Neurofilament Light Chain Related to Longitudinal Decline in Frontotemporal Lobar Degeneration

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ABSTRACT

Objective Accurate diagnosis and prognosis of frontotemporal lobar degeneration (FTLD) during life is an urgent concern in the context of emerging disease-modifying treatment trials. Few CSF markers have been validated longitudinally in patients with known pathology, and we hypothesized that CSF neurofilament light chain (NfL) would be associated with longitudinal cognitive decline in patients with known FTLD-TAR DNA binding protein ~43kD (TDP) pathology. Methods This case-control study evaluated CSF NfL, total tau, phosphorylated tau, and β-amyloid1-42 in patients with known FTLD-tau or FTLD-TDP pathology (n = 50) and healthy controls (n = 65) and an extended cohort of clinically diagnosed patients with likely FTLD-tau or FTLD-TDP (n = 148). Regression analyses related CSF analytes to longitudinal cognitive decline (follow-up ~1 year), controlling for demographic variables and core AD CSF analytes. Results In FTLD-TDP with known pathology, CSF NfL is significantly elevated compared with controls and significantly associated with longitudinal decline on specific executive and language measures, after controlling for age, disease duration, and core AD CSF analytes. Similar findings are found in the extended cohort, also including clinically identified likely FTLD-TDP. Although CSF NfL is elevated in FTLD-tau compared with controls, the association between NfL and longitudinal cognitive decline is limited to executive measures. Conclusion CSF NfL is associated with longitudinal clinical decline in relevant cognitive domains in patients with FTLD-TDP after controlling for demographic factors and core AD CSF analytes and may also be related to longitudinal decline in executive functioning in FTLD-tau.

INTRODUCTION

Frontotemporal lobar degeneration (FTLD) refers to a spectrum of pathological diseases that results in degeneration of the frontal and/or temporal regions in the brain. There is urgent need for a longitudinal marker of likely pathology in living patients with clinical evidence for frontotemporal degeneration (FTD) because of the emergence of disease-modifying treatment trials that target a specific FTLD pathology. The two most common pathological subtypes are FTLD-Tau, characterized by hyperphosphorylated tau-positive inclusions, and FTLD-TDP, characterized by inclusions containing TDP-43 conjugated with ubiquitin. In this study, we examine whether the cerebrospinal fluid (CSF) analyte neurofilament light chain (NfL) can serve as a quantitative biomarker for diagnosis and prognosis of FTD.

Pathologic diagnosis in FTD spectrum cases is currently based on clinical symptoms that imperfectly correspond to FTLD spectrum pathology[1,2]. Some clinical phenotypes have a relatively high association with FTLD-Tau or FTLD-TDP pathologies: FTLD-Tau is often found in progressive supranuclear palsy (PSP) [3], corticobasal degeneration (CBD) [4,5], and non-fluent/agrammatic primary progressive aphasia (naPPA) [6,7], while FTLD-TDP is often associated with FTD when there are additional features of amyotrophic lateral sclerosis (FTD-ALS) [8] and with semantic variant primary progressive aphasia (svPPA) [6]. However, the greatest diagnostic challenge comes from behavioral variant FTD (bvFTD), the most common clinical FTD phenotype, which is equally likely to have FTLD-Tau or FTLD-TDP pathology[9].

In vivo diagnosis of patients with FTD pathology has centered on CSF levels of proteins useful in the diagnosis of Alzheimer's disease (AD). CSF levels of phosphorylated tau (pTau), alone or in combination with total tau (tTau) or beta-amyloid$_{1\text{-}42}$ (Aβ42) have been used as diagnostic markers in FTD spectrum disorders[10,11]. While CSF pTau levels are correlated with

pathologic density of cerebral tau in FTD [12], the diagnostic value of these analytes in FTD is limited. NfL is one of three neurofilament subunits which are needed for axonal growth, transport, and signaling pathways. NfL is the most abundant and soluble neurofilament subunit, and is likely released from neurons during acute axonal damage[13-15]. Some studies have emphasized elevated NfL levels in the CSF of patients with known or likely FTLD-TDP pathology when compared to patients with known or likely FTLD-Tau pathology[16-19]. Other work has underlined the sensitivity of NfL levels to likely FTLD-Tau pathology[20]. One large study of 845 patients showed no differences in CSF NfL level between clinical subtypes of FTD including bvFTD, naPPA, and svPPA[21]. Thus, it is unresolved whether NfL can contribute to the identification of specific FTLD pathology during life, and it is unclear whether CSF levels of NfL provide additional information beyond that available from pTau.

CSF levels of analytes also may be useful at reflecting disease duration and prognosis. Longitudinal studies thus have shown that CSF pTau, alone or as pTau:tTau ratio, has some prognostic value in predicting longitudinal disease course in FTD spectrum patients[11,16,22], although others found little value in longitudinal studies of CSF tau[23,24]. Elevated CSF NfL levels at baseline have been correlated with annualized brain atrophy rate and survival in FTD spectrum disorders[11,18,20,23]. However, it is unclear whether NfL provides additional prognostic information beyond that derived from CSF tau levels. In the present study, we related CSF NfL levels to longitudinal clinical change in patients with known or highly likely FTLD-TDP or FTLD-Tau pathology, and examined whether NfL levels provide additional information beyond that associated with CSF tau levels.

In patients with phenotypes as diverse as those seen in FTD, it is challenging to determine the optimal clinical marker that reflects disease duration or rate of decline. One study

showed correlations of NfL with baseline mini mental state exam (MMSE) scores and annual decreases in MMSE scores in AD and FTD patients, but not in ALS, PSP, or CBD patients, and this difference was attributed to motor or other confounding disease-specific events aside from cognition[21]. Another study reported that NfL correlates positively with Clinical Dementia Rating Sum of Boxes (CDRsb), and negatively with MMSE scores in a biomarker-enriched group with some genetic/autopsy confirmed cases of FTLD[23]. In these patients, as well as in a diverse cohort of sporadic neurodegenerative cases, CSF NfL levels also correlated negatively with backward digit span, phonemic fluency, category fluency, and Stroop color naming interference[23]. In the present study, we examined whether specific cognitive measures are relatively more informative as endpoints in longitudinal studies of CSF analytes in FTLD patients with known pathology.

METHODS

Subjects

This study examined 213 subjects recruited from 1997-2014. Among the 148 clinical cases with FTD spectrum clinical phenotypes were 30 autopsy-confirmed cases established on the basis of published methods[7,9], including 11 with tau pathology (corticobasal degeneration, n=3; PSP, n=6; dementia with Pick bodies, n=1; and argyrophilic grain disease, n=1), and 19 with TDP-43 pathology (ALS spectrum, n=7; bvFTD, n=12). There were also 20 genetic cases with known pathology established on the basis of published genotyping methods[25], including 3 with tau pathology due to a mutation of *MAPT*, and 17 with TDP-43 pathology due to a *C9orf72* repeat expansion (n=11), a *GRN* mutation (n=3), or a *TARDBP* mutation (n=3). The genetic and autopsy cohorts were merged into groups of patients with known FTLD-Tau pathology (n=14) or

known FTLD-TDP pathology (n=36). The remaining 98 of the 148 clinical cases with FTD spectrum clinical phenotypes were patients with a clinical diagnosis of a sporadic disorder established on the basis of published criteria that is frequently associated with tau pathology, including: naPPA (n=15) [6,26] and PSP (n=14) [27]. There were also patients with a clinical diagnosis often associated with TDP-43 pathology, including ALS (n=45) [28], ALS with FTD (n=6) or MCI (n=2) [29], and svPPA (n=16) [6,26]. These groups were combined into likely Tau (n=29) or likely TDP (n=69). We also studied 65 healthy normal controls. One control outlier was removed due to a NfL level >7 SD above the control mean. Some of these samples include CSF levels published previously as part of a larger cohort that are assessed here in a targeted manner with additional data[21]. Written informed consent was obtained from all subjects in accordance with the Institutional Review Board of the University of Pennsylvania.

Materials and Procedures

Cognitive testing was typically performed on the same day as CSF collection, and always within 6 months. We obtained MMSE[30], an overall measure of cognitive impairment sampling a variety of cognitive domains for a total score of 30; forward digit span[31], a measure of attention and short term memory, where participants repeat lengthier sequences of digits and we note the longest correctly reproduced sequence; letter-guided category naming fluency (words beginning with the letter F) [32], a measure of executive functioning, where patients produce as many unique words as possible beginning with a target letter for one minute; visual confrontation naming using an abbreviated version of the Boston Naming test[33]; and delayed word recall[34], a measure of episodic memory, where patients are given 5 trials to learn 9 words, then an interference list, then immediate and delayed recall, and we report the number of correctly recalled words at a delay of 25 minutes.

CSF was collected during routine lumbar puncture into polypropylene collection tubes, and stored at -80°C as previously described[35]. CSF pTau, tTau and Aß42 were measured using the multiplex xMAPLuminex platform (Luminex Corp, Austin, TX, USA) with the INNOBIA AlzBio3 kit (Innogenetics, Ghent, Belgium) [36]. NfL was measured using an in-house ELISA method using two NfL mouse monoclonal antibodies (NfL21 as capture antibody and NfL23 as detector), as previously described in detail [21].

Statistical analyses

This study is a case-control retrospective analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). ANCOVA tests were performed to test for differences in CSF NfL, pTau, tTau, and Aß42 analyte levels between known-or-likely FTLD-Tau, known-or-likely FTLD-TDP, known FTLD-Tau, known FTLD-TDP, and healthy control groups. Similar analyses were performed for MMSE, Forward Digit Span, F word fluency, Boston Naming test, and delayed word recall (PHLTrial9) cognitive measures. We computed annualized neuropsychological difference scores by examining % change values to account for differing baseline performance and differing follow-up durations. Neuropsychological baseline was selected as the testing session closest to the date of CSF collection but never greater than one year difference, compared to follow-up performance for longitudinal data that were between one and three years after baseline, and we calculated % change divided by the number of 12-month periods between tests. Spearman's rank correlations were performed on the longitudinal data, relating demographic, CSF analyte and cognitive data to NfL. Linear mixed model regression analyses were performed on significant correlations between a CSF analyte and a cognitive measure to examine how the CSF analytes could predict the cognitive measures. Three models were used: Model 1: NfL entered as the

only predictor of a specific cognitive measure (Cognitive measure ~ NfL + error); Model 2: NfL, age, and disease duration at time of initial CSF sample entered as predictors of a specific cognitive measure because NfL measures may vary depending on age and disease duration[37] (Cognitive measure ~ NfL + age + disease duration + error); and Model 3: NfL, age, disease duration, pTau, tTau, and Aß42 entered as predictors of a specific cognitive measure (Cognitive measure ~ NfL + age + disease duration + pTau + tTau + Aß42 + error). All tests were two-sided with a significance threshold of $p \leq 0.05$.

RESULTS

Demographic characteristics of participants are summarized in Table 1. Groups were matched for age, education, and disease duration at the time of LP.

CSF NfL, pTau, tTau, and Aß42 levels in patients with known pathology or the extended cohort including highly likely Tau or TDP pathology, and controls are summarized in Table 2. CSF NfL levels differed in all groups, except for the known Tau pathology group, relative to healthy controls. Moreover, patients with known TDP pathology had elevated CSF NfL levels relative to patients with known Tau pathology, and patients with known-or-likely TDP pathology had elevated CSF NfL levels relative to patients with known-or-likely Tau pathology. While these findings were robust to age and other CSF analytes, ANCOVAs covarying for disease duration in the known pathology group resulted in non-significant, marginal NfL differences between groups, suggesting that disease duration impacts CSF NfL levels. ANCOVAs showed a difference in CSF pTau levels between Tau, TDP and controls within the known pathology group, but no differences after pairwise comparisons. CSF tTau levels did not show any differences between groups. While the mean Aß42 level was above our statistical threshold for

likely AD pathology in all groups, it is noteworthy that the mean Aß42 level of Tau patients was significantly lower compared to controls after controlling for age and other CSF analytes in the larger, extended group including all patients with known-or-likely pathology. This suggests the possibility of AD co-pathology in the patients with clinically diagnosed disease. CSF NfL levels thus appear to be relatively more sensitive to the presence of FTD spectrum pathology than other CSF analytes, although the magnitude of the biomarker change depends on disease duration.

Baseline performance on cognitive measures and annualized % performance difference score are summarized in Table 3. Baseline MMSE differed in all patient groups compared to controls. Longitudinal MMSE decline differed from controls in all patients with known pathology and in the extended group of all patients with known-or-likely pathology, and this appears to be due to the subgroup of patients with TDP pathology. Likewise, baseline forward digit span and naming differed in all patient groups compared to controls, and longitudinal decline in forward digit span and naming differed from controls in all patients with known pathology and the extended group of all patients with known-or-likely pathology, and this appeared to be due to the subgroup of patients with TDP pathology. Baseline F letter fluency differed from controls for all patients, but did not differ from controls in longitudinal performance. Performance for delayed memory did not differ between patients and controls at baseline or longitudinally. Thus, MMSE, forward digit span and naming are sensitive to longitudinal change particularly in patients with TDP pathology.

Regression analyses were performed for significant correlations between CSF NfL levels and longitudinal cognitive values, controlling for demographic variables and other CSF analytes. Spearman's rank correlations of CSF NfL levels with longitudinal cognitive data are summarized in Supplementary Table A.

Consider first regressions involving patients with all FTD pathologies (Table 4 and Figure 1). In patients with known pathology, Model 1 showed that elevated CSF NfL significantly predicted % annualized decline in MMSE scores ($F(1,31)=18.825$, $p<.0005$). For Model 2 which included age and disease duration as covariates, elevated CSF NfL significantly predicted % annualized decline in MMSE scores ($F(1,29)=21.870$, $p<.0005$). For Model 3 which included age, disease duration, and other CSF analytes as covariates, CSF NfL predicted % annualized decline in MMSE scores ($F(1,24)=22.323$, $p<.0005$). For specific cognitive measures, elevated CSF NfL predicted decline in F Letter Fluency in Model 1 ($F(1,23)=178.135$, $p<.0005$), Model 2 ($F(1,21)=159.162$, $p<.0005$), and Model 3 ($F(1,17)=42.154$, $p<.0005$). These analyses remained significant after a potentially influential extreme value was removed (Model 1: $F(1,22)=18.428$, $p<.0005$, Model 2: $F(1,20)=14.451$, $p=0.001$, Model 3: $F(1,16)=10.029$, $p=.006$). Elevated CSF NfL predicted % annualized decline in Forward Span in Model 1 ($F(1,28)=37.090$, $p<.0005$), Model 2 ($F(1,26)=33.935$, $p<0.0005$), and Model 3 ($F(1,21)=20.76$, $p<.0005$). Elevated CSF NfL predicted decline in naming in Model 1 ($F(1,20)=7.66$, $p=.012$), Model 2 ($F(1,18)=6.95$, $p=.017$), and Model 3 ($F(1,14)=8.82$, $p=.01$). Elevated CSF NfL also predicted % annualized decline in delayed word recall in known pathology patients (Model 1: $F(1,16)=14.837$, $p=.001$, Model 2: $F(1,14)=12.533$, $p=.003$, Model 3: $F(1,10)=11.695$, $p=.007$).

For the combined group including TDP and Tau pathology that encompassed FTD patients with both known and likely pathology (Table 4), elevated CSF NfL predicted % annualized decline in MMSE scores (Model 1: $F(1,67)=9.752$, $p=.003$; Model 2: $F(1,65)=11.870$, $p=.001$; Model 3: $F(1,51)=9.489$, $p=.003$). For specific cognitive measures, elevated CSF NfL predicted % annualized decline in F Letter Fluency (Model 1: $F(1,45)=69.031$, $p<.0005$, Model 2: $F(1,43)=60.356$, $p<.0005$, Model 3: $F(1,37)=32.473$, $p<.0005$). Model 1 and 2 here remained

significant after an extreme value was removed (Model 1: F(1,44)=6.763, p=0.013, Model 2: F(1,42)=4.543, p=0.039). However, for Model 3, the CSF NfL prediction became marginal after the removal of the outlier (F(1,36)=3.964, p=.054). Age also contributed significantly in Model 2 (F(1,43)=4.410, p=0.042) and Model 3 (F(1,37)=4.467, p=.041). Elevated CSF NfL also predicted % annualized decline in Forward Span in known-or-likely pathology patients (Model 1: F(1,57)=9.694, p=.003, Model 2: F(1,55)=6.300, p=.015, Model 3: F(1,45)=4.357, p=.043). Elevated CSF NfL also predicted % annualized decline in delayed word recall for Models 1 (F(1,36)=5.054, p=.031) and 3 (F(1,26)=4.216, p=.050), but Model 2 was marginal (F(1,34)=3.901, p=.056).

Consider next regressions involving patients with TDP pathology (Table 5). In TDP patients with known pathology, elevated CSF NfL predicted % annualized decline in MMSE scores (Model 1: F(1,22)=14.251, p=.001, Model 2: F(1,20)=14.602, p=.001, Model 3: F(1,16)=18.412, p=.001). For specific cognitive measures, elevated CSF NfL predicted % annualized decline in F Letter Fluency in Model 1 (F(1,16)=129.712, p<.0005), Model 2 (F(1,14)=109.137, p<.0005), and Model 3 (F(1,10)=23.996, p=.001). Model 1 and 2 were still significant after an extreme value was removed (Model 1: F(1,15)=9.480, p=.008, Model 2: F(1,13)=6.528, p=.024), but Model 3 was no longer significant after the outlier was removed (F(1,9)=2.652, p=.138). Elevated CSF NfL also predicted % annualized decline in Forward Span in known TDP pathology patients (Model 1: F(1,19)=34.506, p<.0005, Model 2: F(1,17)=32.983, p<0.0005, Model 3: F(1,13)=20.521, p=.001). Elevated CSF NfL also predicted % annualized decline in naming in known TDP pathology patients (Model 1: F(1,13)=7.88, p=.015, Model 2: F(1,11)=5.69, p=0.036, Model 3: F(1,8)=14.70, p=0.005), and Aß42 also contributed to this association (F(1,8)=7.008, p=.029). Lastly, elevated CSF NfL was

able to predict % annualized decline in delayed word recall in known TDP pathology patients for Model 1 ($F(1,10)=9.405$, $p=.012$) and Model 2 ($F(1,8)=7.356$, $p=.027$). However, Model 3 was not significant ($F(1,5)=3.665$, $p=.114$).

For the combined group of known-or-likely TDP pathology patients (Tables 5), elevated CSF NfL predicted % annualized decline in MMSE scores (Model 1: $F(1,41)=10.478$, $p=.002$, Model 2: $F(1,39)=10.292$, $p=.003$, Model 3: $F(1,32)=6.822$, $p=.014$). For specific cognitive values, higher CSF NfL predicted decline in F Letter Fluency in Model 1 ($F(1,35)=75.086$, $p<.0005$), Model 2 ($F(1,33)=60.832$, $p<.0005$), and Model 3 ($F(1,28)=24.394$, $p<.0005$). Model 1 and 2 were still significant after an extreme value was removed (Model 1: $F(1,34)=7.626$, $p=.009$, Model 2: $F(1,32)=4.268$, $p=.047$), but Model 3 was no longer significant after the outlier removal ($F(1,27)=2.038$, $p=.165$). Elevated CSF NfL predicted % annualized decline in Forward Span in known-or-likely TDP pathology patients (Model 1: $F(1,39)=13.302$, $p=.001$, Model 2: $F(1,37)=9.364$, $p=.004$, Model 3: $F(1,30)=6.378$, $p=.017$). Elevated CSF NfL also was able to predict % annualized decline in delayed word recall in known-or-likely TDP pathology patients (Model 1: $F(1,20)=8.865$, $p=.007$, Model 2: $F(1,18)=7.724$, $p=.012$, Model 3: $F(1,13)=9.674$, $p=.008$). Age and disease duration were not significant contributors in either Model 2 or 3. However, CSF pTau contributed to predicting decline in word recall scores in Model 3 ($F(1,13)=5.055$, $p=.043$).

Linear mixed model analyses of Tau patients (Tables 6) were underpowered due to a small n and thus should be interpreted cautiously. For patients with known Tau pathology, CSF NfL was able to predict MMSE decline in Model 2 only ($F(1,5)=8.031$, $p=.037$). CSF NfL also predicted F Letter Fluency decline in Model 1 ($F(1,5)=15.196$, $p=.011$) and Model 2 ($F(1,3)=39.731$, $p=.008$). One note is that for Model 3 of the extended group including known-

or-likely Tau patients, the analytes CSF Aß42 and CSF tTau were able to predict decline in word list recall scores (CSF Aß42: $F(1,6)=15.049$, $p=.008$, CSF tTau: $F(1,6)=14.820$, $p=.008$) with no other demographic values or analytes showing significance.

DISCUSSION

Our findings indicate that CSF NfL levels are elevated in patients with FTD, including patients with known TDP or Tau pathology, compared to controls, and CSF NfL is elevated in patients with TDP pathology compared to those with Tau pathology, although this may be confounded by disease duration. Moreover, we find that CSF NfL can predict longitudinal cognitive decline in FTD patients with known pathology in multiple cognitive domains, including executive function, attention/short-term memory, and episodic memory difficulty, and these predictions remained statistically robust in patients with known pathology after controlling for demographic factors implicated in longitudinal analyses of NfL levels and other CSF analytes. These effects were most evident in patients with FTLD-TDP pathology, while effects appeared to be attenuated in clinically-defined cohorts that were larger, possibly due to the presence of secondary pathology. We discuss each of these findings below.

Assessments of CSF NfL revealed generally elevated levels in both FTLD-Tau and FTLD-TDP pathology groups compared to healthy controls. These results confirm previous findings in autopsy-confirmed cases of FTD[16-18,20,21]. Previous work attempting to identify patients with FTD pathology has depended on the use of traditional CSF analytes for AD to show an absence of an AD profile (reduced Aß42, elevated pTau) in a clinically appropriate sample to provide evidence consistent with FTD[10,35], and we and others showed elsewhere that CSF NfL levels are significantly elevated in autopsy-defined cases with FTD compared to AD [21,38]. While

we find here that CSF NfL levels are elevated in patients with TDP and Tau pathology, these findings are confounded by disease duration. Other reports also have shown that CSF NfL levels are correlated with disease duration[11,16,23] {Skillback:2014hn}, although this has not been a universal finding[18], and this may reflect increasing axonal degeneration as neurodegenerative disease advances. While age may be a confounding factor in healthy controls[37], we did not find that age impacts CSF NfL levels in patients, consistent with other findings[37].

We also demonstrated differences between subgroups of patients with FTLD pathology. Elevated CSF NfL was most robust in patients with TDP pathology, and patients with TDP pathology had significantly elevated CSF NfL levels compared to patients with Tau pathology. Direct comparisons of NfL levels in patients with known pathology due to FTLD-TDP compared to FTLD-Tau have been published in small cohorts[16], and our finding with a larger cohort replicates these earlier results. While a difference between FTLD-TDP and FTLD-Tau was not found in some studies[11], this may have been related in part to the large proportion of mutation carriers studied in this report. Although not as robust as in patients with FTLD-TDP, CSF NfL levels nevertheless were elevated in patients with FTLD-Tau pathology relative to healthy controls. However, these results were gathered from a small subgroup of patients and thus require replication.

While elevated CSF NfL was evident in both the cohort with known pathology and the larger cohort combining these patients with clinically diagnosed patients thought to have a likely form of pathology compared to controls, a note of caution is warranted here regarding the study of clinically diagnosed patients. Some clinically diagnosed patients in the present study appeared to have lower CSF Aß42 levels. This suggests the presence of AD co-pathology in clinically diagnosed patients, a finding in patients with neurodegenerative disease that is not

uncommon[39,40]. Additionally, some patients may have been misdiagnosed with FTD even though the true underlying primary pathology was AD, another finding that is not uncommon in non-amnestic phenotypes with AD pathology that may be misdiagnosed as having FTD spectrum pathology[41-43].

A correlation between traditional AD CSF analytes and CSF NfL has been reported[11]. We show here that, despite this correlation, CSF NfL explains difference between patients and controls, and between FTLD-TDP and FTLD-Tau patients, that are not otherwise explained by CSF levels of pTau, tTau and Aß42. This is particularly interesting given the common axonal source of Tau and NfL.

Regression analyses were performed to relate CSF NfL levels to % cognitive decline in a cohort of FTD patients followed longitudinally. We found that NfL is associated with declining MMSE in the combined cohort of all FTD patients with known pathology. We replicated this finding in a larger, mixed cohort incorporating both pathology cases and clinical cases where the phenotype is highly likely to be associated with an FTD spectrum pathology. We also assessed whether elevated NfL would be related to longitudinal decline after we controlled for age and disease duration, that is, two factors that have been implicated in elevated NfL. CSF NfL level continued to be associated with declining MMSE even after taking into account these demographic factors. We again replicated these findings in a larger, mixed cohort consisting of both pathology- and clinically-defined cases. This emphasizes the reliability of CSF NfL as a biomarker reflecting cognitive decline in FTLD regardless of age and disease duration. Finally, NfL and traditional AD analytes overlap in part because axonal degeneration is the source of both tau and NfL. We find that CSF NfL predicts declining MMSE despite having taken into account demographic factors as well as CSF levels of pTau, tTau and Aß42. Thus, there is added

value to CSF NfL level beyond that which can be derived from traditional AD CSF analytes. Again, we replicated these findings in a larger, mixed cohort consisting of both pathology- and clinically-defined cases.

It has been difficult to establish a gold standard for overall clinical progression in FTD. Traditional measures such as MMSE and CDR have been used most often to reflect overall clinical decline in FTD, although there are potential problems with this strategy. In particular, these measures were developed to reflect cognitive and functional difficulties primarily in AD, and thus using these measures to track clinical decline may be less than optimal in FTD where patients have primarily language and social disorders and less prominent memory difficulty. In this study, we also found that CSF NfL is associated with declining performance in other specific cognitive domains in patients with known pathology. This includes executive functioning measured by letter-guided category naming fluency, attention and auditory-verbal short-term memory measured by forward digit span, visual confrontation naming, and delayed episodic memory recall. These findings suggest that NfL is associated with varied and widespread measures of cognitive decline. Each of these measures is associated with somewhat distinct neurocognitive networks implicating different brain regions, and these regions are often compromised in FTD spectrum disorders. Category naming fluency is associated with a network of brain regions centered in the frontal lobe; forward digit span is related to a frontal-parietal network thought to be important for attention and short-term memory; visual confrontation naming is related to a left peri-Sylvian network that supports lexical retrieval; and delayed recall is associated with a memory network centered in medial temporal and precuneus regions. Moreover, each of these associations is robust to demographic factors such as age and disease duration, and to CSF levels of other analytes. Each of these networks may be compromised in

patients with FTD pathology, and from this perspective it may be less surprising that CSF NfL predicts decline in these cognitive domains. This may be important because there is not uniform agreement on the measures that should be collected during longitudinal clinical evaluation or endpoints during a treatment trial. It may be noted, however, that there is considerable variability in the robustness of the findings: Category naming fluency is much more robust than MMSE, for example, while naming is less robustly predicted by NfL.

When we examined the usefulness of CSF NfL for predicting cognitive decline in a larger, mixed cohort consisting of pathological and clinical cases, we replicated the findings of the cohort with known pathology only in part. Thus, while NfL was associated with declining category naming fluency, forward digit span and delayed memory recall, we also found that CSF NfL was not associated with progressive naming difficulty. This may have been due in part to the minimal longitudinal change in naming difficulty over time in the FTLD-Tau cohort (see below). Moreover, we found that age appears to impact the predictive capacity of NfL on longitudinal category naming fluency. All of the cognitive measures that we studied are sensitive to changes during aging, and it is possible that healthy aging is relatively more sensitive to executive measures like category naming fluency than the other cognitive measures we used. We did not see this effect for aging in the TDP cases we studied, and we can speculate that this may have bene related in part to the cases with Tau since they were older. However, we cannot fully evaluate a potential role for aging in the participating cases with Tau since this regression was not significant, and additional work is needed to assess this hypothesis.

We examine each pathologic cohort separately because of unclear claims about selective effects for NfL in FTLD-TDP or FTLD-Tau. We found a robust pattern supporting the claim that NfL can predict cognitive decline in patients with known FTLD-TDP pathology. Thus, CSF

NfL levels in patients with known FTLD-TDP pathology were able to predict declining performance on the MMSE as well as decline in each of the more specific cognitive measures. Moreover, this was true after having considered age, disease duration, and CSF levels of traditional AD analytes. The single exception was for naming, where CSF Aß42 appeared to have a minor impact on predicting longitudinal decline.

However, we were unable to extend the longitudinal predictive capacity of CSF NfL to patients with known FTLD-Tau pathology. In patients with known FTLD-Tau pathology, we found only that declining category naming fluency could be predicted by CSF NfL levels. After incorporating demographic factors, CSF NfL was associated with longitudinal decline of MMSE as well. There were too few cases to assess the potential role of traditional AD analytes in the FTLD-Tau cohort.

The basis for this stronger effect in FTLD-TDP than FTLD-Tau is unclear. While not statistically significant, FTLD-Tau cases were older by five years than FTLD-TDP cases, and LP was obtained following a longer disease duration in FTLD-Tau than in FTLD-TDP. Nevertheless, the finding of some predictive value of NfL for declining cognition in FTLD-TDP but not FTLD-Tau may reflect that TDP-43 pathology has a greater impact on axonal degeneration that FTLD-Tau. TDP-43 is implicated in modulation of neuronal inflammatory processes, and disturbances of these processes may have evoked greater axonal degeneration in FTLD-TDP than FTLD-Tau. This would be consistent with the finding that CSF NfL levels were significantly more elevated in FTLD-TDP than FTLD-Tau. Another possibility may be related in part to the smaller cohort of cases with FTLD-Tau that had statistically less power to demonstrate an effect. Additional work is needed to assess these possibilities.

We extended our assessment of more specific measures to a larger cohort that included patients with known pathology as well as clinically-diagnosed patients with a phenotype highly likely to be associated with a specific FTD spectrum pathology. While many findings persisted in the TDP cohort, these were generally less robust, and longitudinal decline in naming was not significantly associated with NfL levels. In the larger Tau cohort including both pathology- and clinically-identified cases, we did not find any significant effects for NfL. However, tTau and Aß42 both were associated with longitudinal decline in episodic memory recall. This suggests that some cases may have had AD co-pathology or may have been misdiagnosed as FTD when they in fact had primary AD pathology. These observations also emphasize the importance of studies in patients with known pathology, even in the setting of larger cohorts.

Recent work has shown a correlation between CSF levels of NfL and serum or plasma levels of NfL[18,44]. It is attractive to study serum or plasma biomarkers compared to CSF biomarkers because of the relative ease and perceived reduction in invasiveness associated with obtaining a blood study compared to obtaining a CSF sample. However, it may be useful to obtain multiple validated biomarkers simultaneously in the setting of differential diagnosis such as discriminating FTD from AD, and CSF may be a superior modality in this context because of persistent doubts associated with the robustness of blood measures of tau and Aß42.

Strengths of this report include the focus on FTLD patients, and the relatively large sample of patients with known pathology. Moreover, we were able to examine the relative contribution of multiple CSF analytes, and were able to relate these to longitudinal decline in multiple cognitive domains. Nevertheless, some limitations should be kept in mind when considering the results of this study. While we examined a relatively large cohort manifesting a rare disease, samples of FTLD-Tau patients with known or likely pathology in particular were

small and additional work is needed with larger cohorts of patients. We assessed longitudinal measures of overall cognitive function as well as some measures that more closely reflect cognitive difficulties on FTD spectrum disorders, but our range of cognitive measures was limited and not every patient had every cognitive test. Future studies should examine additional cognitive measures.

With these caveats in mind, we find that CSF NfL distinguishes patients with known FTLD pathology from healthy controls, and patients with FTLD-TDP pathology have significantly higher CSF NfL levels than patients with FTLD-Tau pathology, but the diagnostic value of these findings is limited by the potential confounding role of disease duration. Moreover, CSF NfL levels are associated with longitudinal decline on a range of cognitive measures, including those that are commonly found to be compromised in patients with an FTD spectrum disorder. These findings were generally robust to demographic factors such as age and disease duration that may impact NfL levels, and provided additional information beyond that available from traditional CSF analytes. We extended these analyses to a larger cohort incorporating patients with known pathology as well as clinically-defined patients, but we found that results may have been less robust due to the possible presence of AD co-pathology or misdiagnosis of AD as a form of FTD.

TABLE 1
Mean ± SD Demographic Features[1, 2]

	ALL FTD		TAU			TDP			CONTROL
	Known-or-likely Tau+TDP	**Known Tau+TDP**	**Known-or-likely Tau**	**Known Tau**	**Clinically likely Tau**	**Known-or-likely TDP**	**Known TDP**	**Clinically likely TDP**	**Healthy Control**
N (male)	148 (90)	50(28)	43 (23)	14 (9)	29 (14)	105 (67)	36 (19)	69 (48)	65 (22)
Age at LP (yr)	62.02±10	63.60±7	65.72±9	65.07±10	66.03±9	60.50±10	63.03±6	59.19±11	68.09±9
Disease Duration at LP (yr)	2.74±2 N=147	2.98±2	3.49±2	3.43±2	3.52±1	2.43±2 N=104	2.81±2	2.24±2 N=68	n/a
Education at LP (yr)	15.27±3 N=137	15.94±3 N=48	14.38±3 N=42	15.23±3 N=13	14.00±3	15.66±2 N=95	16.20±3 N=35	15.35±2 N=60	16.35±3

NOTES

1. Cases included the following pathology and clinical diagnoses:

Known Tau:

Autopsy confirmed Tau: 3 corticobasal degeneration, 6 progressive supranuclear palsy, 1 Pick's disease, and 1 argyrophilic grain disease

Genetically confirmed Tau: 3 MAPT mutation

Clinically Likely Tau:

15 naPPA, 14 PSP

Known TDP:

Autopsy confirmed TDP: ALS spectrum, n=7; bvFTD, n=12

Genetically confirmed TDP: 11 C9orf72, 3 TARDBP, and 3 GRN mutations

Clinically Likely TDP:

45 ALS, 6 ALS with FTD, 2 ALS with MCI, and 16 SD

Healthy Control:

65

2. There are missing values for some demographic features, and the available n is provided in the corresponding cell in the table.

TABLE 2
Mean ± SD Cerebrospinal Fluid Analyte Values[1, 2]

	ALL FTD		TAU		TDP		CONTROL
	Known-or-likely Tau+TDP	**Known Tau+TDP**	**Known-or-likely Tau**	**Known Tau**	**Known-or-likely TDP**	**Known TDP**	**Healthy Control**
Total N	148	50	43	14	105	36	65
NfL (pg/mL)	3668.27±3373 ***	3694.97±3740 ***	2016.30±1257 * ^^^	2241.96±1241 ^	4344.79±3722 *** ^^^	4260.03±4224 *** ^	663.16±573
pTau (pg/mL)	16.03±17 N=136	14.03±7* N=48	16.03±7 N=36	13.67±2 N=13	16.03±20 N=100	14.16±8 N=35	19.70±14
tTau (pg/mL)	61.67±35 N=136	61.06±33 N=48	56.12±25 N=36	58.45±26 N=13	63.67±38 N=100	62.03±35 N=35	54.50±22
Aß42 (pg/mL)	247.86±79* N=137	247.75±67 N=49	222.03±76 N=36	239.99±69 N=13	257.07±79 N=101	250.55±67	255.58±69

NOTES

1. Differs from controls: *0.05; **0.01; ***0.005
Differs known Tau vs known TDP: ^0.05; ^^0.01; ^^^0.005
Differs known-or-likely Tau vs known-or-likely TDP: ^0.05; ^^0.01; ^^^0.005

2. There are missing samples for some analyte values, and the available n is provided in the corresponding cell in the table.

TABLE 3

Mean ± SD Baseline Performance and % Annualized Longitudinal Cognitive Decline[1, 2]

	ALL FTD		TAU		TDP		CONTROL
	Known-or-likely Tau+TDP	**Known Tau+TDP**	**Known-or-likely Tau**	**Known Tau**	**Known-or-likely TDP**	**Known TDP**	**Healthy Control**
Total N	148	49	43	14	105	35	65
Baseline: MMSE (max=30)	24.96±5*** N=91	24.88±5*** N=41	24.49±4*** N=35	25.16±3** N=13	25.25±5*** N=56	24.75±5*** N=28	29.24±1 N=61
Longitudinal: MMSE	-9.50±22* N=69	-11.75±20*** N=33	-7.92±21 N=26	-9.93±10 N=9	-10.45±23* N=43	-12.43±23** N=24	-0.29±3 N=55
Baseline: Forward Span (# accurate repetition)	5.83±1** N=88	5.81±1** N=37	5.54±1** N=28	5.50±1** N=12	5.97±1** N=60	5.96±1** N=25	6.78±1 N=46
Longitudinal: Forward Span	-14.18±27** N=59	-18.75±27*** N=30	-11.53±27 N=18	-6.83±20 N=9	-15.34±28** N=41	-23.86±28*** N=21	1.17±13 N=43
Baseline: F Letter Fluency (#words/min)	8.62±5*** N=69	8.17±5*** N=30	5.00±3*** ^ N=13	4.50±1*** N=8	9.46±5*** ^ N=56	9.50±5** N=22	15.80±4 N=15
Longitudinal: F Letter Fluency	-24.22±115 N=47	-43.98±139 N=25	2.37±80 N=10	-10.08±41 N=7	-31.41±123 N=37	-57.17±162 N=18	-0.70±22 N=10
Baseline: Naming (max=30)	19.99±8*** N=68	21.65±7*** N=33	22.55±6** ^ N=29	22.81±5* N=11	18.09±9*** ^ N=39	21.07±8*** N=22	27.65±2 N=54
Longitudinal: Naming	-9.54±33* N=45	-8.00±16** N=22	-3.62±15 N=17	-2.60±9 N=7	-13.13±40* N=28	-10.52±18** N=15	1.18±5.08 N=48
Baseline: Delayed memory recall (max=9)	5.34±3 N=56	5.34±3 N=55	6.04±2 N=26	5.91±2 N=22	5.33±2 N=9	4.94±3 N=33	6.41±2 N=17
Longitudinal: Delayed memory recall	-22.99±41 N=38	-22.99±41 N=38	-28.10±40 N=18	-24.08±45 N=16	-24.67±40 N=6	-22.20±38 N=22	-29.81±41 N=12

NOTES

1. Differs from controls: *0.05; **0.01; ***0.005

Differs known Tau vs known TDP: ^0.05; ^^0.01; ^^^0.005

Differs known-or-likely Tau vs known-or-likely TDP: ^0.05; ^^0.01; ^^^0.005

2. 10 ALS patients' MMSE scores were originally scored out of a number less than 30 due to motor issues. Their scores were prorated relative to a maximum possible score of 30.

3. There are missing samples for some neuropsychological measures, and the available n is provided in the corresponding cell in the table.

Table 4
Longitudinal linear regression models for All FTD Patients[1]

All FTD: Known Pathology

	COGNITIVE MEASURE				
	MMSE	**F Letter Fluency**	**Forward Span**	**Naming**	**Delayed word recall**
MODEL 1: NfL:	**F(1,31)=18.82**	**F(1,23)=178.13**	**F(1,28)=37.09**	**F(1,20)=7.66**	**F(1,16)=14.83**
	P<0.0005	**P=0.0005**	**P=0.0005**	**P=0.012**	**P=0.001**
MODEL 2: NfL:	**F(1,29)=21.87**	**F(1,21)=159.16**	**F(1,26)=33.93**	**F(1,18)=6.955**	**F(1,14)=12.53**
	P<0.0005	**P<0.0005**	**P<0.0005**	**P=0.017**	**P=0.003**
Age:	F(1,29)=1.62	F(1,21)=0.72	F(1,26)=2.27	F(1,18)=0.001	F(1,14)=0.93
	P=0.212	P=0.404	P=0.144	P= 0.975	P=0.350
Disease Duration:	F(1,29)=0.48	F(1,21)=0.79	F(1,24)=0.12	F(1,18)=0.189	F(1,14)=0.64
	P=0.493	P=0.383	P=0.724	P=0.669	P=0.437
MODEL 3: NfL:	**F(1,24)=22.32**	**F(1,17)=42.15**	**F(1,21)=20.76**	**F(1,14)=8.822**	**F(1,10)=11.69**
	P<0.0005	**P<0.0005**	**P<0.0005**	**P=0.010****	**P=0.007**
Age:	F(1,24)=1.71	F(1,17)=0.01	F(1,21)=1.62	F(1,14)=0.584	F(1,10)=0.47
	P=0.203	P=0.916	P=0.217	P=0.458	P=0.505
Disease Duration:	F(1,24)=1.28	F(1,17)=0.46	F(1,21)=0.00	F(1,14)=0.001	F(1,10)=0.48
	P=0.269	P=0.505	P=0.976	Sig.=0.994	P=0.502
pTau:	F(1,24)=0.60	F(1,17)=1.45	F(1,21)=0.01	F(1,14)=3.544	F(1,10)=1.05
	P=0.443	P=0.244	P=0.920	P=0.081	P=0.329
tTau:	F(1,24)=0.17	F(1,17)=0.31	F(1,21)=0.24	F(1,14)=0.336	F(1,10)=0.48
	P=0.679	P=0.582	P=0.623	P=0.571	P=0.504
Aß42:	F(1,24)=1.14	F(1,17)=0.52	F(1,21)=0.11	F(1,14)=2.935	F(1,10)=0.05
	P=0.295	P=0.479	P=0.737	P=0.109	P=0.821

TABLE 4 (continued)

All FTD: Known-or-Likely Pathology

	COGNITIVE MEASURE				
	MMSE	**F Letter Fluency**	**Forward Span**	**Naming**	**Delayed word recall**
MODEL 1: NfL:	**F(1,67)=9.75**	**F(1,45)=69.03**	**F(1,57)=9.69**	F(1,43)=0.52	**F(1,36)=5.05**
	P=0.003	**P=<0.0005**	**P=0.003**	P=0.471	**P=0.031**
MODEL 2 NfL:	**F(1,65)=11.87**	**F(1,43)=60.35**	**F(1,55)=6.30**	F(1,41)=0.91	F(1,34)=3.90
	P=0.001	**P=<0.0005**	**P=0.015**	P=0.343	P=0.056
Age:	F(1,65)=1.26	**F(1,43)=4.41**	F(1,55)=0.15	F(1,41)=1.41	F(1,34)=0.70
	P=0.265	**P=0.042**	P=0.699	P=0.241	P=0.406
Disease Duration:	F(1,65)=2.33	F(1,43)=1.55	F(1,55)=1.57	F(1,41)=0.45	F(1,34)=2.60
	P=0.132	P=0.220	P=0.215	P=0.505	P=0.116
MODEL 3: NfL:	**F(1,51)=9.48**	**F(1,37)=32.47**	**F(1,45)=4.35**	F(1,33)=1.20	**F(1,26)=4.21**
	P=0.003	**P=<0.0005**	**P=0.043**	P=0.280	**P=0.050**
Age:	F(1,51)=0.35	**F(1,37)=4.46**	F(1,45)=0.20	F(1,33)=1.67	F(1,26)=1.01
	P=0.554	**P=0.041**	P=0.652	P=0.204	P=0.322
Disease Duration:	F(1,51)=0.78	F(1,37)=0.80	F(1,45)=1.15	F(1,33)=0.62	F(1,26)=2.85
	P=0.381	P=0.377	P=0.287	P=0.434	P=0.103
pTau:	F(1,51)=0.01	F(1,37)=0.96	F(1,45)=0.06	F(1,33)=1.26	F(1,26)=2.44
	P=0.980	P=0.332	P=0.795	P=0.269	P=0.130
tTau:	F(1,51)=0.17	F(1,37)=0.17	F(1,45)=1.03	F(1,33)=0.01	F(1,26)=0.48
	P=0.675	P=0.680	P=0.314	P=0.901	P=0.491
Aß42:	F(1,51)=0.05	F(1,37)=3.96	F(1,45)=3.67	F(1,33)=1.19	F(1,26)=3.82
	P=0.997	P=0.054	P=0.062	P=0.282	P=0.061

NOTE

1. Significant models are in bold font.

TABLE 5
Longitudinal linear regression models for TDP Patients[1]

TDP: Known Pathology

	COGNITIVE MEASURE				
	MMSE	**F Letter Fluency**	**Forward Span**	**Naming**	**Delayed word recall**
MODEL 1: NfL:	**F(1,22)=14.25**	**F(1,16)=129.71**	**F(1,19)=34.50**	**F(1,13)=7.88**	**F(1,10)=9.40**
	P=0.001	**P<0.0005**	**P=<0.0005**	**P=0.015**	**P=0.012**
MODEL 2: NfL:	**F(1,20)=14.60**	**F(1,14)=109.13**	**F(1,17)=32.98**	**F(1,11)=5.69**	**F(1,8)=7.35**
	P=0.001	**P<0.0005**	**P<0.0005**	**P=0.036**	**P=0.027**
Age:	F(1,20)=0.75	F(1,14)=1.19	F(1,17)=3.76	F(1,11)=0.31	F(1,8)<0.05
	P=0.397	P=0.293	P=0.069	P=0.589	P=0.985
Disease Duration:	F(1,20)=0.53	F(1,14)=0.65	F(1,17)=0.00	F(1,11)=0.18	F(1,8)=0.95
	P=0.475	P=0.433	P=0.925	P=0.672	P=0.357
MODEL 3: NfL:	**F(1,16)=18.41**	**F(1,10)=23.99**	**F(1,13)=20.52**	**F(1,8)=14.70**	F(1,5)=3.66
	P=0.001	**P=0.001**	**P=0.001**	**P=0.005**	P=0.114
Age:	F(1,16)=2.92	F(1,10)=0.33	F(1,13)=3.62	F(1,8)=2.00	F(1,5)=0.01
	P=0.106	P=0.574	P=0.079	P=0.194	P=0.973
Disease Duration:	F(1,16)=3.05	F(1,10)=0.46	F(1,13)=0.04	F(1,8)=0.13	F(1,5)=0.91
	P=0.100	P=0.512	P=0.835	P=0.727	P=0.383
pTau:	F(1,16)=1.42	F(1,10)=0.07	F(1,13)=0.25	F(1,8)=0.12	F(1,5)=0.001
	P=0.250	P=0.785	P=0.622	P=0.732	P=0.991
tTau:	F(1,16)=0.28	F(1,10)=0.10	F(1,13)=0.34	F(1,8)=0.01	F(1,5)=0.28
	P=0.602	P=0.749	P=0.570	P=0.921	P=0.617
Aß42:	F(1,16)=2.40	F(1,10)=0.17	F(1,13)=0.63	**F(1,8)=7.008**	F(1,5)=0.155
	P=0.140	P=0.689	P=0.439	**P=0.029**	P=0.710

TABLE 5 (continued)

TDP: Known-or-Likely Pathology

	COGNITIVE MEASURE				
	MMSE	**F Letter Fluency**	**Forward Span**	**Naming**	**Delayed word recall**
MODEL 1: NfL:	**F(1,41)=10.47**	**F(1,35)=75.08**	**F(1,39)=13.30**	F(1,26)=0.34	**F(1,20)=8.86**
	P=0.002	**P<0.0005**	**P=0.001**	P=0.565	**P=0.007**
MODEL 2: NfL:	**F(1,39)=10.29**	**F(1,33)=60.83**	**F(1,37)=9.36**	F(1,24)=0.74	**F(1,18)=7.72**
	P=0.003	**P<0.0005**	**P=0.004**	P=0.398	**P=0.012**
Age:	F(1,39)=0.66	F(1,33)=1.88	F(1,37)=0.15	F(1,24)=0.45	F(1,18)=0.28
	P=0.420	P=0.179	P=0.692	P=0.508	P=0.601
Disease Duration:	F(1,39)=0.20	F(1,33)=1.29	F(1,37)=0.43	F(1,24)=0.42	F(1,18)=1.21
	P=0.657	P=0.264	P=0.514	P=0.522	P=0.284
MODEL 3: NfL:	**F(1,32)=6.82**	**F(1,28)=24.39**	**F(1,30)=6.37**	F(1,19)=0.42	**F(1,13)=9.67**
	P=0.014	**P<0.0005**	**P=0.017**	P=0.521	**P=0.008**
Age:	F(1,32)=0.83	F(1,28)=1.24	F(1,30)=0.03	F(1,19)=1.41	F(1,13)=0.14
	P=0.367	P=0.274	P=0.859	P=0.249	P=0.712
Disease Duration:	F(1,32)=0.02	F(1,28)=0.68	F(1,30)=0.52	F(1,19)=0.65	F(1,13)=2.04
	P=0.966	P=0.416	P=0.474	P=0.428	P=0.176
pTau:	F(1,32)=0.18	F(1,28)=0.48	F(1,30)=0.09	F(1,19)=1.77	**F(1,13)=5.05**
	P=0.675	P=0.492	P=0.926	P=0.199	**P=0.043**
tTau:	F(1,32)=0.08	F(1,28)=0.26	F(1,30)=0.06	F(1,19)=0.36	F(1,13)=0.02
	P=0.778	P=0.608	P=0.807	P=0.553	P=0.873
Aß42:	F(1,32)=0.44	F(1,28)=0.76	F(1,30)=1.19	F(1,19)=0.75	F(1,13)=0.30
	P=0.511	P=0.388	P=0.283	P=0.397	P=0.592

NOTE

1. Significant models are in bold.

TABLE 6
Longitudinal linear regression model for Tau Patients[1]

Tau: Known Pathology

	COGNITIVE MEASURE				
	MMSE	**F Letter Fluency**	**Forward Span**	**Naming**	**Delayed word recall**
MODEL 1: NfL:	F(1,7)=3.00	**F(1,5)=15.19**	F(1,7)=0.82	F(1,5)=0.16	F(1,4)=4.45
	P=0.127	**P=0.011**	P=0.393	P=0.702	P=0.102
MODEL 2: NfL:	**F(1,5)=8.03**	**F(1,3)=39.73**	F(1,5)=0.47	F(1,3)=0.47	F(1,2)=5.32
	P=0.037	**P=0.008**	P=0.523	P=0.542	P=0.147
Age:	F(1,5)=4.70	F(1,3)=6.50	F(1,5)<0.005	F(1,3)=0.88	F(1,2)=0.68
	P=0.082	P=0.084	P=0.989	P=0.415	P=0.495
Disease Duration:	F(1,5)=0.28	F(1,3)=6.81	F(1,5)<0.05	F(1,3)=0.02	F(1,2)=0.01
	P=0.616	P=0.080	P=0.995	P=0.876	P=0.984

TABLE 6 (continued)

Tau: Known-or-likely Pathology

	COGNITIVE MEASURE				
	MMSE	**F Letter Fluency**	**Forward Span**	**Naming**	**Delayed word recall**
MODEL 1: NfL:	F(1,24)=0.20	F(1,8)=0.08	F(1,16)=0.201	F(1,15)=1.46	F(1,14)=0.14
	P=0.65	P=0.78	P=0.660	P=0.246	P=0.705
MODEL 2: NfL:	F(1,22)=0.71	F(1,6)=0.09	F(1,14)=0.470	F(1,13)=3.25	F(1,12)=0.14
	P=0.408	P=0.764	P=0.504	P=0.095	P=0.711
Age:	F(1,22)=1.61	F(1,6)=2.58	F(1,14)<0.0005	F(1,13)=3.73	F(1,12)=1.54
	P=0.217	P=0.159	P=0.988	P=0.075	P=0.238
Disease Duration:	F(1,22)=4.04	F(1,6)=0.46	F(1,14)=1.059	F(1,13)=0.43	F(1,12)=1.41
	P=0.057	P=0.521	P=0.321	P=0.520	P=0.257
MODEL 3: NfL:	F(1,12)=0.42	F(1,2)=0.02	F(1,8)=2.850	F(1,7)=1.32	F(1,6)=3.20
	P=0.526	P=0.899	P=0.130	P=0.288	P=0.123
Age:	F(1,12)=0.72	F(1,2)=2.49	F(1,8)=0.324	F(1,7)=2.69	F(1,6)=2.11
	P=0.410	P=0.255	P=0.585	P=0.144	P=0.196
Disease Duration:	F(1,12)=1.85	F(1,2)=0.22	F(1,8)=0.258	F(1,7)=0.14	F(1,6)=1.15
	P=0.199	P=0.682	P=0.625	P=0.711	P=0.324
pTau:	F(1,12)=0.46	F(1,2)=0.40	F(1,8)=0.380	F(1,7)=0.37	F(1,6)=0.12
	P=0.507	P=0.592	P=0.555	P=0.557	P=0.737
tTau:	F(1,12)=0.26	F(1,2)=0.95	**F(1,8)=6.321**	F(1,7)=0.201	**F(1,6)=14.82**
	P=0.618	P=0.433	**P=0.036**	P=0.668	**P=0.008**
Aß42:	F(1,12)=1.36	F(1,2)=2.98	F(1,8)=4.269	F(1,7)=0.38	**F(1,6)=15.04**
	P=0.265	P=0.226	P=0.073	P=0.557	**P=0.008**

NOTE

1. Significant models are in bold.

SUPPLEMENT

Table A: **Spearman Correlations (p-values) of Cerebrospinal Fluid Neurofilament Light Chain Level with Longitudinal Cognitive Measures[1, 2]**

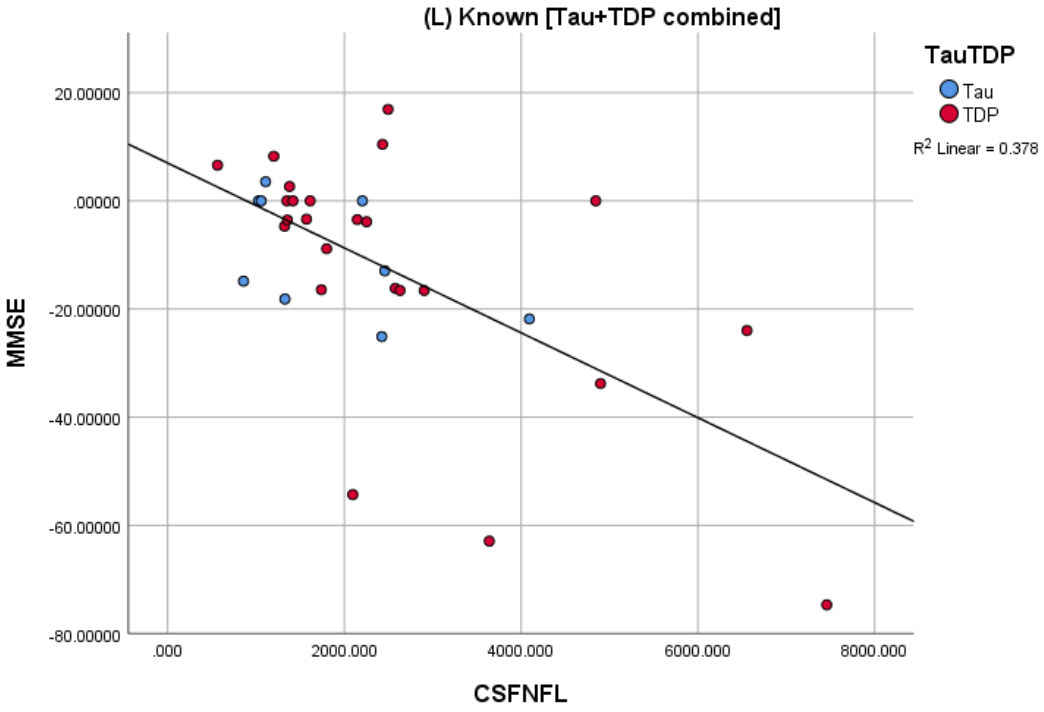
	Known-or-likely Tau+TDP	**Known Tau+TDP**	**Known-or-likely Tau**	**Known Tau**	**Known-or-likely TDP**	**Known TDP**
Cognitive values:						
MMSE% decline	**-0.278 (0.021) N=69**	**-0.527 0(.002) N=33**	-0.111 (0.588) N=26	-0.475 (0.197) N=9	**-0.411 (0.006) N=43**	**-0.579 (0.003) n=24**
Forward Span decline	-0.186 (0.159) N=59	**-0.506 (0.004) N=30**	0.044 (0.864) N=18	-0.373 (0.323) N=9	-0.237 (0.135) N=41	**-0.476 (0.029) N=21**
F Letter Fluency decline	**-0.376 (0.009) N=47**	**-0.699 (<0.0005) N=25**	-0.231 (0.520) N=10	-0.709 (0.074) N=7	**-0.435 (0.007) N=37**	**-0.696 (0.001) N=18**
Naming decline	-0.179 (0.240) N=45	**-0.447 (0.037) N=22**	0.178 (0.495) N=17	0.143 (0.760) N=7	-0.266 (0.172) N=28	**-0.690 (0.004)** N=15
Word Recall decline	-0.156 (0.349) N=38	**-0.596 (0.009) N=18**	-0.027 (0.922) N=16	-0.754 (0.084) N=6	-0.268 (0.227) N=22	-0.469 (0.124) N=12

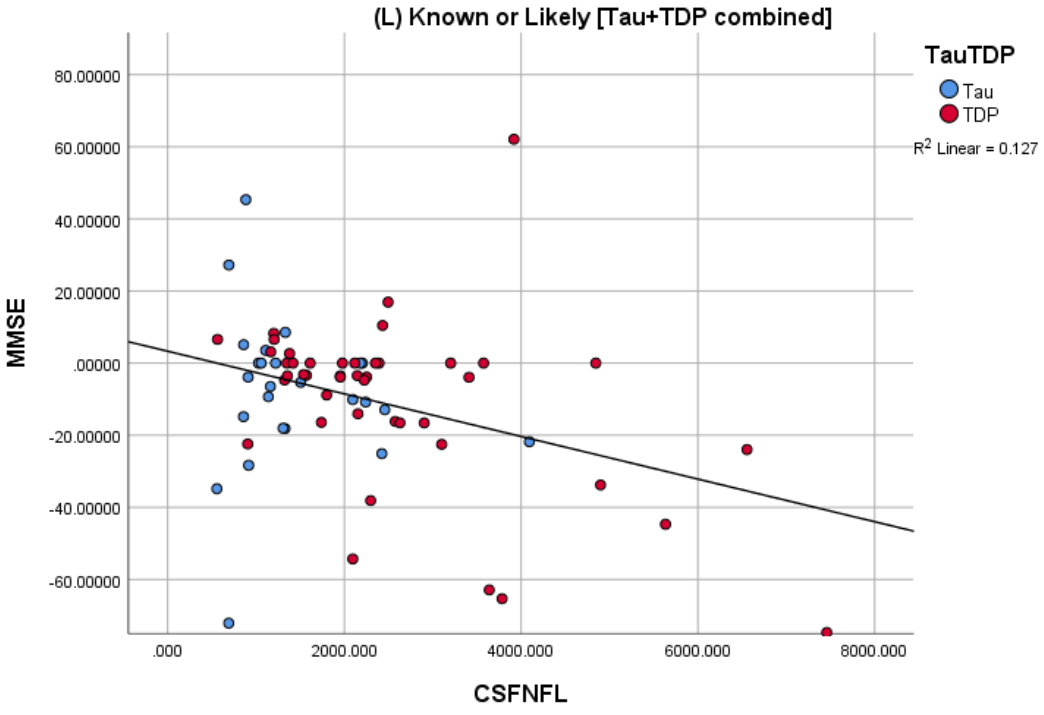
NOTES

1. Significant correlations are in bold.

2. There are missing samples for some neuropsychological measures, and the available n is provided in the corresponding cell in the table.

FIGURE 1


(L) Known [Tau+TDP combined]
TauTDP
Tau
TDP
R2 Linear = 0.378
MMSE
20.00000
.00000
-20.00000
-40.00000
-60.00000
-80.00000
.000
2000.000
4000.000
6000.000
8000.000
CSFNFL


(L) Known or Likely [Tau+TDP combined]
TauTDP
Tau
TDP
R2 Linear = 0.127
MMSE
80.00000
60.00000
40.00000
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-20.00000
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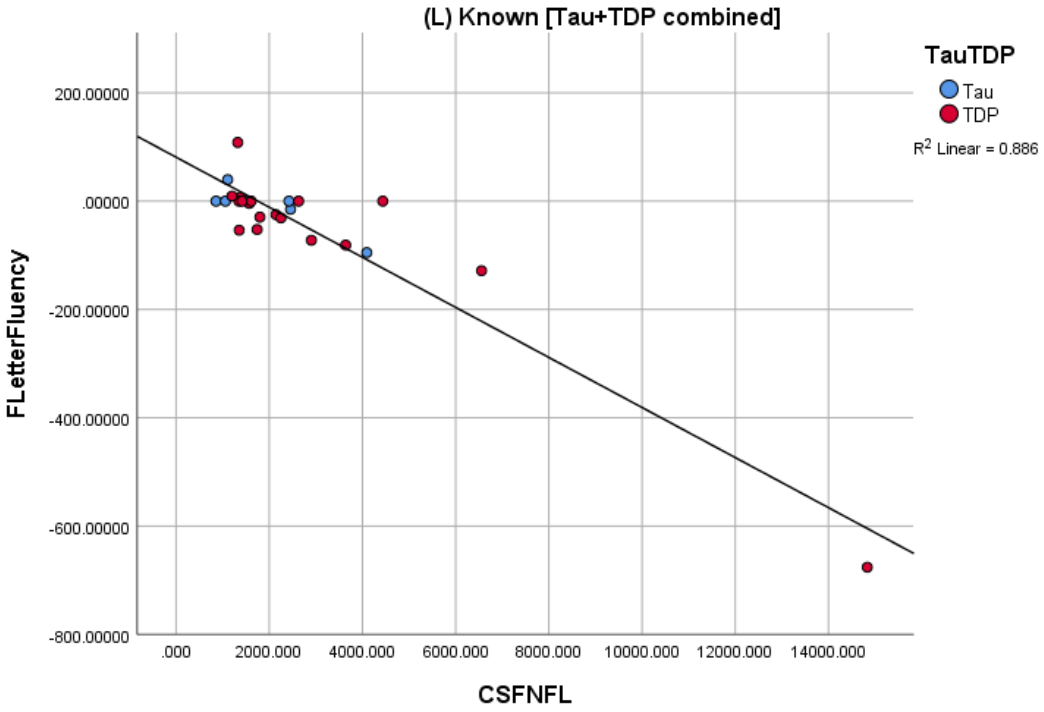
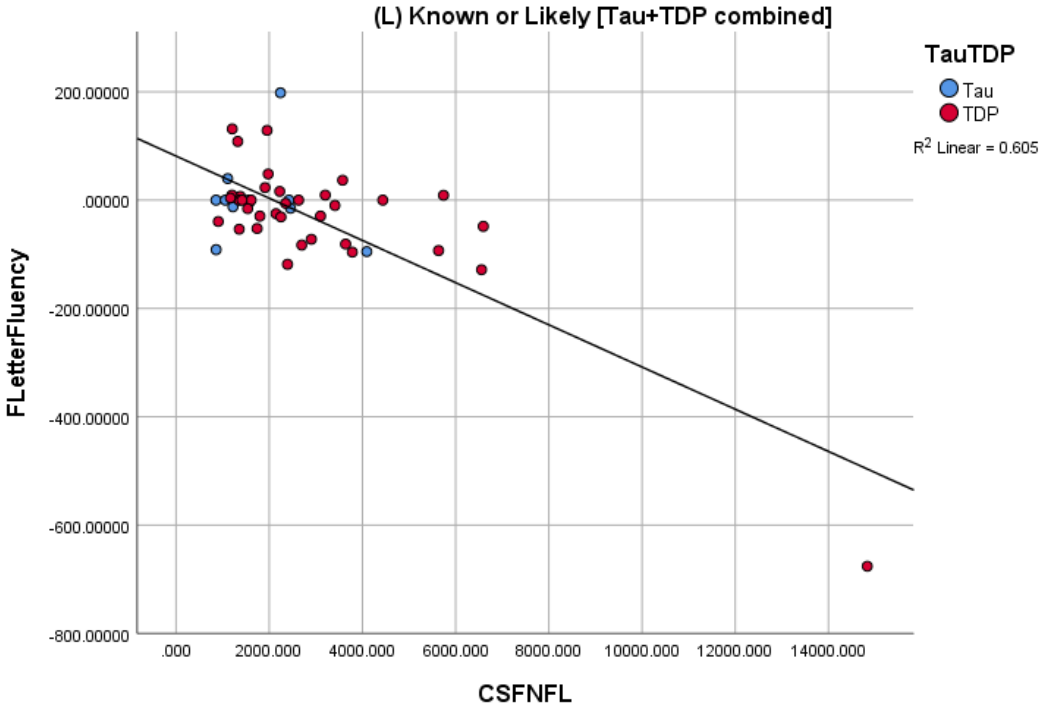
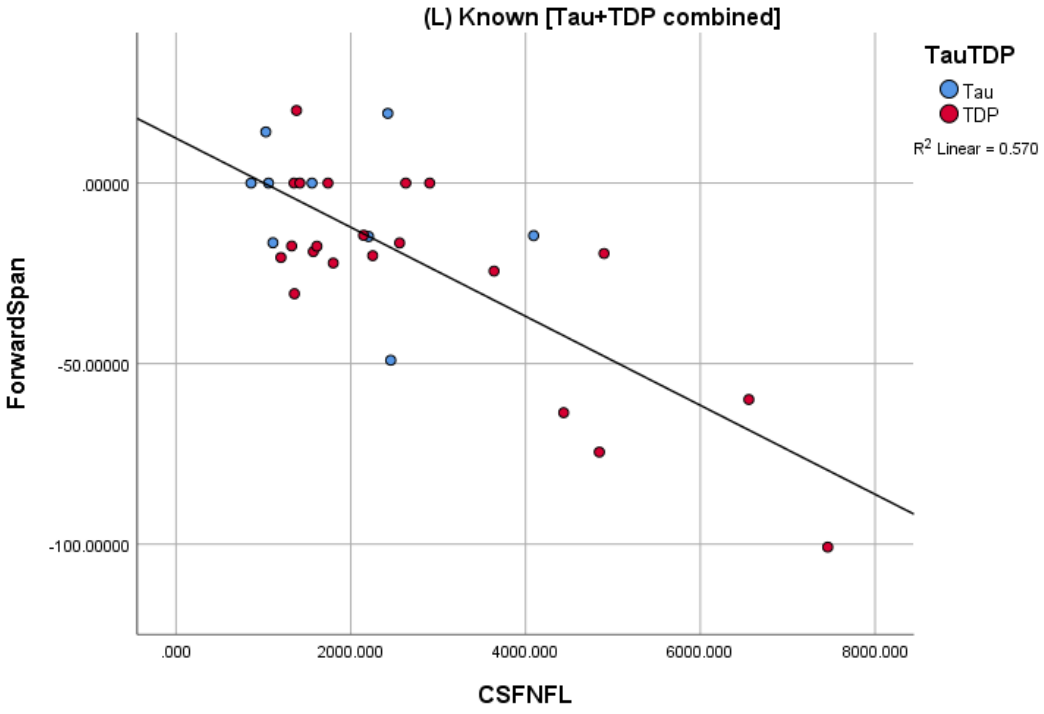
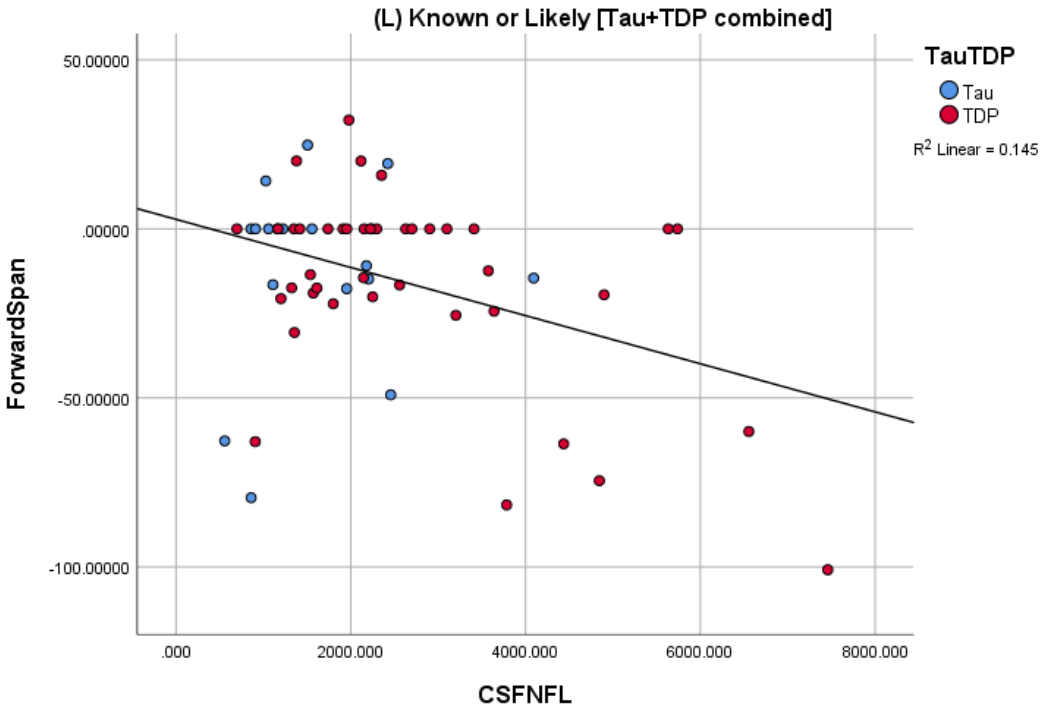
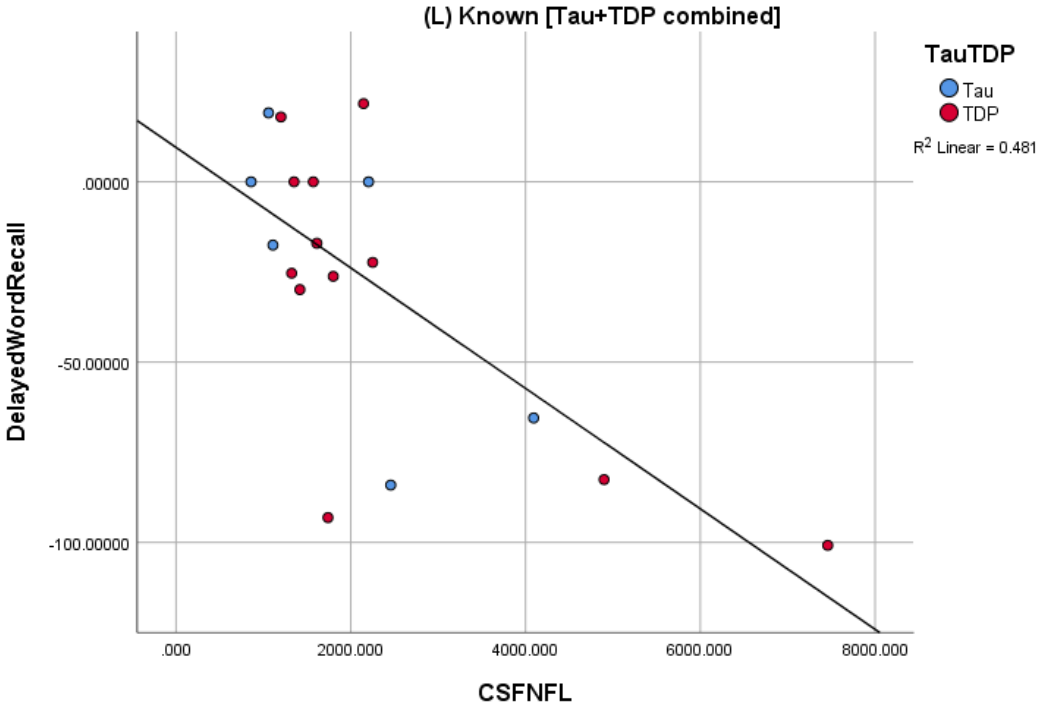
-60.00000
.000
2000.000
4000.000
6000.000
8000.000
CSFNFL

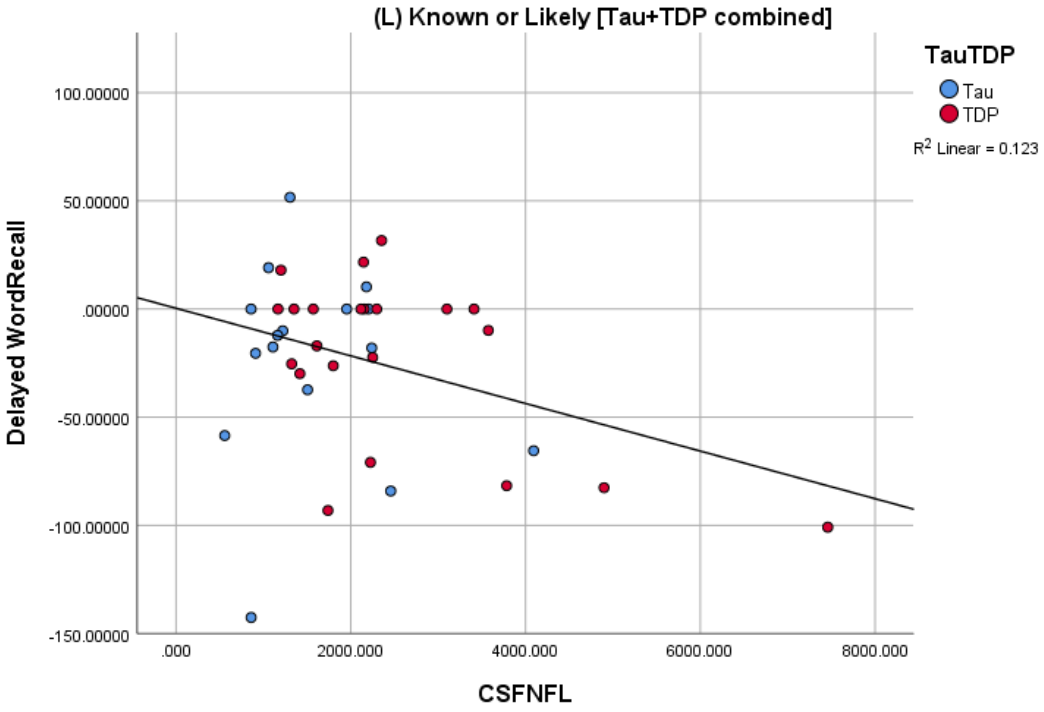

(L) Known [Tau+TDP combined]
TauTDP
Tau
TDP
R2 Linear = 0.886
FLetterFluency
200.00000
.00000
-200.00000
-400.00000
-600.00000
-800.00000
.000
2000.000
4000.000
6000.000
8000.000
10000.000
12000.000
14000.000
CSFNFL

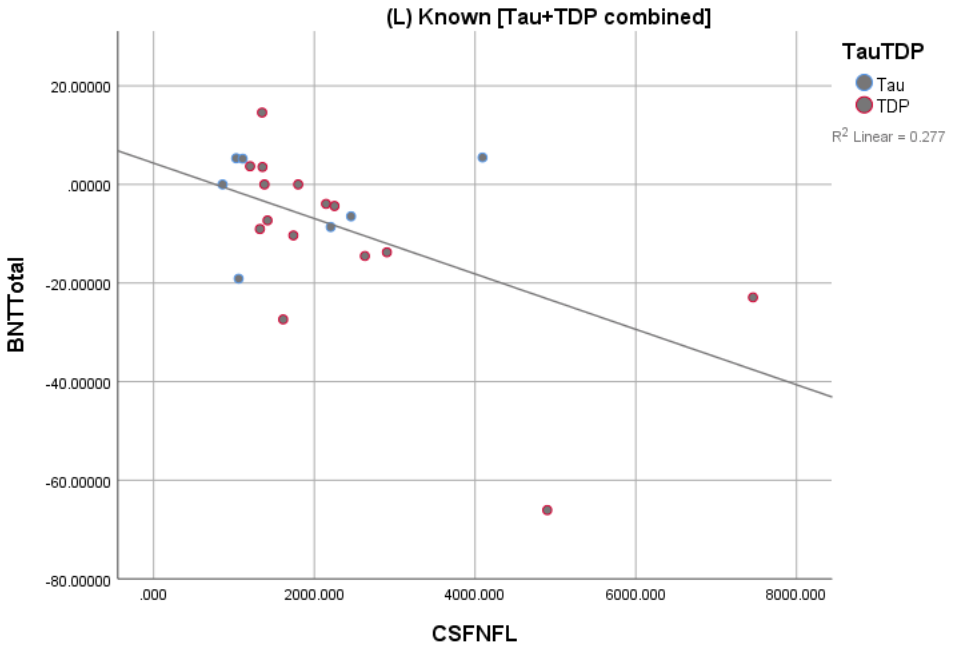

(L) Known or Likely [Tau+TDP combined]
TauTDP
Tau
TDP
R2 Linear = 0.605
FLetterFluency
200.00000
.00000
-200.00000
-400.00000
-600.00000
-800.00000
.000
2000.000
4000.000
6000.000
8000.000
10000.000
12000.000
14000.000
CSFNFL

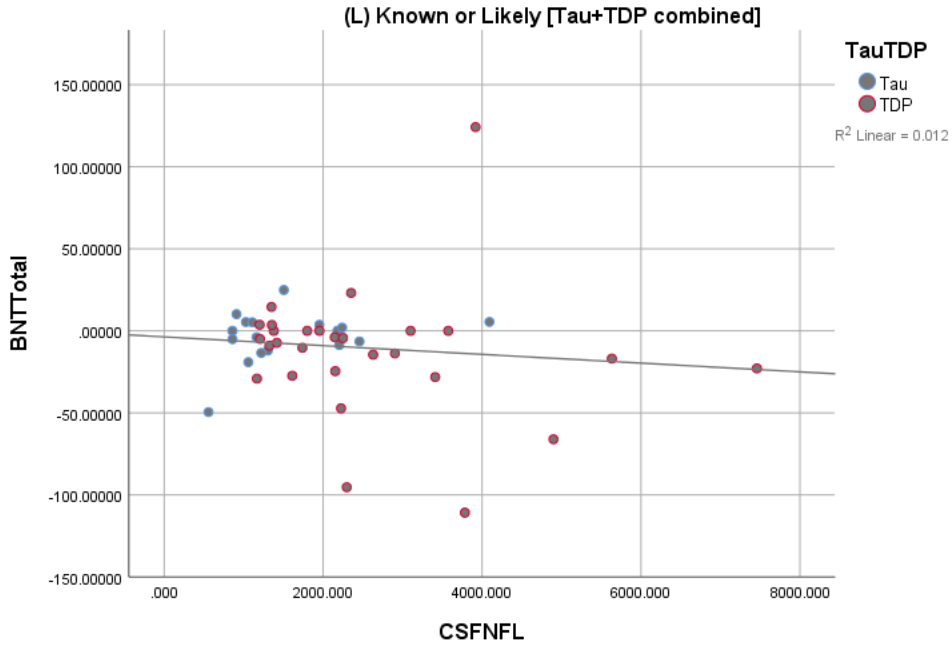

(L) Known [Tau+TDP combined]
TauTDP
Tau
TDP
R2 Linear = 0.570
ForwardSpan
.00000
-50.00000
-100.00000
.000
2000.000
4000.000
6000.000
8000.000
CSFNFL


(L) Known or Likely [Tau+TDP combined]
TauTDP
Tau
TDP
R2 Linear = 0.145
ForwardSpan
50.00000
.00000
-50.00000
-100.00000
.000
2000.000
4000.000
6000.000
8000.000
CSFNFL


(L) Known [Tau+TDP combined]
TauTDP
Tau
TDP
R2 Linear = 0.481
DelayedWordRecall
.00000
-50.00000
-100.00000
.000
2000.000
4000.000
6000.000
8000.000
CSFNFL


(L) Known or Likely [Tau+TDP combined]
TauTDP
Tau
TDP
R2 Linear = 0.123
Delayed WordRecall
100.00000
50.00000
.00000
-50.00000
-100.00000
-150.00000
.000
2000.000
4000.000
6000.000
8000.000
CSFNFL


(L) Known [Tau+TDP combined]
TauTDP
Tau
TDP
R2 Linear = 0.277
BNTTotal
20.00000
.00000
-20.00000
-40.00000
-60.00000
-80.00000
.000
2000.000
4000.000
6000.000
8000.000
CSFNFL


(L) Known or Likely [Tau+TDP combined]
TauTDP
Tau
TDP
R2 Linear = 0.012
BNTTotal
150.00000
100.00000
50.00000
.00000
-50.00000
-100.00000
-150.00000
.000
2000.000
4000.000
6000.000
8000.000
CSFNFL

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