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Left nucleus accumbens atrophy in deficit schizophrenia: A preliminary study

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ABSTRACT

A question that remains to be answered is whether schizophrenia can be characterized by a single etiopathophysiology or whether separate sub-syndromes should be differentiated to define specific mechanisms for each sub-type. Individuals affected by the deficit subtype of schizophrenia (DSZ) display avolitional/amotivational features that respond poorly to conventional treatments. Characterizing DSZ from a neuroanatomical point of view may help clarify this issue and develop new treatment strategies. To determine if DSZ is associated with structural alterations in specific deep grey matter structures linked to its key clinical features, 22 DSZ patients, 22 non-deficit schizophrenia (NDSZ) patients and 22 healthy controls (HC) were recruited for a case-control cross-sectional study. High-resolution magnetic resonance imaging was performed in all subjects and volumes of deep grey matter structures were measured using FreeSurfer. DSZ patients displayed smaller left accumbens volumes compared to both NDSZ patients and HC. Moreover, age and duration of illness were significantly associated with lower volume of the left accumbens in DSZ but not in NDSZ. Findings indicate that DSZ is associated with lower volume of the nucleus accumbens in the dominant hemisphere. This is consistent with the psychopathological features and functional impairments present in DSZ and thus indicates a potential mechanism.

1. Introduction

One of the hallmarks of schizophrenia is impaired volition (Minkowski, 1927; Bleuler, 1950). Recently, several research findings have suggested splitting the negative symptoms of schizophrenia between the motivational dimension, including avolition, anhedonia and asociality, and diminished expressivity, which is characterized by restricted affect and alogia (Blanchard and Cohen, 2006; Strauss et al., 2013). The former have been reported to have a serious impact on clinical and functional outcomes (Strauss et al., 2013).

The quintessence of this motivational impairment is clinically represented in deficit schizophrenia (DSZ), which is characterized by negative symptoms that are primary, stable and enduring (Carpenter et al., 1988; Kirkpatrick et al., 2001). Growing evidence suggests that patients diagnosed with DSZ suffer from a separate disorder and are not simply affected by a more severe form of schizophrenia (Buchanan et al., 1990; Kirkpatrick et al., 1993, 2001). Several studies have explored the socio-demographic characteristics (Galderisi et al., 2002; Messias et al., 2004), risk factors (Kirkpatrick et al., 2000a), clinical outcome (Carpenter, 1994; Tek et al., 2001), response to treatment (Kirkpatrick et al., 2000b) and neurobiological features (Kirkpatrick and Buchanan, 1990; Ross et al., 1997; Hong et al., 2005) associated with DSZ. However, anomalies in the neural substrates of motivational processes have never been selectively investigated.

Nonetheless, a number of neuroimaging studies have attempted to define a "brain map" of DSZ. On one hand, functional studies have described thalamic, frontal and parietal cortical hypometabolism and reduced cerebral blood flow and

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N-acetylaspartate concentrations in bilateral frontal cortex regions (Tamminga et al., 1992; Heckers et al., 1999; Delamillieure et al., 2000; Vaiva et al., 2002; Gonul et al., 2003; Kanahara et al., 2013). On the other hand, structural MRI studies have given more inconsistent results, with some studies reporting cortical and ventricular anomalies (Buchanan et al., 1993; Galderisi et al., 2008; Volpe et al., 2012) and others showing antithetical findings (Arango et al., 2008; Fischer et al., 2012). The only study that compared cortical thickness in DSZ and NDSZ found no difference between them (Voineskos et al., 2013). The four DTI studies (Rowland et al., 2009; Kitis et al., 2012; Voineskos et al., 2013; Spalletta et al., 2015) conducted so far found that different associative white matter tracts were more disrupted in DSZ compared to NDSZ; the only partially replicated result was decreased fractional anisotropy in the left uncinate fasciculus of DSZ patients in two of the four studies (Kitis et al., 2012; Voineskos et al., 2013). Unfortunately, none of these findings pertain directly to reward-related regions or circuitries, perhaps with the exception of Delamillieure and colleagues' MRI spectroscopy results that were localized in the medial prefrontal cortex (Delamillieure et al., 2000).

A recent activation likelihood estimation meta-analysis of functional MRI studies in humans confirmed the pivotal role of the ventral-striatal regions (i.e. nucleus accumbens, ventral nucleus caudatus and putamen) and the medial orbitofrontal cortex in reward processing, with the ventral striatal regions being involved in both prediction and consumption of rewards (Diekhof et al., 2012). Therefore, the pronounced reward processing abnormalities and motivational impairment in DSZ may be the consequence of a disruption localized in the cortical-striatal circuits underlying the various components of reward-related functions such as dopamine-mediated striatal systems. These are critical for reinforcement learning, reward anticipation, prediction of cues that lead to rewarding outcomes and the ability to use positive and negative feedback to guide decision making (Strauss et al., 2014; Stopper and Floresco, 2015). Unfortunately, studies specifically addressing the issue of reward processing in DSZ are lacking. However, since reward processing has been shown to be impaired in schizophrenia (Gold et al., 2008; Strauss et al., 2014) it is reasonable to hypothesize the presence of marked alterations in a subgroup of patients with primary and stable negative symptoms. Other deep grey matter structures (i.e. thalamus, pallidum and amygdala) are involved in volitional and motivational processes according to animal models and functional studies in humans (Smith et al., 2009; Der-Avakian and Markou, 2012; Cho et al., 2013). More specifically, it has been shown that in schizophrenia motivational impairment is selectively associated with functional abnormalities of the ventral striatum rather than the cortex (i.e. the medial orbito-frontal cortex), which is more linked to the hedonic impact of reward (Simon et al., 2010).

In this context, studies investigating whether deep grey matter structures involved in motivation processes and reward-related mechanisms (i.e., nucleus accumbens, caudate, putamen, pallidum, amygdala and thalamus), and possibly involved in DSZ mechanisms, are lacking. Since the core clinical features of DSZ are apathetic and avolitional in nature, attention should be directed to these brain structures, particularly the nucleus accumbens. In fact, the nucleus accumbens is not merely a reward center. It also plays a central role in the integration of cognitive and affective components of appetitively motivated behaviours and represents the interface between the fronto-temporal regions and the subcortex in the acquisition of appetitive responses and motivational control of performance (Yin et al., 2008; Floresco, 2015). Here, we aimed to examine the hypothesis of nucleus accumbens atrophy in DSZ.

2. Methods and materials

2.1. Clinical and diagnostic assessment

Thirty-one right-handed patients diagnosed with deficit schizophrenia (DSZ) were recruited at the IRCCS Santa Lucia Foundation of Rome. Patients were diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders IV-Edition, text revised (DSM-IV-TR) (APA, 2000). They were part of a larger sample of consecutive schizophrenic patients (N=204) and healthy controls (N=505) recruited, assessed and scanned at the Laboratory of Neuropsychiatry of the IRCCS Santa Lucia Foundation of Rome between 2008 and 2013. The preliminary diagnosis was made by the clinician who had been treating the patients and knew their clinical history but was blind to the aims of the study. Subsequently, a senior research psychiatrist confirmed all preliminary diagnoses using the Structured Clinical interview for DSM-IV-TR Patient Edition (SCID-I/P) (APA, 2000). If the clinicians disagreed, more data were gathered and the diagnostic process continued until a final consensus diagnosis was made. If no agreement could be reached, the patient was excluded from the sample.

A structured interview, the Schedule for the Deficit Syndrome (SDS) (Kirkpatrick et al., 1989), was used to diagnose DSZ with standard criteria. The syndrome was diagnosed conservatively to minimize false positive diagnoses. The same senior research psychiatrist who confirmed the DSM diagnosis retrospectively reviewed information regarding the patient's clinical status during the preceding twelve months. The senior psychiatrist (G.S.) was trained by Brian Kirkpatrick at the Maryland Psychiatric Research Center. The training specifically consisted of a detailed description of the clinical construct by Brian Kirkpatrick, who first validated it, and clinical diagnostic training on cases previously diagnosed by B. K. until an inter-rater reliability ≥ 0.8 was achieved. SDS was compiled according to the information obtained from review of records and interviews with psychiatrists and other mental health professionals who treated the patients and had long-standing contact with them. In addition, data obtained from the clinical staff were integrated using reports from the patients and first degree relatives. According to the SDS criteria, the final diagnosis of DSZ requires some combination of two or more primary negative symptoms that are always present during the twelve months preceding admission.

From the initial sample of 31 patients, 9 were excluded because of strong movement artifacts in brain images. The remaining 22 patients were matched one to one according to age (± 2 years), gender (identical), educational level (± 2 years) and handedness (identical) with 22 patients with NDSZ. The researcher who matched the groups was unaware of the aims of the study and the neuroimaging and clinical data.

Age at onset was defined as the age at first onset of positive or negative symptoms based on interviews with the patients and first-degree relatives. If it was impossible to retrieve this information, age at onset was defined as age at first hospitalization. Duration of illness was defined as the difference between the patient's age at assessment and age at onset in years.

Overall severity of schizophrenia symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), a 30-item seven point rating instrument that scores positive (7 items, with a total score ranging from 7 to 49) symptoms, and symptoms of general psychopathology (16 items, with a total score ranging from 16 to 112). PANSS subscales were also evaluated. In particular the factors “anergy” (sum of items N1, N2, G7 and G10), “thought disorder” (sum of items P2, P3, P5 and G9), “activation” (sum of items P4, G4 and G5), “paranoid/belligerence” (sum of items P6, P7 and G8) and “depression” (sum of items G1, G2, G3 and G6) were calculated for each patient.