Research Article

Determinants of confrontation naming deficits on the Boston Naming Test associated with transactive response DNA-binding protein 43 pathology

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Abstract

Objective: To determine whether poorer performance on the Boston Naming Test (BNT) in individuals with transactive response DNA-binding protein 43 pathology (TDP-43+) is due to greater loss of word knowledge compared to retrieval-based deficits. **Methods:** Retrospective clinical-pathologic study of 282 participants with Alzheimer's disease neuropathologic changes (ADNC) and known TDP-43 status. We evaluated item-level performance on the 60-item BNT for first and last available assessment. We fit cross-sectional negative binomial count models that assessed total number of incorrect items, number correct of responses with phonemic cue (reflecting retrieval difficulties), and number of "I don't know" (IDK) responses (suggestive of loss of word knowledge) at both assessments. Models included TDP-43 status and adjusted for sex, age, education, years from test to death, and ADNC severity. Models that evaluated the last assessment adjusted for number of prior BNT exposures. **Results:** 43% were TDP-43+. The TDP-43+ group had worse performance on BNT total score at first ($p = .01$) and last assessments ($p = .01$). At first assessment, TDP-43+ individuals had an estimated 29% (CI: 7%–56%) higher mean number of incorrect items after adjusting for covariates, and a 51% (CI: 15%–98%) higher number of IDK responses compared to TDP-43−. At last assessment, compared to TDP-43−, the TDP-43+ group on average missed 31% (CI: 6%–62%; $p = .01$) more items and had 33% more IDK responses (CI: 1% fewer to 78% more; $p = .06$). **Conclusions:** An important component of poorer performance on the BNT in participants who are TDP-43+ is having loss of word knowledge versus retrieval difficulties.

Keywords: TDP-43 proteinopathy; Alzheimer's disease; neuropsychology; confrontation naming; cognitive decline; Boston Naming Test; LATE-NC

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that is characterized by advancing cognitive impairment in the presence of two abnormal proteins: beta-amyloid (Aβ) and tau (Braak & Braak, 1991; Jack et al., 2018, 2016; Ismail et al., 2020; Latimer & Liachko, 2021; Montine et al., 2012). Aβ is deposited in extracellular plaques as diffuse or neuritic plaques while tau is deposited in neurofibrillary tangles (NFTs). Studies show that the topographic distribution of NFTs progresses in a stereotypical pattern described by the Braak staging scheme (Braak & Braak, 1991) with NFT deposition beginning in the medial temporal limbic areas before spreading to neocortical association areas and then later extending into the primary neocortex in the end-stages of disease (Braak & Braak, 1991; Ehrenberg et al., 2023). This staging scheme corresponds to brain atrophy and deficits in cognitive processes that are observed in typical AD (Braak & Braak, 1991; Whitwell et al., 2008). Aβ progression is described by the Thal phases showing Aβ deposition starting in the cortex and finally extending to the cerebellum (Thal et al., 2002). Even so, a considerable number of participants with AD neuropathologic changes (ADNC) remain clinically normal at the time of death (Davis et al., 1999). Interestingly, an additional protein known as transactive response DNA-binding protein ∼ 43kDa (TDP-43) is present in up to 75% of individuals with neuropathologically diagnosed AD and may

play a role in the neurodegeneration and cognitive impairments observed in AD (Amador-Ortiz et al., 2007; Josephs et al., 2008, 2014; Carlos et al., 2022). Some authors refer to the pathologic deposition of this protein in elderly patients as having Limbic Associated TDP-43 Encephalopathy Neuropathologic Change (LATE-NC) (Nelson et al., 2019).

In normal cells, TDP-43 is primarily present in the nucleus and is responsible for the regulation of RNA including transcription regulation and alternative splicing, in addition to the stabilization of mRNA (Jo et al., 2020; Josephs & Nelson, 2015; Buratti et al., 2004; Latimer & Liachko, 2021). Abnormal TDP-43, however, can become hyperphosphorylated, and ubiquitination of TDP-43 can occur (Jo et al., 2020; Buratti et al., 2004). This can then lead to loss of nuclear TDP-43 with concomitant cytoplasmic accumulation and aggregation of TDP-43, which may be the result of the pathological inclusions of TDP-43 observed in AD (Jo et al., 2020; Zhang et al., 2009, 2019; Hasegawa et al., 2008). Phosphorylated TDP-43 is a recognized agent of neurodegeneration both in individuals who display the presence of Aβ and tau on brain autopsy and in those who do not (Wilson et al., 2013; Nelson et al., 2010; Latimer & Liachko, 2021). TDP-43 is also associated with cognitive impairment (Josephs et al., 2014; Buciuc et al., 2021; Neumann et al., 2006; Nag et al., 2017; Wilson et al., 2013; Nelson et al., 2010; Latimer & Liachko, 2021).

Studies show that in participants with ADNC, the hippocampus has an increased vulnerability to the abnormal deposition of TDP-43 (Buciuc et al., 2020; Josephs et al., 2017). Accordingly, participants with TDP-43 have smaller hippocampal volumes at baseline and a faster rate of hippocampal atrophy overtime, both of which are independent of comorbid ADNC (Buciuc et al., 2021; Josephs et al., 2017; Latimer & Liachko, 2021). The hippocampus is integral for the encoding and recall of memories and also plays a substantial role in visual confrontation naming (van Strien et al., 2009; Sawrie et al., 2000; Squire, 2009). This could explain the more advanced memory and confrontation naming deficits observed in individuals who are TDP-43 positive (TDP-43+) compared to TDP negative (TDP-43-), regardless of ADNC (Buciuc et al., 2021; Josephs et al., 2008; Nag et al., 2017; Wilson et al., 2013; van Strien et al., 2009; Squire, 2009; Josephs et al., 2017).

The ability to recognize and name an object relies on the integrity of the ventral visual stream which supports the process of transforming a visual perception to a conceptual representation. The ventral visual stream begins in the occipital lobe and ends in the anterior temporal lobe, converging in the perirhinal cortex and lateral entorhinal area (Clarke et al., 2013; Dickerson & Eichenbaum, 2010; Jefferies et al., 2020). Loss of word knowledge is typically assessed by determining whether an individual can name a series of objects of varying difficulty level and is deemed present when an individual is unable to name an object when provided with cues. Conversely, naming difficulties can also stem from retrieval-based difficulties rather than loss of word knowledge. This can be differentiated from word-loss by determining whether an individual can name the object when provided with a semantic/ phonemic cue or recognition-type format.

Previous investigations have established that individuals with ADNC who have TDP-43 pathology perform more poorly on measures of confrontation naming, such as the Boston Naming Test (BNT), and have faster rates of decline on the BNT over time compared to individuals with ADNC who do not have TDP-43 pathology (Buciuc et al., 2021; Josephs et al., 2008, 2014). However, it is unknown if the confrontation naming deficits on the BNT in individuals with ADNC who are TDP-43+ is disproportionately

due to loss of word knowledge which can occur in a type of frontotemporal dementia known as semantic dementia (Neary et al., 1998) or a retrieval-based difficulty which is aided when provided with phonemic cuing and thus can provide some evidence as to whether a word is in the individual's lexicon (Kaplan et al., 2001).

The purpose of the current study was to investigate differences in performance on the 60-item BNT in participants with ADNC who are TDP-43+ compared to those who are TDP-43-. We aimed to determine whether the relationship between TDP-43 pathology and poorer performance on the BNT is due to a loss of knowledge about the object versus retrieval difficulties by examining responses to phonemic cues. We hypothesized that TDP-43+ participants would benefit less from phonemic cues during BNT administration, thus reflecting a loss of word knowledge.

Methods

Study design and participants

We conducted a retrospective clinical-pathologic study and evaluated 282 participants with ADNC and known TDP-43 status. All participants were enrolled in the Mayo Clinic Alzheimer's Disease Research Center, Mayo Clinic Study of Aging, or Alzheimer's Disease Patient Registry from the Mayo Clinic in Rochester, MN between January 1991 and July 2019. Participants were included in this study if they had completed the 60-item BNT at their first visit. We excluded participants meeting the clinical diagnostic criteria for frontotemporal dementia (Neary et al., 1998). Participants satisfying the pathological criteria for frontotemporal lobar degeneration with TDP-43 (FTLD-TDP) (Cairns et al., 2007) were also excluded. Item-level data from the BNT protocols were manually extracted by C.G.R. and entered into a Research Electronic Data Capture (REDCap) database.

Neuropsychological evaluations

Confrontation naming was assessed with the 60-item BNT (Kaplan et al., 1983). If the participant misidentified the picture, the psychometrist provided a semantic cue. If the participant could describe the item but couldn't name it or ran out of time, the psychometrist went directly to the phonemic cue. We recorded the number of correct responses without cues, number of correct responses following a stimulus cue, number of correct responses following a phonemic cue, and number of "I don't know" (IDK) responses. Keeping with standardized scoring methods, we considered an item correct (1 point) if a participant gave a spontaneous correct response or gave a correct response following a stimulus cue. The Mini-Mental Status Examination (MMSE) (Folstein et al., 1975) was used to assess general cognitive functioning and the Clinical Dementia Rating sum of boxes (CDR) (Morris, 1993) was used to evaluate functional performance.

Clinical evaluation

All participants were clinically evaluated by a behavioral neurologist. A consensus meeting with study coordinators, physicians, and neuropsychologists was held after a participant's visit to assign a diagnosis of cognitively unimpaired, mild cognitive impairment (MCI), or dementia. A diagnosis of MCI was made if the patient endorsed a cognitive complaint, maintained essentially normal activities of daily living, but had objectively abnormal scores (generally 1.5 standard deviations below the mean range) in 1 or more cognitive domains. A diagnosis of dementia was based on

the criteria in the *DSM-IV* (American Psychiatric Association, 1994). Participants also underwent apolipoprotein Epsilon (APOE) genotyping which was performed using TaqMan genotyping assays (Applied Biosystems, Foster City, CA).

Neuropathologic evaluation

All participants underwent brain autopsy according to standard neuropathologic examination by a board-certified neuropathologist according to the Consortium to Establish a Registry for Alzheimer's Disease (Mirra et al., 1991). Thioflavin S fluorescent microscopy was used to assign Braak NFT stage (0-VI) and a Thal Aβ neuritic plaque density score (0-5) according to the Consortium to Establish a Registry for Alzheimer's Disease (Braak & Braak, 1991; Thal et al., 2002; Mirra et al., 1991). For ADNC rating, participants were rated as high, intermediate, or low likelihoods according to recommendations from published criteria (Montine et al., 2012). Lewy body disease, which is another frequent co-pathology found in patients with ADNC, was also assessed following published guidelines (McKeith et al., 2017). Participants were screened for the presence of TDP-43 pathology in the amygdala by KAJ, MEM, and DWD and were classified as TDP-43+ if TDP-43 immunoreactive neuronal cytoplasmic inclusions, dystrophic neurites, neuronal intranuclear or NFT-associated inclusions were observed in the amygdala as previously described in detail (Josephs et al., 2014; Josephs et al., 2016; Buciuc et al., 2021). All TDP-43+ participants were also assessed for the presence of TDP-43 pathology in the hippocampus, including in the subiculum, Cornu Ammonis (CA) 1 and dentate fascia, and outside the hippocampus, including the entorhinal cortex, occipitotemporal cortex, insula cortex, basal nucleus of Meynert, inferior temporal cortex, medullary inferior olive, midbrain substantia nigra, midbrain tegmentum, basal ganglia, and middle frontal gyrus to determine the extent of distribution or staging (Josephs et al., 2014; Josephs et al., 2016).

Statistical analysis

Descriptive statistics, including median and inter-quartile range or counts (%), were computed for all demographic, clinical, and neuropathological variables. Statistical analyses were performed using R (version 4.1.2). Kruskal-Wallis rank sum tests were used to compare continuous variables, and Pearson's Chi-squared tests were used to compare categorical variables.

We evaluated factors associated with missed items on the BNT at baseline using cross-sectional negative binomial count models. We considered negative binomial models more appropriate than linear regression models because of the discreteness of the BNT scores, and we preferred negative binomial models to Poisson count models because the former relax the Poisson assumption that the variance of the response equals the mean; negative binomial models relax this assumption and thus account for overdispersion (Hilbe, 2011). The outcome in our first model was the total number of missed items on the BNT, and the primary predictor was TDP status. To account for potential confounding, we adjusted for sex, age at the time of the test, years of education, years from the test to death, and ADNC rating modeled as an ordinal variable with levels 0–3. We also fit the same model using the last assessment but further adjusted for the number of prior exposures to the BNT. We then evaluated the relationship between TDP-43 and the number of items named after a phonemic cue (model 2) and the number of items not named after a phonemic cue (i.e., IDK, model 3) using this same negative binomial

modeling approach using data from participants' first BNT and last BNT. Since there is a strong relationship between ADNC level and TDP, we performed a sensitivity analysis by fitting the models separately among participants who were at the highest level of ADNC versus not. In all our analyses we report effect sizes as relative means.

Results

Baseline demographics results

Baseline demographics data are summarized in Table 1. Of the 282 participants selected, 43% were TDP-43+ and 57.4% were TDP-43-. There were no significant differences in sex or education by TDP status at baseline. There was, however, a difference in *APOE e4* genotype between groups with 40.3% of the TDP-43+ group being *APOE e4* carriers compared to 28.4% of the TDP-43- group ($p = .04$). We also observed that among those with cognitive impairment, TDP-43+ participants had an older age at onset (median 77 years vs 70 years; $p = .01$). The TDP-43+ group also had a longer time to death from their baseline BNT assessment (8.3 years vs 6.1 years; $p < .001$) compared to TDP-43- participants and a corresponding older age at death (91 years vs 88 years; $p = 0.01$).

Baseline clinical results

Clinical data at baseline is displayed in Table 2. At the first assessment, there was no difference in the MMSE though the TDP-43+ group had a significantly higher CDR sum of boxes ($p = .003$) and a much higher fraction of individuals with dementia (48% vs 22%; $p < 0.001$). Median BNT total scores were lower in the TDP-43+ group (52 vs 54; $p = 0.01$) as were the correct without cue scores (51 vs 53; $p = 0.02$).

Neuropathological results

Neuropathological results are shown in Table 3. The TDP-43+ group had higher ADNC ratings ($p = .001$) which was driven by higher median Braak NFT stage and higher Thal Aβ neuritic plaque density score in the TDP-43+ group compared to the TDP-43- group. These differences translated into significant differences with respect to the TDP-43+ group in which 41% of participants were rated as high ADNC, 33% as intermediate ADNC, and 12% as low ADNC. In contrast, in the TDP-43- group, 16% of participants were rated as high ADNC, 38% as intermediate ADNC, and 23% as low ADNC.

Negative binomial count models of the total number of BNT errors

Negative binomial count models based on the participants' first assessment are summarized in Figure 1. At first BNT assessment, we found that TDP-43+ participants had a 29% (95% CI, 7%–56%) higher mean number of incorrect items, after accounting for covariates, compared to TDP-43- participants ($p = 0.01$) (Fig. 1a). We also observed a sex effect, with female participants having an estimated 28% higher mean number of incorrect items ($p = 0.01$) at baseline BNT than males. Additionally, higher education was independently associated with fewer incorrect items with an additional year of education associated with 9% fewer incorrect items on average ($p < 0.001$). The TDP-43+ and TDP-43- groups had comparable levels of education with the median years of education in both groups being 14 years. Higher ADNC stage was

Table 1. Demographics

	Negative (*N* = 162)	Positive (*N* = 120)	*p*-value
Female sex	77 (48%)	70 (58%)	0.07
Positive *APOE* e4	46 (28%)	48 (40%)	0.04
Education (years)	14 (12, 16)	14 (12, 16)	0.14
Age at baseline BNT assessment (years)	82 (76, 85)	81 (77, 85)	0.62
Age at onset*	70 (64, 78)	77 (72, 83)	0.01
Time from baseline BNT to death (years)	6.1 (3.7, 8.6)	8.3 (5.0, 12.9)	<0.001
Age at death (years)	88 (83, 93)	91 (87, 94)	0.01
Follow-up data	126 (78%)	97 (81%)	
Time from baseline BNT to death	1 visit (n = 59)	Follow-up visit (n = 223)	
	4.0 (1.3, 6.3)	7.2 (5.1, 12.2)	<0.001

APOE = apolipoprotein; BNT = Boston Naming Test.
Data are shown as number (%) for categorical variables or median (IQR) for continuous variables. P-values are from a Kruskal-Wallis rank sum test or Pearson's Chi-squared test.
* Among those who had cognitive impairment.

Table 2. Clinical results at baseline

	Negative (*N* = 162)	Positive (*N* = 120)	*p*-value
Mini Mental State Exam	28 (26, 28)	27 (25, 28)	0.18
Clinical Dementia Rating sum of boxes score	0.0 (0.0, 0.5)	0.5 (0.0, 1.5)	0.003
Boston Naming Test total score	54 (49, 57)	52 (44, 56)	0.01
Correct without cue score	53 (49, 56)	51 (43, 56)	0.02
Number of correct responses following stimulus cue	0 (0, 1)	0 (0, 1)	0.55
Number of correct responses following a phonemic cue	4 (2, 6)	5 (3, 7)	0.02
Number of "I don't know" responses	2 (1, 5)	3 (1, 7)	0.09
Clinical diagnosis			<0.001
Normal	82 (51%)	31 (26%)	
Mild cognitive impairment	44 (27%)	31 (26%)	
Dementia	36 (22%)	58 (48%)	

Table 3. Neuropathological results

	Negative (*N* = 162)	Positive (*N* = 120)	*p*-value
Braak stage	3 (2, 5)	5 (3, 6)	<0.001
Thal stage	2 (1, 3)	3 (2, 4)	<0.001
Lewy body disease stage			0.62
None	114 (70%)	78 (65%)	
Limbic or amygdala predominant	21 (13%)	16 (13%)	
Neocortical	14 (9%)	18 (15%)	
Brainstem predominant	6 (4%)	4 (3%)	
Region unspecified or found in the olfactory bulb	1 (1%)	0 (0%)	
Unknown	6 (4%)	4 (3%)	
ADNC			<0.001
None	38 (23%)	17 (14%)	
Low	37 (23%)	14 (12%)	
Intermediate	57 (38%)	40 (33%)	
High	26 (16%)	49 (41%)	

ADNC = Alzheimer's Disease Neuropathologic Changes.
*Data are shown median (IQR) for Braak and Thal stages and N (%) for other variables. P-values are from a Kruskal-Wallis rank sum test or Pearson's Chi-squared test.
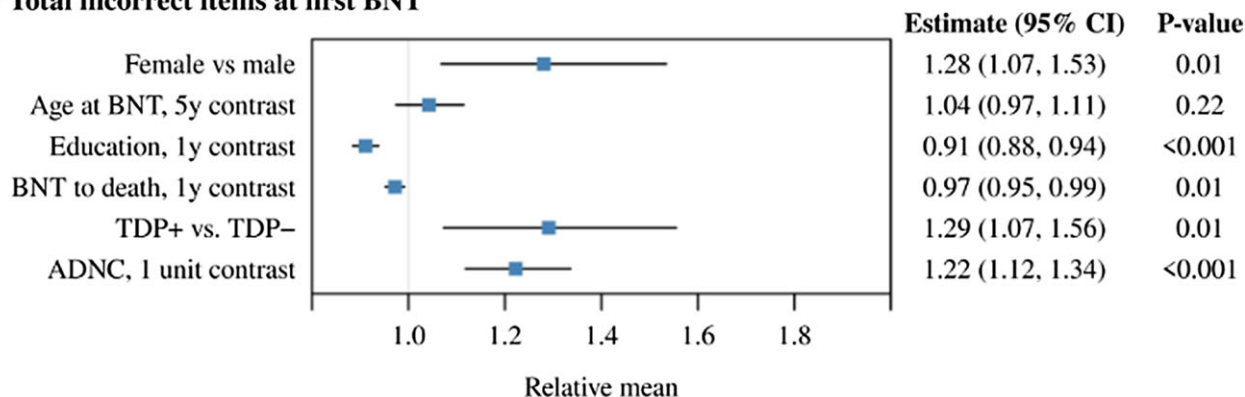
independently associated with a greater number of incorrect items with each additional ADNC stage associated with 22% more incorrect items (95% CI 12%–34%; $p < .001$). Individuals who lived longer after their baseline assessment tended to have fewer incorrect items at their baseline test ($p = 0.01$) after accounting for covariates.

The number of items correctly named only after a phonemic cue was an estimated 14% higher in TDP-43+ participants, a modest association that was not statistically significant (95% CI 5% lower to 37% higher; $p = 0.15$) (Fig. 1b). Factors significantly associated with this endpoint included female sex ($p = 0.003$),

education ($p = 0.001$), years from baseline to death ($p = 0.04$) and ADNC ($p < 0.001$). The mean number of items not named correctly after a phonemic cue (i.e., IDK response) was an estimated 51% higher for TDP-43+ participants (95% CI, 15%–98%; $p = 0.002$) (Fig. 1c). The mean number of IDK responses were an estimated 27% higher in women ($p = 0.07$) and an additional level of ADNC stage was associated with an estimated 29% more IDK responses ($p < 0.001$).

At the last assessment (Fig. 2), we similarly observed that TDP-43+ participants had a 31% (95% CI 6%–62%) increase in the mean number of incorrect items after accounting for covariates,

(A) Total incorrect items at first BNT

	Estimate (95% CI)	P-value
Female vs male	1.28 (1.07, 1.53)	0.01
Age at BNT, 5y contrast	1.04 (0.97, 1.11)	0.22
Education, 1y contrast	0.91 (0.88, 0.94)	<0.001
BNT to death, 1y contrast	0.97 (0.95, 0.99)	0.01
TDP+ vs. TDP−	1.29 (1.07, 1.56)	0.01
ADNC, 1 unit contrast	1.22 (1.12, 1.34)	<0.001

(B) Items named after a phonemic cue at first BNT

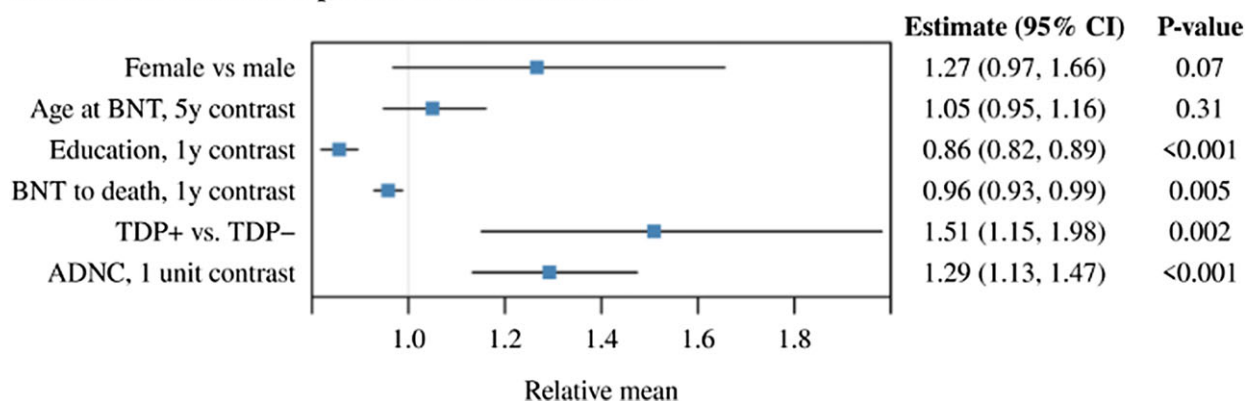|	Estimate (95% CI)	P-value
Female vs male	1.31 (1.10, 1.57)	0.003
Age at BNT, 5y contrast	1.04 (0.97, 1.11)	0.29
Education, 1y contrast	0.95 (0.93, 0.98)	0.001
BNT to death, 1y contrast	0.98 (0.96, 1.00)	0.04
TDP+ vs. TDP−	1.14 (0.95, 1.37)	0.15
ADNC, 1 unit contrast	1.18 (1.08, 1.29)	<0.001

(C) Items not named after a phonemic cue at first BNT

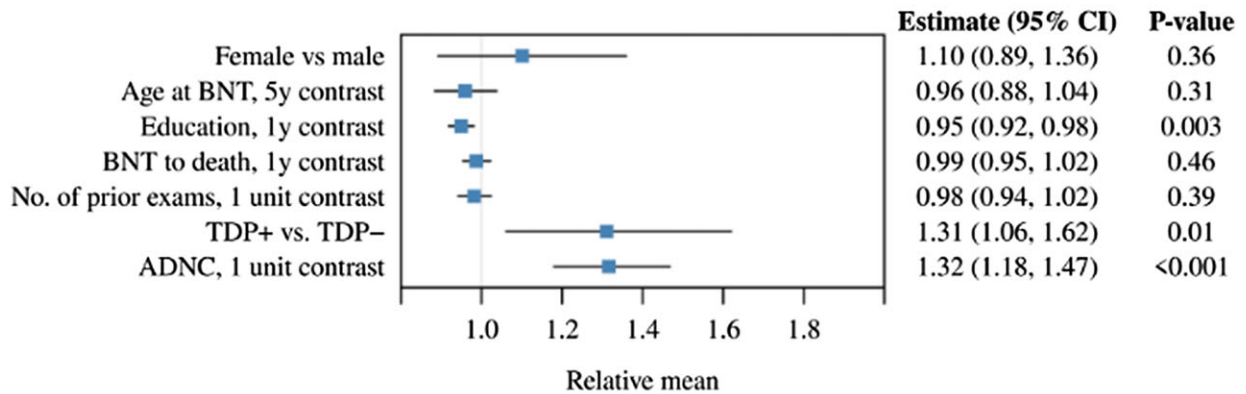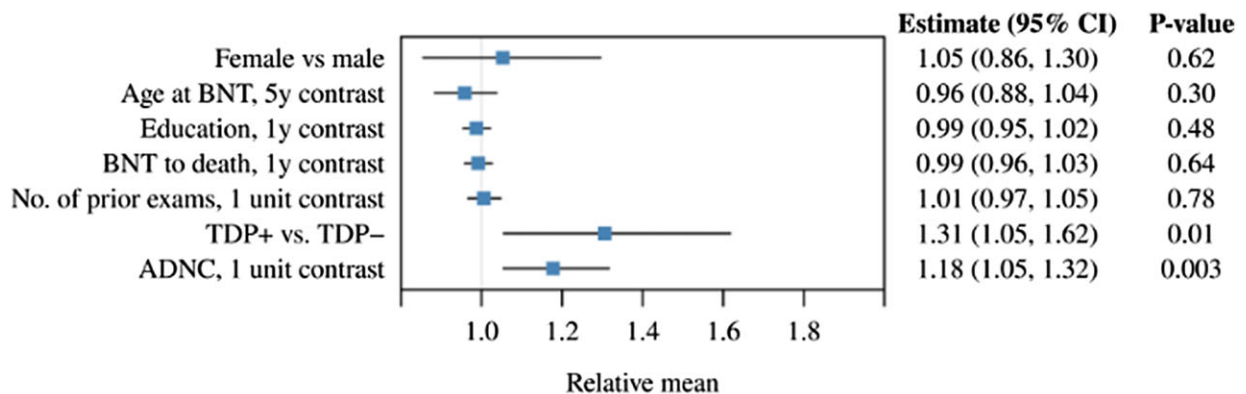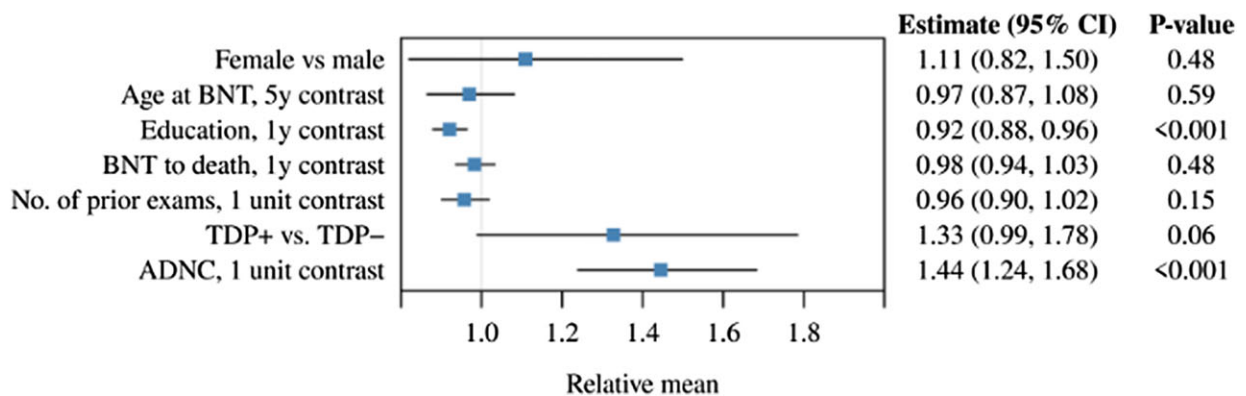|	Estimate (95% CI)	P-value
Female vs male	1.27 (0.97, 1.66)	0.07
Age at BNT, 5y contrast	1.05 (0.95, 1.16)	0.31
Education, 1y contrast	0.86 (0.82, 0.89)	<0.001
BNT to death, 1y contrast	0.96 (0.93, 0.99)	0.005
TDP+ vs. TDP−	1.51 (1.15, 1.98)	0.002
ADNC, 1 unit contrast	1.29 (1.13, 1.47)	<0.001

Figure 1. Negative binomial count models at first assessment. BNT = Boston Naming Test, TAR DNA binding protein 43 (TDP-43), ADNC = Alzheimer's disease neuropathologic changes.

compared to those who were TDP-43- ($p = 0.01$) (Fig. 2a). The previously observed sex effect was attenuated at last BNT assessment (10% difference; $p = 0.36$) while higher education was associated with fewer total incorrect items at last assessment ($p = 0.003$). An additional ADNC level was independently associated with an estimated 32% more incorrect items on the BNT ($p < 0.001$) at last assessment. The TDP-43 effect at last assessment was similar for the number of items correctly identified after a phonemic cue (31%, 95% CI 5%–62%; $p = 0.01$) (Fig. 2b)

and the number of IDK responses (33%, 95% CI 1% smaller to 78% greater, $p = 0.06$) (Fig. 2c). One-unit higher ADNC was also associated with both these endpoints at last BNT (18% [$p = 0.003$] and 44% [$p < 0.001$]).

Sensitivity analysis based on stratifying according to ADNC

As shown in Table 3, TDP-43+ participants were more than twice as likely to be at the highest ADNC level compared to TDP-43-

(A) Total incorrect items at last BNT

	Estimate (95% CI)	P-value
Female vs male	1.10 (0.89, 1.36)	0.36
Age at BNT, 5y contrast	0.96 (0.88, 1.04)	0.31
Education, 1y contrast	0.95 (0.92, 0.98)	0.003
BNT to death, 1y contrast	0.99 (0.95, 1.02)	0.46
No. of prior exams, 1 unit contrast	0.98 (0.94, 1.02)	0.39
TDP+ vs. TDP−	1.31 (1.06, 1.62)	0.01
ADNC, 1 unit contrast	1.32 (1.18, 1.47)	<0.001

(B) Items named after a phonemic cue at last BNT

	Estimate (95% CI)	P-value
Female vs male	1.05 (0.86, 1.30)	0.62
Age at BNT, 5y contrast	0.96 (0.88, 1.04)	0.30
Education, 1y contrast	0.99 (0.95, 1.02)	0.48
BNT to death, 1y contrast	0.99 (0.96, 1.03)	0.64
No. of prior exams, 1 unit contrast	1.01 (0.97, 1.05)	0.78
TDP+ vs. TDP−	1.31 (1.05, 1.62)	0.01
ADNC, 1 unit contrast	1.18 (1.05, 1.32)	0.003

(C) Items not named after a phonemic cue at last BNT

	Estimate (95% CI)	P-value
Female vs male	1.11 (0.82, 1.50)	0.48
Age at BNT, 5y contrast	0.97 (0.87, 1.08)	0.59
Education, 1y contrast	0.92 (0.88, 0.96)	<0.001
BNT to death, 1y contrast	0.98 (0.94, 1.03)	0.48
No. of prior exams, 1 unit contrast	0.96 (0.90, 1.02)	0.15
TDP+ vs. TDP−	1.33 (0.99, 1.78)	0.06
ADNC, 1 unit contrast	1.44 (1.24, 1.68)	<0.001

Figure 2. Negative binomial count models at last assessment. BNT = Boston Naming Test, TAR DNA binding protein 43 (TDP-43), "I don't know" (IDK), ADNC = Alzheimer's disease neuropathologic changes.

participants (41% vs 16%). In our sensitivity analysis stratifying on high ADNC status, we did not find clear evidence that the effect of TDP-43 on number of incorrect items was different for those with high versus low ADNC ($p = 0.28$); however, the estimates did show some variation. Specifically, TDP-43+ participants with the highest level of ADNC ($n = 75$, 27%) tended to have only somewhat more (12%) incorrect items on the BNT ($p = 0.50$) whereas TDP-43+ participants with lower levels of ADNC ($n = 207$; 73%) had an estimated 40% more incorrect items ($p = 0.003$).

Discussion

In this retrospective clinical-pathologic study of 282 autopsied participants with ADNC and known TDP-43 status, we found that TDP-43 was significantly associated with a greater number of incorrect items on the BNT and specifically an increased number of IDK responses. Thus, individuals at baseline who were TDP-43+ were less likely to benefit from phonemic cues, demonstrating that an important component of the relationship between TDP-43

and poorer performance on the BNT is due to an increase in loss of word knowledge. This finding remained after adjusting for sex, age at the time of BNT test, years of education, years from BNT test to death, and ADNC rating suggesting that the differences between groups are related to TDP-43 pathology rather than demographics, disease duration, or ADNC pathology. While our sensitivity analysis found some evidence that the effect of TDP-43 on BNT was attenuated in participants with the highest level of ADNC compared to the participants with lower levels of ADNC, the estimates in the two subgroups were not significantly different. Taken as a whole, our findings suggest TDP-43 is an independent neuropathological component affecting BNT performance in general, and word knowledge specifically.

Our finding that the TDP-43+ group demonstrated poorer performance on the BNT, both at the first and last assessment compared to the TDP-43- group, is in keeping with a previous study from our group (Buciuc et al., 2021) and others (Wilson et al., 2013). The results of the present study add to our understanding of the effect of TDP-43 on BNT performance in two important ways. Firstly, we found an association between TDP-43 status and the total number of incorrect items at the first and last assessments. Participants who were TDP-43+ had about 30% more incorrect items at their first and last assessments compared to participants who were TDP-43-. Secondly, we found that in response to phonemic cues at the first assessment, TDP-43+ participants were about 50% more likely to say IDK rather than name the object. This provides support that the presence of TDP-43 in the brain is particularly associated with loss of word knowledge. We also found an association with TDP-43 positivity and a higher frequency of dementia, which has also been previously reported (Josephs et al., 2008, 2014; Carlos et al., 2022; Wilson et al., 2013; Robinson et al., 2011).

There was a significant effect of sex across models with females having an estimated 28% higher mean number of incorrect items than males at the first assessment. Previous investigations have also reported sex effects with males scoring higher than women across various diagnostic groups and normal controls (Karstens et al., 2023; Randolph et al., 1999; Zec et al., 2007). This sex effect appears to be due to sex differences on specific test items, with some items being more easily recognized and named by men (Randolph et al., 1999).

While individuals in the TDP-43+ group were more likely to have dementia at their last clinical assessment, our models did not adjust for cognitive status because to do so would introduce a circularity since performance on the BNT is one of the items that informs the clinical diagnosis of CU, MCI, or dementia. Further, we do not consider cognitive status to be a potential confounder. (We note that while a confounder will be associated with both the exposure and disease, this is not a sufficient condition since a confounder must not be affected by the exposure or disease [Rothman et al., 2008]). Still, we recognize that our results are suggestive of but do not establish that TDP-43+ has a causal effect on BNT performance.

Strengths and limitations

This study has many strengths including a large cohort with available pathology data for all participants in addition to item-level data for the 60-item BNT. Moreover, rather than solely examining differences in BNT total scores between TDP-43+ and TDP-43- participants, we took it a step further and examined response types following a phonemic cue which provides additional information that is not included in the total score. There

were also limitations including some participants only having a baseline BNT assessment available. We also acknowledge that participants saying "I don't know" is admittedly an ambiguous response and other behavioral phenomenon associated with cognitive impairment may contribute to this other than loss of object knowledge. For example, participants may be reluctant to provide a response to a phonemic cue for fear of making an error or confusion about the task. Finally, we acknowledge that our cohort was well educated and predominantly White.

Conclusions

The present study provides evidence that TDP-43 pathology co-existing with ADNC and referred to as LATE-NC may result in loss of word knowledge and impact performance on the BNT. This finding provides new information on the clinical phenotype of individuals with ADNC and TDP-43. Further, this study suggests that evaluating qualitative responses to phonemic cues on the BNT may be clinically relevant given that TDP-43 positive individuals were less likely to benefit from phonemic cues.

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Data availability statement. Anonymized data are available from the corresponding author upon request from any qualified investigator for purposes of replicating procedures and results.

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