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Persistent Negative Symptoms in Youth at Clinical High Risk for Psychosis: A Longitudinal Study

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Abstract

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Contributors

Drs. Addington, Cannon, Cadenhead, Cornblatt, McGlashan, Perkins, Seidman, Tsuang, Woods, Walker, Mathalon, and Bearden were responsible for the design of the study and for the supervisions of all aspects of data collection. Mr. Devoe and Ms. Liu were responsible for the statistical analyses. Mr. Devoe wrote the initial manuscript. Dr. Addington was involved in writing the subsequent drafts of the manuscript. All authors listed were involved in the study design and have contributed to and approved the final manuscript.

Conflict of Interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study. Dr. Cannon and Dr. Mathalon report that they are consultants to Boerhinger Ingelheim Pharmaceuticals. Dr. Cannon reports that he is a consultant to Lundbeck A/S.

Background: Severity of negative symptoms has been associated with poor functioning, cognitive deficits, and defeatist beliefs in schizophrenia patients. However, one area that remains understudied is persistent negative symptoms (PNS). Negative symptoms, including PNS, have been observed in those at clinical high-risk (CHR) for psychosis. The aim of this study was to determine if PNS were associated with functioning, neurocognition, and defeatist beliefs in a CHR sample.

Method: CHR participants (n=764) were recruited for the North American Prodrome Longitudinal Study. Negative symptoms were rated on the Scale of Psychosis-risk Symptoms. Generalized linear mixed models for repeated measures were used to examine changes over time between and within groups (PNS vs non-PNS).

Results: The PNS group (n=67) had significant deficits in functioning at baseline, 6, 12, 18, and 24-months compared to the non-PNS group (n=673). Functioning improved over time in the non-PNS group, while functioning in the PNS group remained relatively stable and poor over a two-year period. A consistent trend emerged demonstrating higher defeatist beliefs in the PNS group; however, this result was lost when controlling for persistent depressive symptoms. There were no significant differences between the groups on neurocognition, social cognition, and transition to psychosis.

Conclusions: PNS exist in youth at CHR for psychosis, resulting in significant and persistent functional impairment, which remains when controlling for persistent depressive symptoms. PNS remain even in CHR youth who do not transition to psychosis. Thus, PNS may represent an unmet therapeutic need in CHR populations for which there are currently no effective treatments.

Keywords

persistent negative symptoms; clinical high risk; psychosis; functioning; negative-self schemas; defeatist beliefs

1. Introduction

Negative symptoms are a considerable cause of burden for schizophrenia patients, impacting both functioning and quality of life (Galderisi et al., 2018; Kirkpatrick et al., 2006). Although research has advanced our understanding of negative symptoms (Galderisi et al., 2018), one area that has remained relatively understudied is persistent negative symptoms (PNS, (Buchanan, 2007; Kirkpatrick et al., 2006). PNS are defined as clinically stable negative symptoms of moderate severity evident for an extended period of time, whilst controlling for potential sources of secondary negative symptoms (e.g., positive symptoms, extrapyramidal symptoms, or depression (Buchanan, 2007). Although PNS research is limited, it is very clear from existing research that patients with PNS exhibit increased functional deficits (Chang et al., 2011; Galderisi et al., 2013; Hovington et al., 2012; Malla et al., 2004; Puig et al., 2017; Üçok and Ergül, 2014), poorer quality of life (Edwards et al., 1999), greater cognitive deficits (Puig et al., 2017), and have a longer prodrome (Edwards et al., 1999) compared to schizophrenia patients without PNS. Fittingly, the NIMH-MATRICS [National Institute of Mental Health Measurement and Treatment Research to Improve Cognition in Schizophrenia] negative symptom consensus statement, identified PNS as an unmet therapeutic need in schizophrenia, for which longitudinal studies were identified as

being invaluable (Kirkpatrick et al., 2006). The relationship between negative symptoms and functional deficits in patients with schizophrenia has been well documented (Galderisi et al., 2018; Kirkpatrick et al., 2006), with deficits in functioning present long before the onset of illness (Carrion et al., 2013; Cornblatt et al., 2012). One potential mechanism that has been proposed for negative symptoms and functional deficits are maladaptive cognitions such as defeatist performance beliefs (Beck and Rector, 2005; Grant and Beck, 2009). The Beck model reasons that cognitions such as defeatist performance beliefs contribute to overall negative symptoms (e.g., amotivation and asociality) and functional deficits in schizophrenia (Strauss et al., 2015; Ventura et al., 2014). Several observational studies support this model and have found a relationship between negative beliefs and negative symptoms (Beck et al., 2013; Couture et al., 2011; Grant and Beck, 2009; Strauss et al., 2015; Ventura et al., 2014). A recent meta-analysis in schizophrenia studies (k=10) found a significant effect between defeatist performance beliefs and both negative symptoms and functional outcomes (Campellone et al., 2016). Furthermore, research examining pathways contributing to functional deficits in schizophrenia has suggested a relationship between functional capacity, defeatist beliefs, and negative symptoms (Green et al., 2012) with cognition having a direct effect on negative symptoms, and the combination of both cognition and negative symptoms having a direct effect on functional outcomes (Thomas et al., 2017).

Furthermore, negative symptoms have been observed in those at clinical high risk (CHR) for psychosis (Piskulic et al., 2012; Yung et al., 2018). Negative symptoms in those at CHR have associations with a wide range of symptoms and deficits such as social difficulties (Carrión et al., 2016), depressive symptoms (Alvarez et al., 2015), cognitive deficits (Glenthoj et al., 2016), and functional deficits (Cornblatt et al., 2007). However, CHR youth with PNS has rarely been investigated, with only one study to date examining the relationship between functioning and cognition in those with PNS. Moreover, those with predominant negative symptoms are not necessarily perceived as needing treatment (Fusar-Poli and Van Os, 2013). In fact, no treatments to date have specifically targeted PNS in this population (Devoe et al., 2018), thus an in-depth understanding of PNS in CHR is warranted.

CHR youth frequently exhibit functional deficits, doing poorly in school and work, and having increased social isolation (Cornblatt et al., 2012), both of which have been shown to contribute to the likelihood of developing psychosis (Addington et al., 2017; Cornblatt et al., 2007; Cornblatt et al., 2012). Deficits in social functioning appear to remain stable and unrelated to attenuated psychotic symptoms (APS, (Cornblatt et al., 2012). However, many studies have demonstrated a relationship between negative symptoms and functional deficits in CHR (Corcoran et al., 2011; Kim et al., 2013; Lee et al., 2017; Meyer et al., 2014; Schlosser et al., 2015), with long-standing negative symptoms associated with social difficulties (Carrión et al., 2016).

A small study demonstrated that CHR youth endorsed defeatist beliefs more than healthy controls, and that these beliefs were associated with more severe negative symptoms (Perivoliotis et al., 2009). Since defeatist performance beliefs are linked with increased severity of negative symptoms in schizophrenia (Campellone et al., 2016) it may be important to investigate these beliefs in CHR youth who present with PNS. Indeed, previous

studies identified CHR populations in particular as promising for improving our understanding of this relationship (Campellone et al., 2016; Perivoliotis et al., 2009)

A recent meta-analysis demonstrated that CHR youth have poorer cognitive functioning than healthy controls, with the exception of social cognition (Zheng et al., 2018). Negative symptoms in CHR youth have been associated with poorer performance on verbal tasks and slower processing speed (Lindgren et al., 2010; Yung et al., 2018), with poorer performance on neurocognitive tests strongly associated with negative symptom severity (Meyer et al., 2014). Furthermore, one study demonstrated that poorer neurocognition was associated with more severe negative symptoms, while APS were not (Leanza et al., 2018). In terms of social cognition, one study demonstrated that facial affect processing and negative symptoms combined was the best model for predicting transition to psychosis (Amminger et al., 2011), while other studies have not shown a relationship between social cognition and negative symptoms (Barbato et al., 2015; Piskulic et al., 2016).

To date, several studies have demonstrated that negative symptoms typically occur prior to transition to psychosis (Cornblatt et al., 2012; Demjaha et al., 2012; Piskulic et al., 2012; Riecher-Rossler et al., 2009; Rusch et al., 2015; Valmaggia et al., 2013; Velthorst et al., 2010; Zimmermann et al., 2010). With CHR individuals experiencing more severe negative symptoms at baseline having an increased risk of transition to psychosis (Valmaggia et al., 2013) and in some cases negative symptoms have had a higher predictive value than APS (Demjaha et al., 2012; Velthorst et al., 2011). Two studies have looked at the relationship between transition and PNS in CHR participants (Piskulic et al., 2012). One study found no significant associations between PNS and transition to psychosis (Yung et al., 2018). However, the study had few CHR participants with PNS (n=22) and employed the Buchanan PNS criteria (Buchanan, 2007), developed for schizophrenia and first-episode patients in clinical trials, which examines PNS over 6-months. The second study (n=138) demonstrated that negative symptoms were more severe and persistent in those who transitioned to psychosis (Piskulic et al., 2012). Furthermore, this study showed that although severity of baseline negative symptoms predicted transition to psychosis, having PNS over 12-months was more predictive of transition.

Thus, identification and exploration of PNS in a large CHR longitudinal cohort may provide greater insight into when PNS first emerge. Determining whether PNS in CHR youth is directly related to functional deficits, cognitive deficits, defeatist beliefs, and transition may have important treatment implications, which may in turn impact long-term quality of life.

The present study examined PNS in CHR youth in a large longitudinal cohort [North American Prodrome Longitudinal Study (NAPLS 2); (Addington et al., 2012) The aim of this current study was to: (1) determine the prevalence of PNS in a CHR sample, (2) define the relationship between PNS and functioning, defeatist beliefs, neurocognition and social cognition, and (3) to examine whether having PNS was associated with an increased risk of transition to psychosis. We hypothesized that CHR youth with PNS would show significant deficits in functioning, neurocognition, and present with more defeatist beliefs compared to CHR participants without PNS. In addition, we hypothesized that social cognition would not

differ between the two groups. Furthermore, it was hypothesized that those with PNS would have an increased risk of transition to psychosis.

2. Methods

2.1 Setting and participants

All CHR participants (N=764; 436 males, 328 females) were recruited as part of the 8-site North American Prodrome Longitudinal Study [(NAPLS-2); University of California Los Angeles, Emory University, Harvard University, Zucker-Hillside Hospital, University of North Carolina, University of California San Diego, University of Calgary, and Yale University]. CHR participants between the ages of 12 and 35 years old were referred to NAPLS-2 by health care providers, social service agencies, educators, or were self-referred in response to community education efforts. Potential participants underwent a telephone screen to rule out any individuals who may already be psychotic and those for whom it seemed likely that they could meet COPS criteria were subsequently invited to an in-person eligibility evaluation and consent. At baseline, 743 participants met CHR criteria using the Criteria of Psychosis-risk Syndromes (COPS) based on the Structured Interview for Psychosis-risk Syndromes (SIPS; (McGlashan et al., 2010). Twenty-one participants were considered high risk if they were under the age of 19 and presented with schizotypy. Exclusion criteria were any axis I current or lifetime psychotic disorder, IQ <70, past or current history of a central nervous system disorder, and substance dependence in the 6-months prior to enrollment. A more detailed description of the inclusion and exclusion criteria and study measures are described elsewhere (Addington et al., 2012; Addington et al., 2015).

For this study to determine the presence of PNS we included CHR participants who had negative symptoms scoring ≥4 at all 3 assessments: baseline, 6-months, and 12-months. Twenty-four participants did not have sufficient negative symptom data at baseline, leaving a sample of seven hundred and forty CHR participants. We included all CHR subjects with negative symptoms who met criteria for PNS (n=67), as defined below, or who did not meet criteria; non-PNS (n=673), see Figure 1 for flow chart.

2.2 Procedures

The study was approved by institutional review boards at all NAPLS-2 sites (n=8). All participants provided written informed consent, including parental consent. The work described in this article was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Trained raters conducted clinical assessments at baseline, 6, 12, 18, and 24 months, and neurocognition and social cognition at baseline, 12 and 24 months. Intraclass correlations for the total Scale of Psychosis-risk Symptoms (SOPS) scores were in the excellent range (range=0.82–0.93; (Addington et al., 2015).

2.3 Assessments

Negative symptoms were rated on the SOPS (McGlashan et al., 2010). According to the NIMH-MATRICS negative symptom consensus the current domains of negative symptoms include asociality, anhedonia, avolition, blunted affect, and alogia (Kirkpatrick et al., 2006). Therefore, in the current study the SOPS negative symptoms were restricted to social anhedonia (N1), avolition (N2), and expression of emotion (N3), whereas experience of emotions and self (N4), ideational richness (N5), and occupational functioning (N6) were excluded.

To assess for functioning, two well-established scales were used, the Global Functioning: Social (GF:S) and the Global Functioning: Role (GF:R; (Auther et al., 2006; Cornblatt et al., 2007). The GF:S assesses the level of social contact and friendships outside of the family unit. The GF:R assesses the level of role functioning at school or work. The GF:S and GF:R are rated on a 10-point scale, with higher scores representing higher functioning.

Neurocognition was assessed with nine MATRICS MCCB tests (Kern et al., 2008; Nuechterlein et al., 2008), including the Trail Making Test-Part A (TMT-A; (Battery, 1944), Symbol Coding from the Brief Assessment of Cognition in Schizophrenia (SC-BACS; (Keefe et al., 2004), Hopkins Verbal Learning Test-Revised immediate recall (HVLT-R; (Brandt and Benedict, 2001), Spatial Span subtest from the Wechsler Memory Scale-III (WMS-III SS; (Wechsler, 1997), Letter-Number Span (LNS;(Gold et al., 1997), Mazes subtest from the Neuropsychological Assessment Battery (NAB Mazes; (Stern and White, 2003), Brief Visuospatial Memory Test-Revised (BVMT-R; (Benedict et al., 1996), Category Fluency (CF; (Blair and Spreen, 1989), and the Continuous Performance Test-Independent Pairs (CPT-IP; (Cornblatt et al., 1988).

For social cognition, to assess facial affect recognition the Penn Emotion Recognition (ER40) and the Penn Emotion Differentiation (EDF40) tasks were used (Gur et al., 2002; Kohler et al., 2004). Competence in relationship perception was assessed on the abbreviated Relationships Across Domains (RAD-45; (Fiske, 1991, 2004). To assess Theory of Mind (ToM), the Social Inference subscale of The Awareness of Social Inference Test (TASIT) was used (McDonald et al., 2003).

As a proxy to defeatist beliefs, negative-self schemas (e.g., “I am a failure”) were assessed on the Brief Core Schema Scale (BCSS; (Fowler et al., 2006), which is a 24-item self-report scale that assesses concerns about the self and others that has been validated in CHR samples (Addington and Tran, 2009). Higher scores on the negative-self dimension represent increased maladaptive schemas. The BCSS negative-self schemas has similar items to the Dysfunctional Attitude Scale (de Graaf et al., 2009), which is commonly used to measure defeatist beliefs in schizophrenia research.

The Presence of Psychotic Symptoms (POPS; (Miller et al., 2003) criteria was utilized to determine transition to psychosis. Transition to psychosis required at least one of the five SOPS APS to reach a psychotic level of intensity (rating of 6) for a frequency of greater than or equal to 1 hour per day for 4 days per week during the past month or that symptoms seriously impacted functioning (e.g., dangerous to self or others or severely disorganising).

To explore potential sources of secondary negative symptoms, depressive symptoms were assessed with the Calgary Depression Scale for Schizophrenia (CDSS; (Addington et al., 1993), which has been validated in CHR samples (Addington et al., 2014). The SOPS APS subscale was utilized to measure APS.

2.4 Definition of persistent negative symptoms

PNS were defined as having one of the following three negative symptoms: social anhedonia (N1), avolition (N2), and expression of emotion (N3) based on the NIMH-MATRICS negative consensus on current domains of negative symptoms (Kirkpatrick et al., 2006) scored ≥4 (i.e., moderately severe to extreme) for a duration of one year (i.e., scoring ≥4 at all 3 assessments: baseline, 6-months, and 12-months).

2.5 Analyses

Distributions of all variables were inspected using histograms, q-q plots, and Shapiro-Wilks tests before conducting statistical analysis. Participants were divided into two groups, the PNS group (N=67) versus the non-PNS group (N=673). Demographics were examined using chi-square analysis for categorical variables and independent samples t-test for continuous measures.

Generalized linear mixed models for repeated measures were utilized to examine changes over time (i.e., baseline, 6, 12, 18, and 24 months) between and within groups to accommodate for missing data and account for intra-participant correlations. All tests were adjusted for multiple comparisons using Tukey-Kramer, which remains conservative in the case of unequal sample sizes (Hayter, 1984). Participants with PNS were compared with non-PNS participants over time on the GF:S, GF:R, BCSS negative-self schema subscale, MCCB, and social cognitive tests.

As an exploratory analysis we adjusted the PNS criteria to having moderately severe to extreme negative symptoms for a shorter period of six months, because most participants who transitioned to psychosis did so within the first year. Cox proportional hazards regression analysis was utilized to determine the differences in hazard rates between the PNS group and the non-PNS group in transitioning to psychosis.

In order to explore the impact of potential sources of secondary negative symptoms, participants with persistent depressive symptoms measured on the CDSS scored ≥7 for a duration of one year were excluded, and the above-mentioned analyses repeated, comparing the PNS with non-PNS participants over time on the GF:S, GF:R, BCSS negative-self schema subscale, MCCB, social cognitive tests, and transition. A CDSS score for a duration of one year was utilized to ensure that depressive symptoms were accounted for at the same time-points negative symptoms were measured (i.e., baseline, 6-months, and 12-months). A cut-off of ≥7 was chosen based on evidence that a score of at least a 7 on the CDSS yields high sensitivity and specificity in detecting depression in CHR individuals (Rekhi et al., 2018). All statistical tests were 2-sided and an adjusted P value of < 0.05 was considered statistically significant. Analyses were performed using SAS version 9.2 (Der and Everitt, 2008).

3. Results

Seven hundred and forty CHR participants (424 males, 316 females) had sufficient negative symptom data at both baseline and follow-up (i.e., both 6 and 12-months), allowing for the distinction between groups (PNS vs non-PNS). Out of the 740 CHR participants, 67 (9.05%) had PNS and 673 (90.95%) did not. There were significantly more males (71.6% vs 55.9%) in the PNS group, see Table 1 for baseline demographics. The groups did not differ in current employment status, student status, and highest level of education at baseline. There were no significant differences between groups on APS rated on the SOPS or depressive symptoms measured on the CDSS at baseline, 6-months, 12-months, 18-months, and 24-months (See Supplementary Tables 1–2).

3.1 Changes in role functioning over time

Generalized linear mixed models for repeated measures were utilized to examine changes over time for GF:R, the models demonstrated that the PNS group had significantly poorer role functioning on the GF:R compared to the non-PNS group at 6-months (M=5.4, SEM=0.25, vs. M=6.5, SEM=0.09; $p<0.01$), 12-months (M=5.6, SEM=0.26 vs. M=6.5, SEM=0.10; $p<0.05$), and 18-months (M=5.3, SEM=0.31 vs. M=6.5, SEM=0.12; $p<0.01$), see Figure 2. Role functioning did not significantly improve over time compared to baseline within the PNS group, while role functioning within the non-PNS group significantly improved over time compared to baseline, with the exception of 24-months. After removing participants with persistent depressive symptoms, role functioning was significantly poorer in the PNS group (N=30) at 6,12,18, and 24-months compared to the non-PNS group [(N=182); See Supplementary Tables 3–4].

3.2 Changes in social functioning over time

Generalized linear mixed models for repeated measures were utilized to examine changes over time for GF:S, the PNS group had significantly poorer social functioning on the GF:S compared to the non-PNS group at baseline (M=4.7, SEM=0.18, vs. M=6.3, SEM=0.05; $p<0.001$), 6-months (M=4.9, SEM=0.18 vs. M=6.7, SEM=0.06; $p<0.001$), 12-months (M=5.1, SEM=0.17 vs. M=6.9, SEM=0.07; $p<0.001$), 18-months (M=5.3, SEM=0.19 vs. M=6.9, SEM =0.008; $p<0.001$), and 24-months (M=5.5, SEM=0.19 vs. M=7.00, SEM=0.08; $p<0.001$), see Figure 3. Social functioning did not significantly improve over time compared to baseline within the PNS group with the exception of 24-months, while social functioning within the non-PNS group significantly improved over time. After removing participants with persistent depressive symptoms, social functioning remained significantly poorer in the PNS group at all time points (Supplementary Tables 3–4).

3.3 Changes in neurocognition over time

There were no significant differences between the PNS and non-PNS groups on the nine MCCB tests T-scores (i.e., TMT: Part A, BACS-SC, HVLT-R, WMS-III Spatial Span, LNS, NAB Mazes, BVMT-R, CF, and CPT-IP) at baseline, 12-months, or 24-months after adjusting for multiple comparisons (Table 2a and Table 2b), and after removing participants with persistent depressive symptoms (Supplementary Tables 5–6).

3.4 Changes in social cognition over time

There were no significant differences between the PNS and non-PNS groups on the five social cognition tasks (i.e., RAD-45 total, TASIT total, TASIT sarcasm, ER-40, and EDF40) at baseline, 12-months, and 24-months after adjusting for multiple comparisons (Supplementary Tables 7–8), and after removing participants with persistent depressive symptoms (Supplementary Tables 5–6).

3.5 Changes in negative-self schemas over time

Compared to the non-PNS group, PNS participants had significantly higher levels of total negative-self schemas at 12-months (M=6.7, SEM=0.64 vs. M=4.1, SEM=0.26; $p<0.05$) and 24-months (M=5.9, SEM=0.66 vs. M=3.7, SEM=0.27; $p<0.05$), with a trend level in significance for higher negative-self schemas in the PNS group at 6-months ($p=0.08$) and 18-months ($p=0.07$), see Figure 4. The non-PNS group significantly improved on total negative-self schemas at all time points compared to baseline, while the PNS group only significantly improved on total negative-self schemas at 18-months compared to baseline. After removing participants with persistent depressive symptoms, the significance between groups on negative-self schemas was lost (Supplementary Tables 3–4).

3.6 Transition to psychosis

To examine transition to psychosis the PNS criteria was adjusted to having moderately severe to extreme negative symptoms for a period of six months, as most participants who transitioned to psychosis did so within the first year. Using this criterion, 13 of the 139 participants in the PNS group developed psychosis (9.35%) compared to 80 of 601 in the non-PNS group (13.31%). In the Cox proportional hazards regression analysis, it appears that although the non-PNS group have a 77% (Hazard Ratio=1.77) increase in the hazard rate compared to those with PNS, this increase was not significant.

3.7 Proportion meeting PNS criteria over time

The proportion of CHR individuals meeting the 12-month PNS criterion declined over time from 9% (Baseline to 12-months), 7% (6-months to 18-months), to 4% (12-months to 24-months). Using the 6-month PNS criterion, a similar decline was observed from 19% (Baseline to 6-months), 10% (6-months to 12-months), 8% (12-months to 18-months), to 7% (18-months to 24-months).

4. Discussion

This paper examined the prevalence of PNS and their relationship with functioning, neurocognition, social cognition, negative-self schemas, and transition to psychosis. The results indicate that, in the NAPLS cohort, the prevalence of PNS is 9% when exercising a strict 12-month criteria. The PNS group demonstrated significantly more social and role deficits over time compared to the non-PNS group, which remained after controlling for persistent depressive symptoms. Both social and role deficits predominantly improved over time in the non-PNS group compared to baseline, while the PNS group had worse functional deficits that remained relatively stable over two years. There were no differences between the groups on neurocognition and social cognition at any time point. When looking at

negative-self schemas we found a trend for higher negative-self schemas over time in the PNS group, however when controlling for depressive symptoms these results were lost. Lastly, there were no significant differences between the groups on rates of transition to psychosis.

Consistent with our hypothesis, the PNS group had significant deficits in functioning over two years compared to the non-PNS group, controlling for persistent depressive symptoms. These results are supported by previous CHR studies that have shown a relationship between functional deficits and negative symptoms in CHR (Carrión et al., 2016; Corcoran et al., 2011; Kim et al., 2013; Lee et al., 2017; Meyer et al., 2014; Schlosser et al., 2015). In the current study, the PNS group on average demonstrated serious impairment in social functioning (e.g., no close friends, and rarely seeking out others) whereas the non-PNS exhibited mild problems in social functioning (e.g., mild conflicts with peers). The same pattern was observed for role functioning, the PNS group on average demonstrated serious impairment in role functioning (e.g., failing multiple courses) whereas the non-PNS exhibited mild impairment in role functioning (e.g., frequently behind on tasks). Functioning was the main differentiating factor between groups in the current study, which emulates the functional deficits found in FEP with PNS (Chang et al., 2011; Galderisi et al., 2013; Hovington et al., 2012; Malla et al., 2004; Puig et al., 2017; Üçok and Ergül, 2014).

Although these CHR youth have poorer neurocognition than healthy controls on the MCCB domains (Seidman et al., 2016), our results do not support two previous CHR studies that demonstrated a significant relationship between negative symptoms and poor neurocognition (Lindgren et al., 2010; Meyer et al., 2014). One possible reason for this discrepancy is that in CHR studies there are mixed results on neurocognition, in that more often than not CHR participants have poorer neurocognition than healthy controls but the results are not always consistent (Zheng et al., 2018). Alternatively, it is possible that neurocognition is poorer for those that transition to psychosis (Addington et al., 2017), though this relationship was not explored in the current analysis. Interestingly, in the current study the PNS group demonstrated a pattern of persistent poorer neurocognition on most MCCB tests, generally not improving over time compared to baseline, whereas neurocognition predominantly improved over time in the non-PNS group.

As expected, the PNS group did not differ in social cognition compared to the non-PNS group. These results are corroborated by other CHR studies that have not shown a relationship between social cognition and negative symptoms in CHR (Barbato et al., 2015; Piskulic et al., 2016). However, a recent review of FEP patients demonstrated that social cognitive deficits in FEP patients are associated with negative symptoms (Healey et al., 2016). One possible explanation for the discrepancy between FEP and CHR samples is that social cognition in CHR is intermediary between healthy controls and FEP (Piskulic et al., 2016).

We found a trend for higher negative-self schemas over time in the PNS group, however when controlling for persistent depressive symptoms the between-group result was lost. This is contrary to a previous study where defeatist beliefs were associated with increased negative symptom severity (Perivoliotis et al., 2009). This discrepancy may have arisen

because we used a measure of negative-self schemas as a proxy for defeatist beliefs. In schizophrenia research, the Dysfunctional Attitude Scale (e.g., “If I fail at my work, then I am a failure as a person”) is commonly used to measure defeatist performance beliefs in which negative-self beliefs are explicitly linked to functional outcomes (de Graaf et al., 2009). However, negative-self schemas (e.g., I am worthless”) on the BCSS do not relate the negative-self beliefs explicitly to performance nor functional outcomes but rather to how an individual has generally viewed themselves over time. Nevertheless, the non-PNS group improved significantly at all time points on negative self-schemas, whilst the PNS group remained stable. To our knowledge no previous studies have used the BCSS scale as a proxy for defeatist beliefs, nor has negative self-schemas and defeatist beliefs been previously reported to capture the same construct. Future studies in CHR samples may wish to explore the convergent and discriminant validity between these two scales. Several secondary analyses (e.g., negative self-schemas) were not significantly different between the PNS and non-PNS groups after removing participants with persistent depressive symptoms, resulting in a small number of participants in the PNS group. Thus, it is possible that we were unable to detect a difference between the groups due to power constraints and an unbalanced sample size.

Contrary to our hypothesis, those with PNS did not have a significant risk of transition compared to the non-PNS group, which is consistent with one previous study (Yung et al., 2018). With the current focus of identification and treatment of APS, and no treatments established to help negative symptoms nor functioning in CHR (Devoe and Addington, 2019; Devoe et al., 2019; Devoe et al., 2018), an unfortunate trajectory emerges for CHR youth with PNS who may not be identified as needing services and thus do not receive the help they require. One possibility for future treatment of both functioning and negative symptoms in CHR is Cognitive Behavioral and Social Skills Training (CBSST), as findings suggest CBSST improves both functioning and negative symptoms in patients with schizophrenia (Holden et al., 2017). Furthermore, preliminary data suggest that CBSST is a feasible treatment for CHR youth (Addington, 2014).

Other notable points are that the PNS group had significantly more males than the non-PNS group, which is consistent with prior research in CHR samples with more severe negative symptoms (Piskulic et al., 2012) and in FEP patients with PNS (Chang et al., 2011). Secondly, we did not observe any differences on the CDSS nor the SOPS positive subscale between groups at any time-point. This may indicate that future PNS criteria in CHR may not require a cut-off or control for positive symptoms and depressive symptoms as has been required in schizophrenia and FEP studies. Next, the current study was unable to determine whether a particular negative symptom domain was driving PNS categorization as CHR participants could meet criteria for PNS even if the domains of negative symptom they scored changed between baseline and follow-up (e.g., anhedonia is elevated at baseline, and at 6 months only avolition is elevated). Lastly, the number of elevated negative symptom domains were not explored in the current study, however a previous PNS study in FEP demonstrated that certain negative symptom domains (i.e., amotivation) may play an important role in PNS categorization and the relationship with poor functional outcomes (Hovington et al., 2012).

4.1 Strengths and Limitations

This study had the unique opportunity to explore PNS in the absence of frank psychotic symptoms in a large longitudinal cohort. However, several limitations should be considered when interpreting the results. First, due to the transient nature of symptoms in CHR samples we imposed a strict criterion of having at least moderately severe negative symptoms for a duration of one year to qualify for PNS. Utilizing such a strict definition of PNS possibly underestimated the prevalence of this phenomenon in CHR populations. Thus, a limitation of this study was using a 12-month PNS criteria to determine prevalence. Selecting a specific timeframe criterion (i.e., 6 months vs 12 months) for PNS in CHR requires more consideration. One study found that the prevalence of PNS in a CHR sample to be 6.1% at baseline (Yung et al., 2018b). To compare our results, we utilized a less restrictive criteria of 6-months and the prevalence estimates of PNS in CHR doubled (19%), indicating that PNS are certainly evident even in CHR youth. These study results reflect similar results found in FEP patients where the PNS prevalence is between 27% to 13.2%, depending on definitions of PNS (Hovington et al., 2012). In this study the percentage of those meeting PNS criteria declined over time from baseline to 24-months, and as such negative symptoms may have declined.

In a similar vein another one of the limitations of the current study is that we chose a 12-month PNS criterion to look at the outcomes of functioning, neurocognition, and negative-self schemas, which may be of concern. One could consider employing a 6-month PNS criterion to examine outcomes and as such the results may differ. Thus, we re-ran the analyses by creating a PNS 6-month group with those who had negative symptoms for only a 6 month period and the only difference in the results between the two criteria on the primary outcomes of interest was that the groups now differed on GF:R at baseline and the BCSS at baseline and 18 months, with the PNS 6-month group having poorer ratings on these 2 measures. These results are presented in Supplementary Tables 9–12.

A third limitation was that the current study did not use the Buchanan criteria of PNS (Buchanan, 2007), as this criteria was developed for schizophrenia patients and FEP in clinical trials. The current study diverged from the Buchanan criteria by not defining a threshold for both positive symptoms/extrapyramidal symptoms plus having a longer duration of one year. This is a CHR sample and compared to those with full-blown psychosis positive symptoms are attenuated and a defining feature of CHR criteria. Thus, an exclusion criterion within the PNS group based on a severity of APS was not imposed. Rather, since little is known about PNS in CHR samples we explored the relationship between PNS and APS by examining the differences between the groups over time and found no significant differences between groups at any time point. Due to differences in how PNS was operationalized (e.g., 6 months vs 12 months; negative symptom domains; cut-offs) it is possible that the current study measured something different than the Buchanan criteria of PNS.

A fourth limitation was that we followed the NIMH-MATRICS negative consensus on current domains of negative symptoms (Kirkpatrick et al., 2006). Due to the limitations of the SOPS in measuring negative symptoms we measured PNS in only four areas of negative symptoms asociality and anhedonia (i.e., social anhedonia), avolition, and expression of

emotion, whereas no measure of alogia was employed. However, in FEP patients with PNS alogia has been measured and reported to be at significantly lower levels than other negative symptoms (Hovington et al., 2012). It may be that if improved CHR negative symptom scales are validated and aligned with the NIMH-MATRICS negative symptom domains, future studies could incorporate a more precise measure of PNS.

Lastly, although the SOPS negative symptom items may be limited the negative symptom scale on the SIPS has yet to be validated. However, the Prodromal Inventory of Negative Symptoms (PINS), a scale developed in accordance with the NIMH consensus conference recommendations demonstrated that the PINS total score was highly correlated with the SIPS negative symptom factor, signifying good convergent validity (Pelletier-Baldelli et al., 2017). In addition, the adapted version of the Brief Negative Symptom Scale (BNSS) for CHR youth demonstrated significant correlations between BNSS scores and the SIPS negative subscale score, further supporting convergent validity (Strauss and Chapman, 2018).

4.2 Directions for future research

The results of the current study may lead to several avenues for future research. First, future studies may wish to investigate other factors that may be related to PNS in CHR participants such as premorbid functioning, trauma, and quality of life to further improve the evidence base. Second, criteria should be further developed to reach consensus on how best to define PNS in CHR samples, not only to improve prevalence estimates but to establish consistent clinical sub-groups for targeted interventions. Third, no studies have examined the impact of any intervention on PNS. Thus, future trials may want to design interventions that are primarily geared towards impacting PNS.

4.3 Conclusions

PNS are prominent in individuals at CHR for psychosis, resulting in significant and persistent functional impairment. PNS remain even in CHR youth who do not convert to a full-blown psychotic disorder. Thus, PNS may represent an unmet therapeutic need in CHR populations for which there are currently no effective treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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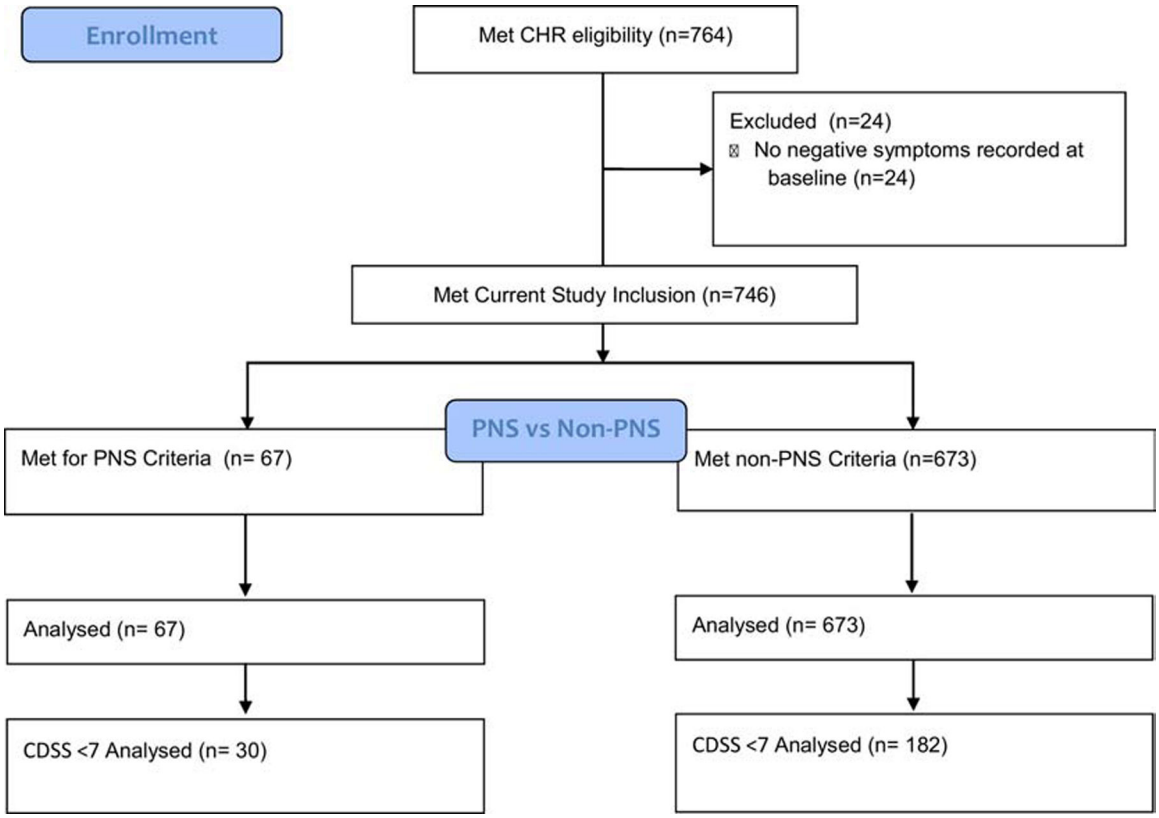

Figure 1.
Flow Diagram

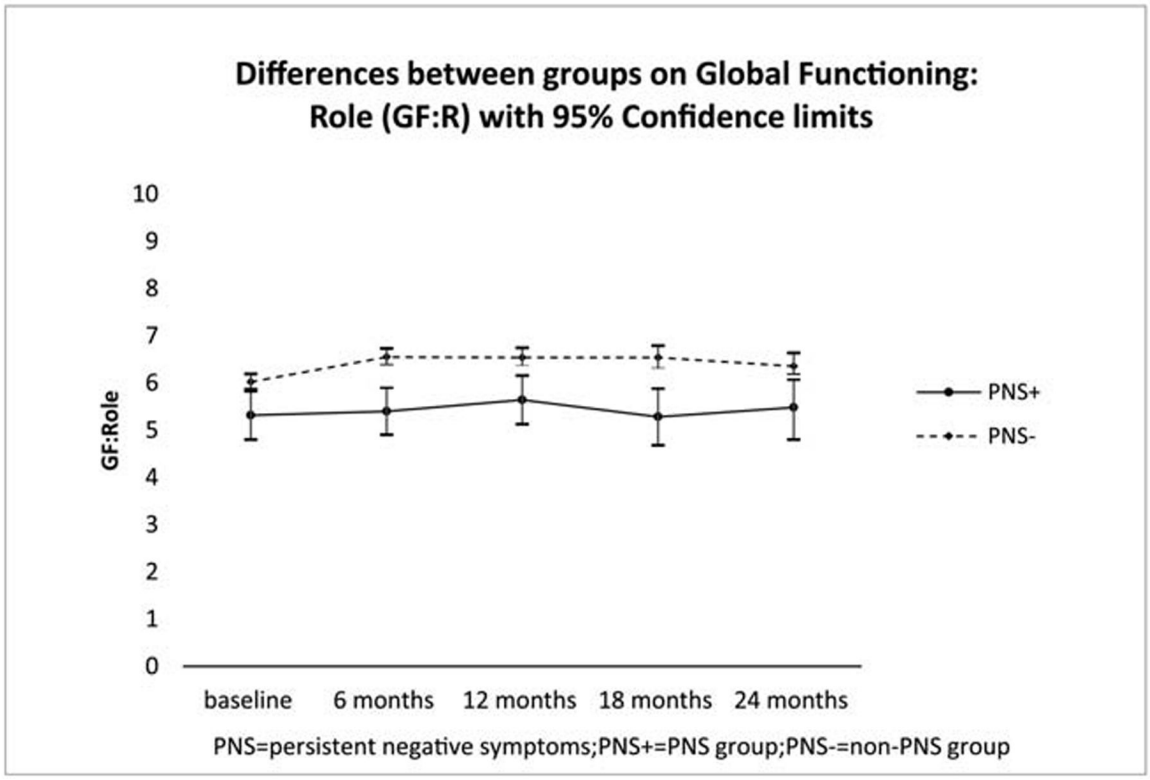

Figure 2.
Differences between groups on Global Functioning: Role (GF:R) with 95% Confidence limits

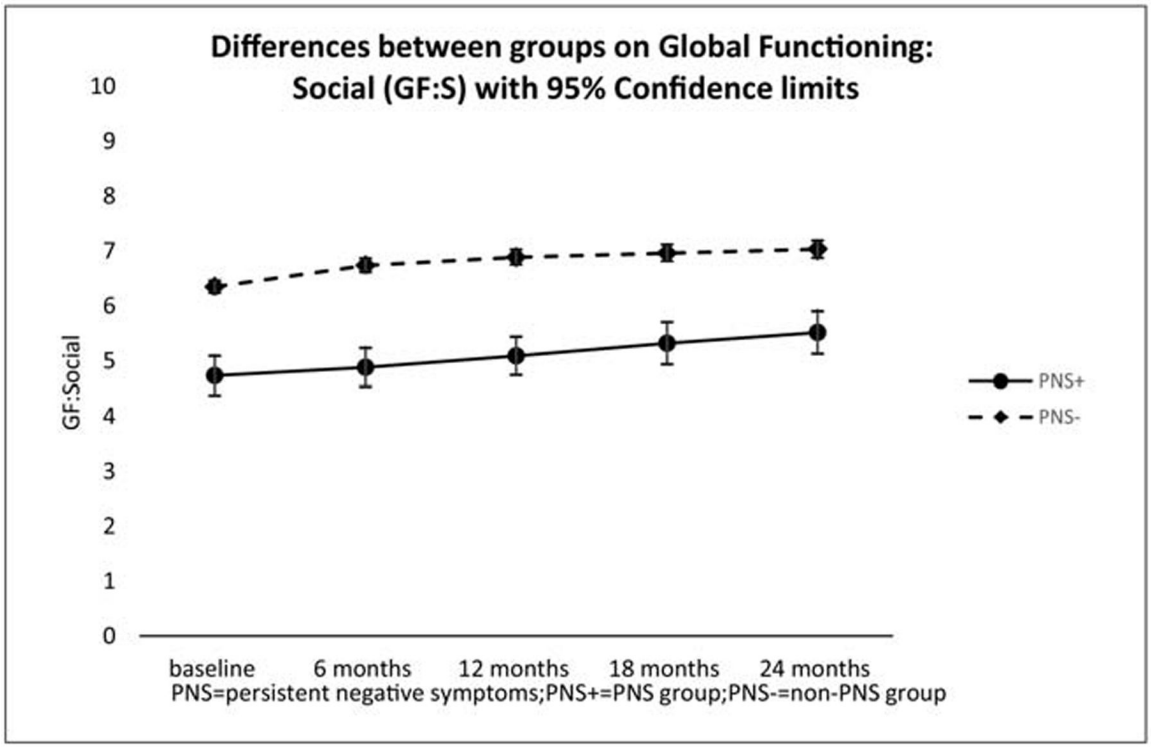

Figure 3.
Differences between groups on Global Functioning: Social (GF:S) with 95% Confidence limits

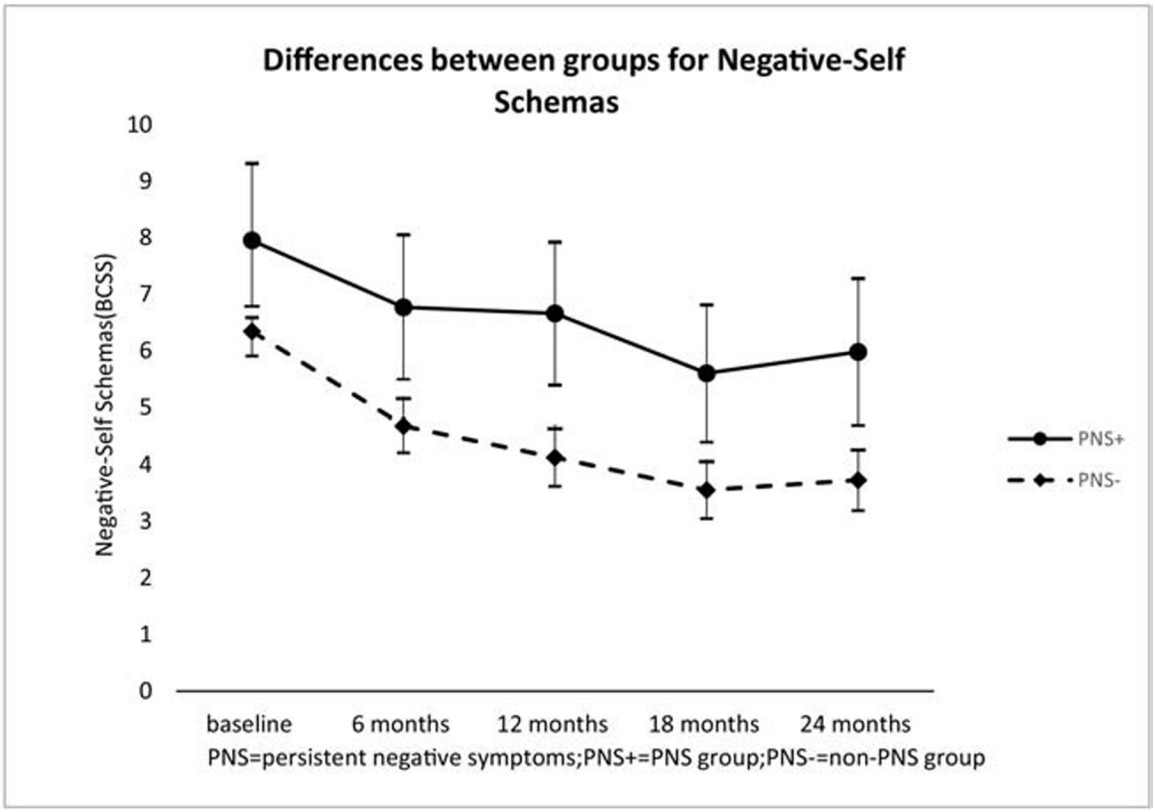

Figure 4.
Differences between groups for Negative-Self Schemas

TABLE 1.

Differences in Baseline Demographics Between Groups

Demographic Characteristic	Non-PNS *n* = 673	PNS *n* = 67	Test Statistic
	Mean (SD)		*t*
Age in years	18.5 (4.28)	18.7 (4.04)	0.10
Years of education	11.3 (2.83)	11.5 (2.59)	0.33
Sex	*Number (%)*		X^2
Male	376 (55.9)	48 (71.6)	6.19 *
Female	297 (44.1)	19 (28.4)	
Current living arrangement			
Living with family	508 (75.6)	53 (79.1)	7.04
Living with spouse/partner	37 (5.5)	1 (1.5)	
Living on own in apartment/house	32 (4.8)	7 (10.5)	
Living in group/rooming home	18 (2.7)	1 (1.5)	
Living with others, not spouse/partner	61 (9.1)	4 (6.0)	
Living in a shelter	2 (0.3)	0 (0.0)	
Other	14 (2.1)	1 (1.5)	
Currently working			
Yes	172 (25.6)	12 (17.9)	1.94
No	499 (74.4)	55 (82.1)	
Highest level of formal education obtained			
High school incomplete	352 (52.4)	37 (55.2)	1.24
High school graduate	260 (38.7)	22 (32.8)	
High school and above	60 (8.9)	8 (11.9)	
Currently enrolled as a student			
Yes	555 (82.6)	53 (79.1)	0.51
No	117 (17.4)	14 (20.9)	
	Mean † *(SE)*		*t*
Clinical Symptoms			
CDSS Total	5.7(0.18)	7.3(0.57)	0.20
SOPS Positive Symptom Total	11.9(0.15)	11.8(0.47)	−2.71
SOPS Negative Symptom Total	11.36(0.23)	17.18(0.54)	−7.78 **
PNS Total (N1 +N2 + N3)	5.80(0.14)	9.76(0.28)	−9.07 **

* p<0.05;

** p<0.001;

† represents the least squares means estimated by the generalized linear models for CDSS and SOPS Positive Symptom Total. Abbreviations: CDSS= The Calgary Depression Scale for Schizophrenia; SD = standard deviation; SOPS = Scale of Psychosis-risk Symptoms; PNS = persistent negative symptoms

Table 2a.

Differences in Cognitive Test Scores (*T-scores*) between groups

Cognitive Tests	Non-PNS *(n=673)*			*PNS(n=67)*		
	Mean (SE)					
	Baseline	***12 months***	***24 months***	***Baseline***	***12 months***	***24 months***
TMT: Part A	41.1(0.45)	44.3(0.59)	45.3(0.68)	42.9(1.42)	43.5(1.54}	46.4(1.73)
BACS Symbol Coding	41.0(0.56)	43.8(0.71)	44.6(0.76)	40.9(1.75)	45.6(1.92}	45.9(2.02)
HVLT-R	43.6(0.41)	45.3(0.53)	45.9(0.62)	44.6(1.29)	44.0(1.37}	45.7(1.58)
WMS-11 Spatial Span	44.3(0.5)	45.6(0.59)	46.3(0.72)	44.1(1.54)	45.6(1.55}	45.7(1.84)
Letter-Number Span	43.1(0.46)	44.8(0.52)	45.9(0.58)	44.5(1.43)	45.2(1.41}	45.1(1.51)
NAB Mazes	42.2(0.42}	44.1(0.51)	45.1(0.60)	44.5(1.32)	45.5(1.34}	45.6(1.53)
BVMT-R	40.7(0.45)	41.3(0.57)	42.3(0.59)	39.9(1.41)	42.2(1.47}	42.3(1.49)
Category Fluency	48.3(0.45)	49.0(0.58)	49.9(0.68)	48.7(1.40)	50.8(1.48}	51.3(1.70)
CPT-IP	38.4(0.50)	41.2(0.58)	42.7(0.69)	38.4(1.54)	41.8(1.59}	41.7(1.79)

Abbreviations: Mean represents the least squares means estimated by the generalized linear model, SE represents the standard error of the mean; TMT = Trail Making Test; BACS = Brief Assessment of Cognition in Schizophrenia; HVLT-R = Hopkins Verbal Learning Test-Revised; WMS: Wechsler Memory Scale; NAB = Neuropsychological Assessment Battery; BVMT-R = Brief Visuospatial Memory Test-Revised; CPT-IP = Continuous Performance Test – Independent Pairs.

Table 2b.

Differences in Cognitive Test Scores (*T-scores*) within groups

Cognitive Tests	Non-PNS (*n*=673)			PNS (*n*=67)		
	Mean (SE)					
	Baseline	***12 months***	***24 months***	***Baseline***	***12 months***	***24 months***
TMT: Part A	41.1(0.45)	44.3(0.59)^{a***}	45.3(0.68)^{a***}	42.9(1.42)	43.5(1.54)	46.4(1.73)
BACS Symbol Coding	41.0(0.56)	43.8(0.71)^{a***}	44.6(0.76)^{a***}	40.9(1.75)	45.6(1.92)^{a*}	45.9(2.02)^{a*}
HVLT-R	43.6(0.41)	45.3(0.53)^{a*}	45.9(0.62)^{a**}	44.6(1.29)	44.0(1.37}	45.7(1.58)
WMS-11 Spatial Span	44.3(0.5)	45.6(0.59)	46.3(0.72)^{a*}	44.1(1.54)	45.6(1.55}	45.7(1.84)
Letter-Number Span	43.1(0.46)	44.8(0.52)^{a**}	45.9(0.58)^{a***}	44.5(1.43)	45.2(1.41}	45.1(1.51)
NAB Mazes	42.2(0.42)	44.1(0.51)^{a**}	45.1(0.60)^{a***}	44.5(1.32)	45.5(1.34}	45.6(1.53)
BVMT-R	40.7(0.45)	41.3(0.57)	42.3(0.59)	39.9(1.41)	42.2(1.47)	42.3(1.49)
Category Fluency	48.3(0.45)	49.0(0.58)	49.9(0.68)	48.7(1.40)	50.8(1.48)	51.3(1.70)
CPT-TP	38.4(0.50)	41.2(0.58)^{a***}	42.7(0.69)^{a***}	38.4(1.54)	41.8(1.59)^{a*}	41.7(1.79)

Abbreviations: Mean represents the least squares means estimated by the generalized linear model, SE represents the standard error of the mean; TMT = Trail Making Test; BACS = Brief Assessment of Cognition in Schizophrenia; HVLT-R = Hopkins Verbal Learning Test-Revised; WMS: Wechsler Memory Scale; NAB = Neuropsychological Assessment Battery; BVMT-R = Brief Visuospatial Memory Test-Revised; CPT-IP = Continuous Performance Test – Independent Pairs. Significance:

^{a}= significantly different from baseline; b= significantly different from 12 months;

* p<0.05,

** p<0.01,

*** p<0.001