The Neuroanatomy of Verbal Working Memory in Schizophrenia: A Voxel-Based Morphometry Study

Gianfranco Spalletta [1,2], Francesco Tomaiuolo [1], Margherita Di Paola [1], Alberto Trequattrini [3], Pietro Bria [4], Emiliano Macaluso [1], Richard S. J. Frackowiak [1,5], Carlo Caltagirone [1,2]

Abstract

Background: Abnormalities of language expression and verbal working memory impairment have been described in schizophrenic subjects. **Purpose:** To investigate the relationship between verbal working memory performance and cerebral structure in schizophrenic patients and control subjects. **Method:** Twenty-one *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV)* schizophrenic subjects and twenty-one control subjects underwent T1-weighted magnetic resonance imaging (MRI). Grey (GM) and white matter (WM) densities were evaluated using voxel-based morphometry (VBM). We administered the verbal n-back task to assess verbal working memory performance. **Findings:** A linear regression model, with illness duration included as a covariate, showed that WM density values in the pars opercularis of the left inferior frontal gyrus were positively and specifically correlated ($t>7.16$, $DF=18$, $r=0.878$, $p<0.05$ corrected for multiple comparisons, at voxel level) with verbal working memory performance in schizophrenic patients. The cluster showing this relationship between performance and WM density extended from the inferior frontal gyrus to the parietal operculum (p-corrected<0.05, at cluster level). Because of its shape and position, the cluster is most probably located in the third component of the superior longitudinal fasciculus. This finding was specific for WM and was not found in control subjects. **Conclusions:** The hypothesis that there is a direct and specific relationship between verbal working memory performance and the integrity of the WM in frontal language areas in schizophrenia is confirmed by the results of this study. Poor working memory is reflected in abnormal frontal WM in the dominant hemisphere and, hence, probably reflects a failure of intercortical connectivity.

Key Words: Schizophrenia, Working Memory, White Matter, Voxel-Based Morphometry (VBM)

Introduction

Schizophrenia is a mental disorder with variable phenomenology that includes positive and negative symptoms and cognitive impairment (1, 2). Cognitive impairment is often present before overt clinical onset in schizophrenic patients; it is also found in attenuated form in nonschizophrenic relatives of patients and is an important risk factor for social dysfunction and unemployment.

One hypothesis concerning the cause of schizophrenia is that there is an impairment in the function of cerebral language areas (3). This results in abnormalities of language expression and difficulty discriminating inner from heard speech. Furthermore, some schizophrenic subjects show working memory impairment (4-6). It has been suggested that the basis for such abnormalities may be an anatomical disconnection between language areas (3, 7).

[1] IRCCS Santa Lucia Foundation, Rome
[2] Department of Neuroscience, University of Rome "Tor Vergata"
[3] Department of Mental Health, ASL Città di Castello (PG)
[4] Institute of Psychiatry, Catholic University of Sacred Heart, Rome
[5] Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College of London, London

Note: G. Spalletta and F. Tomaiuolo contributed equally to this work.

Address for correspondence: Dr. Gianfranco Spalletta, IRCCS Fondazione Santa Lucia, Via Ardeatina, 306-00179 Roma, Italy
Phone: 0039-0651501575; Fax: 0039-0651501575;
E-mail: g.spalletta@hsantalucia.it

Submitted: September 25, 2007; Revised: December 20, 2007; Accepted: December 22, 2007

Working memory is composed of several subsystems - a central executive, the phonological or articulatory loop and a visuospatial sketch pad (8). Each subsystem is associated with activations in different cerebral areas (9). Optimal working memory performance may then be the result of efficient connectivity between component cerebral structures implicated in this system (9). Verbal working memory may have a particularly crucial role in schizophrenia given its function in the temporary storage and manipulation of verbal information and in subvocal rehearsal. It has been shown to be abnormal in schizophrenic subjects in its auditory (10, 11) and visualverbal (12, 13) forms.

Functional imaging studies of verbal working memory in normal subjects have shown activation of the left inferior frontal gyrus and the left posterior parietal cortex by verbal storage and subvocal rehearsal (9, 14). Schizophrenic subjects show reduced activation in the left inferior frontal gyrus (11) and bilaterally in the dorsolateral prefrontal cortex (9, 11), the frontal operculum and both inferior and superior parietal cortices (10). These results support the hypothesis that functional abnormalities of the verbal working memory system in schizophrenic subjects, found mainly in the frontal lobes, are part of the core pathology of schizophrenia. Nevertheless, these results do not distinguish between intrinsic abnormalities of cortical function and/or impaired connections between them (7, 15).

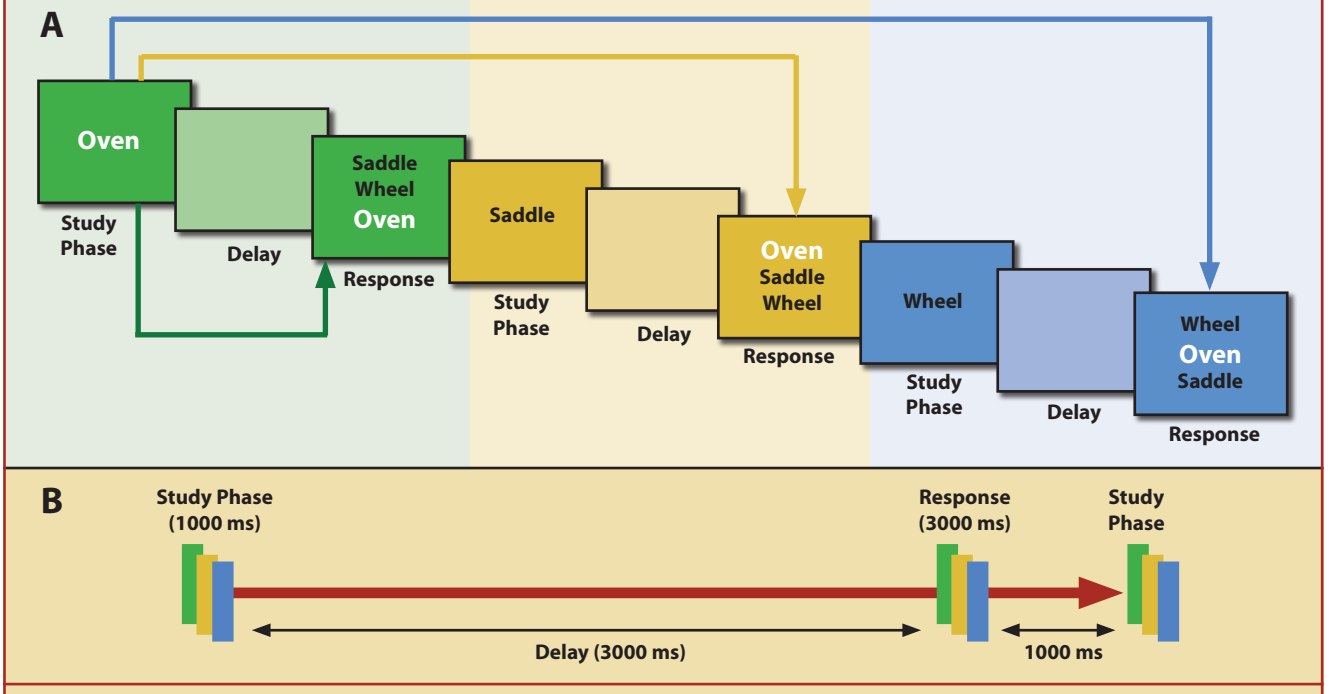
The aim of our study was to explore whether there is a relationship between verbal working memory performance and cerebral WM or GM morphometry in schizophrenic patients. We used the classical verbal "n-back" task to probe working memory (9) and VBM to assess local structural integrity (16, 17). The same analysis was carried out in a group of control subjects matched for age, gender and educational level.

Methods

Schizophrenic Subjects

The clinical sample consisted of twenty-one consecutively recruited outpatients with a diagnosis of schizophrenia in a phase of illness stability. Age at onset was defined as age at first hospitalization. Additional inclusion criteria were: age between eighteen and sixty-five years, Mini-Mental State Examination (MMSE) ≥24 (18) (a characteristic indicating no cognitive deterioration in the Italian population) (19, 20), no major medical or neurological illness, no history of alcohol or drug dependence or head trauma, no tardive dyskinesia as assessed by the Abnormal Involuntary Movement Scale (AIMS) (21) and no additional psychiatric disorder. All patients were receiving stable oral doses of atypical antipsychotic drugs. Antipsychotic dosages were converted to estimated equivalent dosages of olanzapine.

Figure 1 **Verbal "N-Back" Task Experimental Procedure**



A: The green arrow indicates one complete n-back sequence at the n-1 level from the "study phase" to the "response." The yellow arrow indicates one complete n-back sequence at the n-2 level. The blue arrow indicates one complete n-back sequence at the n-3 level. The word "Oven" is the correct item at the n-1, n-2 and n-3 levels.
B: Indicates one complete n-back sequence in terms of time.

The research protocol was approved by the Ethics Committee of the IRCCS Fondazione Santa Lucia. All patients gave written consent after a full verbal explanation of the procedures in the study.

Diagnostic and Neuropsychological Evaluations

A trained psychiatrist diagnosed *DSM-IV* schizophrenia using the Structured Clinical Interview for DSM-IV Patient Edition (SCID-P) (22). A second trained psychiatrist assessed verbal working memory performance (i.e., accuracy as memory load) of patients using the "n-back" verbal working memory task. The experiment was conducted in a soundproof room with soft lighting. Subjects sat comfortably in an armchair approximately 50 cm from a computer monitor (ViewSonic, 19 inches); the center of the monitor was aligned with the subjects' eyes. Subjects were required to monitor continuously a sequence of verbal stimuli (a total of twenty-two items presented as short words) and to select items that appeared n items back in any sequence. (This sequence was generated using locally written software installed on a Pentium® 4 IBM computer.) Furthermore, the item selection was done by the participants using a special keyboard with three keys, one for each stimulus. Also, the computer software automatically generated a file with results of the task with corrected-uncorrected responses. We administered three n-back subtasks at different levels of difficulty. At the n-1 level subjects were required to select an item that appeared one back in a sequence, at the n-2 level subjects selected an item that appeared two back in a sequence, and at the n-3 level they selected an item that appeared three items back in a sequence. The number of corrected responses for each sequence (i.e., n-1, n-2, and n-3) was considered as a possible index of working memory performance. The experimental procedure is described in Figure 1 and has been used with nonverbal stimuli in several previous studies (23-25).

All patients were trained to obtain their maximal performance score. In particular, all subjects were trained using the n-1 back paradigm by means of verbal and written explanations. Furthermore, for training, patients practiced the n-1 back sequence three times before starting the actual experimental procedure. Those subjects who scored less than ten on the n-1 back sequence (n=1) were excluded from the study; "n-back" tasks were performed within fifteen days of MRI.

Control Subjects

Twenty-one control subjects were selected and matched with the schizophrenic patients for age, gender and educational level. They were interviewed with the Structured Clinical Interview for DSM-IV Non-Patient Edition (SCID-NP) (26). None of them suffered from a mental disorder. A different clinical psychiatrist administered the n-back verbal working memory task to the control subjects. Times and modalities of administration for the tasks to the control subjects were identical to those used with the schizophrenic subjects.

Image Acquisition

Magnetic resonance T1-weighted images, Magnetization Prepared Rapid Gradient Echo Sequence (MPRAGE; Erlangen, Germany; 1 mm isotropic voxel, repetition time [TR]=11.4 ms, echo time [TE]=4.4 ms, flip angle=15 deg), were obtained with a Siemens 1.5 T Vision Magnetom MR system. Image distortions and head motion of each image were carefully evaluated by a trained neuroradiologist. Only images without artifact or with very small acceptable problems were used for the analysis.

Image Processing

The procedure we used for VBM followed the methodology described by Bernasconi et al. (27). The following steps were applied to the scans of each subject:

1) The MPRAGE brain volume images underwent a nonuniformity correction to remove variations in MRI intensity related to radio frequency inhomogeneity (28);

2) Subsequently, MRI images were transformed linearly to standardized stereotactic space (29) to adjust for differences in total brain volume and brain orientation. Correct registration is critical for VBM analysis (30); the quality of the transformation was verified using the software Register that allows for the simultaneous visualization in 3D of two brain volumes (www.bic.mni.mcgill.ca/software/distribution). Each individual brain of the subjects who participated in our study was compared with the template of the Montreal Neurological Institute (average of 305 brains) to verify correct resampling in stereotactic space. Variability caused by head structure other than the brain (31) was reduced using the MacDonald algorithm (32);

3) Then the tissue-classification algorithm (INSECT) (33) was applied to classify each voxel into one of three classes: namely, GM, WM or cerebralspinal fluid. A binary volume consisting of GM voxels and another consisting of WM voxels were extracted from the classified image; and,

4) GM and WM binary masks were smoothed using a Gaussian smoothing kernel of 10 mm full width at half maximum to generate 3D maps of GM and WM "density." Smoothing allows one to convert the binary data into a range of continuous data for statistical analyses used in this study (34). The brainstem and cerebellum were not included in the analyses.

Table 1 Sociodemographic and Clinical Characteristics of 21 Schizophrenic Patients and 21 Control Subjects Matched for Age, Gender and Educational Level

	Schizophrenic Patients (n=21)	Control Subjects (n=21)		
Characteristics	**Mean±SD (Range)**	**Mean±SD (Range)**	**t**	**p**
Age (year)	35.1±9.8 (20-58)	34.6±8.3 (20-55)	-0.187	>.05
Educational Level (year)	11.0±3.1 (8-17)	11.8±3.7 (8-17)	0.763	>.05
Age at the Onset of the Illness (year)	23.3±7.0 (15-40)	----	----	----
Duration of Illness (year)	11.8±8.3 (1-34)	----	----	----
Olanzapine Equivalents (mg/day)	21.5±16.3 (3-60)	----	----	----
Verbal Working Memory (1-back)*	19.5±3.2 (10-22)	20.9±2.0 (15-22)	1.782	>.05
Verbal Working Memory (2-back)*	16.4±4.6 (5-21)	19.0±3.4 (9-21)	2.144	<.05
Verbal Working Memory (3-back)*	9.0±3.7 (4-15)	15.1±4.7 (8-20)	4.677	<.0001
Mini-Mental State Examination (MMSE)	27.9±1.6 (24-30)	28.6±1.1 (27-30)	1.661	>.05
	N (%)	**N (%)**	**Chi- square**	**p**
Gender (male)	12 (57)	12 (57)	0.000	>.05
Marital Status (married)	2 (9)	7 (33)	3.535	>.05
***DSM-IV* Subtypes:**				
Paranoid	14 (67)	----	----	----
Disorganized	3 (14)	----	----	----
Undifferentiated	3 (14)	----	----	----
Residual	1 (5)	----	----	----

SD=standard deviation, * Number of corrected responses

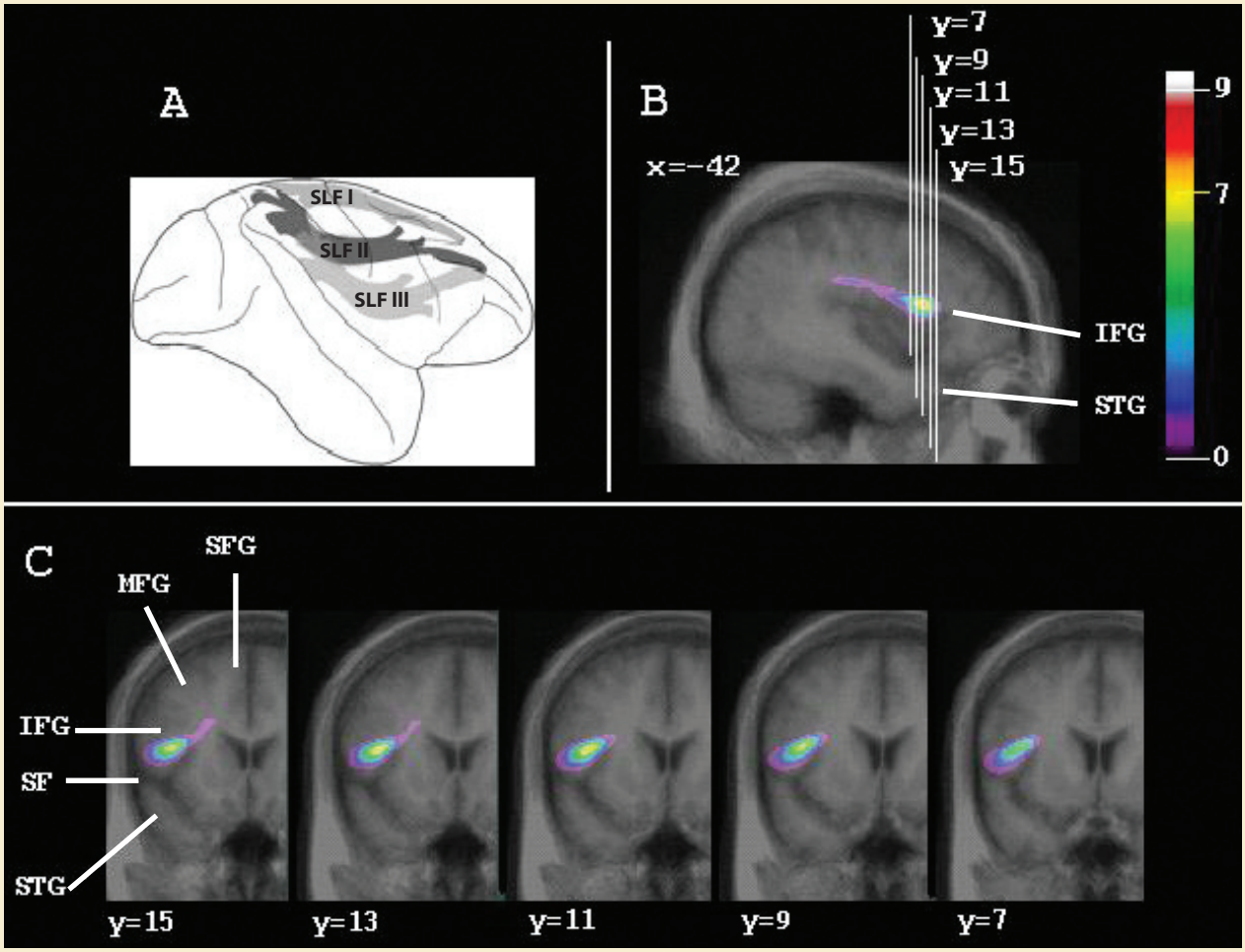
Statistical Analysis

Comparisons with respect to categorical and continuous sociodemographic and clinical variables were made using chi-square and Student's t-tests, respectively. Pearson's correlation was used to analyze the relationship between verbal working memory performance during the n-back task at the 2-back level and antipsychotic dosages in schizophrenic patients. This was done in order to verify whether a statistically significant effect of antipsychotic treatment on verbal working memory performance existed (35). This effect, if present, could influence results of the study.

Using six multivariate linear regression models, we correlated the individual GM and WM density maps with patient and control subject verbal working memory performances during the n-back task. In the first analysis, we correlated the WM density map of the schizophrenic patients with the number of corrected responses at the n-2 level of the n-back task. In the second analysis, we correlated the WM density map of the control subjects with the number of corrected responses at the n-2 level of the n-back task. In the third analysis, we correlated the WM density map ot the control subjects with the number of corrected responses at the n-3 level of the n-back task. The same three analyses were repeated for GM. In all these analyses, the duration of illness was entered as covariate, to correct for possible impact of this variable on the cerebral structures. In schizophrenic subjects we chose to limit statistical analysis to the n-2 level as schizophrenics scored at chance for the n-3 task and at ceiling for the n-1 task. In control subjects, we also analyzed the n-3 level because a range of performances was obtained (36).

The voxel-level statistical threshold for GM maps was set to t>6.85 (r>0.843), based on a voxel size of 1 mm^3, smoothness of 10 mm, a volume of interest of 500 cm^3, 18 degrees of freedom (DF) and a significance level of $p<0.05$ corrected for multiple comparisons (34). The voxel-level threshold for WM maps was set to t>7.16 (r>0.860), based on a voxel size of 1 mm^3, smoothness of 10 mm, a volume of interest of 800 cm^3, 18 degrees of freedom and a significance level of $p<0.05$ corrected for multiple comparisons (34). A positive regression indicated greater GM or WM density associated with more correct items on the n-back task. In

Figure 2 **Verbal Working Memory Task-Related Changes in White Matter Density in the Left Hemisphere**



The map indicating the correlation between verbal working memory performance, at the 2-back level, and white matter density in each voxel is an average across patients, covaried for the duration of the illness. A: Schematic depiction of the 3 branches of the superior longitudinal fasciculus (SLF) in the monkey brain according to Schmahmann and Pandya (49). B: The correlation is superimposed on an average sagittal section (X=-42) constructed from all the schizophrenics in this study. C: Coronal section through a hemisphere of all the schizophrenic brains taken at the level demarcated in B to show the location of the SLF fiber bundle in the white matter.
The colored bar indicates t values. The threshold which is considered statistically significant is set at $p<0.05$ corrected for multiple comparisons (corresponding to a $t>7.16$, at a voxel level, and to $t>3.6$, at a cluster level).
SFG=Superior Frontal Gyrus; MFG=Middle Frontal Gyrus; IFG=Inferior Frontal Gyrus; SF=Silvane Fissure; STG=Superior Temporal Gyrus

addition, we assessed statistical significance at cluster level (p-corrected<0.05) that jointly considers the amplitude of the effects at voxel level (here $p<0.001$) and the number of contiguous voxels passing the threshold (minimum cluster size for WM=782 mm^3). This approach allows us to highlight entire WM structures that correlate with behavioral measures, rather than just specific points in 3D anatomical space.

Results

Sociodemographic and Clinical Variables

The sociodemographic and clinical characteristics of schizophrenic patients and control subjects with statistical comparisons are shown in Table 1.

There were no statistically significant differences in age, educational level or gender between schizophrenic and control subjects. In addition, no statistically significant relationship was found between verbal working memory performance at the 2-back level and atypical antipsychotic dosages in olanzapine equivalents (Pearson's $r=0.039$, $p=0.868$).

A statistically significant difference was found between schizophrenic patients and control subjects in verbal working memory performance at the 2-back and the 3-back levels. Schizophrenic patients performed less well than control subjects.

Relationship between Verbal Working Memory, GM and WM Density

We found a significant positive correlation (see Figure 2) between verbal working memory performance of schizophrenic subjects at the 2-back level and WM density in the pars opercularis of the left inferior frontal gyrus with a maximum peak at x=-42, y=12, z=14 (t>7.16, DF=18, r=0.878, p<0.05 corrected for multiple comparisons, at voxel level). No significant relationship was found with GM density.

To investigate the distribution of the WM density values in the two groups of patients and control subjects at the level of the superior longitudinal fasciculus (SLF), we extracted, for each subject, the value of the white matter density at the voxel with the maximum significant difference (x=-42, y=12, z=14) in the previous analysis. Then, we plotted these values comparing patients versus control subjects (see Figure 3). In this cerebral area, the WM density statistically differed between schizophrenic patients and control subjects (t=2.144, DF=40, p=0.038).

Figure 4 shows the scatterplot of the correlation between working memory scores and white matter density values of schizophrenic patients at the coordinates (x=-42, y=12, z=14) in the schizophrenic patients.

We found no significant relationship in control subjects between either GM or WM density and n-back verbal working memory performance at the 2-back and 3-back levels. Statistical tests for cluster-level significance (p-corrected<0.05) demonstrated that WM density of the fibertracks connecting the pars opercularis of the left inferior frontal gyrus and the parietal operculum in schizophrenic patients showed positive correlation with verbal working memory performance (cluster size=962 mm^3). Because of the characteristic shape and position (see Figure 2) we believe that the result is located and confined to the SLF (37).

Figure 3 White Matter Density Values of Control Subjects and Schizophrenic Patients at the Voxel with the Maximum Significant Difference (x=-42, y=12, z=14)

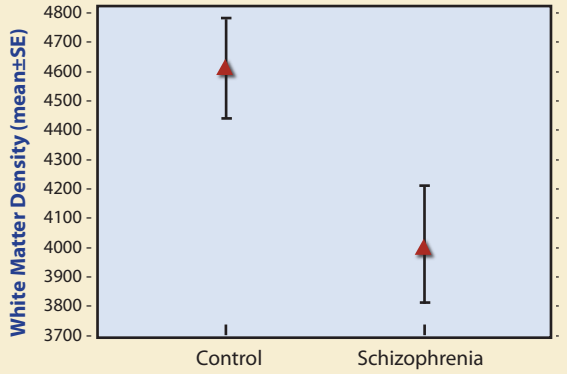
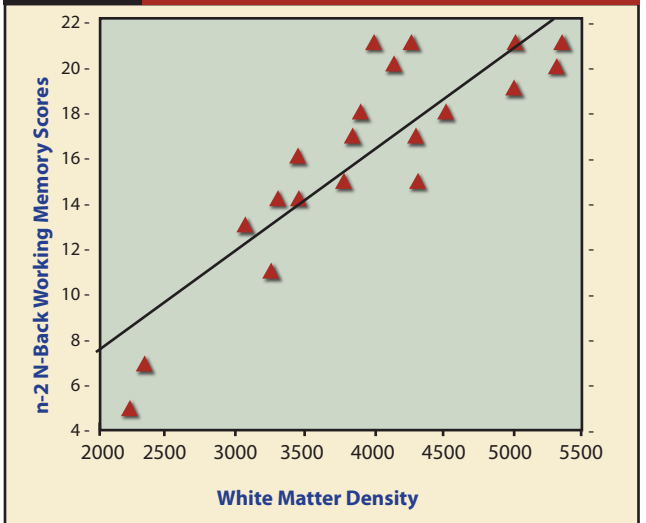


Figure 4 Correlation between Working Memory Scores and White Matter Density Values at the Coordinates (x=-42, y=12, z=14) in the Schizophrenic Patients



Discussion

Our study finds that the WM density of the pars opercularis of the left inferior frontal gyrus of schizophrenic subjects correlates positively with the ability to correctly perform the verbal working memory n–back task at the 2-back level. The peak of this correlation is located in a cluster centered on the frontoparietal operculum. The shape and position of the cluster suggests it is part of the third component of the SLF. We found no significant correlation between verbal working memory and GM density. In control subjects we found no correlation between GM or WM density and verbal working memory performance. The absence of any correlation cannot be explained by a statistical bias induced by a ceiling effect. In control subjects there was also no correlation between performance of the more difficult 3-back task and WM or GM density. The change in WM density found in schizophrenic subjects is, therefore, specific. It could be the result of a modification of axon diameter or myelination, either of which could modify speeds of neural transmission (38, 39).

A very recent study, using diffusion tensor imaging to examine fractional anisotropy, described that recent-onset schizophrenic patients, with a mean illness duration of fifteen months, showed anatomical changes in the left SLF, and this abnormality was associated with the performance in a verbal working memory task (40). Our results, in an older group of patients with longer illness duration, using a different method for assessing WM morphometry, that is VBM, found similar results. This suggests that verbal working memory impairment and its structural correlate may be a constant marker of schizophrenia both at the onset of the

illness and during the later stages. The results are interesting because the affected area is connected to Broca's area (41) and frontal fibers of the SLF. The SLF consists of association fibers that link the frontal to the parietal lobes (37, 42). Anatomical studies in monkeys indicate that it consists of three reciprocal components (37). The third component (i.e., that which is implicated by our results) connects the supramarginal gyrus and the parietal operculum with the premotor area, the pars opercularis of the inferior frontal gyrus, the frontal opercular region and the ventral part of the middorsolateral frontal lobe. Complex somatosensory stimuli related to the face and arm are carried by the third component of the SLF (43, 44). Neural areas connected by the third component of the SLF respond both when a monkey performs a specific movement and when it observes another monkey performing the same action (45). Therefore, the interconnected areas and connecting pathways are involved in action imitation that may be at the basis of gestural communication; a function that probably preceded the evolution of linguistic communication.

From a theoretical point of view, it is possible to interpret our data in the light of Baddeley's model of working memory in which he introduced the concept of "fractionation of working memory" (8). In this model, working memory is a cognitive function composed of various subsystems. The phonological loop constitutes a temporary storage system for language information that may be maintained in memory for two to three seconds. However, when necessary, such information may be retained in memory by continuous subvocal rehearsal, an operation that is mediated by Broca's area (8, 9). Thus, the modification of WM density found in our patients that correlates with verbal working memory performance could represent the structural basis for a specific impairment of phonological loop activity in schizophrenia.

There are some issues to be discussed. Firstly, despite the fact that we found no correlation between atypical antipsychotic dosage and verbal working memory performance, we believe it is important to confirm our findings in drug-naive patients with first-episode schizophrenia. Secondly, how can we explain that: 1) those schizophrenic patients who have a reduced verbal working memory performance have a reduced WM density in the SLF, a WM tract which is involved in the rehearsal process; and that, 2) this was found in schizophrenics only and not in control subjects? On the one hand, it is possible that some insult (e.g., developmental), specifically in this area, can primarily impair the structure of the SLF and, consequently, the working memory performance. Thus, schizophrenics who have decreased verbal working memory performance do not use rehearsal as a strategic choice and may hold verbal materials in other preserved cerebral areas rather than in the damaged phonological areas. However, this strategy could not fully compensate the good performance associated with a preserved SLF structure. An alternative explanation can be found in a precocious primary linguistic problem of environmental or reactive nature, such as a defective phonological problem, that secondarily may compromise the development of language cerebral areas. In reality, there is evidence that those children who will develop schizophrenia have impaired capacity for social interaction, solitary play preference and language problems and, therefore, may use differently, either quantitatively or qualitatively, language for communication (46-48). If this is caused by problems of primary biological nature or secondary environmental or psychological nature, it is difficult to explain. However, the fact that schizophrenic patients have reduced WM density in the SLF area with the strongest correlation with verbal working memory performance, in comparison with control subjects, strongly suggests that this area is primarily damaged in schizophrenia independently from the cognitive performance. Apart from these speculations, the finding of reduced verbal working memory performance in schizophrenia associated with reduced WM density of the SLF is in line with the concept that the structure of fibers connecting Broca's area of the left premotor frontal region and supramarginal gyrus of the inferior parietal lobule may have a pathogenetic role in schizophrenia.

Given the limitations of this study we suggest that future studies should investigate the specificity of these results and analyze the relationship between WM structure (i.e., density, volume or diffusion tensor imaging) and a larger set of cognitive domains.

Conclusions

Results of this study confirm the hypothesis that WM structural abnormality of cerebral language areas, namely the pars opercularis of the left inferior frontal gyrus and the SLF, is implicated in verbal working memory impairment in schizophrenia.

Acknowledgments

The Italian Ministry of Health RC-06/A.

References

1. Andreasen NC. Schizophrenia: the fundamental questions. Brain Res Brain Res Rev 2000;31(2-3):106-112.
2. Mitchell RL, Elliott R, Woodruff PW. fMRI and cognitive dysfunction in schizophrenia. Trends Cogn Sci 2001;5(2):71-81.
3. Crow TJ. Schizophrenia as the price that homo sapiens pays for language: a resolution of the central paradox in the origin of the species. **Brain Res Brain Res Rev 2000;31(2-3):118-129.**
4. Carter CS, Perlstein W, Ganguli R, Brar J, Mintun M,

Cohen JD. Functional hypofrontality and working memory dysfunction in schizophrenia. Am J Psychiatry 1998;155(9):1285-1287.

5. Goldman-Rakic PS. Working memory dysfunction in schizophrenia. J Neuropsychiatry Clin Neurosci 1994;6(4):348-357.

6. Pierri JN, Volk CL, Auh S, Sampson A, Lewis DA. Decreased somal size of deep layer 3 pyramidal neurons in the prefrontal cortex of subjects with schizophrenia. Arch Gen Psychiatry 2001;58(5):466-473.

7. Spalletta G, Tomaiuolo F, Marino V, Bonaviri G, Trequattrini A, Caltagirone C. Chronic schizophrenia as a brain misconnection syndrome: a white matter voxel-based morphometry study. Schizophr Res 2003;64(1):15-23.

8. Baddeley A. The fractionation of working memory. Proc Natl Acad Sci USA 1996;93(24):13468-13472.

9. Smith EE, Jonides J. Storage and executive processes in the frontal lobes. Science 1999;283(5408):1657-1661.

10. Menon V, Anagnoson RT, Mathalon DH, Glover GH, Pfefferbaum A. Functional neuroanatomy of auditory working memory in schizophrenia: relation to positive and negative symptoms. Neuroimage 2001;13(3):433-446.

11. Stevens AA, Goldman-Rakic PS, Gore JC, Fulbright RK, Wexler BE. Cortical dysfunction in schizophrenia during auditory word and tone working memory demonstrated by functional magnetic resonance imaging. Arch Gen Psychiatry 1998;55(12):1097-1103.

12. Conklin HM, Curtis CE, Katsanis J, Iacono WG. Verbal working memory impairment in schizophrenia patients and their first-degree relatives: evidence from the digit span task. Am J Psychiatry 2000;157(2):275-277.

13. Perlstein WM, Carter CS, Noll DC, Cohen JD. Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. Am J Psychiatry 2001;158(7):1105-1113.

14. Honey GD, Bullmore ET, Sharma T. Prolonged reaction time to a verbal working memory task predicts increased power of posterior parietal cortical activation. Neuroimage 2000;12(5):495-503.

15. Crow TJ. Schizophrenia as failure of hemispheric dominance for language. Trends Neurosci 1997;20(8):339-343.

16. Paus T, Zijdenbos A, Worsley K, Collins DL, Blumenthal J, Giedd JN, et al. Structural maturation of neural pathways in children and adolescents: in vivo study. Science 1999;283(5409):1908-1911.

17. Tisserand DJ, van Boxtel MP, Pruessner JC, Hofman P, Evans AC, Jolles J. A voxel-based morphometric study to determine individual differences in gray matter density associated with age and cognitive change over time. Cereb Cortex 2004;14(9):966-973.

18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-198.

19. Measso G, Cavarzeran F, Zappalà G, et al. The Mini-Mental State Examination: normative study of an Italian random sample. Dev Neuropsychol 1993;9:77-85.

20. Grigoletto F, Zappala G, Anderson DW, Lebowitz BD. Norms for the Mini-Mental State Examination in a healthy population. Neurology 1999;53(2):315-320.

21. Guy W. ECDEU assessment manual for psychopharmacology. DHEW publication, no. (ADM) 76-338. Rockville, MD, U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs. 1976.

22. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for Axis I DSM-IV disorders. Research version-patient edition (SCID-I/P, Ver. 2.0). New York (NY): New York State Psychiatric Institute, Biometrics Research Department; 1996.

23. Oliveri M, Turriziani P, Carlesimo GA, Koch G, Tomaiuolo F, Panella M, et al. Parieto-frontal interactions in visual-object and visual-spatial working memory: evidence from transcranial magnetic stimulation. Cereb Cortex 2001;11(7):606-618.

24. Owen AM, Stern CE, Look RB, Tracey I, Rosen BR, Petrides M. Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. Proc Natl Acad Sci USA 1998;95(13):7721-7726.

25. Smith EE, Jonides J. Working memory: a view from neuroimaging. Cognit Psychol 1997;33(1):5-42.

26. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV Axis I Disorders (SCID). New York (NY): New York State Psychiatric Institute, Biometric Research Department; 1995.

27. Bernasconi N, Duchesne S, Janke A, Lerch J, Collins DL, Bernasconi A. Whole-brain voxel-based statistical analysis of gray matter and white matter in temporal lobe epilepsy. Neuroimage 2004;23(2):717-723.

28. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans Med Imaging 1998;17(1):87-97.

29. Collins DL, Neelin P, Peters TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J Comput Assist Tomogr 1994;18(2):192-205.

30. Ashburner J, Friston KJ. Why voxel-based morphometry should be used. Neuroimage 2001;14(6):1238-1243.

31. Burton EJ, Karas G, Paling SM, Barber R, Williams ED, Ballard CG, et al. Patterns of cerebral atrophy in dementia with Lewy bodies using voxel-based morphometry. Neuroimage 2002;17(2):618-630.

32. MacDonald D, Kabani N, Avis D, Evans AC. Automated 3-D extraction of inner and outer surfaces of cerebral cortex from MRI. Neuroimage 2000;12(3):340-356.

33. Zijdenbos AP, Forghani R, Evans AC. Automatic quantification of MS lesion in 3D MRI brain data sets: validation of INSECT. Proceedings of International Conference on Medical Image Computing and Computer-Assisted Intervention (MICCAI). Berlin (Germany): Springer Verlag; 1998.

34. Worsley KJ, Marret S, Neelin P, Vandal AC, Friston KJ, Evans AC. A unified statistical approach for determining significant signals in image of cerebral activation. Hum Brain Mapp 1996;4:58-73.

35. Keefe RS, Young CA, Rock SL, Purdon SE, Gold JM, Breier A; HGGN Study Group. One-year double-blind study of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in schizophrenia. Schizophr Res 2006;81(1):1-15.

36. Honey GD, Fu CH, Kim J, Brammer MJ, Croudace TJ, Suckling J, et al. Effects of verbal working memory load on corticocortical connectivity modeled by path analysis of functional magnetic resonance imaging data. Neuroimage 2002;17(2):573-582.

37. Petrides M, Pandya DN. Association pathways of the prefrontal cortex and functional observations. In: Stuss DT, Knight RT, editors. Principles of frontal lobe function. New York: Oxford University Press; 2002.

38. Aboitiz F, Scheibel AB, Fisher RS, Zaidel E. Fiber composition of the human corpus callosum. Brain Res 1992;598(1-2):143-153.

39. Paus T, Collins DL, Evans AC, Leonard G, Pike B, Zijdenbos A. Maturation of white matter in the human brain: a review of magnetic resonance studies. Brain Res Bull 2001;54(3):255-266.

40. Karlsgodt KH, van Erp TG, Poldrack RA, Bearden CE, Nuechterlein KH, Cannon TD. Diffusion tensor imaging of the superior longitudinal fasciculus and working memory in recent-onset schizophrenia. Biol Psychiatry 2008; 63(5):512-518.

41. Tomaiuolo F, MacDonald JD, Caramanos Z, Posner G, Chiavaras M, Evans AC, et al. Morphology, morphometry and probability mapping of the pars opercularis of the inferior frontal gyrus: an in vivo MRI analysis. Eur J Neurosci 1999;11(9):3033-3046.

42. Tailarach J, Tournoux P. Referentially oriented cerebral MRI anatomy: atlas of sterotaic anatomical correlations for gray and white matter. New York, Stuttgart: Georg Thieme Verlag; 1993.

43. Hyvarinen J, Shelepin Y. Distribution of visual and somatic functions in the parietal associative area 7 of the monkey. Brain Res 1979;169(3):561-564.

44. Leinonen L, Nyman G. II. Functional properties of cells in anterolateral part of area 7 associative face area of awake monkeys. Exp Brain Res 1979;34(2):321-333.

45. Rizzolatti G, Fadiga L, Gallese V, Fogassi L. Premotor cortex and the recognition of motor actions. Brain Res Cogn Brain Res 1996;3(2):131-141.

46. Done DJ, Crow TJ, Johnstone EC, Sacker A. Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. BMJ 1994;309(6956):699-703.

47. Jones P, Rodgers B, Murray R, Marmot M. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 1994;344(8934):1398-1402.

48. Nicolson R, Lenane M, Singaracharlu S, Malaspina D, Giedd JN, Hamburger SD, et al. Premorbid speech and language impairments in childhood-onset schizophrenia: association with risk factors. Am J Psychiatry 2000;157(5):794-800.

49. Schmahmann JD, Pandya DN. Fiber pathways of the brain. New York: Oxford University Press; 2006. Adopted with permission from figures 13-1, 13-3, 13-4.