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Linear and non-linear associations of symptom dimensions and cognitive function in first-onset psychosis

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ABSTRACT

Background: Associations between symptom dimensions and cognition have been mainly studied in non-affective psychosis. The present study investigated whether previously reported associations between cognition and four symptom dimensions (reality distortion, negative symptoms, disorganisation and depression) in non-affective psychosis generalise to a wider spectrum of psychoses. It also extended the research focus to mania, a less studied symptom dimension.
Methods: Linear and non-linear (quadratic, curvilinear or inverted-U-shaped) associations between cognition and the above five symptom dimensions were examined in a population-based cohort of 166 patients with first-onset psychosis using regression analyses.
Results: Negative symptoms showed statistically significant linear associations with IQ and processing speed, and a significant curvilinear association with verbal memory/learning. Significant quadratic associations emerged between mania and processing speed and mania and executive function. The contributions of mania and negative symptoms to processing speed were independent of each other. The findings did not differ between affective and non-affective psychoses, and survived correction for multiple testing.
Conclusions: Mania and negative symptoms are associated with distinct patterns of cerebral dysfunction in first-onset psychosis. A novel finding is that mania relates to cognitive performance by a complex response function (inverted-U-shaped relationship). The associations of negative symptoms with cognition include both linear and quadratic elements, suggesting that this dimension is not a unitary concept. These findings cut across affective and non-affective psychoses, suggesting that different diagnostic entities within the psychosis spectrum lie on a neurobiological continuum.

1. Introduction

Individuals with the same diagnosis within the psychosis spectrum often vary considerably in clinical characteristics (Jablensky, 2006; Joyce and Roiser, 2007; Stroup, 2007). At the same time, different diagnostic categories show overlapping psychopathology, indistinct clinical boundaries and shared etiological factors (Squires and Saederup, 1991; Murray et al., 2004; Kaymaz and Van Os, 2009). Attempts to reconcile the heterogeneity within, and overlap across, psychoses have considered dimensional (e.g. symptom) approaches to classification as a useful adjunct or alternative to categorical (e.g. diagnostic) representations. Exploratory factor analyses in schizophrenia and, more recently, in the full spectrum of psychoses, have identified a discrete number of psychopathological dimensions (e.g. psychomotor poverty, disorganisation, reality distortion, mania, depression) (Liddle, 1987; Dikeos et al., 2006; Demjaha et al., 2009). These have been reported to provide more meaningful information than diagnostic categories in relation to clinically and neurobiologically significant characteristics, including disease course/outcome, likely

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response to treatment (Van Os et al., 1999; Allardyce et al., 2007) and cognitive performance (Dixon et al., 2004; Simonsen et al., 2009).

Despite similar symptom dimensions emerging in factor analytic studies of patients with affective- and those with non-affective psychoses (Peralta et al., 1997; Lindenmayer et al., 2008; Smith et al., 2009), studies exploring relationships between symptom dimensions and neuropsychological performance have mainly focused on non-affective psychoses, especially schizophrenia. A recent meta-analysis of this literature reported modest, statistically significant, and partly dissociable correlations of negative symptoms and disorganisation with neuropsychological performance, but no significant associations of the positive and depressive symptom clusters with cognition (Dominguez et al., 2009). Compared to disorganisation, negative symptoms yielded a significantly stronger correlation with verbal fluency, and significantly less robust associations with reasoning/problem solving and attention/vigilance. The two dimensions did not differ in their strength of correlation with IQ, executive control, speed of processing, verbal working memory, and verbal/visual learning (Dominguez et al., 2009). The latter systematic review identified only four studies exploring the association of cognitive performance with the manic/excitement dimension and excluded the corresponding data as being too limited for an informative synthesis.

The present study addressed the hypothesis that findings from non-affective psychosis in relation to symptom dimensions and neuropsychological performance (specifically, the partly dissociable, significant associations of negative symptoms and disorganisation with cognition, and the non-significant associations of reality distortion and depression with cognition) (Dominguez et al., 2009), replicate in a population-based cohort of patients with first-onset psychoses including both non-affective and affective categories. A further aim was to extend previous findings by exploring associations between neurocognition and manic symptoms.

Although exploring non-linear (quadratic, curvilinear or inverted-U-shaped) associations between psychopathology and cognition was not among the aims of the study, in line with strong statistical evidence of nonlinear processes in brain dysfunction in schizophrenia (Breakspear, 2006), our main analysis suggested potential deviations from linearity for some associations. It was therefore important to follow this indicative finding with post-hoc analyses, particularly in the light of evidence that many relationships in behavioural and social sciences do not follow a straight line. Nonlinear curve fitting is often required in the analysis of biological, biochemical and pharmacological data (Breakspear, 2006), but is less commonly applied to cognition and symptom dimensions. An earlier study of recent-onset schizophrenia reported quadratic associations between negative symptoms and several neuropsychological measures (Van der Does et al., 1993), further underlining the importance of exploring non-linear patterns in our data.

2. Method

2.1. The ÆSOP study

The data were derived from the baseline population-based ÆSOP (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) study, which identified all cases aged 16–64 years with first-onset psychoses (ICD-10 codes F10-F29 and F30-F33 in ICD-10) (World Health Organization, 1992) presenting to specialist mental health services in tightly defined catchment areas in South-east London, Nottingham and Bristol in September 1997–August 2000. Exclusion criteria were previous contact with health services for psychosis, organic causes of psychosis, and transient psychotic symptoms due to acute intoxication. The study further included a random sample of community controls, and was approved by local research ethics committees. Participants gave written informed consent to participate. A detailed overview of the ÆSOP study has been published elsewhere (Fearon et al., 2006; Morgan et al., 2006).

2.2. The analytic cohort

The analytic cohort comprised 166 ÆSOP cases with consensus ICD-10 diagnoses of schizophrenia (F20; $N=64$), schizoaffective disorder (F25; $N=8$), bipolar disorder/mania (F30.2/F31.2/F31.5; $N=31$), depressive psychosis (F32.3/F33.3; $N=27$) or other psychotic disorders, including persistent delusional, acute and transient, other nonorganic, and unspecified nonorganic psychotic disorders (F22/F23/F28/F29; $N=36$). All patients had Item Group Checklist (IGC) ratings on the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (World Health Organization, 1994), Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981) Full-Scale IQ≥70, one or more measurements on the ÆSOP neuropsychological battery, and a good command of English. To satisfy the latter criterion, participants were required to be native speakers of English or migrants to the UK by age 11 (i.e. have completed at least their secondary education in the UK).

Due to being selected for having no learning disability and for being proficient in English (which are standard requirements for neuropsychological testing), as expected, the study sample differed significantly in IQ ($t=4.12$, d.f.$=190$, $P<0.001$) and ethnicity ($\chi^2=20.97$, $P<0.001$) from the remaining ÆSOP cases (of the 370 patients with IGC ratings who were excluded from the current study, 288–318 had available demographic and clinical data, and 26 had available IQ data). The study sample also scored lower on reality distortion compared to the remaining ÆSOP cases ($t=-2.13$, d.f.$=482$, $P=0.033$). The two groups did not differ significantly in gender ($\chi^2=0.001$, $P=0.980$), education ($\chi^2=4.916$, $P=.086$), diagnostic breakdown ($\chi^2=8.108$, $P=0.088$), age at testing ($t=1.030$, d.f.$=482$, $P=0.304$), age at illness onset ($t=1.102$, d.f.$=466$, $P=0.271$), duration of untreated psychosis ($t=0.263$, d.f.$=468$, $P=0.793$), or dimension scores for mania ($t=-0.327$, d.f.$=482$, $P=0.744$), negative symptoms ($t=-1.220$, d.f.$=482$, $P=0.223$), depression ($t=-0.977$, d.f.$=482$, $P=0.329$) and disorganisation ($t=0.987$, d.f.$=482$, $P=0.324$).

2.3. Assessment of socio-demographic and clinical characteristics

Data on age, gender, ethnicity and education were collected by interviews with the participants using the Medical Research Council Sociodemographic Schedule (Mallett, 1997). Clinical data were collected using the SCAN (World Health Organization, 1994). This incorporates the Present State Examination (PSE) Version 10, which was used to elicit symptom-related data at presentation. Ratings on the SCAN are based on clinical interview, case note review and information from informants (e.g. relatives or health professionals). ICD-10 diagnoses were determined using the SCAN data on the basis of consensus meetings involving one of the principal investigators and other members of the research team. The kappa scores for independent diagnostic ratings ranged from 1.0 for psychosis as a category to 0.6–0.8 for individual diagnoses. The participants' demographic, diagnostic and medication characteristics are presented in Table 1.

2.4. Symptom dimensions

Based on a factor analytic study by the ÆSOP Study Group (Demjaha et al., 2009), patients were rated on five symptoms dimensions: *Mania* (6 IGC items: 'heightened subjective functioning', 'expansive mood', 'expansive delusions and hallucinations', 'rapid subjective tempo', 'over-activity', 'socially embarrassing behaviour'), *Reality Distortion* (6 IGC items: 'non-affective auditory hallucinations', 'non-specific auditory hallucinations', 'experience of disordered form of thoughts', 'delusions of reference', 'bizarre delusions and interpretations', 'delusions of persecution'), *Negative Symptoms* (4 IGC items: 'nonverbal communication', 'poverty of speech', 'flat and incongruous affect', 'motor retardation'), *Depressive Symptoms* (3 IGC items: 'special features of depressed mood', 'depressed mood', 'depressive delusions and hallucinations') and *Disorganisation* (2 IGC items: 'incoherent