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Categorical and dimensional approaches to negative symptoms of schizophrenia: Focus on long-term stability and functional outcome

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ABSTRACT

Negative symptoms of schizophrenia represent a heterogeneous psychopathological domain. Both categorical and dimensional approaches have been proposed to reduce negative symptoms heterogeneity.
In the present 5-year follow-up study, long-term stability and impact on outcome of different aspects of negative symptoms were investigated. Following a categorical approach, long-term stability and outcome of deficit schizophrenia (DS), in comparison with nondeficit schizophrenia (NDS), were assessed. Following a dimensional approach, the factor structure and stability of broadly defined negative symptoms and the ability of the identified factors to predict functional outcome were investigated.
DS and NDS subjects included in a previous study were invited to participate. Fifty-one out of 58 patients previously diagnosed as DS and 44 out of 54 NDS patients were included in the present study.
The DS/NDS categorization was confirmed in 82.4% of DS and 79.6% of NDS subjects. At follow-up, DS patients showed more severe negative symptoms and greater social dysfunction than NDS ones.
Schedule for the Deficit Syndrome (SDS) severity scores loaded on two factors: "Poor Emotional Expression" and "Avolition" and the factor structure was stable after 5 years. Avolition was associated to social outcome measures and Poor Emotional Expression to functioning in household activities.
Psychosocial outcome was predicted by SDS factors reflecting the severity of broadly defined negative symptoms, but not by the DS/NDS categorization. This might lend support to the recent shift of research focus from the categorical approach focusing on the presence of primary and enduring negative symptoms to the investigation of key domains of broadly defined negative symptoms.

1. Introduction

Negative symptoms of schizophrenia represent a heterogeneous psychopathological domain. In fact, they include signs and symptoms favourably responding to currently available treatments (for instance, negative symptoms secondary to positive or depressive symptomatology, that might respond well to available antipsychotics or adjunctive antidepressants), but also signs and symptoms still representing a challenge for the development of new pharmacological and non-pharmacological interventions (for instance, primary and persistent negative symptoms, Kirkpatrick and Galderisi, 2008; Galderisi and Maj, 2009). Research focussing on deconstruction of broadly defined negative symptoms might be crucial to identify key targets for new treatments aimed to improve patients' outcome.

A categorical approach within this research field has been represented by the study of deficit schizophrenia (DS). It is regarded as a distinct subtype within the diagnosis of schizophrenia, characterized by the presence of primary and enduring negative symptoms, and showing different clinical, neuropsychological and neurobiological abnormalities with respect to nondeficit schizophrenia (NDS; Carpenter et al., 1988; Kirkpatrick et al., 1998, 2000; Kirkpatrick and Galderisi, 2008; Galderisi and Maj, 2009). Three studies, so far, investigated the stability of the diagnosis across time and the long-term outcome of patients bearing the diagnosis of DS: one was based on a retrospective assessment (Fenton and McGlashan, 1994) and two of them on a prospective design (Amador et al., 1999; Strauss et al., 2010). The frequency of confirmed diagnoses at follow-up ranged from 67% to 83.3%. The lowest figure was reported by Strauss et al. (2010), in a 20-year follow-up study (the longest follow-up interval in the relevant literature), involving 39 patients with schizophrenia categorized as DS (N = 14) or NDS

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(N = 25) using a proxy method; the highest frequency was reported by Amador et al. (1999) in a study involving 43 patients with schizophrenia or schizoaffective disorder, in which the DS/NDS categorization was performed by means of the Schedule for the Deficit Syndrome (SDS). Few prospective studies investigated long-term functional outcome of subjects with DS or NDS. Two of them reported a poorer outcome in DS than in NDS patients (Tek et al., 2001; Strauss et al., 2010), while Chemerinski et al. (2006), in a group of elderly patients with DS or NDS (the latter ones were subdivided into delusional and disorganized type) reported greatest functional impairment in delusional, lowest in disorganized and intermediate in the DS group, at odds with the other studies showing poorer functioning in patients with DS than in those with NDS.

More recently a dimensional approach to the study of negative symptoms has been revived by investigations based on factor analyses of negative symptoms showing that two separate factors, i.e. Avolition and Poor Emotional Expression, can be identified both when the overall negative domain is assessed (Blanchard and Cohen, 2006; Kirkpatrick et al., 2011; Strauss et al., 2012) and when only primary and enduring negative symptoms are evaluated (Kimhy et al., 2006; Nakaya and Ohmori, 2008). No study, so far, examined the SDS factor structure stability across time and the ability of SDS factors to predict functional outcome.

In the present investigation both a categorical and a dimensional approach were used to assess long term-stability and outcome of negative symptoms. In particular, within the former approach, we investigated the long-term stability of the DS and NDS diagnosis and the long-term outcome of patients with DS or NDS. In the frame of a dimensional approach, we assessed the factor structure and stability of broadly defined negative symptoms and the impact of the identified factors on functional outcome.

Premorbid adjustment, general cognitive abilities and other neuropsychological domains, psychopathological dimensions and neurological signs were investigated in the two groups as these variables can influence functional outcome in patients with schizophrenia (Breier et al., 1991; Dickerson et al., 1996, 1999; Green et al., 2000; Galderisi and Maj, 2009; Hunter and Barry, 2012; Peralta et al., 2012).

2. Methods

2.1. Study design

In the baseline study historical, clinical, neuropsychological and neuroradiological aspects had been assessed in 58 subjects with DS and 54 with NDS, recruited in 4 Italian University Departments of Psychiatry (Galderisi et al., 2002, 2008). After 5 years, all patients included in the baseline study and still attending the above mentioned Departments were contacted by their physician. Patients willing to participate in the follow-up study were re-administered the SDS by trained researchers, different from those involved in the baseline study and blind to previous SDS categorization, to verify the stability of the diagnosis of DS or NDS. SDS rating scales were used to assess the severity of 1) restricted affect, 2) diminished emotional range, 3) poverty of speech, 4) curbing of interests, 5) reduction of sense of purpose and 6) reduction of social drive.

Psychopathological evaluation was carried out by the expanded Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), the Scale for the Assessment of Positive Symptoms (SAPS) and the Montgomery-Asberg Depression Rating Scale (MADRS); neurological evaluation was carried out using the Neurological Evaluation Scale (NES), the Abnormal Involuntary Movement Scale and the Simpson-Angus Scale; the recent history of hospitalization and social contacts was explored by the Strauss-Carpenter Outcome Scale (SCOS). Neuropsychological evaluation included tests covering five functional domains: 1) general cognitive abilities, assessed by means of the Full Scale Intelligence Quotient (FSIQ) of the Wechsler Adult Intelligence Scale-Revised (WAIS-R); 2) executive functions, evaluated by a) the number of categories and perseverative errors of the Wisconsin Card Sorting Test (WCST), b) the number of interferences of the Picture Memory and Interference Test (PMIT), c) the flexibility index of the Trail Making Test (TMT) (time to complete Part B minus time to complete Part A) and d) score on the WAIS-R Digit Forward Plus Backward; 3) focused/sustained attention assessed by the WAIS-R Digit Symbol Substitution Test scores and the number of errors on the Continuous Performance Test-AX (CPT-AX); 4) explicit memory evaluated by the number of delayed recalls on the Auditory Verbal Learning Test and the number of identifications on the PMIT; and 5) visuospatial abilities, evaluated by the Benton Judgment of Line Orientation and the WAIS-R Block Design scores. For further details see Galderisi et al. (2002).

A group of healthy controls (HC) was also recruited. All HC were administered the SCID Nonpatient Version (SCID-NP), to exclude the presence and/or history of psychiatric disorders, and the neuropsychological test battery. All patients' scores on neuropsychological tests were expressed as Z-scores from the HC sample.

Only at the follow-up examination, insight and psychosocial functioning were assessed using the Scale for the Unawareness of Mental Disorders (SUMD; Amador et al., 1994) and the Interview for the Assessment of Disability (AD; Morosini et al., 1988). SUMD evaluates the following dimensions of insight: a) having a mental disorder, b) the need for treatment, and c) specific signs and symptoms. AD evaluates functioning in the areas of Self-care, Socialization, Participation in Family Life, Interest and Information and Behavior in Emergency Situations.

Current antipsychotic dose and type of antipsychotic treatment (second/first generation antipsychotic) were recorded for all patients.

2.2. Training of researchers

Researchers involved were different from those who carried out the baseline study. They were trained in the use of the instruments with the same methodology used in the baseline study. Further details and inter-rater reliability data can be found in the supplementary materials.

2.3. Statistical analysis

NES subscale scores, WCST Perseverative errors, Flexibility on the Trail making, Number of interferences on the PMIT did not approach normality and were log-transformed. Categorical variables were analyzed by the chi-square test.

Independent one-way analyses of variance (ANOVAs) were used to test group differences on demographic variables, age of onset, duration of illness, PAS scores, WAIS-R FSIQ and chlorpromazine equivalents of antipsychotic doses in subjects included in the follow-up study. In case of group differences on these indices, they were used as covariates in subsequent analyses. If WAIS-R FSIQ differed between the two groups, a general cognitive ability index (the summed age-corrected scores on the WAIS-R vocabulary and picture completion subscales) was used as a covariate in further analyses on neuropsychological indices to rule out the possible confounding role of an overall deficit of general cognitive abilities on other neuropsychological group differences. To evaluate changes in psychopathological, neurological, neuropsychological and functional outcome measures two-way ANOVAs for repeated measures were carried out in which the between factor was diagnosis and the within factors were time and subdomains of the above listed domains. Group comparisons on insight and psychosocial functioning were carried out by multivariate ANOVAs (MANOVAs). The Fisher's Least Significant Difference Test (LSD) was used for post-hoc comparisons only when a significant main effect or interaction was found in the ANOVA/MANOVA analyses. The rational for using the LSD as a post-hoc test is based on the