Goldowitz, 2010). An additional question is whether the alteration is also found in youth at risk for affective psychoses. To our knowledge, there are no DMN MTL studies directly comparing young relatives at risk for the major psychoses. Thus, future studies should be oriented toward questions of developmental processes, diagnostic specificity and etiology of these alterations.

We do not know when these structural alterations were first present. One causal factor implying neonatal developmental origin is the slightly elevated rates of PPCs in offspring of mothers with schizophrenia (Sacker et al., 1996; Rosso et al., 2000; Cannon et al., 2000). We also cannot rule out the possibility of later occurring alterations in developmental processes such as abnormal synaptic pruning or myelination during adolescence that could account for the abnormal hippocampus. However, consistent with the occurrence of earlier abnormal brain development, children at risk for schizophrenia show signs of neurological, cognitive and social-affective maladjustment as early as the pre-school years (Olin and Mednick, 1996), and the brain structure literature in young relatives suggests that the abnormalities are present in childhood (Thermenos et al., 2013).

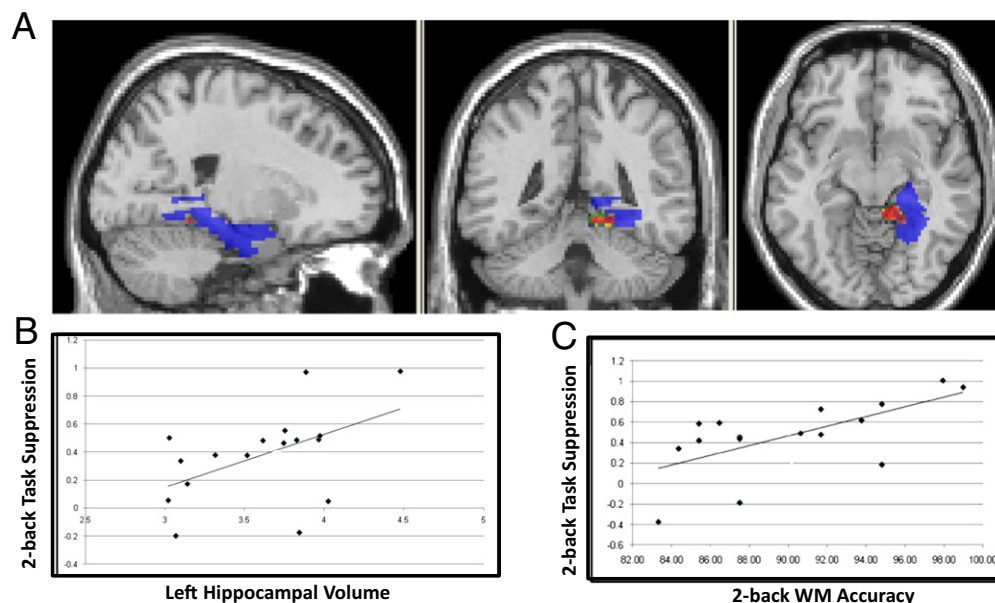


Fig. 3. Brain volumes and task suppression in default mode network.

Table 2Absolute and relative regional medial temporal lobe gray matter volumes (mm³, mean ± SD) in familial high-risk (FHR) and control participants.

	Absolute volumes		Relative volumes ^a			
	FHR n = 27	Controls n = 48	FHR n = 27	Controls n = 48	% difference ^a	Effect sizes (Cohen's <i>d</i>) ^b
Total cerebral volume	1190.9 ± 94.1	1152.6 ± 105.3	–	–	–	–
Left hippocampus	3.6 ± .45	3.8 ± .55	3.04 ± 3.32	3.31 ± 4.29	–8.2%	0.69
Right hippocampus	3.8 ± .38	3.8 ± .55	3.17 ± 2.99	3.33 ± 4.27	–4.8%	0.42
L parahippocampus	4.1 ± .74	4.0 ± .75	3.47 ± 6.88	3.47 ± 5.68	0%	0.00
R parahippocampus	4.0 ± .74	4.0 ± .77	3.37 ± 6.83	3.48 ± 5.68	–3.2%	0.18

^a Absolute volumes divided by total cerebral volume.^b *d* (Cohen, 1988) is calculated as the difference between two means (e.g., control–FHR) divided by the pooled standard deviation.

It would be premature to draw conclusions from the absence of structural abnormalities in the PHG, in part due to a limited literature. We had found morphometric abnormalities in PHG in a prior larger study of adult relatives using these methods (Seidman et al., 2003). To date, two studies of young relatives have shown excessive cortical thinning in FHR (Byun et al., 2012; Karnik-Henry et al., 2012) but there were no significant differences in parahippocampus in the one study that measured volumes.

There is evidence for specialization of functions among the brain regions that constitute the DMN. The posterior cingulate cortex is regularly activated for retrieval of autobiographical episodic memory as well as self-referential tasks (D'Argembeau et al., 2005; Buckner and Vincent, 2007; Schneider and Verbruggen, 2008). The MPFC is activated for social cognitive tasks as well as self-referential tasks (Gusnard et al., 2001; Amodio and Frith, 2006). The MTL, which is sometimes active during rest, is strongly associated with episodic memory. These dissociations raise the possibility of separable subsystems within the DMN, such as medial–prefrontal and medial–temporal lobe subsystems associated, respectively, with self-reference and memory processes within the DMN (Buckner et al., 2008; Andrews-Hanna et al., 2010).

In the healthy brain, greater suppression of the default network is associated with better memory formation (Daselaar et al., 2004), capacity to manage increased task difficulty (McKiernan et al., 2003), fewer lapses of attention (Weissman et al., 2006), better learning of a cognitive skill, and less mind wandering (Mason et al., 2007). There is evidence that cognitive load can modulate the degree of task suppression. Consistent with this, a number of authors (Tomasi et al., 2007; Esposito et al., 2006), found a load-related increase of task-related suppression of neural activity within the DMN, during WM tasks. These findings suggest that the more the regions in the DMN are suppressed, the better people can reallocate attentional resources away from internal self-referential processing toward external stimulus processing.

It is of note that the literature regarding structure–function relationships is limited, including only one paper on schizophrenia (Harms et al., 2013). Interestingly, that study involved hippocampal volumes, and WM, in controls, individuals with schizophrenia and their relatives, but did not report on the DMN. The authors showed that reduced hippocampal volume was associated with hypoactivity in WM regions (the dorsal anterior cingulate and left inferior frontal gyrus) during performance of the 2-back task. Results of Harms et al. (2013) and our study

Table 3

Functional MRI activity in default mode processing in familial high-risk (FHR) and control participants.

	Beta weights		Effect sizes
	FHR n = 17	Controls n = 19	Effect sizes (Cohen's <i>d</i>) ^a
Left hippocampus	0.328	0.610	0.57
Right hippocampus	0.267	0.499	0.55
L parahippocampus	0.397	0.646	0.75
R parahippocampus	0.541	0.752	0.53

^a *d* (Cohen, 1988) is calculated as the difference between two means (e.g., control–FHR) divided by the pooled standard deviation.

suggest that reduced hippocampal volume may be associated with both DMN hyperactivity (non-suppression) and hypoactivity in task-related (e.g., WM) networks, consistent with observed anticorrelations between activity in DMN and WM regions.

4.1. Limitations

Limitations included a small sample size, relatively wide age range for youth, scanning on a 1.5 T magnet, and a selective focus on the MTL. We hope to replicate our effects on a 3.0 T scanner in another sample in which the age range is narrower, or in which the sample size is larger. Moreover, our focus on an a priori replication approach to MTL, based on previous work with independent samples, is a strong one but focusing specifically on the degree of DMN task-related suppression in the MTL could miss important relationships between MTL structures and DMN suppression in other brain regions. We believe that this trade-off to be sound as replication using identical methods is uncommonly carried out. Nevertheless, in a future paper we plan to carry out an analysis using whole brain measurement.

4.2. Conclusions

These results provide support for the hypothesis that expressions of the liability to schizophrenia include a smaller left hippocampus and reduced DMN suppression in the left PHG as well as altered structure and function in MPFC (Whitfield-Gabrieli et al., 2009; Rosso et al., 2010). Thus, structural and functional DMN abnormalities in MTL and MPFC appear to be markers of familial vulnerability to schizophrenia, observable by the teenage years, and likely to precede the onset of psychosis.

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Contributors

Authors LJS, SVF and MTT designed the overarching study and protocol and received funding. LJS supervised all data collection and was responsible for the main hypotheses. IMR performed the majority of hippocampal segmentations and parahippocampal parcellations, and analyzed the structural data. HWT carried out most of the MRI data acquisitions, and worked on a draft of the paper. NM supervised all structural MRI measurements and contributed to the conceptual model of structural brain measurement and the writing up of the MRI structural imaging sections. RJ contributed to the functional MRI data analyses and managed the imaging database. Susan Whitfield-Gabrieli and John Gabrieli were responsible for the focus on default mode network processing, and Susan Whitfield-Gabrieli carried out all the functional MRI analyses. All authors contributed to the contents of the manuscript and approved the final manuscript.

Conflict of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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