Published in final edited form as:

J Clin Neurosci. 2013 December ; 20(12): . doi:10.1016/j.jocn.2013.01.024.

Neurocognitive speed associates with frontotemporal lobar degeneration TDP-43 subtypes

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Abstract

Frontotemporal lobar degeneration (FTLD) is pathologically heterogeneous with TAR DNA binding protein 43 kDa (TDP-43) proteinopathy the most common substrate. Previous work has identified atrophy patterns across TDP-43 subtypes with Type A showing greater frontotemporal and parietal atrophy, Type C predominantly anterior temporal, and Type B predominantly posterior frontal. Despite neuroanatomical correlates of involvement, neuropsychological findings have been inconsistent. The current study utilized broader neurocognitive domains based on aggregated neuropsychological measures to distinguish between subtypes. We hypothesized that patterns of neurocognitive domain impairments would predict FTLD–TDP-43 subtype. Fifty-one patients, aged 38–87, were identified post mortem with pathologically confirmed FTLD with TDP-43. Participants were classified into subtypes A, B, or C. Patients had completed neuropsychological assessments as part of their clinical evaluation. Six cognitive domains were created: Language; Cognitive Speed; Memory; Learning; Visuosperception; and Fluency. Binary logistic regression was conducted. All but three patients could be classified as FTLD–TDP Types A, B, or C: 26 as Type A; nine as Type B; and 13 as Type C. Cognitive Speed scores were associated with Types A and C ($p < 0.001$ and $p = 0.003$, respectively). Impaired performances on the Trail Making Test differentiated Types A and C. Worse Boston Naming Test and Logical Memory (Immediate) ($p < 0.05$) scores also increased the likelihood of Type C phenotype. Findings suggest Cognitive Speed associates with TDP-43 subtypes. Type C also demonstrated language-specific involvement. Differences between TDP-43 subtypes further supports the notion of differences in pathophysiology or topography across these types.

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Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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Keywords

Cognitive speed; Dementia; Frontotemporal lobar degeneration; Neuropathology; Neuropsychology; TDP-43

1. Introduction

Frontotemporal lobar degeneration (FTLD) is an umbrella term that encompasses a clinically and pathologically heterogeneous group of overlapping disorders. These disorders are characterized by varying degrees of behavioral, personality, and cognitive changes, as well as aphasia. While the most common form of dementia for those over the age of 65 is Alzheimer's disease, for those under 65, FTLD approaches comparable incidence rates^{1, 2}.

Neary et al. proposed clinical diagnostic criteria to differentiate three syndromes commonly associated with FTLD³. These included behavioral variant frontotemporal dementia (bvFTD), progressive non-fluent aphasia (PNFA), and semantic dementia (SD). Research has continued to evolve our understanding and clinical definition of these syndromes. We now consider possible, probable, and definite bvFTD categories,⁴ which has been shown to be more sensitive than the older criteria. Research has also demonstrated that PNFA is not a homogeneous group and that PNFA patients can be reclassified into three different groups: agrammatic primary progressive aphasia; logopenic primary progressive aphasia; and primary progressive apraxia of speech^{5, 6}.

Pathologic findings in FTLD have evolved over the past two decades. Originally patients with FTLD were divided into those without any identified inclusions (dementia lacking distinctive histology) and those in which inclusions could be identified with silver impregnation. With the advent of immunohistochemistry, the former group was shown to have inclusions that were identified with ubiquitin immunohistochemistry and the latter with tau immunohistochemistry. Hence, dementia lacking distinctive histology became FTLD–ubiquitin (FTLD–U) while the other group became FTLD–tau. More recent research has shed light on the pathological markers that identify and differentiate FTLD–U into two major protein categories: FTLD–TAR DNA binding protein 43 kDa (FTLD–TDP-43) and FTLD–fused in sarcoma (FTLD–FUS). Therefore, FTLD is now separated into FTLD–tau, FTLD–TDP-43 and FTLD–FUS.

Of these, FTLD–TDP is the most common substrate underlying the FTLD spectrum of disorders, and therefore an important entity for researchers to investigate. Further work on FTLD–TDP-43 identified different distributions and morphological features of the TDP-43 immunoreactive inclusions that lead to the identification of four subtypes of FTLD–TDP-43, Types A–D^{7, 8}. Within the general population, clinicopathologic studies have shown that the most common FTLD–TDP-43 subtype is FTLD–TDP-43 Type A, accounting for 41% of FTLD–TDP patients, followed by Type B (34%), and Type C (25%)^{1, 7, 9–11} (Fig. 1); Type D is extremely rare. It has been demonstrated that there are important clinicopathological associations between clinical syndromes and histological subtype^{7, 10} implying that pathologically subdividing FTLD–TDP-43 is important and not arbitrary. FTLD–TDP-43 Type A is associated most commonly with the bvFTD phenotype, as well as mutations associated with progranulin,¹⁰ Type B with C9ORF72 repeat expansions,¹² and Type C with SD.

One of the inherent challenges in the appropriate diagnoses of FTLD is that the relationship between clinical diagnosis, imaging features, and pathology is not well defined. However imaging studies have been completed and have identified distinct patterns of atrophy across TDP-43 subtypes with Type A showing greater atrophy to frontotemporal and parietal

regions, Type B evidencing posterior frontal changes, and Type C showing predominantly anterior temporal changes¹³. Thus far, studies investigating the neuropsychological profiles of FTLT have revealed modest but inconsistent findings. A review of the literature reveals a multitude of studies that fail to differentiate among the various pathologies that underlie FTLT. Studies investigating the neuropsychological performances reveal arbitrary clustering of neurocognitive domains such as language, executive functioning, and memory, or investigations of specific tests. This is somewhat limiting and potentially contributes to the copious inconsistencies that are reported, further confusing differentiation of the subtypes.

Therefore, the current study sought to investigate whether neurocognitive domains derived from previous factor analytic studies can differentiate pathologically confirmed FTLT–TDP-43 phenotypes utilizing neurocognitive domains. We hypothesized that neurocognitive domains and impairment levels would differentiate between FTLT–TDP-43 subtypes.

2. Methods

2.1 Participants

Fifty-one patients, with antemortem clinical and neuropsychological evaluations and post mortem pathologic diagnosis of FTLT–TDP-43 were identified from the neuropathology files of the Mayo Clinic, Rochester, MN, USA. Participants were classified into TDP-43 subtypes A, B, or C by a neuropathologist (D.W.D.) and neurologist (K.A.J.). All but three patients could be classified as FTLT–TDP-43 Types A, B, or C: 26 as Type A; nine as Type B; and 13 as Type C. Table 1 shows the demographic data for the 51 patients by subtype. Subjects with Type A ranged in age from 46 to 87 years; Type B ranged from 38 to 67; and Type C ranged from 53 to 78. Table 2 shows the associations between final clinical diagnoses and subtypes. Clinical diagnoses were based on the most current clinical criteria.

Data for this study were obtained from the first neuropsychological evaluation. The average disease duration from the time of first neuropsychological evaluation to the date of death was 6.5 years (standard deviation = 4.4 years). This study was approved by the Institutional Review Board at the Mayo Clinic.

2.2 Pathologic methods

All patients had neuropathological examinations according to the recommendations of the Consortium to Establish a Registry for Alzheimer's Disease^{14, 15}. This protocol was utilized based on standard neuropathological practices at the Mayo Clinic. Specifically, all patient samples underwent routine staining methods with hematoxylin and eosin, Bielschowsky silver, and immunohistochemistry to phosphorylated neurofilament, phospho-tau, -synuclein, -amyloid, and TDP-43, as previously described. All patients were diagnosed as FTLT–TDP-43 based on published criteria (i.e., TDP-43 and ubiquitin only immunoreactive inclusions).

2.2.1 FTLT-TDP subclassification—Sections of frontal and medial temporal lobe, including hippocampal dentate granule cells, were restained using a DAKO autostainer with TDP-43 (rabbit polyclonal; 1:3,000, Protein Tech Group, Chicago, IL, USA) and were reviewed by one neuropathologist (D.W.D.) who sub-classified each sample. The neuropathologist was blinded to clinical data. The harmonized classification scheme was chosen in this study to classify all samples¹⁶. Samples were classified as Type A if there were moderate to numerous TDP-43 immunoreactive neuronal cytoplasmic inclusion (NCI), as well as thin and short dystrophic neurites predominantly in layer II of neocortex and variable density of pleomorphic NCI in the dentate gyrus of the hippocampus; Type B if there were NCI in the neocortex and dentate granule cells of hippocampus with absent to

sparse dystrophic neurites; and Type C if there were a predominance of large and thick dystrophic neurites not restricted to any layer of the neocortex with absent, or at most sparse, NCI, and no intranuclear inclusions in the neocortex.

2.3 Neuropsychological measures

Neuropsychological measures were selected from the patient's larger diagnostic battery. Measures used in this study included the Perceptual Organizational Index from the Wechsler Adult Intelligence Scale (WAIS-R or WAIS-III)^{17, 18}, Logical Memory Immediate and Delayed and Visual Reproduction Immediate and Delayed from the Wechsler Memory Scale (WMS-R or WMS-III)^{19, 20}, Rey Auditory Verbal Learning Test²¹, Boston Naming Test (BNT)²², Token test²³, Trail Making Test A and B (TMT-a and TMT-b)²⁴, Stroop Color–Word test²⁵, Controlled Oral Word Association Test (COWAT)²³, and Category Fluency²⁴.

All measures were administered by experienced psychometrists and supervised by clinical neuropsychologists. Scores were converted into Mayo Older American Normative Study (MOANS) age-adjusted scaled scores^{26–30}. For the 13 subjects under the age cut-off for MOANS scores, the youngest normative age was applied (i.e. 56 years). Participants enrolled early in this study were administered the WAIS-R and WMS-R, whereas latter subjects received the WAIS-III and WMS-III. Participants who could not complete the TMT-a or TMT-b within the allotted time were given a score of 316 seconds to reflect a maximal score.

2.4 Data analysis

Six cognitive domain composite scores were developed by transforming raw, scaled, or standard scores into z-scores to allow for direct comparisons. The domains are as follows: Language; Cognitive Speed; Memory; Learning; Visual Perception; and Fluency^{31–33}. Separate binary logistic regression models were developed to differentiate between TPD-43 types within cognitive domains and level of impairment, defined as a z-score surpassing -1.5 . One way (two tailed) analysis of variance was conducted to compare types by individual tests.

3. Results

There was no statistically significant difference between education level or disease duration. Type A subjects were significantly older than Type B subjects with a mean difference of 11.86 years (standard deviation = 4.19; $p = 0.034$). Across all statistical analyses, the Cognitive Speed domain differentiated among types. For each standard deviation decrease (i.e., z-score greater than one standard deviation below the mean), the likelihood of being Type A significantly increased by 2.73 times. Conversely, for each standard deviation increase, the odds of being Type C increased by 8.95 times. Table 3 shows the means and standard deviations by Type for each of the six cognitive domains, as well as the tests that comprised each domain.

Driving the Cognitive Speed domain for Type A was TMT-a ($\text{Exp}(B) = 1.65$) and TMT-b ($\text{Exp}(B) = 1.65$). Type C was also driven by TMT-a ($\text{Exp}(B) = 1.98$) and TMT-b ($\text{Exp}(B) = 2.52$). The Stroop approached significance for Type C ($\text{Exp}(B) = 0.40$). The Cognitive Speed domain was the only domain to differentiate between types based on severity of impairment (Type A: $\text{Exp}(B) = 15.60$, Type C: $\text{Exp}(B) = 0.03$).

At the individual test level, there were significant differences in performances on the TMT-a ($F(2,35) = 4.37$, $p = 0.02$), TMT-b ($F(2,35) = 19.43$, $p < 0.001$), and Stroop tests ($F(2,35) = 7.22$, $p = 0.06$). As seen above with the binary logistic regression, Type A was significantly

slower than Type C on TMT-a ($p = 0.02$) and TMT-b ($p < 0.001$). Type B also was markedly slower when compared to Type C ($p = 0.01$). A similar pattern was observed for Stroop between Types A and C ($p < 0.001$). Interestingly, Type B was also markedly slower on Stroop compared to Type A ($p = 0.01$). BNT was significantly worse for Type C compared to both Types A and B ($p = 0.004$ and $p = 0.01$, respectively). Significance was approached for the Token test ($p = 0.06$) and COWAT ($p = 0.05$).

4. Discussion

The results of the current study suggest that FTLD–TDP-43 Types A and C are associated with differential patterns based on the neurocognitive domain of Cognitive Speed. Type A and Type C differ however on their level of impairment. As cognitive speed scores increase, the likelihood of being Type C significantly increases and impairment level decreases. Although cognitive speed is not localized to one area of the brain, it is believed to be mediated by frontal subcortical circuitry³⁴. However, the finding that Type C was differentiated based on better performance is consistent with the idea that the anterior temporal structures have limited influence on cognitive speed. These findings highlight and support a cognitive signature associated with SD.

Conversely, the likelihood of being Type A increases as cognitive speed declines. Even more striking was the finding that as impairment level surpassed -1.5 standard deviations, the chances of being Type A increased over 15 times. One possible contribution to poorer performances on cognitive speed measures may be related to the fact that some of the Type A subjects had an initial clinical diagnosis of corticobasal syndrome and hence had parkinsonian features. While this may have had some influence on psychomotor speed however, it is unlikely to sufficiently explain the results of this subtype. Type A subjects performed poorly across speed measures including the Stroop, which helps to distinguish between overall cognitive slowing *versus* motor slowing that one might attribute to parkinsonism. Another potential factor that could have accounted for poorer performance was white matter pathology. However to our knowledge there are no studies that have assessed white matter differences across TDP types and our study was not designed to assess for white matter pathology. Of note is the fact that one Type C patient, but no Type A or B patients, was diagnosed with Binswanger's disease, a disease with significant white matter pathology. Instead Type A patients are known to have bilateral frontotemporal and parietal atrophy;^{13, 35} the former can easily explain the neurocognitive findings. More specifically, in order to complete the cognitive speed tasks, recruitment of functions including attention, motor speed, visual scanning, inhibition of learned responses, and cognitive flexibility of set shifting are required. In a sample of asymmetric FTD patients, Boone et al.³⁶ found poorer performances on neuropsychological measures that they classified under "language processing", (the BNT and Stroop color and word reading), as well as "executive functioning" (verbal fluency). With the exception of BNT, these measures require cognitive speed for successful performance. Other studies have also shown executive deficits using the Stroop, TMT-a and TMT-b, Wisconsin Card Sorting, and verbal fluency tests³⁷. As these tasks all require frontal lobe function for their successful completion the findings all seem plausible.

Kipps et al. provided a review of the studies investigating clinical and neuropsychological features of bvFTD, PNFA, and SD³⁸. They were able to differentiate these three clinical presentations based on poorer performances on TMT-b, letter fluency, and verbal memory. Rohrer et al.³⁵ investigated neuropsychological and neuroanatomical patterns using clinical diagnoses as a proxy for TDP-43 subtype. Those with clinical diagnoses primarily of FTD with motor neurone disease, and hence somewhat representing the Type B group, had poorer performances on tasks of working memory including TMT-b and digit span backwards.

Although our Type B patients performed poorly on TMT-b and overall cognitive speed, this group failed to differentiate type based solely on their slowed performance.

Consistent with previous studies, our Type C patients performed poorly on the BNT^{35, 38}. This was expected given the neuroanatomical correlates of the anterior temporal lobe involvement in Type C patients^{13, 35} and the fact that the majority had SD. While it is to be expected that those classified as Type C would have low scores on the BNT, interestingly, participants classified as Type B also struggled on measures that had language components, albeit not on the BNT. One such measure was the Token test which unlike the BNT is a test of sentence comprehension. Studies have demonstrated that poor performance on tests of sentence comprehension is attributed to cortical involvement particularly of the frontal lobe^{39, 40}. Since frontal lobe atrophy occurs in Type B patients^{13, 35}, frontal lobe atrophy could explain the poor performance on the Token test in the Type B patients. However, Type A patients also have frontal lobe atrophy^{13, 35} and did not have a similar degree of impairment on these other measures with a language component. The explanation may therefore rest with the fact that frontal lobe involvement is symmetric in Type B patients and always affects the left hemisphere while Type A patients show asymmetric patterns of frontal lobe atrophy with some patients having right predominant patterns¹³.

Because our conceptualizations or ontologies of these rare conditions are slowly emerging, these findings may not have an immediate clinical impact. Research has highlighted thus far that cognitive speed is associated with differential neuropathology findings, clinical and functional manifestations, and presumably atrophy patterns. Yet, neuropathology can only be assessed post mortem while atrophy patterns can be observed antemortem on neuroimaging. Therefore, neurocognitive patterns and neuroanatomical findings support and lend credence to the importance of differentiating the subtypes of TDP-43 antemortem. As these subtypes are further clarified, emerging information suggests that there are different pathological substrate and differential profiles of functioning, which may have clinical relevance in the long run. As researchers and clinicians continue to learn about the spectrum of FTLT disorders, the goal would be for neurocognitive batteries to be tailored to highlight and draw out the differentials in these subtypes. By understanding TDP-43 pathology, a pathological cascade or pathways can be identified so that we may ultimately be in a better position to provide treatment. Our findings contribute to the notion of differentiation of FTLT–TDP-43 subtypes because neuroanatomical changes, pathological data, and neurocognitive testing appear to cohere. Future research investigating the association between cognitive slowing and white matter tract involvement could potentially contribute to more robust differentiation of these subtypes.

There are a few limitations to the current study. The sample size was relatively small which yielded large variability and may have decreased our power in determining differences. Secondly, the study was retrospective and neuropsychological evaluations were administered as part of the patient's clinical work up, therefore test batteries lacked uniformity, which contributed to some missing variables. Similarly, the normative data set that was selected may have yielded scaled scores that did not fully account for differences in subjects under the age of the norming sample cut off.

In conclusion, the literature by and large has investigated the relationship between antemortem clinical diagnoses of FTLT and neuropsychological test performance with varying results. Because clinical diagnoses may or may not partition well with pathological diagnoses, the current study evaluated those with pathologically confirmed FTLT–TDP-43. To our knowledge, no other studies have specifically evaluated cognitive domains established on the basis of factor analysis, let alone separating cognitive speed as its own domain apart from executive functioning. Our findings suggest that FTLT–TDP-43 subtypes

are associated with a cognitive signature that is associated with differential patterns of speeded information processing. As performance slows (i.e., beyond one and a half standard deviations below the mean) the likelihood of being Type A increases. Conversely, the chance of Type C classification increases as cognitive speed scores increase.

Acknowledgments

This research was supported by the National Institute of Health R01 AG037491 and P50 AG16574. The sponsor had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

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Fig. 1.

Diagram showing the clinical diagnoses and patterns of atrophy associated with the three frontotemporal lobar degeneration–TAR DNA binding protein 43 kDa subtypes.

AD = Alzheimer's disease, bvFTD = behavioral variant frontotemporal dementia, CBS = corticobasal syndrome, FTD–MND = frontotemporal dementia with motor neuron disease, PNFA = progressive nonfluent aphasia, SD = semantic dementia.

Table 1

Demographic information of patients with frontotemporal lobar degeneration by TDP-43 subtype.

	Type A n = 26	Type B n = 9	Type C n = 13
Age at evaluation	66.3 (12.30)	54.4 (10.48)	65.1 (7.52)
Education	13.8 (2.48)	13.9 (10.48)	12.7 (2.19)
Disease duration (years)	7.1 (4.57)	4.5 (4.87)	7.6 (2.42)
Handedness			
Right	92.9%	57.1%	85.7 %
Left	7.1%	42.9%	14.3%
Sex			
Male	38.5%	55.6%	38.5%
Female	61.5%	44.4%	61.5%

Data shown as mean (standard deviation) or percentage.

Table 2

Clinical and pathological diagnosis of frontotemporal lobar degeneration sample by TDP-43 subtype.

Type	PGRN	Clinical diagnosis	Pathological diagnosis
Type A	11 (negative) 9 (positive) 6 not screened	12 bvFTD 2 agPPA 4 CBS 1 FTDP 1 lvPPA 6 other [†]	21 FTLD-U 1 FTLD-U + AD 4 FTLD-MND
Type B	5 (negative) 4 not screened	5 FTD-MND 1 PSP 3 other [†]	1 FTLD-U 8 FTLD-MND
Type C	7 (negative) 6 not screened	10 SD 2 bvFTD 1 other [†]	12 FTLD-U 1 TDP + Binswanger's disease

agPPA = agrammatic variant of primary progressive aphasia, bvFTD = behavioral variant frontotemporal dementia, CBS = corticobasal syndrome, FTDP = frontotemporal dementia with parkinsonism, FTLD-MND = frontotemporal lobar degeneration with motor neuron disease, FTLD-U = frontotemporal lobar degeneration, ubiquitin, lvPPA = logopenic variant of primary progressive aphasia, PGRN = progranulin, PNFA = progressive nonfluent aphasia, PSP = progressive supranuclear palsy, SD = semantic dementia, TDP = TAR DNA binding protein 43.

[†] other = indeterminate, normal, or Alzheimer's disease presentation.

Table 3

Means and standard deviations for composite scores by frontotemporal lobar degeneration–TAR DNA binding protein 43 kDa subtype.

	Type A n = 26	Type B n = 9	Type C n = 13
Cognitive Speed composite	−3.28 (1.21)	−2.64 (1.23)	−0.79 (0.83)
TMT-a	−2.60 (1.79)	−2.33 (1.21)	−0.86 (1.08)
TMT-b	−4.36 (1.25)	−3.15 (1.97)	−1.00 (1.26)
Stroop	−1.75 (1.08)	−2.67 (0.58)	−0.10 (0.47)
Language composite	−1.32 (0.99)	−1.29 (1.39)	−1.06 (1.68)
BNT	−1.24 (1.42)	−0.99 (1.52)	−2.81 (0.31)
Token	−1.35 (1.05)	−3.00 (0.90)	−1.48 (1.16)
Fluency composite	−1.73 (1.34)	−2.50 (0.98)	−1.78 (0.99)
COWAT	−1.61 (1.34)	−2.45 (1.09)	−0.98 (1.29)
Category	−1.96 (1.33)	−2.48 (1.07)	−2.48 (1.05)
Memory composite	−0.90 (1.06)	−0.76 (0.89)	−0.97 (0.97)
AVLT % retention	−0.73 (1.46)	−1.20 (0.99)	−0.51 (1.02)
LM % retention	−0.27 (1.52)	−0.96 (1.25)	−0.94 (1.36)
VR % retention	−1.17 (1.36)	−0.89 (1.10)	−0.54 (1.39)
Perceptual Organizational composite	−1.06 (1.25)	−1.42 (0.66)	−0.57 (0.87)
Learning composite	−0.99 (1.08)	−1.03 (0.70)	−0.99 (1.05)
LMI	−1.45 (1.30)	−1.58 (1.00)	−2.36 (0.48)
AVLT learning coefficient	−0.63 (1.07)	−0.80 (0.80)	−0.51 (1.02)
VRI	−1.04 (1.59)	−0.88 (1.84)	−0.72 (1.81)

All composite and individual scores are represented as z-scores.

AVLT = Rey Auditory Verbal Learning Test, BNT = Boston Naming Test, COWAT = Controlled Oral Word Association Test, LM = Logical Memory, LMI = Logical Memory Immediate, TMT-a = Trail Making Test A, TMT-b = Trail Making Test B, VR = Visual Reproduction, VRI = Visual Reproduction Immediate.