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Predictors of cognition in first episode psychosis

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ABSTRACT

Purpose: Cognitive deficits are common in the first episode of psychosis (FEP) and may begin much earlier. While some evidence suggests that the decline in cognition occurs over the untreated symptomatic period, including the prodromal phase, others point to these deficits being present even earlier. We aimed to investigate the differential effect of untreated symptomatic and pre-morbid phases on cognition in a large sample of FEP.
Methods: Two hundred and sixty eight FEP patients, admitted into a specialized early intervention service, were administered neuro-cognitive tests. The Circumstances of Onset and Relapse Schedule (CORS) was administered for measurement of duration of untreated psychosis (DUP), the duration of untreated illness (DUI) and demographic factors. The Pre-morbid Adjustment Scale (PAS) was used to measure different domains of pre-morbid adjustment. Seventy three healthy controls were also recruited for neuro-cognitive comparison.
Results: We observed no effect of DUP and a minimal effect of DUI on cognitive functioning in FEP. Instead, the early educational pre-morbid adjustment domain was most strongly associated with cognition and predicted both global cognitive and verbal memory outcome in FEP.
Conclusion: Our results suggest that symptoms associated with the symptomatic phase of a FEP do not influence cognitive functioning in FEP. Instead, cognitive deficits in FEP may predate illness onset and may indicate susceptibility to such illness.

1. Introduction

Cognitive deficits are regarded as a fundamental feature of schizophrenia and related psychotic disorders (Milev et al., 2005). Compared to healthy controls, greatest impairments are reported in the domains of memory, attention, and executive function (Dickinson et al., 2004; Mesholam-Gately et al., 2009; Holmen, 2010) and are linked to functional outcomes including independent living, occupational status, social relationships, and overall community behavior (Green and King, 1996; Green et al., 2000; Leeson et al., 2009). As current treatments of these deficits are limited, they often persist throughout the course of illness (Harvey and Penn, 2010).

Cognitive deficits are present at the time of presentation of treatment of the first episode of psychosis (FEP) (Mesholam-Gately et al., 2009) and to a lesser extent, prior to any psychotic symptoms, in both the pre-morbid as well as prodromal phases of illness (MacCabe, 2008; Woodberry et al., 2008; Fusar-Poli et al., 2012). These deficits tend to remain stable from FEP to later stages of the illness with some possible decline in the later stages due to normal aging and medication effects (Zipursky et al., 2012). A recent meta-analysis reported medium deficits (ES = −0.54) in the high risk stage (HR), likely representing the late prodromal phase, compared with larger deficits in FEP (ES = −0.91) that remained relatively unchanged in the chronic phase (ES = −0.96) (Mesholam-Gately et al., 2009).

While the meta-analysis of cognition in the HR phase attempted to delineate the pre-morbid (asymptomatic) from the prodromal phase of illness by separating results of cognitive tests conducted during childhood from those in adolescence (Mesholam-Gately et al., 2009), this division is challenged by the inclusion of studies that did not specify participant age or used overlapping age ranges. Their conclusion of no deterioration in cognition between childhood and adolescence (MeshalomGately et al., 2009) is in contradiction to several studies reporting an increase in deficits over this transitional period (Watt and Lubensky., 1976; Jones et al., 1994; Bilder et al., 2006; Seidman et al., 2010; MacCabe et al., 2013). What remains unclear is the extent to which the severity of cognitive deficits reported at the time of treatment of a FEP is accounted for by a decline that accompanies the onset of non-psychotic (prodromal phase) and/or psychotic symptoms or by cognitive deterioration that predates the onset of any symptoms, in early childhood or the early adolescence pre-morbid period. This may have some practical significance as any deterioration that accompanies onset of symptoms may be subject to intervention through early identification and interventions during the prodromal (such as, high risk mental states) and/or through early treatment of psychotic symptoms (Perkins et al., 2005).

The link between the duration of untreated psychosis (DUP) and outcome is hypothesized to be mediated through a toxic effect on

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brain function (Wyatt, 1991), the latter likely to be represented by cognitive functions should hence reflect an association between duration of untreated psychotic symptoms and cognition. Similarly, the duration of untreated illness (DUI), which incorporates the prodromal as well as the untreated psychotic phase, may have a detrimental effect on long-term cognition but one that begins several years earlier with the start of non-specific symptoms such as depression and anxiety (McGlashan and Johannessen, 1996). While both hypotheses of the effect of DUP and DUI on cognition suggest the impact of either non-psychotic or psychotic symptoms on cognition, measures of pre-morbid adjustment, before the onset of any symptoms, imply a possible role for early neuro-developmental processes (MacCabe and Murray, 2004; Demjaha et al., 2012), early environmental stressors (Wicks et al., 2005) and individual factors such as sex and substance abuse status (Rund et al., 2004).

Among the studies investigating the effect of either DUP or DUI on cognitive functioning in psychosis, six have reported longer DUP to be associated with increased cognitive dysfunction (Scully et al., 1997; Amminger et al., 2002; Joyce et al., 2005; Lappin et al., 2007; Primavera et al., 2012; Chang et al., 2012) while an equal number report no effect (Norman et al., 2001; Ho et al., 2003; Addington et al., 2003; Rund et al., 2007; Barnes et al., 2008; Goldberg et al., 2009). None of the three studies that examined the effect of DUI on cognition found a relationship between the two (Scully et al., 1997; Hoff et al., 2000; Keshavan et al., 2003), although not all used DUI as a primary independent measure. A recent meta-analysis (Bora and Murray, in press) found no deterioration in cognition between baseline and various lengths of follow-up (between 6 months and 5 years) for both those at Ultra High Risk (UHR) and those with an FEP suggesting that the extent of cognitive deficits seen in psychosis occur much earlier, prior to even the prodromal phase (Bora and Murray, in press). Studies that have investigated the association between pre-morbid adjustment and cognition have found either specific (e.g. Silverstein et al., 2002; Larsen et al., 2004; Addington and Addington, 2005; Chang et al., 2013) or general cognitive deficits (Rabinowitz et al., 2006). Another recent study reported the degree of poverty of pre-morbid adjustment to be related to the severity, as opposed to the type, of cognitive deficits in FEP (Bechard-Evans et al., 2010). These discrepancies of the impact of symptomatic stages versus childhood and early adolescence factors on cognitive function in psychosis derived from multiple samples might be resolved by comparing the putative influence of these stages on cognitive functioning within the same group of FEP individuals. Therefore, our objective was to investigate cognitive deficits in the pre-morbid, prodromal, and untreated psychotic phases of illness and their potentially differential effect on cognitive functioning in a large sample of FEP through measures of pre-morbid adjustment, DUI, and DUP, while controlling for additional variables such as sex and substance abuse status that are known to influence cognitive functions. Given the equivocal results of previous research investigating the impact on cognition of the pre-morbid, prodromal, or untreated phases of the psychotic illness, no a-priori hypothesis is presented.

2. Methods

2.1. Overview

In this study, we have used two measures, DUP and DUI, to investigate the association between cognition and duration of different symptoms. DUP is a measure of the duration of psychotic symptoms from their onset until the time of antipsychotic treatment. DUI is defined as the period between the onset of any signs or symptoms to the time that antipsychotics are initiated following FEP. Measures of pre-morbid adjustment are used to assess social and educational functioning before any signs or symptoms of psychosis have occurred. Further putative predictor variables of cognitive functioning in FEP include: age of onset of psychosis (Fusar-Poli et al., 2012), sex (Fusar-Poli et al., 2012), substance use (Potvin et al., 2008; Yücel et al., 2012), socio-economic status (Bertrand et al., 2007), and education level (Norman et al., 2001).

2.2. Treatment setting

This study is part of a larger longitudinal study of FEP in a specialized early intervention service, the Prevention and Early Intervention Program for Psychosis (PEPP — Montreal, Quebec). This program provides comprehensive phase specific treatment including antipsychotic medication, assertive case management, family intervention and other forms of psychosocial therapy. It is the only FEP program serving this catchment area. This study was approved by the institutional research ethics board.

2.3. Participants

All patients consecutively admitted to PEPP between 2003 and 2009 were eligible for participation if they were between the ages of 16–30; from the local catchment area; with a diagnosis of non-affective or affective psychotic disorder; who had not received antipsychotic medication for more than 1 month; and whose IQ was over 70, as assessed by the Wechsler Abbreviated Scale of Intelligence (WAIS-III) (Wechsler, 1997).

Healthy controls ($n = 73$), matched on age and gender, were recruited through local newspaper advertisements. Eligibility criteria included no current or previous history of: any Axis I disorders; any neurological diseases, head trauma causing loss of consciousness; and a 1st degree family member with schizophrenia or related schizophrenia spectrum psychosis.

All subjects signed informed consent for their participation. Those under the age of 18 were also required to have their parent or guardian's signed consent.

2.4. Clinical variables

As part of PEPP protocol, the Structured Clinical Interview for *DSM-IV* (SCID; First et al., 1995) was used to establish a baseline diagnosis and current substance use status (yes or no). Interviews for diagnosis and symptom evaluations were carried out by trained staff who had achieved and maintained a high degree of inter-rater reliability. Final diagnosis was arrived at through consensus by two senior psychiatrists (AM & RJ) at baseline and at follow-up 1 year later. All patients were assessed for age at onset of psychosis, sex, and highest level of education achieved.

Data on DUP and DUI were collected using the Circumstances of Onset and Relapse Schedule (CORS) (Malla et al., 2006), a structured interview instrument for use with patients and families that includes some sections from the Interview for the Retrospective Assessment of Onset of Schizophrenia _ IRAOS (Hafner et al., 1992). Inter-rater reliability for DUP and DUI was relatively high (ICC varying from 0.86 to 0.98). The Hollingshead two-factor index of social position (Hollingshead, 1965) based on a five point Likert scale was used to calculate the highest level of occupational and educational achievement for each of the patient's parents. A higher score on this scale represents lower SES. Due to greater consistency of data available, only the SES of the father was included.

2.5. Pre-morbid adjustment

The Pre-morbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982) was used to assess social and educational pre-morbid functioning across four age ranges: childhood (up to age 11), early adolescence (12–15 years), late adolescence (16–18 years), and adulthood ($\leq$19 years). Only ratings for childhood and early adolescence were included to avoid any overlap with prodromal symptoms that generally occur