Schizophrenia Research 153 (2014) 103–108

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Changes in memory performance over a 12-month period in relation to achieving symptomatic remission after a first-episode psychosis

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ARTICLE INFO

Article history:
Received 12 September 2013
Received in revised form 22 January 2014
Accepted 24 January 2014
Available online 7 February 2014

Keywords:
First-episode psychosis
Remission
Cognitive marker
Verbal memory
Longitudinal

ABSTRACT

With the introduction of a clear definition of symptomatic remission from the Remission in Schizophrenia Working Group (RSWG), studies have sought to characterize cognitive functioning in remitted and non-remitted schizophrenia patients. However, most investigations of cognition and remission are cross-sectional or have studied samples of chronically ill patients. Therefore, the aim of this study was to compare cognitive performance between remitted and non-remitted first-episode psychosis (FEP) patients longitudinally. Seventy patients were categorized as remitted ($n = 17$) or non-remitted ($n = 53$) using the full RSWG criteria after being treated for approximately 15 months, during which cognition was evaluated twice. Since our previous investigations in FEP have isolated verbal memory as a potential cognitive marker of symptomatic remission, analyses were limited to verbal, visual and working memory. We have found that non-remitted patients had a significantly worse verbal memory performance than remitted patients after 3 months ($F_{(1,68)} = 6.47, p = 0.006$) and 15 months of treatment ($F_{(1,68)} = 19.49, p < 0.001$). Visual memory was also significantly lower in non-remitted patients compared to those in remission but only at initial assessment ($F_{(1,68)} = 8.21, p = 0.003$) while working memory performance was similar at both time points. Our findings suggest that verbal memory may be a specific and stable marker of clinical remission in FEP patients. This cognitive domain can easily be evaluated at treatment intake in the hope of identifying early on patients who are less likely to remit.

1. Introduction

A substantial proportion of patients with a first episode of psychosis do not respond adequately to treatment. Previous reports have found symptomatic remission rates for both positive and negative symptoms ranging from 22% to 62% within the first years of treatment (Emsley et al., 2008; Cassidy et al., 2010; Ventura et al., 2011), which leaves a significant proportion of patients struggling with prominent symptoms. These recent investigations of remission have used the Remission in Schizophrenia Working Group (RSWG) criteria for symptomatic remission (Andreasen et al., 2005) according to which patients are remitted when they show mild severity or less on 8 key symptoms, reflecting the 5 diagnostic criteria in the DSM-IV, for at least 6 consecutive months (Andreasen et al., 2005). The introduction of this definition has made it easier to operationalize the concept of remission in schizophrenia and to characterize patients who do not respond favorably to usual treatment.

Since then, studies have investigated the particularities of cognitive performances in remitted and non-remitted patients using the RSGW definition. Non-remitted patients were shown to perform significantly worse than remitted patients in the domains of verbal learning and memory (Helldin et al., 2006; Bodnar et al., 2008; Bodnar et al., 2011), inhibition and executive functions (Hofer et al., 2011; Yun da et al., 2011; Meesters et al., 2013), attention (Hofer et al., 2011), visuospatial skills (Eberhard et al., 2009) and social cognition (Ciudad et al., 2009; Montreuil et al., 2010). However some studies have failed to detect cognitive differences between these subgroups of patients (Li et al., 2010; Brissos et al., 2011; Meesters et al., 2011). Among these previous studies of symptomatic remission in relation to cognition, longitudinal symptom data was only available for the investigation of Eberhard et al. (2009), which limits the interpretations of results. Another limitation of these findings is the use of chronic or enduring schizophrenia samples (Helldin et al., 2006; Ciudad et al., 2009; Eberhard et al., 2009; Li et al., 2010; Brissos et al., 2011; Hofer et al., 2011; Yun da et al., 2011) or even late-life schizophrenia samples (Meesters et al., 2011; Meesters et al., 2013), thereby introducing chronicity and institutionalization confounds. Alternatively, the cognitive characterization of

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http://dx.doi.org/10.1016/j.schres.2014.01.024

clinically remitted and non-remitted first-episode psychosis (FEP) patients in the early years of treatment has the potential to indicate predictors of long-term outcome as well as to inform the development of cognitive rehabilitation plans earlier in the course of treatment.

In our previous work, we have found that FEP patients who did not show symptomatic remission after the first 6 months of treatment had a significantly poorer verbal memory performance at treatment intake compared to remitted patients (Bodnar et al., 2008; Bodnar et al., 2011). However, it remains to be determined whether this difference associated with remission status persists during treatment. Therefore, the goal of this study was to explore the course of memory performance after patients underwent a 1-year follow-up memory assessment in relation to their remission status. Verbal memory is the focus of this investigation since we have previously highlighted this domain as a cognitive marker of remission, and the demonstration of its stability over the first years of treatment would strengthen this suggestion. The formulation of our hypotheses was also influenced by findings that cognition in FEP is relatively stable during the first 2 years of treatment (Addington et al., 2005; Rund et al., 2007; Bozikas and Andreou, 2011). Consequently, we predicted that non-remitted patients would show significantly lower verbal memory performance at initial assessment compared to the remitted patients, and that this difference would persist a year later. If this was the case, we also wanted to assess whether the difference would remain specific to verbal memory or reflect a generally poorer memory performance in non-remitted patients; therefore we included performance in the working memory and visual memory domains in our analysis. We hypothesized that the difference would remain specific to verbal memory.

2. Materials and methods

2.1. Participants and treatment setting

All patients were recruited and treated through the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), a specialized early intervention service with integrated clinical, research, and teaching modules, at the Douglas Mental Health University Institute in Montreal, Canada. Individuals aged 14 to 30 years, suffering from either affective or non-affective psychosis who had not taken antipsychotic medication for more than 1 month and who had an IQ higher than 70 were consecutively admitted to the program as either inpatients or outpatients. For this analysis, only those diagnosed with a non-affective psychotic disorder (schizophrenia spectrum or psychosis NOS) were included since remission in schizophrenia was the focus. The program involves a comprehensive approach with intensive medical and psychosocial management provided primarily through pharmacotherapy, modified case management, family intervention and cognitive behavioral therapy. For complete program details, see Malla et al. (2003) or http://www.douglas.qc.ca/clinical-services/adults/specialized/pepp/contact.asp?l=e.

The data for this study was collected between 2004 and 2010 at which point the cognitive evaluation protocol was modified and different memory tests were administered. Of the patients followed at the time, 70 non-affective patients had received treatment for a minimum of 12 months and had complete baseline and follow-up neuropsychological data pertaining to memory. These patients were subsequently separated into two groups: remitted (n = 17, 24.3%) and non-remitted (n = 53, 75.7%) following the RSWG definition using PANSS ratings of 3 (mild) or less on delusions (P1), unusual thought content (G9), hallucinatory behavior (P3), conceptual disorganization (P2), mannerism/posturing (G5), blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6) maintained for 6 consecutive months. All patients met DSM-IV criteria for schizophrenia (remitted = 12; non-remitted = 42), schizophreniform (remitted = 1), schizoaffective (remitted = 2; non-remitted = 10), or psychosis NOS (remitted = 2; non-remitted = 1) diagnoses according to the Structured Clinical Interview for DSM-IV (First et al., 1998). Diagnoses were confirmed between two senior research psychiatrists (A.M. and R.J.).

After a comprehensive description of the study, written informed consent was obtained from all participants. Research protocols were approved by the Douglas Mental Health University Institute Research Ethics Board and McGill University Faculty of Medicine Review Board.

2.2. Data collection

2.2.1. Symptom, medication, and socio-demographic data

As per PEPP protocol, the following data were obtained at each interview session conducted at the first assessment and at months 1, 2, 3, 6, 9, and 12 following the first assessment; the first assessment took place within 1 month after admission (days; median = 21.8, mean = 23.6, range = 9.3–49.2). Positive and negative symptoms were assessed using the PANSS (Kay et al., 1987); raters had established an overall ICC of 0.75 on this scale. Duration of illness was defined as the period beginning with the first onset of any psychiatric symptoms to the time of first assessment. In dating the onset of first psychiatric symptoms, childhood disorders such as developmental disorders (e.g. autism) or attention deficit disorders were not included. Psychiatric symptoms refer to symptoms indicating behavioral change such as anxiety, depression, suicidal ideation, or social withdrawal. The type and dosage of antipsychotic taken were recorded and subsequently converted into chlorpromazine equivalents (Woods, 2003; Jensen and Regier, 2010). Medication adherence, based on a 5-point scale ranging from 0 (never) to 4 (fully), was obtained from patients or, when possible, from family members. At first assessment, parental socio-economic status (SES) during upbringing was measured with the Hollingshead two-factor index (Hollingshead, 1965).

2.2.2. Memory assessment

A standardized cognitive battery for which the tests were administered in a fixed order and included various measures of memory was completed by all patients at or near admission into PEPP (in months; mean = 2.9, SD = 2.0, range = 0.8–10.7) and again after an average of 15 months after admission (in months; mean = 15.3, SD = 2.9, range = 11.7–23.7). The two groups did not differ with respect to when testing took place for the first cognitive assessment [months, mean (SD): non-remitted = 2.9 (2.0); remitted = 3.0 (2.3); t_{68} = −0.19, p = 0.85] or at follow-up [months, mean (SD): non-remitted = 15.2 (3.0); remitted = 15.4 (3.0); t_{68} = 0.89, p = 0.79]. Testing was administered and scored by a trained professional who was not involved with the treatment of the patient under the supervision of an accredited psychologist (M.L.).

Memory performance was assessed by separating various neuropsychological tests into three cognitive domains as suggested by the MATRICS group (Nuechterlein et al., 2004). The following domains were derived: *verbal learning and memory* from the Logical Memory subtests of the Wechsler Memory Scale—Third Edition (WMS-III) (Wechsler, 1997b); *visual learning and memory* from the Visual Reproduction subtests of the WMS-III; and *working memory* from the Spatial Span subtests of the WMS-III and the Digit Span subtests of the Wechsler Adult Intelligence Scale—Third Edition (WAIS-III) (Wechsler, 1997a). The scaled scores of the abovementioned variables were transformed into normalized scores (z-scores) using a mean = 10 and SD = 3 as stated in the Wechsler testing manuals (Wechsler, 1997a, b). The three memory domains were calculated by averaging the z-scores of the abovementioned subtests.

2.2.3. Statistical analyses

Age at first cognitive assessment and follow-up assessment, duration of untreated illness (DUI), duration of untreated psychosis (DUP) and full scale IQ were compared using independent t-tests, parental SES with a Mann–Whitney U-test, and sex and drug use with cross tabulation and a chi-square test. For clinical data at first assessment and at