

Research Paper

Cognitive and psychopathology correlates of brain white/grey matter structure in severely psychotic schizophrenic inpatients



Nerisa Banaj^a, Federica Piras^a, Fabrizio Piras^{a,b}, Valentina Ciullo^{a,c}, Mariangela Iorio^a, Claudia Battaglia^d, Donatella Pantoli^e, Giuseppe Ducci^d, Gianfranco Spalletta^{a,f,*}

^a Laboratory of Neuropsychiatry, IRCCS Santa Lucia Foundation, 00179 Rome, Italy

^b Museo Storico della Fisica e Centro Studi e Ricerche "Enrico Fermi", 00184 Rome, Italy

^c Department of Neurosciences, Psychology, Drug Research and Child Health, University of Florence, 50139 Florence, Italy

^d Department of Mental Health, ASL, Roma 1, 00135 Rome, Italy

^e Department of Radiology, S. Filippo Neri Hospital, ASL, Roma, 1, 00135 Rome, Italy

^f Division of Neuropsychiatry, Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX 77030, USA

ARTICLE INFO

Keywords:

Psychotic exacerbation
Schizophrenia inpatients
Brain morphometry
Frontal cortex
Temporal cortex
Cerebellum
Cognition

ABSTRACT

The brain structural correlates of cognitive and psychopathological symptoms within the active phase in severely psychotic schizophrenic inpatients have been rarely investigated. Twenty-eight inpatients with a DSM-5 diagnosis of Schizophrenia (SZ), admitted for acute psychotic decompensation, were assessed through a comprehensive neuropsychological and psychopathological battery. All patients underwent a high-resolution T1-weighted magnetic resonance imaging investigation.

Increased psychotic severity was related to reduced grey matter volumes in the medial portion of the right superior frontal cortex, the superior orbitofrontal cortex bilaterally and to white matter volume reduction in the medial portion of the left superior frontal area. Immediate verbal memory performance was related to left insula and inferior parietal cortex volume, while long-term visuo-spatial memory was related to grey matter volume of the right middle temporal cortex, and the right (lobule VII, CRUS1) and left (lobule VI) cerebellum. Moreover, psychotic severity correlated with cognitive inflexibility and negative symptom severity was related to visuo-spatial processing and reasoning disturbances.

These findings indicate that a disruption of the cortical-subcortical-cerebellar circuit, and distorted memory function contribute to the development and maintenance of psychotic exacerbation.

1. Introduction

The majority of patients with schizophrenia (SZ) experience multiple relapses during the course of the illness (Emsley et al., 2013; Robinson et al., 1999) with up to 40% suffering a relapse within a year after being hospitalized (Hogarty and Ulrich, 1998) even under treatment (Gelder et al., 2000). Relapse rates vary from 50% to 92% (Suzuki et al., 2003) and are similar worldwide. Relapse, characterized by acute psychotic exacerbation, may have serious implications, such as progressive deterioration in social and interpersonal functioning (Kane, 2007) and is associated with loss of tissue (Andreasen et al., 2013) either in total cerebral volume and specific subregions (e.g., frontal lobe). Notably, grey matter (GM) density decrease is specifically related to relapse duration and treatment intensity, but unrelated to number of relapses, thus suggesting that acute psychotic exacerbation itself may exert a "toxic" effect on the brain (Andreasen et al., 2013). However,

the loss of brain tissue over time in specific brain regions, and the positive correlation with number of hospitalizations during the scan interval observed in other longitudinal studies (van Haren et al., 2007) may suggest a progressive, not static nature of brain abnormalities in SZ. Nevertheless, it has been suggested that relapse may lead to brain tissue loss via abnormalities in the glutamatergic and/or dopaminergic systems (for a recent review see Landek-Salgado et al., 2016). In a recent elaboration of the dopamine hypothesis, it has been pointed out that dopaminergic hyperfunction, likely due to an increase in pre-synaptic dopamine synthesis, is associated with psychotic exacerbation (Howes et al., 2012; Howes and Kapur, 2009). Indeed, elevated dopamine synthesis has been detected in patients acutely psychotic at the time of investigation (Howes and Kapur, 2009) and associated with poor performance on cognitive tasks (Howes et al., 2009).

Past studies focused exclusively on the relationship between the number and global duration of relapses and brain structural damage, or

* Corresponding author at: Laboratory of Neuropsychiatry, IRCCS Santa Lucia Foundation, Via Ardeatina, 306-00179 Rome, Italy.
E-mail address: g.spalletta@hsantalucia.it (G. Spalletta).

between the severity of acute psychopathological symptoms and cognitive dysfunctions. Unfortunately, no data exist on the relationship between severity of psychopathology and severity of brain structural damage in SZ during the active phase.

Moreover, the interaction between cognition and psychopathology has been studied following different methodological designs. A recently favoured approach for characterizing the psychopathological symptoms of SZ proposes quantitative dimensions to investigate sources of heterogeneity between SZ patients. Indeed, factor analyses have consistently demonstrated that the individual psychopathological symptoms can be grouped, and that they may be better accounted for by three dimensions: psychotic, negative, and disorganized (Andreasen et al., 1995a; Grube et al., 1998). Therefore, assuming that psychopathological dimensions have neurobiological constructs (Andreasen et al., 1995a; Flaum et al., 1995; Koutsouleris et al., 2008) and that cognitive functioning represents an intermediate level between psychopathology and neurobiology (Mortimer and McKenna, 1994), experimental studies focused on different phases of the illness may provide clues about the mediating role of cognition in psychotic activation and the neurobiological mechanisms that underpin such relationship.

To the best of our knowledge, although relapses in SZ represent a crucial part of the illness, they have been scarcely investigated, probably as a consequence of patients' scarce collaboration and hospitalization context, often unsuitable for clinical research. The Italian law 180 (1978) provided that psychiatric patients could be admitted only to hospital psychiatric wards (SPDCs, psychiatric services for diagnosis and treatment), and no other admission (i.e. to psychiatric asylums, which were in fact abolished) shall be allowed. SPDCs are the perfect setting for studying psychotic relapses considering that SZ patients are admitted mainly during the active phase of the illness for their psychotic exacerbation.

The main goal of the present study was to identify the relationships among SZ phenotypic traits (psychopathology/cognition) and their brain structural correlates during psychotic exacerbation. We therefore examined the associations between brain grey/white matter volume, the three symptom dimensions and neurocognitive performance in severely psychotic SZ inpatients. We hypothesized that, similarly to what is observed in the stable phase of the illness (Flaum et al., 1995; Padmanabhan et al., 2014), different symptom dimensions would relate to selective patterns of structural brain alterations and to specific impairments in cognition. Considering that our sample was composed of severely psychotic SZ, the strongest correlations were expected between the psychotic dimension and the cognitive/brain structural markers of SZ.

More specifically, we expected to find an association between severity of psychotic symptoms and regional brain volume within the cortical-subcortical-cerebellar circuit (CSCC), specifically in frontal lobe regions, previously described as functionally impaired (Andreasen, 1999; Barch, 2014; Spoletini et al., 2009), and potentially underlying symptoms such as hallucinations and delusions (Andreasen et al., 1998; Sheffield and Barch, 2016). Moreover, based on recent cognitive models which highlight the importance of cognition in the development and maintenance of psychoses (Garety et al., 2013; Keefe et al., 2011; Krishnan et al., 2011), we predicted that among severely psychotic inpatients, those with more severe symptoms would exhibit a greater cognitive alteration and a more pronounced brain volume reduction in the underlying neural circuitry.

2. Material and methods

2.1. Participants

Patients with a diagnosis of SZ were recruited from the SPDC of San Filippo Neri Hospital in Rome, center Italy. All patients were admitted in the ward for a psychotic exacerbation between November 2013 and February 2015 and were in the active phase of SZ according to DSM-5

(APA, 2013) criteria. They all suffered from clinically significant psychotic symptoms, as defined by a score greater than or equal to 4 in the Hallucination and/or Delusions subscales on the Scale for the Assessment of Positive Symptoms (SAPS). All potentially eligible patients were approached between 24 and 48 h of admission. Diagnoses were confirmed using the Structured Clinical Interview for DSM-5 (SCID)-Clinician Edition (First et al., 2016). No subject had a Major Neurocognitive Disorder according to DSM-5 criteria. Other inclusion criteria were: (a) age between 18 and 65 years; (b) at least 5 years of education; (c) no global cognitive deterioration defined by a Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score lower than 25, consistent with normative data in the Italian population (Measso et al., 1993); and (d) suitability for magnetic resonance imaging (MRI) scan. Exclusion criteria included: a) substance abuse or dependence according to DSM-5 criteria; b) history of neurologic illness or brain injury with loss of consciousness; c) major medical illness (e.g. any clinically significant and unstable blood, renal, gastrointestinal, endocrine or cardiovascular system disorder); d) any potential brain abnormality or vascular lesion as apparent on conventional FLAIR-scans (Iorio et al., 2013).

From the initial 54 inpatients recruited, 16 were excluded (12 for a score < 4 in the hallucinations and/or delusions SAPS and 4 for neuroimaging artefacts or brain lesions) and 10 did not complete the neuropsychological and/or psychopathological assessment. Thus, the final sample consisted of 28 inpatients (64.3% men). Pharmacological therapy was registered for each patient at the time of enrollment. All patients were receiving one or more antipsychotics. The mean (\pm SD) dosage in olanzapine equivalents (Gardner et al., 2010) on the day of evaluation was 22 ± 13 mg/day. Clinical history was collected from the clinicians in charge of patients' psychiatric care, and potentially consolidated by patients' relatives. All patients gave written informed consent to participate after study procedures were explained. The Santa Lucia Foundation ethical review board approved the study protocol.

2.2. Psychopathological and neuropsychological assessment

After the preliminary diagnosis of SZ (GD), a research psychiatrist (GS) confirmed all diagnoses using the Structured Clinical Interview for DSM-5 (SCID) - Clinician Edition (First et al., 2016). Psychopathological assessment included the SAPS (Andreasen, 1984) and the Scale for the assessment of negative symptoms (SANS) (Andreasen, 1989).

Then participants completed a comprehensive neuropsychological battery performed by trained research neuropsychologists. Individual measures included: the Trail-Making Test (TMT) (Reitan, 1992) to evaluate the speed of information processing (TMT-A) and set-switching abilities (TMT-B); the Controlled Word Fluency Test (WFT) from the Mental Deterioration Battery (MDB) (Carlesimo et al., 1996) and the Semantic Fluency Test (SFT) (Lucas et al., 1998) to assess the phonological and semantic processes central to word production; the Wisconsin Card Sorting Test (WCST)- short form (Greve, 2001) to evaluate executive processes and in particular the set-shifting ability; the Rey's 15 word Immediate (RIR) and Delayed Recall (RDR) tests from the MDB (Carlesimo et al., 1996) to assess subjects' declarative verbal memory; the Rey-Osterrieth Complex Figure Test (ROCFT) (Osterrieth, 1944) - delayed recall to measure visuo-spatial memory; the ROCFT - immediate copy (Osterrieth, 1944) to evaluate visuo-constructive abilities; and the Raven's Progressive Matrices' 47 (PM47) to assess logical reasoning on non-verbal stimuli.

Before the beginning of the study, interviewers were trained by didactic instruction, live interviews, and a review of diagnostic rating. They were trained until they demonstrated an inter-rater reliability of at least 0.80 (K coefficient).

2.3. Psychopathological data processing

On the basis of previous evidence by the Andreasen's group

(Andreasen et al., 1995a), we computed three summary dimension measures (psychotic, negative and disorganized) for each patient. Weighted means of each summary measure were calculated such that each global score contributed equally to the final mean. The three dimensional model (Andreasen et al., 1995a) here adopted was chosen on the basis of previous studies suggesting a good reliability for correlating neuropsychological and psychopathological scores. Moreover, the dimensional approach received strong support from studies showing that each dimension has distinct cognitive and neural substrates (Andreasen et al., 1995a; Cuesta and Peralta, 1995; Koutsouleris et al., 2008; Norman et al., 1997).

2.4. Image acquisition and processing

All participants underwent the same imaging protocol, which included 3D T1-weighted, T2-weighted and FLAIR sequences, using a 1.5 T Philips Achieva (Philips Medical Systems, Best, The Netherlands) MR imager with a standard quadrature head coil. Whole-brain T1-weighted images were obtained in the sagittal plane (TE/TR = 3.4/7.5 ms, flip angle 8°, voxel size $1 \times 1 \times 1 \text{ mm}^3$).

T1-weighted images were processed and examined by using the SPM8 software (Wellcome Department of Imaging Neuroscience Group, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) (see Supplementary materials for a detailed description of image data processing).

The segmented, normalized, modulated and smoothed GM and WM images were used for analyses.

2.5. Statistical analysis

2.5.1. Demographic and clinical data

Statistical analyses were performed using the Statview Software v5.0.1 (SAS Institute). Descriptive statistics were computed as mean and frequencies. Correlation coefficients (Pearson r) and Fisher's r to z transformation were calculated to assess the relationship between antipsychotic drug dosage (in olanzapine equivalents) and performance in neuropsychological tests, and between scores of psychopathological dimensions and neuropsychological tests. Bonferroni correction for multiple comparisons ($p < 0.004$, $p = 0.05/11_{(\text{number of comparisons})}$) was applied to analyses.

2.5.2. Image analyses: Relationship with cognitive performance and symptom dimensions

To identify brain regions in which patients showed GM and WM volumetric correlates of phenotypical traits (i.e. psychopathological symptom dimensions and cognitive test scores), a number of multiple regression models was adopted using each behavioral score as regressor.

To avoid type I errors (i.e., accepting false positives) statistical significance ($p < 0.05$) was corrected using the Random Fields Theory Family-wise error (FWE), which controls for the possibility of any false positive across the entire volume (Ashburner and Friston, 2005). Further, results were considered statistically significant if they were part of a spatially contiguous cluster size of 30 voxels or greater.

As ancillary preliminary findings we considered also results reaching significance at $p < 0.0001$ uncorrected for multiple comparisons.

3. Results

Patients' mean age was 39.75 (SD \pm 12.86), the mean years of education was 12.57 (SD \pm 2.97). The mean age at onset of psychotic symptoms was 23.75 (SD \pm 8.53) and the mean duration of illness was 16.21 (SD \pm 12.57) years. Regression analyses did not show any significant relationship between antipsychotic medication dosage and cognitive/psychopathology performance. As expected, only a small correlation was found with the psychotic dimension, which was non-significant after correction for multiple comparisons.

Table 1

Correlations (Pearson's r) between the three symptom dimensions and neuropsychological performances in severely psychotic schizophrenic inpatients.

Characteristics	Negative dimension	Psychotic dimension	Disorganized dimension
RIR	-0.321	-0.322	-0.124
RDR	-0.371	-0.212	-0.090
PM47	-0.549*	0.04	-0.089
TMT-A time (sec)	0.405 [#]	0.347	0.142
TMT-B time (sec)	0.397 [#]	0.439 [#]	-0.137
WFT	-0.388 [#]	-0.368	-0.210
SFT	-0.393 [#]	0.114	-0.117
WCST - category	-0.233	-0.192	0.254
WCST - perseverative errors	0.221	0.533*	-0.224
WCST - non perseverative errors	0.171	0.297	-0.273
ROCFT - immediate copy	-0.536*	-0.058	-0.020
ROCFT - delay recall	-0.359	-0.342	-0.151

Abbreviations: RIR, Rey's 15 word Immediate Recall; RDR, Rey's 15 word Delayed Recall; PM47, Raven's Progressive Matrices' 47; TMT-A, Trail-Making Test-part A; TMT-B, Trail-Making Test-part B; WFT, Controlled Word Fluency Test; SFT, Semantic Fluency Test; WCST, Wisconsin Card Sorting Test- short form, ROCFT - immediate copy, Rey-Osterrieth Complex Figure Test immediate copy; ROCFT- delayed recall, Rey-Osterrieth Complex Figure Test delayed recall.

[#] Significant values at the uncorrected statistical level ($p < 0.05$).

* Significant at the corrected statistical level ($p < 0.004$).

3.1. Cognitive functioning and psychopathological dimensions

Correlations between scores of the three psychopathological dimensions and cognitive functions are reported in Table 1.

The relationship between the severity of negative dimension and performance on neuropsychological tests comprised several cognitive abilities. However, only two correlations survived the correction for multiple comparisons. In particular, we found that increased severity of the negative dimension was associated with decreased performance in the PM47 ($r = -0.549$; $df = 27$; $p = 0.002$) and ROCFT- immediate copy ($r = -0.536$; $df = 27$; $p = 0.002$). Concurrently, increased severity in the psychotic dimension was correlated with a greater number of perseverative errors in the WCST ($r = 0.533$; $df = 27$; $p = 0.003$). No significant correlations were observed between the disorganized dimension and neuropsychological test scores.

3.2. Brain volumes and the three dimensional model of psychopathology

Only negative correlations were observed between GM/WM volumes and the severity of psychotic dimension. The results are summarized in Table 2 and Fig. 1.

In particular, when focusing on GM we found that higher severity of psychotic dimension was significantly associated (FWE-corrected) to lower volume of the medial portion of the right superior frontal cortex- msFC- (Brodmann Area -BA- 8) and the left superior orbitofrontal cortex- SOFC- (BA 11). At a more lenient statistical threshold ($p < 0.0001$ uncorrected for multiple comparisons), we also found a WM area, where higher severity of psychotic dimension was associated to lower volume in the left medial part of the superior frontal area (BA 8), and a GM area where higher severity of psychotic dimension was associated to lower volume in the SOFC (BA 11) of the right hemisphere. No significant correlations were observed between GM/WM volumes and severity of negative or disorganized dimensions.

3.3. Brain volume and neuropsychological performance

Fig. 2 shows that significant positive correlations were present between verbal and visual tests measuring memory performance and volume in different GM areas.

Table 2

Topography of the significant relationship between grey and white matter volumetry and Psychotic Dimension in severely psychotic schizophrenic inpatients.

Anatomical region (BA)	Brain tissue	Extent (n.voxels)	P (FWE corrected)	P (uncorrected)	t	Equiv Z	Coordinates (MNI) x, y, z (mm)
Right frontal cortex (medial/superior) (8)	GM	401	0.011	< 0.0001	6.47	4.95	8; 35; 49
Left frontal area (medial/superior) (8)	WM	46	0.057*	< 0.0001	5.49	4.44	-10; 32; 51
Right orbitofrontal cortex (superior) (11)	GM	750	0.062*	< 0.0001	5.66	4.53	18; 21; -15
Left orbitofrontal cortex (superior) (11)	GM	743	0.036	< 0.0001	5.93	4.67	-12; 12; -24

Abbreviations: GM, grey matter; WM, white matter; BA, Brodmann's area; FWE, Family-wise error; Coordinates are in Montreal Neurological Institute (MNI) Space.

* Approaching significance ($p < 0.0001$ uncorrected).

In fact, Table 3 shows that RIR score was related to volume of areas located in the left inferior parietal cortex (BA 40) and left insular cortex (BA 48). In addition, ROCFT- delayed recall score was related to volume of areas located in the lobule VIIb and CRUS 1 in the right cerebellum (BA 18), in lobule VI in the left cerebellum (BA 18) and in the right middle temporal cortex (BA 22). In all cases, decreased performance in the neuropsychological tests was related to decreased GM volume.

No significant correlations were present between WM volumetric measures and neuropsychological performance.

4. Discussion

We investigated the brain structural correlates of clinical core symptoms (psychopathology/cognition) in hospitalized patients with SZ undergoing a severe psychotic exacerbation. A first finding is that

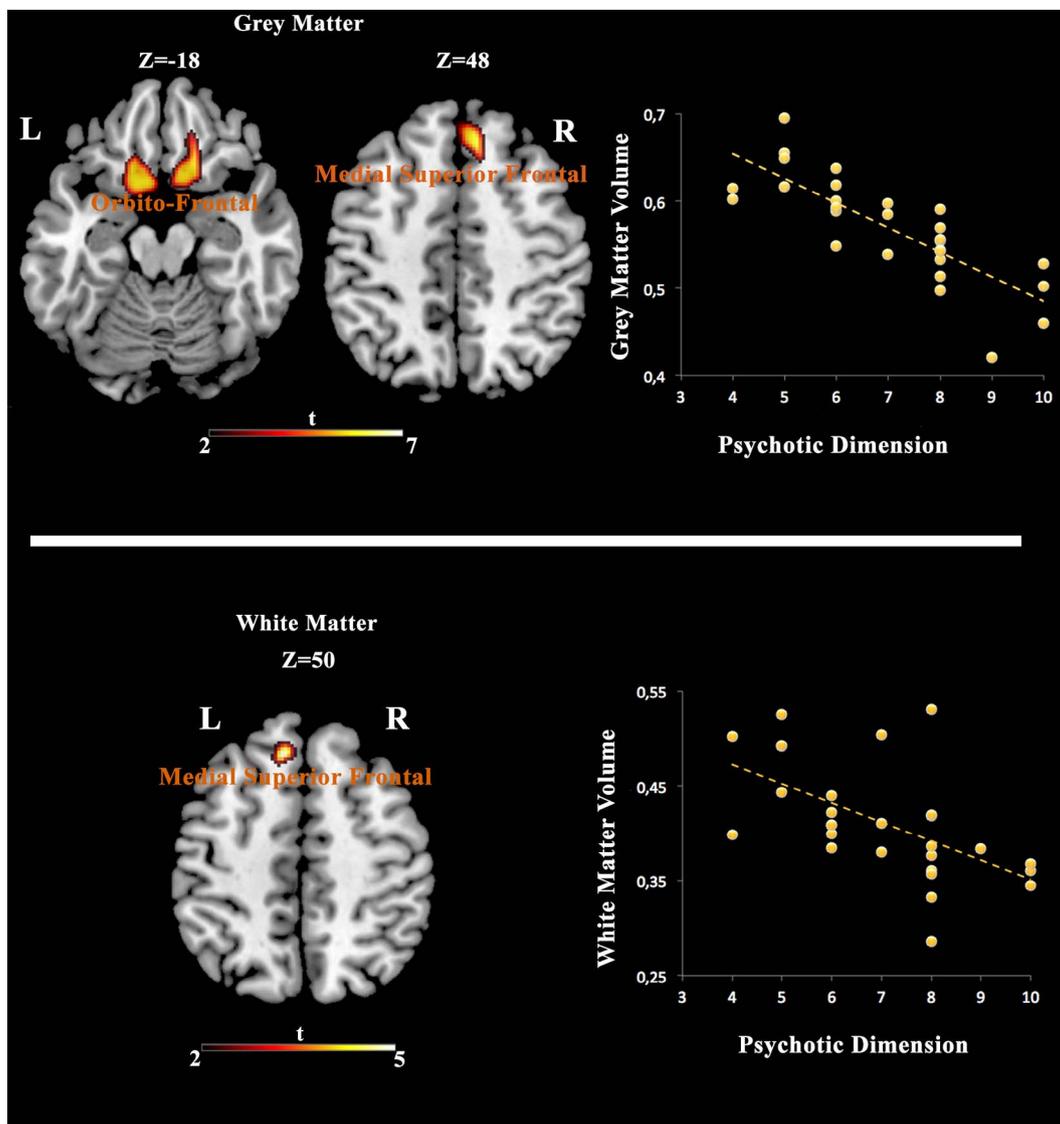


Fig. 1. Grey and white matter volumes related to psychopathology in severely psychotic schizophrenic inpatients. The left side of each panel depicts representative axial slices showing 4 clusters in which lower GM and WM volumes were associated with higher level of Psychotic Dimension scores. The right side reports scatterplots depicting the respective correlation. Yellow circles indicate individual patients' values. Coordinates (z values) are in Montreal Neurological Institute (MNI) space. Linear fits are shown in dotted lines. Abbreviations: L - Left Hemisphere; R - Right Hemisphere. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

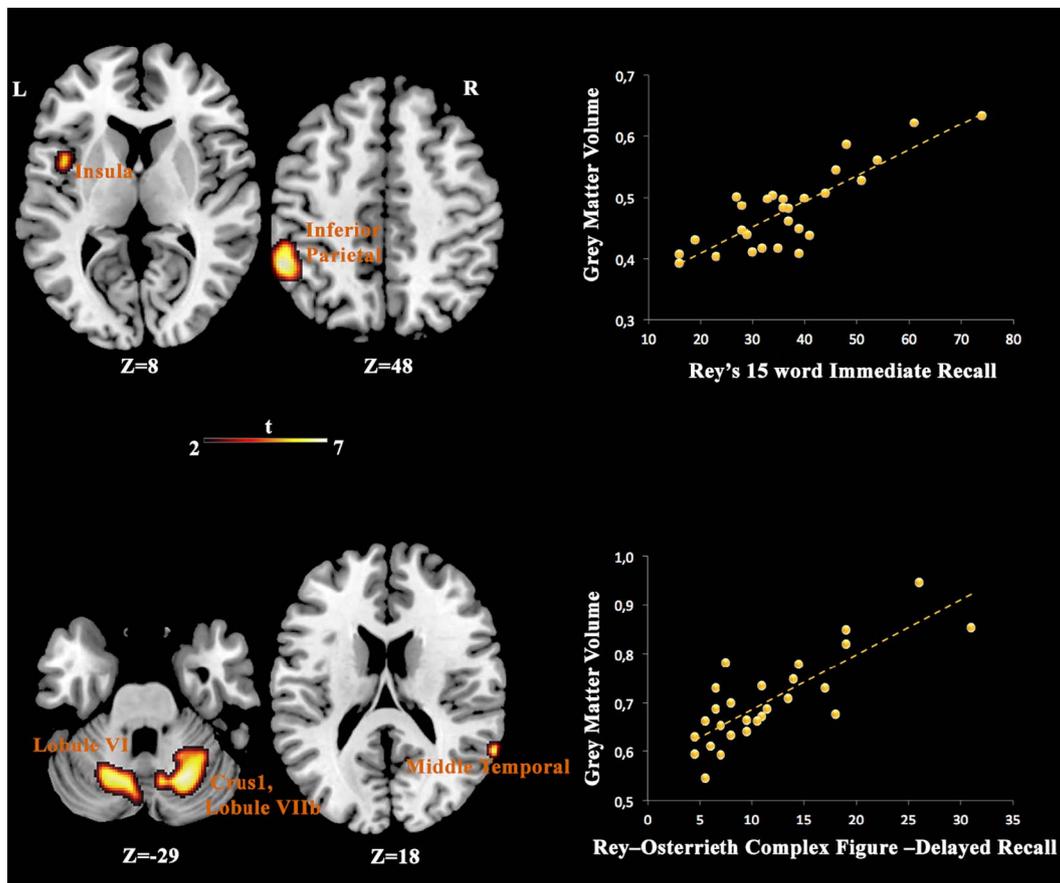


Fig. 2. Grey matter volumes related to cognitive performance in severely psychotic schizophrenic. Left panels depict representative brain axial slices showing 5 clusters in which lower GM volume was associated with decreased performance on memory tests. Right panels show scatter graphs depicting correlations between mean GM volumes of the 5 clusters and performance on the Rey's 15 words - Immediate Recall (upper panel) and the Rey-Osterrieth Complex Figure - Delayed Recall (lower panel). Yellow circles indicate individual patients' values. Coordinates (z values) are in Montreal Neurological Institute (MNI) space. Linear fits are shown in dotted lines. Abbreviations: L - Left Hemisphere; R - Right Hemisphere. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3

Topography of the significant relationship between gray matter volumetry and Neuropsychological test scores in severely psychotic schizophrenic inpatients.

NPS Test	Anatomical region (BA)	Extent (n.voxels)	P (FWE corrected)	P (uncorrected)	t	Equiv Z	Coordinates (MNI) x, y, z (mm)
RIR	Left inferior parietal cortex (40)	437	0.002	< 0.0001	7.32	5.35	-51; -45; 49
	Left insula (48)	131	0.022	< 0.0001	6.16	4.79	-44; 6; 6
ROCFT - delayed recall	Right middle temporal cortex (22)	166	0.003	< 0.0001	7.15	5.27	63; -52; 18
	Left cerebellum - lobule 6 (18)	1042	0.019	< 0.0001	6.23	4.83	-9; -79; -17
	Right cerebellum - lobule VIIb (18)	2321	0.017	< 0.0001	6.27	4.85	45; -63; -56
	Right cerebellum - CRUS 1 (18)	1280	0.011	< 0.0001	6.49	4.96	27; -63; -36

Abbreviations: RIR, Rey's 15 word Test-Immediate recall; ROCFT- delayed recall, Rey-Osterrieth Complex Figure Test delayed recall; NPS, neuropsychological. BA, Brodmann's area; FWE, Family-wise error; Coordinates are in Montreal Neurological Institute (MNI) Space.

bilateral brain tissue reduction in frontal lobe regions subtended the severity of psychotic dimension. Specifically, patients with severe psychotic symptoms showed decreased GM volume bilaterally in the SOFC and in the right msFC as well as reduced WM volume in the medial portion of the left superior frontal area. This is in accordance with evidence of longitudinal studies (Andreasen et al., 2013; van Haren et al., 2007) showing that frontal brain atrophy is related to the number and duration of relapses and that the psychotic dimension measured in the stable phase is associated to frontal tissue loss over time. To the best of our knowledge, this is the first evidence of reduced brain volume in fronto-orbitofrontal regions directly related to the severity of psychotic symptoms in the active phase of SZ, with no relationship with the negative and the disorganized dimensions.

Conversely, previous studies in the stable phase of the illness demonstrated that atrophy of frontal regions is associated with the severity of negative symptoms (Collin et al., 2012; Koutsouleris et al., 2008; Wang et al., 2003; Ziauddeen et al., 2011). However, the finding is not completely unexpected since the neural and cognitive mechanisms underlying symptom expression vary between the active and the stable phases of the illness, while positive symptoms (delusions) are associated with reduced cognitive flexibility (and an hypothesized frontal lobe dysfunction), predominantly in the active phase (Guillem et al., 2005). Moreover, since a dopaminergic dysfunction is linked to psychotic activation (Howes et al., 2015; Howes and Kapur, 2009) and given that the frontal lobe receives strong projections from dopaminergic neurons in the midbrain (Goldman-Rakic et al., 1992), our

findings confirm the possible dopaminergic pathogenic mechanism responsible for positive symptoms in the active phase. The lack of brain volumetric correlate of the negative dimension reinforces the construct of the deficit schizophrenia (Kirkpatrick and Galderisi, 2008). Indeed, clinical and neurobiological correlates of the secondary negative symptoms occurring during active psychotic exacerbations may differ from that of enduring negative symptoms in the stable phase (Tandon et al., 2000).

It is interesting to note that we did not find any association between the disorganized dimension and cognitive performance or brain morphometric measures. The vast majority of previous studies in remitted patients found a significant relationship between disorganization and brain morphometry (Collin et al., 2012; Koutsouleris et al., 2008) and cognitive performance (Guillem et al., 2002, 2005; O'Leary et al., 2000), while only one study (Klingberg et al., 2006) concluded that disorganization and cognitive impairment represent unrelated dimensions. This is in line with the concept of different neurobiological correlates of clinical phenotypes over the stable and active phases of SZ.

It has been hypothesized that the abnormalities in frontal regions consistently observed in SZ (see Mubarik and colleagues for a review) (Mubarik et al., 2016) could impact cognitive processes such as sensory integration, reward mechanisms and executive functioning (Antonova et al., 2004; Barch and Ceaser, 2012; Bechara, 2004; Happaney et al., 2004), thus contributing to positive symptoms. Our findings concerning the relationship between the psychotic dimension and performance in frontal tasks are in line with this evidence, showing increased difficulties in changing a cognitive strategy and increased perseveration as the severity of psychotic symptoms get higher (Liddle and Morris, 1991; Perry and Braff, 1998). In fact, difficulties in exerting and maintaining cognitive inhibition appear to be linked to several clinical symptoms, which are the core of the psychotic activation, such as hallucinations and delusions (Gray et al., 1991). In addition, the observed relationship between increased negative symptoms and poorer visuo-spatial processing and reasoning capacities during a severe psychotic exacerbation, may reflect the difficulty to detect, distinguish and interpret the external stimuli. Indeed, SZ subjects exhibit impaired performance in a wide range of visuo-spatial functions, from the most basic level of visual perception to more complex processes and navigation abilities (Butler et al., 2005; Doniger et al., 2001). Such deficits in perceptual organization abilities and in manipulating visuo-spatial information can negatively affect various daily activities and directly contribute to the lack of interest in the environment, apathy and social withdrawal (Doniger et al., 2001), thus explaining the observed correlation between severity of the negative dimension and visuo-perceptual processing (O'Leary et al., 2000). As previous findings (Cuesta and Peralta, 1995; Guillem et al., 2002) suggested that deluded subjects are probably less willing to gather and encode new environmental information, the correlation between negative symptoms during psychotic activation and poor visuo-spatial abilities may be justified by a reduction of exploratory and processing activity of novel stimuli (Guillem et al., 2002).

A second endpoint of our study is the pattern of neural correlates of neuropsychological performance in severely psychotic SZ. Our results clearly indicate that brain correlates of cognitive impairment are different from those of psychotic exacerbation. In particular, poor performance in immediate verbal memory was associated with decreased volume of the left inferior parietal and insular cortices, known to be associated with memory processes (Hashimoto et al., 2010; Yildiz et al., 2011). Congruently with previous findings (Leiderman and Strejilevich, 2004; Yeganeh-Doost et al., 2011), we also found that reduced visuo-spatial memory performance was related to widespread GM atrophy in temporo-cerebellar regions. Apart from the well-known role of the temporal lobe in memory processes (Karnik-Henry et al., 2012), the crucial cerebellar contribution to the reinforcement and supervision of learning (Doya, 2000; Swain et al., 2011) and to visuo-spatial and executive processes (Yeganeh-Doost et al., 2011) has been increasingly established. Since either region is encompassed in the cortical-

subcortical-cerebellar circuit referred as dysfunctional in SZ (Andreasen, 1999; Barch, 2014), our results are in line with previous studies indicating that the dysfunctional memory circuitry in SZ is characterized by abnormalities within large-scale brain networks (Andreasen et al., 1995b; Kraguljac et al., 2013).

Overall, these findings support recent cognitive models of psychoses (Keefe et al., 2011; Keefe and Kraus, 2009; Kraus et al., 2009) in which memory processes seem to have a special implication. Specifically, according to the memory-prediction model of SZ (Keefe et al., 2011; Keefe and Kraus, 2009; Kraus et al., 2009), primary memory deficits, and the associated altered neural circuitry, disrupt mnemonic processes, thus leading to alterations in learning-dependent predictive perception that present as reality distortion (delusions, thought disorder and hallucinations). Hence, the observed correlation between memory functions (and not other cognitive processes here investigated) and GM volume is coherent with the role attributed to memory alterations in psychotic activation since deficits in brain structure and function, particularly in cortical hubs (including the parietal, temporal and cerebellar cortices), may contribute to the development and maintenance of psychotic exacerbation (Krishnan et al., 2011).

Before reaching the concluding remarks, some potential limitations of the present study should be mentioned. First, we do acknowledge that our conclusions were mainly drawn on the basis of a cross-sectional approach in which, due to lack of a longitudinal perspective, the causal relationship between brain volume, neurocognitive functioning and acute symptoms might be blurred by inter-individual variability. Second, although a small sample size is not uncommon in this vein of research (Guillem et al., 2005), a larger sample would have provided a better understanding of the relationships between the investigated variables, allowing a more assertive interpretation of the findings and generalization beyond the present sample. Nevertheless, by admitting patients with no dementia or gross brain pathology as instantiated by standard MRI, we excluded the confounding factor of potential neurological disorders, which would likely have additive effects on brain structure beyond those of SZ itself. Moreover, the chosen cut-off for the SAPS severity score (i.e. ≥ 4 , severe psychotic symptoms) allowed us to examine only severely psychotic SZ and to purposely investigate the neural and neuropsychological correlates of psychotic exacerbation. Actually, our results are at variance with larger studies outcomes (Keefe et al., 2006) in which neurocognitive deficits were modestly correlated with negative symptom severity, while correlations with positive symptom severity were close to zero. However, heterogeneity within the large sample in such 'all-comer' clinical trial might have obscured relationships that exist within a more homogenous sample like the one here investigated. Indeed, the high inter-individual variability with respect to treatment histories, procedures, and responses should be considered as a general limitation in naturalistic research, which cannot be avoided even when clustering solutions (like in the present study) are adopted.

In conclusion, the findings here exposed suggest that during severe psychotic exacerbation, although cognitive and psychopathological phenotypic markers of SZ have distinct neural correlates, the involved brain areas appear to be functionally linked as part of the cortical-subcortical-cerebellar circuit (CSCC). We therefore experimentally demonstrated the pathogenic model of SZ (Andreasen et al., 1996; Wisner et al., 1998) assuming that a disruption of the CSCC underlies the combination of the vast majority of cognitive and psychotic symptoms. We also added new evidence regarding the role of frontal lobe dysfunction in psychotic exacerbation, and further demonstrated the crucial contribution of distorted memory function in the development and maintenance of psychotic exacerbation.

Future longitudinally studies (also extended to different phases of the illness assessed in the same patients) will help clarifying the causal relationship between clinical and neurobiological factors in SZ, thus contributing to improve outcome prediction and relapses prevention in schizophrenia.

Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

Gianfranco Spalletta, MD, PhD, designed the study, supervised patient recruitment, wrote the final draft of the manuscript and undertook the statistical analyses.

Nerisa Banaj, PhD, wrote the final draft of the manuscript, supervised clinical assessment, undertook the statistical analyses and contributed to the interpretation of the data.

Federica Piras, PhD, wrote the final draft of the manuscript and contributed to the interpretation of the data.

Fabrizio Piras, PhD, designed the study and undertook the statistical analyses.

Valentina Ciullo, PhD, took part at the data collection process.

Mariangela Iorio, PhD, managed neuroimaging data acquisition and processing.

Claudia Battaglia, MD, took part at the data collection process.

Donatella Pantoli, MD, coordinated neuroimaging data collection.

Giuseppe Ducci, MD, contributed to design the study and coordinated patient recruitment.

All authors have contributed to and have approved the final manuscript.

Dr. Gianfranco Spalletta has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Role of funding source

This research has been supported by IRCCS Fondazione “Santa Lucia”. IRCCS has had no further role in study design; in the collection, analysis and interpretation of the data; in the writing of the paper; and in the decision to submit the paper for publication.

Acknowledgement

We express our gratitude to the patients who agreed to participate in this study. The authors acknowledge the valuable collaboration of Gabriella Scifoni, Chiara Cannizzaro and Sara Fraietta.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scog.2018.02.001>.

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