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Altered neuroaxonal integrity in schizophrenia and major depressive disorder assessed with neurofilament light chain in serum

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ABSTRACT

Background: Schizophrenia (SZ) and major depressive disorders (MDD) have been frequently linked to anatomical brain alterations. However, the relationship between brain pathology, inflammation and clinical symptoms in these disorders is still unclear. Thus, by applying novel blood markers of neuroaxonal integrity such as neurofilament light chain (NfL), we can now address main issues in psychiatric research and potentially offer innovative diagnostic tools toward better clinical characterizations and monitoring in both SZ and MDD.
Methods: NfL levels were measured in serum of 44 patients with SZ and in 41 patients with MDD applying single molecule array technology and compared to a healthy norm population. Main inflammatory markers (C- reactive protein, interleukins IL-6 and IL-10) were measured to define patients with inflammatory phenotype. The Digit Symbol Substitution Task (DSST) and the Letter-Number-Sequencing Task were performed to estimate cognitive function in both groups.
Results: NfL levels in MDD group (but not in SZ group) were significantly higher than reference values of healthy norm population. A higher than expected proportion of patients with NfL levels above age-specific cut-off values was observed in both SZ and MDD groups. No correlation was observed between NfL and inflammatory markers. A negative correlation between DSST and NfL-values was observed in patients with MDD.
Conclusions: Both SZ and MDD showed elevated serum levels of NfL, which were independent from inflammatory markers but associated with cognitive performance.

1. Introduction

The role of structural brain alterations in psychiatric disorders such as schizophrenia (SZ) and major depressive disorder (MDD) is still controversial. In SZ, structural brain alterations were consistently observed not only in patients with SZ but across the whole SZ spectrum including individuals at risk for psychosis (Lawrie et al., 2001). However, the presence of progressive brain alterations occurring after the onset of first psychotic symptoms is still an issue of debate (Kanaan et al., 2017; Lieberman, 1999). In MDD, a heterogeneous pattern of structural brain abnormalities was described in patients with recurrent depressive episodes, but the integration of these findings in the physiopathology of the disorders remains unsolved (Liao et al., 2013; Sacher et al., 2012). Looking at symptom dimensions, some consistent findings linked the alteration of long association white matter fibres in SZ to negative symptoms and deficits in several cognitive domains (Karbasforoushan et al., 2015; Surbeck et al., 2020; Wolkin et al., 2003). Also in MDD, structural brain abnormalities (e.g. in white matter, hippocampal and frontal structures) were mostly associated with depressive symptoms and cognitive dysfunctions (Jamieson et al., 2019; Jiang et al., 2017).

An intriguing approach to assess the integrity of brain structures with a minimally invasive procedure, consists in detecting the levels of

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specific brain proteins in extracellular matrices like cerebrospinal fluid (CSF) or serum. In particular, neurofilament proteins (NP) appeared in the last few years as the most promising blood biomarkers of neuro-axonal injury (Khalil et al., 2018). NP are cytoskeletal components, predominantly expressed in long myelinated axons and thought to support axonal stability and high-velocity nerve conduction (Yuan et al., 2017). In pathological processes that cause axonal injury, NP such as neurofilament light chain (NfL) are released in significant amount into CSF and peripheral blood. After the recent introduction of ultrasensitive assays like the Single Molucule Array (SIMOA) method, NfL measure in blood was proposed as a prognostic and monitoring tool in a broad range of neurological and neuropsychiatric disorders (Bridel et al., 2019; Khalil et al., 2018; Kuhle et al., 2019). The sensitivity of NfL response to different structural brain changes was confirmed in imaging studies showing associations of NfL levels with alterations of white matter fibres, global brain volume and local atrophy (e.g. of hippocampus) (Jakimovski et al., 2019; Khalil et al., 2020). The association of NfL with cognitive functioning in healthy individuals, also suggests a high sensitivity of NfL levels in the detection of microstructural alterations at a subclinical level (Beste et al., 2019). Moreover, evidence in patients with neuroinflammatory disorders suggests NfL levels to reflect ongoing pathological processes rather than cumulative brain damage and to be particularly sensitive to acute inflammation (Cantó et al., 2019; Srpova et al., 2021). In this direction, a longitudinal study in patients with multiple sclerosis under immunosuppressive treatment showed that the normalization of the cytokine profile was also accompanied by reduction of NfL levels (Fernández-Velasco et al., 2021).

Importantly, inflammation was frequently discussed as possible etiological factor for the development of structural brain alterations in both SZ and MDD (Kato et al., 2011; Maes et al., 2009). In particular, dysregulation of peripheral cytokines was associated to several structural brain changes including white matter alterations in SZ and hippocampal volume reduction in MDD (Di Biase et al., 2020; Frodl et al., 2012). Microglial activation and neuro-oxidative stress may be main mediators of inflammatory-driven brain pathology (Mondelli et al., 2017). However, clear evidence of an inflammatory role of brain pathology in psychiatric disorders is, to date, still lacking, also due to limitations of in-vivo methods. Preliminary studies on NfL in SZ and MDD reported contrasting findings, with increased CSF levels in a sample of 11 elderly women with MDD history (Gudmundsson et al., 2010), but normal serum levels in other small samples of elderly patients with MDD or SZ (Al Shweiki et al., 2019; Besse et al., 2020; Katisko et al., 2020). Elevated NfL levels were recently observed in a sample of 65 patients with ketamine dependence (Liu et al., 2021). In this study, a marked elevation of NfL levels was reported specifically in a subgroup of patients with ketamine dependence and MDD comorbidity (n = 30). Higher NfL levels were also reported to predict depression after stroke and were associated to peripheral inflammation in the same sample (Zhao et al., 2020). Thus, the possible applicability of NfL measures in the assessment of major psychiatric disorders is promising and requires further investigation.

Based on this background, we aimed to analyze the NfL levels in clinically and pharmacologically stable patients with SZ and MDD as well as their association with inflammatory state and psychiatric symptom severity. In particular, we hypothesized that NfL levels in both groups would be higher than reference values of a healthy norm population (Barro et al., 2018). Moreover, we assessed correlations between NfL levels and peripheral inflammatory state (C- reactive protein [CRP] and interleukins IL-6 and IL-10). CRP was assessed as common surrogate marker of systemic inflammation, while IL-6 and IL-10 were selected as main pro- and anti-inflammatory cytokines, respectively. Notably, CRP and IL-6 levels have been consistently reported to be increased in both SZ and MDD (Goldsmith et al., 2016; Yuan et al., 2019). Differently, IL-10 reduction was frequently linked to neuroinflammation in SZ and MDD (Dhabhar et al., 2009; Xiu et al., 2014). Moreover, a positive association between CRP and NfL levels was previously described in a well-sized cohort of patients after stroke and linked to post-stroke depression (Zhao et al., 2020). Interactions between peripheral levels of IL-6, IL-10 and NfL were also already described in other neurological disorders (Fernández-Velasco et al., 2021; Kimura et al., 2019). Coherently, we hypothesized NfL to be positively correlated with pro-inflammatory markers (CRP, IL-6) and to be negatively correlated with the anti-inflammatory IL-10. Finally, we tested the additional hypothesis that NfL levels would be associated with symptom severity in psychopathological domains known to be related to structural brain alterations such as depressive and negative symptoms and cognitive dysfunction. For this latter point, the Digit Symbol Substitution Task (DSST) was assessed as a sensitive measure of cognitive processing speed, while the Letter-Number-Sequencing task (LNS) was used to evaluate working memory performance. Scores in both tasks were already found to be inversely correlated to NfL levels (Chatterjee et al., 2018; Mattsson et al., 2017). Taken the overall lack of reliable biological markers in psychiatric practice, the introduction of new low-invasive biomarkers represents a priority toward better clinical characterization and individualized treatment for psychiatric patients.

2. Methods

2.1. Ethics

This study was approved by the Research Ethics Committee of the Canton of Zurich. All participants provided written informed consents prior to their enrollment in this study. Clinical and laboratory investigations were strictly conducted according to the principles expressed in the Declaration of Helsinki.

2.2. Participants

44 patients meeting the DSM-V (American Psychiatric Association, 2013) criteria for SZ and 41 meeting the DSM-V criteria for MDD were recruited. Patients were recruited from outpatient and inpatient units of the Psychiatric Hospital of the University of Zurich and affiliated institutions. Diagnoses were confirmed by conducting the Mini-International Neuropsychiatric Interview (Lecrubier et al., 1999). All patients were clinically stable and under a stable dose of medication for at least two weeks prior to testing. Inpatients were at the end of their hospitalization and engaged in a multimodal therapy program and activities outside the hospital. The average duration of hospitalization for patients with SZ and MDD in Swiss psychiatric hospitals is longer than in most other countries, so the majority of patients would have been treated as outpatients in many other health care systems. The inclusion age was between 18 and 65 years. We excluded patients with any other than the above mentioned DSM-IV Axis I disorders, benzodiazepine medication with more than 1 mg of lorazepam equivalents per day and acute psychotic symptoms. Participants with any past or current substance abuse or dependency (including alcohol) according to DSM-IV were excluded. In both groups, participants were also excluded if they had a history of head-injury or any autoimmune or chronic inflammatory disorder or if they took any pain-medication or anti-inflammatory drugs at least one week prior to testing (assessed by a detailed questionnaire and medical records, where available). Furthermore, participants were not included in the study if they had a history of any known acute medical condition associated with inflammation two weeks prior to testing. Clinical data and CRP levels in the SZ sample were already published in previous works (Cathomas et al, 2021a, 2021b; Klaus et al., 2021).

2.3. Psychopathology and cognition scores

Depressive symptoms were assessed using the Hamilton Depression Scale (HAMD) (Hamilton and Guy, 1976) and the Beck Depression Inventory (BDI) (Beck et al., 1961). Negative symptoms were assessed

with the Self-Evaluation of Negative Symptoms (SNS) questionnaire, which is based on five subdomains of negative symptoms (social withdrawal, diminished emotional range, avolition, anhedonia, and alogia) (Dollfus et al., 2016). Negative, positive and disorganized symptoms were also assessed using the five factor model of the Positive and Negative Syndrome Scale (PANSS) (Wallwork et al., 2012). Cognition was assessed with the Brief Neurocognitive Assessment (BNA), consisting of the Digit Symbol Substitution Task (DSST) to assess processing speed ability and the Letter-Number-Sequencing task (LNS) to assess working memory ability (Fervaha et al., 2014).

2.4. Blood biomarkers

Blood collection was performed between 8 and 10 a.m. to obtain serum (NfL and CRP) and plasma (IL-6, IL-10) samples. Patients were instructed to fast for at least 8 h prior to the blood collection. For serum, a silica and gel containing tube (BD Vacutainer) was used and a resting time of 30 min to allow clotting process was applied. Plasma was collected with a EDTA tube and directly processed. After collection, blood was centrifuged for 15min at 1500 g at room temperature. All samples were frozen and stored at −80 °C.

2.4.1. Neurofilament light chain

NfL levels were measured in serum applying single molecule array (SIMOA) technology as previously described at the University Hospital Basel (Disanto et al., 2017). All intra-assay coefficients of variation of duplicate determinations were below 15%. The mean coefficient of variation was 4.3% in the SZ group and 4.3% in the MDD group. There were no missing values and no values below the level of detection. To compare NfL levels in both groups to values of a healthy norm population, NfL percentiles and z-scores for each patient were calculated. Both variables were assessed from a data set consisting of 485 samples from 295 healthy controls by means of GAMLSS models (Generalized additive model for location, scale, and shape) as described in previous work (Barro et al., 2018). From the GAMLSS model, age-group corrected percentiles were derived. These allow to estimate for a given age the proportion of samples in healthy individuals, which are on average below or above a given NfL level. Z-scores were also derived from the same model to quantify how much a given value deviates from the mean values in same age healthy controls, expressed as number of standard deviations.

2.4.2. C- reactive protein

High-sensitivity CRP was measured in serum by immunoturbidimetry on Abbott Architect c16000 or c8000, at Unilabs Medical Analytics in Duebendorf/Zurich, Switzerland. Its measure is commonly used as a surrogate marker of systemic inflammation also in psychiatric populations (Yuan et al., 2019).

2.4.3. Cytokines

Cytokine levels were measured in plasma samples using the Olink® Inflammation panel (Olink Proteomics AB, Uppsala, Sweden) according to the manufacturer's instructions. The Proximity Extension Assay (PEA) technology used for the Olink protocol was described in detail in previous works (Assarsson et al., 2014). IL -6 and IL-10 were selected from the Olink Inflammation panel for the current analysis.

2.5. Data analysis

Group differences in raw and z-scored NfL levels were examined using Mann Whitney U Tests. Chi-square test was used to compare the frequency of categorical percentile allocation (number of individuals above age-group corrected cut-off levels) of SZ and MDD populations to the norm population for each percentile considered (80th, 90th, 95th and 99th percentile) (Barro et al., 2018). One sample t-tests were used to compare mean z-scores in SZ and MDD population to the norm population (mean z-score in norm population = 0). Spearman's correlation coefficients were used to investigate correlations between NfL or z-scores and inflammatory markers, clinical parameters, psychopathology and cognitive scores. Relevant variables identified with a level of significance set at $p < 0.05$ for either NfL or z-score were then included as dependent variables in multivariate linear regression models. All models were performed with forced entry using four preselected independent variables: age, sex, body mass index (BMI), and NfL. Age was included because previous findings demonstrated a strong linkage between advancing age and increased NfL levels (Barro et al., 2018). BMI was also included due to potential effects of BMI on NfL levels, while sex was included to correct for gender frequency differences (Manouchehrinia et al., 2020). For the regression models, interval scaled variables were tested for normal distribution using the Kolmogorov-Smirnov test. Variables showing non-normal distribution were logarithmic transformed prior to entry in regression models. All statistical analyses were computed with SPSS version 25 (IBM Corp., SPSS Inc., Chicago IL, USA) and R-Studio (Version 3.6.1).

3. Results

3.1. Sociodemographic data

Sociodemographic and clinical characteristics of 44 patients with SZ and 41 patients with MDD are summarized in Table 1. Sociodemographic data of the norm population has been described previously (Barro et al., 2018).

3.2. NfL values and percentile distribution

Mean NfL levels in serum were significantly higher in MDD than in SZ group (26.31 ± 10.4 pg/ml vs. 25.51 ± 19.1 pg/ml, U = 666.50, p = 0.038) (see Fig. 1). However, no significant group effect on NfL levels was observed after correcting for age in a linear regression analysis (B = 0.09, β = −0.09, p = 0.321). Coherently with previous findings, age was

Table 1
Sociodemographic, clinical characteristics and psychopathology scores.

Variables	SZ patients (N = 44)	MDD patients (N = 41)
Age, years	34.25 ± 10.46	36.02 ± 10.95
Sex		
Male, N	30 (68.2%)	17 (41.5%)
Female, N	14 (31.8%)	24 (58.5%)
BMI, kg/m^2	26.28 ± 4.63	22.90 ± 4.40
Education years, years	12.30 ± 3.91	14.43 ± 3.13
Current smokers, N	28 (63.6%)	14 (34%)
Cannabis use, N	8 (18.2%)	7 (17%)
Alcohol use, N	23 (52.3%)	32 (78%)
Psychiatric family history, N	14 (31.8%)	18 (43.9%)
Disease onset, months	122.32 ± 102.10	83.39 ± 96.16
Treatment delay, months	9.79 ± 27.73	26.27 ± 51.50
Hospitalizations, number	5.45 ± 5.50	1.22 ± 1.35
Psychotic episodes, number	5.34 ± 5.19	–
Depressive episodes, number	0.07 ± 0.04	3.68 ± 3.24
CPZ-Equivalent, mg	530.98 ± 456.08	–
HAMD_total	7.30 ± 4.96	18.44 ± 7.51
BDI_total	15.18 ± 9.44	25.66 ± 12.68
PANSS_total	51.61 ± 14.10	51.46 ± 9.10
SNS_total	15.82 ± 6.37	18.05 ± 6.97
DSST, score	59.59 ± 13.41	73.58 ± 14.89
LNS, score	18.78 ± 0.30	20.43 ± 0.40

Numerical variables are presented as mean value ± standard deviation. Abbreviations: SZ: Schizophrenia; MDD: Major Depressive Disorder; SD: Standard Deviation; BMI: Body Mass Index; CPZ: Chlorpromazine; HAMD: Hamilton Depression Scale; BDI: Beck Depression Inventory; PANSS: Positive and Negative Syndrome Scale; SNS: Self-Evaluation of Negative Symptoms scale; DSST: Digit Symbol Substitution Test; LNS: Letter-Number-Sequencing task.

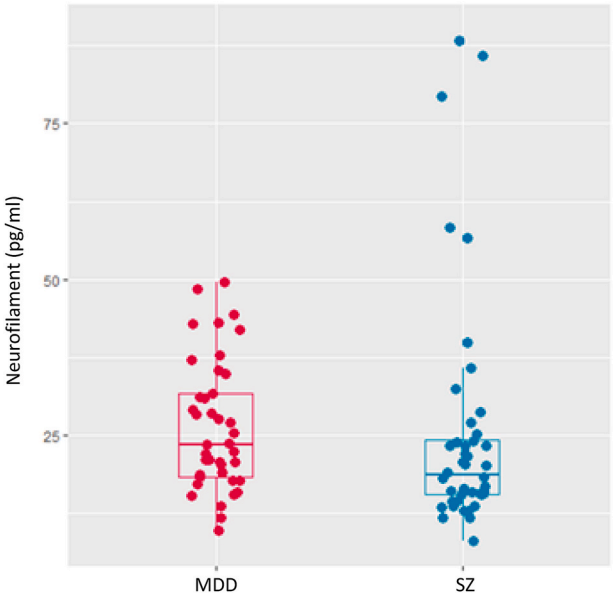

Fig. 1. Comparison of NfL levels in MDD and SZ.
Boxplots showing individual serum NfL levels. Central horizontal lines indicate median values, boxes illustrate the ranges between lower and upper quartiles. Mean/median (interquartile range) NfL levels in pg/ml in MDD group: 26.31/23.60 (18.05–33.30); in SZ group: 25.51/18.75 (15.53–24.83). Abbreviations: MDD: Major Depressive Disorder; SZ: Schizophrenia spectrum disorder; NfL: Neurofilament Light Chain.

positively correlated to NfL levels in both groups (SZ: r(s) = 0.61, p < 0.001; MDD: r(s) = 0.45, p = 0.003) but not with z-scores (SZ: r(s) = 0.02, p = 0.903; MDD: r(s) = -0.10, p = 0.546), which are age-corrected (see Fig. 2). NfL levels were also higher in female patients in both SZ (male vs female: 21.07 ± 15.11 pg/ml vs. 35.01 ± 23.64 pg/ml, U = 96.50, p = 0.004) and MDD groups (male vs female: 21.25 ± 7.59 pg/ml vs. 29.90 ± 10.76 pg/ml, U = 107.50, p = 0.011). However, after inclusion of age and BMI in a linear regression analysis, no significant gender effects on NfL levels were observed (SZ group: B = 0.23, β = −0.20, p = 0.189; MDD group: B = 0.18, β = −0.23, p = 0.122). Compared to age-specific reference values from a healthy norm population, higher NfL levels were observed in the MDD group (t(40) = 3.99; p < 0.001) but not in the SZ group (t(43) = 1.55; p = 0.129) (see Table 2). In the MDD group, an increased proportion of individuals with NfL levels above the 80th, 90th; and 99th percentiles of age-specific distribution curves derived from normative sample (all p < 0.01) was found. Also in the SZ group, an increased proportion of individuals with NfL levels above the 95th and 99th percentiles was observed (both p < 0.01) (see Table 2). Contrary to a previous report in the literature, NfL levels in our SZ patients under clozapine treatment (n = 9) were comparable to those in SZ patients treated with other second-generation antipsychotics (n = 34) (clozapine vs. other antipsychotics: 26.86 ± 24.47 pg/ml vs. 25.22 ± 18.20 pg/ml, U = 137.00, p = 0.649) (Rodrigues-Amorim et al., 2020). Also in the MDD group, NfL levels did not

Table 2
NfL values, percentile distribution and inflammatory markers.

Variables	SZ patients (N = 44)	P value[a] (SZ vs. NP)	MDD patients (N = 41)	P value[a] (MDD vs. NP)	P value[b] (SZ vs. MDD)
NfL levels, pg/mL	25.51 ± 19.13		26.31 ± 10.40		**0.038**
Z-Score, age-group corrected[c]	0.28 ± 1.19	0.129	0.62 ± 0.99	**<0.001**	
80th -Percentile, N	10 (22.7%)	0.666	16 (39.0%)	**0.004**	
90th -Percentile, N	8 (18.2%)	0.098	12 (29.3%)	**<0.001**	
95th -Percentile, N	7 (16.0%)	**0.002**	5 (12.2%)	0.051	
99th -Percentile, N	4 (9.1%)	**<0.001**	3 (7.3%)	**0.002**	
CRP levels, mg/l	2.09 ± 1.69		1.16 ± 1.10		**0.012**
IL-6 levels, ng/l	3.02 ± 0.91		2.68 ± 0.65		0.138
IL-10 levels, ng/l	2.67 ± 0.53		2.59 ± 0.51		0.399

Numerical variables are presented as mean value ± standard deviation.Abbreviations: SZ: Schizophrenia; MDD: major depressive disorder; NP: Norm Population; NfL: Neurofilament Light Chain; CRP: C-Reactive Protein; SD: Standard Deviation.

[a] One sample T-Test [expected value = 0] was used to compare mean z-score in SZ and MDD patients to reference population; Chi-square test used to compare the frequency of percentile allocation in SZ and MDD patients to reference norm population (N = 485).

[b] Mann-Whitney *U* test used for numerical variables.

[c] Z-score was obtained using GAMLSS (Generalized additive model for location, scale and shape) models in a reference population (N = 485) and represent the number of standard deviations a given value deviates from the average values in healthy controls for a given age.

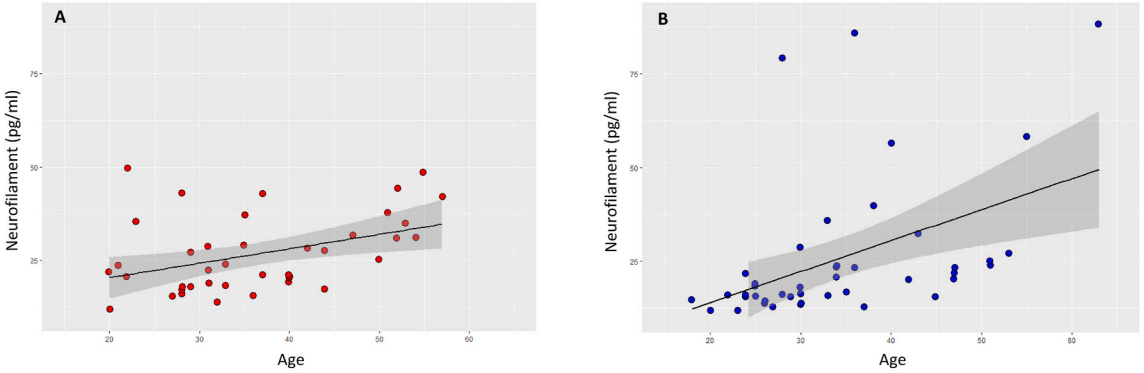

Fig. 2. NfL and age.
Scatterplots showing the relationship between age and serum NfL levels. Age was positively correlated with NfL levels in both MDD (A) and SZ (B). Abbreviations: MDD: Major Depressive Disorder; SZ: Schizophrenia spectrum disorder; NfL: Neurofilament Light Chain.

significantly differ in patients under antidepressant treatment (n = 34) compared to patients without pharmacological treatment (n = 7) (with vs. without antidepressants: 22.93 ± 8.84 pg/ml vs 27.01 ± 10.68 pg/ml, U = 117.00, p = 0.314). Altogether, the findings show increased NfL levels in patients with MDD and higher frequency of individuals with elevated NfL levels in both SZ and MDD.

3.3. NfL and inflammatory markers

None of the inflammatory markers considered (CRP, IL-6, IL-10) showed significant correlations with NfL levels or/and z-scores in each group (see supplementary Table 1). Thus, NfL levels appeared to be independent from inflammatory state in both groups.

3.4. NfL and clinical variables

In order to investigate clinical symptoms that might be associated with NfL levels, we firstly performed a correlation analysis for both NfL and z-scores (see supplementary Table 2). In the SZ group, we identified an inverse correlation between z-score and the number of psychotic episodes and a positive correlation between NfL and disease duration (time since onset, in months) (all $p < 0.05$). In the MDD group, we observed a positive correlation between NfL and HAMD score and a negative correlation between NfL and DSST score (all $p < 0.05$).

To reduce the number of comparisons, clinical variables identified as significant ($p < 0.05$) in correlation analysis were then entered in multivariate regression analysis (see Table 3). In the four models selected (*disease onset* and *psychotic episodes* in SZ group and *HAMD* and *DSST* in MDD group), NfL showed a significant predicting value only for DSST score in the MDD group ($B = -12.89$, $\beta = -0.35$, $p < 0.05$) (see Fig. 3). In DSST model, age was also a significant predicting factor for DSST score ($B = -24.84$, $\beta = -0.52$, $p < 0.001$), coherently with an age-dependent cognitive decline in MDD individuals.

4. Discussion

The aim of the present study was to investigate NfL in blood serum as an innovative blood biomarker of neuroaxonal integrity in schizophrenia and major depressive disorders. Significantly elevated NfL blood levels were observed in clinically stable patients with MDD but not in patients with SZ when compared to a healthy norm population. However, a higher number of patients with NfL levels above age-specific cut-off values was observed in both MDD and SZ groups. Moreover, NfL levels were independent from inflammatory blood markers in both groups. Finally, NfL levels predicted cognitive processing speed in the MDD group.

The increase of NfL levels we observed in the MDD group is consistent with previous neuroimaging studies, which demonstrated subtle widespread white matter alterations and reduced brain volumes in patients with recurrent/chronic MDD (for the ENIGMA-Major Depressive Disorder Working Group et al., 2016; van Velzen et al., 2020). Importantly, evidence in patients with neuroinflammatory disorders suggests that NfL increases reflect active pathological processes rather than cumulative brain damage (Cantó et al., 2019). Consequently, increased NfL levels in MDD group might be considered as a sign of active neuropathological processes and are coherent with the view of accelerated brain aging in this disorder (Dohm et al., 2017; Douillard--Guilloux et al., 2013). Notably, abnormal dynamics of NP assembly were also observed in experimental models of depression (Reinés et al., 2004). Here, hippocampal concentration of NP was shown to be influenced by pharmacological and non-pharmacological interventions, suggesting reversibility potential of NP alterations (Sifonios et al., 2009). As in-vivo markers of brain pathology in psychiatric praxis are lacking, NfL could therefore represent a potential target for future investigations on longitudinal effects of therapeutic interventions.

In our SZ sample, mean NfL levels were not significantly increased compared to reference values of a healthy norm population. Thus, our results would support the idea of structural brain stability in medicated SZ patients (Zipursky et al., 2013). However, a high heterogeneity of NfL levels in SZ was observed, with higher than expected frequency of patients with NfL levels above age-specific cut-off values. Despite the fact that the moderate sample size limits a possible clinical characterization of these outliers, NfL levels may suggest active neuropathological processes at least in a subgroup of SZ patients. This finding is particularly intriguing, as high structural brain heterogeneity was consistently reported in imaging studies and discussed as main feature of SZ (Brugger and Howes, 2017). In this direction, biomarker-driven approaches were recently proposed to guide the identification of putative illness subtypes (Clementz et al., 2016; Wolfers et al., 2018). However, given the dynamic nature of NfL response, its high variance in the SZ group may also reflect different clinical stages, according to the non-linear individual trajectories of white matter integrity on the course of the disorder (Kochunov and Hong, 2014). Thus, longitudinal investigations of NfL in larger SZ cohorts including patients in early and acute phases may provide crucial information toward better characterization of the disorder.

An etiological speculation on the nature of increased NfL levels is limited by the aspecificity of this marker. Studies in animal and humans related NfL levels to neuroaxonal alterations, which are eventually macroscopically detectable as white matter disruption or global brain volume reduction (Khalil et al., 2018; Yuan et al., 2017). However, several neuropathological pathways including inflammatory,

Table 3
Multivariate regression analysis for NfL values predicting psychopathology and cognition scores.

	SZ patients (N = 44)						MDD patients (N = 41)					
	Disease onset[a,b]			Psychotic episodes[a,b]			HAMD[a,b]			DSST[a,b]		
	B	SE	β	B	SE	β	B	SE	β	B	SE	β
Constant	2.20	0.52	0.67	−1.10	1.49		1.82	0.92		214.06	22.45	
Age [b]	0.09	0.28	0.04***	0.66	0.54	0.24	0.27	0.26	0.18	−24.84	6.40	−0.52***
Sex	0.03	0.03	0.12	0.33	0.30	0.19	0.09	0.16	0.09	−0.45	3.95	−0.02
BMI	−0.29	0.26	−0.16	0.04	0.03	0.23	−0.03	0.02 (*)	−0.29	−0.48	0.43	−0.14
NfL [b]	2.20	0.52	0.67	−0.45	0.26	−0.30	0.19	0.22	0.16	−12.89	5.26	−0.35*
R^2		4.45			1.24			0.52			1203.72	
F		7.70***			2.10			2.80*			11.01***	

Abbreviations: SZ: Schizophrenia; NfL: Neurofilament Light Chain; HAMD: Hamilton Depression Scale; BDI: Beck Depression Inventory; SNS: Self-Evaluation of Negative Symptoms scale; DSST: Digit Symbol Substitution Test; B: unstandardized regression coefficient; SE: unstandardized Standard Error; β: standardized Beta; BMI: Body Mass Index.variables (age, sex, BMI) and NfL as independent variables. P-value symbols: (*)p < 0.10; *p < 0.05; **p < 0.01; ***p < 0.001.

[a] Multivariate linear regression models with clinical variables (Onset, Psychotic Episodes, HAMD, DSST) as a dependent variables and sociodemographic.

[b] Logarithmic transformed variables: age, NfL, onset, psychotic episodes, HAMD, DSST.

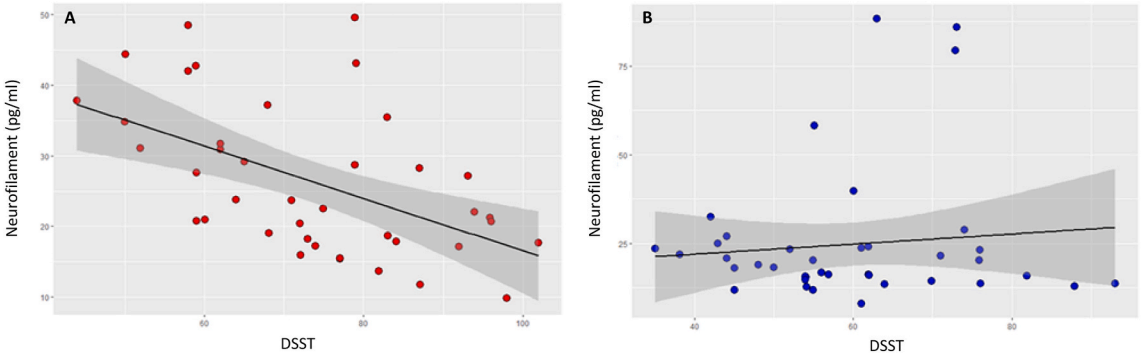

Fig. 3. NfL and cognitive processing speed.
Scatterplots showing the relationship between DSST score and NfL levels. DSST score was negatively correlated to NfL in MDD group (A) but not in SZ group (B). Abbreviations: MDD: Major Depressive Disorder; SZ: Schizophrenia spectrum disorder; NfL: Neurofilament Light Chain, DSST: Digit Symbol Substitution Task.

neurodegenerative, and vascular processes may be involved. In our study, no correlation between peripheral inflammatory markers and NfL levels was observed. This finding is particularly intriguing in the light of the putative role of the inflammatory system in both SZ and MDD. Meta-analytic reviews described an inflammatory phenotype in major psychiatric disorders with similar magnitude and frequency of cytokine alterations in both SZ and MDD (Goldsmith et al., 2016; Köhler et al., 2017). These common inflammatory findings were alternatively discussed as an unspecific vulnerability trait of psychiatric patients or rather as a response of the immune system to (illness-related) chronic stress, through dysregulation of glucocorticoid signaling and consequent induction of neurodegenerative processes (Howes and McCutcheon, 2017; Maes et al., 2009; Raison and Miller, 2003). Our finding, however, does not support an association of peripheral inflammation with active neuroaxonal pathology in both SZ and MDD. As our sample only consists of medically stable patients, one may argue that pharmacological treatment could influence the inflammatory state and that a cytokine effect on brain structure could rather characterize the acute phase of disorder. In this direction, Goldsmith et al. (2016) suggested that treatment of acute state may lead to resolution of inflammation. Nonetheless, alterations of cytokines levels have also been observed in chronic psychiatric patients and were related to structural brain alterations in neuroimaging studies in both SZ and MDD (Di Biase et al., 2020; Haroon et al., 2018). As the nature of brain alterations in psychiatric disorders remains poorly understood, NfL could represent a promising marker for further investigations on in-vivo relevance of different neuropathological pathways.

Looking at symptom dimensions, the negative association between cognitive processing speed (DSST score) and NfL levels in MDD is not surprising. DSST is an unspecific but sensitive marker of cognitive functioning and is widely used as monitoring tool in MDD (Jaeger, 2018). Physiologically, cognitive processing speed is dependent on the integrity of long caliber brain fibres, in which NfL is abundantly expressed (Turken et al., 2008). An association between white matter integrity and cognitive functioning was also described in several imaging studies on MDD (Jamieson et al., 2019; Jiang et al., 2017). Moreover, DSST score was already demonstrated to negatively correlate with NfL levels in elderly individuals and in patients with neurodegenerative disorders (Chatterjee et al., 2018; Mattsson et al., 2017). Thus, our findings support the idea of NfL being a sensitive marker for microstructural brain alterations (e.g., of white matter fiber tracts) that are relevant for cognitive functioning (Beste et al., 2019). As DSST score was predicted by both age and NfL levels, the decline of processing speed in patients with MDD should be seen as an interaction of physiological (age-related) and pathological (disorder-related) degenerative brain processes.

The present study bears several limitations. First, its cross-sectional design and limited sample size prevented us from drawing conclusions about causal relationship between disease activity and NfL alterations. Furthermore, our sample is limited to patients under stable pharmacological treatment. As NfL represents a dynamic biomarker of active neuropathological processes, it is plausible to suspect a role of medical treatment and disease relapses on NfL levels. Although we did not find significant relationships between NfL and several clinical variables in multivariate regression models, we cannot exclude that the selection of patients with chronic/recurrent symptomatology in our sample had a crucial influence on observed NfL levels. In addition, cardiovascular risk factors, renal function and physical activity were not systematically assessed in our samples but they may have an influence on NfL levels (Barro et al., 2020). Finally, we used a previously published norm sample as a reference population instead of a specifically matched healthy control group, which might have impacted our result. However, the norm population was relatively large (N = 285), which is an advantage above a matched control sample of a similar size as the case samples (n = 41–44). Nonetheless, our study offers intriguing findings on the highly relevant topic of biomarkers implementation in psychiatry. To date, only few studies had applied SIMOA technology to measure NfL levels in blood of patients with SZ and MDD and were limited to smaller samples of elderly patients (Al Shweiki et al., 2019; Besse et al., 2020; Katisko et al., 2020). Moreover, the integration of clinical variables, psychopathology, and inflammatory markers provided us with relevant information on interpretation of NfL levels in psychiatric patients. To further understand the trajectories of neuroaxonal involvement in the course SZ and MDD, future investigations should focus on longitudinal observations including patients across different phases of their illness.

Taken together, our findings suggest the presence of active neuroaxonal deterioration in patients with MDD, which negatively influenced cognitive functioning. Moreover, we described a high heterogeneity of NfL levels in patients with SZ, with potential implications for clinical phenotyping. Based on our findings, we support the introduction of NfL as low-invasive biomarkers in psychiatric research and speculate a possible application for treatment monitoring.

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CRediT authorship contribution statement

Francesco Bavato: Conceptualization, Formal analysis, Writing – original draft. **Flurin Cathomas:** Investigation, Writing – review & editing. **Federica Klaus:** Investigation, Writing – review & editing. **Karoline Gütter:** Investigation, Writing – review & editing. **Christian Barro:** Conceptualization, Writing – review & editing. **Aleksandra Maceski:** Investigation. **Erich Seifritz:** Resources, Supervision, Writing – review & editing. **Jens Kuhle:** Resources, Methodology, Writing – review & editing. **Stefan Kaiser:** Supervision, Writing – review & editing. **Boris B. Quednow:** Supervision, Formal analysis, Writing – original draft, Funding acquisition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.05.072.

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