Clinical and functional characteristics of youth at clinical high-risk for psychosis who do not transition to psychosis

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Abstract

Background. Much of the interest in youth at clinical high risk (CHR) of psychosis has been in understanding conversion. Recent literature has suggested that less than 25% of those who meet established criteria for being at CHR of psychosis go on to develop a psychotic illness. However, little is known about the outcome of those who do not make the transition to psychosis. The aim of this paper was to examine clinical symptoms and functioning in the second North American Prodrome Longitudinal Study (NAPLS 2) of those individuals whose by the end of 2 years in the study had not developed psychosis.

Methods. In NAPLS-2 278 CHR participants completed 2-year follow-ups and had not made the transition to psychosis. At 2-years the sample was divided into three groups – those whose symptoms were in remission, those who were still symptomatic and those whose symptoms had become more severe.

Results. There was no difference between those who remitted early in the study compared with those who remitted at one or 2 years. At 2-years, those in remission had fewer symptoms and improved functioning compared with the two symptomatic groups. However, all three groups had poorer social functioning and cognition than healthy controls.

Conclusions. A detailed examination of the clinical and functional outcomes of those who did not make the transition to psychosis did not contribute to predicting who may make the transition or who may have an earlier remission of attenuated psychotic symptoms.

Introduction

Over the past two decades, there has been an international attempt to better understand and identify the early stages of psychosis (McGorry, 2015). Reliable criteria have been developed (McGlashan *et al.*, 2010) which has enabled researchers to prospectively follow individuals considered to be at clinical high risk (CHR) of psychosis, with the goal of being able to distinguish differences between those who go on to develop psychosis and those who do not. However, despite advances in this research, nearly two-thirds of these individuals who meet CHR criteria will not go on to develop a psychotic illness (Fusar-Poli *et al.*, 2012*a*). This has led to an increase in interest regarding the outcome of CHR individuals who do not make the transition to psychosis. A recent meta-analysis has shown that over a 2-year follow-up approximately 73% of recruited CHR individuals did not convert to psychosis, and that of these individuals, about 43% fully remitted from their attenuated psychotic symptoms (APS) (Simon *et al.*, 2013). Since this meta-analysis, a few other studies have attempted to better understand the outcome of those who do not make the transition to psychosis. Armando *et al.* (2015) reported that in their small sample of children aged 9–17, they found that only the non-converters who remitted from CHR status improved on functioning. Additionally, although there were no variables that predicted remission, the absence of unusual

thought content and lower score on disorganized symptoms were related to better outcome (Armando *et al.*, 2015). Typically, remission has referred to remission of APS severity. However, a recent publication from Korea found that when only APS was considered the remission rate was 56% but when improvement in functioning was added only 39.7% were in remission (Lee *et al.*, 2014).

There has been some interest in better understanding the presence of poor functioning and comorbid psychopathology amongst those who do not go on to convert to psychosis. In an earlier paper with our first cohort in the North American Prodrome Longitudinal Study, we reported that there was significant poor functioning even for those who had remission of APS (Addington *et al.*, 2011). In the OASIS study, in the UK, 71.6% had not made the transition to psychosis (Rutigliano *et al.*, 2016). After a 6-year follow-up, 28.3% reported APS, 45.4% had a functional impairment and 56.8% had at least one co-morbid disorder at follow-up (Rutigliano *et al.*, 2016). Interestingly if a disorder was present at baseline, 61.5% had persistence of it at follow-up. In the PACE follow-up of 2–14 years, Lin *et al* reported that of those who had not made the transition to psychosis, 28.3% had persistent APS, and 68% had a non-psychotic disorder, typically depression and/or anxiety (Lin *et al.*, 2015).

The present study, the second North American Prodrome Longitudinal Study (NAPLS 2) aimed to add to the body of existing research on the outcome of individuals who do not convert to psychosis. However, we will further differentiate those who do not make a transition into three groups based on 24-month symptom ratings: (1) those in remission, determined by scores ≤2 on all five APS on The Scale of Psychosis-risk Symptoms (SOPS); (2) symptomatic, determined by still having a rating of 3–5 on any one of the five APS on the SOPS; and (3) prodromal progression, determined by continuing to meet the Criteria of Psychosis-risk Syndromes (COPS). We will attempt to address some of the limitations of previous research in that we will include information on medications as well as provide more specific (*v.* global) measures of social and role functioning.

We hypothesize that among the non-converter sample, those who continue to evidence APS will have increased psychopathology and poorer social, role and cognitive functioning compared with those who remit from their symptoms.

Methods

Participants

All participants are part of the second North American Prodrome Longitudinal Study (NAPLS-2). Participants in this study were help-seeking and were recruited through various resources. Most of the participants were referred from family physicians, mental health clinics, social services, and school and college counsellors. Many self-referred in response to community educational efforts. Recruitment efforts have been described in detail elsewhere (Addington *et al.*, 2012). The NAPLS-2 sample consisted of a total of 764 youth at CHR (436 males, 328 females) and 279 healthy controls (HC) (141 males, 138 females) recruited across the eight NAPLS-2 sites. All participants were assessed with the Structured Interview for Psychosis-risk Syndromes (SIPS) (McGlashan *et al.*, 2010) to determine if they met the COPS, i.e. one or more of the following high risk syndromes: APS syndrome (APSS); brief intermittent psychotic symptoms syndrome; or genetic risk and deterioration syndrome. Of the

total 764 NAPLS-2 sample, 86 made the transition to psychosis, 390 did not complete the 2-year study (see Stowkowy *et al.*, 2017), 10 did stay for 2 years but had minimal 2-year data and 278 CHR had not made the transition to psychosis and had completed 2 years of follow-up and thus will be the sample described in this paper. Of the 278 who completed 2 years, 66% completed all five assessments, 24% missed one assessment, 5% missed two and 5% missed three. In total 143 HCs completed the 2-year follow-up. Participants were between 12 and 35 years of age. Exclusion criteria included meeting criteria for any current or past axis I psychotic disorder, IQ less than 70, or past or current history of a clinically significant central nervous system disorder. Exclusion criteria for HCs was a first-degree relative with a current or past psychotic disorder.

Measures

The Structured Interview for SIPS (McGlashan *et al.*, 2010) was used to determine whether an individual met COPS criteria. The Scale of Psychosis-risk Symptoms (SOPS) was used to rate the severity of APS. The SOPS consists of 19 items in four symptom domains (i.e. positive, negative, general, and disorganized symptoms).

The Structured Clinical Interview for DSM-IV (SCID) (First *et al.*, 1995) was used to determine the presence of current and past psychiatric diagnoses, including conversion to a psychotic disorder. Conversion to psychosis was determined by meeting the Presence of Psychotic Symptoms (POPS) (McGlashan *et al.*, 2010) criteria. The POPS require that at least one of the five SOPS APS had reached a psychotic level of intensity (rated 6) for a frequency of less than or equal to 1 h per day for 4 days per week, or that psychotic symptoms were seriously impacting functioning (e.g. disorganizing or dangerous to self or others).

Four different clinical outcomes were determined at each of the follow-up assessments. These were: (1) remission is defined as remission from all CHR syndromes, i.e. participants had to have scores of 2 or less on all five positive symptoms on the SOPS scale; (2) symptomatic but not currently meeting criteria for a prodromal risk syndrome. This means that participants should have ratings of 3–5 on any one of the five positive symptoms on the SOPS but the symptoms had neither worsened or begun in the previous 12 months; (3) prodromal progression which meant that the participant at a given assessment would currently meet criteria for APSS; that is one of the five positive symptoms had to have begun or increased in the previous 12 months and (4) psychotic which would mean that the participant currently met criteria for a psychotic disorder or evidencing scores of 6 on one or more positive symptoms of the SOPS , i.e. one of the positive symptoms had reached psychotic intensity (McGlashan *et al.*, 2010).

The functional outcome measures included the Global Functioning-Social (GF:S) and Role (GF:R) scales. Both scales were developed specifically to address functioning in youth at risk of psychosis and are psychometrically sound, with good construct validity (Cornblatt *et al.*, 2007).

For cognition tasks from the MATRICS battery (Nuechterlein *et al.*, 2008) that reflected areas of cognition most often seen as problematic in CHR such as speed of processing, verbal learning and working memory (Fusar-Poli *et al.*, 2012*b*; Seidman *et al.*, 2016) were chosen. These include Trails A, letter-number span, the BACS and the Hopkins Verbal Learning Test.

Procedures

Both CHR individuals and HCs were recruited for the study, which was approved by the Institutional Review Boards of all eight NAPLS-2 sites. Written informed consent, including parental consent, was obtained from all adult participants and parents/guardians of minors.

After the initial screening assessment that included administering the SCID and the SIPS, vignettes were developed for each CHR participant to obtain a consensus decision on meeting COPS criteria. The APS rated on the SOPS are described at length and include both recent and longstanding symptoms. The vignettes are written so that raters from all eight sites can review the information under each symptom category and provide a reliable rating. Once approved at the site level, the vignette is presented on a conference call for a consensus decision on the symptom ratings as well as the diagnosis. The NAPLS-2 consensus call, chaired by JA, was held once a week and attended by the clinical raters from each of the eight sites. Submitted vignettes are individually reviewed and a consensus must be reached on each symptom rating, diagnosis and ultimate admission into the study. Clinical raters were experienced research clinicians. Gold standard post-training agreement on determining the prodromal diagnoses was excellent ($\kappa = 0.90$) (Addington *et al.*, 2012). Diagnostic interviews at all sites were conducted by trained raters. Data were collected at five-time points: baseline, 6-, 12-, 18- and 24-month follow-up.

Statistical analysis

One-way ANOVA was used to compare groups on all continuous variables. χ^2 tests were used to compare the groups on SCID diagnoses at both baseline and 24 months.

The analysis of medication differences was performed using SAS 9.4. We used the generalized estimating equations (GEE) models to determine the differences in the use of antipsychotics, antidepressants and anxiolytics across all assessments (baseline, 6, 12, 18 and 24 months) for four remitter groups (remission at 6 months, 12 months, 18 months and 24 months) as well as for the overall 3 groups (in remission, symptomatic and prodromal progression). The same analyses were used to compare the overall three groups on the use of non-pharmacological treatments.

Results

Of the total NAPLS 2 sample, 278 CHR had not made the transition to psychosis and had completed 2 years of follow-up. This is the sample described in this paper. Among these participants, 110 (39.57%) were in remission, 93 (33.45%) symptomatic, and 75 (26.98%) continued to meet criteria for APSS and thus are experiencing prodromal progression. Further examination of these groups across time showed that the symptomatic group was symptomatic across all follow-up assessments and that the prodromal progression group tended to meet prodromal progression or be symptomatic across all follow-up assessments. However, those in remission at 24 months could be divided into those who remitted at 6 months, at 12 months, 18 months and then 24 months. Once an individual remitted they typically remained in remission. We did, however, compare these four remission groups on all the variables under study. Differences were that the 12-month remitters had significantly lower ratings on the SOPS total positive symptoms compared with those who remitted at 24 months at baseline ($p < 0.05$) and at 24 months ($p < 0.01$) and at 24 months anxiety

disorders were more common in those who remitted at 18 and 24 months. See online Supplementary Tables S1 and S2. Thus, since there were not many differences among the remitters in symptoms, cognition, functioning and other disorders for all further analyses we have the remitters as one group.

Comparison of in-remission, symptomatic and prodromal progression groups

Demographics are presented in Table 1. There were no significant differences between the groups on any demographic variables.

We compared the three groups on symptoms at baseline and at 2-years. To avoid multiple comparisons, we only examined individual SOPS symptoms if the groups differed on any of the total scores. At baseline the prodromal progression group had significantly higher ratings on unusual thought content compared with the remission group and the symptomatic group had significantly higher ratings on suspiciousness compared with the remission group. Both the symptomatic and prodromal progression groups had significantly higher ratings on total positive symptoms than the remission group. The groups did not differ on any other of the SOPS symptom domains. Comparison of the three groups at 24 months demonstrated that both the symptomatic and prodromal progression groups had significantly higher ratings not only on positive symptoms as would be expected but on all SOPS domains. The remission group had significantly less total negative symptoms, and lower ratings on avolition and decreased expression of emotion than the other groups. The symptomatic and prodromal progression groups did not differ on any of the general symptoms or disorganized symptoms and received more severe ratings than the remission group. The one exception was impaired personal hygiene that was not a problem in any group. See Table 2.

Lifetime and current DSM-IV diagnoses were assessed at baseline and current diagnoses at 24 months. The most common diagnoses in all groups were depression and anxiety. The groups did not differ on lifetime diagnoses and the only diagnoses that the groups differed on at baseline was anxiety and post-traumatic stress disorder (PTSD). At the 2-year follow-up, the remission group had significantly fewer cases of depression and the symptomatic groups significantly more cases of anxiety. These results are presented in Table 3.

See online Supplementary Table S3 for frequencies of all diagnoses lifetime, baseline and 24 months. In addition, a comparison of DSM-IV diagnoses between the HCs and remitted participants revealed that those who had remitted in terms of APS still had increased comorbid diagnoses compared with HCs. See online Supplementary Table S4.

Table 4 shows that the groups did not differ at baseline on either role or social functioning nor at 24 months in role functioning. The remission group had improved social functioning at 24 months. Online Supplementary Table S5 shows that the groups did not differ on any of the cognitive tasks.

Since the remission group typically had improved functioning relative to the symptomatic and prodromal progression group, the three CHR groups were compared with the HC on social, role and neurocognitive functioning. All three CHR groups had significantly poorer ratings on both social and role functioning compared with HC. For neurocognition, the prodromal progression group had poorer ratings on 3 of the 4 neurocognitive tasks compared with the HC and on the 4th task, the remission and symptomatic groups had poorer scores. See Table 5.

Table 1. Demographic information

Variable	Remission $n = 110$	Symptomatic $n = 93$	Prodromal progression $n = 75$	Test statistic
	Mean (s.d.)			F
Age (years)	18.2 (4.3)	19.0 (3.9)	19.33 (5.0)	1.91
Years of education	11.06 (2.95)	11.66 (2.64)	11.53 (2.58)	1.31
Sex	N (%)			
Female	53 (48.2)	37 (39.8)	34 (45.3)	1.46
Male	57 (51.8)	56 (60.2)	41 (54.7)	
Race				
First nations/Indigenous American	2 (1.8)	1 (1.1)	2 (2.7)	0.87
Asian	7 (6.4)	7 (7.5)	5 (6.7)	
Black	20 (18.2)	20 (21.5)	13 (17.3)	
Caucasian	64 (58.2)	52 (55.9)	45 (60)	
Mixed Race	17 (15.4)	13 (14.0)	10 (13.3)	
Marital status				
Single, never married	105 (95.5)	91 (97.8)	72 (96.0)	0.71
Other	5 (4.5)	2 (2.2)	3 (4.0)	

Treatment comparisons

First, the 3 CHR groups were compared on their use of medication (antipsychotics, antidepressants and anxiolytics) over time. The remission group (remission at 6 months, 12 months, 18 months and 24 months) were also compared on their use of medication. There were no significant differences between any of the groups in their use of medication over the 2 years in the study. These results are presented in online Supplementary Tables S6 and S7. Psychosocial treatments included individual, family and group therapies, case-management and school counselling. There were no significant differences between any of the groups in their use of psychosocial treatments. See online Supplementary Table S8.

Discussion

Since the majority of CHR participants do not make the transition to psychosis, the purpose of this paper was to report on youth in the NAPLS 2 project who completed 2 years in the study but who did not make the transition to psychosis. This may be becoming more important since in the literature there seems to be a trend for declining transition rates. (Fusar-Poli *et al.*, 2012*a*; Riecher-Rossler and Studerus, 2017) Furthermore, since amongst those who do not make the transition there is a range of specific symptomatic outcomes, we wanted to examine sub-groups that included those who had a complete remission of APS, those who continued to have symptoms and those whose symptoms seemed to be increasing in severity. Of our sample that completed the 2-year follow-up without a transition approximately one third fell into each of these three groups. Our rates for the remission of APS for those who completed the study fit with other reports in the literature.

We first explored those who were in remission at 2-years. It seemed possible that perhaps there would be something we could learn about those who had a complete remission from

APS at 6 or even 12 months compared with those whose remission occurred later in the project but we were unable to find any clinical or functional variable that really differentiated these groups. Most notable was that the later remitters evidenced more anxiety disorders at 24 months which might have accounted for the longer time to remission. Those who remained symptomatic or whose symptoms increased tended to have higher ratings on APS at baseline and 2-years which is not surprising. They did, however, have increased symptoms overall, i.e. negative, disorganized and general symptoms, compared with remitters at 2-years, as well as more anxiety and mood diagnoses. This suggests that they are generally more symptomatic overall compared with those who remit.

An examination of social and role functioning demonstrated that although the remission group had somewhat improved social functioning at 2 years compared with the other CHR groups they were still functioning below the HC. Interestingly all CHR groups continued to have poorer role functioning than the HC. This suggests that perhaps poorer social and functioning may be independent of attenuated symptoms in those at CHR. A recent meta-analysis supports this possibility in that poor functioning in adolescence, in terms of education and employment accomplishments, was predictive of later CHR status (Fusar-Poli *et al.*, 2017).

For neurocognitive functioning, the speed of processing and working memory seemed to be the key functions that differentiated the symptomatic CHR groups from the others. In both schizophrenia and in those at CHR speed of processing and memory are key common neurocognitive deficits (Seidman *et al.*, 2016). However, recent publications have demonstrated that working memory and/or speed of processing can be predictive of later transition to psychosis, suggesting that these are the cognitive functions most likely to be impaired for those at CHR (Cornblatt *et al.*, 2015; Addington *et al.*, 2016; Cannon *et al.*, 2016) and perhaps ones that could be addressed in terms of remediation (Choi *et al.*, 2017).

Table 2. Group comparisons of symptoms at baseline & 24 months

Variable	In Remission $n = 110$	Symptomatic $n = 93$	Prodromal progression $n = 75$	Test statistic
	Mean (S.D.)			F
Baseline comparisons				
Total positive symptoms	10.70 (4.34)	12.41 (3.62)[a]	12.23 (4.13)[a]	5.40**
P1 – Unusual thought content	2.91 (1.48)	3.26 (1.13)	3.61 (1.36)[a]	6.24**
P2 – Suspiciousness	2.30 (1.57)	2.99 (1.28)[a]	2.71 (1.56)	5.59**
P3 – Grandiose ideas	0.91 (1.30)	1.19 (1.35)	1.09 (1.33)	1.20
P4 – Perceptual abnormalities	3.00 (1.51)	3.22 (1.26)	3.25 (1.55)	0.87
P5 – Disorganized thought	1.58 (1.41)	1.75 (1.34)	1.56 (1.53)	0.50
Total negative symptoms	11.67 (6.02)	12.26 (6.13)	11.81 (5.93)	0.25
Total general symptoms	8.72 (4.36)	9.39 (4.36)	8.75 (4.38)	0.70
Total disorganized symptoms	4.62 (3.04)	5.29 (3.58)	5.48 (3.20)	1.94
24 month comparisons				
Total positive symptoms	2.70 (2.10)	8.58 (3.57)[a]	9.85 (4.24)[a,b]	130.52****
P1 – Unusual thought content	0.70 (0.84)	2.27 (1.44)[a]	2.76 (1.65)[a,b]	65.24****
P2 – Suspiciousness	0.65 (0.80)	2.39 (1.18)[a]	2.43 (1.50)[a]	77.84****
P3 – Grandiose ideas	0.21 (0.54)	0.87 (1.16)[a]	0.91 (1.24)[a]	15.52****
P4 – Perceptual abnormalities	0.58 (0.81)	1.84 (1.45)[a]	2.59 (1.67)[a,b]	55.83****
P5 – Disorganized thought	0.56 (0.77)	1.22 (1.09)[a]	1.17 (1.11)[a]	13.82****
Total negative symptoms	5.99 (5.41)	8.84 (6.10)[a]	9.19 (5.39)[a]	9.49****
N1 – Social anhedonia	1.43 (1.63)	2.01 (1.76)[a]	1.69 (1.53)	3.15*
N2 – Avolition	1.25 (1.44)	1.94 (1.60)[a]	2.19 (1.74)[a]	8.99****
N3 – Expression of emotion	0.66 (1.12)	1.00 (1.44)	0.96 (1.23)	2.14
N4 – Decreased exp. of emo. & self	0.49 (0.93)	1.01 (1.40)[a]	0.97 (1.46)[a]	5.37**
N5 – Decreased ideational richness	0.55 (0.92)	0.66 (0.96)	0.84 (1.04)	2.09
N6 – Occupational functioning	1.61 (2.17)	2.23 (2.15)	2.53 (2.28)[a]	4.35*
Total general symptoms	3.47 (3.43)	6.72 (3.94)[a]	7.73 (4.68)[a]	30.26****
G1 – Sleep disturbance	1.18 (1.45)	1.73 (1.45)[a]	2.20 (1.74)[a]	10.05****
G2 – Dysphoric mood	1.17 (1.34)	2.39 (1.56)[a]	2.71 (2.06)[a]	23.75****
G3 – Motor disturbances	0.20 (0.56)	0.53 (0.86)[a]	0.52 (0.88)[a]	6.09**
G4 – Impaired tol. to normal stress	0.92 (1.30)	2.08 (1.73)[a]	2.31 (1.83)[a]	20.92****
Total disorganized symptoms	2.15 (2.10)	3.90 (2.78)[a]	4.40 (3.13)[a]	19.43****
D1 – Odd behaviour or appearance	0.36 (0.75)	0.76 (1.10)[a]	0.64 (1.00)	4.78**
D2 – Bizarre thinking	0.13 (0.47)	0.69 (0.92)[a]	0.84 (1.19)[a]	18.15****
D3 – Trouble with focus and atten.	1.26 (1.25)	1.88 (1.18)[a]	2.20 (1.29)[a]	13.85****
D4 – Impairment in personal hygiene	0.39 (0.79)	0.57 (1.10)	0.72 (1.30)	2.24

[a]Significantly different from remission group.
[b]Significantly different from symptomatic group.
*$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$.

Thus, the more severe the APS the more likely there was increased general symptoms, the presence of DSM-IV mood or anxiety disorders, poorer social functioning and poorer neurocognitive functioning. Interestingly, we did not see many differences between the prodromal progression group and the symptomatic group. The key difference was that the prodromal progression group had marginally increased APS at follow-up and the symptomatic group had more anxiety. Since the groups did not differ at baseline it is possible that the groups only differed in the stability of their APS rather than the prodromal progression group being the more severe of the two symptomatic groups. The symptomatic group continues to present with APS throughout the 2 years whereas for the prodromal progression group, there was more evidence of fluctuating symptoms. In order to meet prodromal criteria at 24 months, for some participants, there may have been an increase in symptoms over time, for others perhaps a new

Table 3. Group comparisons of DSM-IV disorders

Variable	In remission	Symptomatic	Prodromal progression	χ^2
Lifetime diagnoses at baseline	N = 110 (%)	N = 93 (%)	N = 75 (%)	
Any depression disorders	36 (32.7)	28 (30.4)	31 (41.3)	2.38
Post-traumatic stress disorder	1 (0.9)	3 (1.1)	2 (2.7)	1.43
Any anxiety disorder	20 (18.2)	29 (31.5)	18 (24.0)	4.87
Attention-deficit hyperactivity disorder	14 (12.7)	10 (10.9)	9 (12.0)	0.17
Other disorders	41 (37.2)	34 (36.9)	31 (41.4)	3.77
Diagnoses at baseline				
Any depression disorders	33 (30.0)	32 (34.8)	26 (34.7)	0.67
Post-traumatic stress disorder	0 (0.0)	0 (0.0)	5 (6.7)	13.71**
Any anxiety disorder	30 (27.3)	50 (54.3)	34 (29.8)	15.91****
Attention-deficit hyperactivity disorder	17 (15.5)	16 (17.4)	10 (13.3)	0.52
Other disorders	39 (35.5)	30 (32.7)	27 (34.5)	4.04
Diagnoses at 24 months	N = 100 (%)	N = 84 (%)	N = 63 (%)	
Any depression disorder	21 (21.0)	26 (31.0)	25 (39.7)	6.73*
Post-traumatic stress disorder	1 (1.0)	0 (0.0)	3 (4.8)	5.53
Any anxiety disorder	25 (25.0)	37 (44.0)	24 (38.1)	7.70*
Attention-deficit hyperactivity disorder	11 (11.0)	15 (17.9)	4 (6.3)	4.68
Other disorders	21 (21.0)	20 (23.9)	34 (54.0)	11.74

*$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$.
Note: Anxiety disorder included all anxiety disorders except Obsessive-Compulsive Disorder (OCD) and Post-traumatic Stress Disorder (PTSD). Other disorders include all other disorders – see online Supplementary Table S1.

Table 4. Group comparisons of baseline and 24 month social and role functioning

Variable	In remission	Symptomatic	Prodromal progression	Test statistic
		Mean (s.d.)		F
Baseline comparisons	n = 110	n = 93	n = 75	
Global functioning: Social	6.16 (1.66)	6.04 (1.51)	6.35 (1.47)	0.79
Global functioning: Role	6.22 (2.12)	6.16 (2.22)	6.01 (2.23)	0.20
24 month comparisons	n = 109	n = 91	n = 75	
Global functioning: Social	7.20 (1.51)	6.56 (1.52)[a]	6.68 (1.36)[a]	5.37**
Global functioning: Role	6.68 (2.33)	6.42 (2.55)	5.89 (2.39)	2.35

[a]Significantly different from remission group.
**$p < 0.01$.

symptom developed and for others there would have been some improvement and then a return to a previous level.

It has been suggested that the initial presentation of CHR symptoms might actually be predictive of other disorders (van and Guloksuz, 2017). However, although these CHR individuals do present with a range of other disorders, in particular, mood and anxiety, this does not seem to be the case in this data set (Webb et al., 2015; Woods et al., 2018) or in in other samples (Lin et al., 2015; Fusar-Poli et al., 2016). Lin et al in their longitudinal study of non-transitioned cases reported in their follow-up period 68% experienced a non-psychotic disorder and that 52% continued to experience a persistent or recurrent disorder (Lin et al., 2015). Thus, as a general summary it seems as if, at least clinically, after presenting with a prodromal syndrome those who do not make the transition to psychosis are on a continuum of severity of APS, that is accompanied by, although to a lesser degree, severity of poor social, role and neurocognitive functioning. Of course, it is possible that individuals in the symptomatic or prodromal progression groups may experience a later transition, even though most transitions occur within the first 2 years there are reports of later transitions (Cannon et al., 2008; Nelson et al., 2013).

Another consideration is that these individuals who remain symptomatic fit with the psychosis proneness- persistence-impairment model proposed by van Os et al. (2009). Our symptomatic and prodromal progression individuals may well be similar to those described as initially presenting with a transitory developmental expression of psychosis that becomes abnormally persistent and subsequently clinically relevant. In this model, persistence depends on the degree of environmental risk

Table 5. Social and role functioning and neurocognition comparisons between groups and HC's at 24-months

Variable	HCs n = 143[a]	In remission n = 110[a]	Symptomatic n = 93[a]	Prodromal progression n = 75[a]	Test statistic
			Mean (S.D.)		F
Functioning					
GF: Social	8.73 (0.90)	7.20 (1.51)[b]	6.56 (1.52)[b,c]	6.68 (1.36)[b,c]	70.21****
GF: Role	8.62 (0.97)	6.68 (2.33)[b]	6.42 (2.55)[b]	5.89 (2.39)[b]	39.99****
Neurocognition					
TMT A	24.15 (7.68)	25.44 (8.89)	26.75 (9.98)	30.57 (19.90)[b,c]	4.54**
BACS	66.89 (13.78)	61.69 (12.64)[b]	61.97 (15.46)	59.21 (15.53)[b]	5.07**
HVLT TOTAL	28.67 (3.86)	26.63 (5.03)[b]	26.73 (4.78)[b]	27.16 (3.93)	5.28***
LNS	16.85 (3.17)	15.67 (3.44)	15.44 (3.72)[b]	15.42 (3.70)[b]	4.21**

HCs, healthy controls; TMT, Trail Making Test; LNS, Letter-Number Span; BACS, Brief Assessment of Cognition in Schizophrenia; HVLT, Hopkins Verbal Learning Test.
[a]n may not add up for each measure due to missing data.
[b]Significantly different from healthy control group.
[c]Significantly different from in remission group.
**$p \leqslant 0.05$; ***$p \leqslant 0.001$; ****$p < 0.0001$.

to which the person is additionally exposed. Interestingly, in our sample we observed increased cannabis use, trauma and perceived discrimination compared with HC that did not necessarily predict transition to psychosis (Addington et al., 2013; Saleem et al., 2013; Buchy et al., 2015; Stowkowy et al., 2016).

The strength of this paper is that we could examine in a large cohort over a 2-year period a range of clinical outcomes for those who did not make the transition to psychosis. These clinical outcome groups were compared on a range of clinical and functional outcomes as well as treatment. There are several limitations to this study. First, the sample was only followed for 2 years which is typical of many other studies but to better address the issue of non-transition longer follow-ups are required. We do not know if once participants are no longer being followed if there would be a change in clinical outcome. Monitoring is often helpful for people especially knowing they have immediate contact should they experience a change. Secondly, it is possible that over the course of 2 years with dropouts that more of the healthy people might have dropped out. In a recent publication (Stowkowy et al., 2017) examining in detail dropouts from the NAPLS-2 project, we were unable to observe any clinical, functional or demographic variables that might indicate the likelihood of dropping out. Furthermore, our examinations of SOPS ratings suggested that at the time of dropout, dropouts had neither more nor less severe SOPS symptoms, ruling out the possibility that these CHR individuals leave the study because of either increased or improved symptoms. Thirdly, our first assessment occurred at 6 months it is possible that there might be a small subgroup of those who were in remission by 6 months who had a speedier remission and who may have improved ratings on the functional measures. Fourthly, we are unable to determine with confidence whether our prodromal progression group were given this designation due to an increase in severity or due to the appearance of a new symptom. Some participants had some improvement and then later had an increase in the symptoms. Fifthly, our comparison of the different groups was based on clinical or functional variables. There may be biological markers that might differentiate these different outcome groups more precisely and in a more meaningful way. Finally, we chose to pre-define our groups on clinical status at 2-years. It is possible that alternative approaches such as statistically identifying sub-groups with latent class analyses or machine learning may offer more information about the nature

of CHR syndromes. However, this current approach is more readily translatable into real-world settings.

In conclusion, detailed examination of clinical and functional outcomes of those who by 2-years do not make the transition to psychosis does not contribute to predicting who may make the transition to psychosis or who may have an earlier remission of APS. It is possible that there are other factors that might help this distinction but based on our current data it appears as if those who present with a prodromal syndrome of APS have an outcome that is on a continuum of severity. The implications are that this is a group that requires treatment albeit at different levels of intensity that would address the attenuated symptoms, mood and/or anxiety and functioning.

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