Published in final edited form as:
Neuroimage. 2011 June 15; 56(4): 1865–1874. doi:10.1016/j.neuroimage.2011.03.079.

Covariance Modeling of MRI Brain Volumes in Memory Circuitry in Schizophrenia: Sex Differences are Critical

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Abstract

Women have consistently demonstrated better verbal memory on tests that evaluate immediate and delayed free recall. In patients with schizophrenia, these verbal memory processes are relatively more preserved in women than men. However an understanding of the brain anatomy of the female advantage for verbal memory is still unclear.

29 females and 59 males with schizophrenia made comparable to 21 female and 27 male healthy volunteers were scanned using structural magnetic resonance imaging (sMRI) in order to assess volumes of regions across the entire brain. Sex differences within and between groups in the covariance structure of memory circuitry regions were evaluated using a novel approach to covariance analysis (the Box M Test). Brain areas of interest included prefrontal cortex (PFC), inferior parietal lobule (iPAR), anterior cingulate gyrus (ACG), parahippocampus, and hippocampus (HIPP).

Results showed significant differences in the covariance matrices of females and males with schizophrenia compared with their healthy counterparts, in particular the relationships between iPAR-PFC, iPAR-ACG, and HIPP-PFC. Sex differences in the iPAR-PFC relationship were

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significantly associated with sex differences in verbal memory performance. In control women, but not in men ACG volume correlated strongly with memory performance. In schizophrenia, ACG volume was reduced in females, but not in men, relative to controls.

Findings suggest that the relationship between iPAR and PFC is particularly important for understanding the relative preservation of verbal memory processing in females with schizophrenia and may compensate for ACG volume reductions. These results illustrate the utility of a unique covariance structure modeling approach that yields important new knowledge for understanding the nature of schizophrenia.

Keywords

Verbal memory; sex differences; schizophrenia; magnetic resonance imaging; brain morphometry; covariance

1. Introduction

There is a well-documented tendency for healthy adult women to score higher than healthy men on verbal memory tests (Herlitz et al., 1999; Joseph et al., 1982; Kail and Siegel, 1977; Kramer et al., 1988; Larrabee and Crook, 1993; Larrabee et al., 2000; Norman et al., 2000; Schaie and Willis, 1993; Trahan and Quintana, 1990; Van Der Elst et al., 2005; West et al., 1992; Youngjohn et al., 1991; Zelinski et al., 1993), particularly on free and delayed recall measures of verbal declarative memory (e.g., Delis et al., 1988; Gale et al., 2007; Hazlett et al., 2010; Herlitz et al., 1999; Kail and Siegel, 1977; Kramer et al., 1988; Larrabee and Crook, 1993; Larrabee et al., 2000; Van Der Elst et al., 2005). However, there is little understanding of the anatomy underlying the effect. Typically, differences are on the order of a quarter to half of a standard deviation and are independent of age, education, and other sociodemographic characteristics (Norman et al., 2000; Paolo et al., 1997; Rabbitt et al., 1995; Schaie and Willis, 1993; West et al., 1992; Zelinski et al., 1993). Reports suggest that the female advantage in memory in part is due to the organization of recall and efficient use of memory strategies, such as a semantic-based organizational strategy (Kramer et al., 1988, 1997; Van Der Elst et al., 2005). In fact, even on visual declarative memory tasks where it is possible to verbally encode items, women have shown better memory than men (Kramer et al., 1997; Lewin et al., 2001).

When no significant difference between males and females is reported, the measure of recall typically involves a limited (or closed) set of items, such as digits and letters (Jahoda, 1981; Orsini et al., 1987). Closed stimulus sets may make the memory task easier or raise the potential for guessing (Larrabee and Crook, 1993; Larrabee et al., 2000). Differences also have not been found on tests of recognition memory (Herlitz et al., 1999; Joseph et al., 1982; Kramer et al., 1988, 1997, 2003), cued recall (Saykin et al., 1995) or other forced-recall strategies, including the story-based recall associated with the Wechsler Memory Scale (e.g., Wechsler, 1997) Logical Memories subtests (Dodrill, 1979; Saykin et al., 1995).

This cognitive sex difference raises the possibility that these effects, at least in part, are associated with structural brain differences between the sexes. Sex differences in memory performance in healthy individuals are consistent with sex differences in structural brain volumes (relative to cerebrum size) in areas known to contribute to verbal declarative memory function, including the prefrontal cortex (PFC; Allen et al., 2003; Goldstein et al., 2001; Luders et al., 2009; Schlaepfer et al., 1995), anterior cingulate gyrus (ACG; Allen et al., 2003; Chen et al., 2007; Goldstein et al., 2001; Good et al., 2001; Pujol et al., 2002), hippocampus (HIPP; Filipek et al., 1994; Giedd et al., 1996; Goldstein et al., 2001), and

parietal cortex (PAR; Allen et al., 2003; Chen et al., 2007; Goldstein et al., 2001; Good et al., 2001; Nopoulos et al., 2000; Schlaepfer et al., 1995). These studies show that the PFC, ACG, HIPP, and PAR are larger in the healthy female brain, relative to the size of the cerebrum, than in males. Women have also been found to have larger neuron somata in these regions (Rabinowicz et al., 1999, 2002), larger gray/white matter ratio (Allen et al., 2003; Rabinowicz et al., 1999, 2002; Sowell et al., 2007), and thicker gray matter in the dorsolateral prefrontal cortex (DLPFC; (Luders et al., 2009; Sowell et al., 2007) and PAR (Cosgrove et al., 2007; Luders et al., 2009; Sowell et al., 2007; Witelson et al., 1995).

Systematic examinations of sex differences in declarative verbal memory using functional magnetic resonance imaging (fMRI) are lacking, but other imaging work suggests a functional sexual dimorphism that complements the structural one. A positron emission tomography (PET) study by Nyberg and colleagues (2000) compared glucose metabolism during encoding and retrieval using a CVLT-like task. Women showed a greater increase in relative glucose metabolism during retrieval in bilateral ACG and right anterior PAR. Men showed a greater increase in relative metabolism in a more posterior area of PAR, which was bilateral rather than the lateralized effect seen in women (Nyberg et al., 2000). This higher glucose metabolism in women during retrieval in a CVLT-like task has recently been replicated (Hazlett et al., 2010). Furthermore, an fMRI study of estrogen replacement therapy (ERT) in post-menopausal women showed higher blood-oxygen-level-dependent (BOLD) signal change during encoding in DLPFC and PAR with ERT (Persad et al., 2009). In fact, most study participants are tested without regard to menstrual cycle, thereby potentially obscuring beneficial effects of cycle-time-dependent hormones, which have been found on verbal memory measures in regularly cycling females (Otero Dadin et al., 2009; Rosenberg and Park, 2002), postmenopausal females (e.g., Maki and Resnick, 2000), and transsexual males (Miles et al., 1998).

Taken together, previous studies indicate that healthy women compared to healthy men perform better on verbal memory tasks, have larger volumes of memory-related brain areas (relative to overall brain volume), and show greater activation in brain areas related to verbal declarative memory function. Additionally, these differences have been shown to be driven, in part, by gonadal hormones (e.g., McEwen and Woolley, 1994; Protopopescu et al., 2008). The present investigation examines the extent to which the covariance of structural brain regions can explain sex differences in verbal memory. Specifically, we are interested in explaining a relative preservation of verbal memory in females with schizophrenia compared to their male counterparts.

Sex differences in the healthy population have implications for understanding cognitive and anatomical abnormalities in schizophrenia, the magnitude of which varies by sex. Verbal memory is one of the most affected cognitive domains in first-episode and chronic patients with schizophrenia (Aleman et al., 1999; Cirillo and Seidman, 2003; Heinrichs and Zakzanis, 1998; Mesholam-Gately et al., 2009). Brain regions, such as frontal, temporal, and hippocampal areas, underlie verbal declarative memory and show some of the largest volumetric reductions in schizophrenia (Ellison-Wright et al., 2008; Honea et al., 2008; Seidman et al., 2002; Shenton et al., 1992; Wright et al., 2000). Within the frontal cortex, there are reductions in ACG and DLPFC, with a greater DLPFC reduction in chronic patients with schizophrenia (Ellison-Wright et al., 2008), that are related to verbal memory impairments, especially impairments to encoding processes (Antonova et al., 2004; Baaré et al., 1999; Ho et al., 2006; Maher et al., 1995; Matsui et al., 2008; Olli et al., 2009; Sanfilipo et al., 2002; Seidman et al., 2002; Thoma et al., 2009; Turetsky et al., 2002; Wexler et al., 2009).

Men with schizophrenia are more impaired on verbal memory tasks than women in small samples when controlled for sampling and other potential confounds (Goldstein et al., 1998, 1994; Nopoulos et al., 2000). Importantly, sex differences between patients with schizophrenia are larger than sex differences in verbal memory in the healthy population, which suggests that sex differences in patients are not simply a reflection of normative sex differences. This cognitive difference may be related to the propensity for greater severity of illness among men than women with schizophrenia (Goldstein, 1988; Goldstein et al., 1990; Haas and Castle, 1997; Häfner et al., 1993; Leung and Chue, 2000).

The goal of the analysis presented here is to contribute to understanding the neuroanatomical underpinnings of sex differences in verbal memory function in schizophrenia. We will examine the covariance structure of memory-related brain regions (i.e., a memory network) in males and females with and without schizophrenia. These areas include posterior cingulate (BA 23, 29, & 30), inferior parietal (BA 40), parahippocampus (as well as entorhinal cortex), HIPP, ACG (BA 24, 33, 32), inferior frontal gyrus (BA 44 & 45), and PFC (BA 8, 9, 6, 36) (Cabeza et al., 2008; Cirillo and Seidman, 2003; Eichenbaum, 2004; Golby et al., 2001; Goldman-Rakic, 1988, 1984; Krause et al., 1999; Mesulam, 1990; Moscovitch, 2008; Petrides et al., 1993; Schacter et al., 2007; Skinner and Fernandes, 2007; Squire et al., 2004; Stone et al., 2005; Thermenos et al., 2007; Tulving, 2002). Relating observed sex differences in covariance structure to sex differences in verbal memory performance will contribute to understanding the relative preservation of verbal memory performance in women compared to men with schizophrenia. To achieve these aims, we applied the Box M Test (Box, 1949) in a novel way to test for covariance differences between the sexes for patients and healthy controls. Our goal was to study the *network* of brain regions supporting memory function, test whether the illness *differentially* affected the relationships between brain volumes by sex, and determine what role this *differential* effect might play in explaining sex differences in verbal memory in schizophrenia.

2. Methods

2.1 Subjects

The present sample included subjects reported in previous work (Goldstein et al., 2002; Seidman et al., 2002) and additional schizophrenia cases (n=50) from the Harvard cohort of the NIMH Genetics Schizophrenia Initiative (GSI) scanned in one of our previous studies (NIMH MH56956 (JMG, P.I.; Makris et al., 2010). Patients with schizophrenia (n=90) were recruited from three public Boston area psychiatric hospitals serving primarily psychotic patients (Goldstein et al., 1999) and from the New England region for the NIMH GSI sample. Subjects were excluded if they were found to have any of the following conditions: substance abuse for the past six months, history of head injury with documented cognitive sequelae or loss of consciousness > five minutes, neurological disease or damage, or medical illnesses that significantly impaired neurocognitive function. Cases were DSM-III-R schizophrenia probands diagnosed based on interviews conducted by experienced diagnostic interviewers and systematic review of medical records. Senior investigators (JMG, LJS) reviewed all material to determine diagnosis (see previous work listed above for details and excellent reliability). In addition to diagnosis, subjects were selected to be between the ages of 23 and 68 years at MR imaging, have at least an eighth-grade education, speak English as their first language, and have an estimated IQ of 65 or more. Two case subjects were excluded due to motion artifacts leaving a sample of 88 individuals with schizophrenia.

Healthy comparison subjects (n=48) were recruited through advertisements in the Boston area and notices posted on bulletin boards at the hospitals from which the patients were ascertained. Comparison subjects were selected to be comparable to patients in (Goldstein et al., 1999) on age, sex, ethnicity, parental socioeconomic status, and handedness. They were

screened for current psychopathology by means of a short form of the Minnesota Multiphasic Personality Inventory (MMPI-168) and family history of psychoses or psychiatric hospitalizations. We excluded control subjects if they had current psychopathology or lifetime history of any psychosis, family history of psychosis, or psychiatric hospitalization, or if any MMPI clinical or validity scale score, except Masculinity-Femininity, was above 70.

Written informed consent was obtained from all subjects after providing a complete description of the study, and they were compensated for their time and participation. This study was approved by the Harvard Medical School and hospital (Massachusetts Mental Health Center and Massachusetts General Hospital) Human Studies committees.

2.2 Neuropsychological Testing

The Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) estimated current general intelligence (Brooker and Cyr, 1986) using adjusted scales from Sattler's tables (Sattler, 1982). The Reading subtest of the Wide Range Achievement Test – Revised (Jastak and Wilkinson, 1984) was used as an estimate of intellectual potential (Kremen et al., 1995). Memory was tested using the California Verbal Learning Test (CVLT; Delis et al., 1988). The CVLT is a measure of list learning using recall and recognition. The measures that are reported here are total number of items recalled on the last trial of the task, an estimate of the use of semantic recall strategies ("Semantic cluster score"), and an estimate of the use of serial recall strategies ("Serial processing score"). The semantic cluster score was calculated by counting the number of items from the same category that were recalled together and then adjusting for the baseline probability of these items being recalled together given the number of words (n=16) and categories (n=4). The serial cluster score was calculated by counting the number of items that were recalled in the same order as they were presented and then adjusting for the baseline probability given the number of items. Due to changes in post-scan protocol during the study approximately half of the cases completed the CVLT (31 males, 14 females), and the other half received the Wechsler Memory Scale-III (Wechsler, 1997). However, given that we were interested in sex differences in verbal memory, and given that the WMS-III Logical Memory Stories, which as cited in the Introduction does not yield sex differences (e.g. Dodrill, 1979; Saykin et al., 1995), we changed the post-scan protocol during the study to the CVLT.

2.3 MRI Scanning

MRI scans were acquired at the Athinoula Martinos Biomedical Imaging Center at Massachusetts General Hospital (MGH) with a 1.5 Tesla General Electric Signa scanner.Contiguous 3.1 mm coronal spoiled gradient echo images of the entire brain were obtained with the following acquisition parameters: TR = 40 msec, TE = 8 msec, flip angle = 50°, field of view = 30 cm, matrix = 256 × 256, and averages = 1. MR images were analyzed at the MGH Center for Morphometric Analysis (CMA). Images were normalized in space to adjust for variation in head position by imposing a standard 3-dimensional (3D) coordinate system on MR scans (Caviness et al., 1996; Filipek et al., 1994), and resliced into normalized 3.1 mm coronal scans.

We restricted the network to areas that (as discussed in the Introduction) demonstrate: *1.) Involvement in memory across all tasks and methods found in a PubMed* (National Center for Biotechnology Information, U.S. National Library of Medicines, Bethesda, Maryland) *search of studies using or reviewing the use of representative methods for studying the cognitive neuroscience of memory* (Cabeza et al., 2008; Cirillo and Seidman, 2003; Eichenbaum, 2004; Golby et al., 2001; Goldman-Rakic, 1988, 1984; Krause et al., 1999;

Mesulam, 1990; Moscovitch, 2008; Petrides et al., 1993; Schacter et al., 2007; Skinner and Fernandes, 2007; Squire et al., 2004; Stone et al., 2005; Thermenos et al., 2007; Tulving, 2002) *2.) Anatomical abnormalities found in schizophrenia* (Ellison-Wright et al., 2008; Goldstein et al., 1999; Honea et al., 2008; Seidman et al., 2002; Shenton et al., 1992; Wright et al., 2000), *3.) Sexual dimorphisms* (Allen et al., 2003; Chen et al., 2007; Filipek et al., 1994; Giedd et al., 1996; Goldstein et al., 2001, 2002; Good et al., 2001; Nopoulos et al., 2000; Schlaepfer et al., 1995), and *4.) Anatomical connections between regions* (Barbas and Pandya, 1989; Fletcher et al., 1999; Goldman-Rakic, 1988, 1984; Petrides and Pandya, 1984; Seltzer and Van Hoesen, 1979; Sesack et al., 1989). These criteria yielded a network of ACG, PFC, HIPP, parahippocampus (parHIPP), and inferior parietal cortex (iPAR) regions.

MR Segmentation and Parcellation—Scans were segmented using a semi-automated technique described in (Caviness et al., 1996; Filipek et al., 1994; Goldstein et al., 1999; Rademacher et al., 1992; Seidman et al., 1999), which uses automatic algorithms for tissue classification and manual delineation using Caviness and colleagues' (1996) CARDVIEWS software (CMA, Boston, Massachusetts; see details below). As a general overview, tissue classification yields separate compartments of neocortex, subcortical gray nuclei, white matter, and ventricular system subdivisions generally corresponding to natural tissue boundaries distinguished by signal intensities in the T1-weighted images. The neocortex was then manually subdivided into bilateral parcellation units based on the system in (Caviness et al., 1996) and applied in (Goldstein et al., 1999) to schizophrenia.

The only pre-processing that was done was a reorientation of each subject's scan to control for differences in head position during scanning. For this, images were oriented by imposing a standard 3D coordinate system on each 3D MRI scan, using the midpoints of the decussations of the anterior and posterior commissures and the midsagittal plane at the level of the posterior commissure as points of reference for rotation and (nondeformation) transformation. Scans were then resliced into normalized 3.0-mm coronal, 1.0-mm axial, and 1.0-mm sagittal scans and were analyzed according to the semi-automated technique described below (Filipek et al., 1994; Goldstein et al., 1999). No deformation or normalization was applied to the scan; all structural analysis was completed in each subject's native space.

Each slice of the oriented coronal scans was segmented into gray and white matter and ventricular structures using a semiautomated intensity-contour–mapping algorithm (Caviness et al., 1996) and signal-intensity histogram distributions. The segmentation algorithms first define image intensity contours by interpolating across signal intensity transition zones and creating a border formed by the pixels with intensity values closest to the contour value (Note: This procedure does not rely on absolute signal value as do global-threshold techniques (Filipek et al., 1994). Once the external borders of the hemispheres and ventricles are defined, a histogram of the signal intensity distribution for each hemisphere is used to classify voxels as gray or white matter. The histogram of each hemisphere resulted in a bimodal distribution of voxel intensity values, the nadir of which defines the gray-white border (Filipek et al., 1994).

Specific regions of interest were defined as follows using the definitions given by Filipek and colleagues (1994) and Caviness and colleagues (1996). **HIPP** was defined superolaterally by the interface with the inferior horn of the lateral ventricle, inferolaterally by white matter, and inferomedially by a secondary border connecting the medial tip of the subjacent white matter with the subiculum-parahippocampal gyrus interface. The secondary ventromedial transition from the amygdala to hippocampus was calculated as occurring at 10/24 of the distance between the anterior and posterior commissure. HIPP served as the

medial border to **parHIPP** and the collateral sulculs served as the lateral border. The parHIPP extends in the anterior direction until the first coronal slice that contains the temporofrontal junction and in the posterior direction to the anterior end of the calcarine sulcus. **iPAR** was a large area that included anterior supramarginal gyrus, posterior supramarginal gyrus, and angular gyrus. It was on the lateral surface of the cortex, and encompassed an area from the postcentral gyrus, back in a dorsal and posterior direction along the sylvian fissure and intraparietal sulcus on its dorsal edge and the superior temporal sulcus on its ventral edge to the posterior extent of the angular gyrus. This point was defined as the point where the parietoccipital sulcus meets the dorsal hemispheric margin. **PFC** was defined as the region between the superior and inferior frontal sulcus, with its posterior border defined by the intersection of these sulci and the precentral gyrus, and the anterior border defined by the edge of the frontal pole, which runs perpendicular to the AC-PC axis at the rostral end of the anterior horizontal ramus of the sylvian fissure. **ACG** was defined as the cingulate gyrus from the genu of the corpus callosum to the precentral sulcus, with the dorsal and ventral boundaries defined by the cingulate and callosal sulci, respectively.

Volumes, measured in cubic centimeters (cm^3), were calculated for each region by multiplying the slice thickness by the area measurement on each slice and summing the slices on which the region appeared. All measurements were divided by the volume of the subject's total cerebrum to adjust for potential group differences in total brain volume. Very good inter- and intra-rater reliability of regions has been established in numerous previous studies [e.g. (Goldstein et al., 1999; Herbert et al., 2005)].

The 136 brains in the current study were randomly assigned to 7 raters. The raters' measurements of the above brain regions were made as part of a whole-brain analysis carried out by the laboratory from 1992–1997 using a standardized protocol. All raters met laboratory standards for reliability (Filipek et al., 1994; Goldstein et al., 1999; Herbert et al., 2005), defined as intraclass correlations that were excellent (ICC > .80) or very good (ICC <.70), in all of the regions examined here. Raters were blind to the subject's diagnosis, sex, and memory ability.

2.4 Statistical Analysis

A general linear model (GLM) was used to test for differences in memory performance by group (patients versus controls), sex, and the sex by group interaction. To test the equality of covariance matrices across groups, we employed the Box M test (Box, 1949). The Box M statistic is calculated as follows:

$$M=(n-T)\ln|C|-\sum_{i=1}^{T}(n_i-1)|C_i|$$

$$C=\frac{1}{n-T}\sum_{i=1}^{T}(n_i-1)C_i$$

where C_i is the variance-covariance matrix calculated from the sample group i; T is the total number of sub-groups where the equality of matrices is tested; $n=n_1+n_2+\ldots n_Y$; n_i is the sample size of group i.

Box showed that the M statistic can be approximated by either a chi-square statistic or an F statistic. The chi-square approximation of the Box M statistic is appropriate for small dimensional problems of five variables or less (Morrison, 1990). Hence, we employed the chi-square statistic in our analysis. Box (1949) showed that the product Mh is a chi-square with $p(p+1)(T-1)/2$ degrees of freedom where:

$$h=1-\frac{2p^2+3p-1}{6(p+1)(T-1)}\left[\sum_{i=1}^{T}\frac{1}{n_i-1}-\frac{1}{n-T}\right]$$

p=number of variables in the matrix

If the observed chi-square, *Mh*, is larger than the critical value, then one would reject the null hypothesis (the equality of the covariance matrix).

However, the rejection of the equality of the covariance matrix does not necessarily indicate differences between individual correlations. In order to test the equality of individual correlation coefficients after rejecting the equality of the covariance matrix, we adapted the methodology described in (Papoulis, 1990). First, correlation coefficients were converted to a normal distribution by Fisher's z-transform (Fisher, 1925) using the following equation,

$$z_{i,j,k}=(1/2)[\ln(1+r_{,j,ki})-\ln(1-r_{i,j,k})]$$

where $r_{i,j,k}$ is correlation between region *i* and region *j* in group *k*.

For a given pair of groups *u*, *v*, with sample size n_u, n_v the difference:

$$\bar{z}_{i,j}=\frac{z_{i,j,u}-z_{i,j,v}}{\sqrt{1/(n_u-1)+1/(n_v-1)}}$$

is approximately standard normally distributed (i.e. zero mean, unit variance, Gaussian distributions). Therefore, we can use the z-value to test for differences between correlations by setting a threshold for rejection of equal correlations based on the probability of Type I and Type II errors of a given $\bar{z}_{i,j}$.

We set a significance threshold of $p < .05$ for the Box M test, the differences between mean brain volumes, the correlations between memory performance and anatomical volume, and z-tests of group differences based on a Fisher's z transformation of these correlations. We set a threshold of $p < .10$ for the simple correlations between the volumes of anatomical areas and z-tests for group differences in these correlations. The latter threshold is more liberal than the other tests given that the overall Box-test was significant and therefore allowed for "protection" of multiple testing for the simple correlations. The weak power associated with a small sample size meant that the probability of a Type II error was more likely than in the other tests, therefore the threshold was adjusted to protect against this error in order to view any trends in the data. Threshold selection ultimately did not impact the significance of results involving the case group.

3. Results

3.1 Sample Demographics

There were no significant sex differences or significant interactions between sex and case-control status on sociodemographic variables (see Table 1). There were significant differences (at $p < .05$) between patients with schizophrenia and the healthy comparisons as a whole on age (a small difference), education, WAIS-R vocabulary, WAIS-R block design, Sattler IQ, WRAT-reading subtest, and socioeconomic status (SES). However, the mean and standard deviation (as well median and range) of age in the male and female case groups were comparable and the interaction of age with group status was not significant.

Additionally, education and IQ differences between patients and controls most likely reflects illness differences in both males and females, as demonstrated in many previous studies [see (Isohanni et al., 2001) or (Woodberry et al., 2008) for a review]. In fact, parental education, which serves as a reflection of SES of origin, did not differ between groups. Male and female patients were not significantly different on any clinical measures.

3.2 Sex Differences in Verbal Memory

There was a significant sex difference in the number of items recalled on Trial 5, with females (78.0%) recalling more than males (64.4%) [$F(1,88) = 9.94$, $p < .01$], and healthy controls (78.3%) recalling more than the patients (60.4%) [$F(1,88) = 26.91$ $p < .01$] (see Table 2). Further, there was a significant sex difference in the use of semantic clustering for recall, which was higher among females than males [$F(1,88) = 13.76$, $p < .01$] and higher among healthy adults than patients [$F(1, 88) = 16.27$, $p < .01$]. There was no significant interaction on Trial 5 recall [$F(1,88) = 1.82$, p =.18], although the effect size between female cases and controls (Cohen's d=.64) was substantially less than that of male cases and controls (d=1.01). Further, the effect size between female and male controls (d=.49) was less than that between female and male cases (d=.82). There were no significant differences as a function of sex, group (patient or comparison group), or sex by group in the number of items recalled as serial clusters. For the whole sample and within patients alone, GLMs that included age, age by sex, and age by sex by group showed no significant effects.

Table 3A shows the correlations between regions of interest by sex and group and Table 3B shows the means and standard deviations of the brain volumes. The Box M Test of differences between the correlation matrices of regional brain volumes showed a significant sex by group interaction, wherein there was a significant difference between female and male cases [χ^2 (15) = 38.30, $p < .001$], but no significant difference between female and male controls [χ^2 (15) = 12.32, $p = .65$]. Further, there was a greater difference between female cases and female controls [χ^2 (15) = 20.03, $p = .17$] than between male cases and controls [χ^2 (15) = 12.27, $p = .66$]. There was no significant difference between patients and controls when sex was ignored: [χ^2 (15) = 9.30, $p = .86$].

The overall covariance difference between female and male cases was driven by differences in three relationships (see Figure 1): iPAR-PFC (z = 2.54, $p = .01$), iPAR-ACG (z = 2.16, $p < .05$), and HIPP-ACG (3.31, $p < .01$). For each of these correlations, men showed no relationship or the opposite relationship compared to women. Females showed a negative correlation between iPAR-PFC (r = −.30, $p = .10$) and HIPP-ACG (r = −.55, $p < .01$) and a positive correlation between iPAR-ACG (r = .35, p =.06). In contrast, men showed a positive correlation between iPAR-PFC (r = .28, $p < .05$) and no relationship in HIPP-ACG (r = .17, p =.20) or iPAR-ACG (r = −.15, $p = .26$).

These differences were not simply a reflection of normal sex differences between male and female controls for three reasons. First, as reported above, there was no significant sex difference between the covariance matrices of controls. Second, male and female controls showed no significant post-hoc differences between iPAR-ACG correlations (z = 0.00, p = .99) or HIPP-ACG correlations (z = 1.00, $p = .50$), which is a more liberal test of sex differences than the Box M Test. Third, female controls showed a positive relationship between iPAR-PFC (r = .36), while female cases showed a negative relationship (r = −.30).

In order to investigate the functional significance of the sex differences in covariance among brain regions, the brain volumes were correlated with memory performance in men and women (see Table 4). In fact, in female cases, there was a negative correlation between CVLT Trial 5 performance and semantic clustering and the volume of PFC (r = −.51, p = .06 and r = − .45, $p = .10$). However, females who performed well on the CVLT due to the

use of semantic clustering had larger iPAR even though they had smaller PFC volumes. These women also had a larger HIPP in relation to ACG (r = −.55). Fisher's z tests resulted in significant sex differences between memory measures and PFC volumes (see Table 4).

The ACG was the only brain region for which there was an interaction (although at a trend level) between illness status and gender [F(1,132) = 2.86, $p = .09$; see Table 5]. For female controls, the ACG had the strongest relationship with memory performance. Trial 5 recall (r = .44, $p < .05$), semantic clustering (r = .26, $p = .26$), and serial clustering (r = .33, $p = .15$) all had positive correlations with ACG, though not all were significant. Female cases had volumes that were reduced by about 12% ($\bar{x}$ = 1.06 cm^3, SD = .23) compared to their control counterparts ($\bar{x}$ = 1.20, SD = .26), but were similar to male patients ($\bar{x}$ = 1.08, SD = .22), and their controls ($\bar{x}$ = 1.09, SD = .19). The only other area where female patients had a smaller volume compared to controls was in the HIPP, where there was an approximately 5% decrease [$\bar{x}$ = .74, SD = .09 for patients; $\bar{x}$ = .78, SD = .08 for female controls; F(1,132) = 4.39, $p = .04$].

4. Discussion

These findings demonstrate a significant sex difference in schizophrenia, but not healthy controls, in the covariance of structural brain volumes in regions implicated in verbal memory circuitry. Further, these sex differences were significantly associated with sex differences in memory function. Females with schizophrenia compared with female controls demonstrated significant covariance differences between hippocampus (HIPP) and anterior cingulate gyrus (ACG), inferior parietal lobule (iPAR) and prefrontal cortex (PFC), and iPAR and ACG, suggesting variability in volumetric reductions in female patients. In males, these relationships were not significantly different between cases and controls, given that volumes in male patients were reduced in a consistent way across all regions in the network. Male patients showed volumetric reductions in HIPP, paraHIPP, PFC and iPAR, and their HIPP and PFC volumes were significantly related to memory performance, which was poorer than in female patients.

We interpret this pattern of findings as suggesting that female cases may be able to recruit less affected brain regions (such as iPAR) better, which contributes to better memory performance through the semantic organization of material for recall. These findings are underscored by the fact that there were no significant IQ or WRAT-Reading differences within sex by group or within group by sex. Aging has important effects on changes in brain structure over time, which differs for men and women. However, our data do not represent the full aging spectrum (and we found no significant age by sex by group effects). Therefore gender and illness had stronger relationships with differential patterns of regional brain volume associations, which were significantly associated with better memory function in female patients compared to their male counterparts.

A previous study of primarily male subjects has demonstrated that correlations between frontal regions and the rest of the cerebral cortex are significantly different from non-ill subjects and differ between "good" outcome and "poor" outcome patients (Mitelman et al., 2005). Fronto-cingulate and fronto-mediotemporal correlations were positively correlated in good outcome patients and fronto-superiotemporal correlations were negative. The correlations were reduced in patients with poor outcomes. These data, along with our findings, suggest that the consistent reductions in HIPP and ACG in male patients are clinically important, even though the *covariance* between them was not statistically significant.

Our results in women with regard to iPAR are consistent with relatively new evidence implicating iPAR in memory function as seen in fMRI and lesion studies (Cabeza et al., 2008; Wagner et al., 2005). iPAR is involved in assessing the level of confidence in memory retrieval (Moscovitch, 2008; Skinner and Fernandes, 2007) and recall (Squire et al., 2004) through the coordination of iPAR with PFC and iPAR with HIPP (Addis et al., 2007; Krause et al., 1999). The involvement of HIPP and paraHIPP in memory has been well established (see reviews in (Eichenbaum, 2004; Mesulam, 1990; Moscovitch, 2008; Squire et al., 2004). ParaHIPP (including entorhinal cortex) has reciprocal connections to heteromodal association cortex, which in turn connects to primary sensory areas (Mesulam, 1990; Squire et al., 2004). These cortical regions were not finely segmented and (because they shared an anatomical border) not independent of HIPP in the present study, which may explain the lack of correlation between paraHIPP and the other cortical regions. This pathway forms one input through which sensory experience gains access to the HIPP with reciprocal connections that separately connect HIPP to PFC and ACG. Coordination between HIPP and PFC, and HIPP with ACG, is important for encoding and later recall of relational information (Golby et al., 2001; Krause et al., 1999; Skinner and Fernandes, 2007; Tulving, 2002; Woodward et al., 2006) and assessment of the accuracy and confidence in recalled memories (Moscovitch, 2008; Schacter and Addis, 2007; Skinner and Fernandes, 2007). During recall then, ACG serves a similar function to iPAR. We suggest here that the disruption of the coordination between HIPP and ACG in females may be “offset” by the recruitment of iPAR in female patients, resulting in significant covariance differences among female patients compared to their healthy controls between iPAR with PFC and iPAR with ACG.

Indeed, these regions have documented direct and indirect anatomical connections between one another (Goldman-Rakic, 1988, Goldman-Rakic et al., 1984; Petrides and Pandya, 1984). Connections between HIPP-iPAR terminate in similar regions within HIPP as those connecting HIPP-PFC (Seltzer and Van Hoesen, 1979). ACG connects with PFC (Barbas and Pandya, 1989) and other parts of the cingulate gyrus, entorhinal cortex, thalamus and amygdala (Sesack et al., 1989), each of which provides an indirect connection between ACG and HIPP. It has been proposed that the ACG plays a modulatory role in directing the interaction between PFC and the temporal lobe (Fletcher et al., 1999). Entorhinal and PFC connections provide a way for HIPP to send information to ACG, and for ACG to modulate information sent to HIPP. Direct reciprocal connections between PFC-paraHIPP and PFC-HIPP travel along the cingulum bundle and the fronto-occipital fasciculus. Finally, iPAR connects directly with PFC and the cingulate (Petrides and Pandya, 1984).

Verbal memory is one of the primary cognitive deficits associated with schizophrenia (Cirillo and Seidman, 2003; Shenton et al., 1992), and one in which we and others demonstrated sex differences in performance (Goldstein et al., 1998, 1994). Our data suggest that the connection between PFC-iPAR and ACG-HIPP have implications for understanding why females with schizophrenia consistently demonstrate higher verbal memory function than males. We previously found that the cingulum bundle and white matter tracts connecting PFC-iPAR were abnormal in patients as compared with controls in this sample (Makris et al., 2010). This abnormality was not subjected to a sex differences analysis, but the finding we report here (i.e., a sex difference in PFC-iPAR correlation and its relation to verbal memory) leads us to predict that females will show attenuated white matter abnormalities compared to males, and this preservation of white matter structure will also be associated with better verbal memory performance. Moreover, white matter integrity may in fact mediate the gray matter relationship, which would strengthen our current argument that these gray matter relationships are indicative of functional connectivity differences in these areas during verbal memory processing. We are conducting these analyses now. Therefore, findings in this study begin to identify the anatomy associated with

understanding sex differences in verbal memory performance in schizophrenia. This understanding could only be achieved in the context of analyzing the covariance between regions in the memory network rather than the reliance on analyses of mean volumetric differences alone.

Covariance structure modeling of structural brain volumes assumes, as in any covariance structure modeling, that the brain regions are correlated due to a shared underlying process that connects them. In fact, there are previous studies demonstrating the use of correlative techniques similar to ours to understand gray-matter variation in brain networks (Allen et al., 2003; Chen et al., 2008; Colibazzi et al., 2008; He et al., 2008; Lerch et al., 2006; Mechelli et al., 2005; Mitelman et al., 2005; Seeley et al., 2009), including areas of the visual system (Andrews et al., 1997), the aging brain (Raz et al., 2004, 1997, 2005), and neurodegenerative diseases (Buckner et al., 2005; Seeley et al., 2009). These studies have supported the hypothesis that correlations between the brain volumes of a known functional network reflect shared neurodevelopmental processes (see also Caviness and Takahashi, 1995; Herrup and Busser, 1995).

The preservation of verbal memory function in females with schizophrenia is unlikely due to a single factor, just as schizophrenia itself is not the result of a single factor. However, developmental factors in particular, such as prenatal and early-life stress, are known to impact risk for psychiatric disorders, including schizophrenia, and have been shown in animals to affect signaling pathways implicated in long-term potentiation, the structure of memory-related brain areas, and connections between memory-related brain areas, thereby affecting memory function (Bruce-Keller et al., 2000; Brunson et al., 2005; Buka et al., 2001a,b; Shors, 2004, 2006; Vegeto et al., 2004). Prenatal stress can disrupt the function of neurotransmitters, such as GABA and glutamate, and growth factors, such as brain derived neurotrophic factor, both of which can cause structural changes to memory-related brain areas (Horner et al., 1990; Kadekaro et al., 1988; Radley et al., 2004; Roth et al., 2009; Virgin et al., 1991). These effects are perhaps most pronounced in HIPP and PFC where they can impact neurogenesis in HIPP and synaptic and dendritic remodeling. Importantly, these effects are mediated by gonadal and adrenal hormones (Handa et al., 1994; Shors, 2004, 2006; Solum and Handa, 2002), and are therefore dependent on the sex of the affected individual. While the present study obviously does not implicate one neurodevelopmental process over another, it does suggest that sex-mediated neurodevelopmental processes that affect risk for schizophrenia and memory function may do so through measurable changes to brain regions and the *relationships between* brain regions in a sex-dependent way (Goldstein and Walder, 2006; Goldstein et al., 2002). The present study measures these changes via gray-matter volumes in both males and females and will be complemented by future studies on the covariance of functional activations and white-matter structure in the context of sex-specific differences in verbal memory function in schizophrenia.

5. Conclusions

The findings in this study are an important step toward understanding the biological basis of cognitive symptoms in schizophrenia. The novelty of these analyses lies in the holistic consideration of sex differences in verbal memory function in schizophrenia and their relationship to the pattern of structural volume differences in the brain. We identified sex differences in the *covariance* of verbal-memory-related brain regions in schizophrenia and linked these covariance differences to sex differences in verbal memory performance in regions that have been shown in previous human and animal studies to be sexually dimorphic in the healthy brain. While these analyses are not traditionally thought of as a connectivity analysis, in fact the *a priori* knowledge of anatomical connections between these regions, and the substantial literature on structural covariation in known functional

brain networks, strongly implicate shared neurodevelopmental factors in determining the ultimate structural and functional relationship between regions of the memory circuitry. In as much as memory deficits are particularly detrimental cognitive symptoms in schizophrenia, these findings are an important step toward understanding the relative preservation of memory function in females, its biological underpinning, and implications for sex-specific rehabilitative treatments in patients with schizophrenia.

Findings suggest that the relationship between iPAR and PFC is particularly important for understanding the relative preservation of verbal memory processing in females with schizophrenia and may compensate for ACG volume reductions. We would argue that there are shared underlying neurodevelopmental processes that disrupt the memory circuitry in a sexually-dimorphic way, which results in vulnerability to sex differences in brain anatomy and memory function in adult schizophrenia. Therefore, this study underscores the importance of investigating sex effects in understanding verbal memory deficits in schizophrenia. Findings also demonstrate the need for more structural MRI investigations of *networks* implicated in cognitive functioning rather than sole reliance on individual regions, a practice that is common in functional imaging studies and less so for structural imaging studies of gray matter volumes. These results also illustrate the utility of a unique covariance structure modeling approach to studying such networks. Understanding these complex relationships in the anatomy and sexual dimorphisms in schizophrenia is a challenging prospect, but one that will lead to a more sophisticated understanding of the disease processes associated with schizophrenia and their impact on cognitive function and behavior in schizophrenia.

Acknowledgments

This study was supported by National Institute of Mental Health (NIMH) Grant RO1MH56956 and Mental Health Centers for Intervention Development and Applied Research (CIDAR) Grant P50MH08272-02 (JMG, P.I. – Sex Differences, Hormones and Memory Project). Dr. Abbs's time also was supported in part by NIMH Grant T32MH16259-31. In addition, data collection was in part supported by NIMH Grants R01MH43518 and R01MH46318 (MT, P.I.). The authors wish to thank George Papadimitriou for his assistance in figure preparation.

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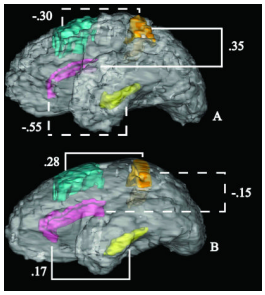

Figure 1.

Two cortical parcellations, one for a female (A) and male (B) patient with schizophrenia, which illustrate the location of the regions we defined as PFC (blue), ACG (pink), HIPP (yellow), and iPAR (orange). Overlaid on these parcellations are the correlations between the volumes of these brain regions for all females with schizophrenia (A) and all males with schizophrenia (B). Solid lines indicate a positive correlation and dashed lines indicate a negative correlation. Note: Brains are rotated slightly in the x and y plane to display clearly these regions of interest.

Table 1

Sociodemographic, Clinical, and Cognitive Characteristics[a] of Schizophrenia Cases compared with healthy controls

	Schizophrenia				Comparison Group			
Demographic Variable	**Females (N=29)**		**Males (N=59)**		**Females (N=21)**		**Males (N=27)**	
	x̄	**SD**	**x̄**	**SD**	**x̄**	**SD**	**x̄**	**SD**
Age at MRI[*]	**43.8**	9.7	**45.1**	9.5	**39.0**	9.9	**41.6**	11.6
Education[*]	**12.7**	2.6	**12.4**	2.4	**14.9**	2.3	**14.7**	2.3
WAIS-R Vocabulary[*]	**9.8**	2.9	**10.4**	3.8	**13.3**	3.7	**12.9**	3.4
WAIS-R Block Design[*]	**8.7**	3.4	**9.00**	2.9	**10.7**	2.5	**11.8**	2.3
Sattler IQ[*]	**95.7**	16.3	**97.2**	16.3	**111.5**	14.7	**113.4**	11.9
WRAT-Reading Subtest[*]	**97.5**	17.1	**99.6**	18.5	**105.8**	11.9	**104.6**	11.7
SES[*]	**3.2**	1.2	**3.3**	1.0	**2.5**	.93	**2.6**	1.0
Parental Education	**10.9**	5.4	**11.9**	2.5	**12.2**	2.2	**12.1**	2.5
Age at First Hospitalization	**24.7**	6.4	**23.5**	6.7	**n/a**		**n/a**	
Number of Hospitalizations (Median)	**4.0**	5.5	**7.0**	85.2	**n/a**		**n/a**	
Months of Hospitalizations	**56.2**	63.7	**60.5**	46.2	**n/a**		**n/a**	
Chlorpromazine Equivalent Medication	**619.9**	296.2	**663.4**	333.7	**n/a**		**n/a**	

[a] All measures are means, except where indicated.

[*] $p<.05$ for difference between subjects with schizophrenia and the comparison group. No significant within group or across diagnostic groups by sex.

Neuroimage. Author manuscript; available in PMC 2012 June 15.

Table 2

Average Scores on Memory Tests for Females (A) and Males (B).

A.)	**Females (N=50)**							
	Case		**Control**				**All Females**	
	x̄	**SD**	**x̄**	**SD**	**Sig.**[1]	**d**[2]	**x̄**	**SD**
CVLT[3]								
Trial 5	**71.9**%	19.0	**82.4**%	12.5	*	.64	**78.4**%	16.0
Sem.[4] Clust.	**4.1**	3.0	**6.4**	3.2	*	.68	**5.5**	3.9
Ser.[5] Clust	**.86**	1.3	**.67**	.97		−.17	**.74**	1.1
Short Delay	**63.4**%	16.4	**72.6**%	15.5	*	.49	**68.9**%	18.7
Long Delay	**65.6**%	18.8	**75.0**%	18.2	*	.53	**71.3**%	1.7

B.)	**Males (N=86)**							
	Case		**Control**				**All Males**	
	x̄	**SD**	**x̄**	**SD**	**Sig.**	**d**	**x̄**	**SD**
CVLT								
Trial 5	**55.2**%	19.3	**75.2**%	14.7	*	1.01	**64.4**%	19.8
Sem. Clust.	**2.1**	1.8	**4.0**	3.2	*	.71	**3.00**	2.7
Ser. Clust	**1.1**	1.5	**1.2**	1.4		.12	**1.1**	1.3
Short Delay	**47.8**%	23.9	**69.7**%	18.3	*	.99	**57.8**%	22.3
Long Delay	**48.0**%	20.5	**71.9**%	18.3	*	.99	**58.9**%	24.2

[1] Significance between cases and controls within sex indicated by a

* ($p < .05$)

[2] Cohen's d (effect size difference between cases and controls within sex).

[3] CVLT = California Verbal Learning Test

[4] Sem. Clust. = Semantic Clustering

[5] Ser. Clust. = Serial Clustering.

Table 3-A

Pairwise Correlations between in Volumes of Memory Circuitry Regions of Interest

A.)	**Male Patients**	**Female Patients**
Brain Areas		
*HIPP-ACG***	.17	−.55
*iPAR-ACG***	−.15	.35
*iPAR-PFC***	.28	−.30
	Male Controls	**Female Controls**
Brain Areas		
HIPP-ACG	.34	−.04
iPAR-ACG	−.05	.07
*iPAR-PFC**	−.13	.36
	All Males	**All Females**
Brain Areas		
*HIPP-ACG***	.21	−.26
*iPAR-ACG**	−.13	.20
iPAR-PFC	.18	.00

Table 3-B. Mean Brain Volumes (cm^3) on which Correlations are Based

B.)	**Females**				**Male**			
	Case		**Control**		**Case**		**Control**	
	x̄	**SD**	**x̄**	**SD**	**x̄**	**SD**	**x̄**	**SD**
Total Cerebrum	986.92	97.53	1023.55	89.70	1122.00	106.30	1116.22	92.13
Unadjusted								
HIPP[a,b]	7.28	1.05	7.89	.64	8.08	1.01	8.33	.91
pHIPP[b]	8.00	1.52	8.52	1.22	8.63	1.32	8.96	1.34
PFC	23.07	2.38	23.82	4.45	24.85	4.51	24.38	4.35
ACG[a]	10.47	2.34	12.47	3.00	12.09	2.53	12.07	2.13
iPAR[b]	32.94	5.34	33.65	6.00	37.48	7.16	36.77	6.03
Adjusted								

Table 3-B. Mean Brain Volumes (cm^3) on which Correlations are Based

B.)	Females				Male			
	Case		Control		Case		Control	
	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
HIPP[a]	.74	.09	.78	.08	.72	.08	.75	.08
pHIPP[b]	.81	.16	.83	.12	.77	.10	.80	.10
PFC[b]	2.35	.32	2.33	.39	2.21	.35	2.18	.28
ACG	1.06	.23	1.20	.26	1.08	.22	1.09	.19
iPAR	3.34	.43	3.28	.41	3.33	.47	3.29	.42

A Box-M test showed a significant sex difference between the covariance matrices of memory-related brain areas in patients, but not controls. This table shows the correlations that showed significant sex differences in patients following a post-hoc z-test on the Fisher z-transformations of these correlations. All correlations are based on volumes adjusted for total cerebrum size (see Table 3-B). The correlations and z-test results for controls and the entire sample are presented for comparison despite the Box-M tests not being significant in these groups:

** $p<.05$,

* $p<.10$

[a] indicates significant ($p<.05$) differences between cases and controls.

[b] indicates significant ($p<.05$) differences between males and females. *Adjusted* volumes are adjusted for total cerebrum size (see Methods).

Table 4

Correlations Between Memory Measures and Brain Volumes of Memory Circuitry Regions of Interest.

	Male Patients (N=59)	Female Patients (N=29)	Significance
CVLT	r-value	r-value	
Trial5-PFC	**.40**	**−.51**	**
Semantic-PFC	.09	**−.45**	†
Sem.-iPAR	−.04	**.38**	Ns
Sem.-HIPP	**.32**	.03	Ns
Serial-PFC	**.49**	**−.32**	**

PFC, HIPP, and iPAR were chosen given they are the regions that covaried significantly based on the Box-M and z-tests of the covariance matrices comparing groups. Fisher's z-test showed that these correlations are significantly different for male patients compared with female patients.

* ($p < .05$);

† $p < .10$