Neurocognitive functions in persistent negative symptoms following a first episode of psychosis

Martin Lepage [a, b, 1] PhD & Michael Bodnar, PhD [c, 1]
Delphine Raucher-Chéné, MD, PhD [a, b, d, e]
Katie M. Lavigne, PhD [a, b, f]
Carolina Makowski [g]
Ridha Joober, MD, PhD [a, b]
Ashok K. Malla, MBBS, FRCPC [a, b]

[a] Douglas Mental Health University Institute, McGill University, Montreal, Canada

[b] Department of Psychiatry, McGill University, Montreal, Canada

[c] The Royal's Institute of Mental Health Research, Ottawa, Canada

[d] Cognition, Health, and Society Laboratory (EA 6291), University of Reims Champagne-Ardenne, Reims, France

[e] Academic Department of Psychiatry, University Hospital of Reims, EPSM Marne, Reims, France

[f] McGill Centre for Integrative Neuroscience, Montreal Neurological Institute, McGill University, Montreal, Canada

[g] Department of Radiology, University of California San Diego, La Jolla, California

[1] These authors contributed equally to the manuscript

Corresponding author:
Martin Lepage, PhD
Douglas Mental Health University Institute
6875 LaSalle Blvd.,Verdun, Quebec
H4H 1R3, CANADA
Tel.: +1 (514) 761-6131 ext. 4393
Fax: +1 (514) 888-4064
Email address: martin.lepage@mcgill.ca

Abstract word count: 248
Total word count: 5928

Abstract

Negative symptoms are present at the onset of psychosis and their persistence is significantly associated with poor psychosocial functioning and lower quality of life. Persistent negative symptoms (PNS) may be idiopathic or secondary to other factors such as depression, positive symptoms, and medication side-effects. Several studies have examined neurocognitive functions in early psychosis patients with PNS relative to non-PNS, but have not systematically controlled for secondary PNS (sPNS). The latter may have a distinct neurocognitive profile that could obscure differences between PNS and non-PNS. Using a large (n=425) sample, we examined neurocognitive functions in PNS, sPNS, and non-PNS and hypothesized that PNS would be associated with greater impairments relative to non-PNS. Following admission to an early intervention program, a neurocognitive battery was administered after at least 3 months of treatment, and symptom data collected during a subsequent 6-month period were used to classify patients as PNS, sPNS and non-PNS. At month 12, both PNS and sPNS groups had significantly lower level of functioning relative to the non-PNS group but the sPNS group experienced higher levels of depressive and positive symptoms and were on a higher dose of antipsychotics. Relative to non-PNS, PNS patients exhibited significant impairments in verbal memory and working memory, whereas sPNS patients exhibited a trend towards greater impairments in verbal memory. This study confirms that the presence of PNS or sPNS negatively influences functioning with more selective cognitive impairments found in PNS, providing evidence that these groups of patients could benefit from different personalised interventions.

Keywords: neurocognition; verbal memory; working memory; first-episode psychosis; persistent negative symptoms

1. Introduction

Negative symptoms represent an important dimension of psychopathology in schizophrenia and related psychoses, as they are known to adversely impact functioning and quality of life (Correll and Schooler, 2020; Foussias et al., 2014; Jordan et al., 2014). Multiple studies have shown a significant association between negative symptoms and neurocognitive impairments (Eack and Keshavan, 2020; Harvey et al., 2006; Milev et al., 2005) and both dimensions have been linked to brain abnormalities (Galderisi et al., 2015; Harrison, 2004; Ince and Ucok, 2018). The study of the association between negative symptoms and neurocognitive functions (or brain imaging correlates) is however complicated by the presence of negative symptoms that may be secondary to other factors such as positive symptoms, depressive symptoms and medication side-effects (Correll and Schooler, 2020; Kirschner et al., 2017; Mucci et al., 2017). Hence, there is a need to adopt a research approach that facilitates the identification of primary or idiopathic negative symptoms by using objective measures. Expert consensus (Kirkpatrick et al., 2006) and recent empirical work on large datasets (Strauss et al., 2019; Strauss et al., 2018) confirm that negative symptoms are best represented by a constellation of five symptoms consisting of blunted affect, alogia, anhedonia, avolition, and asociality.

The study of negative symptoms requires a systematic and replicable operational definition of a group of patients presenting with such

psychopathology. To that end, Buchanan (2007) proposed the construct of persistent negative symptoms (PNS) as a way to operationally define a subgroup of patients with negative symptoms of at least moderate severity but with a low level of potential confounds. Such confounds include positive (psychotic), depressive and extrapyramidal symptoms, which together or separately could lead to secondary negative symptoms. Finally, there should be clinical stability for an extended period of time for the presence/absence of negative symptoms. Using well-established rating scales (such as PANSS and SANS), it has become possible to identify patients with PNS that are putatively primary or idiopathic, while minimizing potential confounds in the ratings of negative symptoms using other complementary scales assessing positive, depressive and extrapyramidal symptoms (Hovington et al., 2012).

Negative symptoms are significantly present even in the early phase of psychosis (Chang et al., 2011; Galderisi et al., 2013; Hovington et al., 2012; Malla et al., 2004; Rammou et al., 2019; Wunderink et al., 2020). The examination of potential etiological factors at this stage is key, as it limits the confounding effects of long-term medication use, recurrent hospitalizations and sedentary lifestyle, among other factors (Correll and Schooler, 2020; Kirschner et al., 2017; Mucci et al., 2017). Studies that have examined PNS in cohorts of first episode of psychosis (FEP) patients have reported a prevalence ranging from 8 to 31% during the first year following the initiation of treatment (Bucci et al., 2020; Chang et al., 2011; Galderisi et al., 2013; Hovington et al., 2012; Malla et al., 2004; Puig et al., 2017; Ucok and Ergul, 2014). PNS have also been examined in relation to neuroimaging (Hovington et al., 2015; Hovington and Lepage, 2012; Ince and

Ucok, 2018; Li et al., 2018; Makowski et al., 2016; Makowski et al., 2017; Mucci et al., 2017), neurocognitive (Hovington et al., 2013; Ince and Ucok, 2018; Puig et al., 2017), and functional (Bucci et al., 2020; Chang et al., 2011; Galderisi et al., 2013; Hovington et al., 2012; Puig et al., 2017; Ucok and Ergul, 2014) markers.

While the evidence for an association between PNS and poorer functioning has been firmly established, results on neurocognitive function and PNS have been more equivocal. Some studies have identified specific cognitive domains as being significantly impaired in PNS. Notably, evidence for poorer verbal memory (Hovington et al., 2013), working memory (Ucok and Ergul, 2014), and executive function (Puig et al., 2017; Ucok and Ergul, 2014) have been reported, but other studies failed to observe a significant difference in performance between PNS and non-PNS subgroups (Chang et al., 2011; Galderisi et al., 2013; Malla et al., 2004). In the studies with null findings, the samples of PNS patients with neurocognitive data tended to be relatively small (n=17 in Galderisi et al., 2013; n=22 in Chang et al., 2011; and n=36 in Malla et al., 2004). In addition, the first assessments of negative symptoms were often performed near the initiation of treatment, a time when such symptoms are often contaminated by depressive and positive symptomatology (see for example Buchy et al., 2010; Cotton et al., 2012; Sonmez et al., 2013). Finally and importantly, the non-PNS group by definition includes patients with varying symptomatic profiles. This includes remitted patients with no or mild positive and negative symptoms but also patients with negative symptoms that are secondary to other factors. These include positive symptoms, depressive symptoms, medication side-effects, social deprivation, and substance abuse (Kirschner et al., 2017). This is an important

consideration as the etiology, clinical trajectories and treatment are likely to be different for both categories of negative symptoms. Further, recent brain imaging studies suggest evidence of different structural neural correlates underlying PNS and secondary PNS (sPNS) patients (Makowski et al., 2016; Makowski et al., 2017).

The sPNS group has received scant attention thus far from a research perspective. It is possible that their presence within the non-PNS group may represent a confounding effect, as this group is likely to have a worse clinical status than those without negative symptoms. Hence, there is a need to study this sPNS group further at multiple levels including symptomatology, functioning, and neurocognitive functions. Furthermore, the isolation of such a sPNS group would allow for better characterization of the difference in neurocognitive functions between PNS and non-PNS in early psychosis.

The current study combines three important methodological considerations while examining neurocognitive functions in PNS. First, it examines a large and representative sample of FEP patients from a single catchment area. Second, the determination or categorization of early PNS was based on longitudinal ratings of negative symptoms and potential confounds (depression, extrapyramidal symptoms and positive symptoms) and were examined 6 months after the initiation of treatment (and for a continuous period of 6 months). As such, this window of observation on negative symptoms allows for significant improvement of overall symptoms and clinical stabilization for a large proportion of patients (see for example Buchy et al., 2010). Finally, a group of patients with sPNS is identified which allows a novel characterization of that group in FEP while allowing for a better examination of differences between PNS and non-PNS

patients. We categorized participants from a large sample (n=425) of FEP into PNS, sPNS and non-PNS using longitudinal clinical data during the first year of treatment and compared their neurocognitive profiles. Based on our preliminary report with a smaller sample of 136 FEP patients (Hovington et al., 2013), and our more recent work on verbal memory and negative symptoms (e.g. Makowski et al., 2020a; Makowski et al., 2020b), we hypothesized that verbal memory will significantly differ between the PNS and non-PNS groups. Given that there is a dearth of knowledge of sPNS patients, we also explored functioning, symptom and antipsychotics use in this group.

2. Experimental procedures

2.1 Participants

Patients were treated at the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), a specialized early intervention service with integrated clinical, research, and teaching modules, at the Douglas Mental Health University Institute in Montreal, Canada. PEPP-Montréal serves a local catchment area (~300,000 people) providing services to 14- to 35-year-olds with a first episode of affective or non-affective psychosis. Entry criteria include: an IQ over 70; no or less than one month of antipsychotic treatment; absence of organic brain conditions or a pervasive developmental disorder. A complete description of the services provided in this program can be found in Iyer et al., (2015). All patients were free to withdraw from research-based activities at any point without any consequences for their treatment.

Non-clinical controls (n=138) were recruited through advertisements within the same local catchment area. In addition to exclusion criteria listed for FEP

patients, controls were excluded if they had any current/past history of Axis I disorders, and/or a first-degree relative suffering from a schizophrenia spectrum disorder. After a comprehensive description of the study, written informed consent was obtained from all participants. Research protocols were approved by the Research Ethics Boards of the Douglas Mental Health University Institute and the McGill University Faculty of Medicine.

2.2 Study design and data collection

Following admission to PEPP-Montréal between 2003 and 2018, participants took part in a systematic assessment protocol with multiple timepoints across a two-year span (See Jordan et al., 2014 for more information of the assessment protocol). For the purpose of the current study, symptom assessment performed at the time of the neurocognitive testing (Month 3 following admission) were examined in addition to month 6 and 12 following admission. The two latter assessments were used to categorize patients into PNS, sPNS, or non-PNS groups. Symptom rating data during that period was available from 515 participants. From those, 90 did not complete the neurocognitive assessment for various reasons including clinical instability, lack of interest, or disengagement with services. A comparison of baseline sociodemographical and clinical characteristics did not reveal any significant differences between this group and those who completed the neurocognitive assessments (age at entry p=.12, years of education p=.50, SAPS total p=.78, SANS total p=.12, CDSS p=.08, SOFAS p=.13).

Evaluations were performed by multiple research personnel over the 15-year span of the study, but none were involved with patient treatment. All received

extensive training and continued supervision. Yearly inter-rater reliability sessions were held to calculate intraclass correlations (ICC), and serve as continuing education for staff. The ICCs have consistently been high over the 15 years of data collection (0.73 – 0.80 for SAPS and 0.62 – 0.71 for SANS), indicating good reliability.

The type and dosage of antipsychotics prescribed were noted at each time point; dosage was converted into chlorpromazine equivalents (Woods, 2003, 2011). Education level (years completed), Full Scale IQ (Wechsler, 1997a, 1999), duration of untreated psychosis (DUP), and duration of untreated illness (DUI) were collected at baseline. Diagnoses were determined using the Structured Clinical Interview for DSM-IV-TR (SCID patient version; First et al., 2002) and validated through consensus with a staff research psychiatrist. Functioning was examined at month 12 using the Social and Occupational Functioning Assessment Scale (SOFAS; Morosini et al., 2000). This scale evaluates social and occupational functioning independent of overall severity of psychiatric symptoms. The ratings are done first to allocate a category (1-10 ranging from lack of autonomy in basic functions to excellent functioning) based on the description of that category and how it applies to the individual, followed by a numerical score within that category.

2.3 Neurocognitive assessment

Neurocognitive assessments were administered in pen and paper format with the Wechsler Memory Scale—Third Edition WMS-III (Wechsler, 1997b) to participants recruited between 2003 and 2010 (FEP: n=246; non-clinical controls: n=69) and in computerized format with the CogState Research Battery (CSRB;

Pietrzak et al., 2009) to participants recruited thereafter (FEP: n=179; non-clinical controls: n=69). Table 1 provides a complete list of neurocognitive tests included in each battery.

Neurocognitive assessments took place on a single occasion, when patients were in a stable but not necessarily asymptomatic condition (approximately 3 months following admission to PEPP), and were not repeated on subsequent timepoints. Average z-scores from non-clinical controls were used as normative data to transform individual patient data into battery-specific z-scores. A composite score was calculated for each cognitive domain in both neurocognitive batteries by averaging z-scores for all tests within each domain (Benoit et al., 2015).

2.4 Classification of Persistent Negative Symptoms

Following our previous work (see Bodnar et al., 2014; Hovington et al., 2012; Makowski et al., 2017), the PNS group was defined by three criteria. First, patients required a global rating of moderate (3) or more on at least one global rating of a negative symptom (flat affect, alogia, avolition-apathy, or anhedonia-asociality) as measured with the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a). Second, this group was characterized by the absence of factors that can lead to secondary negative symptoms. To that end they needed to have: i) a global rating of mild (2) or less on all global ratings of positive symptoms, as measured with the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b), ii) a total score of 4 or less on the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1990), and iii) no extrapyramidal symptoms or very mild presence of such symptoms that did not

require treatment with anticholinergic medication based on the Extrapyramidal Symptom Rating Scale (ESRS; Chouinard and Margolese, 2005). Third, these symptom severity criteria had to be maintained for at least 6 consecutive months during the first year of treatment (specifically between months 6 and 12). Patients who displayed moderate or more levels of negative symptoms in the presence of clinically relevant positive, depressive, or extrapyramidal symptoms were considered to have secondary PNS (sPNS). This definition is consistent with recent work on secondary negative symptoms (Correll and Schooler, 2020; Kirschner et al., 2017), which we have also successfully applied to brain imaging studies (Makowski et al., 2016; Makowski et al., 2017). The remaining patients were classified as not having PNS (non-PNS).

2.5 Statistical Analyses

Differences in demographic and clinical characteristics between groups were tested with unpaired *t* tests, χ^2 tests, and Mann-Whitney tests as appropriate. A Multivariate Analysis of Covariance (MANCOVA) was conducted with group as the independent variable and each neurocognitive domain (speed of processing, attention, working memory, visual memory, verbal memory, executive function) as the dependent variable, covarying for sex and battery type (WMS-III, CSRB). This test was followed by ANCOVAs on each cognitive domain using the same covariates. In previous studies (Benoit et al., 2015; Buck et al., 2020), we found sex- and battery-specific differences in neurocognitive performance, thus justifying our rationale for including these variables as covariates. All analyses were conducted: 1) between FEP and controls and 2) between PNS subgroups (PNS, sPNS, non-PNS) and 3) between PNS and

combining sPNS and non-PNS groups as in previous studies. Bonferroni correction was used for *post-hoc* tests. All statistical tests were performed on SPSS version 27 (SPSS, Chicago, IL, USA) and were two-tailed with an alpha level of 0.05.

3. Results

3.1 Demographical/Clinical

Our sample included 425 FEP patients including 118 (27.8%) with PNS, 87 (20.5%) with sPNS, and 220 (51.8%) without PNS (non-PNS). The sPNS patients displayed clinically relevant positive symptoms (n = 45), depressive symptoms (n = 21), positive and depressive symptoms (n = 1), extrapyramidal symptoms (n = 6), and positive and extrapyramidal symptoms (n = 3).

As can be seen in **Table 2**, non-clinical controls significantly differed from all patient groups on full-scale IQ, years of education and age. When examining FEP as a whole group, there was no significant difference on the sex or handedness proportions relative to non-clinical controls. When FEP patients were categorized into PNS groups (PNS, sPNS and non-PNS), significant differences were noted for age at entry ($F(2,422)=3.22$, $p=.041$; PNS < non-PNS ($p=.042$)), sex ($\chi^2(2)=14.76$, $p=.001$; PNS<non-PNS), years of education ($F(2,405)=10.99$, $p<.001$; non-PNS > PNS/sPNS ($p<.001$ and $p=.047$ respectively)), and IQ ($F(2,417)=6.18$, $p=.002$; PNS < non-PNS ($p=.002$)) (see **Table 2** for descriptive data). ANOVAs examined the effect of Time and Group on positive (SAPS), negative (SANS), and depressive (CDSS) symptoms. No significant effect of Time was observed on SAPS ($F(2,341)=1.48$, $p=.23$), SANS($F(2,341)=2.33$, $p=0.10$), nor CDSS ($F(2,341)=2.23$, $p=0.11$). A significant group effect was observed on SAPS ($F(2,341)=38.32$, $p<.001$), SANS($F(2,341)=110.55$, $p=0.001$), and CDSS ($F(2,341)=28.63$, $p<0.001$).

Finally a significant interaction between Time and Group was noted for SAPS ($F(4,341)=5.11$, $p<.001$), SANS($F(4,341)=12.22$, $p<0.001$), but not on the CDSS ($F(2,341)=1.41$, $p=0.23$). As expected, the sPNS patient subgroup had significantly higher SAPS totals compared to the PNS and non-PNS subgroups at 6 and 12 months. Also, the PNS and sPNS subgroups had significantly higher SANS totals compared to the non-PNS subgroup across all timepoints. FEP subgroups differed in distribution of diagnosis, with a higher proportion of non-PNS diagnosed with affective psychotic disorders (major depression, bipolar), and higher proportions of schizophrenia/schizophreniform diagnoses in the PNS and sPNS subgroups. Additionally, the amount of antipsychotic prescribed in chlorpromazine equivalents at 6 and 12 months was significantly higher for sPNS patients compared to non-PNS. **Table 3** summarizes symptom data and antipsychotic information at the time of neurocognitive assessment and at 6- and 12-month timepoints.

3.2 Association of PNS with neurocognitive domains

A first series of analyses compared all FEP participants together with the non-clinical controls. An omnibus MANCOVA analysis, performed to determine whether FEP as a group showed neurocognitive impairments relative to controls, revealed a significant effect of group ($F(6,519)=23.12$, $p<.001$) when all cognitive domains were considered. This was followed by ANCOVAs on individual cognitive domains, revealing significant differences between groups across all domains: verbal memory ($F(1,524)=112.52$, $p<.001$), visual memory ($F(1,524)=60.85$, $p<.001$), working memory ($F(1,524)=54.81$, $p<.001$), executive

functions (F(1,524)= 66.02, p<.001), speed of processing (F(1,524)=19.72, p<.001), and attention (F(1,524)=37.29, p<.001).

A second series of analyses specifically examined the 3 groups of FEP patients (PNS, sPNS and non-PNS). A MANCOVA revealed a significant effect of group (F(12,760)=2.18, p=.011) and subsequent ANCOVAs on individual cognitive domains revealed significant differences between groups for verbal memory (F(2,385)=9.06, p<.001, $\eta^2_{partial}$ = .045) and working memory (F(2,385)=3.95, p<.02, $\eta^2_{partial}$ = .020) only. All other domains (visual memory, executive functions, speed of processing, and attention) failed to reach significance (p's>.18). Simple effects analyses for verbal memory revealed a significant difference between PNS and non-PNS (p<.001) and a trend towards significance for the comparison between sPNS and non-PNS (p=.059). No significant difference was observed between PNS and sPNS (p=.53). Similar simple effects analyses for working memory revealed a significant difference between PNS and non-PNS (p<.02) but no significant differences between sPNS and non-PNS (p=1.0) nor between PNS and sPNS (p=.17). **Figure 1** illustrates the neuropsychological profile of all three FEP groups as a function of cognitive domains.

To better characterize how the inclusion of patients presenting with sPNS with non-PNS patients may have influenced results of previous studies, we conducted additional analyses in which we combined the sPNS and non-PNS groups together. This two-group MANCOVA revealed a significant effect of group (F(6,381)=2.95, p=.008) and subsequent ANCOVAs on individual cognitive domains revealed significant differences between groups for verbal memory (F(1,386)=12.48, p<.001, $\eta^2_{partial}$ = .031), working memory (F(1,386)=7.71, p<.006,

$\eta^2_{partial}$ = .020) and executive functions (F(1,386)=4.09, p<.044, $\eta^2_{partial}$ = .010). Visual memory, speed of processing, and attention did not reach significance (all ps >.10). It is of interest to note that the measure of effect size (Partial Eta-Squared, $\eta^2_{partial}$), was stronger for verbal memory ($\eta^2_{partial}$ = .045) in the ANCOVA with 3 groups relative to the ANCOVA with 2 groups ($\eta^2_{partial}$ = .031).

3.3 Effects of early and secondary PNS on psychosocial functioning

Functioning was examined at month 12 using the SOFAS and an ANOVA revealed a significant difference between patient groups (F(2,323)=84.31, p<.001). Simple effect analyses showed that the non-PNS group had significantly higher level of functioning relative to PNS (p<.001) and sPNS (p<.001). In addition, the PNS group had significantly higher level of functioning than the sPNS group (p<.001).

4. Discussion

This study used a large sample of patients to examine the neurocognitive correlates of persistent negative symptoms following a first episode of psychosis. Unlike previous studies on PNS in early psychosis, we identified a group of patients with secondary PNS, thus minimizing potential confounds contributed by this group which has traditionally been pooled with non-PNS patients. Using two cognitive batteries that reproduced the MATRICS consensus battery (Nuechterlein et al., 2008), we observed significant differences between PNS and non-PNS groups limited to verbal memory and working memory. The sPNS group exhibited a trend towards significance relative to the non-PNS group on verbal memory, suggesting that some participants of this group clearly manifest

cognitive impairments. Finally, the isolation of a group of FEP patients with sPNS allowed for their characterization on multiple dimensions. In particular, this group exhibited significant impairments in functioning similar to the PNS group and higher levels of positive and depressive symptomatology and finally, higher dose of antipsychotics.

The finding of verbal and working memory measures significantly distinguishing PNS from the non-PNS subgroup replicates and extends our previous work (Hovington et al., 2013) in a larger sample. The subgroup with sPNS only exhibited a trend toward significance on verbal memory measures relative to non-PNS patients. The association between verbal memory impairment and PNS is consistent with the observation that both are related to functional impairments. For instance, we reported previously that baseline verbal episodic memory and persistence of negative symptoms represented the strongest predictors of functioning outcome after two years of care (Jordan et al., 2014; Jordan et al., 2018) and a recent independent study similarly revealed both factors to predict future employment status in FEP (Karambelas et al., 2019). Working memory also differed between PNS and non-PNS, an observation reported before (Ucok and Ergul, 2014) using the digit span. It should also be noted that several studies on neurocognitive functions and PNS did not administer a measure of working memory (for example Galderisi et al., 2013; Malla et al., 2004), hence the paucity of evidence for this relationship.

We did not observe significant differences on measures of executive functions, unlike other studies (Puig et al., 2017; Ucok and Ergul, 2014). Interestingly, when the sPNS and non-PNS groups were combined together into a

single group, we did observe a significant difference relative to the PNS group. Hence, this suggests that the pattern of results is sensitive to the composition of the non-PNS group and whether or not sPNS patients are included. Another factor to consider from previous studies which observed significant differences between PNS and non-PNS relates to the nature of the neurocognitive tasks administered. Specifically, these studies administered the Wisconsin Card Sorting Task (WCST), an arguably more complex task compared to our assessments of executive function (e.g. Trail-B and set-shifting). This raises the possibility that using the WCST may be a more sensitive, albeit more complex, measure tapping into various cognitive processes of executive function.

The three FEP groups included in the present study significantly differed on multiple clinical and functional dimensions. At the end of the first year of treatment, both PNS and sPNS groups had poorer functioning relative to non-PNS, a finding that has been consistently reported (Bucci et al., 2020; Chang et al., 2011; Galderisi et al., 2013; Hovington et al., 2012; Puig et al., 2017; Ucok and Ergul, 2014). By design, sPNS presented more severe positive and depressive symptoms than the other two groups, but they also received higher doses of antipsychotics at 6 and 12 months and showed poorer functioning at 12 months relative to non-PNS. It follows that the sPNS group encompass multiple factors influencing ratings of negative symptoms and as such, may capture a heterogeneous collection of patients with varying etiologies that all converge on poor functioning.

Brain imaging evidence in PNS may provide converging evidence for some of our findings. In a smaller cross-sectional sample, we have previously observed

right medial temporal lobe abnormalities in PNS patients relative to non-PNS patients (Benoit et al., 2012; Bodnar et al., 2014). These findings are consistent with the results of a recent meta-analysis (Li et al., 2018) of 12 VBM studies in PNS that reported grey matter reduction in the parahippocampal gyrus bilaterally, left caudate and left prefrontal cortex. In a longitudinal brain imaging study separating PNS from sPNS, we further confirmed these cortical abnormalities and reported that thinner cortex in temporal regions seems specific to PNS patients (Makowski et al., 2016). We also found altered maturational trajectories of cortical thickness in PNS patients with age, with younger patients showing reduced thickness and subsequent thickening with age in multiple prefrontal regions. In a subsequent longitudinal imaging study of limbic structures using the same cohort, it was found that PNS patients had significantly reduced amygdalar and right hippocampal volumes, as well as different maturational trajectories of these structures, relative to sPNS and non-PNS groups (Makowski et al., 2017). Hence, these results confirm the potentially different etiologies between PNS and sPNS and provide further evidence for medial temporal and frontal structural abnormalities in PNS, which may contribute to the observed memory deficits in this group observed in this study. Considering these imaging findings between PNS and sPNS, it would be of great interest to examine neurodevelopmental trajectories and determine whether differences exist in factors such as premorbid functioning and history of trauma.

The involvement of hippocampal pathology in psychotic disorders is well established (Harrison, 2004; Heckers and Konradi, 2010) and significant associations in schizophrenia have been reported between hippocampal

volume and verbal memory (Antoniades et al., 2018). Several studies have shown an association between measures of the integrity of the hippocampus such as total volume and the severity of negative symptoms (e.g. Duan et al., 2020; Matsumoto et al., 2001; Rajarethinam et al., 2001). In a recent paper (Makowski et al., 2020a) used a novel brain imaging measure of the nature of hippocampal connectivity with the rest of the brain (termed hippocampal centrality) and examined the hypothesis that longitudinal changes in the hippocampal circuit are altered in FEP and that such changes are associated with negative symptoms and verbal memory. Importantly, this study observed that lower centrality (or reduced coupling) of the hippocampal circuit with other cortical networks was associated with worse negative symptoms over time, a relationship that was mediated by changes in verbal memory. Hence, this study demonstrated the important role of the hippocampal circuit (subfields and surrounding white matter) underlying the trajectory of negative symptoms following a FEP and the contributions of verbal memory to this relationship.

One interesting avenue to further study the association between neurocognitive functions and negative symptoms is to examine their interplay prior to the onset of psychosis. There has been recent interest in clinical high risk and negative symptoms (Azar et al., 2018; Sauve et al., 2019). This is of particular interest as negative symptoms and cognitive impairments seem to be emerging during this period (Gerritsen et al., 2020). Recent studies have now examined PNS in this population in relation to functioning and neurocognitive capacity and one report described a significant difference in verbal fluency between clinical high risk individuals with and without PNS (Yung et al., 2019); although no such

differences were observed in another recent and large longitudinal study (Devoe et al., 2020). Finally, another recent study (Ucok et al., 2020) found that negative symptoms had an impact on functioning in a cohort of clinical high risk. Interestingly, an association of cognitive flexibility and attention with functioning was mediated by negative symptoms in clinical high risk. Hence, the current literature in clinical high risk is still in its early stages but seems to suggest associations between neurocognitive functions, negative symptoms, and functioning.

The current study has some important limitations to consider. First, measures of social cognition were not systematically examined in this study and growing evidence suggests a strong association of social cognition with negative symptoms (Green, 2020; Kalin et al., 2015; Lincoln et al., 2011; Lysaker et al., 2012; Pelletier-Baldelli and Holt, 2020; Piskulic and Addington, 2011). Although the Cogstate battery includes a measure of social cognition (social emotional cognitive test), this test is a stronger measure of emotion recognition or processing rather than theory of mind, which shows the strongest relation to functioning relative to other social cognitive domains (Fett et al., 2011). Recent evidence also suggests a link between social cognition, episodic memory and the medial temporal lobe including the hippocampus (Laurita and Spreng, 2017; Montagrin et al., 2018; Thibaudeau et al., 2020). As such, future studies need to examine the association between social cognition and verbal memory in PNS with respect to both behavior and brain structure/function. Another important limitation is the difference in proportion of affective and non-affective psychosis across FEP groups. However, we aimed to focus on the evolution of negative

symptoms after a FEP regardless of diagnosis to maximize the clinical utility of our work. Considering that our interest resided in the characterization of FEP patients at time of entry in a specialized program and as a function of the evolution of their negative symptoms in order to maximize the clinical utility of such findings, the current work nonetheless provides new insights into the neurocognitive correlates of PNS. Finally, another important limitation is the relatively narrow definition of sPNS that considered only positive, depressive, and extra-pyramidal symptoms. As recent reviews suggest (Correll and Schooler, 2020; Kirschner et al., 2017), other factors could be examined including symptoms of anxiety, substance abuse and environmental factors such as social deprivation. Hence, future studies on sPNS are encouraged to comprehensively assess all these factors.

In sum, our study identified measures of verbal memory and working memory as important differentiators between PNS and non-PNS patients. The sPNS subgroup exhibited a trend towards significance on verbal memory. It is quite possible that the mechanism for neurocognitive impairment may be different between PNS and sPNS. Another possibility is that the sPNS subgroup may represent a superposition of secondary factors on primary negative symptoms. Hence, the treatment for negative symptoms should be adapted to the different profiles of PNS and sPNS to maximize their effectiveness. This could involve varying pharmacological and psychosocial interventions based on the nature of the negative symptoms and accompanying cognitive impairments.

Author Disclosure

Role of funding source

Funding for this study was provided by CIHR Grant 68961; the CIHR had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

M.B., M.L., and A.K.M. designed the study and wrote the protocol. M.B., M.L. D.R-C, K.L. C.M. managed the literature searches and analyses. M.B, M.L., and D.R-C. undertook the statistical analysis and wrote the first draft of the manuscript. A.K.M and R.J. provided expertise with clinical assessments. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

Salary awards include: FRSQ to J.L.S., R.J., M.B., and M.L.; a Canada Research Chair to A.M.; and a James McGill Professorship to M.L. M.L. reports grants from Otsuka Lundbeck Alliance, diaMentis personal fees from Otsuka Canada, personal fees from Lundbeck Canada, grants and personal fees from Janssen, and personal fees from MedAvante-Prophase, outside the submitted work. R.J. reports receipt of grants, speaker's and consultant's honoraria from Janssen, Lundbeck, Otsuka, Pfizer, Shire, Perdue, HLS and Myelin and royalties from Henry Stewart Talks. A.M. reports research funding for an investigator-initiated project from BMS Canada and honoraria for lectures and consulting activities (e.g. advisory board participation) with Otsuka and Lundbeck, all unrelated to the present article. All other authors report no competing interests.

Acknowledgements

We thank PEPP-Montreal research staff for their help with recruitment and for conducting the clinical assessments. Finally, we are grateful to all the people who participated in the study.

References

Addington, D., Addington, J., Schissel, B., 1990. A depression rating scale for schizophrenics. Schizophrenia research 3, 247-251.

Andreasen, N.C., 1984a. Modified scale for the assessment of Negative Symptoms (SANS). University of Iowa, Iowa City.

Andreasen, N.C., 1984b. Scale for the Assessment of Positive Symptoms (SAPS). University of Iowa, Iowa City.

Antoniades, M., Schoeler, T., Radua, J., Valli, I., Allen, P., Kempton, M.J., McGuire, P., 2018. Verbal learning and hippocampal dysfunction in schizophrenia: A meta-analysis. Neurosci Biobehav Rev 86, 166-175.

Azar, M., Pruessner, M., Baer, L.H., Iyer, S., Malla, A.K., Lepage, M., 2018. A study on negative and depressive symptom prevalence in individuals at ultra-high risk for psychosis. Early Interv Psychiatry 12, 900-906.

Benoit, A., Bodnar, M., Malla, A.K., Joober, R., Lepage, M., 2012. The structural neural substrates of persistent negative symptoms in first-episode of non-affective psychosis: a voxel-based morphometry study. Front Psychiatry 3, 42.

Benoit, A., Malla, A.K., Iyer, S.N., Joober, R., Bherer, L., Lepage, M., 2015. Cognitive deficits characterization using the CogState Research Battery in first-episode psychosis patients. Schizophr Res Cogn 2, 140-145.

Bodnar, M., Hovington, C.L., Buchy, L., Malla, A.K., Joober, R., Lepage, M., 2014. Cortical thinning in temporo-parietal junction (TPJ) in non-affective first-episode of psychosis patients with persistent negative symptoms. PLoS One 9, e101372.

Brickenkamp, R., Zilmer, E., 1998. d2–Test of Attention Hogrefe & Huber Publishers. Göttingen.

Bucci, P., Mucci, A., van Rossum, I.W., Aiello, C., Arango, C., Baandrup, L., Buchanan, R.W., Dazzan, P., Demjaha, A., Diaz-Caneja, C.M., Giordano, G.M., Glenthoj, B.Y., Leucht, S., McGuire, P., Rodriguez-Jimenez, R., Vignapiano, A., Kahn, R.S., Galderisi, S., 2020. Persistent negative symptoms in recent-onset psychosis: Relationship to treatment response and psychosocial functioning. Eur Neuropsychopharmacol 34, 76-86.

Buchanan, R.W., 2007. Persistent negative symptoms in schizophrenia: an overview. Schizophrenia bulletin 33, 1013-1022.

Buchy, L., Bodnar, M., Malla, A., Joober, R., Lepage, M., 2010. A 12-month outcome study of insight and symptom change in first-episode psychosis. Early Interv Psychiatry 4, 79-88.

Buck, G., Lavigne, K.M., Makowski, C., Joober, R., Malla, A., Lepage, M., 2020. Sex Differences in Verbal Memory Predict Functioning Through Negative Symptoms in Early Psychosis. Schizophrenia bulletin.

Chang, W.C., Hui, C.L., Tang, J.Y., Wong, G.H., Lam, M.M., Chan, S.K., Chen, E.Y., 2011. Persistent negative symptoms in first-episode schizophrenia: a prospective three-year follow-up study. Schizophrenia research 133, 22-28.

Chouinard, G., Margolese, H.C., 2005. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). Schizophr Res 76, 247-265.

Correll, C.U., Schooler, N.R., 2020. Negative Symptoms in Schizophrenia: A Review and Clinical Guide for Recognition, Assessment, and Treatment. Neuropsychiatric disease and treatment 16, 519-534.

Cotton, S.M., Lambert, M., Schimmelmann, B.G., Mackinnon, A., Gleeson, J.F., Berk, M., Hides, L., Chanen, A., McGorry, P.D., Conus, P., 2012. Depressive symptoms in first episode schizophrenia spectrum disorder. Schizophrenia research 134, 20-26.

Devoe, D.J., Lu, L., Cannon, T.D., Cadenhead, K.S., Cornblatt, B.A., McGlashan, T.H., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Woods, S.W., Walker, E.F., Mathalon, D.H., Bearden, C.E., Addington, J., 2020. Persistent negative symptoms in youth at clinical high risk for psychosis: A longitudinal study. Schizophrenia research.

Duan, X., He, C., Ou, J., Wang, R., Xiao, J., Li, L., Wu, R., Zhang, Y., Zhao, J., Chen, H., 2020. Reduced Hippocampal Volume and Its Relationship With Verbal Memory and Negative Symptoms in Treatment-Naive First-Episode Adolescent-Onset Schizophrenia. Schizophrenia bulletin.

Eack, S.M., Keshavan, M.S., 2020. Cognition, negative symptoms, and functional outcome in psychosis. Schizophrenia research.

Fett, A.K., Viechtbauer, W., Dominguez, M.D., Penn, D.L., van Os, J., Krabbendam, L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci Biobehav Rev 35, 573-588.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B., 2002. Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition. SCID-I/P New York, NY, USA:.

Foussias, G., Agid, O., Fervaha, G., Remington, G., 2014. Negative symptoms of schizophrenia: clinical features, relevance to real world functioning and specificity versus other CNS disorders. Eur Neuropsychopharmacol 24, 693-709.

Galderisi, S., Merlotti, E., Mucci, A., 2015. Neurobiological background of negative symptoms. European archives of psychiatry and clinical neuroscience 265, 543-558.

Galderisi, S., Mucci, A., Bitter, I., Libiger, J., Bucci, P., Fleischhacker, W.W., Kahn, R.S., Eufest Study, G., 2013. Persistent negative symptoms in first episode patients with schizophrenia: results from the European First Episode Schizophrenia Trial. Eur Neuropsychopharmacol 23, 196-204.

Gerritsen, C., Maheandiran, M., Lepock, J., Ahmed, S., Kiang, M., Bagby, R.M., Mizrahi, R., 2020. Negative symptoms in the clinical high-risk state for psychosis: Connection with cognition and primacy in impacting functioning. Early Interv Psychiatry 14, 188-195.

Green, M.F., 2020. From Social Cognition to Negative Symptoms in Schizophrenia: How Do We Get There From Here? Schizophrenia bulletin 46, 225-226.

Harrison, P.J., 2004. The hippocampus in schizophrenia: a review of the neuropathological evidence and its pathophysiological implications. Psychopharmacology 174, 151-162.

Harvey, P.D., Koren, D., Reichenberg, A., Bowie, C.R., 2006. Negative symptoms and cognitive deficits: what is the nature of their relationship? Schizophrenia bulletin 32, 250-258.

Heckers, S., Konradi, C., 2010. Hippocampal pathology in schizophrenia. Curr Top Behav Neurosci 4, 529-553.

Hovington, C.L., Bodnar, M., Chakravarty, M.M., Joober, R., Malla, A.K., Lepage, M., 2015. Investigation of white matter abnormalities in first episode psychosis patients with persistent negative symptoms. Psychiatry Res 233, 402-408.

Hovington, C.L., Bodnar, M., Joober, R., Malla, A.K., Lepage, M., 2012. Identifying persistent negative symptoms in first episode psychosis. BMC Psychiatry 12, 224.

Hovington, C.L., Bodnar, M., Joober, R., Malla, A.K., Lepage, M., 2013. Impairment in verbal memory observed in first episode psychosis patients with persistent negative symptoms. Schizophrenia research 147, 223-229.

Hovington, C.L., Lepage, M., 2012. Neurocognition and neuroimaging of persistent negative symptoms of schizophrenia. Expert Rev Neurother 12, 53-69.

Ince, E., Ucok, A., 2018. Relationship Between Persistent Negative Symptoms and Findings of Neurocognition and Neuroimaging in Schizophrenia. Clin EEG Neurosci 49, 27-35.

Iyer, S., Jordan, G., MacDonald, K., Joober, R., Malla, A., 2015. Early intervention for psychosis: a Canadian perspective. J Nerv Ment Dis 203, 356-364.

Jordan, G., Lutgens, D., Joober, R., Lepage, M., Iyer, S.N., Malla, A., 2014. The relative contribution of cognition and symptomatic remission to functional outcome following treatment of a first episode of psychosis. The Journal of clinical psychiatry 75, e566-572.

Jordan, G., Veru, F., Lepage, M., Joober, R., Malla, A., Iyer, S.N., 2018. Pathways to functional outcomes following a first episode of psychosis: The roles of premorbid adjustment, verbal memory and symptom remission. Aust N Z J Psychiatry 52, 793-803.

Kalin, M., Kaplan, S., Gould, F., Pinkham, A.E., Penn, D.L., Harvey, P.D., 2015. Social cognition, social competence, negative symptoms and social outcomes: Inter-relationships in people with schizophrenia. Journal of psychiatric research 68, 254-260.

Karambelas, G.J., Cotton, S.M., Farhall, J., Killackey, E., Allott, K.A., 2019. Contribution of neurocognition to 18-month employment outcomes in first-episode psychosis. Early Interv Psychiatry 13, 453-460.

Kirkpatrick, B., Fenton, W.S., Carpenter, W.T., Jr., Marder, S.R., 2006. The NIMH-MATRICS consensus statement on negative symptoms. Schizophrenia bulletin 32, 214-219.

Kirschner, M., Aleman, A., Kaiser, S., 2017. Secondary negative symptoms - A review of mechanisms, assessment and treatment. Schizophrenia research 186, 29-38.

Laurita, A.C., Spreng, R.N., 2017. The hippocampus and social cognition, in: Hannula, D.E., Duff, M.C. (Eds.), The hippocampus from cells to systems: Structure, connectivity, and functional contributions to memory and flexible cognition. Springer International Publishing, Cham, Switzerland, pp. 537-558.

Li, Y., Li, W.X., Xie, D.J., Wang, Y., Cheung, E.F.C., Chan, R.C.K., 2018. Grey matter reduction in the caudate nucleus in patients with persistent negative symptoms: An ALE meta-analysis. Schizophrenia research 192, 9-15.

Lincoln, T.M., Mehl, S., Kesting, M.L., Rief, W., 2011. Negative symptoms and social cognition: identifying targets for psychological interventions. Schizophrenia bulletin 37 Suppl 2, S23-32.

Lysaker, P.H., Erikson, M., Macapagal, K.R., Tunze, C., Gilmore, E., Ringer, J.M., 2012. Development of personal narratives as a mediator of the impact of deficits in social cognition and social withdrawal on negative symptoms in schizophrenia. J Nerv Ment Dis 200, 290-295.

Makowski, C., Bodnar, M., Malla, A.K., Joober, R., Lepage, M., 2016. Age-related cortical thickness trajectories in first episode psychosis patients presenting with early persistent negative symptoms. NPJ Schizophr 2, 16029.

Makowski, C., Bodnar, M., Shenker, J.J., Malla, A.K., Joober, R., Chakravarty, M.M., Lepage, M., 2017. Linking persistent negative symptoms to amygdala-hippocampus structure in first-episode psychosis. Transl Psychiatry 7, e1195.

Makowski, C., Lewis, J.D., Khundrakpam, B., Tardif, C.L., Palaniyappan, L., Joober, R., Malla, A., Shah, J.L., Bodnar, M., Chakravarty, M.M., Evans, A.C., Lepage, M., 2020a. Altered hippocampal centrality and dynamic anatomical covariance of intracortical microstructure in first episode psychosis. Hippocampus 30, 1058-1072.

Makowski, C., Lewis, J.D., Lepage, C., Malla, A.K., Joober, R., Evans, A.C., Lepage, M., 2020b. Intersection of verbal memory and expressivity on cortical contrast and thickness in first episode psychosis. Psychol Med 50, 1923-1936.

Malla, A.K., Norman, R.M., Takhar, J., Manchanda, R., Townsend, L., Scholten, D., Haricharan, R., 2004. Can patients at risk for persistent negative symptoms be identified during their first episode of psychosis? J Nerv Ment Dis 192, 455-463.

Matsumoto, H., Simmons, A., Williams, S., Pipe, R., Murray, R., Frangou, S., 2001. Structural magnetic imaging of the hippocampus in early onset schizophrenia. Biol Psychiatry 49, 824-831.

Milev, P., Ho, B.C., Arndt, S., Andreasen, N.C., 2005. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. The American journal of psychiatry 162, 495-506.

Montagrin, A., Saiote, C., Schiller, D., 2018. The social hippocampus. Hippocampus 28, 672-679.

Morosini, P.L., Magliano, L., Brambilla, L., Ugolini, S., Pioli, R., 2000. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. Acta Psychiatr Scand 101, 323-329.

Mucci, A., Merlotti, E., Ucok, A., Aleman, A., Galderisi, S., 2017. Primary and persistent negative symptoms: Concepts, assessments and neurobiological bases. Schizophrenia research 186, 19-28.

Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese, F.J., 3rd, Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., Zalcman, S., Marder, S.R., 2008. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. The American journal of psychiatry 165, 203-213.

Pelletier-Baldelli, A., Holt, D.J., 2020. Are Negative Symptoms Merely the "Real World" Consequences of Deficits in Social Cognition? Schizophrenia bulletin 46, 236-241.

Pietrzak, R.H., Olver, J., Norman, T., Piskulic, D., Maruff, P., Snyder, P.J., 2009. A comparison of the CogState Schizophrenia Battery and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Battery in assessing cognitive impairment in chronic schizophrenia. Journal of clinical and experimental neuropsychology 31, 848-859.

Piskulic, D., Addington, J., 2011. Social cognition and negative symptoms in psychosis. Psychiatry Res 188, 283-285.

Puig, O., Baeza, I., de la Serna, E., Cabrera, B., Mezquida, G., Bioque, M., Lobo, A., Gonzalez-Pinto, A., Parellada, M., Corripio, I., Vieta, E., Bobes, J., Usall, J., Contreras, F., Cuesta, M.J., Bernardo, M., Castro-Fornieles, J., Group, P.E., 2017. Persistent Negative Symptoms in First-Episode Psychosis: Early Cognitive and Social Functioning Correlates and Differences Between Early and Adult Onset. The Journal of clinical psychiatry 78, 1414-1422.

Rajarethinam, R., DeQuardo, J.R., Miedler, J., Arndt, S., Kirbat, R., Brunberg, J.A., Tandon, R., 2001. Hippocampus and amygdala in schizophrenia: assessment of the relationship of neuroanatomy to psychopathology. Psychiatry Res 108, 79-87.

Rammou, A., Fisher, H.L., Johnson, S., Major, B., Rahaman, N., Chamberlain-Kent, N., Stone, J.M., 2019. Negative symptoms in first-episode psychosis: Clinical correlates and 1-year follow-up outcomes in London Early Intervention Services. Early Interv Psychiatry 13, 443-452.

Reitan, R.M., 1992. Trail Making Test: Manual for administration and scoring. Reitan Neuropsychology Laboratory.

Sauve, G., Brodeur, M.B., Shah, J.L., Lepage, M., 2019. The Prevalence of Negative Symptoms Across the Stages of the Psychosis Continuum. Harv Rev Psychiatry 27, 15-32.

Sonmez, N., Romm, K.L., Andreasssen, O.A., Melle, I., Rossberg, J.I., 2013. Depressive symptoms in first episode psychosis: a one-year follow-up study. BMC Psychiatry 13, 106.

Strauss, G.P., Esfahlani, F.Z., Galderisi, S., Mucci, A., Rossi, A., Bucci, P., Rocca, P., Maj, M., Kirkpatrick, B., Ruiz, I., Sayama, H., 2019. Network Analysis Reveals the Latent Structure of Negative Symptoms in Schizophrenia. Schizophrenia bulletin 45, 1033-1041.

Strauss, G.P., Nunez, A., Ahmed, A.O., Barchard, K.A., Granholm, E., Kirkpatrick, B., Gold, J.M., Allen, D.N., 2018. The Latent Structure of Negative Symptoms in Schizophrenia. JAMA Psychiatry 75, 1271-1279.

Stroop, J.R., 1992. Studies of interference in serial verbal reactions. Journal of Experimental Psychology: General 121, 15.

Thibaudeau, E., Achim, A.M., Parent, C., Turcotte, M., Cellard, C., 2020. A meta-analysis of the associations between theory of mind and neurocognition in schizophrenia. Schizophrenia research 216, 118-128.

Ucok, A., Direk, N., Kaya, H., Caglar, N., Cikrikcili, U., Noyan, H., Yokusoglu, C., Devrim-Ucok, M., 2020. Relationship of negative symptom severity with cognitive symptoms and functioning in subjects at ultra-high risk for psychosis. Early Interv Psychiatry.

Ucok, A., Ergul, C., 2014. Persistent negative symptoms after first episode schizophrenia: A 2-year follow-up study. Schizophrenia research 158, 241-246.

Wechsler, D., 1997a. Wechsler Adult Intelligence Scale. 3rd edn. The Psychological Corporation, San Antonio, TX.

Wechsler, D., 1997b. Weschsler Memory Scale-III. The Psychological Corporation, San Antonio, TX.

Wechsler, D., 1999. Weschler Abbreviated Scale of Intelligence. The Psychological Corporation, San Antonia, TX.

Woods, S.W., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. The Journal of clinical psychiatry 64, 663-667.

Woods, S.W., 2011. Chlorpromazine Equivalent Doses for Atypical Antipsychotics: An Update 2003-2010, pp. 1-8.

Wunderink, L., van Bebber, J., Sytema, S., Boonstra, N., Meijer, R.R., Wigman, J.T.W., 2020. Negative symptoms predict high relapse rates and both predict less favorable functional outcome in first episode psychosis, independent of treatment strategy. Schizophrenia research 216, 192-199.

Yung, A.R., Nelson, B., McGorry, P.D., Wood, S.J., Lin, A., 2019. Persistent negative symptoms in individuals at Ultra High Risk for psychosis. Schizophrenia research 206, 355-361.

Table 1. List of Cognitive Measures for Each Domain of Cognition Assessed

Cognitive Domain	Pen and Paper Battery	CogState Research Battery
Speed of processing	Digit Symbol[a] Trail Making Test A[b] Stroop Test: Word[c] Stroop Test: Color[c]	Groton Maze Chase Test Detection Task
Attention	D2 Test[d] Stroop Test: Inhibition[c]	Identification Task
Working memory	Digit Span[a] Corsi Spatial Span[e]	One-back Task Two-back Task
Visual memory	Visual Reproduction: Immediate Recall[e] Visual Reproduction: Delayed Recall[e]	One-Card Learning Task Continuous Paired Associate Groton Maze Learning Task: Delayed Recall
Verbal memory	Logical Memory: Immediate Recall[e] Logical Memory: Delayed Recall[e]	International Shopping List: Immediate Recall International Shopping List: Delayed Recall
Executive function	Block Design[a] Trail Making Test B[b]	Groton Maze Learning Task Set-Shifting Task

[a] (Wechsler, 1997a)
[b] Reitan (1992)
[c] Stroop (1992)
[d] Brickenkamp and Zilmer (1998)
[e] (Wechsler, 1997b)

Table 2. Sociodemographic and diagnostic information for the different FEP groups and non-clinical controls.

		FEP			Controls (n=138)	Statistic$_{(df)}$	*p*-value
		PNS (n=118)	sPNS (n=87)	Non-PNS (n=220)			
General Demographics and clinical data							
	Age at entry (years), *M* (*SD*)	22.47 (4.11)	23.64 (4.69)	23.77 (4.85)	24.46 (5.14)	t(554)=-2.25	0.025
	Male, n (%) [a]	96 (81.36) [a]	59 (67.82) [a, b]	134 (60.91) [b]	96	χ^2(1)=0.12	0.731
	Education (years), *M* (*SD*) [n]	10.93 (2.60) [113]	11.54 (2.96) [83]	12.43 (2.87) [212]	14 (2.32) [136]	t(542)=-7.88	<0.001
	Socioeconomic Status						
	Right-handed, n (%) [a]	80 (67.80) [a]	53 (60.92) [a]	154 (70) [a]	113 (81.88)	χ^2(2)=3.27	0.195
	Full Scale IQ, *M* (*SD*) [n]	93.17 (15.46) [117]	96.63 (16.89) [87]	99.16 (15.07) [216]	110.14 (14.42) [138]	t(556)=-9.01	<0.001
	DUP (weeks), *M (SD)* [n] [c]	50.86 (85.66)	70.01 (122.91)	51.85 (130.88)			
	DUI (weeks), *M (SD)* [n] [c]	270.72 (249.17)	361.76 (303.66)	314.68 (307.67)			
Diagnosis (to be decided how to present the data) n (%)[a]							
	Schizophrenia/Schizophreniform	79 (66.95) [a]	66 (75.86) [a]	112 (50.91) [b]			
	Affective Disorder	28 (23.73) [a, b]	14 (16.09) [b]	77 (35) [a]			
	Delusional Disorder/ Psychosis NOS	11 (9.32) [a]	7 (8.05) [a]	31 (14.09) [a]			

Abbreviations: *M* = mean; *SD* = standard deviation; n = number of participants for whom data were available; PNS, persistent negative symptoms; PNS, early-PNS; 2nd-PNS, secondary-PNS; non-PNS, non-PNS; IQ: Intelligent Quotient; DUP, duration of untreated psychosis; DUI, duration of untreated illness.

[a] Each subscript letter denotes whose proportions significantly differ from each other at the *P*=0.05 level; across columns for sex and diagnosis.
[c] Analysed using transformed (square-root) data.

Table 3. Clinical data for the FEP groups as a function of timepoints and neurocognitive data.

		FEP			Statistic$_{(df)}$	*p*-value	Post-hoc comparisons (*p*-value)
		PNS (n=118)	sPNS (n=87)	Non-PNS (n=220)			
Clinical data at time of neurocognitive assessment		n = 111	n = 82	n = 204			
	SAPS total	11.36 (15.33)	13.80 (13.80)	11.69 (14.83)	F(2,394)= 0.76	0.47	-
	SANS total	29.55 (12.86)	25.83 (12.47)	17.31 (12.23)	F(2,394)= 38.42	<0.001	PNS>non-PNS (<0.001); sPNS>non-PNS (<0.001)
	CDSS	1.72 (2.97)	3.51 (4.65)	2.93 (4.06)	F(2,369)= 5.12	0.006	PNS<sPNS (0.009); PNS<non-PNS (0.036);
	CPZ equivalent (in mg)	188.81 (143.51)	179.12 (149.66)	163.20 (130.96)	F(2,370)= 1.23	0.293	-
Clinical data at month 6 assessment		n = 108	n= 78	n = 203			
	SAPS total	7.52 (10.71)	15.44 (10.84)	5.01 (8.89)	F(2,386)= 31.74	<0.001	PNS<2nd-PNS (<0.001); sPNS>non-PNS (<0.001)
	SANS total	27.65 (12.55)	25.60 (11.95)	10.91 (9.34)	F(2,386)= 104.65	<0.001	PNS>non-PNS (<0.001); sPNS>non-PNS (<0.001)
	CDSS	1.80 (3.35)	4.36 (4.42)	1.90 (3.26)	F(2,386)= 15.49	<0.001	PNS<sPNS (<0.001); sPNS>non-PNS (<0.001)
	CPZ equivalent (in mg)	184.33 (199.19)	245.14 (273.41)	178.02 (180.30)	F(2,414)= 3.37	0.035	sPNS>non-PNS (0.035)
Clinical data at month 12 assessment		n = 108	n = 84	n = 204			
	SAPS total	6.08 (7.24)	17.52 (13.95)	5.69 (9.71)	F(2,393)=43.59	<0.001	PNS<sPNS (<0.001); 2nd-PNS>non-PNS (<0.001)
	SANS total	26.28 (12.18)	26.87 (14.11)	9.04 (9.06)	F(2,393)= 121.30	<0.001	PNS>non-PNS (<0.001); sPNS>non-PNS (<0.001)
	CDSS	1.13 (2.01)	4.24 (4.34)	1.36 (2.74)	F(2,393)= 32.58	<0.001	PNS<sPNS (<0.001); 2nd-PNS>non-PNS (<0.001)
	CPZ equivalent (in mg)	217.37 (260.23)	304.37 (329.25)	156.74 (166.63)	F(2,393)= 12.35	<0.001	PNS<sPNS (0.031); 2nd-PNS>non-PNS (<0.001)
	SOFAS [a]	53.61 (14.35)	48.71 (12.84)	71.61 (14.65)	F(2,323)=84.31	<.001	PNS<non-PNS (<0.001); sPNS<non-PNS (<0.001);
Neurocognitive data		n = 107	n = 82	n = 201	F(12,760)=2.17	0.011	
	Verbal memory	-1.66	-1.34	-0.85	F(2,385)=9.06	<0.001	PNS<non-PNS (<0.001); sPNS<non-PNS (0.059)

	Visual memory	-1.36	-1.22	-0.97	F(2,385)=1.20	0.301	-
	Working memory	-1.01	-0.72	-0.64	F(2,385)=3.95	0.020	PNS<non-PNS (0.018)
	Executive functions	-1.51	-1.05	-1.08	F(2,385)=2.15	0.118	-
	Speed of processing	-0.83	-0.72	-0.45	F(2,385)=1.64	0.196	-
	Attention	-0.93	-0.96	-0.59	F(2,385)=0.72	0.486	-

Abbreviations: n = number of participants for whom data were available; PNS, persistent negative symptoms; PNS, early-PNS; sPNS, secondary-PNS; non-PNS, non-PNS; SAPS: Scale for the Assessment of Positive Symptoms; SANS: Scale for the Assessment of Negative Symptoms; CDSS: Calgary Depression Scale for Schizophrenia; CPZ: Chlorpromazine; SOFAS: Social and Occupational Functioning Assessment Scale.
[a] for SOFAS, n = 326 (PNS: 85, sPNS: 69; non-PNS: 172).

Figure 1:Neurocognitive profile across domains (in Z-scores) as a function of FEP groups