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Covariation between motor signs and negative symptoms in drug-naive subjects with schizophrenia-spectrum disorders before and after antipsychotic treatment

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ABSTRACT

Objective
To examine the covariation between negative symptoms and motor signs in a broad sample of drug-naïve subjects with schizophrenia-spectrum psychoses before and after inception of antipsychotic medication.
Methods: One-hundred and eighty-nine antipsychotic-naïve subjects with DSM-IV schizophrenia-spectrum psychoses were assessed for negative symptoms including affective flattening, alogia, avolition/apathy and anhedonia/associality, and motor signs including catatonia, parkinsonism and dyskinesia. We examined the association between negative and motor features at baseline, 4-weeks after inception of antipsychotic treatment and that of their mean change over the treatment period, such as their trajectories and treatment response pattern.
Results: At the drug-naïve state, motor signs were strongly related to affective flattening and alogia ($p < 0.01$); at 4-weeks, most negative and motor features were significantly interrelated ($p < 0.01$); mean change of motor signs and negative symptoms tended to be unrelated. This association pattern was irrespective of levels of positive symptoms. Ratings of negative symptoms, excepting affective flattening, improved after treatment ($p < 0.001$) while motor ratings showed divergent trajectories with catatonia improving ($p < 0.001$), parkinsonism worsening ($p < 0.001$) and dyskinesia remaining unchanged ($p > 0.01$). Although to a different extent, motor and negative features showed drug-responsive, drug-worsening, of drug-unchanged patterns of response to antipsychotic medication. The main predictors of negative and motor features in treated subjects were their corresponding baseline ratings ($p < 0.001$).
Conclusions: Negative and motor features are differentiated, but to some extent, overlapping domains that are meaningfully influenced by antipsychotic medication. At the drug-naïve state, motor signs and the diminished expression domain of negative symptoms may share underlying neurobiological mechanisms.

1. Introduction

Both negative symptoms and motor abnormalities may be indigenous features of schizophrenia (Crow, 1980; Whitty et al., 2009, Peralta et al., 2010a, 2010b) and the expression of the underlying pathophysiology of the illness with important repercussions in the functional outcome of the subjects (Tandon et al., 2000; Sánchez-Torres et al., 2017). The relationship between negative symptoms and motor signs has long been recognized in subjects with chronic schizophrenia both during the preneuroleptic era (Kraepelin, 1919; Leonhard, 1957) and in subjects treated with antipsychotic medication (Kay et al., 1987; Peralta and Cuesta, 1999; Ungvari et al., 2005; Docx et al., 2012). Otherwise, negative symptoms and motor signs have been found to be meaningfully influenced by antipsychotic medication, and thus, the question arises as to whether in treated subjects this association is an intrinsic feature of the two symptomatic domains or due to the effect of antipsychotic medication.

Previous studies conducted in drug-naïve subjects have reported an association of motor signs with negative or deficit symptoms (Honer et al., 2005; Fenton et al., 1994; Chatterjee et al., 1995; Peralta et al., 2000; Peralta and Cuesta, 2011; Peralta et al., 2014), although only a few studies have examined this association using a comprehensive motor assessment including parkinsonism, dyskinesia and catatonia (Peralta and Cuesta, 2011; Peralta et al., 2014). Regarding the influence of antipsychotic medication on such an association, only two previous studies using small samples of drug-naïve subjects ($n < 48$) treated with mixed

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antipsychotic regimes and examining only parkinsonism showed that, after incepting antipsychotics, change in negative and parkinsonian ratings were unrelated (Peralta et al., 2000; Cortese et al., 2005). Neither of the two studies controlled for antipsychotic potency or concomitant medications, and while negative symptoms tended to improve in the two studies, the studies differed in that parkinsonism tended to remain stable over a 6-month period (Cortese et al., 2005) or worsen over a 3-week period (Peralta et al., 2000).

With the aim of obtaining a more comprehensive picture about the relationships between negative and motor features, in this study we examined the covariation between negative symptoms including affective fattening, alogia, avolition/apathy and anhedonia/associality and motor signs including catatonia, parkinsonism and dyskinesia in a wide sample of drug-naïve subjects with schizophrenia-spectrum psychoses before and after inception of antipsychotic medication. The specific objectives that we pursued were: 1) to examine the association between motor and negative symptoms at the drug-naïve state, after 4 weeks of exposure to antipsychotic medication, as well as their mean change (variation) as a consequence of antipsychotic exposure; 2) to examine the baseline predictors of motor signs and negative symptoms in treated subjects; and 3) to examine the specific treatment response pattern of individual negative and motor features. Using this strategy, we can explore both, the nature of the association of primary features from the two symptom realms and the effect of antipsychotic medication (or the lack of it) on such an association.

2. Methods

2.1. Subjects

The study population was drawn from 200 drug-naïve subjects with schizophrenia-spectrum disorders (Peralta et al., 2010a, 2010b). Eleven subjects did not complete a 4-weeks trial with antipsychotic medication and were excluded from the study, thus the final study sample comprised 189 subjects. The main demographic and clinical characteristics of the subjects in this subsample are described in Table 1.

Criteria for inclusion were: (a) patients experiencing their first episode of a DSM-IV (APA, 1994) nonaffective psychotic disorder (i.e. schizophrenia-spectrum disorders), (b) no previous exposition to antipsychotic drugs as documented by the patients, relatives and medical registers, and (c) age 15–65 years. Exclusion criteria were: (a) a history of drug abuse, (b) evidence of organic brain disorder including mental retardation, epilepsy, a history of head trauma resulting in loss of consciousness and neurodegenerative disorders, and (c) meaningful somatic disease. The study was approved by the local ethical committee and all the patients or their legal representatives gave written informed consent to participate in the study. Subjects were treated according to clinical choice with haloperidol, risperidone or olanzapine, and they initially received a low dose of antipsychotic that was gradually titrated up over the course of the episode, and other psychotropic medications were allowed if necessary. The mean dose of antipsychotic medication over the treatment period was transformed to Chlorpromazine (CPZ) equivalents (Woods, 2003). As a proxy measure of antipsychotic potency reflecting D2 dopamine blockage we created a variable coded as 1 (olanzapine), 2 (risperidone) and 3 (haloperidol).

2.2. Clinical assessments

Demographics, clinical features, psychopathology and diagnosis were all rated using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). Age at illness onset was assessed by means of the Symptom Onset in Schizophrenia scale (Perkins et al., 2000) and defined as the age at the first presentation of any illness-related symptom. Because patients had not been previously exposed to antipsychotic medication, illness duration and duration of untreated illness figures are the same.

Table 1
Demographic and clinical characteristics of the subjects (n = 189).

	Mean	s.d.	N	%
Age	29.8	10.3		
Duration of untreated illness, months	40.8	70.0		
Baseline SAPS	10.4	3.45		
Daily average dose of CPZ equivalents	276.7	136.9		
CASH global ratings of psychopathology				
Mania	0.47	1.06		
Depression	0.84	1.30		
Catatonia	0.53	1.08		
Reality-distortion	3.77	1.04		
Disorganization	1.74	1.43		
Negative	1.51	1.42		
Gender (male)			126	66.7
Civil status (single)			154	81.5
DSM-IV diagnosis				
Schizophrenia			88	46.6
Schizophreniform disorder			36	19.0
Schizoaffective disorder			13	6.9
Brief psychotic disorder			35	18.5
Delusional disorder			13	6.9
Psychosis not otherwise specified			4	2.1
Antipsychotic drug				
Haloperidol			23	12.2
Risperidone			93	49.2
Olanzapine			57	30.1
Mixed antipsychotic treatment			16	8.5
Other medications				
Biperiden			34	18.0
Benzodiazepines/hypnotics			110	58.2
Antidepressants			43	22.8
Mood stabilizers			15	7.9

CASH: Comprehensive Assessment of Symptoms and History; CPZ: Chlorpromazine; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. 4th ed.; SAPS: Scale for the Assessment of Positive Symptoms.

Clinical symptoms were evaluated by VP or MJC before starting antipsychotic treatment and four weeks after. We used the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS), which are built-in the CASH, to rate negative and positive symptoms, respectively. Motor signs were assessed using a structured procedure; catatonia was specifically assessed by means of the Modified Rogers Scale, catatonia subscore (MRS-C) (Lund et al., 1991); parkinsonism was rated with the Simpson-Angus Rating Scale (SARS) (Simpson and Angus, 1970), and dyskinesia with the Abnormal Involuntary Movements Scale (AIMS) (Guy, 1976).

We also examined the differential treatment response pattern of motor and negative symptoms to antipsychotic drugs on the basis of pre-treatment and 4-week scores. For each rating score, we defined drug-responsiveness if the rating score at baseline was higher than at 4-weeks, drug-unchanged if ratings at the two assessments points were the same, and drug-worsening if the 4-weeks rating was higher that the baseline rating.

2.3. Statistics

Scores for the negative symptoms and motor signs were examined with the Kolmogorov-Smirnov test to determine whether they were normally distributed. All the scores showed a non-normal, positively skewed distribution, and thus they were Z transformed, and parametric procedures were performed. Pearson correlation coefficients were used to examine the association between motor signs and negative symptom scores at admission, discharge and mean change scores between the two assessment points. To control for the effect of psychotic symptoms as assessed with the SAPS on such associations, partial correlation coefficients were used. Within-group differences in symptom scores at admission and 4-weeks were examined by paired *t*-test on untransformed scores.

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