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Verbal memory impairments in schizophrenia associated with cortical thinning

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ABSTRACT

Verbal memory (VM) represents one of the most affected cognitive domains in schizophrenia. Multiple studies have shown that schizophrenia is associated with cortical abnormalities, but it remains unclear whether these are related to VM impairments. Considering the vast literature demonstrating the role of the frontal cortex, the parahippocampal cortex, and the hippocampus in VM, we examined the cortical thickness/volume of these regions. We used a categorical approach whereby 27 schizophrenia patients with 'moderate to severe' VM impairments were compared to 23 patients with 'low to mild' VM impairments and 23 healthy controls. A series of between-group vertex-wise GLM on cortical thickness were performed for specific regions of interest defining the parahippocampal gyrus and the frontal cortex. When compared to healthy controls, patients with 'moderate to severe' VM impairments revealed significantly thinner cortex in the left frontal lobe, and the parahippocampal gyri. When compared to patients with 'low to mild' VM impairments, patients with 'moderate to severe' VM impairments showed a trend of thinner cortex in similar regions. Virtually no differences were observed in the frontal area of patients with 'low to mild' VM impairments relative to controls. No significant group differences were observed in the hippocampus. Our results indicate that patients with greater VM impairments demonstrate significant cortical thinning in regions known to be important in VM performance. Treating VM deficits in schizophrenia could have a positive effect on the brain; thus, subgroups of patients with more severe VM deficits should be a prioritized target in the development of new cognitive treatments.

1. Introduction

Schizophrenia patients consistently display lower brain volumes and reduced cortical thickness when compared to healthy controls (Edgar et al., 2012; Kuperberg et al., 2003; Olabi et al., 2011; Shenton et al., 2001; van Haren et al., 2011; Venkatasubramanian et al., 2008). However, there is growing evidence of heterogeneity of brain structural patterns in schizophrenia patients. That is, different subgroups of patients seem to show different degrees and extent of structural alterations depending on their clinical or cognitive profile (Cobia et al., 2011; Nenadic et al., 2012, 2015). While verbal memory (VM) is considered a core cognitive domain affected in schizophrenia (Aleman et al., 1999; Cirillo and Seidman, 2003; Dickinson, et al., 2008; Keefe et al., 2005; Lewis and Gonzalez-Burgos, 2006), some studies have also revealed different subgroups of patients with a close to normal VM profile (Brazo et al., 2013; Bruder et al., 2004; Kremen et al., 2004; Turetsky et al., 2002). Yet, little is known about how cortical thickness is associated with the level of VM capacity in schizophrenia.

A large number of functional neuroimaging studies investigating VM impairments in schizophrenia have linked lower performance to abnormal brain activity in the medial temporal lobes (i.e. the hippocampus and the parahippocampal gyrus (PHG)) and frontal lobes (Achim and Lepage, 2005a; Francis et al., 2015; Haut et al., 2015; Hawco et al., 2015; Hutcheson et al., 2015; Ragland et al., 2004, 2009; Weiss et al., 2003). Nonetheless, it remains unclear whether VM impairments in schizophrenia are related to cortical thinning in these regions. One correlational study reported a similar positive and significant relationship between cortical thickness and VM capacity in these regions in schizophrenia, and in healthy controls (Hartberg et al., 2010). A more recent study failed to show any association between cortical thickness and VM performance in schizophrenia, nor in healthy controls (Ehrlich et al., 2012). The only positive relationship with VM observed by the authors pinpointed hippocampal volume in schizophrenia patients, but not in healthy controls.

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Table 1
Demographic, clinical and neuropsychological data.

	Controls (N = 23)			'Low to mild' VM impairments (N = 23)			'Moderate to severe' VM impairments (N = 27)			*p-value*
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	
Age	33.26	8.17	22:50	34.57	8.7	24:50	35.85	8.66	21:50	0.49
IQ	112.50	14.21	80:133	99.43	12.53	75:116	90.19	12.80	70:120	<0.001
ISLT										
Learning recall	27.27	3.13	20:31	24.67	2.96	21:33	16.75	4.02	7:24	
Delayed recall	9.14	2.03	5:12	9.00	1.55	6:11	4.61	2.00	1:8	
z-scores	0.00	0.92	−1.93:1.14	−0.47	0.75	−1.30:1.37	−2.85	1.00	−5.24 :− 1.44	<0.001
		N	%		N	%		N	%	
Gender										0.16
Male		15	65		13	57		22	81	
Female		8	35		10	43		5	19	
Parental socioeconomic status										0.15
Lower		1	4		4	20		3	14	
Lower-middle		6	26		5	25		4	19	
Middle		8	35		8	40		12	57	
Upper-middle		4	17		1	5		2	10	
Upper		4	17		2	10		0	0	
Handeness category										0.28
Right		15	65		14	61		11	40	
Moderately right		3	13		4	17		8	30	
Ambidextrous		2	9		2	9		3	11	
Moderately left		2	9		2	9		4	15	
Left		1	4		1	4		1	4	
		Mean	SD	Range	Mean	SD	Range			
SANS (without attention total)		19.13	8.7	4:34	25.52	9.93	6:51			0.03
SAPS		17.13	18.05	0:60	20.15	15.85	1:53			0.63
Age of onset		21.74	4.56	15:33	24.22	7.69	14:43			0.19
Duration of illness		12.83	7.41	4:28	11.63	7.61	3:33			0.48
Medication (mg chlorpromazine)		632.63	472.13	45:1774	480.83	456.32	11:2179			0.26

Note: VM = verbal memory, ISLT = International Shopping List Task, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms. Post-hoc Bonferroni correction (with a criteria of $p < .05$) was applied for IQ (each group differed from each other) and ISLT (a significant difference existed between the patient subgroups). Due to incomplete records, 3 patients with 'low to mild' VM impairments and 6 with 'moderate to severe' VM impairments having missing datapoints for parental socioeconomic status.

One possible explanation for the discrepancy in these results is that VM performance may not be linearly related to cortical thickness; thus using a regression approach may not be optimal. Considering the inconsistency of previous findings, further investigation of VM impairments in schizophrenia and cortical thickness are warranted, and using a categorical approach based on a clinical threshold of VM

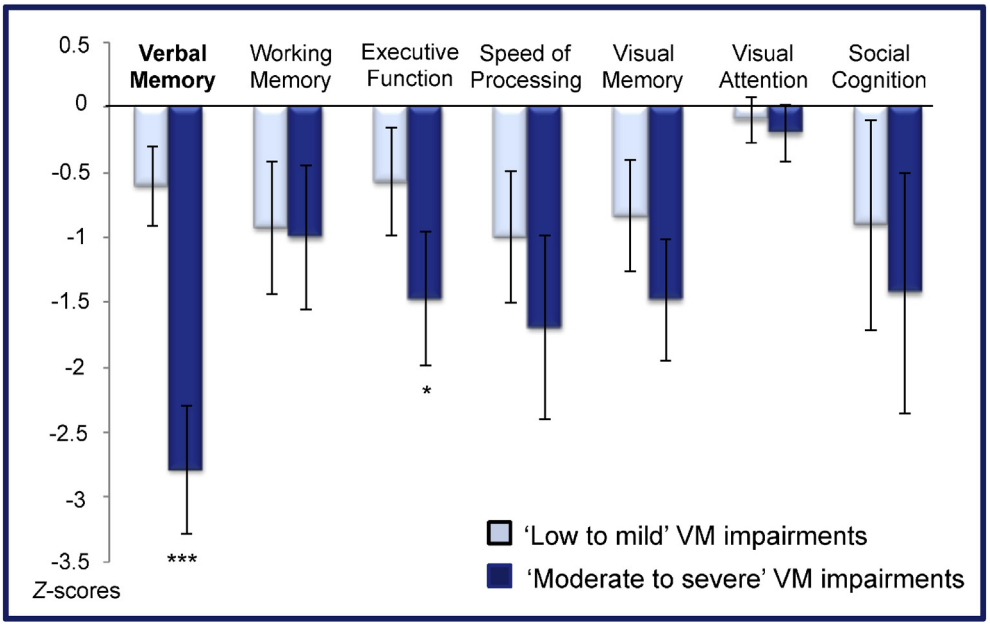

Fig. 1. Mean z-scores for cognitive domain evaluated by the Cogstate battery in the 'moderate to severe' verbal memory (VM) impairments group compared to the group with 'low to mild' VM impairments.

deficits could provide new insight on the matter. In this context, we investigated whether schizophrenia patients with significant VM impairments also have greater cortical thinning in key brain regions associated with this cognitive function. We used a novel subgroup approach, comparing patients with 'moderate to severe' VM impairments to patients with 'low to mild' VM impairments, and a group of healthy controls. We predicted that schizophrenia patients displaying 'moderate to severe' VM impairments would have thinner cortex in the PHG and the frontal cortex, and reduced hippocampal volume relative to patients with 'low to mild' VM impairments, and healthy controls.

2. Methods

2.1. Study participants

Participants were recruited from different outpatient and inpatient units at the Douglas Mental Health University Institute, Montreal, QC, Canada; from external and community-based mental health clinics; and from advertisements. Fifty patients with schizophrenia aged 21–50 were matched to 23 healthy control subjects on age, sex, handedness, and highest parental level of education. Control subjects were recruited through advertisements and were from socio-demographic areas similar to patients. We excluded individuals with (1) a lifetime history of a medical or neurological condition that has been shown to affect cognition, (2) a family history of hereditary neurological disorders, (3) a diagnosis of substance dependence (within the past three months), (4) presence of depression or Parkinsonism, or (5) presence of metallic objects in the body which are contraindicated for magnetic resonance imaging (MRI).

All participants were assessed with the Edinburgh Handedness Inventory (Oldfield, 1971), the Hollingshead two-factor index of social position (Hollingshead, 1965), and either the SCID-I (patient version) to confirm diagnosis for patients, or the SCID-I (non-patient version) to confirm absence of any Axis I disorders in healthy controls. Patients further underwent an exhaustive clinical assessment. Clinical symptoms were assessed using the Scale for the Assessment of Negative Symptoms

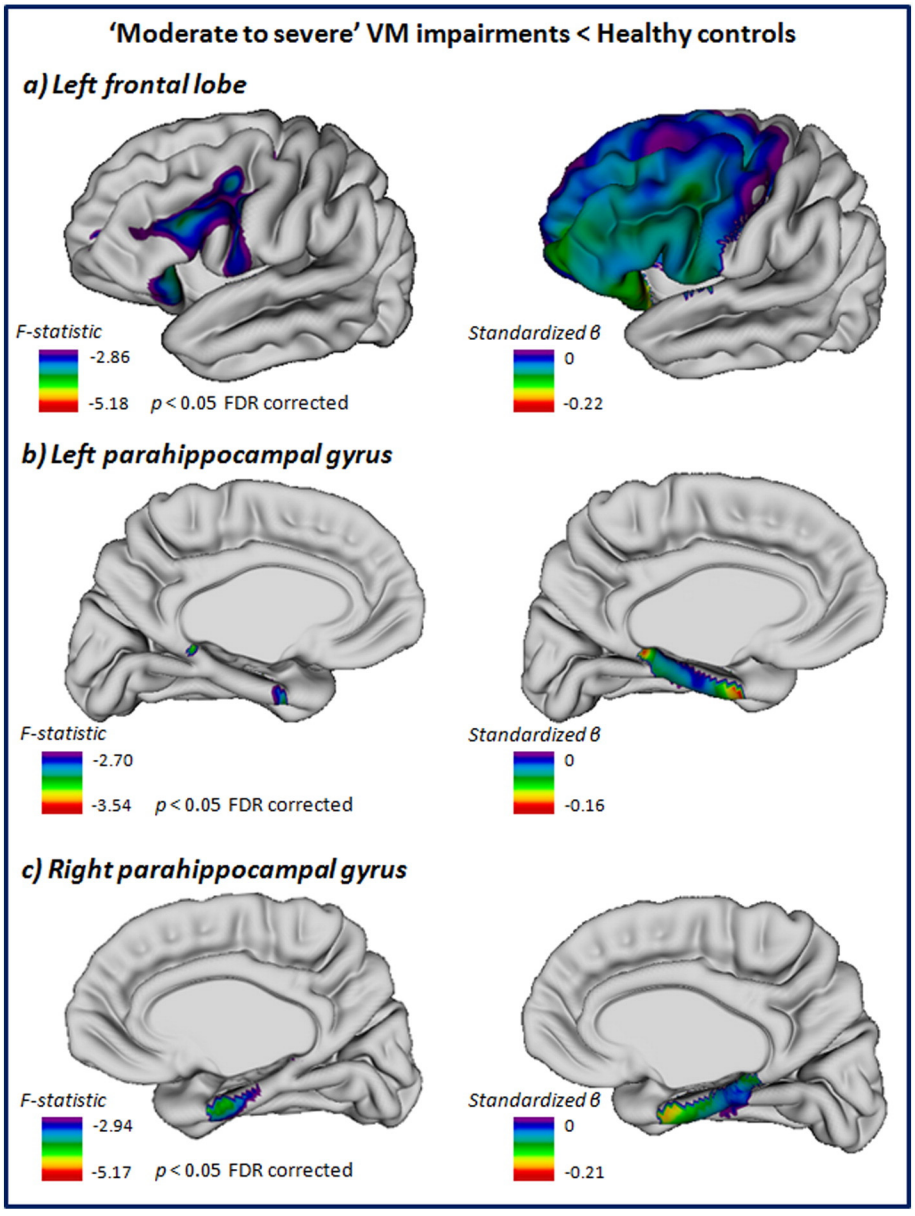

Fig. 2. Statistical maps demonstrating cortical thickness differences between patients with 'moderate to severe' verbal memory (VM) impairments and healthy controls, within frontal and parahippocampal ROIs.

(SANS) (Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b). Medication histories were obtained via self-report and verified when necessary with the treating psychiatrist. Antipsychotic doses were converted to chlorpromazine equivalents according to the literature (Jensen and Regier, 2010; Leucht et al., 2014; Woods, 2003) to allow comparison between patient groups. The Douglas Mental Health University Institute's Research Ethics Board approved the study and all participants provided informed written consent.

As part of a larger neurocognitive assessment using the CogState battery for schizophrenia research (Pietrzak et al., 2009), all participants performed the VM International Shopping List Task (ISLT). Participants underwent 3 trials to learn a list of 16 words, and were later tested using delayed recall. The performance of the matched control group (n = 25) was then used as normative data to transform individual patient data into *z*-scores. The average of the z-scores for the total recall of the 3 learning trials and for the delayed recall was computed and kept for further comparison. Schizophrenia patients were subsequently classified into two subgroups: patients with 'moderate to severe' VM impairments (n = 27, *z*-score ≤ −1.4), and patients with 'low to mild' VM impairments (n = 23, *z*-score > −1.4), following the criteria of the Compendium of Neuropsychological Tests (Spreen and Strauss, 1998). Other cognitive domains were also assessed using CogState. Intellectual quotient (IQ) was estimated in all participants using the Wechsler Abbreviated Scale of Intelligence (WASI) (Hays et al., 2002). The other neurocognitive measures described above were collected and reported for informational purposes, and to provide a complete cognitive profile of our two subgroups of patients.

2.2. Statistical analysis of demographic, clinical and neuropsychological data

To verify that groups were matched, the two patient groups and the control group were compared on age using one-way ANOVAs. Sex, parental SES, and handedness between-group differences were evaluated using Kruskal–Wallis tests. To examine differences in overall cognitive profile between the two groups of patients, independent *t*-tests (with Bonferroni correction) were applied to all neurocognitive domains of the CogState battery. A one-way ANOVA was computed to test for a difference in IQ. Finally, independent *t*-tests were used to compare antipsychotic dosages, negative and positive symptoms, age of onset, and duration of the illness between the two groups of patients. All analyses were conducted using SPSS version 20 (SPSS, Chicago, IL, USA) and were two-tailed with a critical *p*-value of .05.

2.3. Image acquisitions and processing

We used a similar cortical thickness analytical procedure as reported in previous studies (Buchy et al., 2011, 2012; Cassidy et al., 2014; Emami et al., 2016). T1-weighted MR images were acquired using an 8-channel head coil on a Siemens 3T Tim trio MRI at the Douglas Mental Health University Institute's Brain Imaging Center in Montreal. The anatomical scan was MPRAGE (TR = 2300 ms, TE = 2.98 ms, FOV 256 mm, 1 mm × 1 mm × 1 mm voxels, flip angle = 9) and lasted 9 min. Cortical thickness was analyzed using the CIVET processing pipeline (version 1.1.10; Montreal Neurological Institute at McGill University, Montreal, Quebec, Canada). T1-weighted images were registered to the ICBM152 nonlinear template with a 9-parameter linear transformation (Collins et al., 1994). The T1s were then corrected for inhomogeneities (Sled et al., 1998) and classified into different tissue types (Zijdenbos et al., 2002). Deformable models were used to create white and gray matter surfaces for each hemisphere separately (Kim et al., 2005; MacDonald et al., 2000) From these surfaces, the distance between the white and gray surfaces was measured (Lerch and Evans, 2005) and was subsequently blurred using a 20-mm surface-based diffusion blurring kernel in preparation for statistical analyses (Lerch et al., 2008).

2.4. Cortical thickness analyses

The bilateral PHG and bilateral frontal lobes were defined as ROIs using the cortical parcellations available in the LPBA40 atlas by using the intersection of atlas regions and the cortical surface (Shattuck et al., 2008). A mask was then created to exclude all other vertices from the analyses. The RMINC package (version 1.0) was used to analyze the vertex-wise cortical thickness within the ROIs. Vertex-wise GLMs using group membership (healthy controls, patients with 'low to mild' VM impairments, and patients with 'moderate to severe' VM impairments) as the independent variable, and cortical thickness as the dependent variable, including age and sex, were then performed at each vertex within the ROI in order to reduce the burden of multiple comparisons, and to perform a comparison in line with our hypotheses. Correction for multiple comparisons across all vertices included in each ROI was determined using the false discovery rate (FDR; Genovese et al., 2002). Vertices surviving 5% FDR were considered statistically significant. For the ROI where a significant between-group effect was found, we performed the same GLM analyses, but used each pair of groups independently to investigate where these differences were. Effect sizes were also explored using standardized beta values.

2.5. Hippocampal volumes analyses

Due to the prominent role of the hippocampus in schizophrenia (Heckers, 2001), we also explored between-group differences in the hippocampal volumes. Fully-automated segmentation of the hippocampus was carried out using the MAGeT Brain algorithm (Chakravarty et al., 2013; Pipitone, et al., 2014; Voineskos et al., 2015; https://github.com/CobraLab/MAGeTbrain). This modified multi-atlas segmentation technique is designed to use a limited number of high-quality manually segmented atlases of the hippocampal subfields as input (Winterburn et al., 2013; http://cobralab.ca/digital-atlases). Atlas segmentations are propagated to a template library and then to subjects using nonlinear registration, and a subset of the population under study is used as the template library through which the final segmentation is bootstrapped. Each subject in the template library is segmented through nonlinear

Table 2
Brain regions displaying thinner cortex in the between-group comparisons.

Region	Brodmann area	Stereotaxic coordinates of local maxima (MNI space)		
		x	y	z
'Moderate to severe' < healthy controls (p < 0.05, FDR corrected)				
L anterior middle frontal gyrus	10	−29	58	−2
L posterior middle frontal gyrus	9	−44	16	32
L orbitofrontal gyrus	47	−48	24	−12
L inferior frontal gyrus	46/44	−51	30	16
L precentral gyrus	6	−62	5	18
L anterior parahippocampal gyrus	35	−23	−12	−35
L posterior parahippocampal gyrus	30	−8	−43	2
R anterior parahippocampal gyrus	35	17	−12	−31
'Moderate to severe' < 'low to mild' (p < 0.05, uncorrected)				
L anterior inferior frontal gyrus	10	−45	49	4
L posterior inferior frontal gyrus	45/9	−57	17	23
L orbitofrontal gyrus	47	−46	24	−8
L middle frontal gyrus	46	−46	40	21
L precentral gyrus	6	−58	−1	9
L anterior parahippocampal gyrus	35	−19	−9	32
L posterior parahippocampal gyrus	30	−8	−45	2
R anterior parahippocampal gyrus	35	18	−12	−27
'Low to mild' < healthy controls (p < 0.05, uncorrected)				
L precentral gyrus	4	−44	−17	53
L anterior parahippocampal gyrus	28	−18	−16	−29
R posterior parahippocampal gyrus	35	18	−27	−18

atlas-to-template registration followed by label propagation, yielding 5 unique definitions of the hippocampus for each of the templates. In the current study, 21 templates, a number shown to be optimal in previous work (Pipitone et al., 2014), were used from the overall subject pool. Ten controls and eleven patients were chosen to ensure a representative template set. This resulted in 105 candidate labels for each subject, and labels were then fused using a majority vote to complete the segmentation process. Nonlinear registration was performed using a version of the Automatic Normalization Tools (ANTS) registration technique (Avants et al., 2008) that is compatible with the minc toolkit (https://github.com/vfonov/mincANTS). As the dentate gyrus and subiculum are included within the MAGeT Brain algorithm, the term "hippocampus" used throughout this manuscript encompasses the hippocampal formation. Hippocampal differences were explored using a 2 × 3 MANCOVA, with hemisphere (left and right) as a within-group factor, group membership (healthy controls, patients with 'moderate to severe' VM impairments, and patients with 'low to mild' VM impairments) as the between-group factor, and covarying for age, sex, and total brain volume. Exploratory MANCOVAs using the same group membership as the between-group factor were also performed for each hippocampal subfield, using Bonferroni correction.

3. Results

3.1. Demographic, clinical and neuropsychological results

Demographic, clinical and neuropsychological data are presented in Table 1. All groups were matched on demographic variables. 'Low to mild' VM impaired patients did not significantly differ on VM when compared with healthy controls. 'Moderate to severe' VM impaired patients had significantly lower verbal memory ($p < .005$), as well as significantly lower executive functioning ($p < .05$), than 'low to mild' VM impaired patients, and healthy controls. Importantly, both subgroups of patients did not significantly differ from each other on any other cognitive domain. Moreover, as illustrated by their cognitive profile, represented in Fig. 1, both subgroups differ mainly on VM capacity. A significant difference in IQ was also present between all groups ($p < .05$). Post-hoc Pearson correlations showed strong positive

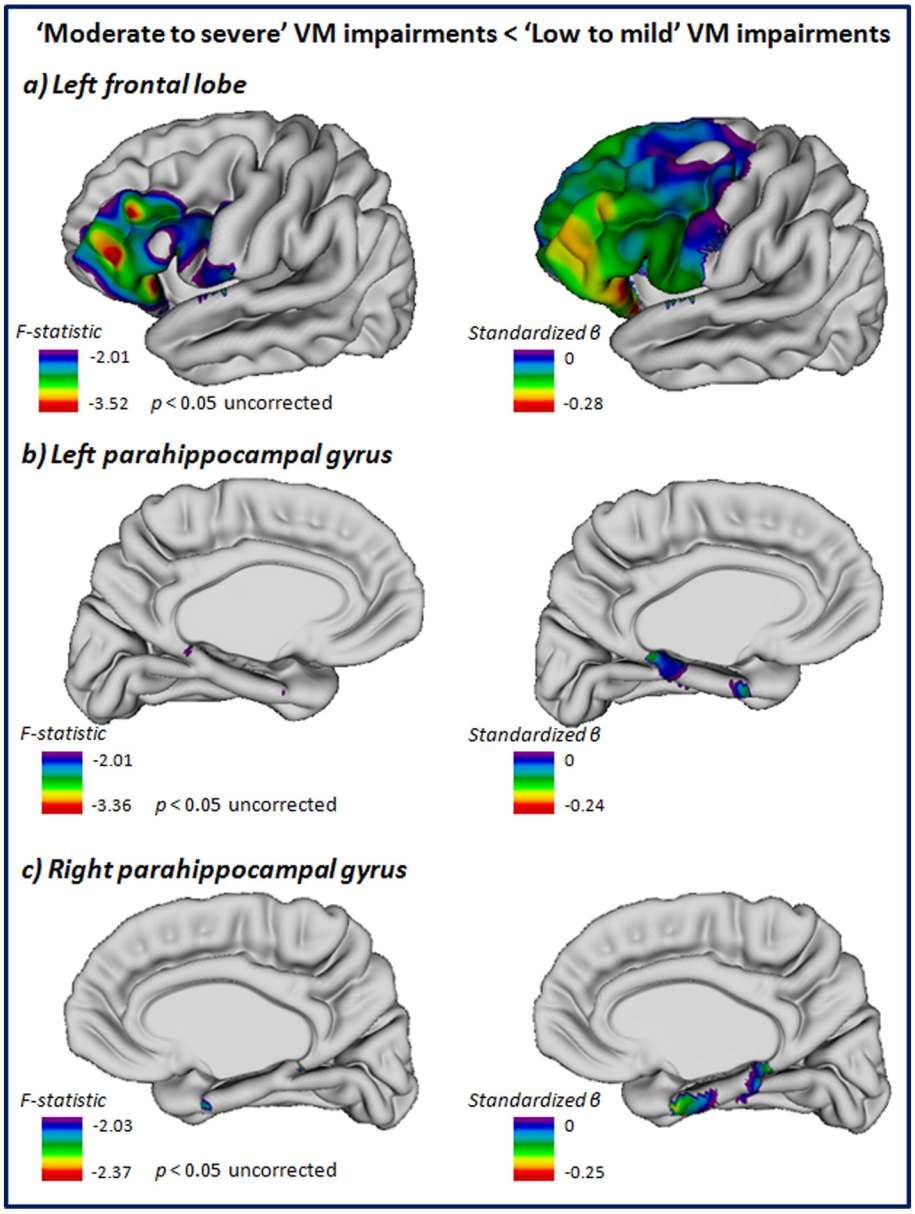

Fig. 3. Statistical maps demonstrating cortical thickness differences between patients with 'moderate to severe' verbal memory (VM) impairments and patients with 'low to mild' VM impairments, within frontal and parahippocampal ROIs.

correlations between VM and executive function ($r = .58$, $p < .0001$, $R^2 = .33$), as well as between VM and IQ ($r = .60$, $p < .0001$, $R^2 = .36$). Finally, the subgroup of patients with 'moderate to severe' VM impairments also had more severe negative symptoms (SANS total; $p < .05$). All other clinical features were similar in both subgroups.

3.2. Cortical thickness results

3.2.1. Between-group comparison

The ROI vertex-wise GLM analyses showed significant between-group differences for the left frontal lobes ($F_{(3, 69)} = -2.77$, $p < .05$), and for the bilateral PHG (left: $F_{(3, 69)} = -2.60$, $p < .05$; right: $F_{(3,69)} = -2.81$, $p < .05$). No significant between-group differences were observed in the right frontal lobe. We then performed the same GLM analyses but used each pair of groups separately to investigate where these differences were. Statistical cortical thickness maps (Fig. 2) revealed significantly thinner cortex in 'moderate to severe' VM impaired patients compared to healthy controls, in the left frontal lobe ($F_{(3, 46)} = -2.86$, $p < .05$; this included the middle frontal gyrus, the inferior frontal gyrus, the orbitofrontal gyrus, and the precentral gyrus; see Table 2). We also observed significantly thinner cortex in patients with 'moderate to severe' VM impairments in the bilateral PHG when compared to healthy controls (left: $F_{(3, 46)} = -2.70$, $p < .05$; right: $F_{(3, 46)} = -2.94$, $p < .05$).

As shown in Fig. 3, the comparison between both groups of patients revealed a trend for thinner cortex in patients with 'moderate to severe' VM impairments in the left frontal lobe ($F_{(3, 46)} = -2.01$, $p < .05$ uncorrected; this included the middle frontal gyrus, the inferior frontal gyrus, the orbitofrontal gyrus and the precentral gyrus; see Table 2). We also observed a trend of thinner cortex in the PHG for patients with 'moderate to severe' VM impairments, compared to patients with 'low to mild' VM impairments (Left: $F_{(3, 46)} = -2.01$, $p < .05$; right: $F_{(3, 46)} = -2.03$, $p < .05$).

Patients with 'low to mild' VM impairments compared to healthy controls (Fig. 4) showed a trend of thinner cortex in the bilateral PHG (left: $F_{(3, 42)} = -2.03$, $p < .05$ uncorrected; right: $F_{(3, 42)} = -2.03$, $p < .05$ uncorrected), and in a negligible amount of cortex in the precentral gyrus ($F_{(3, 42)} = -2.01$, $p < .05$ uncorrected). Examination

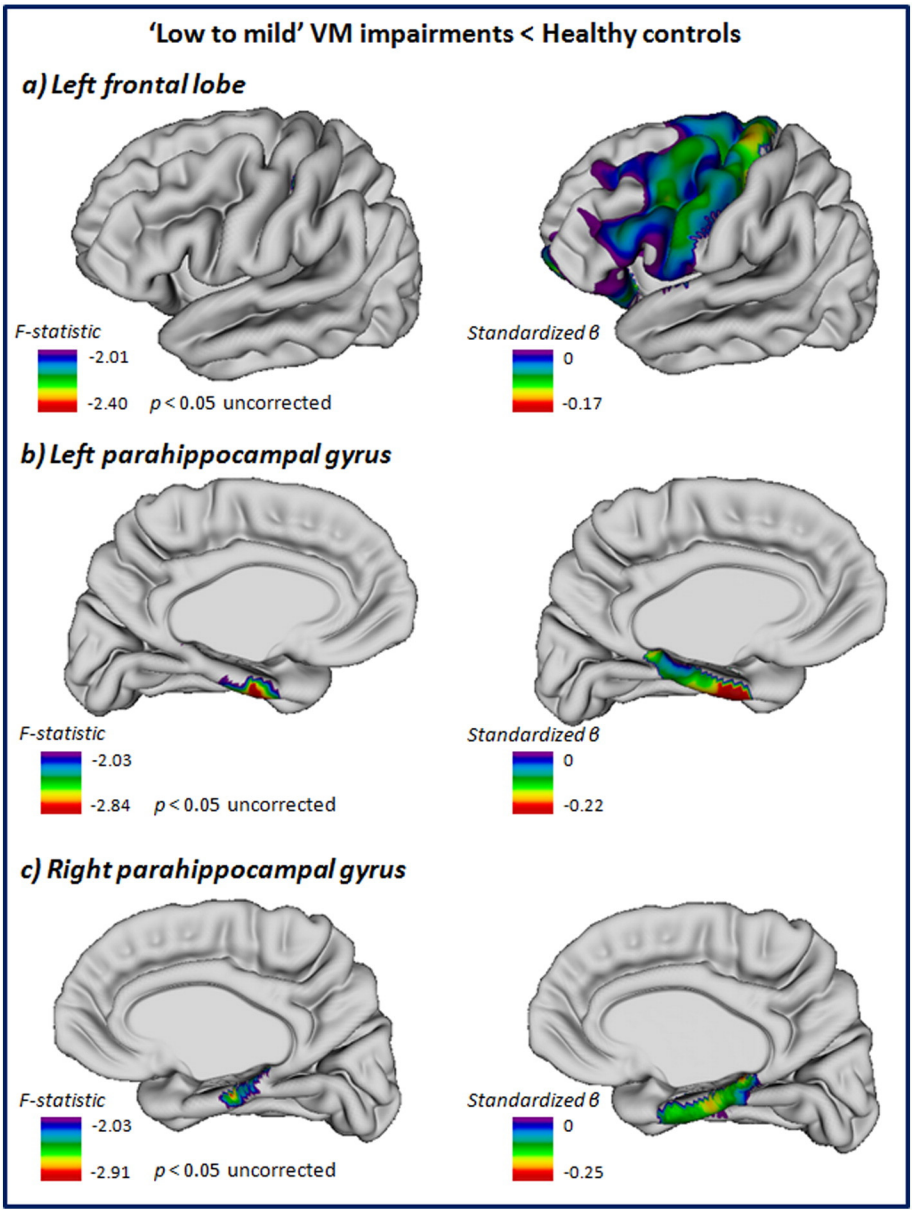

Fig. 4. Statistical maps demonstrating cortical thickness differences between patients with 'low to mild' verbal memory (VM) impairments and healthy controls, within frontal and parahippocampal ROIs.

of effect-size maps of these results supports that contrary to the 'moderate to severe' VM impairments patients (Figs. 2a and 3a), 'low to mild' VM impairments patients seem to have cortical thickness indices comparable to controls within the left prefrontal cortex (Fig. 4a).

Post-hoc GLM (sex and age controlled) revealed no significant differences ($p < 0.05$ FDR corrected) when all patients (as a single group) were compared to the healthy controls, for any ROI.

3.3. Hippocampal volumes

As presented in Fig. 5, the 2 × 3 (hemisphere x group) MANCOVA did not reveal any significant main effects of hemisphere ($F_{(1, 67)} = 0.08$, $p = 0.78$) or group ($F_{2, 67} = 2.4$, $p = 0.10$). No significant interactions were found ($F_{(2, 67)} = 1.41$, $p = 0.25$). Exploratory investigation of the hippocampal subfields did not show any differences between the groups after Bonferroni correction.

4. Discussion

Our findings demonstrate that schizophrenia patients with more severe VM dysfunction have greater cortical thinning in key brain regions associated with VM capacity. In the current study, we compared schizophrenia patients with 'moderate to severe' VM impairments, to patients with 'low to mild' VM impairments and to healthy controls. As predicted, we observed significantly thinner cortex in the PHG and in the left frontal cortex in the 'moderate to severe' VM impairments group when compared to healthy controls, and with a more liberal threshold, when compared to 'low to mild' VM impaired patients. More specifically, we observed thinner cortex in the left inferior frontal gyrus, which is associated with VM performance in healthy populations (Baker et al., 2001; Casasanto, et al., 2002), the left middle frontal gyrus, which is involved in complex post-retrieval monitoring (Achim and Lepage, 2005b), and the orbitofrontal cortex, which plays a role in the mobilization of efficient encoding strategies in VM (Savage et al., 2001). Abnormalities in neural activity in relation to VM deficits in schizophrenia have been previously observed in these regions of the frontal cortex, as well as in the PHG (Achim and Lepage, 2005a; Francis et al., 2015; Haut et al., 2014; Hawco et al., 2015; Hutcheson et al., 2015; Ragland et al., 2004, 2009; Weiss et al., 2003). Therefore, in addition to previous functional neuroimaging studies, our results strongly support the relationship between VM and structural abnormality observed in the left frontal cortex and the PHG in schizophrenia patients.

Separating patients into two subgroups depending on their level of VM capacity contributes to a better understanding of previous inconsistent relationships reported between cortical thickness and VM in schizophrenia. Indeed, previous studies have found opposing results regarding whether there is a relationship between cortical thickness and VM in schizophrenia when compared to healthy controls (Hartberg et al., 2010; Ehrlich et al., 2012). One possible explanation is that VM may not be linearly related to cortical thickness. Nonetheless, our results suggest that patients who display more severe VM impairments also have thinner cortex in key regions responsible for this cognitive domain. Thus, the level of VM capacity in previous studies sample may have influenced their findings.

In the present study, we did not find any significant differences in our ROIs when all patients were compared to the healthy control group. This could be explained by the selection of our healthy controls, who share similar socio-demographic features to that of our patient groups. This also highlights that the sole differences surviving FDR correction were between the healthy control group and the patient group with 'moderate to severe' VM deficits. No significant differences were observed between patients with 'low to mild' VM impairments and healthy controls. Even when utilizing a more liberal threshold of $p < .05$ uncorrected, this group of patients showed similar cortical thickness in the left prefrontal cortex when compared to healthy controls. These results provide strong support for the work of Cobia et al. (2011), where no significant cortical differences were found between their healthy control group and a cognitively intact group of schizophrenia patients. These results also suggest that differences in the left prefrontal cortex observed in previous studies comparing schizophrenia patients with healthy controls (e.g., Kuperberg et al., 2003; van Haren et al., 2011) could have been driven in part by the level of VM impairments in patients, which many studies do not account for.

Results from the exploratory hippocampal volume analysis are not in line with the previously reported positive relationship between this region and VM (Gur et al., 2000; Ehrlich et al., 2012). In addition, we only observed a trend between-group effect ($p = 0.10$), and did not replicate hippocampal volume differences between patients and healthy controls that were previously obtained (Honea et al., 2005; Wright et al., 2000). Nonetheless, some previous studies also failed to show

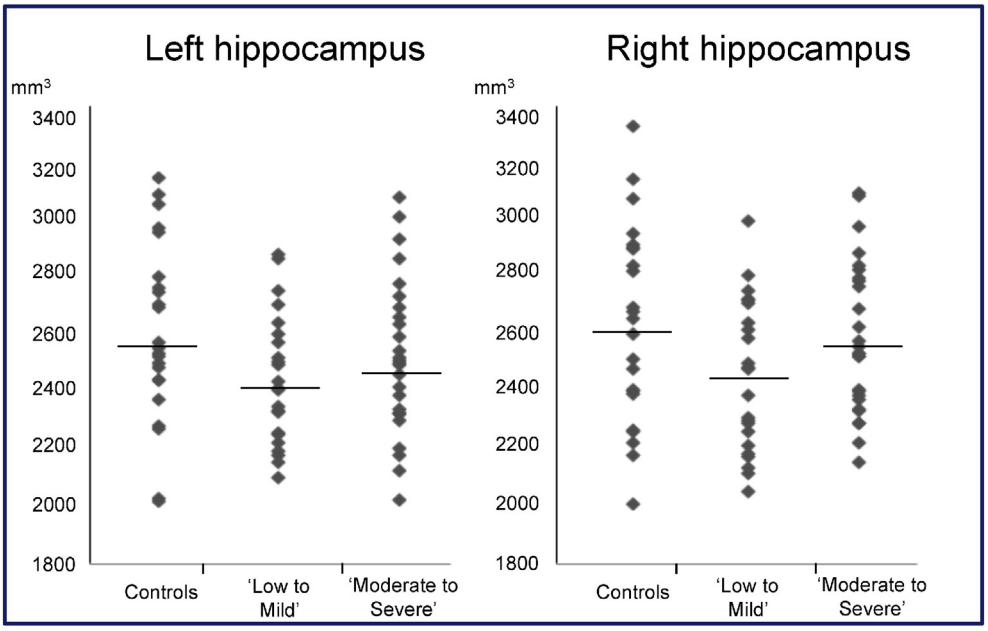

Fig. 5. Left and right hippocampal volumes (mm^3) for each group (VM = verbal memory). Bars indicate the means.

any structural hippocampal differences in schizophrenia patients (Niemann et al., 2000; Sanfilipo et al., 2000; Walker et al., 2002). In a recent review, Adriano et al. (2012) suggest that variations in image segmentation techniques could explain these differences. As noted by our group (Pipitone et al., 2014) and others (Morey et al., 2010), some segmentation pipelines such as FreeSurfer may be prone to false positives due to proportional bias in the way that large and small hippocampi volumes are estimated. The novel method of using the MAGeT Brain algorithm to extract hippocampal volumes, as well as the relatively small sample size, could explain our results. However, future research should be conducted to elucidate these inconsistencies.

While we reported multiple cognitive and demographic measures to better characterize our subgroups, it is highly unlikely that our two subgroups of patients differ only on their level of VM capacity. Indeed, patients with 'moderate to severe' VM impairments also had lower IQ and lower executive functioning, but were similar on all other neuropsychological measures. IQ is known to be generally lower in schizophrenia (Aylward et al., 1984; Khandaker et al., 2011) and accounts for part of the variance in VM performance among these patients (Kopald et al., 2012). Both IQ and executive function strongly correlated with VM in our study, and thus might account for a part of the variance in cortical thickness observed between our groups. Some researchers have proposed that IQ, executive function, and VM impairments in schizophrenia could reflect a common abnormality of information processing in prefrontal cortex rather than specific deficits in different cognitive domains (Leeson et al., 2009). However, further studies with greater statistical power should investigate the specific effect of cortical thickness on VM performance in relation to other cognitive domains known to be affected in schizophrenia.

Our two subgroups of patients were relatively similar on all other demographic and clinical measures, with the exception of negative symptom severity. Negative symptoms in schizophrenia are related to VM deficits (Harvey et al., 2006; Hovington et al., 2013) and as such, this difference is not surprising. There are several studies that have not found significant cortical thickness associations with negative symptom severity in schizophrenia (Sigmundsson et al., 2001; Kuperberg et al., 2003; Rimol et al., 2012; Xiao et al., 2015). However, other volumetric studies revealed associations between persistent negative symptoms and brain volume reductions in schizophrenia, specifically in the prefrontal and temporal cortices (Bodnar et al., 2014; Hovington and Lepage, 2012; Galderisi et al., 2015). Our results add an important contribution to previous studies that compare cortical thickness between subgroups of patients based solely on clinical features, without reporting any neurocognitive information. Recently, Nenadic et al. (2015) reported more extensive cortical thinning within a subgroup of schizophrenia patients who have more negative symptoms, implicating the prefrontal cortex and the PHG. Considering the strong associations between the two, it is possible that both VM and negative symptoms share common neural substrates involving prefrontal and PHG regions. Therefore, further investigation is necessary to better understand the specific and/or common effects of VM and negative symptoms on these areas.

Finally, our results suggest that schizophrenia patients with VM memory deficits are more likely to have thinner cortex, which may have significant clinical implications. VM deficits are associated with poor community functioning and poor response to psychosocial rehabilitation programs (Green et al., 2000; Evans et al., 2004). For example, schizophrenia patients who demonstrate greater VM impairments also tend to have poorer clinical and functional outcomes (Bodnar et al., 2008; Lepage et al., 2014). Investigating the association between VM impairments and cortical thickness in schizophrenia could provide important insights into the neuronal markers of poor clinical trajectories. A recent study observed associations between higher social withdrawal and reduced bilateral PHG volume in first-episode schizophrenia (Bodnar et al., 2012). This region is significantly reduced in the present study and appears to be related to both VM and clinical outcome. Further studies should explore the relationship between neural correlates of VM and daily functioning. Considering the importance of VM in a patient's global functioning and clinical outcome (Benoit et al., 2014; Bodnar et al., 2008; Evans et al., 2004; Green et al., 2000; Lepage et al., 2014), treatments targeting this type of memory and improving neurocognition should be encouraged. Administration of cognitive remediation to schizophrenia patients has shown a small to moderate positive effect on memory (McGurk et al., 2007; Wykes et al., 2011). Interestingly, cognitive enhancement therapy demonstrates significantly greater preservation of gray matter volume over 2 years in the left hippocampus, PHG, and fusiform gyrus, and significantly greater gray matter increases in the left amygdala in early schizophrenia (Eack et al., 2010). Additionally, specific cognitive training focusing on semantic encoding strategies has recently been shown to have a positive impact on VM in chronic schizophrenia (Guimond and Lepage, 2015). It would be of great interest to investigate to what extent deficits in semantic encoding strategies may explain VM impairments in schizophrenia, as well as related structural and functional brain abnormalities. Moreover, studies examining the impact of the aforementioned therapies on VM and associated brain structures at every stage of schizophrenia (i.e. prodromal, acute, and residual) are warranted.

5. Conclusion

In summary, we investigated whether schizophrenia patients with more severe VM deficits demonstrate greater cortical thinning. We observed that patients with 'moderate to severe' VM impairments have significantly thinner cortex in the left frontal cortex and bilateral PHG compared to healthy controls. Furthermore, using a more liberal threshold, we observed thinner cortex in these regions in patients with 'moderate to severe' VM impairments compared to patients with 'low to mild' VM impairments. However, even given this more liberal threshold, patients with 'low to mild' VM impairments showed similar cortical thickness compared to healthy controls in the left prefrontal cortex. Therefore, our results posit that a subgroup of patients with more severe VM impairments show greater cortical thinning in regions previously linked to this cognitive domain. Considering that patients with schizophrenia and VM deficits are more likely to have poor outcomes, gaining a better understanding of correlated brain abnormalities of this subgroup of patients is critical. Furthermore, our findings demonstrate that treatments targeting VM impairments in schizophrenia are warranted and should be encouraged.

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Contributors

SG drafted the first manuscript. SG, ML and MMC contributed to the design of the study. SG, LBG and RP carried out the data analysis. All authors contributed significantly to the interpretation of the data as well as having read and approved the final manuscript.

Conflict of interest

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

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