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Characterization of premorbid functioning during childhood in patients with deficit vs. non-deficit schizophrenia and in their healthy siblings

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ABSTRACT

Impaired premorbid adjustment has been reported in patients with schizophrenia, generally in association with unfavorable aspects of the illness (e.g., poor outcome and severe negative symptoms). Several studies attempted to define the domains of premorbid dysfunction associated with negative symptoms and poor outcome; however, most of them assessed broadly defined negative symptoms. The present study was aimed to characterize premorbid functioning in a group of patients with deficit schizophrenia (DS), characterized by the presence of at least two primary and persistent negative symptoms (PPNS), and one of patients with a diagnosis of schizophrenia who did not meet criteria for DS (NDS).

The presence of emotional/behavioral problems during childhood was investigated using the Childhood Behavior Checklist (CBCL) in both patient groups and in their respective healthy siblings. The Premorbid Adjustment Scale (PAS) was also used to assess premorbid functioning during childhood in the two patient groups. PPNS were also treated as a continuous variable and correlated with the indices of premorbid functioning regardless the DS/NDS categorization.

DS patients, as compared to NDS, showed higher scores on the CBCL subscale "Withdrawn". Both DS and NDS patients showed, as compared to their healthy siblings, a greater impairment on almost all CBCL subscales. PAS findings revealed that DS patients had poorer premorbid adjustment than NDS. No significant correlation between premorbid functioning and PPNS was observed.

These findings support the hypothesis that DS has a different developmental trajectory with respect to NDS, and that premorbid adjustment is one of the essential aspects of its characterization.

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1. Introduction

In patients with schizophrenia, an impairment of premorbid adjustment involving several areas of functioning has been widely reported (Hans et al., 1992; Addington and Addington, 1993; Cannon et al., 2001; Reichenberg et al., 2002). Such an impairment is not found in all patients, as a proportion of them present an abrupt onset with a relatively good premorbid functioning (Neumann et al., 1995; McGlashan, 2008). Moreover, when present, the impairment may vary in its age of onset and course over time, degree of severity, and functional domains involved (Neumann et al., 1995). Many authors reported associations between impaired premorbid functioning and some unfavorable aspects of schizophrenia, including a chronic clinical course, a poor

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outcome and a higher severity of negative symptoms (Kelley et al., 1992; Haim et al., 2006; Rabinowitz et al., 2002, 2006; Galderisi et al., 2002, 2013; Ayesa-Arriola et al., 2013). Several studies attempted to define the domains of premorbid dysfunction associated with negative symptoms and poor outcome. Most of them used the Premorbid Adjustment Scale (PAS, Cannon-Spoor et al., 1982), extracting two distinct functional subdomains, i.e. a social and an academic one, and found that the impairment of the social domain was more strongly related to the severity of negative symptoms than the impairment of the academic domain (McClellan et al., 2003; Monte et al., 2008; Chang et al., 2013; Strauss et al., 2012).

In these studies, broadly defined negative symptoms were considered, notwithstanding the largely acknowledged heterogeneity within this psychopathological dimension, including negative symptoms that are inherent to the disease (generally referred to as primary) and negative symptoms caused by factors other than the core disease process (generally referred to as secondary negative symptoms, and due to

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medication side-effects, concurrent depression, and limited social stimulation). Primary negative symptoms are usually enduring and resistant to pharmacological and non-pharmacological interventions, contrary to secondary negative symptoms that are related to identifiable sources, are generally not enduring and are often modifiable with adequate treatment interventions addressing their causes.

Primary and persistent negative symptoms (PPNS) are considered as the main clinical aspect of deficit schizophrenia, a diagnosis requiring the presence during the 12 months preceding the diagnosis of at least two primary negative symptoms.

A poor premorbid adjustment, in conjunction with an insidious onset and a poor response to treatment with antipsychotic drugs, has been reported among the characteristics of deficit schizophrenia (DS) (Carpenter et al., 1988; Kirkpatrick et al., 1996; Fenton and McGlashan, 1994; Galderisi et al., 2002; Kirkpatrick and Galderisi, 2008; Galderisi and Maj, 2009).

Two investigations (Strous et al., 2004; Strauss et al., 2012) focused on PPNS so far. In the former one, the criteria proposed by Mayerhoff et al. (1994) to assess the deficit state in first-episode schizophrenia were used, while in the latter one the Schedule for the Deficit Syndrome was administered to assess PPNS. The two PAS subdomains (i.e., Social and Academic) were analyzed only in the study by Strauss et al. (2012): a greater deterioration of academic than social premorbid functioning was observed in NDS patients, while DS showed comparable deterioration in both premorbid domains, as well as a poorer social premorbid adjustment as compared to NDS.

Two studies (Baum and Walker, 1995; Rossi et al., 2000) explored the relationships between negative symptoms and premorbid adjustment assessed by the Childhood Behavioral Checklist (CBCL; Achenbach, 1991), an instrument evaluating several behavioral and emotional aspects in five age periods in patients as compared to their siblings. Baum and Walker (1995) found that the negative psychopathological dimension was associated with withdrawn behavior, while Rossi et al. (2000) found that patients showing a higher level of behavioral abnormalities during childhood and adolescence had more severe negative symptoms. Neither study assessed PPNS.

The present study was aimed to characterize premorbid functioning in patients with PPNS. In particular, here we tested the hypothesis that patients with DS, as compared to those with NDS, have poorer premorbid functioning since childhood, and that aspects relevant to the negative dimensions (i.e., withdrawal) are also found in healthy siblings of subjects with DS, due to their high genetic load (Smyrnis et al., 2007; Pelayo-Terán et al., 2011; Li et al., 2012). To this aim, the presence of emotional/behavioral problems during childhood was investigated by means of the CBCL in both DS and NDS patients, as well as in their respective healthy siblings; the assessment of premorbid functioning during childhood was also carried out by means of the PAS in the two patient groups. Moreover, since PPNS can still be present in patients with NDS, we also treated them as a continuous quantitative variable and investigated their correlations with the indices of premorbid functioning regardless the DS/NDS categorization.

2. Methods

2.1. Subjects

Subjects were recruited in four university departments of psychiatry (Naples, L'Aquila, Milan and Pisa) within a multicenter project aimed at characterizing historical, clinical, neuropsychological and neuroradiological aspects of DS (Galderisi et al., 2013).

Before entering the study, patients participated in a 1-h clinical interview to verify their conformity to the following inclusion criteria: 1) a DSM-IV diagnosis of schizophrenia, confirmed by the Structured Clinical Interview for DSM-IV (SCID); 2) age between 16 and 55 years; 3) no history of severe mental retardation, alcoholism, or drug abuse or dependence in the last 12 months and no previous ECT; 4) no

significant changes in the clinical state or in drug treatment during the preceding 3 months; and 5) willingness to participate in the study procedures, expressed by providing written informed consent after complete description of the study.

Patients meeting these criteria were then classified as having either DS or NDS after being interviewed with the Schedule for the Deficit Syndrome (SDS, Kirkpatrick et al., 1989). According to this instrument, patients are classified as having DS when meeting the following criteria: 1) presence of at least two negative symptoms among the following: restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose, diminished social drive; 2) some combination of two or more of the negative symptoms listed above are persistent, i.e., have been present for the preceding 12 months and always present during periods of clinical stability; 3) the abovementioned negative symptoms must be primary or idiopathic, i.e., not secondary to factors other than the disease process, such as anxiety, drug effect, suspiciousness or other psychotic symptoms, mental retardation or depression.

2.2. Clinical assessment

Psychopathological evaluation was carried out by the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1981) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). Measures from the SANS and SAPS were grouped into three dimensions (Liddle, 1987; Liddle and Barnes, 1990; Peralta et al., 1992; Galderisi et al., 1999): 1) negative symptoms (sum of global scores on the alogia, anhedonia, affective flattening, and avolition subscales of the SANS); 2) reality distortion (sum of global scores on the hallucinations and delusions subscales of the SAPS); and 3) disorganization (sum of global scores on the formal thought disorder and bizarre behavior subscales of the SAPS).

2.3. Assessment of premorbid characteristics

In all patients with at least one sibling and whose mother (or father) was available for the interview, premorbid functioning was assessed by Baum and Walker's (1995) modified version of the CBCL. In this version of the instrument, the 124 CBCL items were changed to the past tense to evaluate five age periods (0–3 years, 4–7 years, 8–11 years, 12–15 years, 16–18 years). The CBCL items measure a broad range of emotional/behavioral problems. For each item, at each time period, one of the parents (usually the mother, when available) rates the patient and the sibling closest in age on a three point scale (0 = not true; 1 = somewhat or sometimes true; 2 = very true or often true).

Scores obtained on the 124 items were converted by means of the Assessment Data Manager (ADM) software into the composite scores for the eight CBCL subscales suggested by Achenbach (1991): "Withdrawn", "Somatic Complaints", "Anxious/depressed", "Social Problems", "Thought Problems", "Attention Problems", "Delinquent Behaviour", "Aggressive Behavior", plus a residual category called "Other". The age periods 12–15 and 16–18 years were excluded from the analysis in order to minimize possible contamination with early prodromal and psychotic symptoms of the illness, since for some recruited patients the age at onset was 14 years. Outlier values, identified as those with a z-score \geq 3, were replaced by the mean of the group.

A further assessment of patients' premorbid functioning was carried out by using the PAS. Similarly to the CBCL, only the age period ≤11 years (childhood) was included in the analysis. The PAS assesses five psychosocial domains, i.e. sociability and withdrawal, peer relationships, scholastic performance, adaptation to school, and social-sexual functioning. Ratings are made on a 0 to 6 point Likert scale, with 0 indicating normal adjustment and 6 indicating severe impairment. To gather information about the premorbid period, a semi-structured interview was utilized with the participant and her/his family members. According to the procedure followed in previous studies (Allen et al., 2005;

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