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Predictors of a clinical high risk status among individuals with a family history of psychosis

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ABSTRACT

Background: Risk for psychosis can be assessed on the basis of genetic risk, referred to in the literature as family high risk (FHR) or through the presence of clinical high risk symptoms (CHR). Recent studies have also shown that certain risk factors (i.e. trauma, cannabis, migration) may play a role in the development of psychosis, possibly in combination with one another and in particular in combination with a family history of psychosis. It is unknown which risk factors may play a role in the prediction of CHR status among individuals whom are already genetically vulnerable. This study compared FHR individuals who also met CHR criteria to FHR individuals who did not on various risk factors, psychopathology and functioning.

Method: Participants were 25 who met FHR and CHR criteria (FHR + CHR) as determined by Structured Interview for Prodromal Syndromes, 25 who met only FHR criteria (FHR-non-CHR), and 25 healthy controls. A binary logistic regression was performed to determine the best predictors of belonging to the FHR + CHR group.

Results: FHR + CHR and FHR-non CHR were significantly different on measures of age first tried cannabis ($F = 3.65$, $p < 0.05$) and IQ ($F = 3.32$, $p < 0.05$). FHR groups also differed on self-reported anxiety ($F = 11.79$, $p < 0.001$) and current scores of social ($F = 19.74$, $p < 0.0001$) and role ($F = 17.71$, $p < 0.0001$) functioning. The most significant predictor of belonging to the FHR + CHR group was an earlier age of cannabis use (OR = 0.44, $p = 0.05$).

Conclusion: These preliminary results are promising in determining potential risk factors for the development of psychosis in those who are at risk for psychosis on the basis of a family history.

1. Introduction

One way to determine an individual's risk for developing psychosis is based on the relationship to an affected individual, usually a first-degree relative and often a parent (Cannon et al., 2003). The risk here for developing psychosis is approximately 10% compared to 1% in the general population, risk that increases with the degree of the genetic relationship (de la Serna et al., 2011). There have been several seminal studies of individuals with a family risk of psychosis (FHR) (Fish, 1960; Nagler et al., 1985; Mednick et al., 1987; Erlenmeyer-Kimling et al., 2000; Johnstone et al., 2005). A review of this literature suggests that around 25–60% of high risk children display poor timing of developmental milestones, and deficits in cognition social functioning, attention and information processing (Cannon et al., 2003). While there are many advantages of these FHR studies, such as the power of prospective data, standard assessments, and true blindness as to outcome, these types of studies take a long time with both subject and investigator dropout and what once may have been state of the art tools easily become out-dated.

Recent research focuses on those who may be at risk of developing psychosis based on clinical symptoms and thus experiencing a potential prodrome for psychosis (Addington and Heinssen, 2012). Reliable criteria have been developed (McGlashan et al., 2010) and researchers are able to prospectively follow the course of the illness with the goal of being able to distinguish differences between those who go on to develop psychosis and those who do not. A recent meta-analysis indicates that approximately 29% of these at risk individuals will go on to develop a full blown illness within two years (Fusar-Poli et al., 2012). Since risk is determined on the basis of clinical symptoms these individuals are considered to be at clinical high risk (CHR) of developing psychosis.

There is a growing literature linking risk for psychosis to certain biological and psychosocial risk factors such as urban upbringing (Krabbendam and van Os, 2005; Kelly et al., 2010), migration (Veling and Susser, 2011), discrimination or more likely perceived discrimination (Janssen et al., 2003; Karlsen et al., 2005), history of trauma in childhood (Arseneault et al., 2011; Bendall et al., 2013), cannabis use

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and the age of first using cannabis (Arseneault et al., 2002; Stefanis et al., 2004; Henquet et al., 2005, 2008; Konings et al., 2008), traumatic brain injury (AbdelMalik et al., 2003), obstetric complications (Cannon et al., 2002), paternal age at conception (Miller et al., 2011) as well as a wide range of other factors such as infections (Torrey et al., 2012), motor dysfunction (Dickson et al., 2012), or internalizing and externalizing disorders (Tarbox and Pogue-Geile, 2008). There is also evidence that individuals that later develop schizophrenia display clinically significant intellectual impairments (Reichenberg et al., 2006) and a recent systematic review found that low IQ was among one of the strongest antecedents of schizophrenia (Matheson et al., 2011).

It has further been suggested that many of these factors are working in combination with one another (van Os et al., 2004; Houston et al., 2008; Konings et al., 2012) or additively (Cougnard et al., 2007; Harley et al., 2009; Kuepper et al., 2011) to even further increase risk of developing psychosis. Furthermore, these types of interactions have been reported in some FHR studies, suggesting that environmental factors may synergistically combine with pre-existing psychosis liability to cause symptoms of psychosis (Mirsky et al., 1985; Cannon and Mednick, 1993; van Os et al., 2008; GROUP, 2010). Thus, if there is a combination of factors that may explain why some individuals at FHR of psychosis go on to develop the illness and some do not, it may be important to consider why some individuals at FHR develop subthreshold symptoms and why some do not. However, since many of the early FHR studies did not distinguish between those who had subthreshold symptoms and those who did not, it is possible that there may be the same synergy between family risk and other risk factors to predict CHR status.

The overall purpose of this project was to determine differences between individuals at FHR of psychosis who have developed subthreshold psychotic symptoms, that is, are at CHR for psychosis and FHR individuals who do not. The primary hypothesis is that the FHR group at CHR of psychosis would evidence more risk factors defined as previous traumatic experiences, greater sense of discrimination, ever having had a head injury, cannabis use before age 15 and lower IQ compared to FHR individuals who do not meet CHR criteria. Secondly, the samples will be compared on functioning and psychopathology. A sample of healthy controls (HC) will be included to aid interpretability of results; particularly should the two FHR groups not differ on a given variable.

2. Methods

2.1. Participants

The sample consists of 50 participants with a family high risk of psychosis; 25 of whom were at clinical high risk of psychosis (FHR + CHR), 25 with no clinical high risk symptoms (FHR-non-CHR) and 25 healthy controls with neither a family history of psychosis or evidence of CHR symptoms. All participants were between the ages of 12 and 35 and were required to understand and sign informed consent. The FHR + CHR group and the healthy controls were recruited as part of the ongoing North American Prodrome Longitudinal Study 2 (NAPLS 2) at the Calgary site. FHR participants all had a first degree relative with a psychotic illness. Exclusion criteria were not meeting criteria for any current or lifetime axis I psychotic disorder, no prior history of treatment with an antipsychotic, IQ < than 70 or past and no current history of a clinically significant central nervous system disorder. The FHR + CHR participants met the Criteria of Prodromal Syndromes (COPS) using the Structured Interview for Prodromal Symptoms (SIPS) (McGlashan et al., 2010) and the FHR-non-CHR had no evidence of current or past subthreshold psychotic symptoms. The FHR-non-CHR participants were recruited from a variety of sources. Notices were posted in mental health clinics as well as other community settings and mass emails were sent out to various departments throughout the University. Further details on ascertainment, inclusion and exclusion criteria have been described in detail elsewhere (Addington et al., 2012). The distribution of affected family member was as follows; for the FHR + CHR sample: mother (n = 7, 28%), father (n = 10, 40%), brother (n = 5, 20%), or sister (n = 3, 12%) with psychosis. For the FHR-non-CHR group: mother (n = 11, 44%), father (n = 5, 20%), brother (n = 8, 32%), or sister (n = 1, 4%) with psychosis. Groups did not significantly differ on the distribution of affected family member.

2.2. Measures

The *Family Interview for Genetics Studies* (*FIGS*) (Maxwell, 1996) was used to determine a family history of mental illness, as well as the presence of a psychotic disorder in a first degree relative. The *Structured Clinical Interview for DSM-IV Disorders* (*SCID-1*) (First et al., 1995) was used to determine the presence of any axis 1 disorders and the *Structured Interview for Prodromal Syndromes* (*SIPS*) (McGlashan et al., 2010) was used to determine the presence and severity of prodromal symptoms. The COPS have three possible prodromal syndromes — attenuated positive symptom syndrome (APSS), genetic risk and deterioration (GRD) and/or brief intermittent psychotic syndrome (BIPS). APSS requires the presence of at least one particular positive psychotic symptom (unusual thought content, suspiciousness, grandiose ideas, perceptual abnormalities, or disorganized communication) of insufficient severity to meet diagnostic criteria for a psychotic disorder. The GRD state requires having a combination of both functional decline (at least a 30% drop in GAF score over the last month as compared to 12 months ago) and genetic risk; genetic risk refers to having either schizotypal personality disorder or a first-degree relative with a schizophrenia spectrum disorder. The BIPS state requires the presence of any one or more threshold positive psychotic symptoms (unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and disorganized communication) that are too brief to meet diagnostic criteria for psychosis.

Clinical measures included the *Calgary Depression Scale for Schizophrenia* (*CDSS*) (Addington et al., 1993) and the *Social Interaction Anxiety Scale* (*SIAS*) & *Social Anxiety Scale (SAS)* (Olivares et al., 2001).

Table 1
Demographic characteristics.

Variable	Healthy controls n = 25	FHR-non-CHR n = 25	FHR + CHR n = 25	Test statistic
	Mean (SD)			*F value*
Age	19.64 (5.23)	20.76 (5.85)	17.88 (3.24)	2.18
Years of education	12.44 (4.32)	12.00 (3.27)	11.04 (2.77)	1.01
	Number (%)			X^2
Sex				
Male	10 (40.0%)	10 (40.0%)	12 (48.0%)	0.47
Female	15 (60%)	15 (60.0%)	13 (52.0%)	
Race				
Asian	3 (12.0%)	1 (4.0%)	1 (4.0%)	14.23
West/Central Asia/ Middle East	0 (0.0%)	0 (0.0%)	2 (8.0%)	
White	22 (88.0%)	21 (84.0%)	19 (76.0%)	
Interracial	0 (0.0%)	3 (12.0%)	3 (12.0%)	
Marital status				
Single never married	24 (96.0%)	22 (88.0%)	24 (96.0%)	3.11
Married/Common law	0 (0.0%)	2 (8.0%)	1 (4.0%)	
Living with significant other	1 (4.0%)	1 (4.0%)	0 (0.0%)	
Currently working				
Yes, full time	6 (24.0%)	6 (24.0%)	1 (4.2%)	7.97
Yes, half time	3 (12.0%)	5 (20.0%)	7 (29.2%)	
No, have in last year	6 (24.0%)	6 (24.0%)	10 (41.7%)	
No, have not in last year	10 (40.0%)	8 (32.0%)	6 (25.0%)	
Currently enrolled as a student	22 (88.0%)	19 (76.0%)	20 (83.3%)	1.26