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Medial temporal lobe structure and cognition in individuals with schizophrenia and in their non-psychotic siblings

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ABSTRACT

Medial temporal lobe (MTL) structures play a central role in episodic memory. Prior studies suggest that individuals with schizophrenia have deficits in episodic memory as well as structural abnormalities of the medial temporal lobe (MTL). While correlations have been reported between MTL volume loss and episodic memory deficits in such individuals, it is not clear whether such correlations reflect the influence of the disease state or of underlying genetic influences that might contribute to risk.

We used high resolution magnetic resonance imaging and probabilistic algorithms for image analysis to determine whether MTL structure, episodic memory performance and the relationship between the two differed among groups of 47 healthy control subjects, 50 control siblings, 39 schizophrenia subjects, and 33 siblings of schizophrenia subjects. High-dimensional large deformation brain mapping was used to obtain volume measures of the hippocampus. Cortical distance mapping was used to obtain volume and thickness measures of the parahippocampal gyrus (PHG) and its substructures: the entorhinal cortex (ERC), the perirhinal cortex (PRC), and the parahippocampal cortex (PHC). Neuropsychological data was used to establish an episodic memory domain score for each subject.

Both schizophrenia subjects and their siblings displayed abnormalities in episodic memory performance. Siblings of individuals with schizophrenia, and to a lesser extent, individuals with schizophrenia themselves, displayed abnormalities in measures of MTL structure (volume loss or cortical thinning) as compared to control groups. Further, we observed correlations between structural measures and memory performance in both schizophrenia subjects and their siblings, but not in their respective control groups. These findings suggest that disease-specific genetic factors present in both patients and their relatives may be responsible for correlated abnormalities of MTL structure and memory impairment. The observed attenuated effect of such factors on MTL structure in individuals with schizophrenia may be due to non-genetic influences related to the development and progression of the disease on global brain structure and cognitive processing.

1. Introduction

Within the medial temporal lobe (MTL), the hippocampus and parahippocampal cortex (PHC, the posterior sub-region of the parahippocampal gyrus, or PHG) play a critical role in recollection (Davachi et al., 2003; Kahn et al., 2004; Ranganath et al., 2004; Lehn et al., 2009), while the entorhinal cortex (ERC) and perirhinal cortex (PRC), are involved in semantic (Davies et al., 2004; Lee et al., 2006) and item memory (Davachi et al., 2003; Ranganath et al., 2004). These cognitive processes are involved in episodic memory, and individuals with schizophrenia have been found to show impairment in both verbal and visual/spatial episodic memory (Aleman et al., 1999 (meta-analysis); Heinrichs and Zakzanis, 1998; Saykin et al., 1991). Furthermore, the results of in vivo neuroimaging studies suggest that abnormalities in MTL structure and function are central to the pathophysiology of schizophrenia (Freedman and Goldowitz, 2010; Tamminga et al., 2010). These abnormalities include hippocampal volume reductions and shape changes (Csernansky et al., 2002; Seidman et al., 2002; Sim et al., 2006) and cortical volume loss and thinning within the PHG (Job et al., 2002; Joyal et al., 2002; Turetsky et al., 2003; Prasad et al., 2004).

To understand the etiology of these abnormalities — more specifically, whether they are due to the disease state or due to genetic

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influences that predispose to the disease state, relatives of individuals with schizophrenia have been studied. Such studies are in keeping with the goal of discovering neuroanatomical and cognitive "endophenotypes" (i.e., phenotypes related to disease-related genetic influences) (Gottesman and Gould, 2003). Some studies have reported attenuated episodic memory impairments and MTL abnormalities in the relatives of patients with schizophrenia (O'Driscoll et al., 2001; Tepest et al., 2003; van Haren et al., 2003; Sitskoorn et al., 2004; Delawalla et al., 2006; Ho and Magnotta, 2010), which suggests that genetic influences associated with the disease may impact both MTL structure and function.

To the best of our knowledge, no study to date has examined the structure of sub-regions of the PHG in schizophrenia siblings, or the relationship between abnormalities in MTL structure and episodic memory deficits in individuals with schizophrenia and their siblings. In this study, we hypothesized that MTL (i.e., hippocampus and PHG) structural abnormalities and memory deficits would be present in individuals with schizophrenia and in their siblings, thus suggesting that both are endophenotypes for schizophrenia. Moreover, we hypothesized that a relationship between MTL structure and memory performance would be found in both individuals with schizophrenia and their siblings, suggesting that the memory deficits observed in schizophrenia are mediated by genetically influenced structural abnormalities of the MTL.

2. Methods

2.1. Subjects

The subjects in this study were recruited through the Conte Center for the Neuroscience of Mental Disorders (CCNMD) at Washington University in St. Louis. The sample included 39 individuals with DSM-IV schizophrenia (33 male, 6 female; 22 White, 17 Black; mean age = 22.5, age range = 17–31); 33 siblings of individuals with schizophrenia (15 males, 18 female; 21 White, 12 Black; mean age = 22.1, age range = 14–28); 47 healthy control participants (26 male, 21 female; 38 White, 9 Black; mean age = 21.1, age range = 14–27); and 50 siblings of healthy controls (14 male, 36 female; 38 White, 11 Black and 1 Other; mean age = 20.4, age range = 15–27). Schizophrenia participants were recruited from local inpatient and outpatient treatment facilities. Control subjects were recruited using local advertisements from the same community. Clinical, structural, and general neuropsychological testing data from a group of subjects largely overlapping with this sample have been reported previously (Delawalla et al., 2006; Harms et al., 2007; Calabrese et al., 2008; Mamah et al., 2008; Harms et al., 2010). Additional details related to subject recruitment procedures can be found in those publications.

Participants from any of the four groups were excluded if they (1) met DSM-IV criteria for substance abuse or dependence within the past 6 months; (2) had a clinically unstable or severe medical disorder, or a medical disorder that would confound the assessment of psychiatric diagnosis or render research participation dangerous; (3) had head injury (past or present) with documented neurological sequelae or loss of consciousness; and (4) met DSM-IV criteria for mental retardation (mild or greater in severity). In addition, control participants were excluded if they had a lifetime history of any Axis I psychotic or major mood disorder,(i.e., major depression or bipolar disorder) or a first-degree relative with a psychotic disorder. Further, participants in the schizophrenia sibling and control sibling groups were excluded if they had a lifetime history of any Axis I psychotic disorder, but not other Axis I disorders.

2.2. Cognitive measures

We developed a single domain measure for episodic memory in each subject by averaging the z-scores from the following tests: Logical Memory I (WMS-III) (Wechsler, 1987), Family Pictures I (WMS-III) (Wechsler, 1987) and the California Verbal Learning Test (CVLT) (Delis et al., 1988). These tasks are routinely used to assess episodic memory and have been reported to be sensitive to cognitive deficits in schizophrenia subjects (Hawkins, 1999; Weickert et al., 2000). Each subject's raw scores on the above tasks were converted to z-scores using the entire cohort of subjects as reference. This procedure is described in greater detail in Delawalla et al. (2006).

2.3. MR scanning

All MR scans were collected on the same Siemen's 1.5-Tesla Siemens imaging system with a standard head coil. The MR scanning protocol included the collection of multiple (2–4) high-resolution, 3D T1-weighted MPRAGE volumes which were used for quantifying parahippocampal cortex (voxel size: $1\times1\times1.25$ mm^3, TR: 1765 ms, TI: 640 ms, TE: 4.0 ms, flip angle: 10°, scan time: 6.5 min per acquisition) and a single 3D T1-weighted FLASH scan which was used for quantifying the hippocampus (voxel size: $1\times1\times1$ mm^3, TR: 20 ms, TE: 5.4 ms, flip angle: 30°, scanning time: 13.5 min). The MPRAGE scans for each subject were aligned with the first scan and averaged to create a low-noise image volume. In order to have the largest sample possible, we analyzed all available data, including that of individuals whose siblings' data had not yet been collected or processed. As such, of our 169 subjects, 122 subjects formed sibling pairs.

2.4. Hippocampal mapping

Landmark-based, large-deformation high-dimensional brain mapping (HDBM-LD) from a template was used to map the hippocampal structure in each subject as previously described (Csernansky et al., 2002). Left and right hippocampal volumes in the target scans were determined by calculating the volumes enclosed by these transformed surfaces.

2.5. PHG mapping

We quantified the gray matter volume and thickness of the PHG and its component subregions using validated labeled cortical distance mapping procedures (Ratnanather et al., 2004). Briefly, a region of interest (ROI) containing the PHG was manually defined in each MR scan and non-brain tissue (e.g., tentorium) manually removed. Gaussian mixture modelling segmentation (Priebe, et al., 2006) was then used to classify the voxels within the ROI as gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) by fitting the ROI histogram typically with three Gaussian curves representing each tissue type. The validity of this approach to cortical segmentation has been previously established (Lee et al., 2008). A topologically correct surface (i.e., no "holes" or "handles" in the surface mesh) was then generated at the WM/GM interface in the ROI (Han et al., 2002).

We then used dynamic programming (Ratnanather et al., 2004) to manually delineate the boundaries of the PHG as well as those of its subdivisions (i.e., PHC, ERC and PRC) on the ROI WM/GM interface according to the following anatomical rules: For the PHG, the anterior-most boundary was the temporal pole, the posterior-most boundary was the calcarine sulcus, the medial boundary was the inflection point of the subiculum, and the lateral-most boundary was the collateral sulcus (Fig. 1). In a reliability analysis comparing the surface areas of 10 re-cut PHG surfaces to the original surfaces, the Case 3 intraclass correlation coefficient (ICC) as defined by Shrout and Fleiss (1979) for this procedure was 0.93. The PHC was next parcellated from the posterior portion of the PHG, where the boundary was identified as the first appearance of the lateral geniculate nucleus of the thalamus (Fig. 2). The anterior portion of the PHG was parcellated into ERC and PRC by distinguishing between exposed cortex (ERC) and buried cortex (PRC). We were able to include most of the histologically defined ERC (Mai et al., 1997), while still using a

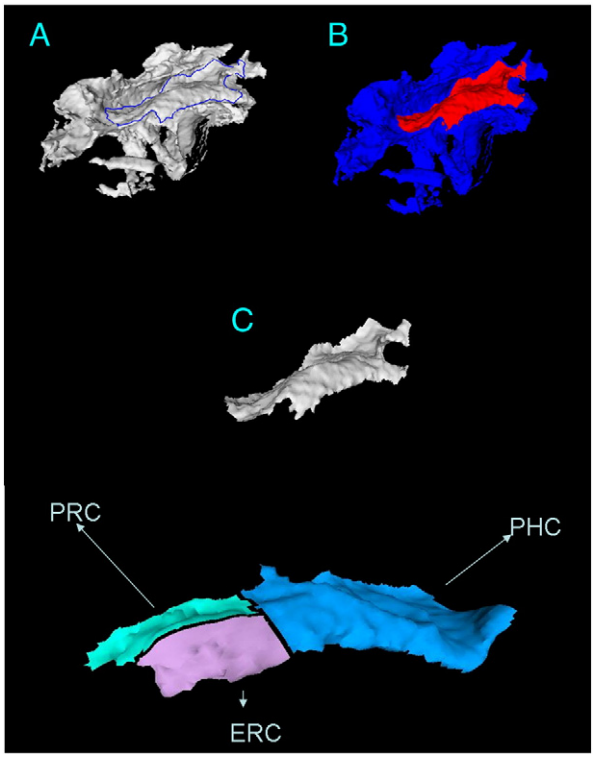

Fig. 1. PHG gray–white surface cutting. A: delineating the path of cut, calcarine sulcus, depth of collateral sulcus, temporal pole mark boundaries of PHG surface. B: the cut made by the path, Red is PHG surface. C: extracted PHG surface. D: WM surface parcellated into PHG substructures.

consistent and clearly identifiable boundary. The medial portion is then the ERC and the lateral portion the PRC.

Our definitions of the PHG (and subsequently PHC, ERC and PRC) included BA 35 and completely excluded BA 36 since the part of PRC that overlaps BA 36 is thought to more closely resemble the neighboring visual association area TE (Blaizot et al., 2004). In the subjects where the collateral sulcus morphology appeared ambiguous and could either be considered branched, or shallow, we followed the protocol outlined by Insausti et al. (1998) and defined the sulcus as shallow. We also excluded the medial portion of the fusiform gyrus. Our boundary between the PRC and ERC, and our anterior boundary for the PHC were similar to those used by Feczko et al. (2009), where FreeSurfer generated surfaces of PHG were segmented. Since FreeSurfer was unable to separately segment the PRC when both we and Feczko's group were processing data, and remained unable to do so as of 2009 (Fischl, 2009), Feczko et al. manually parcellated the FreeSurfer generated surfaces. However, our anterior and posterior boundaries for the PHG extended beyond those used in that study

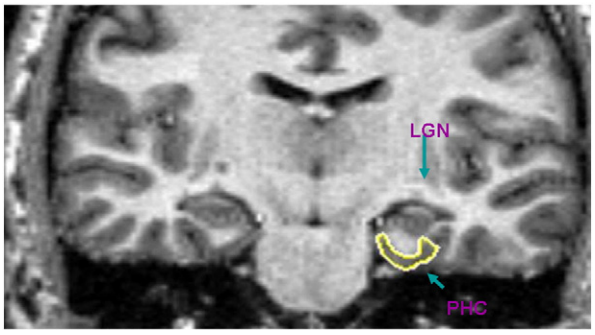

Fig. 2. Moving posteriorly, first appearance of LGN, the boundary of the PHC and the rhinal cortices.

which included cortex that began 3 mm anterior to the start of the hippocampus, and extended through the most posterior appearance of the hippocampus (Feczko et al., 2009), thereby excluding substantial portions of PHG cortex.

2.6. Brain volume

Total cerebral volume (excluding the brainstem, ventricles, and cerebellum) and cerebral gray matter thickness were derived using FreeSurfer software (Fischl et al., 2002) to be used as covariates in statistical analysis.

2.7. Statistical analysis

Group differences in episodic memory performance and the structural measures were assessed using mixed-model methods that explicitly estimated the covariance (correlation) in the residuals attributable to the sibling relationships. Specifically, sibling status was entered as a 'REPEATED' variable in PROC MIXED of SAS 9.1 (SAS Institute, Cary, North Carolina) to specify the desired covariance structure in the residuals of the mixed model. The selected covariance structure within a sibling pair was "unstructured" (i.e., 'TYPE = UN'). Group status and gender were used as fixed effect predictors in all models. For the structural measures, hemisphere and group * hemisphere were included as additional fixed-effect predictors, and an appropriate whole brain measure was included as a covariate. This measure was whole brain volume for analyses of the MTL volume measures, and mean cortical thickness for analyses of the MTL thickness measures. Additionally, for analyses of the structural measures, the mixed model included the correlation across hemispheres as part of the covariance structure (i.e., 'TYPE = UN@UN'). In all mixed model analyses the two different sibling pairs were allowed to be heterogeneous in their covariance structure, and the degrees of freedom calculation used the method of Kenward and Roger (1997).

In order to investigate the effect of schizophrenia and risk for schizophrenia on brain structure, we included the following group contrasts in the mixed model: schizophrenia subjects vs. controls, schizophrenia subjects vs. schizophrenia siblings, schizophrenia siblings vs. controls, schizophrenia siblings vs. control siblings, controls vs. control siblings.

Finally, we performed a Pearson correlation analysis between neuroanatomical measures of MTL and the episodic memory domain scores in each group, partialling out gender (below). We limited our correlational analyses to structures with an observed group effect.

3. Results

3.1. Subjects

Calculating χ^2 with the Yates Correction for significant differences in group composition using a 2×4 contingency table, we found significant differences in gender compositions between our four groups [χ^2 (3) = 26.37, $p < 0.0001$]. As such, we controlled for gender in our analyses. We found no significant difference in racial composition [χ^2 (3) = 6.37, $p = 0.10$] in our four groups. There was also no significant age difference between either of our experimental groups and our healthy controls ($F_{2,\ 118} = 1.99$, $p = 0.15$. We found no significant difference in parental socio-economic status between our groups [χ^2 (12) = 8.53, $p = 0.74$].

3.2. Episodic memory performance

A significant effect of group was observed on memory performance ($F_{3,\ 64} = 19.41$, $p < 0.0001$). Least Squared means for between-group comparisons can be found in Table 2. Individuals with schizophrenia performed significantly worse than both control

groups ($p<0.0001$) and their unaffected siblings ($p<0.0001$). Unaffected siblings of individuals with schizophrenia also performed significantly worse than healthy control subjects ($p=0.02$) and the siblings of healthy controls ($p=0.04$).

3.3. Hippocampus

Hippocampal volume showed a trend level effect for a group∗hemisphere interaction ($F_{3,\ 80}=2.24$, $p=0.09$). Least square mean values of MTL structure and episodic memory performance can be found in Table 1; scatter plots of average MTL structural measures for individuals from each group can be found in Fig. 3. The group∗hemisphere effect seemed to be driven by the difference between the schizophrenia group and the three other groups in left hippocampal volume. In a post hoc analysis where the left hippocampus was analyzed separately, the observed group effect became non-significant with the inclusion of left brain volume as a covariate ($F_{5,\ 156}=1.63$, $p=0.18$).

3.4. PHG

We did not observe a significant group∗hemisphere or group effect on PHG volume ($F_{3,\ 86}=0.40$, $p=0.75$, $F_{3,\ 92}=1.90$, $p=0.14$, respectively). However there was a significant group effect on PHG thickness, ($F_{3,\ 86}=3.25$, $p=0.03$), for which schizophrenia subjects differed from control siblings at the trend level ($p=0.09$), and schizophrenia siblings differed from both controls ($p=0.01$) and control siblings ($p=0.004$). We did not observe a significant group∗hemisphere effect on PHG thickness ($F_{3,\ 82}=0.91$, $p=0.44$).

3.5. PHG substructures

There was no significant group effect on either ERC volume ($F_{3,\ 93}=0.85$, $p=0.47$), or ERC thickness ($F_{3,\ 79}=1.00$, $p=0.40$). Nor was there a significant group∗hemisphere effect on either measure ($F_{3,\ 84}=0.51$, $p=0.67$, $F_{3,\ 83}=1.98$, $p=0.12$, respectively).

The effects of group∗hemisphere and group on the volume of the PRC were not significant ($F_{3,\ 83}=0.76$, $p=0.52$, $F_{3,\ 93}=0.51$, $p=0.67$, respectively). However, there was a significant effect of group on the thickness of the PRC ($F_{3,\ 91}=3.15$, $p=0.03$). The group effect appeared to be due to the difference between the schizophrenia siblings and healthy controls ($p=0.01$) and control siblings ($p=0.01$). The PRC of schizophrenia siblings was approximately 6% thinner than that of the two control groups. There was not a significant group∗hemisphere effect on thickness of the PRC ($F_{3,\ 83}=0.99$, $p=0.40$).

The effect of group on the gray matter volume of the PHC was significant at the trend level ($F_{3,\ 92}=2.28$, $p=0.084$) with the effect being driven by the difference between unaffected siblings of individuals with schizophrenia and the other groups (vs. affected siblings: $p=0.02$; vs. healthy controls: $p=0.06$; vs. control siblings: $p=0.07$). The effect of group on the thickness of the PHC was also significant at the trend level ($F_{3,\ 87}=2.30$, $p=0.08$), and again, the schizophrenia siblings differed significantly from both the healthy controls ($p=0.03$) and their siblings ($p=0.01$). No significant effect of group∗hemisphere was observed (on volume of PHC $F_{3,\ 84}=1.34$, $p=0.27$) or on thickness of this structure ($F_{3,\ 83}=0.11$, $p=0.95$).

3.6. Structural correlations with episodic memory performance

In the schizophrenia sibling group, episodic memory performance was significantly correlated with left hippocampal volume ($r=0.48$, $p=0.007$) (Fig. 4), PHG thickness ($r=0.37$, $p=0.04$), and PHC thickness ($r=0.40$, $p=0.03$) (Fig. 5). In the schizophrenia subjects, there was a correlation at trend-level significance between left hippocampal volume and episodic memory performance ($r=0.29$, $p=0.10$). No structural measure was correlated with episodic memory performance in either the healthy controls or their siblings.

4. Discussion

In this study, we found a trend level effect of group by hemisphere interaction on hippocampal volume such that left hippocampal volumes in individuals with schizophrenia appeared to be smaller than those of unaffected siblings of individuals with schizophrenia, and of both control groups. However, in our post hoc analysis of left hippocampal volume, when left cerebral volume was included as a covariate, the above effect became non-significant. On measures of PHG structure, siblings of individuals with schizophrenia had significantly smaller values compared to the control groups. We also observed that individuals with schizophrenia and their siblings performed significantly worse than the two control groups on tasks of memory performance. These findings together suggest that disease-related genetic factors may influence memory performance and

Table 1
Least square mean values of average MTL structural measures and standardized episodic memory performance with standard errors in parentheses. Volume measured in cubic millimeters; thickness in millimeters; episodic memory in z-scores. *For hippocampal volume, schizophrenia subjects n=36; schizophrenia siblings n=31; controls n=46; control siblings n=49.

	Schizophrenia subjects n=39*	Schizophrenia siblings n=33*	Controls n=47*	Control siblings n=50*
Hippocampal volume	2528	2660	2672	2664
	(48)	(43)	(38)	(39)
PHG volume	2938	2890	3183	3289
	(82)	(83)	(92)	(91)
ERC volume	406	401	439	467
	(23)	(19)	(21)	(24)
PRC volume	635	604	626	667
	(40)	(39)	(33)	(38)
PHC volume	1953	1888	2107	2123
	(53)	(55)	(61)	(56)
PHG thickness	3.27	3.20	3.36	3.40
	(0.04)	(0.04)	(0.05)	(0.04)
ERC thickness	3.66	3.59	3.74	3.78
	(0.07)	(0.07)	(0.07)	(0.06)
PRC thickness	3.66	3.53	3.75	3.76
	(0.06)	(0.05)	(0.06)	(0.07)
PHC thickness	3.02	2.97	3.10	3.14
	(0.04)	(0.04)	(0.04)	(0.04)
Episodic memory	−0.87	0.05	0.40	0.39
	(0.14)	(0.09)	(0.09)	(0.09)

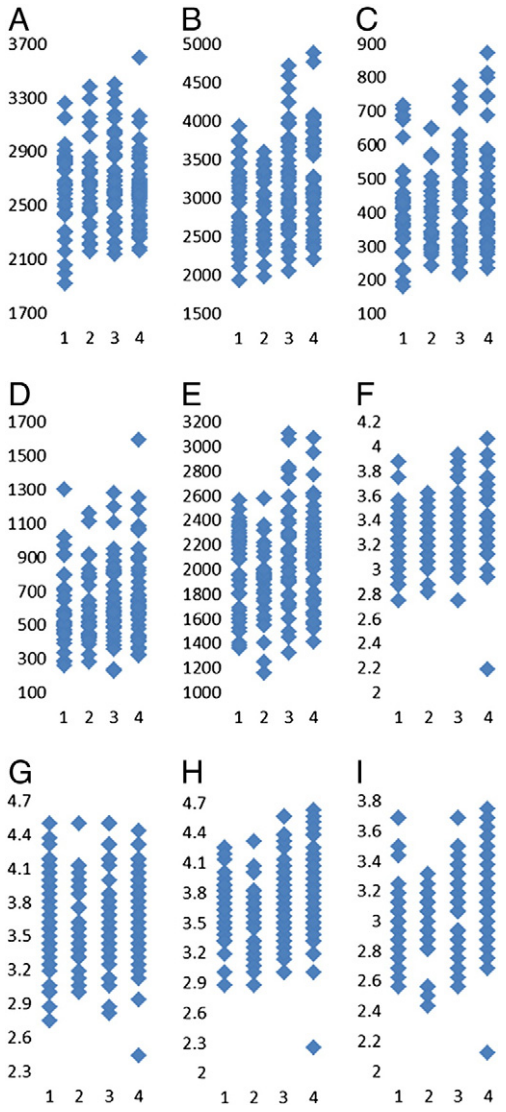

Fig. 3. Scatter plots of average MTL structural measures in individuals (volume in cubic millimeters; thickness in millimeters); individuals with schizophrenia = 1, unaffected siblings of individuals with schizophrenia = 2, healthy control subjects = 3, siblings of healthy control subjects = 4. Panels A–E show average hippocampal volume (A), average PHG volume (B), average ERC volume (C), average PRC volume (D), average PHC volume (E) by group; panels F–I show average PHG (F), ERC (G), PRC (H) and PHC (I) thickness by group.

structural measures within the PHG, whereas structural abnormalities of the hippocampus in schizophrenia may be more related to the disease state. Furthermore, the correlations between memory performance and PHG structure found in schizophrenia siblings suggest that the memory deficits observed in individuals with schizophrenia and their siblings may be due, in part, to abnormalities in PHG structure.

Our findings are consistent with prior findings of reduced hippocampal (Baaré et al., 2001; Csernansky et al., 2002; Seidman et al., 2002; Tepest et al., 2003; Sim et al., 2006; Goldman et al., 2008) and PHG (Job et al., 2002; Joyal et al., 2002; Turetsky et al., 2003; Prasad et al., 2004) volumes in individuals with schizophrenia. However, not all studies have reported hippocampal (Colombo et al., 1993; Deicken et al., 1999; Niemann et al., 2000; Staal et al., 2000) or PHG (DeLisi et al., 1997; Krabbendam et al., 2000; Sanfilipo et al., 2002; Sim et al., 2006) volume reductions. Unlike some others (O'Driscoll et al., 2001; Tepest et al., 2003; van Haren et al., 2003; Ho and Magnotta, 2010), we did not find hippocampal abnormalities in first-degree relatives of individuals with schizophrenia. Four studies to date have reported varying findings of PHG (no studies of PHG

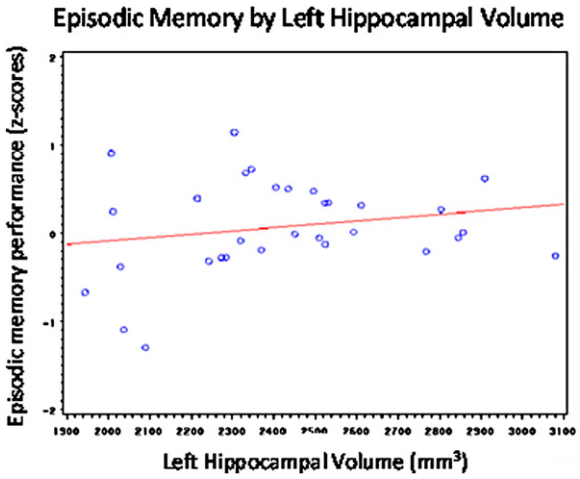

Fig. 4. Scatter plot of episodic memory domain z-scores by left hippocampal volume ($r = 0.48$, $p = 0.007$) in schizophrenia siblings. Significant correlations between left hippocampus and episodic memory performance were not observed in other groups.

sub-structures) in schizophrenia siblings. DeLisi et al. (1997) and Yang et al. (2010) showed evidence for deficits in the vicinity of the PHG. In contrast, Staal et al. (2000) reported no significant differences between schizophrenia siblings and healthy controls for PHG where a large segment of both PRC and ERC were excluded. Goghari et al. (2007) reported that siblings of schizophrenia subjects had larger

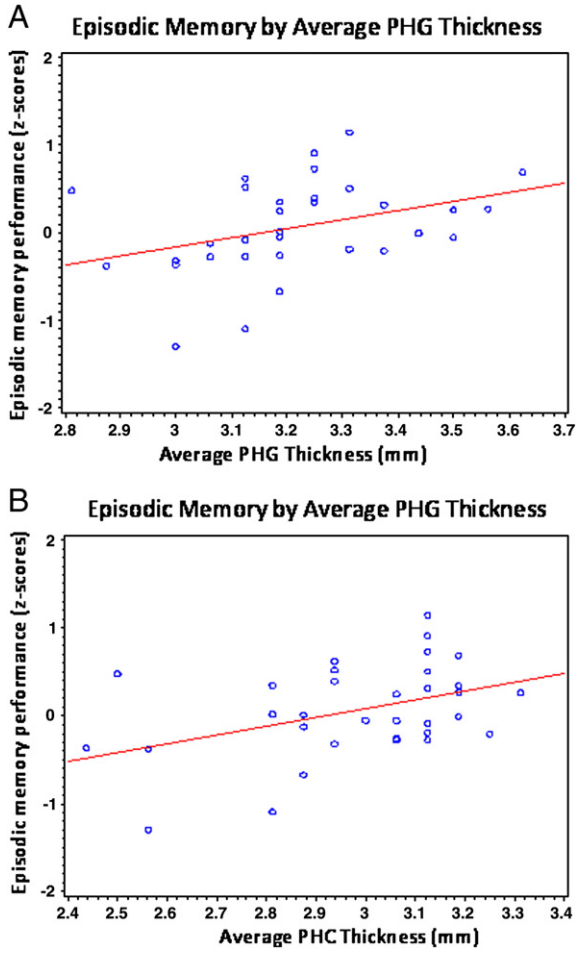

Fig. 5. Scatter plot of episodic memory domain z-scores by (A) average PHG thickness ($r = 0.37$, $p = 0.04$) and by (B) average PHC thickness ($r = 0.40$, $p = 0.03$) in schizophrenia siblings. Significant correlations between PHG structural measures and episodic memory performance were not observed in other groups.

volumes of PHG relative to control subjects. However, due to a lack of consistency in defining structures, comparing our MTL findings to those of others may prove difficult. For example, our definition of PHC included posterior PHC, whereas the PHC as delineated by Sim et al. did not. Similarly, the definitions of PHG structural boundaries used by other groups also differed from ours (Turetsky et al., 2003; Prasad et al. 2004).

The lack of significant group effects observed in some of our MTL measures may be explained in a number of ways. One possibility is, of course, that the disease-related and risk for disease-related reductions of these structures are proportional to reductions throughout the brain. However, in the case of the hippocampus, based on our prior findings (Csernansky et al., 1998; Wang et al., 2001; Csernansky et al., 2002), it is likely that this result reflects a change in specific sub-regions of the hippocampus, rather than a uniform abnormality across the entire structure. A small but significant volume reduction in a sub-region of the hippocampus in subjects with schizophrenia may not be powerful enough to survive the inclusion of whole brain volume as a covariate. Our above studies, which have failed to find significant differences in hippocampal volume between schizophrenia subjects and control subjects after covarying for whole brain volume, have found significant inward deformation in the head of the hippocampus of schizophrenia subjects compared to healthy controls.

Similarly, in the PHG, a lack of sensitivity in our measures may explain our lack of significance upon including whole-brain covariates. Recent evidence suggests that the anterior and posterior portions of PHC may subserve different functions (Aminoff et al., 2007; Saleem et al., 2007). The results of these studies in both people and non-human primates suggest that the more posterior region of the PHC may be more closely related to visual-spatial processing, and the more anterior region may be more deeply involved in memory and non-spatial context processing. However, by measuring the average thickness of this structure with both anterior and posterior PHC together, we may have missed a subtle relationship between the anterior PHC and memory performance in individuals with schizophrenia or the risk of developing schizophrenia.

As a neural substrate for memory, several researchers have examined hippocampal structure in schizophrenia, but very few have examined the other structures of the MTL in the context of this disorder. Significant differences in activation of the PHG have been reported in patients with schizophrenia who are hallucinating as compared to healthy controls (Diederen, et al., 2010; Jardri et al., 2011). Deficits of emotional processing observed in schizophrenia subjects have also been linked to abnormal activation of PHG (Escartí et al., 2010; Li et al., 2010, meta-analysis). Additionally, schizophrenia subjects show significant deficits in MTL activation during the encoding and retrieval periods of episodic memory tasks (Ragland et al., 2004; Achim et al., 2007; Ragland et al., 2009, meta-analysis). Taken together, these findings, suggest that the disruption of PHG connections with multimodal association cortices, single sensory cortices and the hippocampus may be the basis for at least some of the psychopathology and cognitive impairments associated with schizophrenia (Kalus et al., 2005; Acioly et al., 2010).

Our correlational findings suggest that this may be the case for episodic memory deficits observed in both individuals with schizophrenia and, their first-degree relatives. Notably, we observed that measures of MTL structure were positively correlated with episodic memory performance in siblings of subjects with schizophrenia, and to a lesser extent, in individuals with schizophrenia themselves. However, we found that normative variation in MTL measures among the control groups was not related to memory performance. Additionally, our findings of memory deficits in individuals with schizophrenia and their siblings were as expected, and consistent with previous findings (meta-analysis Sitskoorn et al., 2004; Delawalla et al., 2006).

Surprisingly, we found that the siblings of individuals with schizophrenia showed greater abnormalities of MTL structure than their affected siblings, and that the observable relationship between MTL structure and memory performance was also more pronounced in these subjects than in individuals with schizophrenia. There are a number of potential explanations for these findings. For example, it is possible that MTL structural abnormalities are an endophenotype of schizophrenia, but that thinning of other vast expanses of cortex reflects a disease-specific process not mediated by genetic factors. As such, we would expect to see significant abnormalities in unaffected siblings of patients, while at the same time observing attenuated levels of abnormality in individuals with schizophrenia when covarying for whole-brain measures. An alternate analysis of PHG measures (not reported here) without whole-brain covariates revealed several significant structural abnormalities in individuals with schizophrenia. Furthermore, recent functional imaging studies of neural activity during episodic memory tasks have shown different activation patterns involving increased recruitment of frontal regions in individuals with schizophrenia compared to those observed in healthy control subjects during deep-encoding (Bonner-Jackson et al., 2005). These findings suggest that the recruitment of frontal regions may compensate for abnormalities in the structures of the MTL, a region that normally subserves memory tasks. Such compensation may explain our lack of a significant correlation between memory performance and MTL structural measures in patients.

Alternatively, given the reported effects of antipsychotic treatment on brain structure, we considered the possibility that the type and duration of treatment received by individuals with schizophrenia may have affected our measures of MTL structure. Several studies have reported that in individuals with schizophrenia, typical antipsychotic treatment is associated with reductions in parietal and temporal cortical volume (Dazzan et al., 2005 and Lieberman et al., 2005), and that atypical antipsychotic treatment is associated with increases in cortical volume (Garver et al., 2005). Upon conducting a post-hoc correlation analysis of our schizophrenia subjects based on number of months on kind of antipsychotic and our various measures of MTL structure, we found that several structural measures were positively correlated with number of months on only atypical antipsychotic medication (left PHG volume, $r = 0.38$; left ERC volume, $r = 0.72$; left ERC thickness, $r = 0.45$; left PHC volume, $r = 0.30$; right ERC volume, $r = 0.42$; right ERC thickness, $r = 0.30$; right hippocampal volume, $r = 0.32$, whereas others were negatively correlated with number of months on typical antipsychotic medication (right PHG thickness, $r = -0.30$; left PHC thickness, $r = -0.47$; right PHC thickness $r = -0.63$). It should be noted that there were several measures that were positively correlated with number of months on typical antipsychotic medication, but this may be due to the composition of the sample in that, 10 of the 11 subjects who had been treated with typical antipsychotic medication had also been treated with atypical medication. Unlike these subjects, our 22 subjects who had been treated with atypical antipsychotic medication, as far as we know, had been treated exclusively with atypical medication. Though not conclusive, these findings suggest that antipsychotic drug treatment may have had an impact on MTL measures in the individuals with schizophrenia and may have precluded us from seeing some of the differences from controls that we found in the schizophrenia sibling participants.

Additionally, a number of disease-related factors could have impacted memory performance in individuals with schizophrenia. These factors include a history of drug or alcohol abuse (Smith et al., 2008) in our subjects, which could have disrupted the structure and function of other brain regions associated with memory performance. Such influences may have influenced the appearance of the relationship between memory performance and MTL structure in our subjects.

In light of the above potential disease-related confounding factors, the significance of our observations in unaffected first-degree

relatives of individuals with schizophrenia may provide insights into the etiology of schizophrenia and its effects on cognition. By producing a reliable means of mapping the PHG and its substructures, we have extended the findings on the PHG in schizophrenia subjects. In addition, our findings, though not conclusive, suggest that genetic factors underlying the risk of developing schizophrenia (as represented in siblings) may influence the structure of the MTL. Our correlation findings relating MTL structure to episodic memory performance in the siblings of schizophrenia subjects and to a lesser extent in the subjects themselves, though not conclusive, also suggest that genetic factors related to the risk of developing schizophrenia may contribute to disease-related abnormalities in MTL structure and episodic memory deficits.

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Contributions

John G. Csernansky, Deanna Barch, and Lei Wang designed the study and wrote the protocol. Meghana Karnik and Carolina Campanella defined the PHG segmentation, Meghana Karnik also managed the literature searches and the data processing, undertook the statistical analyses and wrote the manuscript. Michael Harms constructed the Mixed Models used in the analyses. All authors contributed to 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 doi:10.1016/j.schres.2012.03.015.

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