Neurofilament light protein as a biomarker in depression and cognitive function

Nikolaj Travica, Michael Berk, and Wolfgang Marx

Purpose of review
Converging evidence suggest axonal damage is implicated in depression and cognitive function. Neurofilament light protein, measured within serum and cerebrospinal fluid, may be a biomarker of axonal damage. This article examines the emerging evidence implicating neurofilament light protein in depression and cognitive function.

Recent findings
Preliminary cross-sectional and case–control studies in cohorts with depression have yielded inconsistent results regarding the association between neurofilament light protein and symptomatology. However, these studies had methodological limitations, requiring further investigation. Importantly, neurofilament light protein concentrations may be a marker of progression of cognitive decline and may be associated with cognitive performance within cognitively intact cohorts.

Summary
Axonal damage is implicated in the neuropathology of depression and cognitive dysfunction. Consequently, neurofilament light protein is an emerging biomarker with potential in depression and cognitive function. Results are more consistent for cognition, requiring more research to assess neurofilament light protein in depression as well as other psychiatric disorders. Future longitudinal studies are necessary to determine whether neurofilament light protein can predict the onset and progression of depression and measure the effectiveness of potential psychiatric interventions and medications.

Keywords
biomarker, cognition, depression, neurofilament light protein, psychiatry

INTRODUCTION

The neuropathology of psychiatric disorders drives symptomatology [1,2]. However, the mechanisms involved in the onset and progression of depression remain poorly understood. Impairments in cognitive function are a frequent and debilitating symptom of depression and other psychiatric disorders [3]. An evolving and promising area is the identification of reliable biomarkers of depression. This includes cognitive function, which can be recognized prior to the onset of and during the progression of clinical symptoms [4]. Identification of such biomarkers reflecting pathological pathways associated with mood and cognitive changes is needed to develop therapeutic interventions and create earlier, more tailored intervention regimens [5].

Aided by advances in immunoassay technology, a promising biomarker linked to neuronal axonal damage is neurofilament light protein (NfL) [6▪▪]. NfL concentrations appear to be correlated with symptom severity and cases across several neurodegenerative diseases including Alzheimer's disease and multiple sclerosis [7,8]. Given that NfL is not a disease specific biomarker, it may also have potential in depression. This is the first review of the recent literature that explores NfL concentrations in cohorts with depression and its association with cognitive function.

NEUROFILAMENTS AND NEUROFILAMENT LIGHT CHAIN

NfL is an emerging biomarker of neural health or injury [9]. Neurofilaments are vital constituents of the neuronal cytoskeleton and are particularly

Deakin University, IMPACT – the Institute for Mental and Physical Health and Clinical Translation, Food & Mood Centre, School of Medicine, Barwon Health, Geelong, Victoria, Australia

Correspondence to Nikolaj Travica, 1 Gheringhap Street, Geelong, VIC 3220, Australia. Tel: +61 3 5227 8288;
e-mail: nikolaj.travica@deakin.edu.au

Curr Opin Psychiatry 2022, 35:30–37
DOI:10.1097/YCO.0000000000000756

KEY POINTS

- Neurofilament light protein (NfL) is an emerging blood and cerebrospinal fluid marker representative of neuronal axonal damage.
- Due to study limitations, inconsistent results were observed between NfL concentrations in depression and additional psychiatric disorders.
- NfL concentrations have potential to predict disease progression and cognitive performance.
- Larger, prospective cohort studies are required to establish the viability of NfL as a potential biomarker in depression, cognitive function and clinical change.

abundant in the axons of neurons [10]. Neurofilaments form the assembly and stability of the cytoskeleton through cross-bridging and interconnecting with other components of the cytoskeleton [11▪]. Neurofilaments provide structural support by maintaining size, shape, and calibre of axons [12]. In addition, neurofilaments constitute a dynamic network involved in neuronal differentiation, axon outgrowth, and regeneration [13]. In large myelinated axons, the high density of neurofilaments promote increased radial axonal growth [11▪]. At a molecular level, neurofilaments help shape the cellular environment, position the nucleus, and support organelles, such as mitochondria and endoplasmic reticulum. NfL also participates in intracellular signalling, neuromodulation, and transcription [11▪].

Given that NfL is the most abundant and soluble intermediate filament, they are the most extensively studied neurofilament [14]. Low levels of NfL are constantly released from axons under normal conditions in an age-dependent manner, increasing by an estimated 2.2% per year [15▪]. Following axonal damage, NfL release substantially increases whereby NfL leave the axon and enter the interstitial fluid [15▪]. After reaching the interstitial fluid, NfL is detectable in CSF and peripheral circulation. All diseases that lead to neuronal and axonal damage can increase the cerebrospinal fluid (CSF) levels of these proteins [16]. Other factors that may alter NfL levels include BMI, vascular risk factors and the accumulation of subclinical comorbidities [15▪,17].

NfL can be measured by immunoassays in both cerebrospinal fluid and plasma/serum. Recent advancements in ultrasensitive analytical methods have enabled improved detection of NfL in blood samples [18], with many studies utilizing serum to reliably measure NfL [19▪]. Research in neurodegenerative diseases indicates that NfL concentrations reliably reflect the degree of axonal damage in the brain [20]. Accordingly, the relevance of NfL may potentially extend to a range of psychiatric and cognitive conditions.

AXONAL DAMAGE IN DEPRESSION

Various neurobiological pathologies are related to axonal damage accompany depression [21]. Disruptions of axon-myelin adhesion seen in participants diagnosed with depression can initiate axonal damage by altering the axonal cytoskeleton. In depression, there are decreases in myelin cross-sectional areas across specific regions and at a whole brain level [2,22].

Furthermore, oligodendrocyte lineage cells, which serve important functions in forming myelin, are dysfunctional in depression and may play a role in reduced myelin content and axon numbers [23]. Although matter lesions are an established biomarker of depression, especially in the elderly [24], while white matter atrophy is a further indicator of axonal loss or injury in depression [25]. A recent investigation further displayed CSF proteome changes in proteins associated with myelination in depression [26▪].

Additional pathophysiologies in depression may indirectly contribute to or exacerbate axonal damage. These include mitochondrial dysfunction, increased oxidative stress, neuronal apoptosis, immunoinflammation, imbalances in metabolic pathways and disturbed energy metabolism [21,27]. As such, elevated NfL concentrations have been linked with neuroinflammation [28], mitochondrial dysfunction [29], kynurenine pathway metabolite changes [30▪▪] and brain atrophy [6▪▪].

It remains unclear exactly how axonal damage is implicated in the aetiology/manifestation of depressive-like symptomatology. However, axonal damage may affect neural transmission within subcortical circuits that regulate mood [31]. Treatment resistance in depression may be related to persistent axonal damage within neural networks involved in processing emotion [31].

AXONAL DAMAGE AND COGNITIVE FUNCTION

A range of neurological structures and networks play a pivotal role in maintaining optimal cognitive function [32]. Axonal integrity plays a fundamental part in maintaining optimal neurological functioning that is concomitant with cognitive capacity [33]. Given that axons primarily function to transmit and receive electrical and chemical signals, neurons cannot communicate properly if axons are damaged, thereby disrupting neuronal communication and cognitive function [34,35].

Axonal degeneration is a common feature of neurodegenerative diseases and traumatic brain injury (TBI), constituting an important contributor to cognitive dysfunction in these conditions [32,36]. Empirical investigations suggest that white matter degradation, indicative of significant myelin and axonal loss, is associated with reduced general cognition [37].

Increasing evidence suggests that axonal degeneration occurs before cell body loss [38], a process occurring prior to the onset of clinical symptomatology that is observed in various neurological diseases. In addition, given that axonal integrity is compromised during ageing, this may be one of many contributing factors to age-associated cognitive decline.

NEUROFILAMENT LIGHT PROTEIN IN DEPRESSION AND PSYCHIATRIC DISORDERS

To date, there is only one published animal study that has explored the role of NfL in depression. In this study, a rat model of depression reported decreased levels of NfL immunostaining in the hippocampus [39]. These findings suggest that hippocampal depression-associated alterations may have resulted from changes to the dynamics of the neurofilament assembly and NfL release from the cytoskeleton.

Supporting this animal study, there are now several small, mainly cross-sectional and case–control, human studies of NfL (Table 1). These preliminary

Table 1. Neurofilament light protein concentrations in depression and psychiatric disorders

Study	Sample size	Age (mean ± SD)	Diagnosis/ comorbidity	Specimen (blood/CSF)	Result
Depression					
Besse *et al.* [40▪▪]	15 (11 female)	49.2 ± 14	Depression	Serum	NfL concentrations did not differ between patients and healthy controls
Dickstein *et al.* [41]	17 males	44.5 ± 9.5	Depression/mild traumatic brain injury	Serum	Elevated NfL after mTBI, associated with depression
Gudmundsson *et al.* [42]	78 females	73.9 ± 3.2	Depression	CSF	Sample diagnosed with MDD exhibited significantly higher levels of CSF NfL
Guedes *et al.* [43]	195 (167 males)	37.5 ± 16.5	Depression/mild traumatic brain injury	Plasma	Elevated NfL were associated with repetitive mTBIs and with chronic depressive symptoms
Katisko *et al.* [18]	125 (71 females)	42.5 ± 8.1	Primary psychiatric mood disorder, frontotemporal lobar degeneration	Serum	NfL levels were significantly higher in those with FTLD compared with the PPD group
Linnemann *et al.* [44▪]	33	72.5 ± 5.0	Depression/ dementia	Serum	NfL values were significantly higher in patients with depression and consecutive dementia than those with cognitive recovery
Tauil *et al.* [45]	40 (majority female)	18-62	Depression/multiple sclerosis	CSF	The significant relationship between depression scores and NfL concentration
Zhao *et al.* [46]	236 (142 male)	54-80	Depression/ ischaemic stroke	Serum	Higher NfL levels were associated with a higher risk of developing poststroke depression
Additional psychiatric conditions					
Hellerhoff *et al.* [47▪▪]	108 adolescent females	16.4 ± 2.3	AN, depression	Serum	Higher NfL observed in AN, alongside higher depressive scores
Nilsson *et al.* [48]	35 females	29 ± 1.9	AN	Serum	Increased NfL in AN in contrast to healthy controls and those who recovered from AN
Rodrigues-Amorim [49▪▪]	82 (51 males)	43 ± 14.5	Schizophrenia	Serum	Raised NfL in schizophrenia groups compared with healthy controls

AN, anorexia nervosa; CSF, cerebrospinal fluid; MDD, major depressive disorder; mTBI, mild traumatic brain injury; Na, not assessed; NfL, neurofilament light protein; SD, standard deviation.

human studies have utilized a variety of specimens (blood and CSF) to determine NfL concentrations in cohorts either primarily diagnosed with depression or presenting with comorbid depressive symptoms.

One study examined the cross-sectional relationship between depression and CSF NfL levels in elderly women ($n = 78$) [42]. Those diagnosed with depression had significantly higher levels of CSF NfL compared with those without depression. A further study involving elderly participants reported that the mean serum NfL of participants with depression and subsequent dementia was significantly higher than in a study group of depressive participants who exhibited cognitive recovery [44▪].

Additional research has assessed NfL concentrations in cohorts with mild TBI (mTBI) exhibiting comorbid depressive symptoms. One longitudinal study involving a cohort of 195 war veterans showed that elevated plasma levels of NfL were associated with both repetitive mTBIs and chronic depressive symptoms [43]. Increased levels of plasma NfL were also correlated with the length of time since the injury, suggestive of a progressive axonal dysregulation. Similarly, elevated levels of serum NfL in addition to abnormal hyperphosphorylated tau were observed in a small cohort following mTBI ($n = 10$), alongside significantly higher levels of depression and reduced fine motor dexterity than a control group [41].

Similar NfL levels independently predicted the development of poststroke depression ($n = 236$), after adjusting for a series of potential confounding factors, such as age and inflammatory markers [46]. The study further demonstrated that higher serum NfL levels were associated with a higher risk of developing 3-month poststroke depression.

In contrast, there are number of studies that failed to establish an association between NfL and depression outcomes. A cohort of participants with multiple sclerosis, for example, found no significant association between CSF NfL concentrations and measures of depression [45]. A further study failed to establish a link between serum NfL and depression in a cohort ($n = 15$) of participants diagnosed with depression. In this study, NfL was measured before and 24 h and 7 days after receiving electroconvulsive therapy (ECT) [40▪▪]. NfL concentrations did not differ between participants and healthy controls, with no significant change in NfL levels in the course of ECT. It remains unknown if other antidepressant interventions impact NfL concentrations.

NfLs have been explored as potential biomarkers for neuronal damage in other psychiatric disorders including anorexia nervosa and schizophrenia. Blood samples were obtained from 54 adolescent females diagnosed with anorexia and 54 age-matched healthy control participants [47▪▪]. Group comparisons displayed significantly higher levels of NfL in the anorexia nervosa group, alongside higher depressive scores on the Beck Depression Inventory-II, with reductions in NfL following weight restoration. Similarly, in a sample of 35 participants with anorexia, a decrease in NfL was observed after short-term partial weight restoration alongside increased levels in anorexia in contrast to healthy controls and those who recovered from anorexia [48].

NfL concentrations have also been explored in schizophrenia. In a study of 40 healthy controls and 42 participants with schizophrenia, serum NfL was elevated in both first-episode psychosis and chronic schizophrenia groups compared with the control group [49▪▪]. Significantly elevated levels of NfL were also seen in the subgroup of clozapine-treated participants with schizophrenia compared with the remaining schizophrenia group. This is interesting as clozapine is reserved for the most refractory individuals, which suggests that the elevated NfL concentrations in this cohort may indicate that symptom severity is related to greater axonal damage.

A recent review of 21 CSF and 6 blood studies examined whether NfL may differentiate behavioural frontotemporal dementia from primary psychiatric disorders [50▪▪]. There was low NfL variability within groups, with comparable values in psychiatric disorders and healthy controls, both of whom displayed significantly lower NfL levels than Behavioural Frontotemporal Dementia patients.

NEUROFILAMENT LIGHT PROTEIN AND COGNITIVE FUNCTION

A limited number of studies have investigated the association between NfL and cognition prior to the diagnosis of a neurodegenerative disease (Table 2). These data suggest that NfL may be more sensitive to subclinical cognitive decline compared with other proposed biomarkers for cognitive deterioration [51].

A large cross-sectional investigation ($n = 544$) revealed that elevated NfL concentrations were associated with reduced performance on processing speed, attention, executive function and delayed and recognition memory in a sample of cognitively intact participants and those with mild cognitive impairment [53▪]. NfL may, therefore, be a marker of early changes in cognition.

Similarly, a large cross-sectional study ($n = 860$) of non-Hispanic participants revealed that higher NfL levels were related to poorer neuropsychological test performance across measures of attention,

Table 2. Studies assessing neurofilament light protein and cognitive function in asymptomatic cohorts

Study	Sample size	Age (mean ± SD)	Retrospective disease onset (if any)	Specimen (Blood/CSF)	Result
de Wolf *et al.* [52▪▪]	4444 (2555 females)	71.9 ± 7.5	Dementia	Plasma	Higher baseline NfL level was associated with a higher risk of all-cause dementia
Hall *et al.* [53▪]	544	NA	MCI	Plasma	Elevated NfL had a negative impact on processing speed, attention, executive functions and delayed and recognition memory
Hu *et al.* [54]	243 (117 females)	72.76 ± 6.8	AD	Plasma	NfL played a predictive role in cognitive decline and hippocampal atrophy
Mielke *et al.* [55]	79 males	76	General cognitive function	CSF	Higher NfL associated with worsening in cortical thickness and NfL change impacted global cognition
Naude *et al.* [56]	584 (269 females)	73 ± 7.4	Mild behavioural impairment	Serum	Greater increases in NfL predicted mild behavioural impairment
Petersen *et al.* [57]	860	NA	MCI/dementia	Plasma	NfL related to poorer performance on attention, processing speed, verbal fluency in non-Hispanics, and attention, processing speed, executive functioning, and verbal fluency in Hispanics
Verberk *et al.* [58]	300 (125 women)	61 ± 9	AD	Serum	NfL rates of change abnormally elevated in the preclinical AD

AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MDD, major depressive disorder; Na, not assessed; NfL, neurofilament light protein; SD, standard deviation.

processing speed, verbal fluency and immediate memory [57]. Conversely, among Hispanic Mexican Americans, elevated NfL was only associated with poorer performance on verbal fluency.

Recent longitudinal studies have indicated that serum NfL were elevated approximately 6 years before the onset of a clinical phenotype [6▪▪,59]. Multiple investigations have demonstrated that serum NfL concentration and their rates of change are abnormally elevated in the preclinical phase of Alzheimer's disease predicting cognitive decline, future diagnosis [58] and hippocampal atrophy [54].

Higher baseline plasma NfL is associated with worsening of a series of neuroimaging measures and global cognition in a 30-month prospective study [55]. Plasma NfL at 2 years was also associated with faster progression towards mild behavioural impairment in cohorts presenting with no dementia at baseline [56]. In line with these results, a population-based study of 4444 participants without dementia identified that higher baseline plasma NfL levels were associated with a higher risk of all-cause dementia or Alzheimer's [52▪▪]. Additional analyses revealed that NfL levels increased 3.4 times faster in participants who developed Alzheimer's disease compared with those who remained dementia-free.

NfL concentrations were associated with the degree of cognitive impairment that accompanies Alzheimer's disease and mild cognitive impairment, indexed by cognitive scores in a prospective study [60]. Additionally, there is evidence to suggest a link between the severity of anatomical MRI changes, cognitive deterioration and NfL concentrations in neurodegeneration (Table 3) [60–62].

FUTURE DIRECTIONS

Various limitations are evident in the studies investigating NfL in psychiatric disorders, particularly depression. Across multiple investigations, primary conditions were not depression or a psychiatric disorder, instead, these studies explored depressive symptoms in other conditions, such as TBI or stroke, which are known to influence both NfL concentrations and mood states. Numerous studies focused on younger samples, failing to consider the age-dependant increases of NfL [26▪,50▪▪]. Furthermore, few large-scale studies had a control group with no clinical diagnosis, making it difficult to distinguish abnormal NfL levels [18,63].

Although strong correlations have been proposed between CSF and blood NfL measurements [64], others have postulated that NfL in CSF is increased at an earlier time point than in serum [65▪▪] and may be associated with different components of cognition [66]. The type of samples from which NfL concentrations are derived from should be considered in future studies involving depression.

Table 3. Studies assessing neurofilament light protein and cognition in neurodegenerative disease

Study	Sample size	Age (mean ± SD)	Type of neurodegenerative disease	Specimen (blood/CSF)	Result
Delaby *et al.* [7]	535	37–82	AD, DS, FTD, ALS, DLB, PSP, CBS	CSF	Highest NfL levels in patients with ALS, PSP, CBS and FTD, NfL associated with degree of cognitive impairment
Dhiman *et al.* [60]	221 (112 males)	73.8 ± 6.9	AD	CSF	Higher NfL predicted cortical amyloid load, brain atrophy and cognitive impairment
Mattioli *et al.* [62]	18 (9 females)	45	MS	Serum	Higher NfL in MS compared with controls, NfL predicted greater cognitive impairment

AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; CBS, corticobasal syndrome; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; DS, down syndrome; FTD, frontotemporal dementia; MDD, major depressive disorder; MS, multiple sclerosis; Na, not assessed; NfL, neurofilament light protein; PSP, progressive supranuclear palsy; SD, standard deviation.

In addition to the limited sample sizes of participants diagnosed with depression, most studies were cross-sectional, measuring NfL levels and disease severity at only one-time point, with the use of single diagnostic scales [45]. Consequently, there is a lack of insight into how the severity of depressive symptoms, cognitive decline, and their progression is associated with NfL concentrations. Further longitudinal, prospective studies with well defined samples are required to investigate whether NfL concentrations may serve as a risk factor for the onset of depression. Longitudinal studies are particularly important for psychiatric disorders in which the disease course can vary significantly [67].

There remains a large heterogeneity between NfL concentrations that are considered pathological, concentrations used to estimate the risk of conversion from preclinical to clinical symptoms, and determine adequate treatment response (concentration changes that reflect treatment response). More research is required to determine whether certain reference ranges may be considered disease-specific.

At present, it is unclear whether axonal damage and subsequent NfL concentrations are associated with psychiatric conditions, such as depression or whether they are a cause or consequence of the condition. NfL concentrations seem to rise during the preclinical phase; however, it is uncertain where in the sequence of neurological damage, an increase in NfL occurs. Identifying molecular and cellular mechanisms responsible for NfL increases, combined with repeated NfL measurements along the trajectory of disease progression may clarify this question.

Finally, further understanding of the effects of antidepressant medications, somatic therapies and lifestyle interventions on NfL concentrations may provide vital insight into treatment effectiveness. Studies have begun to measure the effects of lifestyle factors, such as exercise [68▪▪,69] and diet [70] on NfL concentrations; however, similar investigation on antidepressant medications is currently lacking.

CONCLUSION

On the basis of recent emerging data, axonal damage, as reflected by elevated NfL levels may represent one of many pathological hallmarks that accompany a series of psychiatric disorders, such as depression as well as cognitive function. The limited number of studies investigating the association between NfL and depression leave many unanswered questions regarding the role of NfL in these conditions. Future longitudinal studies are needed to establish the utility of NfL concentrations in depression and cognitive function, particularly in the onset and progression of depression and assessment of treatment effectiveness.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

M.B. is supported by a NHMRC Senior Principal Research Fellowship (1156072). M.B. has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical

Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Abbot, Astra Zeneca, Janssen and Janssen, Lundbeck and Merck and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Janssen and Janssen, Lundbeck Merck, Pfizer and Servier – all unrelated to this work. W.M. is currently funded by an Alfred Deakin Postdoctoral Research Fellowship and a Multiple Sclerosis Research Australia early-career fellowship. W.M. has previously received funding from the NHMRC, Clifford Craig Foundation, Cancer Council Queensland and university grants/fellowships from La Trobe University, Deakin University, University of Queensland, and Bond University, received industry funding and has attended events funded by Cobram Estate Pty. Ltd, received travel funding from Nutrition Society of Australia, received consultancy funding from Nutrition Research Australia, and has received speakers honoraria from The Cancer Council Queensland and the Princess Alexandra Research Foundation. N.T. has received funding from Deakin University for an Executive Dean's Post-Doctoral Fellowship.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Nelson ME, Jester DJ, Petkus AJ, Andel R. Cognitive reserve, Alzheimer's neuropathology, and risk of dementia: a systematic review and meta-analysis. Neuropsychol Rev 2021; 31:233–250.
2. Boda E. Myelin and oligodendrocyte lineage cell dysfunctions: new players in the etiology and treatment of depression and stress-related disorders. Eur J Neurosci 2021; 53:281–297.
3. Kim J, Kim Y-K. Crosstalk between depression and dementia with resting-state fMRI studies and its relationship with cognitive functioning. Biomedicines 2021; 9:82.
4. Simrén J, Ashton NJ, Blennow K, Zetterberg H. An update on fluid biomarkers for neurodegenerative diseases: recent success and challenges ahead. Curr Opin Neurobiol 2020; 61:29–39.
5. García-Gutiérrez MS, Navarrete F, Sala F, *et al.* Biomarkers in psychiatry: concept, definition, types and relevance to the clinical reality. Front Psychiatry 2020; 11:432.
6. ■■ Khalil M, Pirpamer L, Hofer E, *et al.* Serum neurofilament light levels in normal aging and their association with morphologic brain changes. Nat Commun 2020; 11:812.

This study measured serum neurofilament light protein in a healthy cohort of participants and after a mean follow-up time of 5.9 years. Results demonstrated rising and more variable neurofilament light protein levels in participants older than 60 years, indicative of accelerated neuronal injury and subclinical comorbid pathologies in a longitudinal manner.

7. Delaby C, Alcolea D, Carmona-Iragui M, *et al.* Differential levels of Neurofilament Light protein in cerebrospinal fluid in patients with a wide range of neurodegenerative disorders. Sci Rep 2020; 10:9161.
8. Moscoso A, Grothe MJ, Ashton NJ, *et al.*, Alzheimer's Disease Neuroimaging Initiative. Longitudinal associations of blood phosphorylated Tau181 and neurofilament light chain with neurodegeneration in Alzheimer disease. JAMA Neurol 2021; 78:396–406.
9. Ramani S, Berard JA, Walker LA. The relationship between neurofilament light chain and cognition in neurological disorders: a scoping review. J Neurol Sci 2020; 420:117229.
10. Bozzetti S, Ferrari S, Gajofatto A, Mariotto S. Neurofilament light chain in demyelinating conditions of the central nervous system: a promising biomarker. Neuroimmunol Neuroinflamm 2021; 8:1–13.
11. ■ Bomont P. The dazzling rise of neurofilaments: physiological functions and roles as biomarkers. Curr Opin Cell Biol 2021; 68:181–191.

This thorough review highlighted the important functions of neurofilaments, such as neurofilament light protein in the central nervous system, in addition to the broad clinical value of these biomarkers.

12. Bott CJ, Winckler B. Intermediate filaments in developing neurons: beyond structure. Cytoskeleton 2020; 77:110–128.
13. Petrova V, Nieuwenhuis B, Fawcett JW, Eva R. Axonal organelles as molecular platforms for axon growth and regeneration after injury. Int J Mol Sci 2021; 22:1798.
14. Xiong Y-l, Meng T, Luo J, Zhang H. The potential of neurofilament light as a biomarker in Alzheimer's disease. Eur Neurol 2021; 84:6–15.
15. ■ Thebault S, Booth RA, Freedman MS. Blood neurofilament light chain: the neurologist's troponin? Biomedicines 2020; 8:523.

This review summarizes the physiology, pathophysiology of neurofilaments, also focuses on the technological advancements that have enabled reliable measurement of NfL in blood.

16. Lambertsen KL, Soares CB, Gaist D, Nielsen HH. Neurofilaments: the C-reactive protein of neurology. Brain Sci 2020; 10:56.
17. Manouchehrinia A, Piehl F, Hillert J, *et al.* Confounding effect of blood volume and body mass index on blood neurofilament light chain levels. Ann Clin Transl Neurol 2020; 7:139–143.
18. Katisko K, Cajanus A, Jääskeläinen O, *et al.* Serum neurofilament light chain is a discriminative biomarker between frontotemporal lobar degeneration and primary psychiatric disorders. J Neurol 2020; 267:162–167.
19. ■ Thebault S, Booth RA, Rush CA, *et al.* Serum neurofilament light chain measurement in MS: hurdles to clinical translation. Front Neurosci 2021; 15:654942.

This review highlighted the present hurdles that are faced before serum neurofilament light protein can be implemented clinically in relation to neurodegenerative diseases, such as MS and further discusses the biomarker's clinical and analytical validity.

20. Barro C, Chitnis T, Weiner HL. Blood neurofilament light: a critical review of its application to neurologic disease. Ann Clin Transl Neurol 2020; 7:2508–2523.
21. Marx W, Lane M, Hockey M, *et al.* Diet and depression: exploring the biological mechanisms of action. Mol Psychiatry 2021; 26:134–150.
22. Baranger DAA, Halchenko Y, Satz S, *et al.* Aberrant levels of cortical myelin distinguish individuals with unipolar depression from healthy controls. medRxiv 2021. https://pubmed.ncbi.nlm.nih.gov/34455188/.
23. Zhou B, Zhu Z, Ransom BR, Tong X. Oligodendrocyte lineage cells and depression. Mol Psychiatry 2020; 26:103–117.
24. Oudega ML, Siddiqui A, Wattjes MP, *et al.* Are apathy and depressive symptoms related to vascular white matter hyperintensities in severe late life depression? J Geriatr Psychiatry Neurol 2021; 34:21–28.
25. Binnewies J, Nawijn L, van Tol M-J, *et al.* Associations between depression, lifestyle and brain structure: a longitudinal MRI study. Neuroimage 2021; 231:117834.
26. ■ Al Shweiki MHDR, Oeckl P, Steinacker P, *et al.* Proteomic analysis reveals a biosignature of decreased synaptic protein in cerebrospinal fluid of major depressive disorder. Transl Psychiatry 2020; 10:144.

This study investigated the cerebrospinal fluid proteome of psychiatric patients focusing on MDD by deep proteomic profiling approach and targeted mass spectrometry. Results indicated changes in proteins associated with synaptic transmission and myelination.

27. Allen J, Caruncho HJ, Kalynchuk LE. Severe life stress, mitochondrial dysfunction, and depressive behavior: a pathophysiological and therapeutic perspective. Mitochondrion 2021; 56:111–117.
28. Srpova B, Uher T, Hrnciarova T, *et al.* Serum neurofilament light chain reflects inflammation-driven neurodegeneration and predicts delayed brain volume loss in early stage of multiple sclerosis. Mult Scler 2020; 27:52–60.
29. Zheng Y-S, Sun C, Wang R, *et al.* Neurofilament light is a novel biomarker for mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes. Sci Rep 2021; 11:2001.
30. ■■ Rajda C, Galla Z, Polyák H, *et al.* Cerebrospinal fluid neurofilament light chain is associated with kynurenine pathway metabolite changes in multiple sclerosis. Int J Mol Sci 2020; 21:2665.

This is the first study to display an association between cerebrospinal fluid neurofilament light protein and markers representative of neuroinflammation, such as kynurenine metabolites. Results provide important information on the underlying pathomechanism of disease activity.

31. Spanier S, Kilian HM, Meyer DM, Schlaepfer TE. Treatment resistance in major depression is correlated with increased plasma levels of neurofilament light protein reflecting axonal damage. Med Hypotheses 2019; 127:159–161.
32. Guo W, Dittlau KS, Van Den Bosch L, editors. Axonal transport defects and neurodegeneration: Molecular mechanisms and therapeutic implications. Semin Cell Dev Biol; 2020: Elsevier.
33. Van Eijck MM, Herklots MW, Peluso J, *et al.* Accuracy in prediction of long-term functional outcome in patients with traumatic axonal injury: a comparison of MRI scales. Brain Inj 2020; 34:595–601.
34. Guo B, Huang Y, Gao Q, Zhou Q. Stabilization of microtubules improves cognitive functions and axonal transport of mitochondria in Alzheimer's disease model mice. Neurobiol Aging 2020; 96:223–232.

35. Vitet H, Brandt V, Saudou F. Traffic signaling: new functions of huntingtin and axonal transport in neurological disease. Curr Opin Neurobiol 2020; 63:122–130.

36. Jolly AE, Bălăeţ M, Azor A, *et al.* Detecting axonal injury in individual patients after traumatic brain injury. Brain 2020; 144:92–113.

37. Coelho A, Fernandes HM, Magalhães R, *et al.* Signatures of white-matter microstructure degradation during aging and its association with cognitive status. Sci Rep 2021; 11:1–12.

38. Pemberton JM, Pogmore JP, Andrews DW. Neuronal cell life, death, and axonal degeneration as regulated by the BCL-2 family proteins. Cell Death Differ 2020; 28:108–122.

39. Reinés A, Cereseto M, Ferrero A, *et al.* Neuronal cytoskeletal alterations in an experimental model of depression. Neuroscience 2004; 129:529–538.

40. ■■ Besse M, Belz M, Folsche T, *et al.* Serum neurofilament light chain (NFL) remains unchanged during electroconvulsive therapy. World J Biol Psychiatry 2020; 21:148–154.

This is the first study to examine whether ECT has any affects on serum neurofilament light protein concentrations in patients with major depressive disorder. Results demonstrated no significant change in concentrations 7 days following the therapy. However, the sample was restricted to only 15 patients.

41. Dickstein DL, De Gasperi R, Sosa MAG, *et al.* Brain and blood biomarkers of tauopathy and neuronal injury in humans and rats with neurobehavioral syndromes following blast exposure. Mol Psychiatry 2020. https://pubmed.ncbi.nlm.nih.gov/32094584/.

42. Gudmundsson P, Skoog I, Waern M, *et al.* Is there a CSF biomarker profile related to depression in elderly women? Psychiatry Res 2010; 176: 174–178.

43. Guedes VA, Kenney K, Shahim P, *et al.,* CENC Multisite Observational Study Investigators. Exosomal neurofilament light: a prognostic biomarker for remote symptoms after mild traumatic brain injury? Neurology 2020; 94:e2412–e2423.

44. ■ Linnemann C, Caviezel MP, Cramer L, *et al.* Predictive value of serum neurofilament light chain for persistent cognitive deficits in elderly depressive patients. J Affect Disord Rep 2021; 4:100095.

Serum neurofilament light protein measurements were able to predict a consecutive dementia diagnosis after remission of depressive symptoms in a cohort of depressive patients aged at least 60 years, with these clinically important findings requiring further investigation.

45. Tauil CB, Rocha-Lima AD, Ferrari BB, *et al.* Depression and anxiety disorders in patients with multiple sclerosis: association with neurodegeneration and neurofilaments. raz J Med Biol Res 2021; 54:e10428.

46. Zhao H, Mo M, Miao C, *et al.* Association of serum biomarker neurofilament light concentration with poststroke depression: a preliminary study. Gen Hosp Psychiatry 2020; 64:17–25.

47. ■■ Hellerhoff I, King JA, Tam FI, *et al.* Differential longitudinal changes of neuronal and glial damage markers in anorexia nervosa after partial weight restoration. Transl Psychiatry 2021; 11:86.

This cohort study investigated serum neurofilament light protein levels longitudinally in anorexia patients undergoing weight restoration. Longitudinally, based on 54 diagnosed patients, a decrease in neurofilament light protein was observed in the patients with anorexia upon short-term partial weight restoration.

48. Nilsson IA, Millischer V, Karrenbauer VD, *et al.* Plasma neurofilament light chain concentration is increased in anorexia nervosa. Transl Psychiatry 2019; 9:1–6.

49. ■■ Rodrigues-Amorim D, Rivera-Baltanás T, del Carmen Vallejo-Curto M, *et al.* Plasma β-III tubulin, neurofilament light chain and glial fibrillary acidic protein are associated with neurodegeneration and progression in schizophrenia. Sci Rep 2020; 10:1–10.

This is the first study to demonstrate significantly elevated plasma neurofilament light protein concentrations in patients diagnosed with schizophrenia in comparison to a healthy control group. Results also demonstrated that patients treated with clozapine still had higher neurofilament light protein than nontreated patients.

50. ■■ Davy V, Dumurgier J, Fayosse A, *et al.* Neurofilaments as emerging biomarkers of neuroaxonal damage to differentiate behavioral frontotemporal dementia from primary psychiatric disorders: a systematic review. Diagnostics (Basel) 2021; 11:754.

This systematic review compared neurofilament light protein concentrations between behavioral frontotemporal dementia and psychiatric conditions derived from a number of previous studies. results demonstrated higher concentrations in those diagnosed with behavioral frontotemporal dementia, however, various limitations were present amongst the reviewed studies.

51. Merluzzi AP, Vogt NM, Norton D, *et al.* Differential effects of neurodegeneration biomarkers on subclinical cognitive decline. Alzheimers Dement (N Y) 2019; 5:129–138.

52. ■■ de Wolf F, Ghanbari M, Licher S, *et al.* Plasma tau, neurofilament light chain and amyloid-β levels and risk of dementia; a population-based cohort study. Brain 2020; 143:1220–1232.

This cohort study, which obtained plasma neurofilament light protein from 4444 nondemented participants revealed that higher concentrations were associated with a higher risk of all-cause dementia and Alzheimer's disease during a 14-year follow-up, suggesting that neurofilament light protein may be useful in monitoring progression of Alzheimer's disease dementia.

53. ■ Hall JR, Johnson LA, Peterson M, *et al.* Relationship of neurofilament light (NfL) and cognitive performance in a sample of Mexican Americans with normal cognition, mild cognitive impairment and dementia. Curr Alzheimer Res 2020; 17:1214–1220.

In a sample of 544 cognitively intact participants, plasma neurofilament light protein concentrations were related to a series of cognitive assessments, suggesting that neurofilament light protein may be a marker of early changes in cognition in those with normal cognition.

54. Hu H, Chen KL, Ou YN, *et al.,* Alzheimer's Disease Neuroimaging Initiative. Neurofilament light chain plasma concentration predicts neurodegeneration and clinical progression in nondemented elderly adults. Aging 2019; 11:6904–6914.

55. Mielke MM, Syrjanen JA, Blennow K, *et al.* Plasma and CSF neurofilament light. Relation to longitudinal neuroimaging and cognitive measures 2019; 93:e252–e260.

56. Naude JP, Gill S, Hu S, *et al.* Plasma neurofilament light: a marker of neurodegeneration in mild behavioral impairment. J Alzheimers Dis 2020; 76:1017–1027.

57. Petersen M, Hall JR, Mozdbar S, *et al.* Plasma neurofilament light chain (NFL) is differentially associated with neuropsychological test performance among non-Hispanic whites and Hispanic, Mexican Americans: a HABLE study. Alzheimers Dement 2020; 16:e043423.

58. Verberk IMW, Laarhuis MB, van den Bosch KA, *et al.* Serum markers glial fibrillary acidic protein and neurofilament light for prognosis and monitoring in cognitively normal older people: a prospective memory clinic-based cohort study. Lancet Healthy Longevity 2021; 2:e87–e95.

59. Bjornevik K, Munger KL, Cortese M, *et al.* Serum neurofilament light chain levels in patients with presymptomatic multiple sclerosis. JAMA Neurol 2020; 77:58–64.

60. Dhiman K, Gupta VB, Villemagne VL, *et al.* Cerebrospinal fluid neurofilament light concentration predicts brain atrophy and cognition in Alzheimer's disease. Alzheimers Dement (Amst) 2020; 12:e12005.

61. Alirezaei Z, Pourhanifeh MH, Borran S, *et al.* Neurofilament light chain as a biomarker, and correlation with magnetic resonance imaging in diagnosis of CNS-related disorders. Mol Neurobiol 2020; 57:469–491.

62. Mattioli F, Bellomi F, Stampatori C, *et al.* Longitudinal serum neurofilament light chain (sNfL) concentration relates to cognitive function in multiple sclerosis patients. J Neurol 2020; 267:2245–2251.

63. Fourier A, Formaglio M, Kaczorowski F, *et al.* A combination of total tau and neurofilaments discriminates between neurodegenerative and primary psychiatric disorders. Eur J Neurol 2020; 27:1164–1169.

64. Sejbaek T, Mendoza JP, Penner N, *et al.* Comparison of neurofilament light chain results between two independent facilities. BMJ Neurol Open 2020; 2:e000063.

65. ■■ Andersson E, Janelidze S, Lampinen B, *et al.* Blood and cerebrospinal fluid neurofilament light differentially detect neurodegeneration in early Alzheimer's disease. Neurobiol Aging 2020; 95:143–153.

This study directly compared the reliability of neurofilament light chain in blood and cerebrospinal fluid. Results found that the concentration of neurofilament light protein in cerebrospinal fluid, but not in plasma, was increased in response to beta amyloid pathology in cognitively intact participants and that concentrations in cerebrospinal fluid may be a more reliable biomarker of neurodegeneration than in blood during preclinical AD.

66. Osborn KE, Khan OA, Kresge HA, *et al.* Cerebrospinal fluid and plasma neurofilament light relate to abnormal cognition. Alzheimers Dement (Amst) 2019; 11:700–709.

67. Kirkpatrick RH, Munoz DP, Khalid-Khan S, Booij L. Methodological and clinical challenges associated with biomarkers for psychiatric disease: a scoping review. J Psychiatr Res 2020. https://pubmed.ncbi.nlm.nih.gov/33221025/.

68. ■■ Joisten N, Rademacher A, Warnke C, *et al.* Exercise diminishes plasma neurofilament light chain and reroutes the kynurenine pathway in multiple sclerosis. Neurol Neuroimmunol Neuroinflamm 2021; 8. https://pubmed.ncbi.nlm.nih.gov/33782190/.

This is the first investigation to demonstrate that an acute bout of exercise was able to reduce plasma levels of neurofilament light protein while increasing the kynurenine pathway flux toward the neuroprotective kynurenic acid, 3 h after a training session in patients with multiple sclerosis.

69. Cruickshank T, Bartlett D, Govus A, *et al.* The relationship between lifestyle and serum neurofilament light protein in Huntington's disease. Brain Behav 2020; 10:e01578.

70. Nilholm C, Roth B, Höglund P, *et al.* Dietary intervention with an Okinawan-based Nordic diet in type 2 diabetes renders decreased interleukin-18 concentrations and increased neurofilament light concentrations in plasma. Nutr Res 2018; 60:13–25.