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Research Paper

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

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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 presynaptic 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

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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 $\pm$ 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