Medial temporal lobe and basal ganglia volume trajectories in persistent negative symptoms following a first episode of psychosis

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Highlights

- Distinct 24-month brain volume trajectories for PNS in first-episode psychosis
- Medial temporal lobe volumes decreased in PNS, stable in sPNS, increased in non-PNS
- Basal ganglia trajectories did not distinguish PNS groups
- Peak volume reductions at 12 to 24 months in PNS support early interventions

Abstract

Background: Persistent negative symptoms (PNS, e.g., avolition, anhedonia, alogia) are present in up to 30% of individuals diagnosed with a first episode of psychosis and greatly impact functional outcomes. PNS and secondary PNS (sPNS: concomitant with positive, depressive, or extrapyramidal symptoms) may index distinct pathophysiologies reflected by structural brain changes, particularly in the medial temporal lobe (MTL) and basal ganglia. Aims: We sought to characterize dynamic brain changes related to PNS over the course of 2 years following a first episode of psychosis. Method: Longitudinal volumetric trajectories within the MTL (hippocampus, parahippocampal gyrus, entorhinal cortex, perirhinal cortex) and basal ganglia (caudate, putamen, pallidum) were investigated in 98 patients with first-episode psychosis and 86 healthy controls using generalized estimating equations. Results: In left hippocampus, PNS (n = 25 at baseline) showed decreased volumes over time, sPNS (n = 26) volumes remained stable, and non-PNS (n = 47) volumes increased over time to control levels. PNS-specific changes were observed in left hippocampus and left perirhinal cortex, with the greatest decline from 12 to 24 months to levels significantly below those of non-PNS and controls. Affective/non-affective diagnosis, antipsychotic medication dosage and adherence at baseline did not significantly impact these findings. Basal ganglia volume trajectories did not distinguish between PNS and sPNS. Conclusions: The current study highlights distinct structural brain trajectories in PNS that are prominent in the left MTL. Basal ganglia alterations may contribute to PNS irrespective of their etiology. Left MTL volume reductions were most evident after 1 year of treatment, highlighting the importance of targeted early interventions.

Introduction

Persistent negative symptoms (PNS) refer to a reduction of either motivation (e.g., avolition, asociality, anhedonia) or expression (e.g., flat affect, alogia) that are present for at minimum 6 months, are unresponsive to treatment, and persist during periods of relative clinical stability (1, 2). PNS are observed in between 23% to 40% of patients diagnosed with either an affective or non-affective first episode of psychosis (FEP) and are associated with poor clinical outcomes (3-8). PNS in FEP have also been clearly linked to impaired neurocognition (4, 9, 10), poor insight (11), and worse functional outcome (3, 4, 12), including reduced educational and occupational attainment, lower quality of life and real-life functioning.

Previous reviews have demonstrated associations between structural brain alterations and negative symptoms or PNS in schizophrenia-spectrum disorders, including ventricular enlargement and widespread volume reductions within frontal, medial temporal, and subcortical regions (5, 10, 13-15). In PNS, structural brain alterations within the medial temporal lobe (MTL; e.g., hippocampus, parahippocampal gyrus) and basal ganglia (e.g., caudate, putamen) have been strongly implicated (5, 10, 14-17). A recent meta-analysis noted decreased brain volume in PNS in right parahippocampal gyrus, left caudate nucleus, and frontal regions (15), suggesting PNS might be understood from the perspective of dysfunction in reward-related (striatal-based) and/or memory-related (MTL-based) processes reliant on connectivity with frontal regions (14).

A better understanding of the neurobiological mechanisms underlying PNS is hampered by heterogeneity within the negative symptoms dimension as well as confounding factors of chronicity and medication in studies using enduring schizophrenia samples. FEP studies can help mitigate some of the confounding effects of medication and illness duration, which are known to affect brain morphology (18, 19). However, most neuroimaging research on PNS is confounded with secondary PNS (sPNS), which are PNS putatively caused by other factors (e.g., positive, depressive, or extrapyramidal symptoms; 20) and

may represent distinct pathophysiology (9, 16). Clinical recommendations for distinguishing between PNS and sPNS have recently been put forth, which highlight the importance of longitudinal assessments and taking into account a broader range of positive, depressive, and extrapyramidal symptoms (21). In addition, previous reviews have called for the separation of PNS and sPNS in neurobiological studies to allow for investigation of potentially distinct neurobiological mechanisms (13). Thus, longitudinal neuroimaging studies distinguishing between PNS and sPNS should provide a clearer picture of the temporal progression of brain changes underlying negative symptoms driven by different etiologies.

Nevertheless, few longitudinal studies of structural brain changes in PNS and sPNS have been conducted and none have focused on the basal ganglia. We previously noted PNS-related cortical thinning in inferior temporal regions and distinct age-related thickness trajectories in PNS and sPNS (17). A follow-up study focusing on amygdala-hippocampal structure also supported distinct age-related volume and shape trajectories in PNS relative to sPNS (16), suggesting diverging progressive brain changes in PNS and sPNS that could represent longitudinal biomarkers or dynamic endophenotypes.

The purpose of this study was to explore progressive brain changes in PNS and sPNS within cross-sectionally implicated brain regions in previous PNS studies. We thus examined longitudinal volume trajectories in the MTL and basal ganglia over two years in healthy controls and early FEP patients (approximately 3 months post-admission). Though frontal volume reductions have been observed in PNS, it has been suggested that diffusion-based structural connectivity and functional connectivity may play a greater role than regional volume reductions in frontal regions (14). We, therefore, restricted our region of interest analyses to MTL and basal ganglia, but performed supplemental exploratory whole-brain analyses. FEP patients were classified into PNS, sPNS, or non-PNS groups based on their symptom severity from 6 to 12 months post-admission. Specifically, both PNS and sPNS exhibited moderate to severe negative symptoms that persisted over 6 months. However, sPNS also presented with moderate to severe positive, depressive, or extrapyramidal symptoms. In contrast, non-PNS experienced little to

no negative symptoms over this period or negative symptoms that were not sustained over time. We hypothesized that PNS and sPNS patients would show distinct trajectories in MTL, consistent with our previous work in hippocampus (16) and temporal cortex (17). Regions of the basal ganglia were examined in an exploratory manner, but were expected to relate to both PNS and sPNS given previous findings of associations with negative symptoms more generally (15, 20).

Materials and Methods

Participants

Patients were treated at the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), a specialized early intervention service at the Douglas Mental Health University Institute in Montreal, Canada. This sample represents the neuroimaging subsample of our two recent PNS studies (9, 11). Treatment involves a comprehensive approach towards recovery with intensive medical and psychosocial management provided primarily through modified assertive case management. Individuals from a local catchment area presenting with either a non-affective or an affective FEP and between 14 to 35 years of age are accepted as either in- or out-patients. For the current neuroimaging study, the lower age limit was restricted to 18 years. PEPP-Montreal entry criteria include: IQ higher than 70; previous antipsychotic medication use less than 1 month; and no organic brain damage, pervasive developmental disorder, or epilepsy. Patients were clinically stable at the time of assessment. Diagnoses were confirmed at one-year post-admission using the SCID-IV (22) and were validated through consensus with research-staff psychiatrists. For further details, see Iyer et al (23).

Non-clinical controls were recruited from within the same catchment area as patients. Additional exclusion criteria for controls included current or past history of Axis I disorders and/or a first-degree relative diagnosed with a schizophrenia spectrum disorder. MRI exclusion criteria for both patients and controls included head trauma causing loss of consciousness or MRI contraindications (e.g., irremovable metal within the body, claustrophobia, pacemaker, pregnancy). Written informed consent was obtained

from all participants and all patients were free to withdraw from the research at any time without compromising treatment. The study was approved by the Research Ethics Board of the Douglas Mental Health University Institute and the McGill University Faculty of Medicine.

Longitudinal Procedure

Neuroimaging data were acquired at baseline (mean = 3.48 months post-admission, SD = 1.37 months, range = 1.18-5.95), and at least 12 months (mean = 16.67, SD = 1.89, range = 12.94-21.42) and 24 months (mean = 29.40, SD = 2.28, range = 26.12-36.21) thereafter. Sociodemographic and clinical data were collected at each timepoint, with an additional assessment at 6 months to allow for assignment into PNS groups (see below).

Measures

Key symptomatic data were collected using the Scale for the Assessment of Negative Symptoms (SANS; 24), Scale for the Assessment of Positive Symptoms (SAPS; 25), and Calgary Depression Scale for Schizophrenia (CDSS; 26). SANS and SAPS global scores were used to define PNS groups and the total scale scores were used in analyses, except that SANS attention items were excluded as they are more closely related to disorganization (7). At each assessment, the type and dosage of antipsychotic prescribed were noted and converted into chlorpromazine equivalents (CPZeq; 27, 28). Medication adherence was measured at each time point using a 5-point scale [0 = never (0%), 1 = infrequently (1% to 25%), 2 = sometimes (26% to 50%), 3 = often (51% to 75%), 4 = fully (76% to 100%)] based on composite information obtained from the client, family members, and treatment team; ICC = 0.84 (29). Demographic data (e.g., sex, handedness, age, education) were also obtained.

Classification of Persistent Negative Symptoms (PNS)

PNS patients were identified as in our previous research (9, 11, 12, 16, 30) consistent with Buchanan's (1) conceptualization: 1) global rating of moderate or more (≥ 3) on at least one negative symptom of the SANS; 2) global rating of mild or less (≤ 2) on all positive symptoms of the SAPS; 3) a

total score of 4 or less on the CDSS; 4) low or absent level of extrapyramidal symptoms as measured with the Extrapyramidal Symptom Rating Scale (31) and not requiring anticholinergic medication; and 5) all criteria maintained for six months (6-12 months post-admission in the current study). Accordingly, those with marked negative symptoms in the presence of clinically relevant positive, depressive, or extrapyramidal symptoms formed the secondary PNS (sPNS) subgroup, which is in line with current conceptualizations of sPNS (2, 20). Patients not categorized into either PNS or sPNS were classified as non-PNS.

Magnetic Resonance Imaging (MRI) Acquisition

T1-weighted MRI images were acquired at the Montreal Neurological Institute on a 1.5T Siemens whole-body MRI system using a 3D gradient-echo pulse sequence (TR = 22ms; TE = 9.2ms; flip angle = 30º; FOV = 256mm SI x 204mm AP; 180 sagittal slices; voxel size = $1mm^3$).The same scanner and identical parameters were used for all subjects and timepoints.

MRI Preprocessing

MR images were preprocessed in FreeSurfer version 6.0 (https://surfer.nmr.mgh.harvard.edu) via the longitudinal stream (32, 33). Though we've previously shown that MAGeTBrain (34) provides a closer approximation to manual segmentation and may be more sensitive to group differences in the hippocampus and basal ganglia (35), we chose FreeSurfer for this study to leverage its longitudinal pipeline. First, each scan was independently processed through the standard FreeSurfer pipeline (recon-all -all). Then, a within-subject template was created representing the median volume across all available timepoints for a given subject (recon-all -base). This template was then processed through the standard FreeSurfer pipeline. Longitudinal processing (recon-all -long) involved aligning each timepoint to the respective template and processing the images using common information derived from the within-subject template. Left and right hemisphere volumes for hippocampus, parahippocampal gyrus, entorhinal cortex, perirhinal cortex, caudate, putamen, and pallidum were extracted for analysis.

Quality Control and Exclusions

Of the 482 MRI scans (baseline = 141 FEP, 92 controls; 12 months = 94 FEP, 46 controls; 24 months = 77 FEP, 32 controls), 101 scans were excluded due to: withdrawn consent (n = 2 FEP, 6 scans), baseline scan more than 6 months past entry (n = 29 FEP, 60 scans), diagnosis (e.g., substance-induced psychosis, n = 3 FEP, 3 scans), missing clinical data (n = 3 patients, 4 scans), MRI signal loss (n = 3 controls, 7 scans), incidental MRI findings (n = 3 FEP, 4 scans), and FreeSurfer processing failures (n = 3 FEP, 3 control, 17 scans). The final sample consisted of 381 scans (baseline = 98 FEP, 86 controls; 12 months = 72 FEP, 44 controls; 24 months = 54 FEP, 27 controls). Table 1 displays quality-controlled sample sizes per group (PNS, sPNS, non-PNS, control) and timepoint (baseline, 12 months, 24 months).

Statistical Analysis.

Group differences were assessed at each timepoint for sociodemographic and clinical variables using one-way ANOVA or Chi-square, as appropriate. Longitudinal volumetric data were analyzed using full factorial generalized estimating equations (GEEs; first order autoregressive [AR(1)] correlation matrix; normal distribution; identity link function; 36) with group (PNS, sPNS, non-PNS, control) and Time (baseline, 12 months, 24 months) as predictors and volume as the dependent variable. Fourteen GEEs were computed to examine longitudinal trajectories in the MTL (hippocampus, parahippocampal gyrus, entorhinal cortex, perirhinal cortex) and basal ganglia (caudate, putamen, pallidum) in the left and right hemispheres separately. Covariates for all analyses consisted of age at baseline, handedness (right, left, mixed), sex (male, female), education, and estimated total intracranial volume. Significant interactions between group and timepoint were followed up with pairwise contrasts, corrected for multiple comparisons using the Benjamini-Hochberg procedure (37). To examine whether observed effects were driven by controls or by potential confounds of diagnosis (affective, non-affective), antipsychotic dose, and antipsychotic adherence in patients, we performed follow-up analyses in patients only, with diagnosis (affective/non-affective) and Chlorpromazine equivalent weighted by adherence (CPZeq

adherence) as additional covariates (see supplement). We also performed exploratory whole-brain GEEs, which are detailed in the supplement.

Results

Sociodemographic and clinical group differences

Group differences on sociodemographic and clinical variables are displayed per group and timepoint in Table 1. At baseline, groups differed on education, $F(3,180) = 14.47$, $p<0.001$, with PNS completing fewer years of education than non-PNS ($p<0.05$) and controls ($p<0.001$). Both sPNS ($p<0.001$) and non-PNS ($p<0.001$) also completed fewer years or education than controls. Consistent with the PNS group definitions, both SAPS, $F(2,95) = 11.79$, $p<0.001$, and SANS, $F(2,95) = 16.92$, $p<0.001$, differed between the groups. PNS had lower SAPS total scores than sPNS ($p<0.01$), who had higher SAPS total scores than non-PNS ($p<0.001$). Both PNS ($p<0.001$) and sPNS ($p<0.001$) had higher SANS scores than non-PNS. Proportions of affective and non-affective psychosis also differed between the groups at baseline, $\chi^2 = 7.07$, $df = 2$, $p<0.05$, with fewer patients diagnosed with affective psychosis in the sPNS group. No significant differences were noted for CPZeq adherence, illness duration, or CDSS at baseline ($ps > 0.13$). These patterns were similar across timepoints, though CPZeq was higher in sPNS than PNS and non-PNS at 12 months ($ps<0.05$) and affective/non-affective diagnosis proportions did not differ at 12 months (see Table 1).

Longitudinal volume changes in PNS

Figure 1 summarizes the overall GEE results for each region of interest, with interaction effects and pairwise comparisons displayed in Figures 2A-D. Mean volumes are shown in Table S1 per group, timepoint, and hemisphere for MTL (hippocampus, parahippocampal gyrus, entorhinal cortex, perirhinal cortex) and basal ganglia (caudate, putamen, pallidum). Pairwise comparisons following significant effects are detailed in Table S2 (between-groups) and Table S3 (within-groups over time). Results of the whole-brain GEEs are described in the supplement.

Hippocampus

Left hippocampus showed a significant Group × Time interaction, $\chi^2 = 18.65$, $df = 6$, $p < 0.005$. Pairwise between-group comparisons at each timepoint (Figure 2A) revealed PNS, sPNS, and non-PNS had lower volumes at baseline than controls ($ps < 0.09$, $ps_{ADJ} > 0.05$) but did not differ from one another ($ps > 0.65$). No group differences were observed at 12 months ($ps > 0.12$). At 24 months, PNS had significantly lower volume than non-PNS and controls ($ps < 0.05$, $ps_{ADJ} > 0.05$). None of these findings remained significant after correcting for multiple comparisons.

Pairwise within-group comparisons (Figure 2A, Figure 3) revealed decreased volume in PNS from baseline to 24 months and from 12 months to 24 months, as well as increased volume in non-PNS from baseline to 12 months and from baseline to 24 months ($ps < 0.05$, $ps_{ADJ} < 0.06$). Controls showed a decrease in volume from baseline to 12 months ($p < 0.05$, $p_{ADJ} < 0.06$) and a trend from baseline to 24 months ($p < 0.05$, $p_{ADJ} > 0.05$). These findings remained significant or trending after correcting for multiple comparisons, except for the decrease in controls from baseline to 24 months.

A trending Group × Time interaction was observed for right hippocampus (Figure 2B), $\chi^2 = 12.22$, $df = 6$, $p < 0.06$, $p_{ADJ} > 0.05$. Pairwise between-group comparisons showed a trend between PNS and controls at 24 months ($p = 0.06$) that was non-significant after adjusting for multiple comparisons ($p_{ADJ} = 0.62$). Within-group comparisons revealed decreased volume in non-PNS from baseline to 12 months ($p < 0.005$, $p_{ADJ} < 0.01$) and increased volume from 12 to 24 months ($p < 0.001$, $p_{ADJ} < 0.05$).

Parahippocampal Gyrus

A significant main effect of Time was observed in left parahippocampal gyrus, $\chi^2 = 6.79$, $df = 2$, $p < 0.05$, due to decreased volume from baseline to 24 months ($p < 0.05$, $p_{ADJ} < 0.05$), and from 12 to 24 months ($p < 0.05$, $p_{ADJ} < 0.05$). Right parahippocampal gyrus showed significant main effects of Group, $\chi^2 = 8.57$, $df = 3$, $p < 0.05$, and Time, $\chi^2 = 9.56$, $df = 2$, $p < 0.01$. The Group effect was due to decreased volume in PNS relative to non-PNS ($p < 0.05$, $p_{ADJ} < 0.05$) and controls ($p < 0.01$, $p_{ADJ} < 0.05$). The Time

effect was due to decreased volume from baseline and 12 months ($p < 0.05$, $p_{ADJ} = 0.06$) and from baseline to 24 months ($p < 0.005$, $p_{ADJ} < 0.01$).

Entorhinal Cortex

Left entorhinal cortex showed a trending interaction between Group and Time (Figure 1 and 2C), $\chi^2 = 12.19$, $df = 6$, $p < 0.06$. This interaction was driven by increased volume in non-PNS from 12 to 24 months ($p < 0.05$, $p_{ADJ} = 0.16$) as well as in controls from baseline to 12 months ($p < 0.05$, $p_{ADJ} = 0.16$) and from baseline to 24 months ($p = 0.05$, $p_{ADJ} = 0.18$). No significant effects emerged for right entorhinal cortex.

Perirhinal Cortex

A significant Group × Time interaction, $\chi^2 = 16.41$, $df = 6$, $p < 0.05$, was observed in left perirhinal cortex (Figure 1 and 2D). Between-groups, PNS showed lower volumes than non-PNS ($p < 0.05$, $p_{ADJ} = 0.40$) and controls ($p < 0.05$, $p_{ADJ} = 0.40$) at 24 months. Pairwise within-group comparisons revealed decreased volume in PNS from 12 to 24 months ($p < 0.01$, $p_{ADJ} = 0.05$) and increased volume in non-PNS from baseline to 24 months ($p < 0.005$, $p_{ADJ} < 0.05$) and a from 12 to 24 months ($p < 0.05$, $p_{ADJ} = 0.17$). No significant effects emerged for right perirhinal cortex.

Caudate Nucleus

A significant main effect of Time was observed for the left caudate, $\chi^2 = 7.34$, $df = 2$, $p < 0.05$, due to decreased volume from baseline to 24 months ($p < 0.01$, $p_{ADJ} < 0.05$) and from 12 to 24 months ($p < 0.05$, $p_{ADJ} < 0.05$) that was observed across groups. The right caudate also showed a significant main effect of Time, $\chi^2 = 7.53$, $df = 2$, $p < 0.05$, due to decreased volume from baseline to 24 months ($p<0.01$, $p_{ADJ}<0.05$) and from 12 to 24 months ($p<0.05$, $p_{ADJ}<0.05$).

Putamen

A significant main effect of Group was observed in the left putamen, $\chi^2 = 9.91$, $df = 3$, $p < 0.05$. Relative to controls, PNS ($p < 0.05$, $p_{ADJ} = 0.07$) and sPNS ($p < 0.05$, $p_{ADJ} = 0.07$) had decreased volumes,

but did not differ from each other ($p = 0.88$). Right putamen also showed a significant main effect of Group, $\chi^2 = 9.30$, $df = 3$, $p < 0.05$, with lower volumes in PNS ($p < 0.05$, $p_{ADJ} = 0.06$) and sPNS ($p < 0.05$, $p_{ADJ} = 0.06$) versus controls.

Pallidum

A significant main effect of Time was observed for the left pallidum, $\chi^2 = 6.25$, $df = 2$, $p < 0.05$, due to increased volume from baseline to 24 months ($p < 0.01$, $p_{ADJ} = 0.05$). A trending main effect of Group was also observed, $\chi^2 = 6.77$, $df = 3$, $p < 0.08$, driven by increased volumes in sPNS relative to controls ($p<0.05$, $p_{ADJ} = 0.13$).

Roles of diagnosis, baseline Chlorpromazine equivalent (CPZeq), and adherence

After controlling for diagnosis (affective, non-affective), and CPZeq weighted by adherence, observed effects within and between patient groups remained significant in left hippocampus, right parahippocampal gyrus, left perirhinal cortex, and bilateral caudate. Effects in right hippocampus, left parahippocampal gyrus, bilateral entorhinal cortex, putamen, and pallidum were not retained. In addition, a trending interaction emerged in right entorhinal cortex, due to decreased volume in PNS from 12 to 24 months (see supplement).

Discussion

In the current study, we investigated longitudinal brain volume trajectories in relation to persistent negative symptoms in FEP. Our distinction between PNS and secondary PNS allowed us to identify progressive changes in PNS separable from other symptom confounds (e.g., positive, depressive, extrapyramidal) as well as shared and diverging effects in these groups. Distinct group trajectories were observed primarily in left hippocampus and left perirhinal cortex, with decreasing volumes in PNS, increasing volumes in non-PNS and relative stability in sPNS over the 24-month period. At 24 months, left hippocampal and perirhinal volumes were significantly reduced in PNS relative to non-PNS and controls, who were indistinguishable from each other. PNS changes were most prominent between 12

and 24 months and were not the result of affective or non-affective diagnosis, antipsychotic medication dosage or adherence. While some effects of time and group were observed in the basal ganglia, these did not distinguish PNS and sPNS patients and no interactions emerged. These findings support a biological distinction between PNS and sPNS, suggesting that PNS is driven in part by changes in left MTL (especially hippocampus and perirhinal cortex) and that basal ganglia changes known to be associated with negative symptoms may not be specific to PNS.

Persistent negative symptoms and left medial temporal lobe

Though all patient groups had reduced left hippocampal volumes relative to controls at baseline, they demonstrated distinct volume trajectories in left MTL, particularly in the hippocampus and perirhinal cortex. In PNS, this involved reductions over time that were most prominent between 12 and 24 months. In contrast, sPNS showed stability of volumes in these regions over the 24-month period, which were situated between PNS and controls/non-PNS (who did not differ from each other at 12 and 24 months). These findings suggest that progressive volume reductions in left MTL are characteristic of PNS, but not sPNS, where negative symptoms are secondary to other symptoms. By definition, sPNS patients present positive, depressive, or extrapyramidal symptoms for at least 6 months (6 to 12 months following admission in the current study), which explains the increased antipsychotic dosage at 12 months in sPNS relative to the PNS and non-PNS groups. Our supplemental MTL analyses controlling for medication dose and adherence were largely consistent with the main results, suggesting antipsychotic medication does not account for PNS-related trajectories in left MTL. However, the stability of MTL volumes in sPNS and its relation to potential treatment-resistance should be examined in more detail in future work.

Hippocampal volume reductions are a robust finding in schizophrenia (38) and play a key role in many theoretical accounts of psychosis (39-42). These accounts point to glutamate and/or serotonergic dysregulation in anterior subregions of the hippocampus (e.g., CA1, anterior portions of CA4/dentate

gyrus) prior to psychosis onset, leading to hippocampal volume loss primarily via reduction in GABAergic interneurons. In turn, this may lead to a progressive cascade of volume reductions in early psychosis throughout the medial temporal lobe and frontal regions via altered hippocampal projections to these regions, which is thought to contribute to memory impairments and psychotic symptoms.

Consistent with this model, left perirhinal cortex followed a similar volumetric trajectory to the hippocampus, with decreasing volumes in PNS, increasing volumes in non-PNS, and stable volumes in sPNS and controls. This region may not have emerged in previous cross-sectional studies due to group differences only becoming evident at 24 months. The perirhinal cortex is reciprocally connected to the hippocampus, among other MTL and frontal regions, and is a key region involved in memory processes (43). Thus, both memory and PNS may rely on overlapping neural substrates (e.g., MTL). This is supported by previous findings of strong associations between memory and negative symptoms in psychosis (14), disproportionate impairments in verbal memory in PNS (9, 44), and growing evidence that verbal memory may mediate the relationship between hippocampal brain structure and negative symptoms in first-episode psychosis (45, 46). Moreover, some treatment studies have shown promise in increasing hippocampal volume in psychosis along with beneficial effects on cognition and negative symptoms, particularly through newer antipsychotic medications with partial agonism at dopamine and serotonin receptors (47) and through exercise-induced plasticity (48). Future work is warranted to extend these findings to PNS and to broader MTL regions, such as the perirhinal cortex.

In addition, our findings indicate that previous longitudinal studies in FEP demonstrating early decreases in hippocampal volume that stabilize over time (49) may be specific to a subgroup of patients or the result of averaging across patients with different trajectories. Our previous cortical thickness findings in PNS and sPNS, using a subsample of these data, also revealed decreases in left temporal cortex in PNS relative to non-PNS (17). Interestingly, a follow up study (16) including hippocampal volumes and surface area implicated the right hippocampus in PNS versus sPNS, which was only

trending in the current study and appeared to be driven by increased volume in the non-PNS group. Inconsistencies between studies may be due to differences in preprocessing and selected structural measure (volume, thickness, or surface area), but may also be the result of different comparisons (single- or multi-group comparisons) and analysis techniques. For example, the previous studies employed linear mixed models, whereas the current study took a GEE approach, which allowed for a more fine-grained examination of volumetric changes between time-points. This allowed us to determine that left MTL changes in PNS are most prominent from 12 to 24 months following a FEP, which provides a window for early interventions targeting negative symptoms.

Negative symptoms and basal ganglia

Our study is novel in exploring longitudinal basal ganglia changes in relation to PNS in FEP. Across the 24-month period, bilateral caudate volume reductions and left pallidum volume increases were noted and were consistent across groups. Our findings of volume reductions in bilateral caudate over time were observed across groups suggesting they were not specifically related to PNS. A recent cross-sectional meta-analysis primarily in enduring schizophrenia (15) noted volume reductions in the left caudate in PNS relative to controls. The current FEP study indicates that these differences may not be evident early in the illness and warrants further investigation. In contrast, bilateral putamen volumes were significantly reduced in both PNS and sPNS when compared to controls, which was expectedly suppressed following removal of controls in our supplementary analyses. Striatal associations with negative symptoms are well-documented, yet the relative contributions of the caudate and putamen to negative symptoms and to PNS, specifically, require further investigation. Volume reductions are observed early in the course of schizophrenia-spectrum disorders (50), are related to symptomatology (51). Notably, there is indirect evidence that striatal alterations may contribute to secondary negative symptoms (20). Altered resting-state connectivity between striatal regions and cortical areas may predict improvement in negative symptoms (52). The basal ganglia, particularly the putamen and

pallidum, is also sensitive to antipsychotic treatment (18). In the current study, basal ganglia results were attenuated after controlling for antipsychotic dose, though these supplemental analyses also excluded controls. Nonetheless, our findings suggest that group differences observed in the basal ganglia may be indicative of negative symptoms, irrespective of etiology. Future research is necessary to tease apart specificity to negative symptoms versus general psychopathology and the potential moderating effects of medication.

Strengths and Limitations

This longitudinal MRI study conducted on PNS in FEP offers a unique view of the potential subcortical brain changes that can occur during early disease course and provides insight into potential dynamic endophenotypes specific to PNS. Indeed, dynamic processes of cortical reorganization (53) likely underlie the development and maintenance of psychotic disorders and longitudinal analyses of brain structure are necessary to highlight relationships with specific stages or clinical subgroups of patients that require adapted care, such as PNS.

The distinction between PNS and sPNS allows for investigation into PNS in the absence of factors known to contribute to negative symptoms, particularly positive, depressive, and extrapyramidal symptoms. However, due to the definitions used in the current study, the non-PNS group would have combined individuals with no/low negative symptoms and negative symptoms that did not persist over the 6-month period. In addition, examining PNS in FEP mitigates the effects of medication and illness severity that can affect both clinical and neurobiological outcomes. In the current study, we demonstrated that neither medication dosage nor adherence accounted for our primary MTL findings nor were they driven by affective or non-affective diagnoses. In addition, these findings remained significant in patients only, confirming that the interactions were not driven by larger patient versus control differences. Attenuated basal ganglia effects after covarying for medication and diagnosis may be due to either medication/diagnosis or the necessary exclusion of control participants and should be

further examined. Attrition is an important factor to consider for longitudinal studies and contributed to our small group sizes, particularly at 12- and 24-month follow-up. Though GEE provides accurate estimates for missing data when it is missing at random, this is not often the case in longitudinal clinical studies, where patients might drop out for reasons related to variables of interest (e.g., symptomatology).

Thus, longitudinal studies in larger samples are warranted and could be realized through larger collaborative efforts (e.g., ENIGMA). Longitudinal studies at higher field strengths (e.g., 3T, 7T) would also clarify whether PNS-specific trajectories in the hippocampus are driven by certain subfields or white matter output regions, as noted for negative symptoms (45, 49) or vary across the longitudinal axis of the hippocampus, recently shown to relate to memory impairment in schizophrenia using functional connectivity (54). Structural MRI-derived connectivity (e.g., structural covariance) between MTL and cortical regions in PNS and sPNS is also a ripe area for future research as hippocampal-cortical connectivity has been recently implicated in both negative symptoms and memory impairment in first-episode psychosis (45).

Conclusion

We observed distinct brain volume trajectories in FEP patients with PNS, sPNS and non-PNS over 24 months. Group differences at baseline were minimal and PNS volume reductions were most evident between 12 and 24 months, suggesting a progressive deterioration in the MTL that is specific to PNS. Given the significant impact of PNS on functional outcomes and the observed progressive changes in this group, early interventions targeting negative symptoms, such as social skills training or non-invasive brain stimulation (55), may be essential for improving health outcomes in PNS.

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Table 1. Sample characteristics per group (PNS, sPNS, non-PNS, Control) and timepoint (baseline, 12 months, 24 months).

	PNS	*sPNS*	*non-PNS*	*Control*
Baseline				
N	25	26	47	86
Sex (male:female)	19:6	16:10	33:14	54:32
Handedness (R:L:M)	21:1:3	23:1:2	37:4:6	77:2:7
Age	23.49 (3.54)	24.69 (3.96)	24.07 (3.74)	24.22 (3.56)
Years of Education[a*,c**,e**,f**]	11.20 (2.53)	12.12 (2.05)	12.51 (2.46)	14.29 (2.46)
CPZeq with Adherence	146.80 (132.80)	115.84 (103.80)	170.00 (205.65)	-
SAPS Total[a*d**]	7.84 (9.31)	14.81 (11.33)	4.47 (6.47)	-
SANS Total[b**,d**]	28.68 (11.97)	23.31 (13.70)	13.02 (9.74)	-
CDSS Total	3.04 (3.37)	3.00 (2.99)	1.68 (3.32)	-
Illness Duration (years)	1.14 (1.48)	1.21 (1.76)	1.14 (1.84)	-
Diagnosis (affective:non-affective)[a*,d*]	17:18	1:25	14:33	-
12 months				
N	19	19	34	44
Sex (male:female)	13:6	12:7	24:10	24:20
Handedness (R:L:M)	16:0:3	16:1:2	28:3:3	38:1:5
Age	24.85 (3.83)	26.38 (3.92)	25.22 (3.80)	24.64 (3.62)
Years of Education[c**,e**,f**]	11.47 (2.52)	12.00 (2.29)	12.74 (2.31)	14.36 (2.51)
CPZeq with Adherence[a*d*]	115.88 (143.92)	239.00 (296.91)	78.87 (101.78)	-
SAPS Total[a**d**]	6.11 (6.09)	16.21 (11.12)	2.32 (5.45)	-
SANS Total[b**d**]	22.11 (12.82)	23.53 (11.99)	8.26 (9.91)	-
CDSS Total	1.11 (1.49)	1.42 (2.01)	1.53 (2.92)	-
Illness Duration (years)	1.97 (0.99)	2.36 (1.96)	2.38 (2.09)	-
Diagnosis (affective:non-affective)	4:15	1:18	11:23	-
24 months				
N	16	11	27	27
Sex (male:female)	10:6	8:3	20:7	15:12
Handedness (R:L:M)	13:0:3	11:0:0	24:1:2	23:1:3
Age	25.84 (3.95)	26.79 (3.78)	26.24 (3.99)	26.63 (3.18)
Years of Education[c**,e**,f**]	11.38 (2.58)	12.09 (1.51)	12.52 (2.49)	14.81 (2.54)
CPZeq with Adherence	101.10 (93.33)	197.53 (327.40)	100.64 (123.26)	-

	PNS	*sPNS*	*non-PNS*	*Control*
SAPS Total [a*d**]	7.88 (11.26)	16.27 (18.62)	2.11 (3.45)	-
SANS Total [b**d*]	21.13 (12.18)	16.18 (17.67)	6.96 (7.55)	-
CDSS Total	3.07 (3.52)	1.91 (2.74)	1.40 (2.02)	-
Illness Duration (years)	3.09 (0.99)	3.69 (2.60)	3.40 (2.24)	-
Diagnosis (affective:non-affective)[a*b*]	3:13	0:11	10:17	-

Note. PNS = persistent negative symptoms; sPNS = secondary PNS; R = right; L = left; M = mixed; CPZeq = Chlorpromazine equivalent; SAPS = Scales for the Assessment of Positive Symptoms total score; SANS = Scales for the Assessment of Negative Symptoms total score, excluding attention items, CDSS = Calgary Depression Scale for Schizophrenia; [a] = PNS vs. sPNS, [b] = PNS vs. non-PNS, [c] = PNS vs. Control; [d] = sPNS vs. non-PNS, [e] = sPNS vs. Control; [f] = non-PNS vs. Control, * = $p<0.05$, ** = $p<0.001$.

Figure 1. Overall generalized estimating equation results (color = significant; light gray = non-significant) for hippocampus and basal ganglia displayed using ggseg for R (56). Cortical regions were segmented and overlaid on the Desikan-Killiany atlas, except perirhinal cortex (exvivo atlas), which is combined with entorhinal cortex for visualization purposes as it followed the same pattern of results. Subcortical regions were segmented and displayed using FreeSurfer's aseg atlas. INT = interaction, L = left, ME = main effect.

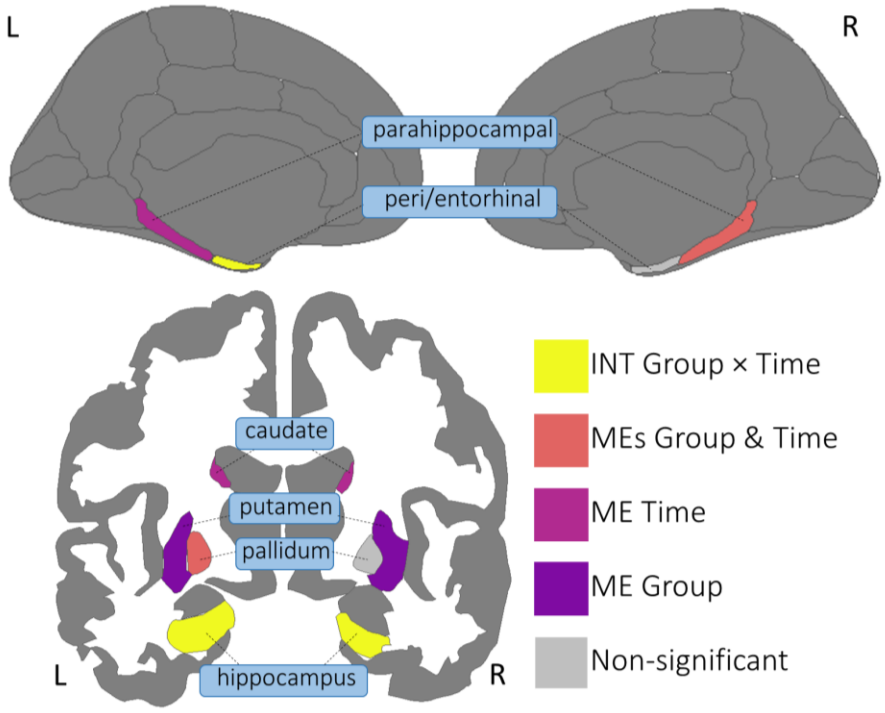


Figure 2. Group × Time interaction results for left hippocampus (A), right hippocampus (B), left entorhinal cortex (C) and left perirhinal cortex (D). Volumes reflect estimated marginal means adjusting for age, sex, and intracranial volume. Upper group labels and asterisks indicate pairwise within-group comparisons, whereas lower letters and asterisks indicate pairwise between-group comparisons at each timepoint. PNS = persistent negative symptoms, a = PNS vs. Control, b = PNS vs. non-PNS, c = secondary PNS vs. Control, d = non-PNS vs. Control, ** = p<0.005, * = p<0.05, † = p<0.09.

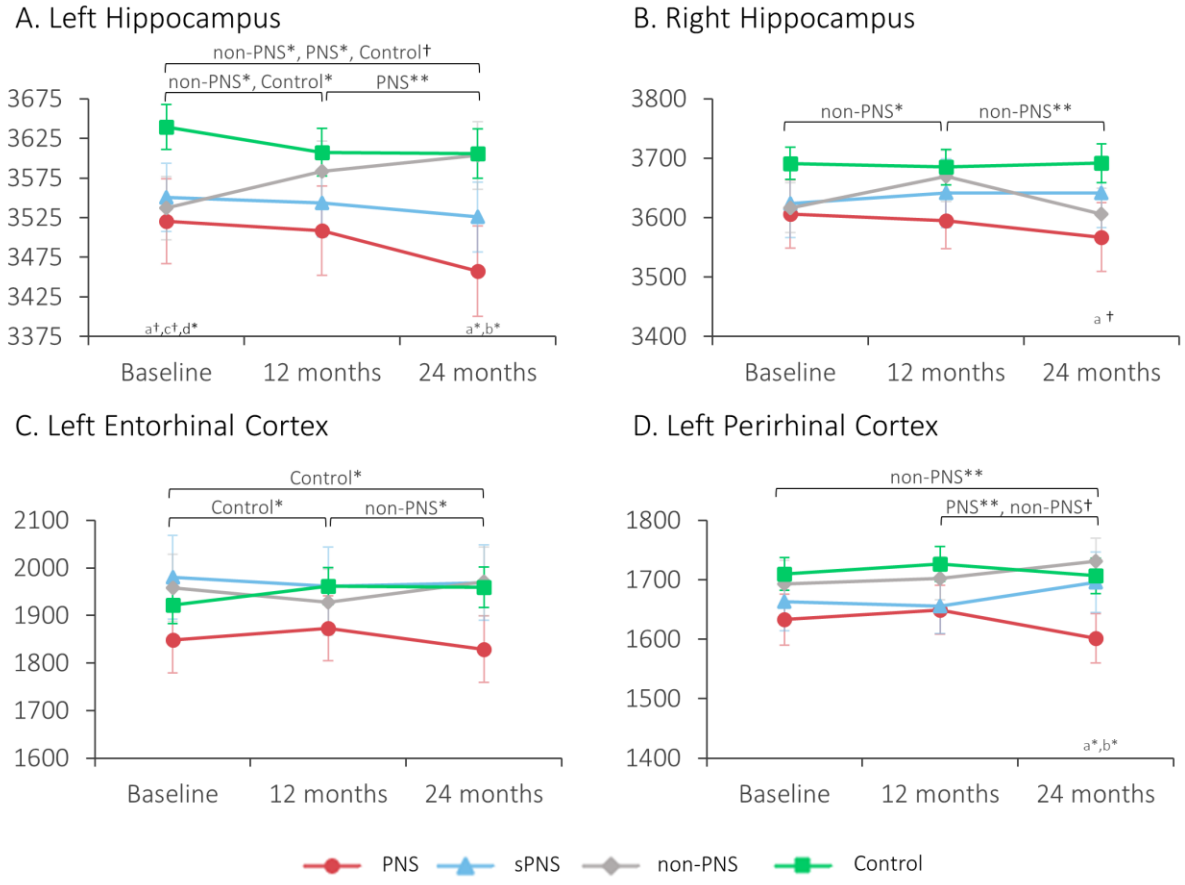
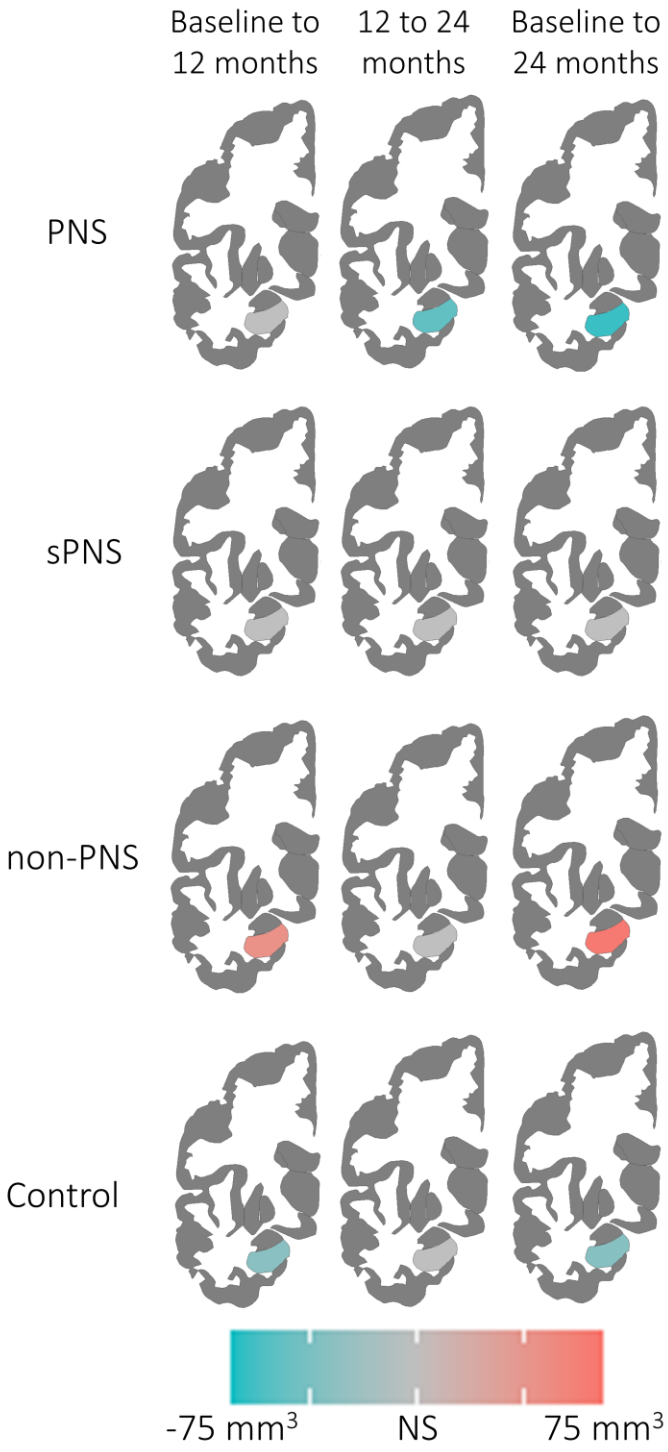


Figure 3. Left hippocampus Group × Time interaction results showing pairwise within-group differences over time (light gray = non-significant (NS), blue = volume decrease, red = volume increase). Volumes in cubic millimeters (mm^3) reflect estimated marginal means adjusting for age, sex, and intracranial volume. PNS = persistent negative symptoms, sPNS = secondary PNS.



Conflict of Interest

ML 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. RJ 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. AM 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. KML reports grants and speaker's honoraria from Otsuka Canada. All reported interests are unrelated to the present work. All other authors report no competing interests.

Author Contribution

Katie M. Lavigne: conceptualization, study design, data processing, data analysis, interpretation, writing, editing. Delphine Raucher-Chéné: interpretation, writing, editing. Michael Bodnar: conceptualization, study design, data collection, writing, editing. Carolina Makowski: conceptualization, study design, interpretation, editing. Ridha Joober: conceptualization, interpretation, editing. Ashok Malla: conceptualization, interpretation, editing. Alan C. Evans: interpretation, editing. Martin Lepage: conceptualization, study design, data collection, interpretation, writing, editing.

Supplemental Material

Medial temporal lobe and basal ganglia volume trajectories in persistent negative symptoms following a first episode of psychosis

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Longitudinal volume changes in PNS – Role of affective/non-affective diagnosis and antipsychotic dose and adherence

To examine whether the inclusion of controls, diagnosis (affective, non-affective), antipsychotic dose, or medication adherence may have accounted for longitudinal changes reported in the main text, we re-ran the generalized estimating equations in patients only with baseline Chlorpromazine equivalent (CPZ) weighted by adherence and diagnosis (affective, non-affective) as additional covariates.

Hippocampus

The significant Group × Time interaction in the left hippocampus was retained, $\chi^2 = 12.54$, $df = 4$, $p < 0.05$. Pairwise comparisons revealed the interaction was driven by decreased volume in the PNS group from baseline to 24 months (Δ = 66.93, 95% CI: [9.33,124.54], $p < 0.05$) and from 12 months to 24 months (Δ = 55.22, 95% CI: [18.76,91.69], $p < 0.005$), as well as increased volume in non-PNS from baseline to 12 months (Δ = -42.26, 95% CI: [-79.73,-4.79], $p < 0.05$) and from baseline to 24 months (Δ = -63.80, 95% CI: [-118.16, -9.44], $p < 0.05$, Figure 1). At 24 months, PNS had significantly lower left hippocampal volume than non-PNS (Δ = -151.56, 95% CI: [-296.86,-6.27], $p < 0.05$). The significant interaction in the right hippocampus was not retained in the patients only after covarying for diagnosis and CPZ adherence.

Parahippocampal Gyrus

Right parahippocampal gyrus showed significant main effects of Group, $\chi^2 = 7.63$, $df = 2$, $p < 0.05$, and Time, $\chi^2 = 9.24$, $df = 2$ $p < 0.01$. The Group effect was due to decreased volume in PNS relative to non-PNS (Δ = -151.87, 95% CI: [-261.62,-42.12], $p < 0.05$). A trend was also observed for decreased volume in PNS relative to sPNS (Δ = -116.79, 95% CI: [-243.23,9.65], $p = 0.07$). The Time effect was due to decreased volume from baseline to 24 months (Δ = 31.59, 95% CI: [10.43,52.76], $p < 0.005$) and a trend between baseline and 12 months (Δ = 15.14, 95% CI: [-1.07,31.34], $p < 0.07$).

Entorhinal Cortex

A trending interaction between Group and Timepoint, $\chi^2 = 7.96$, *df* = 2, $p < 0.10$, emerged in the right entorhinal cortex, driven by decreased volume in PNS from 12 to 24 months (Δ = 65.68, 95% CI: [10.98,120.37], $p < 0.05$).

Perirhinal Cortex

A significant Group × Time interaction, $\chi^2 = 11.89$, *df* = 4, $p < 0.05$, was found in left perirhinal cortex. Pairwise comparisons revealed this interaction was driven by decreased volume in PNS from 12 to 24 months (Δ = 51.88, 95% CI: [11.86,91.91], $p < 0.01$) and increased volume in non-PNS from baseline to 24 months (Δ = -33.11, 95% CI: [-59.60,-6.62], $p < 0.05$) and a trend from 12 to 24 months (Δ = -25.83, 95% CI: [-54.80,3.14], $p = 0.08$). At 24 months, PNS showed a trend towards lower volumes than sPNS (Δ = -127.47, 95% CI: [-255.05,0.11], $p = 0.05$) and significant lower volumes than non-PNS (Δ = -120.75, 95% CI: [-231.04,-10.47], $p < 0.05$). No significant effects emerged in the right hemisphere.

Caudate Nucleus

A trend towards a significant main effect of Timepoint was observed for the left caudate, $\chi^2 = 5.26$, *df* = 4, $p = 0.07$, due to decreased volume from baseline to 24 months (Δ = 42.41, 95% CI: [6.13,78.69], $p < 0.05$) and a trend from 12 to 24 months (Δ = 32.48, 95% CI: [-2.06,67.02], $p < 0.07$). A trend towards a significant main effect of Time was observed in the right caudate, $\chi^2 = 4.95$, *df* = 4, $p = 0.09$, due to decreased volume from baseline to 24 months (Δ = 31.68, 95% CI: [0.30, 63.06], $p < 0.05$) and from 12 to 24 months (Δ = 30.35, 95% CI: [1.50,59.20], $p < 0.07$).

Putamen

No significant main effects or interactions were noted for left or right putamen.

Pallidum

No significant main effects or interactions were noted for left or right pallidum.

Longitudinal volume changes in PNS – Whole-brain exploratory analyses

To explore longitudinal volumetric changes across the whole brain, we performed GEEs on the 62 brain regions defined by the Desikan-Killiany Tourville atlas (57) and corrected for multiple comparisons using the Benjamini-Hochberg procedure (37). These analyses were identical to those in the main text: creation of a first-order autoregressive [AR(1)] correlation matrix, with a normal distribution and identity link function. Group (PNS, sPNS, non-PNS, control) and time (baseline, 12 months, 24 months) were included as predictors and brain volume (each of 62 DKT regions) as the dependent variable, with covariates of age at baseline, handedness, sex, education, and estimated total intracranial volume.

Significant corrected Time × Group interactions were observed for left superior frontal gyrus, χ^2 = 20.97, *df* = 6, $p < 0.005$, left insula, χ^2 = 21.59, *df* = 6, $p < 0.005$, right inferior frontal gyrus, pars orbitalis, χ^2 = 22.24, *df* = 6, $p < 0.005$, right rostral middle frontal gyrus, χ^2 = 21.25, *df* = 6, $p < 0.005$, and right caudal middle frontal gyrus, χ^2 = 20.08, *df* = 6, $p < 0.005$. These interactions were primarily due to decreasing volumes over time in PNS and controls, with no significant changes in the other two groups, except for sPNS, who showed the same decreasing pattern in the left insula and right inferior frontal gyrus. The only group difference observed was in the left insula at 24 months, with PNS having lower volumes than sPNS ($p < 0.05$).

Table S1. Uncorrected brain volumes (standard deviations) per group (PNS, sPNS, non-PNS, Control) and timepoint (baseline, 12 months, 24 months).

	PNS	*sPNS*	*non-PNS*	*Control*
Baseline				
ICV	1679695.91 (186191.30)	1658009.90 (163926.62)	1732268.31 (146039.43)	1710322.60 (197011.06)
L Hippocampus	3489.15 (322.21)	3492.23 (353.43)	3585.82 (357.14)	3656.40 (392.71)
R Hippocampus	3574.75 (340.82)	3565.17 (408.45)	3665.23 (377.03)	3708.58 (377.75)
L Parahippocampal	2223.88 (318.10)	2211.88 (294.17)	2326.91 (364.96)	2344.95 (382.30)
R Parahippocampal	2089.88 (240.35)	2154.62 (291.18)	2276.66 (283.31)	2240.27 (325.36)
L Entorhinal	1848.64 (388.47)	1943.12 (505.59)	1990.26 (559.69)	1928.13 (376.89)
R Entorhinal	1861.04 (336.91)	1728.62 (425.09)	1964.87 (439.96)	1891.12 (393.11)
L Perirhinal	1627.28 (250.46)	1632.54 (290.35)	1718.62 (326.68)	1716.24 (283.49)
R Perirhinal	1917.52 (274.41)	1855.04 (345.40)	2046.15 (315.98)	1955.20 (320.18)
L Caudate	4232.05 (380.41)	4032.96 (596.93)	4172.42 (484.73)	4104.70 (500.07)
R Caudate	4185.38 (384.35)	4131.81 (589.12)	4180.83 (471.38)	4170.98 (512.99)
L Putamen	5645.42 (479.05)	5512.63 (689.23)	5603.43 (708.34)	5422.28 (596.03)
R Putamen	5717.87 (396.59)	5621.12 (673.49)	5635.77 (692.80)	5507.22 (647.25)
L Pallidum	2311.40 (216.06)	2286.57 (271.97)	2304.01 (265.58)	2256.00 (264.35)
R Pallidum	2232.74 (177.09)	2216.83 (259.16)	2226.62 (227.55)	2202.10 (282.25)
12 months				
ICV	1629464.26 (151417.86)	1668082.67 (167006.77)	1747312.48 (148374.71)	1685248.95 (181443.06)
L Hippocampus	3424.35 (284.60)	3489.73 (350.33)	3648.99 (376.30)	3561.49 (364.50)
R Hippocampus	3516.15 (286.68)	3575.73 (414.15)	3762.82 (410.48)	3631.53 (338.77)
L Parahippocampal	2229.79 (287.10)	2213.16 (187.86)	2369.91 (358.36)	2301.52 (354.23)
R Parahippocampal	2041.16 (263.33)	2123.37 (219.75)	2296.82 (274.12)	2189.43 (277.20)
L Entorhinal	1788.84 (309.63)	1979.42 (516.93)	1995.03 (606.91)	1939.27 (361.00)
R Entorhinal	1835.42 (336.69)	1788.89 (464.20)	2001.32 (439.93)	1880.07 (350.10)
L Perirhinal	1599.26 (192.38)	1628.58 (262.92)	1752.94 (325.54)	1674.14 (240.22)
R Perirhinal	1877.68 (265.50)	1903.00 (352.47)	2096.65 (305.42)	1929.59 (332.66)
L Caudate	4196.50 (404.10)	3982.67 (682.43)	4154.09 (476.67)	4050.93 (448.77)
R Caudate	4168.71 (404.12)	4082.37 (661.01)	4181.65 (481.35)	4106.62 (461.42)

	PNS	*sPNS*	*non-PNS*	*Control*
L Putamen	5623.04 (481.85)	5632.89 (666.94)	5681.94 (682.91)	5389.99 (569.37)
R Putamen	5664.82 (470.39)	5725.57 (668.71)	5737.49 (730.71)	5453.78 (612.66)
L Pallidum	2273.86 (234.45)	2335.46 (278.02)	2311.54 (285.93)	2230.82 (279.22)
R Pallidum	2222.63 (172.35)	2266.55 (278.43)	2219.39 (233.46)	2155.15 (252.49)
24 months				
ICV	1603125.83 (147513.47)	1718899.72 (170172.54)	1762358.16 (142972.36)	1677925.88 (176691.85)
L Hippocampus	3402.35 (279.60)	3576.63 (408.93)	3722.22 (364.86)	3606.76 (388.77)
R Hippocampus	3507.57 (346.56)	3692.13 (413.62)	3751.87 (367.43)	3656.48 (386.58)
L Parahippocampal	2151.50 (283.73)	2316.27 (187.06)	2434.48 (399.31)	2316.59 (378.20)
R Parahippocampal	1972.44 (263.31)	2117.73 (201.86)	2307.96 (316.30)	2185.11 (345.45)
L Entorhinal	1773.88 (316.11)	2037.55 (594.74)	2156.78 (639.18)	1959.59 (411.78)
R Entorhinal	1777.13 (277.07)	1789.55 (583.59)	2094.56 (474.00)	1894.63 (332.51)
L Perirhinal	1546.13 (205.91)	1702.27 (319.40)	1852.41 (345.27)	1681.07 (235.50)
R Perirhinal	1794.69 (203.80)	1887.27 (388.66)	2135.41 (293.58)	1943.33 (333.99)
L Caudate	4153.41 (389.40)	3981.14 (700.31)	4233.01 (457.87)	3959.50 (427.34)
R Caudate	4124.26 (370.52)	4117.59 (691.35)	4248.59 (451.84)	4034.97 (455.06)
L Putamen	5619.14 (481.45)	5703.82 (801.79)	5753.23 (694.03)	5360.22 (565.71)
R Putamen	5655.89 (512.65)	5802.58 (790.17)	5773.50 (707.92)	5435.86 (583.47)
L Pallidum	2270.91 (231.26)	2362.84 (325.03)	2319.65 (273.47)	2220.83 (274.86)
R Pallidum	2223.01 (176.91)	2297.65 (288.74)	2251.56 (254.32)	2153.29 (261.46)

Note. ICV = intracranial volume; L = left; R = right; PNS = persistent negative symptoms; sPNS = secondary persistent negative symptoms.

Table S2. Significant between-group pairwise comparisons (mean difference [95% confidence interval]) of regional brain volumes for generalised estimating equations per region and group.

Region	Group Comparison	Baseline	24 months	All Timepoints (ME Group)
L Hippocampus	PNS vs. Control	-118.86 [-237.84, 0.13] *[c]	-148.29 [-275.97, -20.61] *[c]	
	sPNS vs. Control	-88.83, [-190.60, 12.94] †[c]		
	Non-PNS vs. Control	-102.56 [-197.35, -7.76] *[c]		
	PNS vs. Non-PNS		-145.95 [-287.45, -4.45] *[c]	
R Hippocampus	PNS vs. Control		-124.32 [-254.52, 5.43] †[c]	
R Parahippocampal	PNS vs. Control			-137.18 [-238.49, -35.87] *[a]
	PNS vs. Non-PNS			-153.74 [-270.77, -36.71] *[a]
L Perirhinal	PNS vs. Control		-105.23 [-206.68, -3.78] *[c]	
	PNS vs. Non-PNS		-129.63 [-242.92, -16.33] *[c]	
L Putamen	PNS vs. Control			-253.30 [-53.48, -453.12] *[b]
	sPNS vs. Control			-233.27 [-29.81, -436.73] *[b]
R Putamen	PNS vs. Control			-255.58 [-41.10, -470.06] *[b]
	sPNS vs. Control			-261.42 [-54.96, -467.87] *[b]
L Pallidum	sPNS vs. Control			97.90 [13.15, 182.64] *[c]

Note. a = *p*ADJ < 0.05, b = *p*ADJ < 0.09, c = *p*ADJ > 0.05, L = left, ME = main effect, pADJ = benjamini-hochberg adjusted p-value, PNS = persistent negative symptoms, R = right, sPNS = secondary PNS, * = $p < .0.05$, † = $p < 0.09$.

Table S3. Significant within-group pairwise comparisons (mean difference (standard error), [95% confidence interval]) of regional brain volumes for generalised estimating equations per region and group.

Region	Group Comparison	Baseline to 12 months	12 to 24 months	Baseline to 24 months
L Hippocampus	PNS		50.71 [17.51, 83.91] *[a]	63.11 [6.6, 119.61] *[b]
	Non-PNS	-46.23 [-84.24, -8.23] *[b]		-66.54 [-122.36, -10.72] *[b]
	Control	32.12 [4.08, 60.14] *[b]		33.68 [-4.51, 71.88] †[c]
R Hippocampus	Non-PNS	-53.53 [-89.14, -17.93] *[a]	-64.32 [26.59, 102.07] *[a]	
L Parahippocampal	All Groups (ME Time)		21.48 [2.55, 40.72] *[a]	23.00 [5.27, 40.72] *[a]
R Parahippocampal	All Groups (ME Time)	14.05 [0.57, 27.53] *[b]		32.38 [11.14, 53.62] *[a]
L Entorhinal	Non-PNS		-43.46 [-81.19, -5.73] *[c]	
	Control	-38.82 [-73.61, -4.03] *[c]		-36.97 [-73.97, 0.03] *[c]
L Perirhinal	PNS		48.00 [11.80, 84.20] *[a]	
	Non-PNS		-28.58 [-57.01, -0.16] *[c]	-38.29 [-64.61, -11.96] *[a]
L Caudate	All Groups (ME Time)		30.64 [3.43, 57.84] *[a]	38.46 [10.52, 66.41] *[a]
R Caudate	All Groups (ME Time)		24.32 [2.38, 46.26] *[a]	33.72 [9.09, 58.36] *[a]
L Pallidum	All Groups (ME Time)			-20.45 [-37.24, -3.67] *[a]

Note. a = *p*ADJ < 0.05, b = *p*ADJ < 0.09, c = *p*ADJ > 0.05, L = left, ME = main effect, pADJ = benjamini-hochberg adjusted p-value, PNS = persistent negative symptoms, R = right, * = $p < .0.05$, † = $p < 0.09$.

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