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Depression and clinical high-risk states: Baseline presentation of depressed vs. non-depressed participants in the NAPLS-2 cohort

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ABSTRACT

Depressed mood appears to be highly prevalent in clinical high risk (CHR) samples. However, many prior CHR studies utilize modest size samples and do not report on the specific impact of depression on CHR symptoms. The aim of the current paper is to investigate the prevalence of depressive disorders and the impact of lifetime depression on baseline clinical presentation and longitudinal outcomes in a large cohort of individuals meeting CHR criteria in the second phase of the North American Prodrome Longitudinal Study (NAPLS-2). Depression was assessed both categorically (via DSM-IV-TR diagnoses) and symptomatically (using a clinician-rated scale of depressive symptoms) within a sample of 764 individuals at CHR and 279 controls. Current and lifetime depressive disorders were highly prevalent (60%) in this sample. Depression diagnoses were associated with more pronounced negative and general symptoms; individuals with remitted depression had significantly less severe negative, disorganized, and general symptoms and better social and role functioning relative to those with current depression. Current mood disturbance, as measured by scores on a clinician-rated symptom scale, contributed beyond the impact of positive and negative symptoms to impairments in social functioning. Both symptomatic and diagnostic baseline depression was significantly associated with decreased likelihood of remission from CHR status; however depression did not differentially distinguish persistent CHR status from transition to psychosis at follow-up. These findings suggest that depressed mood may function as a marker of poor prognosis in CHR, yet effective treatment of depression within this population can yield improvements in symptoms and functioning.

1. Introduction

Interest in early detection and prevention of schizophrenia and other psychotic disorders has focused attention on teenagers and young adults who may be at risk of developing a psychotic illness. Identifying predictors and mechanisms of transition to psychosis among individuals deemed to be at clinical high risk (CHR) for psychosis is necessary for the development of effective early interventions. Identification and intervention early in the course of psychosis appears to maximize treatment effectiveness and quality of life (Marshall et al., 2005; Woodberry et al., 2016b).

Although criteria for CHR states focus mainly on attenuated psychotic symptoms, depressed mood appears to be highly prevalent in CHR samples. One meta-analysis found that 41% of CHR individuals meet DSM-IV criteria for a depressive disorder (Fusar-Poli et al., 2014). In the first phase of the North American Prodrome Longitudinal Study (NAPLS-1) sample of 377 CHR participants, 55% met DSM-IV criteria for a non-bipolar mood disorder (Woods et al., 2009). The prevalence of depressive symptoms such as dysphoric mood and suicidal ideation in CHR cohorts is likely far higher than the prevalence of diagnosed

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depressive disorders (Hui et al., 2013). Dysphoric mood appears to contribute uniquely to impairments in social and role functioning (Fulford et al., 2013), and has been associated with poor prognosis (though not necessarily increased conversion to psychosis) within CHR cohorts (Falkenberg et al., 2015; Lim et al., 2015; Schlosser et al., 2012). Thus depression appears to constitute a central clinical feature and risk factor within this already vulnerable population.

The high prevalence of depressed mood within CHR cohorts complicates the conceptualization of CHR youth as primarily 'prodromal' to non-affective psychotic disorders. One theory is that depression is a common but ultimately transient feature of the early course of schizophrenia (Häfner et al., 2005). In a review of 23 studies involving 2182 participants at risk for psychosis, only 11% of those who transitioned to psychosis received an outcome diagnosis of affective psychosis (i.e. depression [5%] or bipolar disorder [6%] with psychotic features), and an additional 8% developed schizoaffective disorder (Fusar-Poli et al., 2013). This low proportion of affective disorder outcomes among converters could suggest that although depression is common during a prodromal phase of illness, mood dysfunction remains secondary to emerging psychosis for those at highest risk for conversion.

A different hypothesis holds that the prevalence of depression is high in CHR samples because of the inclusion of individuals with primarily affective disorders who experience waxing and waning subthreshold psychotic symptoms over the course of mood episodes (Sullivan et al., 2014; Wigman et al., 2012); attenuated psychotic symptoms among such individuals may never progress to frank psychosis. Additionally, psychosis occurring in the context of anxiety and depressive disorders may be more common than previously thought (Koyanagi et al., 2016; Wigman et al., 2012). A third potential explanation for the high prevalence of depression in CHR samples is that depressive appraisals of positive symptoms, reduced functioning due to negative symptoms, and/or stigma related to emerging mental illness could trigger depression for individuals experiencing subthreshold psychosis (Krabbendam et al., 2005). In this scenario, depressive mood that *follows* the onset of attenuated psychotic symptoms further increases the risk of poor outcome through the interactive effects of thought disorder and affect dysregulation; this "negative appraisal" model also aligns with the common clinical observation of depression among patients dealing with shame and loss following a first psychotic episode (Upthegrove et al., 2014). A related conceptualization of the role of depression in psychosis is that depressive symptoms (e.g., dysphoric mood, low self-worth, negative evaluations) exacerbate existing psychotic disorders by worsening distress, pre-occupation, and conviction related to delusional experiences (Smith et al., 2006; Vorontsova et al., 2013); this may be mechanistically related to abnormalities in limbic-prefrontal activity and connectivity observed in schizophrenia spectrum disorders (Phillips and Seidman, 2008). Finally, given evidence for shared genetic etiology (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), simultaneous emergence of depressive and psychotic symptoms during adolescence may represent a phenotype that is poorly captured by our current nosologic system (Murray and Jones, 2012; Smoller, 2013). In this model, depressed mood may be an intrinsic feature of psychosis even among individuals with "non-affective" or "primary" psychotic disorders (Stochl et al., 2015). The CHR construct likely reflects a heterogeneous population that includes individuals at-risk for worsening psychosis, patients already manifesting the full expression of an affective illness, as well as persons with both symptomatic manifestations.

Despite the body of recent literature describing the prevalence of depression in CHR population, the specific influence of depression on CHR symptom presentation, and the role of depression as a prognostic marker within CHR, is poorly understood. Many prior CHR studies utilize small or modest size samples and do not report on the specific associations between depression and attenuated psychosis symptoms. The aim of the current paper is to investigate the prevalence of depressive disorders and the impact of depression on baseline clinical presentation and CHR-status outcomes in the largest cohort of individuals meeting criteria for a CHR syndrome studied to date (NAPLS-2). We also wish to examine whether the impact of depression on symptoms and functioning is better explained by an altered mood "state" vs. a persistent subgroup "trait" model. Informed by models emphasizing shared etiology of mood and psychotic disorders as well as models positing an interactive effect in which psychotic and mood symptoms are seen as mutually exacerbating, we hypothesize that depression is highly prevalent in this CHR sample relative to the control sample, and that CHR participants with a depressive disorder will experience more severe positive and negative symptoms than CHR participants with no depression. An additional exploratory aim is to examine whether the presence of baseline depression may heighten risk for conversion to psychosis over time.

2. Methods

2.1. Sample

The NAPLS-2 sample comprises 764 help-seeking teens and young adults ages 12–35, and 279 controls. Participants were recruited across the eight sites between January 2009 and March 2013. Referrals to the study were made by health care providers, community mental health practitioners, schools, and self/family inquiries. Inclusion/exclusion criteria for the CHR group were: participants met criteria of a prodromal syndrome (COPS) per the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan et al., 2010), or were under age 19 and met criteria for schizotypal personality disorder (SPD). Participants could not meet criteria for a current or lifetime Axis I psychotic disorder (including affective psychoses). Other exclusion criteria were estimated IQ < 70, a central nervous system disorder, or substance dependence in the past 6 months. CHR participants could be included if they met DSM-IV criteria for any other non-psychotic disorder, as long as the disorder did not clearly account for the individual's prodromal symptoms. Control subjects could not meet criteria for any prodromal syndrome, any current or past psychotic disorder, or a Cluster A personality disorder. They could not have a family history (in first-degree relatives) of any psychotic disorder or any other disorder involving psychotic symptoms.

2.2. Baseline clinical measures

2.2.1. Structured Clinical Interview for Psychosis-Risk Syndromes (SIPS)

The SIPS is a semi-structured interview targeting interviewees' experiences of attenuated symptoms and other indicators of psychosis risk (McGlashan et al., 2010; Miller et al., 1999). The SIPS contains probes and rating conventions for 19 symptom constructs, referred to as the Scale of Psychosis-Risk Symptoms or "SOPS." Items sum to four symptom subscales (positive, negative, disorganized, and general). Each item is rated by the interviewing clinician on a Likert-style scale ranging from zero to six. Reliability was assessed annually based on a video-taped interview. Intraclass correlations, over 4 years, for the total SOPS scores ranged from 0.82 to 0.93 (Addington et al., 2015). The SIPS was administered at baseline and at six, twelve, eighteen, and twenty-four months after study entry.

At follow-up assessments, conversion to psychosis was defined by SIPS presence of psychosis (POPS) criteria (McGlashan et al., 2010). Remission from CHR was defined by failure to meet any of the SIPS psychosis risk syndrome criteria. At follow-up assessments, individuals with "persistent CHR" were those who did not convert to psychosis or remit but continued to experience positive symptoms at a SIPS level of 3–5 even if their symptoms showed no increase in the past year (see Addington et al., 2015).

2.2.2. Structured Clinical Interview for the DSM-IV (SCID-IV)

The structured clinical interview for DSM-IV (SCID) (First, 1995) was used to assess current and lifetime depression as well as other Axis 1 disorders.

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