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Neurofilament light-chain (NfL) and 18 kDa translocator protein in early psychosis and its putative high-risk

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ABSTRACT

Evidence of elevated peripheral Neurofilament light-chain (NfL) as a biomarker of neuronal injury can be utilized to reveal nonspecific axonal damage, which could reflect altered neuroimmune function. To date, only a few studies have investigated NfL as a fluid biomarker in schizophrenia primarily, though none in its putative prodrome (Clinical High-Risk, CHR) or in untreated first-episode psychosis (FEP). Further, it is unknown whether peripheral NfL is associated with 18 kDa translocator protein (TSPO), a validated neuroimmune marker. In this secondary study, we investigated for the first time (1) serum NfL in early stages of psychosis including CHR and FEP as compared to healthy controls, and (2) examined its association with brain TSPO, using [^{18}F]FEPPA positron emission tomography (PET). Further, in the exploratory analyses, we aimed to assess associations between serum NfL and symptom severity in patient group and cognitive impairment in the combined cohort. A large cohort of 84 participants including 27 FEP (24 antipsychotic-naive), 41 CHR (34 antipsychotic-naive) and 16 healthy controls underwent structural brain MRI and [^{18}F]FEPPA PET scan and their blood samples were obtained and assessed for serum NfL concentrations. We found no significant differences in serum NfL levels across clinical groups, controlling for age. We also found no significant association between NfL levels and brain TSPO in the entire cohort. We observed a negative association between serum NfL and negative symptom severity in CHR. Our findings suggest that neither active neuroaxonal deterioration as measured with NfL nor associated neuroimmune activation (TSPO) is clearly identifiable in an early mostly untreated psychosis sample including its putative high-risk.

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1. Introduction

Schizophrenia is a complex mental disorder affecting about 1% of the world population (Freedman, 2003), causing significant social and cognitive disability (Kahn et al., 2015). The pathophysiology of schizophrenia is multifactorial (Forsyth and Lewis, 2017), with some evidence pointing to altered immune function (Doorduin et al., 2009; Plavén-Sigray et al., 2018). The presence of progressive brain alterations including non-specific damage to axons occurring after the onset of first psychotic symptoms, and the progression of the damage dependence on the length of the episode are still debatable (Kanaan et al., 2017). Evidence suggests that, in the periphery, neurofilament light-chain (NfL) is a reliable marker of neuroaxonal integrity. NfL protein, an essential component of the neuroaxonal cytoskeleton, is central to the growth and stability of axons (Khalil et al., 2018). Elevated levels of NfL in cerebrospinal fluid (CSF) and blood have been demonstrated in a wide range of progressive neurological diseases (Yuan et al., 2017; Zhao et al., 2019; Karantali et al., 2021; Ashton et al., 2021; Bridel et al., 2019; Gaetani et al., 2019), and is used as a biomarker in grading and distinguishing types of dementia from primary psychiatric disorders (Katisko et al., 2020; Vijverberg et al., 2017). To date, only a few studies (Ceylan et al., 2023; Rodrigues-Amorim et al., 2020; Zhang et al., 2021; Popovic et al., 2023; Eratne et al., 2020, 2021, 2024; Bavato et al., 2021) have investigated NfL as a fluid biomarker in schizophrenia, with contradictory results. Some studies have shown elevated NfL levels in specific schizophrenia populations, including adolescents (Ceylan et al., 2023), individuals on clozapine (Rodrigues-Amorim et al., 2020), male first-episode schizophrenia patients (NfL gene expression) (Zhang et al., 2021), and unmedicated patients with acute schizophrenia (Popovic et al., 2023) compared to controls. Additionally, a mixed cohort study found mildly elevated CSF NfL levels in individuals with primary psychiatric disorders, including those with schizophrenia spectrum disorders (Eratne et al., 2020). In contrast, one study reported lower plasma NfL levels in treatment-resistant schizophrenia (TRS) compared to other psychiatric disorders (Eratne et al., 2024). However, in the largest sample of well-characterized patients on clozapine with treatment-resistant schizophrenia and their first-degree relatives, found no differences in plasma NfL levels compared to healthy controls (Eratne et al., 2021). Similarly, another study found no differences in serum NfL levels in individuals with schizophrenia compared to reference controls, but found a high heterogeneity in a subgroup of schizophrenia patients with NfL levels above age-specific cut-off values (Bavato et al., 2021). These studies had varying sample sizes, age groups, treatment regimens (including clozapine), and less comprehensive patient characterizations in mixed psychiatric cohorts, making it challenging to assess NfL changes in schizophrenia. Overall, these data suggest that NfL alterations maybe present in schizophrenia patients. One important question is if neuroaxonal damage occurs in the putative early course of schizophrenia such as the first-episode psychosis (FEP) and the clinical high-risk (CHR) state for psychosis where subacute prodromal clinical symptoms and decline in cognitive function manifest.

Preclinical studies have linked excessive microglial activation to brain tissue damage (Loane et al., 2014). Supporting this evidence, studies on neurodegenerative conditions such as Alzheimer's disease (AD), Parkinson disease, multiple sclerosis have demonstrated increased TSPO density alongside neurodegenerative alterations in the brain (Liu and Hong, 2003). Brain immune cells, in particular microglia and brain macrophages, are important players of the neuroinflammatory response also expressed in schizophrenia (Barron et al., 2017; Zhu et al., 2022; Gandal et al., 2018). In response to brain damage, microglia cells (and other cell types, see (Notter et al., 2018) for review) become activated and increase the expression of mitochondrial 18 kDa translocator protein (TSPO). These activated glial cells secrete pro-inflammatory cytokines and reactive oxygen species, which may contribute to neurodegeneration (Perry et al., 2007). Alternatively, a previous study in early AD has investigated interactions between plasma NfL and microglial activation and reported an inverse correlation of increased brain TSPO levels with reduced plasma NfL levels (Parbo et al., 2020). However, an interaction between neuroimmune and neurodegenerative markers in schizophrenia has never been tested previously.

Currently, positron emission tomography (PET) using radioligands that target TSPO can reliably quantify TSPO in vivo (Hafizi et al., 2017a, 2017b; Kenk et al., 2015; Coughlin et al., 2016). Compared to some other neuropsychiatric disorders, TSPO PET findings in schizophrenia exhibit heterogeneity (De Picker and Morrens, 2020). These include the use of first-generation TSPO tracer, [11C]PK11195 with a low signal-to-noise ratio; use of distribution volume ratio (instead of total volume of distribution) as outcome measure (Bloomfield et al., 2016), and possible effects of antipsychotic medication (Holmes et al., 2016), etc. Our own research in CHR state (Hafizi et al., 2017b) and FEP including schizophrenia (Hafizi et al., 2017a; Kenk et al., 2015) found no difference in TSPO labels. Nevertheless, using individual participant data and meta-analytic methods, incorporating our data (Hafizi et al., 2017a; Kenk et al., 2015) among seven TSPO PET studies, in the largest sample to date reported reduced TSPO levels in schizophrenia patients (Plavén-Sigray et al., 2021), in line with microglia suppression at the transcriptional level (Zhu et al., 2022; Gandal et al., 2018) and hence, neurodegeneration (elevations in NfL) may be non-identifiable. However, in acute psychosis, structural axonal damage might manifest in a subset of patients, rendering them more vulnerable to adverse disease outcomes. A recent study in acutely ill unmedicated schizophrenia patients found that serum NfL was increased in approximately 25% of schizophrenia patients (versus healthy control) which correlated positively with positive symptom severity and predicted long-term treatment outcome and likelihood of future relapses in schizophrenia combined with other biological variables (Popovic et al., 2023). Additionally, evidence suggests that schizophrenia individuals may have neuroimaging abnormalities that are consistent with neurodegenerative changes (Keshavan et al., 2020) and whether these processes are primary contributors to the development of schizophrenia or secondary effects of the disease remains unclear, requiring further investigation. Thus, in vivo imaging of microglial response by PET combined with peripheral NfL would provide new insights into the disease process.

Previously, we have demonstrated a relationship between elevated brain TSPO and the complement system (genetically predicted C4A) (Da Silva et al., 2021) consistent with previous studies investigating microglia-complement factor interactions (Sellgren et al., 2019). However, it is unknown whether peripheral NfL, a proxy for neuroaxonal integrity, is associated with altered neuroimmune function as quantified with PET-TSPO reflecting ongoing neuroimmunological or neuroinflammatory processes in response to brain insults relevant to the disease. Here, we primarily aimed to 1) test differences in serum NfL concentrations in the early stages of psychosis spectrum of mostly untreated CHR and FEP, as compared to healthy controls (HCs) and 2) investigate the association between serum NfL and TSPO expression in the brain as indexed by PET-TSPO ([^{18}F]FEPPA V_T) in the total sample covarying for potential confounders (i.e., sex, BMI, cannabis, tobacco, and antipsychotic use) as we expected their effect on serum NfL to be different within study groups. We hypothesized that serum NfL will be 1) significantly different between study groups (HC < CHR < FEP) and 2) positively associated with brain TSPO V_T, respectively. Exploratorily, we also aimed to assess the association between serum NfL levels and symptom severity in the patient cohort and cognitive impairment in the combined sample. Given the recent evidence in acutely ill unmedicated schizophrenia patients that demonstrated increased serum NfL in schizophrenia patients which correlated positively with positive symptom severity and inversely with global functioning (Popovic et al., 2023), we hypothesized that higher serum NfL levels will be significantly correlated with worse symptomatology/poor cognition.

Table 1
Demographics and clinical characteristics of the participants.

Variable		HC (n = 16)	CHR (n = 41)	FEP (n = 27)	F Test or χ^2 Test	*p* value
Age (years), Mean ± SD		21.38 ± 1.93	21.20 ± 2.85	27.33 ± 6.20	F = 19.94	$\mathbf{p < 0.001}$
Sex, Male/Female, n		6/10	25/16	17/10	$\chi^2 = 3.14$	$p = 0.21$
BMI (kg/m^2), Mean ± SD[a]		19.75 ± 11.41	22.02 ± 17.67	21.25 ± 8.73	F = 0.33	$p = 0.72$
TSPO rs6971 genotype[b], HAB/MAB, n		11/4	23/14	17/5	$\chi^2 = 1.64$	$p = 0.44$
PET Parameters[b], Mean ± SD	Specific activity (mCi/μmol)	1811.99± 2038.06	1777.36± 1810.99	2240.83± 3022.98	F = 0.27	$p = 0.76$
	Mass injected (μg)	1.89 ± 1.40	1.84 ± 1.49	1.48 ± 0.66	F = 0.53	$p = 0.59$
	Amount injected (mCi)	4.90 ± 0.33	5.11 ± 0.25	5.09 ± 0.27	F = 3.63	$\mathbf{p = 0.03}$
Antipsychotic use,AP-free/AP-current, n		16/0	34/7	24/3	$\chi^2 = 3.22$	$p = 0.20$
Cannabis use[c], non-cannabis users/cannabis users, n		16/0	36/5	24/3	$\chi^2 = 2.10$	$p = 0.35$
Tobacco use,Non-smokers/Smokers, n		16/0	32/9	15/12	$\chi^2 = 10.98$	$\mathbf{p = 0.004}$
Total RBANS Score, Mean ± SD		89.88 ± 13.66	91.13 ± 13.69	82.37 ± 17.74	F = 2.91	$p = 0.06$
Total PANSS Score, Mean ± SD		NA	NA	66.33 ± 12.91	NA	NA
SOPS Total Symptom Severity Score, Mean ± SD		NA	36.39 ± 11.66	NA	NA	NA

Abbreviations: AP – antipsychotic; X^2 – Chi-squared statistic; CHR – Clinical High-Risk; F value – ANOVA test statistic; FEP – First-episode Psychosis; HC – healthy control; HAB - high-affinity binder; μg – micrograms; μmol – micromole; mCi – millicurie; MAB - mixed-affinity binder; NA – not applicable; PANSS - Positive and Negative Syndrome Scale; PET – positron emission tomography; RBANS - Repeatable Battery for the Assessment of Neuropsychological Status; SOPS - Scale of Prodromal Symptoms; SD – standard deviation; TSPO – 18 kDa translocator protein.

[a] BMI value was not available for one CHR.

[b] See Fig. S1 for the participant flow diagram indicating the PET analysis exclusions (n, 74 participants (22 FEP, 37 CHR and 15 healthy controls were included in the PET analyses)).

[c] 5 CHR and 3 FEP had a positive urine drug screen for cannabis.

2. Methods and materials

2.1. Participants

Eighty-four participants including 27 FEP (Age range, 19–40 years), 41 CHR (Age range, 18–33 years) and 16 HCs (Age range, 18–25 years) were included in this study (Table 1). Most individuals in the FEP (n = 24, ~89%) and CHR group (n = 34, ~83%) were antipsychotic naive. For the PET analyses, 4 FEPs and 3 CHRs were excluded due to technical issues with the quantification of [^{18}F]FEPPA binding or insufficient quality of the PET images yielding an unreliable outcome measure or unavailability of PET/MRI data owing to early discharges, and 3 other participants (1 HC, 1 CHR and 1 FEP) were excluded due to low-affinity binder (LAB) genotype which cannot be quantified with [^{18}F]FEPPA. Additionally, 2 CHR subjects with extreme NfL outlier values were not included in the main NfL analysis. Thus, a total of 82 participants were included for the main NfL analysis and 72 participants were included for the main NfL-TSPO analysis [excluding the 2 CHR subjects with extreme NfL outlier values] (see Fig. S1 for the participant flow diagram).

The study was performed under a repository protocol that allowed a re-analysis of previously acquired data approved by the Centre for Addiction and Mental Health Research Ethics Board and now approved under Clinical and Translational Sciences (CaTS) BioBank by Research Ethics Board (REB) of the Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Ouest-de-l'Île-de-Montréal – Mental Health and Neuroscience subcommittee for secondary analyses. Participants included in the study were subset of a larger dataset recruited from July 20, 2011 to March 12, 2019 (Ontario, Canada). The study was performed in accordance with Good Clinical Practice guidelines, regulatory requirements, and the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from all participants at the beginning of screening after a full explanation of anticipated study procedures. This is a secondary analysis and hence the majority of the participants (healthy controls, n = 16; CHR, n = 37 and FEP, n = 27) in this study were also part of our previous studies (Hafizi et al., 2017a, 2017b, 2018; Da Silva et al., 2019, 2021).

To be eligible, FEP patients had to have a diagnosis of one of the following psychotic disorders: schizophrenia, schizophreniform, delusional disorder, and psychosis not otherwise specified (NOS), as determined using the Structured Clinical Interview for DSM-IV (SCID) (First and Gibbon, 2004). Individuals in the CHR group were included if they met diagnostic criteria for prodromal risk syndrome as assessed using the Criteria of Prodromal Syndromes (Miller et al., 2003). Healthy controls did not have any history of Axis I disorders as determined by the Structured Clinical Interview for DSM-IV (except for cannabis use disorder), current psychoactive drug use (except for cannabis and nicotine), and/or first-degree relatives with a major psychotic disorder. All participants were excluded if they had a clinically significant medical illness, current diagnosis of alcohol or substance use/dependence (except for cannabis and tobacco use), were pregnant or breastfeeding, or had metal implants that precluded a MRI scan. Positive and negative syndrome scale (PANSS) (Kay et al., 1987) was used to assess severity of symptoms in the first-episode psychosis group. In the CHR group, we assessed clinical status and severity of prodromal symptoms using the Structured Interview for Psychosis-Risk Syndromes (SIPS) (Miller et al., 2003) and the Scale of Prodromal Symptoms (SOPS). We assessed neurocognitive performance using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Holzer et al., 2007).

2.2. PET and structural MRI data acquisition and analysis

PET and MRI data acquisition have been described in detail elsewhere (Kenk et al., 2015) and are summarized below. A proton density-weighted (PD) brain MRI scan was obtained for each participant using a 3T MR-750 scanner (General Electric Medical Systems). All [^{18}F]FEPPA scans were performed using a high-resolution research tomograph neuro-PET camera system (HRRT, Siemens Molecular Imaging, Knoxville, TN, USA) for 125 min following an intravenous bolus injection of 187.11 ± 10.83 MBq of [^{18}F]FEPPA. Arterial blood samples were collected using an automatic blood sampling system (ABSS Model PBS-101, Veenstra Instrument, Joure, Netherlands) for the first 22.5 min after radioligand injection at a rate of 2.5 mL/min and manually at −5, 2.5, 7, 12, 15, 20, 30, 45, 60, 90, and 120 min to measure radioactivity in blood and determine the relative proportion of radiolabelled metabolites. Dispersion and metabolite-corrected plasma input functions were generated as previously described (Kenk et al., 2015).

2.3. PET image processing and calculation of total distribution volume (V_T)

Time-activity curves were extracted for dorsolateral prefrontal cortex (DLPFC), hippocampus, anterior cingulate cortex (ACC), medial prefrontal cortex (MPFC), temporal cortex and cerebellum using validated in-house imaging pipeline ROMI (Rusjan et al., 2006). The regions

of interest were delineated using individual PD MRI. Kinetic parameters of [^{18}F]FEPPA were derived from the time-activity curves using the two-tissue compartment model (2-TCM) and plasma input function to calculate the total distribution volume (V_T) for each region of interest, which has been validated for [^{18}F]FEPPA quantification and described elsewhere (Rusjan et al., 2011).

2.4. TSPO rs6971 polymorphism genotyping

Using high salt extraction method, DNA samples were extracted from venous peripheral white blood cells (collected and centrifuged from the blood samples acquired on the PET scan day). Further each participant was genotyped for their TSPO rs6971 polymorphism and based on the results categorized the individuals into high-(HAB), mixed- (MAB), or low-affinity binders (LAB), as described elsewhere (Mizrahi et al., 2012). LABs were excluded as they cannot be reliably quantified with second generation radioligands. All PET analyses have been adjusted for TSPO *rs6971* polymorphism (HAB and MAB).

2.5. Sample collection, storage and measurement of serum NfL

Whole blood samples collected from participants on the PET scan day as part of the PET-TSPO [^{18}F]FEPPA study were collected into 4 ml lavender/EDTA tubes by venipuncture. EDTA/whole blood was mixed well by inversion and spun at 900*g* for 15 min. The supernatant was isolated, aliquoted into 1 ml cryovials, snap frozen and stored at −80 °C. The measurement of serum NfL levels (assay) was performed in Dr. Bazinet's lab at University of Toronto. Serum samples were thawed once and R-Plex assay of serum NfL levels were measured in duplicate according to the manufacturer's instructions with appropriate standards and internal controls using fully automated ultra-sensitive Meso Scale Discovery (MSD) Sector 2400A (https://cfi3d.utoronto.ca/meso-scale-discovery-sector-2400a/) present at the 3D centre in University of Toronto equipment facility. Dilutions in this process included: biotinylated capture antibody (R-PLEX Human Neurofilament L Antibody Set), 1:100 in MSD Diluent 11 (Cat# R55BA-3); samples and calibrators, 1:2 in MSD Diluent 12 (Cat#: R50JA-3); SULFO-TAG™ detection antibody, 1:100 in MSD Diluent 11 (Cat# R55BA-3) and MSD Gold Read Buffer (CAT# R92TG-4),1:2 in dH2O. The serum NfL standard curve spanned from 6.1 pg/ml to 12,500 pg/ml, with a manufacturer determined assay lower limit of detection (LLOD) of 5.5 pg/ml. Serum NfL readout was obtained, and concentrations were calculated using the MSD Discovery Workbench. Inter-assay variation of the data was reduced by determining the average NfL value ratio of samples run on the final assay plate over the values of those same samples when run on previous plates. These average ratios were then multiplied by the sample values on plates other than the final plate run to obtain normalized serum NfL values.

2.6. Statistical analyses

We report differences in participant characteristics between the clinical groups (CHR and FEP) and healthy controls using χ^2 tests for categorical variables (e.g., sex) and analysis of variance (ANOVA) for continuous variables (e.g., age). Missing NfL values or serum NfL concentration values below the detection range (<5.5 pg/mL) were replaced by values generated using expectation maximization algorithm (Do and Batzoglou, 2008) to retain as many cases as possible in each group. Additionally, any extreme serum NfL outliers (NfL values outside 3rd quartile + 3*interquartile and 1st quartile – 3*interquartile ranges) were removed prior to reporting the results of primary analyses and other exploratory analyses (see Supplement Fig. S1 for the schematic illustration of the analyses). The primary analysis was conducted using expectation maximization replaced NfL values and following removal of extreme outliers, however additional sensitivity analyses were conducted removing missing cases/replaced values and with outliers, respectively.

To test our primary hypothesis of differences in serum NfL levels between groups, we used univariate analysis of variance, with serum NfL levels as the dependent variable and clinical group (CHR, FEP, healthy controls) as fixed factor, controlling for age, given previous findings suggesting a strong link between advancing age and increased NfL levels (Khalil et al., 2020). Analyses including covariates (sex, BMI, cannabis, tobacco, and antipsychotic use) are presented by adding them as fixed factors in separated models after reporting primary results without these variables.

To test the association between serum NfL levels and TSPO, we used linear mixed model with group, TSPO rs6971 genotype, regions of interest (ROI), BMI and age as fixed factors; ROI is also specified as a repeated within-subject factor with a diagonal covariance structure (allowed for different residual variances at different ROIs); participants as random effects; regional [^{18}F]FEPPA V_T as the dependent variable and serum NfL levels as predictor. The ROIs included in the model were DLPFC, hippocampus, ACC, MPFC, temporal cortex, and cerebellum. Brain regions were selected based on the previous post-mortem evidence on TSPO expression (Kreisl et al., 2013; Busse et al., 2012) or increase in microglia density (Gober et al., 2022) and structural alterations (Pantelis et al., 2003; Fornito et al., 2009; Pomarol-Clotet et al., 2010) relevant to schizophrenia and CHR. We also tested for Nfl-by-group and NfL-by-ROI interactions in the same model as we expected the NfL effect on [^{18}F]FEPPA V_T to be depended on the study groups or ROI effect. Potential confounding factors as previously described were tested by including them as fixed factors in separated models.

As exploratory analyses, we explored the associations between serum NfL levels and clinical symptoms' severity across clinical groups (FEP and CHR) using Pearson's partial correlations, controlling for age. We also explored the relationship between serum NfL levels and neuropsychological measures across study groups using univariate analyses (controlling for group and age). Investigation of the associations for these exploratory analyses were exploratory in nature. All statistical analyses were implemented using SPSS 27.0 (SPSS 27.0; IBM Corp., Armonk, NY), with 2-sided $p \leq 00.05$ considered to be statistically significant.

3. Results

3.1. Demographics and clinical characteristics

Demographics and clinical characteristics of the participants are presented in Table 1. Group comparisons for differences in age, sex, BMI, TSPO rs6971 genotype, antipsychotic use, cannabis use, and tobacco use are described in the primary NfL analysis. Three out of 27 FEP participants were taking low-dose antipsychotic medications (risperidone 1 mg, 2 mg, and quetiapine 100 mg) and seven out of 41 CHR individuals were also on low doses (risperidone 0.5 mg, 1 mg (n = 2), aripiprazole 2 mg (n = 2), and quetiapine 20 mg and 50 mg), respectively. Except for amount injected, which was significantly higher in the clinical high-risk group, PET radiotracer injection parameters did not differ between the patient and healthy groups.

3.2. Serum NfL levels were not different across clinical groups

3 HC, 1 CHR and 4 FEP either had missing serum NfL values or concentration below the detection range (<5.5 pg/mL) and hence were replaced by values generated using expectation maximization algorithm (see Supplement S2 for the main analysis excluding these replaced values). Additionally, two extreme serum NfL outliers (CHR, n = 2 [116.62 pg/mL, 58.33 pg/mL]) were noted and removed (see S3 for results with their inclusion). We did not find any significant differences in serum NfL levels across study groups (main group effect: $F_{(2,\ 78)} = 0.14$, $p = 0.87$) (Fig. 1). However, there was a significant effect of age on serum NfL levels across study groups ($F_{(1,\ 78)} = 5.12$, $p = 0.03$) (see S4a for the main analysis non-adjusted for age). These results remained after

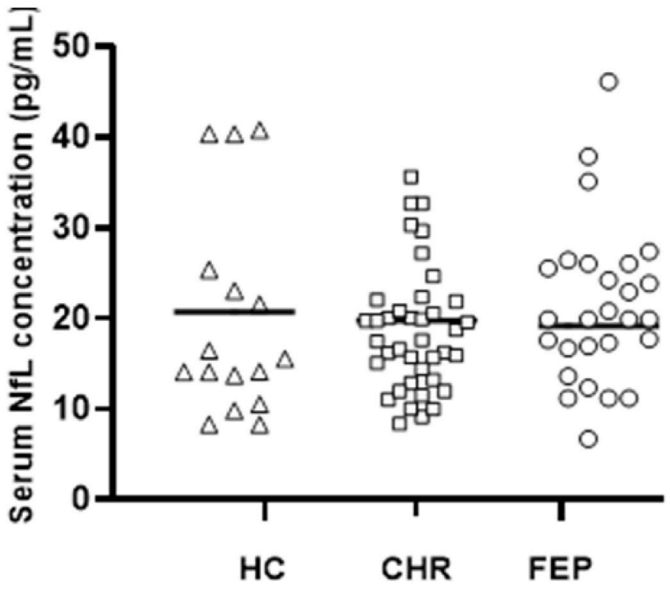

Fig. 1. Peripheral neurofilament light-chain (NfL) serum levels across the psychosis spectrum. The scatter plot graph reflects serum NfL concentration levels in healthy controls (HCs) and clinical groups (CHR and FEP). Horizontal bar indicates group means adjusted for age.
Abbreviations: CHR – Clinical High-risk; HC – Healthy control; FEP – First-episode Psychosis; NfL – Neurofilament Light-Chain; pg/mL – picogram/milliliter.

controlling for sex, BMI, tobacco use, cannabis use and antipsychotic use (see S4b).

3.3. No association between [^{18}F]FEPPA V_T and serum NfL levels

Serum NfL extreme outliers (CHR, n = 2 [116.62 pg/mL, 58.33 pg/mL]) were removed in the main analysis (see S5a for results with their inclusion). After controlling for the TSPO rs6971 polymorphism and BMI effect, no significant effect of group was observed on [^{18}F]FEPPA V_T ($F_{(2,\ 71.98)} = 0.76$, $p = 0.47$; ROI effect: $F_{(5,123.57)} = 20.9$, $p < 0.001$).

Importantly, NfL concentration was not significantly associated with [^{18}F]FEPPA V_T (main serum NfL concentration effect: $F_{(1,73.30)} = 1.71$, $p = 0.19$; group effect: $F_{(2,\ 71.98)} = 0.38$, $p = 0.69$; ROI effect: $F_{(5,\ 121.95)} = 6.12$, $p < 0.001$), controlling for TSPO rs6971 genotype, BMI, and age (see S5b for the main analyses non-adjusted for age). We did not find any NfL-by-group ($F_{(2,\ 71.98)} = 0.21$, $p = 0.82$) or NfL-by-ROI ($F_{(5,\ 121.99)} = 1.06$, $p = 0.39$) interactions in the model (see Supplement S5c, Fig. S4 A-F). These results held after controlling for sex, tobacco use, cannabis use and antipsychotic use (see S5d).

3.4. No significant association between serum NfL levels and symptom severity or cognition

In FEP, we found no significant correlations between serum NfL concentration and PANSS total symptom severity score (r (24) = 0.14, $p = 0.49$). However, in CHR, we found a trend for negative between serum NfL levels and SOPS total symptom severity score ($r(36) = -0.29$, $p = 0.076$, (see Supplement S6, Fig. S5a), controlling for age. Further, investigation of individual SOPS clinical symptom dimensions revealed a negative correlation between serum NfL levels and negative symptom severity ($r(36) = -0.39$, $p = 0.02$) (see Fig. S5b), non-surviving Bonferroni corrections for multiple comparisons for the SOPS sub-scales tested.

No significant association was observed between serum NfL levels and cognition (RBANS total score: $F_{(1,73)} = 0.39$, p = 0.54), including individual RBANS subscales [immediate memory, visuospatial ability, language, attention, delayed memory subscale (data not shown)], controlling for age and clinical group tested across all 3 cohorts (HC, CHR and FEP). We did not find any significant age-by-RBANS ($F_{(1,73)} = 0.69$, p = 0.41) or group-by-RBANS ($F_{(2,73)} = 2.14$, p = 0.13) interactions in the model.

4. Discussion

To our knowledge, this is the first study to examine serum NfL levels and investigate its relation to brain TSPO concentration across a large, mostly untreated psychosis spectrum cohort including individuals at CHR. In this study, serum NfL levels were not significantly different across clinical groups. We also found no significant association between serum NfL levels and brain TSPO expression.

Our findings of similar NfL levels across clinical groups are in line with a recent study in schizophrenia including at-risk cohort (siblings of individuals with treatment-resistant schizophrenia) and TRS group that reported no differences in NfL levels when compared to healthy controls (Eratne et al., 2021). Alternatively, another recent study in a similar group of unmedicated individuals with acute schizophrenia reported increased NfL levels compared to controls, while yet another study reported relatively lower plasma NfL levels in TRS group compared to other psychiatric disorders and controls (Eratne et al., 2024). Our results are consistent with other studies in schizophrenia that found no significant group differences in NfL levels (Eratne et al., 2021; Bavato et al., 2021) but observed an age-related increase in serum NfL in a subset of schizophrenia patients. In this context, it is noteworthy to emphasize the young age of our study sample, as all of them were below 40 years of age, perhaps explaining the negative findings. The notable age effect on serum NfL levels in our sample (5.1 (SE = 2.3) units/10 years) corresponds to a 1.3% rise in average serum NfL levels from a baseline of 19.7 pg/mL (average sample NfL levels). This finding aligns with previous studies that demonstrated a 2.2% annual increase in blood NfL levels between the ages of 18 and 70 years (Disanto et al., 2017). However, this age effect was not prominent enough to cause the separation of groups as analysis of the data non-adjusted for age still found no differences in serum NfL levels among study groups.

Additionally, a recent study reported slightly elevated serum NfL levels in schizophrenia as compared to age-matched adolescents with bipolar disorder and controls indicating early neuronal damage (Ceylan et al., 2023). A few other studies also reported mildly elevated NfL levels in schizophrenia patients, however, these observations were more pronounced in older medicated (Rodrigues-Amorim et al., 2020; Eratne et al., 2020) or forensic psychiatric patients experiencing acute conditions with a higher risk of neural injury (Fernqvist et al., 2023). On the contrary, our sample constituted mostly unmedicated or patients on a very low dose of antipsychotic use (<250 mg of chlorpromazine (CPZ) equivalent), perhaps explaining our study findings. Interestingly, the recent study in acutely ill schizophrenia patients (Popovic et al., 2023) showed increased NfL in schizophrenia versus healthy control which was positively correlated with positive and negative syndrome scale-positive scores and inversely with global assessment of functioning-scores.

We found that serum NfL levels were not significantly associated with brain TSPO across the psychosis spectrum. This finding is consistent with recent studies which showed that peripheral NfL levels did not appear to be sensitive to modest structural brain changes in patients with psychosis (Fernqvist et al., 2023), in comparison to neuroaxonal degeneration processes associated with neurodegenerative disorders (Walia et al., 2023). A recent study in AD also reported no significant interactions between plasma NfL and PET imaging measurements of AD-related neurodegeneration (Malek-Ahmadi et al., 2023). In contrast, another study in early AD specifically investigating NfL-TSPO association reported an inverse correlation between raised brain TSPO levels and reduced plasma NfL levels (Parbo et al., 2020). Coincidentally, a meta-analysis combining 7 TSPO PET studies, including our own data

(Hafizi et al., 2017a; Kenk et al., 2015), reported lower TSPO levels in schizophrenia patients compared to healthy control subjects (Plavén-Sigray et al., 2021). Moreover, the median serum NfL levels in our FEP and CHR groups were consistent with previously reported healthy control concentration ranges (median concentration range in neurological conditions: ~150–220 pg/mL; median concentration range in healthy controls: ~26–51 pg/mL) (Stengelin et al., 2019). Together, this may explain the lack of association in our sample implying lack of neuroaxonal damage and associated abnormal neuroimmune response in the early psychosis spectrum. Supporting this evidence, a more recent study distinguishing Anti-NMDAR Encephalitis (NMDARe) and FEP found that 96% of FEP patients had serum NfL<15 pg/mL comparable to healthy controls while only 15% of NMDARe with isolated psychosis had values less than 15 pg/mL (Guasp et al., 2022).

We found a negative correlation between serum NfL levels and negative symptom severity in individuals at CHR but found no associations in FEP. In contrast, a recent study in acute schizophrenia patients found increased serum NfL levels compared to healthy controls, which correlated positively with positive symptom severity (Popovic et al., 2023). Previous studies that employed peripheral NfL levels in neurological (Khalil et al., 2018) and neuroinflammatory conditions (Kuhle et al., 2019; Srpova et al., 2021) also reported elevated NfL levels. These abnormal NfL elevations were closely associated with pathologic brain changes shown via imaging studies (Khalil et al., 2020; Jakimovski et al., 2019; Mattsson et al., 2017). A previous study in medicated (clozapine-treated) schizophrenia patients presenting with worse outcomes and cognitive decline had higher concentration of NfL proteins when compared to those who responded to first-line antipsychotics (Rodrigues-Amorim et al., 2020). In our study, we did not observe clinical associations in FEP and the negative correlation observed in CHR needs to be investigated in well-powered studies.

Finally, we found no correlations between serum NfL levels and cognitive function as assessed by the RBANS scale. This contrasts with the findings by multiple studies that demonstrated the effectiveness of peripheral NfL levels in predicting cognitive decline (Beste et al., 2019) in psychiatric disorders (Popovic et al., 2023) and neurodegenerative disorders (Mattsson et al., 2017). However, the RBANS scale is also influenced by age and our relatively younger cohort, with preserved cognitive function, can explain these results.

The results of this study should be interpreted considering the following limitations. First, some of the participants in the CHR (n = 5) and FEP (n = 3) groups tested positive for cannabis in urine drug screening. However, adding positive urine drug screen results as a covariate in our statistical analyses did not change our findings. Second, in this study we replaced NfL values that were missing or below detection range using the EMM to retain as many cases as possible. Despite the relatively small sample size limiting its use and possible clinical validity, this method has been implemented in psychosis studies with similar sample sizes (Boerrigter et al., 2017). The results remained unchanged after analysis of the data removing these replaced NfL values (S2). Third, several types of cells in the brain including microglia, astrocytes, neurons, and vascular endothelial cells express TSPO (Lavisse et al., 2012). Nonetheless, these other cell types are also involved in the immune response, and thus the overall conclusion of this study remains unaffected. Fourth, studies suggest that CSF NfL levels are more reliable compared to its concentration in blood (Gagliardi et al., 2019). Although previous studies have shown a strong correlation between CSF and blood NfL levels (Khalil et al., 2018; Wilke et al., 2016) independent of the diagnosis, this should be specifically examined in psychosis cohorts. Fifth, the cross-sectional design and lack of serial NfL levels prevented us from assessing the causal relationship between disease progression and NfL levels. Longitudinal clinical follow-up revealed that 6 of the 41 individuals at CHR in this study (~12%) converted to psychosis. Although conclusions were limited by small sample size for conversion, we found no significant differences in serum NfL levels between individuals at CHR who converted to psychosis and non-converters (data not shown). Lastly, while our samples sizes are relatively large for PET studies, the study may be underpowered to test multiple associations. Nevertheless, our previous studies (Da Silva et al., 2021) with similar sample sizes, allow us to consider this study to be sufficiently powered to test associations between serum NfL levels and TSPO levels.

5. Conclusion

In conclusion, our findings of similar NfL levels across clinical groups fill an important gap in the literature regarding the relevance of serum NfL in early psychosis. These findings coupled with the lack of association between serum NfL and brain TSPO expression may point towards the lack of active neuroaxonal alterations and related elevated neuroimmune response early in the psychosis spectrum.

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CRediT authorship contribution statement

Kankana Nisha Aji: Formal analysis, Writing – original draft, Writing – review & editing, Data curation. **Giulia Cisbani:** Methodology, Resources, Formal analysis, Validation, Writing – review & editing. **Ana Weidenauer:** Formal analysis, Writing – review & editing. **Alex Koppel:** Data curation, Methodology, Writing – review & editing. **Sina Hafizi:** Data curation, Formal analysis, Project administration, Writing – review & editing. **Tania Da Silva:** Data curation, Formal analysis, Project administration, Writing – review & editing. **Michael Kiang:** Writing – review & editing, Visualization. **Pablo M. Rusjan:** Formal analysis, Methodology, Software, Validation, Writing – review & editing. **Richard P. Bazinet:** Methodology, Resources, Supervision, Validation, Writing – review & editing. **Romina Mizrahi:** Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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