

Hippocampus volume and episodic memory in schizophrenia

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Abstract

Previous studies of schizophrenia have suggested a linkage between neuropsychological (NP) deficits and hippocampus abnormality. The relationship between hippocampus volume and NP functioning was investigated in 24 patients with chronic schizophrenia and 24 matched healthy controls. Overall intracranial, white and gray matter, and anterior (AH) and posterior (PH) hippocampus volumes were assessed from magnetic resonance images (MRI). NP domains of IQ, attention, and executive function were also evaluated with respect to volumetric measures. It was hypothesized that AH and PH volumes and episodic memory scores would be positively associated in controls and that the schizophrenia group would depart from this normative pattern. NP functioning was impaired overall and AH volume was smaller in the schizophrenia group. In the controls, the hippocampus–memory relationships involved AH and PH, and correlations were significant for verbal memory measures. In the schizophrenia group, positive correlations were constrained to PH. Negative correlations emerged between AH and verbal and visual memory measures. For both groups, cortical volume negatively correlated with age, but a negative correlation between age and hippocampus volume was found only in the schizophrenia group. In this sample of adults with schizophrenia, atypical relationships between regional hippocampus volumes and episodic memory ability were found, as was an atypical negative association between hippocampus volume and age. (*JINS*, 2009, *15*, 182–195.)

Keywords: Magnetic resonance imaging, Cognition, Neuropsychology, Memory, Temporal lobe, Antipsychotic agents

INTRODUCTION

Declarative, episodic, and working memory have long been recognized as being dependent on the function of an intact hippocampus, a medial temporal lobe structure necessary for encoding and consolidating new memories. Schizophrenia is a disorder characterized by both episodic memory deficits and hippocampus abnormality. Because selective memory impairment has been observed in never-medicated patients

experiencing first-episode schizophrenia, episodic memory has been posed as a core deficit of the disorder rather than an effect of chronicity or antipsychotic medication (Saykin et al., 1994). Episodic memory deficits appear to be present in schizophrenia before the onset of frank psychosis. In a study of patients at high risk of developing psychosis (predominantly schizophrenia), impairments in the Visual Reproduction and Logical Memory subtests of the Wechsler Memory Scale-Revised (WMS-R) differentiated patients who went on to develop psychosis within the next 12 months from those who did not (Brewer et al., 2005). While it is possible for lower scores on neuropsychological tests of memory to be secondary to any number of environmental or individual attributes, episodic memory impairment in schizophrenia is

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not commensurate with global impairment, nor is it attributable to lack of motivation, attention, or cooperation (Gold et al., 1992; Saykin et al., 1991; Tamlyn et al., 1992).

Functional neuroimaging has linked hippocampus dysfunction to impaired performance on memory tasks in schizophrenia. In a positron emission tomography (PET) study, Heckers et al. (1998) identified lesser hippocampus activity in patients than controls during attempts to recall studied words. In a functional magnetic resonance imaging (fMRI) study, controls exhibited greater activation than patients in left anterior hippocampus during encoding and in hippocampus bilaterally during recognition (Jessen et al., 2003). Functional impairment related to the hippocampus extends to the ability to comprehend relationships and draw inferences, as demonstrated by a selective deficit in discrimination accuracy when cognitive flexibility is required, which has been observed in schizophrenia using fMRI (Öngur et al., 2006). Using a similar relational-memory task, Hanlon et al. (2005) directly assessed hippocampus activity with magnetoencephalography (MEG), reporting abnormal right hemisphere processing of nonverbal stimuli accompanied by a possibly compensatory, left-lateralized activation in schizophrenia.

Structural abnormalities of the medial temporal lobe, which includes the hippocampus, are among the most robust findings in schizophrenia research. A number of studies have reported smaller volume of the medial temporal lobe in schizophrenia (Bogerts et al., 1993; Gur et al., 2000; McCarley et al., 1999; Wright et al., 2000), particularly in the left hemisphere (DeLisi et al., 1991; Honea et al., 2005; Shenton et al., 1992). However, while hippocampus abnormality is consistently found, the precise nature of the results has varied. Meta-analyses have posited that smaller hippocampus volume is equivalent across hemispheres (Nelson et al., 1998), even when limited to studies of first-episode patients (Steen et al., 2006). However, other first-episode studies have resulted in findings of significant left-less-than-right hippocampus asymmetry (Bogerts et al., 1990; Hirayasu et al., 1998). In a longitudinal study, Velakoulis et al. (2006) demonstrated hippocampus volume deficits bilaterally in chronic schizophrenia, in the left hemisphere only in first-episode schizophrenia, and not at all in schizophreniform psychosis. It is also important to note that there have been scattered reports of null findings with regard to hippocampus volume in schizophrenia. For example, Marsh et al. (1997) reported no group difference in hippocampal volume in an inpatient sample with severe and chronic schizophrenia. Because of the variability in group differences across reports, the etiological role of hippocampal anomaly in schizophrenia and its association with subsequent symptoms and course of the disorder remains a critical area for research (White et al., 2008).

With some degree of hippocampal volume deficits in schizophrenia well established but the nature and mechanisms of its functional consequences unclear, attention is turning to localizing hippocampus volume decrements along the anterior-posterior axis. One study confirmed the pres-

ence of overall hippocampus volume deficits in schizophrenia but maintained that the loss was diffuse rather than topographically specific (Weiss et al., 2005). However, Narr et al. (2004) made a strong argument for factoring regional specificity into hippocampus measurements in a study that demonstrated volume deficits localized to midbody and anterior hippocampus in first-episode schizophrenia. Consistent with Narr et al.'s finding, smaller anterior hippocampus volumes have been observed in both first-episode and chronic schizophrenia (Lieberman et al., 2001; Pegues et al., 2003; Szeszko et al., 2003). Other studies have found deficits localized to posterior hippocampus in chronic schizophrenia (Narr et al., 2001) and in first-episode patients (Hirayasu et al., 1998).

The relationship of neuropsychological function to structural abnormality in the hippocampus is under debate. Lack of a relationship between hippocampus volume and episodic memory in people with schizophrenia or controls has been reported by some studies (DeLisi et al., 1991; Torres et al., 1997). Gur et al. (2000), on the other hand, found a positive correlation between gray matter volume of the hippocampus and episodic memory scores across patients and controls of both sexes. This finding is supported by other studies reporting similar correlations between verbal memory and left hippocampus volume (Goldberg et al., 1994; Seidman et al., 2002) or amygdala-anterior hippocampus volume (O'Driscoll et al., 2001) in people with schizophrenia, their relatives, and controls. However, some investigations of structure-function relationships have found differential patterns of correlations between hippocampus volume and verbal IQ or verbal or visual memory in controls and people with schizophrenia (Kuroki et al., 2006; Sachdev et al., 2000; Sanfilippo et al., 2002; Touloupoulou et al., 2004). Findings of differential patterns of correlations for patients and controls are thought to indicate a loss of normal structure-function relationships, possibly arising from aberrant neurodevelopment.

One reason for discrepancies among volumetric studies may be that critical hippocampus subregions are not being discriminated, as few studies have combined neuropsychological assessment with hippocampus subregion measurements as discussed earlier. Anterior hippocampus volume deficits have been correlated with decrements in executive and motor function, but not memory, in first-episode schizophrenia (Bilder et al., 1995), with the effect present for men but not for women in a similar study (Szeszko et al., 2002). Given the substantial evidence for episodic memory dysfunction and hippocampus volume deficits in schizophrenia, further investigation taking subregional measurements into account seems warranted.

The present study was conceived to investigate how measures of cognitive function track structural abnormalities in specific hippocampus subregions. Based on prior research, it was expected that (1) episodic memory would be impaired and (2) hippocampus volume would show deficits in the schizophrenia group. It was also predicted that (3) there would be positive correlations between hippocampus volumes and episodic memory scores in the control group,

establishing an assemblage of correlational relationships that represent normal brain-behavioral functioning. It was further predicted that (4) correlations between regional hippocampus volumes and episodic memory scores would differentiate the groups, supporting the presence of abnormal brain-behavioral relationships in schizophrenia. Demographic variables that are known to affect hippocampus volume, such as age and gender, were also investigated.

METHOD

Participants

Participants in this study were 24 schizophrenia patients and 24 healthy control subjects matched for age, education, and sex (see Table 1). Group membership was determined with the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV; First et al., 1996). No subject had a history of head injury, neurological disorder, or severe medical illness.

The schizophrenia group consisted of volunteers and referrals who were relatively stable patients, well known to their providers. They met predetermined criteria for clinical stability, as they had been treated with the same antipsychotic medications for at least 3 months and had had no inpatient stays during the past year. Absence of other current psychiatric disorders was determined using the SCID-CV. Patients with schizophrenia were all taking antipsychotic medications, either haloperidol ($n=6$), olanzapine ($n=4$), risperidone ($n=5$), clozapine ($n=4$), aripiprazole ($n=2$), or quetiapine ($n=3$).

The control group consisted of healthy volunteers recruited via advertisements in local newspapers. Control subjects were screened for the presence of Axis-I psychopathology via SCID-CV with a licensed clinical psychologist (Thoma) or with a psychology graduate student under his direct supervision. Axis II psychopathology was ruled out with a diagnostic clinical interview with a licensed clinical psychologist (Thoma) if necessary. If there was a question of the presence of schizotypal or schizoid symptoms, scores on the Social Anhedonia Scale (Chapman et al., 1994) and the Magical Ideation Scale (Eckblad & Chapman, 1983) were reviewed. During the clinical interview, potential control subjects were asked if they had a first-degree relative with schizophrenia or other psychotic disorder, and if so, they were not included in the study.

Table 1. Sample demographics

	Control	Schizophrenia	Statistic
Age	41.74	40.09	$t=.52$ ($p=.61$)
Education (in years)	13.56	12.47	$t=1.47$ ($p=.15$)
Sex			
Male	16	20	$\chi^2=1.78$ ($p=.32$)
Female	8	4	

Institutional Review Board approval was obtained prior to running subjects, and subjects were informed that they could leave the study at any time. Appropriate informed consent was obtained from all subjects, and data was obtained in compliance with institutional regulations.

Hippocampus volume data from these subjects was previously published elsewhere as part of an analysis of psychophysiological anomalies (Thoma et al., 2008).

Procedures

Magnetic resonance images

Three-dimensional structural magnetic resonance images (MRI), T1 weighted, were collected with a 1.5 Picker Edge Imager at the NMVAHCS Magnetic Source Imaging center. A gradient echo 3-D sagittal sequence with parameters TR=15 ms; TE=4.4 ms; FOV=256 mm; 192 x 256 matrix, flip angle=25; slice thickness=1.5 mm, with no gap, was used.

Structural MRI analysis

The method used for this hippocampus volumetric analysis was first described in detail elsewhere (Thoma et al., in press). MRIs were first resliced into coronal images of 1.0 mm thickness (Figure 1a). The skull was then stripped from each MRI image using Brain Extraction Tool software (BET: fMRIB Image Analysis Group, Oxford, UK). Intracranial volume (ICV) was calculated from the mask produced from this program. Images were then segmented using an automated k-means clustering segmentation algorithm, and the volumes of gray matter (GM; not including cerebellum; see Figure 1b), white matter (WM; not including cerebellum), cerebrospinal fluid (CSF), and total ICV (including cerebellum) were determined by the number of pixels in each of their respective clusters (Petropoulos et al., 1999). Pixels that could not be assigned exclusively to GM or CSF were considered partial volume (PV). The number of PV pixels was divided in half and then added to the GM for a final count.

The k-means algorithm segmented GM from WM to assist raters in selecting the hippocampus, and as a result hippocampus WM was excluded from the overall hippocampus volume measurement (Figure 1c). Two independent raters used interactive software (Driscoll, et al., 2003) to conduct volumetric assessment of the hippocampus using the already k-means segmented coronal T1-weighted images. The software was designed to interact with the segmented imaging data for quantification and allows the user to select a segmented brain section. The user is able to magnify the area of interest to remove sections of segmented data from the volumetric analysis and allow the user to specify brain structures and easily quantify the selection via a pixel-counting algorithm (Figure 1d).

Raters followed the anatomical guidelines outlined by Watson et al. (1992) to measure hippocampus, except in regard to the posterior hippocampus definition. Watson et al. (1992) defined the most posterior slice as where the crux of

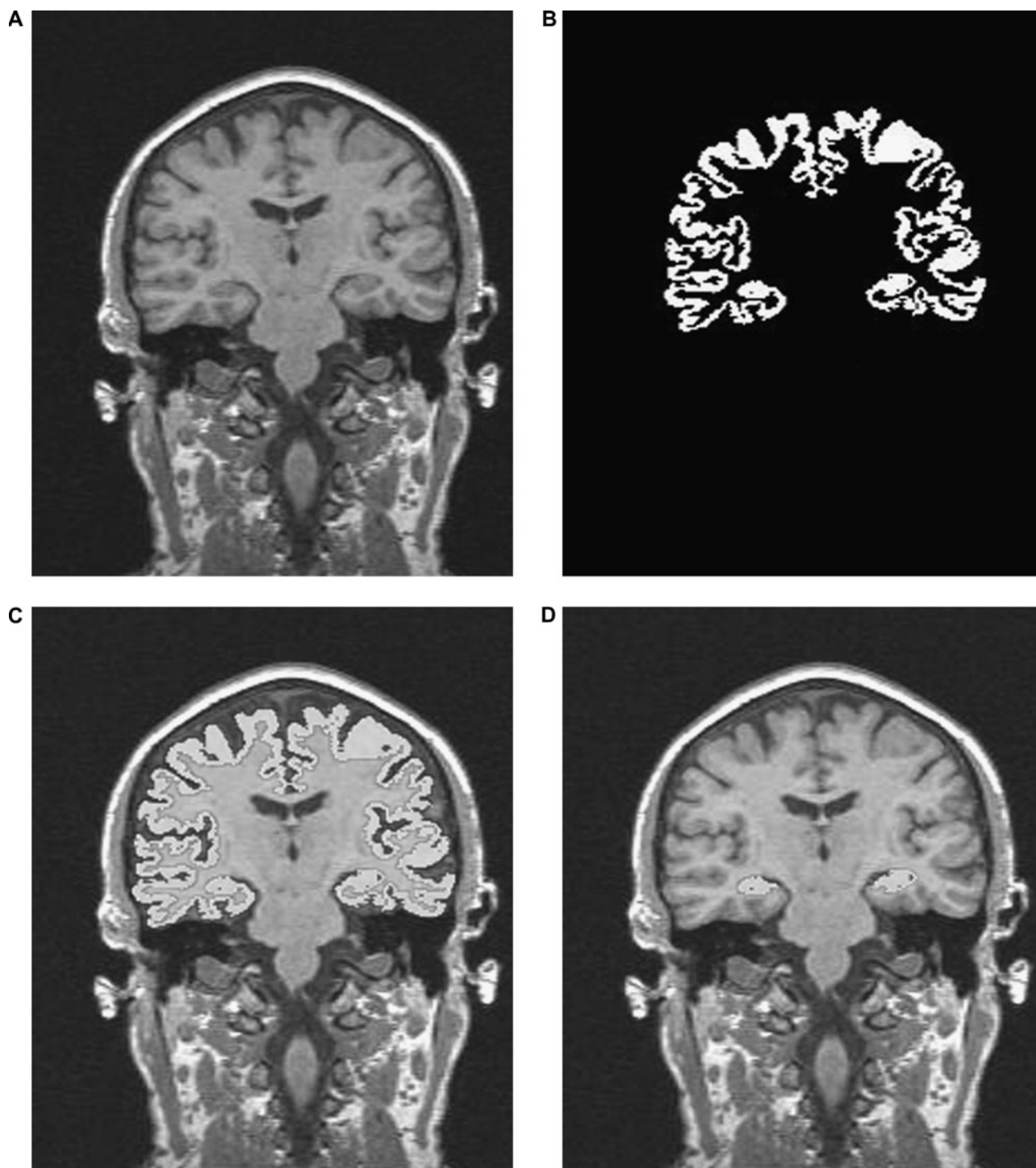


Fig. 1. A pictorial representation of the steps involved in the hippocampus quantification routine. (1a) Sagittal MRI series is resliced into 1-mm coronal images. (1b) An example of cortical gray matter segmentation. (1c) Cortical mask “overlay” on T1 image. (1d) Hippocampus tissue extracted by trained rater utilizing manual editing to separate the body of the hippocampus from the cortex.

the fornix separated from the hippocampus. This method, however, eliminates the most posterior slices of the hippocampus. Since active hippocampus MEG source dipoles have been previously found on these most posterior slices of the hippocampus (Hanlon et al., 2005), they were included in the present measurements. Consequently, the most posterior slice was defined in this study as the slice in which the

hippocampus connects laterally to the lateral ventricle and medially to the midline. Hippocampus volume was determined for total, right, left, anterior (anterior 9 slices), and posterior (posterior 9 slices) (Maguire et al., 2000). Total hippocampus volume was the sum of the measurements collected for the images available, around 40 (1.0 mm) slices. The mean measurements from the two raters were used.

Inter-rater reliability between two raters was established in a subset of 20 hippocampi ($\alpha = .82$).

Neuropsychological battery

While the primary hypotheses focused on the relationship between hippocampus volume and episodic memory, a broad neuropsychological battery was administered to assess a wide array of cognitive functions, including intelligence, attention, working memory, and executive functioning, in addition to episodic memory function. Intelligence was assessed with the Shipley Institute for Living Scale (Shipley, 1940), attention with the Conners' Continuous Performance Test (CPT; Conners, 2000), working memory with the auditory consonant trigrams test (ACT), as well as Digit Span Forward (DSF) and Back (DSB), and executive functioning with the Trail Making Test (Trails A & B). For the episodic memory assessment, the Wechsler Memory Scale-Revised (WMS-R) Logical Memory I (LM I) and II (LM II) and Visual Reproduction I (VR I) and II (VR II) subtests were used (Wechsler, 1987).

RESULTS

Hypothesis 1

The schizophrenia group was impaired across all neuropsychological tests (p -values ranged from $<.001$ to $.034$) with two exceptions. There was a marginal group difference for digit span forward ($p = .052$), and no difference for digit span back ($p = .187$; see Figure 2).

Hypothesis 2

Group differences in hippocampus substructure volumes were assessed using a mixed-model multivariate analyses of

variance (MANOVA), with Hemisphere (right and left) \times Region (anterior and posterior hippocampus) entered as repeated measures. Overall hippocampus volume was smaller in the schizophrenia group than in controls [Group main effect, $F(1, 46) = 6.689, p = .013$]. Across groups, anterior hippocampus volume was larger than posterior hippocampus volume [Region main effect, $F(1, 46) = 254.554, p < .001$], and left hippocampus was larger than right [Hemisphere main effect, $F(1, 46) = 4.195, p = .046$].

The Group \times Region interaction was marginally significant, $F(1, 44) = 3.122, p = .084$, two-tailed test, and investigation of this predicted interaction using simple-effects tests demonstrated a trend toward smaller anterior hippocampus in the schizophrenia group than in controls, $t(46) = 2.701, p = .010$, with no group difference for posterior hippocampus ($p = .821$). No other main effects or interactions approached significance.

Hypotheses 3 and 4

Table 2 shows partial correlations between hippocampus subregional volumes and neuropsychological memory test scores for each group, controlling for ICV. Groups did not differ in ICV, GM, or WM, so using ICV as a covariate is appropriate (Miller & Chapman, 2001). In the control group, LM I and LM II scores correlated positively with right anterior and left posterior hippocampus volumes. No significant brain-behavior correlations associated with VR I or VR II emerged for this group.

In the schizophrenia group, the pattern of correlations was markedly different. Only a single correlation was noted with LM: LM I was *negatively* correlated with right anterior hippocampus volume. VR I and VR II were also *negatively* correlated with right anterior hippocampus volume. VR I and VR II were positively correlated with bilateral posterior

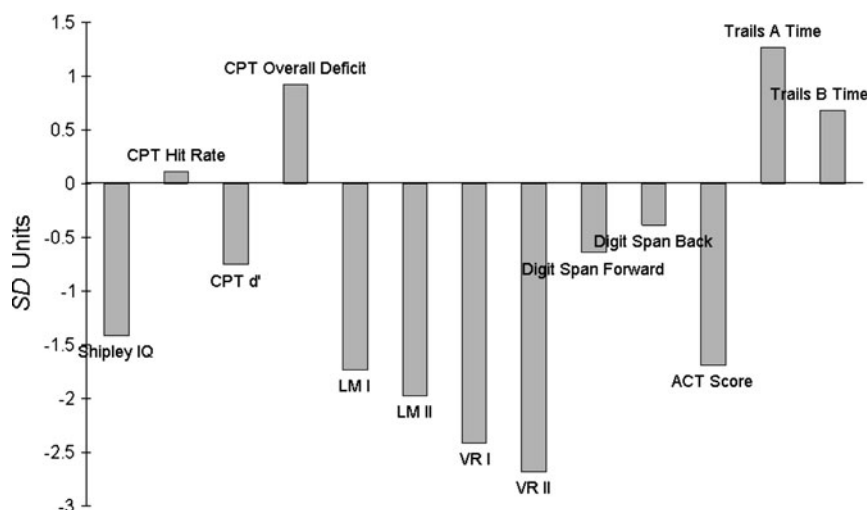


Fig. 2. Standardized representation of cognitive deficits in schizophrenia. Each bar represents mean schizophrenia group score as a z -score relative to normal control mean and standard deviation. For most tests, negative scores indicate a schizophrenia group deficit. Trails A, Trails B, and CPT Overall Deficit measures reflect schizophrenia group deficit in terms of increased time on task.

Table 2. Correlations between neuropsychological tests and hippocampus subregions

Test	Right anterior	Left anterior	Right posterior	Left posterior
Control group (<i>n</i> =24)				
LM I	.436**	.052	.268	.497**
LM II	.494**	.048	.281	.414**
VR I	.020	.095	-.097	.224
VR II	.184	.352	.001	.022
Schizophrenia group (<i>n</i> =24)				
LM I	-0.471***a	-0.284	0.189	0.250
LM II	-0.298	-0.179	0.108	0.140 ^b
VR I	-0.529***a	-0.246	0.365**a	0.650***a
VR II	-0.450***a	-0.271 ^b	0.427***a	0.509***a

Note. Values represent partial correlations controlling for intracranial volume (ICV).

LM I, LM II=Wechsler Memory Scale-Revised (WMS-R) Logical Memory scores; VR I, VR II=WMS-R Visual Reproduction scores.

^aGroup difference in correlations, $p < .05$.

^bGroup difference in correlations, $p < .10$.

* $p < .10$. ** $p < .05$. *** $p < .01$.

hippocampus volumes. See Figure 3 for scatterplots of relationships between episodic memory scores and hippocampus subregions.

Cohen's statistical tables were used to test group differences between brain-behavior correlations (Cohen, 1988). Group correlational differences fell into two basic clusters. First, the schizophrenia group correlations between right anterior hippocampus volume and episodic memory test scores (i.e., LM I, VR I, VR II) were significantly different from those in the control group. In this cluster, the schizophrenia group correlations were strongly negative versus positive or absent in controls. Second, bilateral posterior hippocampus volume correlations with VR I and VR II were significantly different, in this case more positive in the schizophrenia group than those correlations in the control group. In addition, differences between correlations for left anterior volume and VR II and left posterior volume and LM II approached significance ($p < .10$).

To provide some context for the findings presented in Table 2, Tables 3a and 3b show the zero-order correlations between most test scores derived from the neuropsychological battery and all brain regional volumetric data assessed for this study. Tables 4a and 4b show partial correlation coefficients between test scores and hippocampus regions controlling for gray matter volume.

Demographic Variables

As a result of the nature of the population from which these samples were drawn (i.e., a VA population consisting largely of middle-aged veterans), only 13 women were included in the study. When sex was considered as a covariate in the mixed model MANOVA described earlier, there was no main effect ($p = .381$) or significant interactions between sex and hippocampus volume variables.

There was a group difference in how age related to hippocampus volume [Group x Age interaction, $F(2, 45) = 4.513$, $p = .016$]. Further correlational analysis indicated that there

was no effect of age on hippocampus volumes for control subjects but that age was negatively correlated with left anterior hippocampus ($r(24) = -.406$, $p = .049$) and marginally correlated with right posterior ($r(24) = -.382$, $p = .065$) and left posterior ($r(24) = -.383$, $p = .065$) hippocampus volumes in the schizophrenia group (see Figure 4).

Consistent with the prevailing literature, GM volume correlated negatively with age for both groups. In a regression, no effect was found for Group, or for the Group x Age interaction term, indicating that GM volume decreased equally with age for control and schizophrenia groups. A series of hierarchical regressions was used to investigate whether this generalized GM diminution might account for the age-hippocampus volume correlations in the schizophrenia group. With age used as a dependent variable, and GM as a lone predictor variable, the overall regression was significant for the schizophrenia group ($R^2 = .386$, $p = .001$). However, there was no additional variance accounted for when hippocampus volumes were added as predictors. Taken together, these analyses suggest that age-hippocampus volume correlations in schizophrenia are proportionate to age-GM correlations, whereas in controls, age predicts only smaller GM and there was no evidence of a correlation with hippocampus volume.

The mean number of years since schizophrenia symptom onset was 16.18 ($SD = 8.34$) and was considered as a demographic covariate for the schizophrenia group. To investigate an effect for time since first diagnosis, a mixed-model MANOVA was used with Region and Hemisphere as repeated measures and Years since symptom onset entered as a covariate. There was a three-way Hemisphere x Region x Years interaction, $F(1, 19) = 7.233$, $p = .015$. *Post-hoc* investigation with correlations suggested that Years was most significantly correlated with right hemisphere posterior hippocampus volume ($r = -.505$, $p = .017$).

To investigate possible medication effects, Medication type (typical, atypical) was entered as a covariate for the schizophrenia group. Although there was no main effect of Medication type, there was a significant Medication

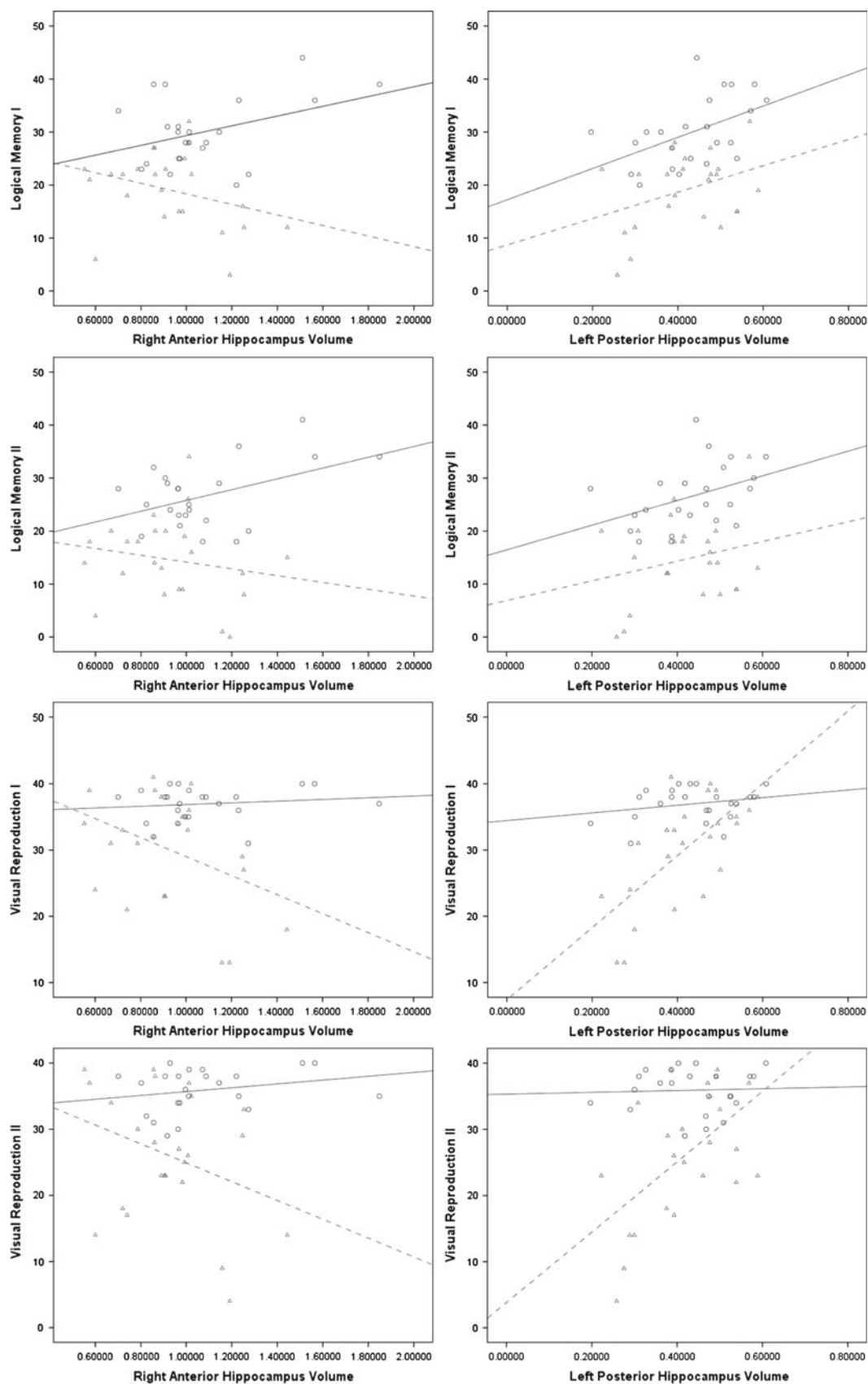


Fig. 3. The most dramatic correlational group differences were between memory test scores and right anterior and left posterior hippocampus. The scatterplots depict bivariate correlations between the variables (hippocampus volumes are in cc). Solid line = control group, dashed line = schizophrenia group.

Table 3a. Bivariate correlations between neuropsychological tests and hippocampus regional volumes, overall WM and GM, and ICV for the control group ($n = 24$)

Test	Right anterior	Left anterior	Right posterior	Left posterior	White matter	Gray matter	ICV
Shipley	.082	.092	.050	.025	.395*	.278	.529***
CPT d'	-.188	-.294	-.209	.263	-.068	-.005	-.061
CPT Overall	.112	-.046	.191	.137	-.274	-.201	-.201
LM I	.383*	-.019	.256	.481**	-.111	-.137	-.113
LM II	.449**	.004	.272	.404*	.049	-.108	-.080
VR I	.254	.318	-.048	.220	.429**	.220	.424
VR II	.276	.420**	-.013	.091	.101	.251	.234
DSF	.214	.133	.133	.028	.085	.137	.175
DSB	-.041	.192	-.098	.013	.168	.086	.218
ACT	.262	.144	.441**	.262	.334	.292	.376*
Trails A	-.264	-.120	-.383*	-.132	-.238	-.332	-.163
Trails B	-.151	.148	-.311	.038	-.390*	-.169	-.231

Note. ICV = intracranial volume, GM = gray matter, WM = white matter, CPT Overall = Continuous Performance Test Overall Deficit, CPT d' = CPT detectability, DSF = Digit Span Forward, DSB = Digit Span Back, ACT = Auditory Consonant Trigrams, Trails A, B = Trail-Making Tests A & B. * $p < .10$. ** $p < .05$. *** $p < .01$.

type x Region interaction, $F(1, 22) = 5.267$, $p = .032$; schizophrenia subjects taking atypical antipsychotic medications had larger anterior hippocampus and smaller posterior hippocampus than those taking typical antipsychotic medications (see Figure 5). When Medication type was entered as a covariate in the correlation matrix relating neuropsychological tests and hippocampal subregions, there were no significant changes from Table 2 evident in the pattern or size of the correlations.

DISCUSSION

Associations between hippocampus and memory are one of the core findings in neuropsychology (Milner, 2005). Both hippocampus abnormality and normal variability in volume have been linked to episodic memory measures. Because hippocampus volume deficits are among the most consistent findings in schizophrenia, a key focus of this study was to better characterize the relationship between hippocampus

subregion volume and episodic memory function in healthy control subjects and patients with schizophrenia.

The first hypothesis was that the schizophrenia group would be impaired on neuropsychological measures relative to controls. Across measures and presumed cognitive domains, with a single exception, neuropsychological function was impaired in the schizophrenia group, a finding consistent with the majority of studies investigating the extent of cognitive changes associated with schizophrenia (e.g., Goldberg et al., 1993; Gruzelier et al., 1988; Saykin et al., 1991; 1994). The exception was for the digit span backward portion of the digit span test. Further analysis indicated that a single, high-scoring subject in the schizophrenia group accounted for the lack of group difference, as he achieved the highest score of either group. With his data removed from the analysis, patients scored significantly worse than controls on the digit span backward test.

The second hypothesis was that hippocampus volume would be smaller in the schizophrenia group. This hypothesis

Table 3b. Bivariate correlations between neuropsychological tests and hippocampus regional volumes, overall WM and GM, and ICV for the schizophrenia group ($n = 24$)

Test	Right anterior	Left anterior	Right posterior	Left posterior	White matter	Gray matter	ICV
Shipley	-.463**	-.248	.318	.312	.173	.153	.208
CPT d'	-.387	-.322	-.177	.096	.037	-.238	-.117
CPT Overall	.270	-.001	-.132	-.424**	-.336	-.231	-.276
LM I	-.203	-.019	.334	.266	.321	.238	.343
LM II	-.172	.092	.100	.117	.328	.167	.284
VR I	-.398*	-.065	.393*	.685**	.278	.233	.285
VR II	-.330	-.092	.452*	.560**	.301	.244	.274
DSF	-.278	.071	-.008	.208	.239	.202	.323
DSB	-.350*	-.061	.035	.190	.329	.213	.323
ACT	-.477**	.153	.296	.197	-.003	-.017	-.066
Trails A	.404**	.180	-.256	-.602**	-.134	-.466**	-.329
Trails B	.350*	.136	-.153	-.436**	-.104	-.369*	-.229

Note. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 4a. Partial correlations between neuropsychological tests and hippocampus regional volumes for the control group, controlling for GM ($n = 24$)

Test	Right anterior	Left anterior	Right posterior	Left posterior
Shipley	.127	.215	.043	.041
CPT d'	-.215	-.195	-.179	.212
CPT Overall	.236	.008	.138	.172
LM I	.408**	.142	.262	.411**
LM II	.393*	.075	.243	.309
VR I	.112	.104	-.077	.366
VR II	.180	.303	.000	.149
DSF	.159	.196	.135	.008
DSB	-.120	.089	-.119	.025
ACT	.129	.076	.425**	.272
Trails A	-.246	-.106	-.278	-.056
Trails B	-.247	.179	-.080	-.126

Note. * $p < .10$. ** $p < .05$. *** $p < .01$.

was supported, but of particular interest was the finding that the group difference was specific to bilateral anterior (not posterior) hippocampus. Overall intracranial, GM, and WM volumes were statistically equivalent across groups, although these three measures were smaller in mean size. With increased power, that is, larger sample size, group differences may have been found. Certainly, such a finding would not be unusual and would be well supported by the prevailing literature (Andreone et al., 2007; Sanfilipo et al., 2000; 2002; Steen et al., 2006; Zipursky et al., 1998). In any case, however, none of these measures accounted for the group difference in anterior hippocampus when considered as statistical covariates, indicating that smaller hippocampus volume is not part of a more general effect for GM or WM volume, but is specific to anterior hippocampus.

Because of the importance of an intact hippocampus for episodic memory, the third hypothesis predicted that hippocampus volumes would positively correlate with episodic memory scores. Again, there was support for this hypothesis, but the answer was more complicated than initially supposed. Correlations between hippocampus and episodic

memory scores were first evaluated in healthy control subjects to establish a frame of reference. In the control group, strong positive correlations between the size of hippocampus and episodic memory test performance were observed only for LM I and LM II, tests of immediate and delayed verbal memory. Verbal memory is often thought to be lateralized to the left hemisphere, yet positive correlations with both left posterior and right anterior hippocampus volumes indicate that current models of episodic memory may be oversimplified. Certainly, frontotemporal interaction and intrahippocampus circuitry are critical to the encoding, storage, and retrieval of relevant information. VR I and VR II, tests of memory for nonverbal information, evinced no correlations with any measure of hippocampus volume in controls.

A fourth prediction was that the pattern of correlations established in controls would not hold for the schizophrenia group, and this hypothesis was supported. Patterns of correlations between episodic memory scores and hippocampus volumes differed markedly according to diagnosis. Bilateral posterior hippocampus volumes correlated positively with

Table 4b. Partial correlations between neuropsychological tests and hippocampus regional volumes for the schizophrenia group, controlling for GM ($n = 24$)

Test	Right anterior	Left anterior	Right posterior	Left posterior
Shipley	-.529**	-.380*	-.230	.174
CPT d'	-.373*	-.240	-.137	.210
CPT Overall	.330	.126	-.050	-.304
LM I	-.391*	-.184	.099	.149
LM II	-.243	-.092	.057	.097
VR I	-.466**	-.183	.253	.486**
VR II	-.404**	-.213	.293	.330
DSF	-.323	.029	-.075	.101
DSB	-.406**	-.186	-.047	.045
ACT	-.495**	-.178	.250	.146
Trails A	.531***	.430**	-.031	-.235
Trails B	.432**	.285	.071	-.050

Note. * $p < .10$. ** $p < .05$. *** $p < .01$.

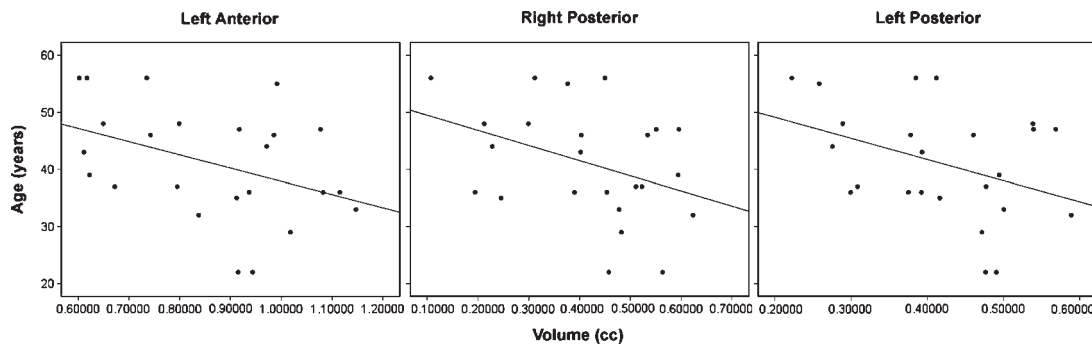


Fig. 4. Scatterplots represent the significant correlations between age and hippocampus subregional volumes in the schizophrenia group.

performance on VR I and VR II in the schizophrenia group. Since mean posterior hippocampus volumes did not differ by group, this finding suggests that hippocampus organization in service to episodic memory is quite different in schizophrenia. Perhaps most damaging to a simple “bigger-is-better” model was the finding that right anterior hippocampus volume was *negatively* correlated with both verbal and non-verbal memory functions (i.e., LM I, VR I, and VR II) in schizophrenia. That these partial correlations were weaker and generally nonsignificant (but still negative) in bivariate correlations suggests that the effect is partially, but not entirely, accounted for by overall brain size in schizophrenia. It may be that smaller size reflects more efficient design or some developmental anomaly associated with schizophre-

nia. For example, anomalous schizophrenia neurodevelopment is thought to involve neurodevelopmental delays interacting with a fixed “developmental window” (see Yeo et al., 2007). To the extent that a “smaller-is-better” model applies to hippocampus function in normal childhood (Van Petten, 2004), it is possible that the present negative correlations simply reflect a straightforward schizophrenia neurodevelopmental delay. Of course, the current negative association between hippocampal volume and episodic memory score runs contrary to the typical findings in this literature and requires replication.

Beyond the main hypotheses, the effects of demographic variables were considered. The age of subjects in this study ranged from 20 to 62 years. There was a strong negative association between overall GM volume and age that was equivalent for both groups. In controls, however, there was no effect for age on hippocampus volume, which appeared to remain relatively constant across the lifespan (at least ages 20–62). In contrast, hippocampus volume in the schizophrenia group correlated with age to the same extent as overall cortical volume. The cross-sectional design and limited sample size in the present study allow only for speculation as to the cause of this finding. Other researchers have demonstrated similar effects among controls (Sullivan et al., 1995) and subjects with schizophrenia (Chakos et al., 2005). These findings invite further investigation into possibly differential aging of neocortical versus limbic cortical tissue. Another demographic variable effect investigated was gender. This sample was drawn from the population of a veteran’s hospital, and the small number of women included reflects the representation of women in that population. Because of the small sample size, this study was not an ideal test of population-typical gender differences. When sex was considered as a covariate in the analysis, there was no evidence of an effect.

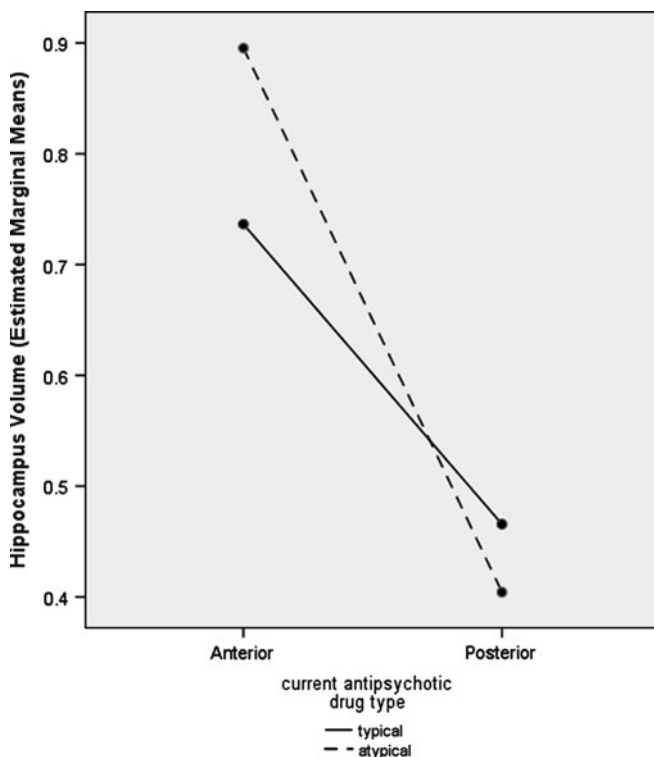


Fig. 5. Schizophrenia patients taking atypical antipsychotic medications had larger anterior hippocampi and smaller posterior hippocampi than those taking typical antipsychotic medications.

In brain-behavioral studies of schizophrenia, the effect of medication must be considered. When included as a covariate, medication type had no effect on the hippocampus–memory correlations, suggesting that medication does not mediate this relationship. Rather, schizophrenia subjects taking atypical antipsychotic medications were found to have

larger anterior hippocampi and smaller posterior hippocampi than those taking typical antipsychotic medications. This group was a chronic population and had been on medication for years or decades. Medication decisions for these patients were based on clinical criteria of maximizing good effects and limiting side effects, using the standard VA formulary. It may be that this pattern of hippocampal structure is an indicator of who will derive the best outcome from each medication type; however, this result was unexpected and will require replication.

Hippocampus volume is consistently and positively associated with episodic memory performance across both the normal lifespan and a host of disorders, including temporal lobe epilepsy, neurodegenerative disease, depression, post-traumatic stress disorder, dementia, and Alzheimer's disease (Griffith et al., 2004; Hickie et al., 2005; Kramer et al., 2004; 2005; Mungas et al., 2005; Nemeroff et al., 2006; Petersen et al., 2000; Reminger et al., 2004; Walhovd et al., 2004). In none of these disorders has the relationship between hippocampus volume and episodic memory function differed notably from that for normal samples. Hence, growing evidence for a divergent pattern of correlations between hippocampus volumes and episodic memory scores in schizophrenia suggests the presence of multiple processes in this disorder. These processes may be more complex than the hippocampus atrophic changes found in dementia or epilepsy that result in a relatively linear correspondence between reduced hippocampus volume and impaired episodic memory. Although the present study did identify an inverse correlation of hippocampus volume and age in the schizophrenia group, this effect was not associated with decrements in episodic memory performance. It may be that the abnormal structure-function relationship between hippocampus and episodic memory in schizophrenia precedes the onset of the disorder and catalyzes an abnormal aging process throughout the lifespan.

Several weaknesses in this research remain to be addressed. The generalizability of the present conclusions regarding hippocampus volume and episodic memory relationships is limited by the relatively small sample size. The use of a longitudinal design in the future would allow for stronger conclusions regarding aging and hippocampus-memory relationships in schizophrenia. Further, the investigation of sex differences was weakened by the gender bias in this VA sample. Moreover, very recent research by Squire and colleagues (i.e., Bayley et al., 2008) suggests that certain aspects of semantic memory processing traditionally assumed to be based in the hippocampus actually involve neocortical structures while minimally engaging the hippocampus. To the extent that this is true, some of the variance unaccounted for in episodic memory scores might be explained by abnormalities in distal neocortical regions. It may be that schizophrenia hippocampus-memory relationships are best considered in the context of a distributed brain network (Eyler et al., 2008; Nestor et al., 2007), and future research will be necessary to investigate this possibility. Our current results require replication prior to drawing any strong conclusions, but the data

serve as an incremental step in our understanding of brain-behavioral relationships in schizophrenia.

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