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Duration of attenuated positive and negative symptoms in individuals at clinical high risk: Associations with risk of conversion to psychosis and functional outcome

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ABSTRACT

Research in individuals at clinical high-risk (CHR) for psychosis has focused on subjects with no more than 12 months of present or worsened attenuated positive symptoms. However, the impact of long duration attenuated positive and/or negative prodromal symptoms on outcomes is unclear. Seventy-six CHR subjects with attenuated positive symptoms and at least moderate severity level negative symptoms rated on the Scale of Prodromal Symptoms (SOPS) were prospectively followed for a mean of 3.0 ± 1.6 years. Social and Role functioning was assessed with the Global Functioning: Social and Role scales. Correlations between attenuated positive and negative symptom duration and severity and conversion to psychosis and functional outcomes were analyzed. The average onset of SOPS rated negative symptoms (M = 53.24 months, SD = 48.90, median = 37.27) was approximately twelve months prior to the emergence of attenuated positive symptom (M = 40.15 months, SD = 40.33, median = 24.77, $P < 0.05$). More severe positive symptoms ($P = 0.004$), but not longer duration of positive ($P = 0.412$) or negative ($P = 0.754$) symptoms, predicted conversion to psychosis. Neither positive symptom duration ($P = 0.181$) nor severity ($P = 0.469$) predicted role or social functioning at study endpoint. Conversely, longer negative symptom duration predicted poor social functioning ($P = 0.004$). Overall, our findings suggest that the severity of attenuated positive symptoms at baseline may be more important than symptom duration for determining individuals at increased risk of developing psychosis. In contrast, long-standing negative symptoms may be associated with persistent social difficulties and therefore have an important position in the treatment of disability.

Interventions designed to prevent psychosis by starting treatment during the prodromal (or pre-illness) stage were based on the assumption that the longer early symptoms were present, the more severe the underlying illness and risk for leading to psychosis (McGlashan, 1998, 1999; McGlashan and Johannessen, 1996). The prevention assumption was derived from the notion that in already fully psychotic patients, the duration of untreated symptoms was related to prognosis in general, and that the earlier treatment was started after onset, the better the outcome (McGorry et al., 2007). While there has been evidence to support the latter (Boonstra et al., 2012; Bottlender et al., 2003; Buchanan, 2007; Keshavan et al., 2003; Perkins et al., 2005), there are few findings to support the pre-illness association between a longer symptom duration and increased symptom severity leading to full-blown psychosis. The current assumption is that accurately identifying individuals at clinical high-risk [(CHR) also called ultra high risk (UHR), or at-risk mental state (ARMS)] of developing psychosis may provide an opportunity to reduce the duration of the untreated illness by targeting the first appearance of subtle (i.e., attenuated) forms of positive and negative symptoms (Cornblatt et al., 2003; Yung and McGorry, 1996; Yung et al., 1996). However, there is little information on the impact of long duration attenuated positive and

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negative symptoms on the severity of prodromal symptoms or conversion to full-blown psychosis and functional outcomes. Given the possibility that long-term outcomes may be improved by reducing the duration of prodromal symptoms (Keshavan et al., 2003), this information may provide new insights for establishing effective early intervention programs (Yung and McGorry, 1996).

The few prospective studies with individuals at CHR that have examined the duration of prodromal symptoms prior to study entry have yielded mixed results (Chung et al., 2010; Fusar-Poli et al., 2009; Yung et al., 2003, 2007). For example, an earlier study by Yung and colleagues (Yung et al., 2003) found that a longer duration of attenuated positive symptoms increased the likelihood of conversion to psychosis. CHR individuals who developed psychosis had a longer time between the onset of positive symptoms and first contact with a prodromal service compared to those who did not (2.5 vs. 0.9 years), suggesting that shortening the window between early symptom onset and first contact may delay or reduce likelihood of developing psychosis. In fact, a reduction in the time between the onset of attenuated positive symptoms and first contact may be partially responsible for a decline in conversion rates in recent CHR cohorts (Yung et al., 2007). However, a recent study by Chung et al. (2010) found no relationship between the duration and severity of attenuated positive symptoms in CHR individuals, making it difficult to draw any conclusions regarding the relationship between attenuated positive symptoms and outcome.

Along with positive symptom duration, there is some evidence from patients with schizophrenia that longer duration negative symptoms may adversely impact functional outcomes (Choi et al., 2009; Cuesta et al., 2012; Murphy et al., 2008). In contrast to positive symptoms, negative symptoms (i.e., social anhedonia, avolition) are now understood as most likely to begin early in development and pre-date psychosis by many years, with positive symptoms appearing in relatively later stages of the illness (Haas and Sweeney, 1992; Häfner, 2000; 1999; 2013; 2003; Iyer et al., 2008; Tan and Ang, 2001). This trajectory would imply that a longer duration of attenuated negative symptoms would relate to increased functional impairments in CHR individuals. Surprisingly, however, no study to date has investigated a relationship between the duration of negative symptoms and outcome in this vulnerable population. Given that early declines in social functioning and academic performance have a prominent role in determining functional outcome (Carrión et al., 2011, 2013; Cornblatt et al., 2012), establishing the onset and time course of negative symptoms before the emergence of full-blown psychosis in individuals at CHR for psychosis may have important implications for the treatment and prevention of long-term functional disability. While positive and negative symptoms are related to the disease process, the relative onset of attenuated positive symptoms and negative symptoms may indicate differing stages of symptom progression (Lencz et al., 2004). Along the same lines, attenuated positive and negative symptom duration may be differentially related to the risk of psychosis onset and poor functional outcomes, indicating that different stages of the prodrome and different levels of attenuated positive symptoms and/or clinically relevant negative symptoms may require different interventions (Cornblatt et al., 2003).

The goal of the present study was therefore to explore the severity and duration of attenuated positive symptoms and negative symptoms present at study entry and determine the association between higher symptom severity and longer symptom duration and the risk of conversion to psychosis and functional outcomes in a prospective sample of individuals at CHR for psychosis. In the current study, individuals were included only if they exhibited attenuated positive symptoms at clinically significant severity levels as defined by the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2003, 2002, 1999). In contrast to most CHR studies, duration of symptoms was treated as a continuous variable and was not limited to an onset or worsening over the year prior to baseline, as specified by the criteria in standard use (Correll et al., 2010). Based on prior findings, we hypothesized the following: (1) Negative symptoms would precede the onset of attenuated positive symptoms; (2) Longer duration attenuated positive symptoms would be related to a higher likelihood of conversion to full-blown psychosis; and (3) A longer duration of negative symptoms would be related to an increased likelihood of poorer functioning at study outcome rather than conversion to psychosis.

1. Methods and materials

1.1. Participants

The Recognition and Prevention (RAP) program is an ongoing longitudinal study of treatment-seeking adolescents and young adults considered to be at CHR for psychosis initiated in 1998 and funded by the National Institute of Mental Health in 2000. This article reports data for participants recruited during Phase 1 (2000–2006) of the study. Patient referrals were made to the RAP Program by affiliated outpatient and inpatient psychiatry departments, local mental health providers, school psychologists or counselors, or were self-referred. All procedures were approved by the Institutional Review Board at Northwell Health (formerly the North Shore-Long Island Jewish Health System). Written informed consent (with assent from participants under 18) was obtained from all participants.

The original intake sample consisted of 101 participants that met criteria for Clinical High-Risk, Positive (CHR+) derived from the Scale of Prodromal Symptoms (SOPS) with its companion interview the SIPS (Miller et al., 2003, 2002, 1999). Inclusion criteria were based on the presence of one or more moderate, moderately severe, or severe (scores of 3, 4, or 5) SOPS rated (scale of 0–6) attenuated positive symptoms. A score of 6 (severe and psychotic) on any item was exclusionary for the CHR group. Although not used as entry criteria, in addition to the positive symptoms, CHR+ subjects also received ratings on the SOPS Negative Symptom scale: 1. Social Anhedonia, 2. Avolition, 3. Expression of emotion, 4. Experience of emotions and self, 5. Ideational richness, and 6. Occupational Functioning. Additional inclusion criteria required participants to be between the ages of 12 and 22 years. Exclusion criteria for all participants included: (1) Schizophrenia-spectrum diagnosis; (2) Non-English speaking; (3) A medical or neurological disorder; (3) Estimated IQ < 70. Detailed sample characteristics, including full demographics and clinical characteristics are presented elsewhere (Cornblatt et al., 2015).

Symptom onset was calculated relative to the baseline assessment date. In most cases specific dates were obtained from the SIPS interview in which time of first onset the prodromal symptom is estimated from a retrospective account and logged on the SOPS summary sheet located at the end of the SIPS. Informant and patient interview versions were used to provide the most accurate date of onset. In the cases where dates were not recorded on the SOPS summary sheet, clinician based best-estimates were made by extensive review of all available intake information. Inconsistent reports from the subject and family members were reconciled by consensus based on all available information. Only attenuated positive symptoms rated at a moderate, moderately severe, or severe (scores of 3, 4, or 5) level and negative symptoms rated at a moderate, moderately severe, severe, or extreme (scores of 3–6) level were used for determining symptom onsets (i.e., symptoms that met CHR criteria or were at least at a “prodromal” level of intensity).