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Impairment in verbal memory observed in first episode psychosis patients with persistent negative symptoms

Cindy L. Hovington [a,b], Michael Bodnar [a], Ridha Joober [a,c], Ashok K. Malla [a,b,c], Martin Lepage [a,b,c,*]

[a] Prevention and Early Intervention Program for Psychoses (PEPP—Montreal), Douglas Mental Health University Institute, Montreal, Quebec, Canada
[b] Department of Neurology & Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada
[c] Department of Psychiatry, McGill University, Montreal, Quebec, Canada

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ABSTRACT

Negative symptoms are present early on during the first episode of psychosis (FEP). The severity of these symptoms has been linked to cognitive deficits, including memory; however, its relationship with persistent negative symptoms (PNS) remains unclear. Thus, the goals of the current paper were to explore memory profiles in FEP patients identified as having PNS and to delineate this relationship in PNS over a 1-year period. Patients diagnosed as having a first episode of psychosis were segregated into groups of patients who met the criteria for PNS (N = 39) and patients who did not, or non-PNS (N = 97). At an initial assessment, all subjects were administered neurocognitive tests for three memory domains including verbal, visual and working memory. In addition, in FEP patients, clinical symptoms including negative, positive and depressive symptoms were also measured at the initial assessment as well as months 1, 2, 3, 6, 9, and 12. A significant interaction of memory × group was observed (F = 4.997, d.f. = 1,181, P = 0.002), with post hoc comparisons indicating that the PNS group performed more poorly than non-PNS only in the verbal memory domain. All three-memory domains remained stable over time. Hence, in comparison to non-PNS patients, FEP patients with PNS appear to have greater (selective) verbal memory impairments throughout the first year of treatment.

1. Introduction

Since Kraepelin's first description of dementia praecox (Kraepelin, 1971) and Blueler's emphasis on primary vs. accessory (psychotic) symptoms, negative symptoms, as well as cognitive impairments, have been recognized as core features of schizophrenia. Negative symptoms refer to an impoverishment of normal behavior and include poverty of speech (alogia), reduced ability to feel pleasure (anhedonia), decreased motivation (avolition) and emotional unresponsiveness (blunted affect) (Andreasen, 1989; Kirkpatrick et al., 2006). Several studies suggest a modest association between poor cognitive ability and negative symptom severity (Gold et al., 1999; Fitzgerald et al., 2004; Harvey et al., 2006). This relationship is not as strongly evidenced with positive symptoms (Gold et al., 1999; Bilder et al., 2000; Keefe et al., 2006; Ventura et al., 2009).

Memory impairments manifesting across various memory domains including verbal, visual and working memory are well documented in schizophrenia (for review see (Aleman et al., 1999) (Fridberg et al., 2010; Harvey et al., 2011; Leeson et al., 2010; Lepage et al., 2010; Bodnar et al., 2012; Ragland et al., 2012; Zhou et al., 2012); however, what is of clinical concern is the presence of these deficits earlier in the illness. Some have suggested that memory deficits documented during early stages of psychosis are associated with the severity of negative symptoms (Bodnar et al., 2008; Leeson et al., 2010), while others have shown that memory deficits present in the prodrome may predict transition to psychosis (Brewer et al., 2005; Lencz et al., 2006; Pukrop et al., 2006; Woodberry et al., 2010). Nonetheless, three major caveats of past studies investigating this relationship are: 1) the employment of correlational analyses, 2) variable degrees of negative symptoms between studies (O'Leary et al., 2000; Hughes et al., 2003; Bozikas et al., 2004; Rund et al., 2004) and 3) a lack of a clear distinction between PNS and non-PNS. Thus, identifying a group of FEP patients with set criteria for PNS may help strengthen findings and further our understanding of negative symptoms.

Research on persistent negative symptoms (PNS) has recently gained substantial momentum (Edwards et al., 1999; Heckers et al., 1999; Malla et al., 2004; Kirkpatrick et al., 2006; Buchanan, 2007; Chang et al., 2011; Hovington and Lepage, 2012; Stauffer et al., 2012). These symptoms are present at the first episode and represent approximately 24–27% of FEP patients (Malla et al., 2004; Chang et al., 2011; Hovington et al., 2012). Persistent negative symptoms must be present for a minimum of 6 consecutive months after the initial symptom stabilization (Buchanan, 2007; Hovington and Lepage, 2012); hence, longitudinal rather than cross-sectional studies seem more suitable to investigate these symptoms. The stability of the relationship between memory and PNS remains

* Corresponding author at: Douglas Mental Health University Institute, Frank B Common Pavilion, F1143, 6875 LaSalle Blvd., Verdun, Quebec H4H 1R3, Canada. Tel.: +1 514 761 6131x4393; fax: +1 514 888 4064.
E-mail address: martin.lepage@mcgill.ca (M. Lepage).

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equivocally unclear (Gold et al., 1999; Milev et al., 2005) [for review see (Bozikas and Andreou, 2011)].

Given the ambiguity of this relationship, it may be beneficial to assess a more homogenous subgroup of FEP. Thus, the objectives of this study were: 1) to compare memory ability (working, verbal and visual memory) in a sample of FEP subjects with PNS to subjects without PNS as well as healthy controls; and 2) to assess the trajectory of these three memory domains in relation to PNS at 1-year follow-up. Based on previous reports on the relationship between the severity of negative symptoms and memory deficits, we hypothesize that the group with PNS will have greater memory deficits compared to non-PNS patients and healthy controls. Further, based on reports of relative stability of cognition over time (Aleman et al., 1999; Vaz and Heinrichs, 2002; Hughes et al., 2003), we hypothesized that all memory domains would remain stable.

2. Methods

2.1. Participants

All FEP patients were part of a longitudinal study and were treated in 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 35 years from the local catchment area suffering from either affective or non-affective psychosis who had not taken antipsychotic medication for more than one month and with an IQ higher than 70 were admitted to the program as either in- or out-patients (for details see (Malla et al., 2003) or visit http://www.douglasresearch.qc.ca/pages/view?section_id=165). Diagnosis of schizophrenia or related spectrum disorders was established with the Structured Clinical Interview for DSM-IV (SCID-IV) (First et al., 1998). Written informed consent was obtained from all participants. Research protocols were approved by the Douglas Institute Human Ethics Review Board. Sixty-two healthy controls were recruited through advertisements in local newspapers and were included only if they had no current or previous history of (a) any Axis I disorders, (b) any neurological diseases, (c) head trauma causing loss of consciousness, and (d) a first-degree family member with schizophrenia or related schizophrenia-spectrum psychosis. Current IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI-III) (Wechsler, 1997a).

2.2. Clinical assessment

An initial assessment was conducted on average, within one month after admission (in days; mean = 22.7, s.d. = 8.6, range = 8.3–54.8). Education level (number of school years completed), parental socioeconomic status (SES) with the Hollingshead two-factor index (Miller, 1991), Social and Occupational Functioning Assessment Scale (SOFAS), The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982) and handedness (Oldfield, 1971) were acquired at the initial assessment. As part of the longitudinal study, the following clinical variables were assessed at the initial assessment as well as at months 1, 2, 3, 6, 9 and 12 following the first evaluation. Negative and positive symptoms were quantified using the SANS (Andreasen, 1984) and the SAPS (Andreasen, 1983), respectively. The domain of attention in the SANS scale was not included in our analyses because previous factor analytical studies have shown that it loads on both negative and disorganization (Peralta and Cuesta, 1999; Malla et al., 2002). Evaluators at PEPP established an ICC of 0.74 on the SAPS and 0.71 on the SANS; all evaluators participated in inter-rater reliability sessions at least once a year to avoid evaluator drift (i.e. evaluators must maintain consistency with themselves as well as with other evaluators). Depressive symptoms were assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993) and extrapyramidal symptoms with the Extrapyramidal Symptoms Rating Scale (ESRS) (Chouinard and Margolese, 2005). If prescribed, type and dose of anticholinergic medications taken were recorded. The type and dosage of antipsychotics taken were also recorded and subsequently converted into chlorpromazine equivalents (Woods, 2003).

2.3. Neuropsychological assessment

Trained research staff administered a standardized battery of neuropsychological tests to all participants under the supervision of an accredited neuropsychologist (M.L). As part of a larger cognitive study, a total of seven cognitive domains as suggested by the NIMH—Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) group (Nuechterlein et al., 2004) were assessed at the first evaluation and at the 1-year follow-up in the patient group and only at the first assessment in the healthy control group. We have described these domains in further detail elsewhere (Bodnar et al., 2008; Lepage et al., 2008). The following cognitive domains were derived: *verbal learning and memory* from the Logical Memory (LM) 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; *working memory* from the Spatial Span subtests of the WMS-III and the Digit Span subtest of the Wechsler Adult Intelligence Scale—Third Edition (WAIS-III); *speed of processing* from Trail Making Test A (completion time) (Reitan, 1992) and the digit symbol subtest of the WAIS-III; *reasoning and problem solving* from the Trail Making Test B (completion time) and the block design subtest of the WAIS-III; *attention* from the d2 Test of Attention (concentration performance score) (Brinkenkamp and Zilmer, 1998) and *social cognition* from the Four Factor Tests of Social Intelligence (O'Sullivan and Guilford, 1976) and Hinting Task (Corcoran et al., 1995).

2.4. Identifying persistent negative symptoms

Clinical data from the first assessment as well as months 1, 2, 3, 6, 9, and 12 were analyzed to identify patients with PNS. PNS was defined as having a minimum score of three on one or more global items of the SANS (Malla et al., 2004) (Hovington et al., 2012). These negative symptoms were required to be present after the initial stabilization of positive symptoms (month 3) and to be maintained for 6 consecutive months (months 6, 9 and 12) (Buchanan, 2007) (Hovington et al., 2012). Subjects with global ratings on "affective flattening" or "alogia" entirely based as a result of items "inappropriate affect" or "poverty of content of speech", respectively were excluded as having negative symptoms based on previous findings suggesting that these items are not part of the negative symptom construct (Malla et al., 2004). After the completion of the 12-month assessment, FEP patients were segregated into two groups (PNS and non-PNS).

Patients in the PNS group had primary negative symptoms absent of any positive (global rating of mild (2) or less, as measured by the SAPS), depressive (a total score of 4 or less on the CDSS) (Addington et al., 1993) or extrapyramidal symptoms (low to mild levels). Lastly, FEP patients who were administered their initial neuropsychological assessment later than nine months after entry into our program were also excluded since this was deemed too late given our PNS criteria.

2.5. Statistical analysis

For clinical data, DUP and DUI were log transformed and duration of prodrome was square-root transformed; all other clinical data characteristics were normally distributed. Independent t-tests were used to compare clinical characteristics between PNS and non-PNS groups. Categorical variables were compared using a chi-squared test, while continuous variables were compared using independent t-tests. All clinical scales (SOFAS, SANS, SAPS, CDSS) were compared between groups at both first assessment and month 12.