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The course of negative symptoms over the first five years of treatment: Data from an early intervention program for psychosis

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ABSTRACT

Background: Cross-sectional studies suggest that negative symptoms are constituted by separable domains of reduced expressiveness and reduced motivation, but there is little data on the longitudinal course of these symptoms. We examined evidence for differences in the course and correlates of these two domains in a prospective study of patients presenting with a first episode of psychosis.

Methods: Of 132 patients who were followed up for five years, it was possible to monitor reduced expressiveness and motivation on a weekly basis for 127. Information on treatment delay, premorbid adjustment, intellectual functioning, anxiety, depression and psychosocial functioning were also collected.

Results: Over the five year follow-up, symptoms of reduced motivation occurred in 95.3% of patients and reduced expressiveness in 68.5%; and deficits in motivation were more likely to be unremitting (15.7%) than expressive deficits (5.5%). There were differences in the correlates of the proportion of time each patient experienced symptoms of each domain. Depression, weeks of full time occupation and weeks on a disability pension were associated with both domains. Anxiety was associated only with diminished motivation. Lower performance IQ; extrapyramidal symptoms (EPS) and dysrhythmic EEG were associated only with proportion of time showing reduced expressiveness.

Conclusions: The prospective data support previous cross-sectional findings that, while these domains of negative symptoms are correlated, they do show differences in prevalence over time and in their correlates.

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1. Introduction

Issues related to the course of negative symptoms can be complex and may involve multiple influences (Millan et al., 2014). Of possible significance are findings from cross-sectional studies of the structure of negative symptoms suggesting two separable dimensions, one reflecting diminished emotional expression including affective flattening and poverty of speech, and another consisting of diminished motivation and social interest (Foussias and Remington, 2010; Kimhy et al., 2006; Peralta and Cuesta, 1999; Sayers et al., 1996). This structure appears to be independent of medication status, chronicity, or whether symptoms are considered primary (Kelley et al., 1999; Kimhy et al., 2006; Nakaya and Ohmori, 2008).

There is evidence that symptoms related to the motivational component are more prevalent than diminished expression (Kelley et al., 2008; Kimhy et al., 2006), and more stable (Keefe et al., 1991), and that these domains have different correlates and pathophysiology (Foussias and Remington, 2010; Keefe et al., 1992; Kelley et al., 1999;

Kimhy et al., 2006; Kirkpatrick et al., 2006; Kirkpatrick and Fischer, 2006). Mayer et al. (1985) and Stolar et al. (1994) found evidence that reduced expressiveness may be specifically related to poor performance on non-verbal cognitive tasks, although subsequent findings are not consistent (Gur et al., 2006). In the only study directly comparing neurocognitive correlates of each domain in the same sample, Ventura et al. (2014) reported symptoms of both reduced expressiveness and motivation correlated with a composite index of neurocognitive functioning.

One neurophysiological index that has been found related to prominence of negative symptoms up to five years after initiation of treatment is abnormality of resting state EEG (Manchanda et al., 2008; Manchanda et al., 2014). Although there is some evidence that reduced motivation and expressiveness differ in their correlations with neurobiological impairments (Barch et al., 2013; Gur et al., 2007), this has yet to be examined with respect to EEG anomalies.

Social withdrawal, which is a prominent aspect of the motivation component of negative symptoms, may partially reflect anxiety (Birchwood, 2003; Chudleigh et al., 2011; Lysaker et al., 2010; Penn et al., 1994), whereas diminished expressiveness appears unrelated to anxiety (Cohen et al., 2012; Huppert and Smith, 2001; Kelley et al., 1999). There is also evidence that the motivational component has

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more implications for everyday functioning than diminished expression (Fervaha et al., 2014; Green et al., 2012; Rocca et al., 2014; Sayers et al., 1996; Strauss et al., 2013), although these findings may be confounded by the prominence of observed functioning in the assessment of negative symptoms related to motivation (Leifker et al., 2009; Ventura et al., 2009).

There are no published reports that compare the long-term course of the specific domains of reduced motivation and expressiveness, and their correlates, although such studies have been identified as a priority (Kirkpatrick and Fischer, 2006; Schooler et al., 2015). In the current paper, we examine the occurrence and correlates of these two domains of negative symptoms over a five year period in a sample of first episode patients. Given the past literature reviewed above, we hypothesize that there will be significant differences in the prevalence over time, and correlates of the domains.

2. Method

Participants were recruited from successive admissions to the Prevention and Early Intervention Program for Psychoses (PEPP) in London, Canada between March of 1997 and February 2002. Criteria for admission to PEPP and inclusion in the sample were having a psychotic disorder, not having previous treatment with antipsychotic medication for four weeks or longer, and living within the catchment area for PEPP. Treatment within PEPP includes intensive psychosocial intervention and treatment with second generation antipsychotic medication (Manchanda et al., 2007; Norman et al., 2011). A total of 132 previously untreated patients were recruited. All participants provided informed consent as approved by Western University's Ethics Board for Health Sciences Research.

2.1. Measures and procedures

2.1.1. Diagnosis and pretreatment characteristics

Diagnosis was based on a Structured Clinical Interview for DSM-IV (SCID; First et al., 1995). The SCID was also used to identify a comorbid substance use disorder.

Information regarding onset and treatment delay was obtained using a structured interview (Norman and Malla, 2002), which includes items from the Retrospective Assessment of Onset of Schizophrenia (Häfner et al., 1992), administered to patients and collateral sources. Duration of untreated psychosis (DUP) was identified by the length of active psychosis (in weeks) before the initiation of treatment, and duration of untreated illness (DUI) was the length of time between the onset of any noticeable changes in behavior leading up to psychosis (Norman et al., 2012).

Premorbid adjustment was assessed at entry into treatment using the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982) based on information provided by patients and family. Scores on the academic and social components of adjustment were calculated for childhood and early adolescence, unless psychosis emerged during early adolescence, in which case this period was omitted (Norman et al., 2005).

2.1.2. Symptom course

Assessments that allow a refined temporal resolution of symptoms are advantageous (Addington et al., 1991; Schooler et al., 2015; Ventura et al., 2004). In addition, examining the course in terms of remission is likely to be most clinically meaningful (Andreasen et al., 2005; Kelley et al., 2008; Schooler et al., 2015).

Current data were collected to allow monitoring of remission and relapse on a relatively continuous basis. Clinicians, including psychiatrists and case managers, were asked to rate separately the severity of diminished emotional expression and amotivation at every clinical appointment, which usually occurred at least monthly. These summary ratings reflected the extent to which each of the domains was present.

Clinicians were very familiar with, and experienced in, the use of the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). The summary rating of diminished expressions reflected the extent to which affective flattening (SANS item 8) and poverty of speech (SANS item 9) were present; and the summary rating of amotivation/asociality reflected the extent of avolition/apathy (SANS item 17) and anhedonia/asociality (SANS item 22). Ratings were based on a 6-point scale identical to that used in the SANS. Raters were asked to indicate if there was evidence of weekly fluctuation in level of the relevant symptoms over the time covered and make separate weekly ratings accordingly. All staff completing these assessments had completed extensive training in the assessment of negative symptoms using the SANS. Every six months, inter-rater reliability was assessed on varying video recorded interviews, and inter-rater reliabilities based on intra-class correlation coefficients were consistently at least .80.

The timelines of symptoms were formulated by two research personnel who carefully reviewed all case notes for patients, which included the above ratings, and cross-checked them with full SANS assessments that were completed by the patient's psychiatrist on a semi-annual basis for the first two years, and annually thereafter up to five years. Consistent with recommended criteria (Andreasen et al., 2005; Schooler et al., 2015), patients were considered to be in remission of a symptom domain when ratings were less than or equal to 2. Derived timelines were cross-checked with case managers and psychiatrists. For 15 patients, the time chart was completed independently by the two raters and examined for interrater reliability, which was good (Kappa coefficients above .80).

2.1.3. Mood

As part of the clinical assessment protocol, clients were assessed annually for level of anxiety and depression using the Calgary Depression Scale (CDS; Addington et al., 1990) and the Hamilton Anxiety Rating Scales (HARS; Riskind et al., 1987). In addition to the annual assessments, average scores across the five years were calculated to reflect an estimate of overall mood during the follow-up.

2.1.4. Cognitive functioning

As noted earlier, it has been suggested that reduced expressiveness may be specifically related to performance rather than verbal indices of cognition. The WAIS-III (Wechsler, 1997) was used to provide indices of verbal and performance IQ. The WAIS was completed for 104 of the patients after admission to the program when the individual was stable and able to complete the assessment. The primary reasons for non-completion of the WAIS were patient refusal to complete the testing, or difficulty in scheduling assessment. There were no significant differences between completers and non-completers of the WAIS on other measures relevant to the course of negative symptoms.

2.1.5. EEG

EEG assessments were completed on 99 of the patients shortly after admission to PEPP. Recordings were made in accordance with the International 10–20 Electrode Placement System and results were classified according to the Mayo Clinic Classification System (Mayo Clinic, 1991): normal indicating that findings are within normal limits; essentially normal indicating one or more elements of doubtful normality; and dysrhythmia reflecting the presence of three levels of varying intensity and frequency of theta-delta or rhythmic activity including spikes or recorded seizures. Interpretation and classification of the EEG data was carried out by a neurologist specializing in EEG and epilepsy, who had no knowledge of the patient's psychiatric condition.

EEG assessments were part of the clinical protocol within PEPP, but were ordered at the discretion of the treating psychiatrist. There were non-significant differences on measures related to course of negative symptoms between patients for whom EEG findings were and were not available.

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