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Exploring Abstract Semantic Associations in the Frontotemporal Dementia Spectrum in a Dutch Population

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Abstract

Objective: To investigate the differential ability of the "Test Relaties Abstracte Concepten" (TRACE), a Dutch test for abstract semantic knowledge, in frontotemporal dementia (FTD).
Methods: The TRACE was administered in patients with behavioral variant FTD (bvFTD; $n = 16$), nonfluent variant (nfvPPA; $n = 10$), logopenic variant (lvPPA; $n = 10$), and semantic variant primary progressive aphasia (svPPA; $n = 9$), and controls ($n = 59$). We examined group differences, performed correlational analyses with other neuropsychological tests and investigated discriminative ability. We compared the TRACE with a semantic association test for concrete stimuli (SAT).
Results: All patient groups, except nfvPPA, performed worse on the TRACE than controls ($p < .01$). svPPA patients performed worse than the other patient groups ($p < .05$). The TRACE discriminated well between patient groups, except nfvPPA, versus controls (all $p < .01$) and between svPPA versus other patient groups with high sensitivity (75–100%) and specificity (86%–92%). In bvFTD and nfvPPA the TRACE correlated with language tests ($\rho > 0.6$), whereas in svPPA the concrete task correlated ($\rho \geq 0.75$) with language tests. Patients with bvFTD, nfvPPA and lvPPA performed lower on the TRACE than the SAT ($p < .05$), whereas patients with svPPA were equally impaired on both tasks ($p = .2$).
Discussion: We demonstrated impaired abstract semantic knowledge in patients with bvFTD, lvPPA, and svPPA, but not nfvPPA, with svPPA patients performing worse than the other subtypes. The TRACE was a good classifier between each patient group versus controls and between svPPA versus other patient groups. This highlights the value of incorporating semantic tests with abstract stimuli into standard neuropsychological assessment for early differential diagnosis of FTD subtypes.

Keywords: Frontotemporal dementia; Aphasia; Language and language disorders; Assessment; Dementia; Learning and memory

Introduction

Semantic memory refers to a long-term memory system for the storage of lexical, concept and object knowledge, that is essential for the ability to generalize information (Cousins & Grossman, 2017). Degradation of semantic memory can have devastating effects on daily living, as is apparent in patients with temporal lobe degeneration, most notably in patients with subtypes of frontotemporal dementia (FTD) (Cousins, Ash, Irwin, & Grossman, 2017). FTD constitutes a spectrum of

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clinically and pathologically heterogeneous diseases, with patients typically presenting with primarily behavioral and executive functioning impairments (behavioral variant FTD (bvFTD)) or language impairments (primary progressive aphasia (PPA)) (Gorno-Tempini et al., 2011; Lashley, Rohrer, Mead, & Revesz, 2015; Rascovsky et al., 2011; Seelaar, Rohrer, Pijnenburg, Fox, & Van Swieten, 2011). Three subtypes of PPA are distinguished: semantic variant PPA (svPPA), nonfluent variant PPA (nfvPPA) and logopenic variant PPA (lvPPA) (Gorno-Tempini et al., 2011), with the latter also manifesting as a result of Alzheimer's disease (AD) pathology (Giannini et al., 2017). Degradation of semantic memory is the main deficit in svPPA (Gorno-Tempini et al., 2004; Gorno-Tempini et al., 2011; Grossman, 2018; Hodges & Patterson, 2007; Marshall et al., 2018; Patterson, Nestor, & Rogers, 2007), but can occur in other clinical FTD subtypes as well. For example, semantic deficits are often seen in patients with bvFTD and can be present in combination with other core symptoms of nfvPPA, lvPPA, or mixed subtypes of PPA (Cousins & Grossman, 2017; Heim, McMillan, Olm, & Grossman, 2020; Liu et al., 2004; Marczinski, Davidson, & Kertesz, 2004; Marshall et al., 2018; Rohrer & Warren, 2010; Rosen et al., 2006; Seeley et al., 2005; Utianski et al., 2019). This clinical overlap complicates the differential diagnosis in these patient populations, and together with the subtlety of symptoms in the early stages of the disease misdiagnosis and/or diagnostic delay may occur. Yet, early diagnosis is crucial for proper patient management and early treatment planning.

Standard diagnostic neuropsychological evaluation in FTD syndromes often includes semantic memory tests that focus on concrete stimuli, such as the Pyramid and Palm Trees test (Howard & Patterson, 1992). Concrete nouns refer to entities that are tangible, exist in the real world and can be experienced through our senses, e.g., "umbrella" (Cousins et al., 2017). In contrast, abstract nouns have minimal physical or tangible qualities, and primarily refer to entities that only exist within language and thought, and are therefore less dependent on sensory information, but rely more on contextual and linguistic information, e.g., "honour" (Cousins et al., 2017). In general, individuals are better at identifying and remembering concrete than abstract words, a phenomenon which is referred to as the concreteness effect (Wiemer-Hastings & Xu, 2005; Macoir, 2009). This effect typically becomes even stronger after brain damage, e.g., aphasia after stroke (Saffran & Sholl, 1999; Sandberg & Kiran, 2014). As a result, semantic tests focusing on concrete concepts are often not sensitive enough to detect subtle semantic deficits in the early stages of the disease. Fundamental studies using experimental materials have indeed shown a specific degradation of abstract semantic concepts in patients with bvFTD (Cousins et al., 2017; Cousins, York, Bauer, & Grossman, 2016), whereas a reversal of this concreteness effect is seen in patients with svPPA, that is, patients are better at identifying abstract than concrete words (***Breedin, Saffran, & Coslett, 1994; Cousins et al., 2017; Cousins et al., 2016; Macoir, 2009; Papagno, Capasso, & Miceli, 2009; Warrington, 1975; Yi, Moore, & Grossman, 2007). Yet, clinically validated tests to measure the understanding of abstract words are currently lacking. The Dutch "Test Relaties Abstracte Concepten" (free translation from Dutch: "Test of the relations between abstract concepts (TRACE)") was specifically developed for this purpose and has been validated in Dutch-speaking patients with AD, patients with aphasia after stroke and cognitively healthy individuals in different age categories (Sonneville & Visch-Brink, 2016). In these validation studies, the TRACE discriminated between patient groups and control participants, and all three groups performed significantly worse on the TRACE as compared to a Dutch task that uses concrete stimuli. The TRACE has not been investigated in the FTD spectrum yet, and it is unknown how patients with nfvPPA and lvPPA perform on semantic tests for the understanding of abstract words. However, results from previous studies indicate that a test for abstract semantic knowledge, complementary to traditional semantic tests with more concrete stimuli could provide important additional diagnostic information about subtle semantic impairments in the early stages of the disease as well as help in the differential diagnosis between FTD subtypes in the early stages.

The aim of the current study was therefore to investigate the differential ability of the TRACE in the FTD spectrum. We compared Dutch-speaking patients with bvFTD, PPA subtypes (svPPA, nfvPPA, and lvPPA) and cognitively healthy controls and investigated discriminative ability, sensitivity, and specificity of the TRACE. In addition, we investigated correlations with other relevant neuropsychological tests, and more specifically compared the TRACE with the verbal Semantic Association Test (SAT) (Visch-Brink, Stronks, & Denes, 2005), the concrete counterpart of the TRACE.

Methods

Participants

Data for this study were retrospectively collected via two different ways; the outpatient clinic of the Erasmus Medical Center (cohort 1) and an ongoing cohort study of Dutch genetic FTD families (the FTD Risk cohort, FTD-RisC) (Dopper et al., 2014, Papma et al., 2017) (cohort 2). A STROBE participant flowchart can be seen in Fig. 1.

Cohort 1: In total, 111 individuals were seen for diagnostic neuropsychological evaluation at the outpatient clinic of the Erasmus Medical Center between January 2017 and March 2020, and received a dementia diagnosis in the FTLD spectrum (bvFTD: $n = 53$; PPA: $n = 58$). From this group, six patients with bvFTD, nine patients with nfvPPA, 10 patients with lvPPA and

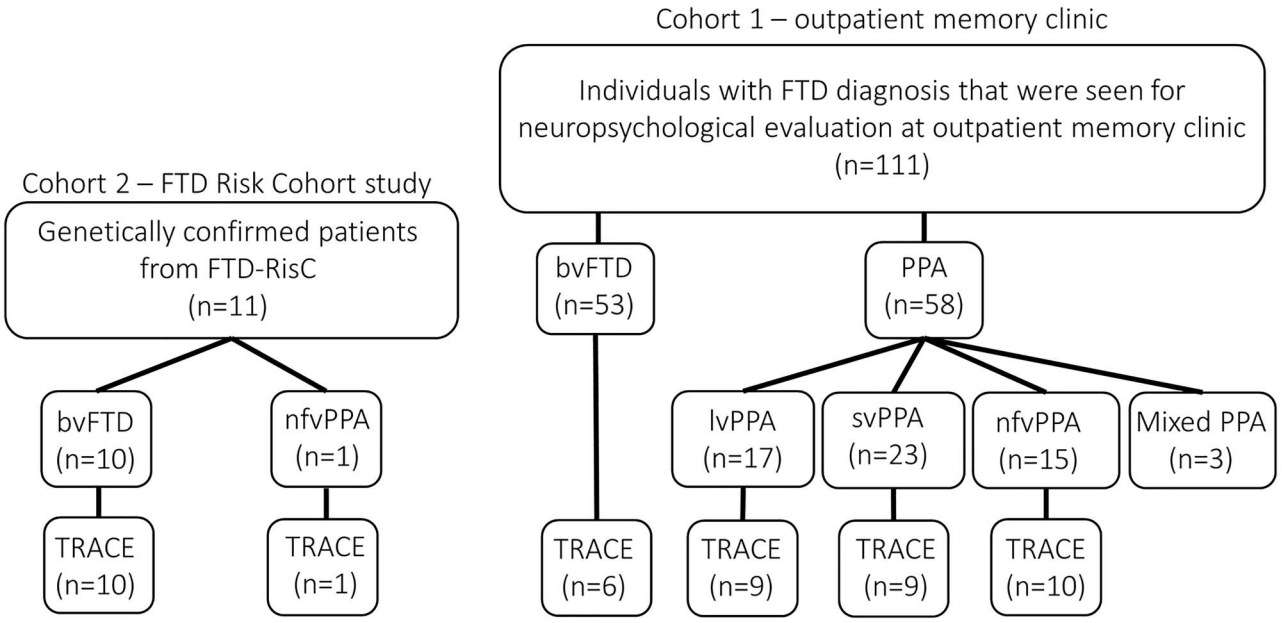

Fig. 1. STROBE participant flowchart. FTD = Frontotemporal dementia; FTD-RisC = Frontotemporal dementia risk cohort; bvFTD = behavioral variant frontotemporal dementia; PPA = primary progressive aphasia; nfvPPA = nonfluent variant primary progressive aphasia; lvPPA = logopenic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia; TRACE = Test Relaties Abstracte Concepten

nine patients with svPPA performed the TRACE and were included in this study. Patients with a mixed type of PPA ($n = 3$) were excluded. Based on the referral question and clinical suspicion of PPA, the TRACE was administered as part of the diagnostic neuropsychological evaluation according to the judgment of experienced neuropsychologists (LCJ, EvB, SF, JvH). Reasons for not administering the TRACE were for example when patients were too cognitively impaired to perform the task or if the concerning neuropsychologist not deemed it necessary/relevant to answer the referral question (e.g., other cognitive tests had priority).

Cohort 2: 11 genetically confirmed patients (bvFTD: $n = 10$; nfvPPA: $n = 1$) carrying FTD mutations were recruited via FTD-RisC (Dopper et al., 2014, Papma et al., 2017) in which the TRACE is a standard part of the neuropsychological test protocol. In addition, 59 control participants from the FTD-RisC study were used as a reference group (matched for age, education, and sex). This control group consists of healthy first-degree family members of genetic FTD patients who tested mutation-negative, upon DNA genotyping (described in more detail in Dopper et al., 2014 and Papma et al., 2017).

In all patients, diagnoses were made in a multidisciplinary consensus meeting, involving experienced neurologists, neuropsychologists, (neuro) radiologists, geriatricians, and a care consultant. Patients had a probable ($n = 31$) or definite ($n = 14$) diagnosis according to established diagnostic criteria for bvFTD (Rascovsky et al., 2011), PPA (Gorno-Tempini et al., 2011), and FTD-ALS (Brooks, Miller, Swash, & Munsat, 2000). DNA genotyping was performed as a part of the FTD-RisC study ($n = 11$) or as part of diagnosis setting ($n = 3$). Two patients with bvFTD had concomitant amyotrophic lateral sclerosis (FTD-ALS) (Brooks et al., 2000). Cerebrospinal fluid (CSF) biomarkers were analyzed as part of the diagnosis setting in 15 patients (lvPPA: $n = 4$; nfvPPA: $n = 2$; svPPA: $n = 4$; bvFTD: $n = 1$; FTD-ALS: $n = 2$) and indicated AD as underlying etiology in four patients with lvPPA (Duits et al., 2014). The study was approved by the local Medical and Ethical Review Committee. All patients with dementia that were recruited via the outpatient clinic of the Erasmus Medical Center were part of a local biobank study, for which they provided written informed consent for the use of their anonymized medical and clinical data for research purposes. Participants of the FTD-RisC study provided written informed consent for the use of their anonymized research data.

Procedure

The TRACE was administered as part of a larger standardized neuropsychological assessment protocol for bvFTD and PPA. We administered the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and Frontal Assessment Battery (FAB) (Dubois, Slachevsky, Litvan, & Pillon, 2000) as measures of respectively global and frontal cognitive functioning. Additional tests from the neuropsychological assessment battery that were available in all four patients groups and controls

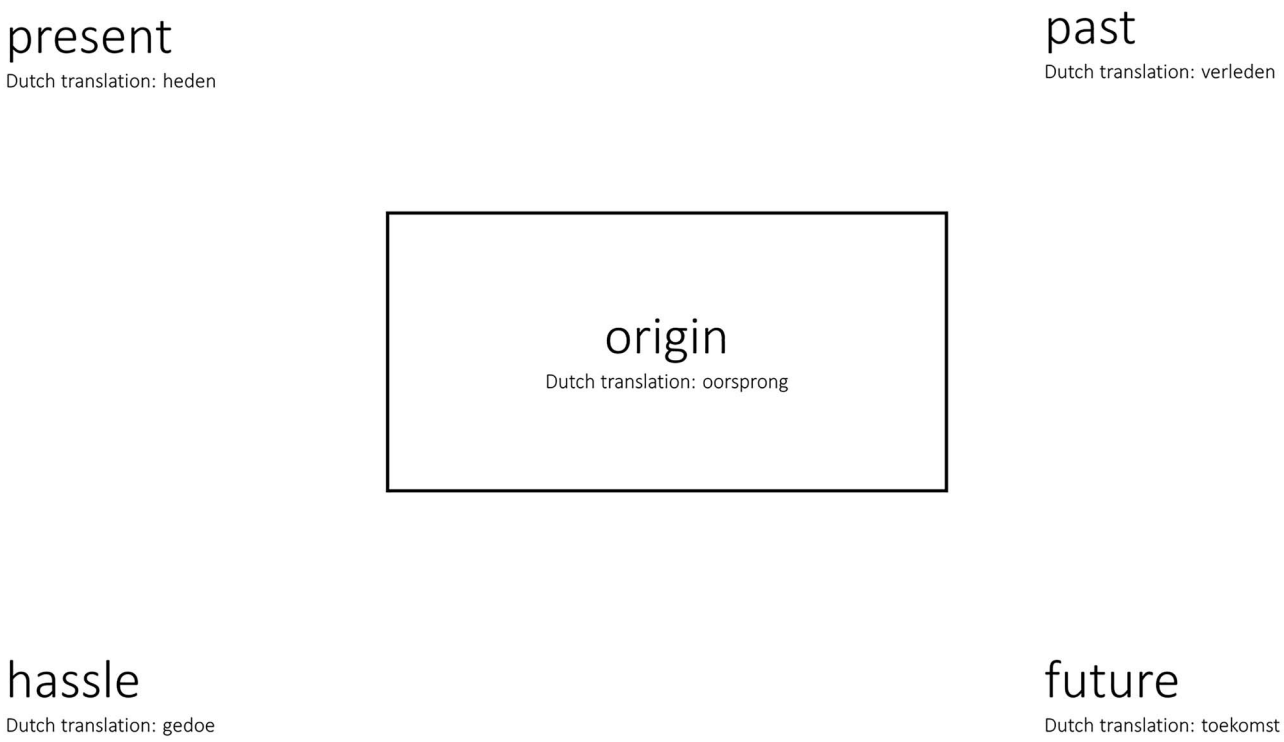

Fig. 2. Example item from the TRACE with Dutch translations.

included tests for language (i.e., the Boston Naming Test 60 items (BNT) (Kaplan et al., 1983), category fluency (Schmand, Groenink, & Van den Dungen, 2008) and the verbal SAT (Visch-Brink et al., 2005)), attention and executive functioning (i.e., the Trail Making Test (TMT) part A and B (Corrigan & Hinkeldey, 1987) and letter fluency (Schmand, Groenink, & Van den Dungen, 2008)), social cognition (i.e., the Emotion Recognition Test (ERT) (Kessels, Montagne, Hendriks, Perrett, & de Haan, 2014)), and memory (i.e., the Visual Association Test (VAT) (Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002)).

Test Relaties Abstracte Concepten (TRACE)

The TRACE is a Dutch neuropsychological test measuring a patient's understanding of abstract words (Sonneville & Visch-Brink, 2016). The design of the TRACE is analogous to that of the Pyramids and Palm Trees Test (Howard & Patterson, 1992) where patients have to associate words based on the meaning. The TRACE consists of two practice and 30 test items that are presented visually on successive cards which each shows five abstract words in Dutch: one in the center (target) and four (one correct answer and three distractors) in each corner. An example item from the TRACE, including English translations, can be seen in Fig. 2. Two distractors on each card are semantically related to the correct answer, whereas one distractor is semantically unrelated to both the target and the correct answer. Participants have to choose the item that relates best to the target on an abstract semantic level (Sonneville & Visch-Brink, 2016). Typical administration time of the TRACE is 20–30 min. Performance on the TRACE is defined by the number of correct items (maximum = 30). Information regarding the development, administration, validity, and reliability of the TRACE as provided in the Dutch test manual (Sonneville & Visch-Brink, 2016) is described in the following two paragraphs.

There is a thematic relation between the target and correct answer, which means that the words can be used in a syntagmatic association (i.e., a linear relationship between elements that are able to precede or follow each other in a sentence, e.g., target = "origin", correct answer = "past") (Jackendoff, 1983; Lyons, 1977) and that the target and correct answer do not belong to the same semantic category. The semantic distractors were chosen from the same semantic category as the correct answer with a paradigmatic relation to the correct answer (i.e., a vertical relation between elements that can be substituted for each other, e.g., "past" could be replaced by "present" or "future") (Jackendoff, 1983; Lyons, 1977). The most important factor in item-selection was imageability of the words, as it is assumed to underlie the abstractness of a word (Paivio et al., 1968; Sonneville & Visch-Brink, 2016). Only words with low imageability (i.e., imageability score of $\leq$3.5 on a 7-point scale) were selected

from an inventory of imagery values of Dutch words (van Loon-Vervoorn, 1985). Items from different semantic categories were used and the use of synonyms was avoided as much as possible. Factors such as typical acquisition age, word length, and word frequency were taken into account and words belonging to multiple parts of speech were not considered (e.g., words that could function as both a noun and verb). The first set of items ($n = 57$) were rated by 20 healthy individuals. Some items were adjusted when there was a large variation between participants in how the responses were grouped. This procedure was repeated three times which resulted in 35 items with a high level of agreement. The first version of the TRACE was tested in patients with AD and a healthy elderly control group. Five items were removed based on factor analysis and reliability data to correspond the number of items on the SAT (=30).

Reliability and validity of the TRACE was evaluated in patients with aphasia after stroke ($n = 59$), AD ($n = 23$), and control participants ($n = 164$) (Sonneville & Visch-Brink, 2016). There was a high internal consistency for all three groups (Cronbach's alphas of respectively 0.79, 0.84, and 0.86), and the mean corrected item-total correlation was sufficient (respectively 0.30, 0.38, and 0.36). Test–retest reliability was investigated in 11 patients with aphasia and showed a strong association between test moments ($r = 0.8$, $p = .003$; $\rho = 0.83$, $p = .002$). Construct validity was determined by investigating the distribution of scores per item and the correlation between the TRACE and demographic factors, and other cognitive tests. There were no items with a ceiling effect, but there were five items that had a possible floor effect which was mediated by education level. There was no significant effect of sex on TRACE performance, but there was a strong correlation between the TRACE and age ($r = -0.5$, $p < .0001$, $\rho = -0.51$, $p < .0001$), as well as a significant effect of education level in control participants ($p < .0001$). There were strong correlations between the TRACE and SAT ($r = 0.64$; $\rho = 0.72$, $p < .0001$), between the TRACE and abbreviated Token Test (Renzi & Faglioni, 1978) ($r = 0.56$, $p < .0001$; $\rho = 0.51$, $p < .0001$) and between the TRACE and the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) -49 task (Bastiaanse, Bosje, & Visch-Brink, 1995) ($r = 0.7$; $\rho = 0.68$) (all $p < .0001$). All groups performed significantly lower on the TRACE than the SAT and the PALPA-49 task ($p < .0001$). There was no association between the TRACE and the repetition subtest of the Aachen Aphasia Test (AAT, Graetz et al., 1992). Criterion validity was determined by receiver operating characteristic (ROC) analysis which showed a 90% sensitivity and 40% specificity in patients with aphasia after stroke and 96% sensitivity and 44% specificity in patients with AD, with a cutoff of 27 compared to controls. Norms are available in the test manual of the TRACE (Sonneville & Visch-Brink, 2016). A detailed description as well as psychometric properties of the SAT can be found in the Supplementary Material. There was no SAT data available in the control group.

Statistical Analysis

Statistical analyses were performed using STATA version 16 (Texas, USA). The significance level was set at $p < .05$ (two-tailed) across all comparisons. Statistical assumptions were checked by visually inspecting the data as well as statistical tests (Shapiro–Wilk and Levene's Test). We compared age (one-way ANOVA), sex (chi square test), education level (Kruskal–Wallis and Wilcoxon Rank Sum Test), and disease duration (Kruskal–Wallis and Wilcoxon Rank Sum Test) between groups.

Performance in controls was assessed by calculating the cumulative frequency of test scores (and therefore percentile scores) as well as investigating the effect of sex (Wilcoxon Rank Sum Test), age (Spearman rank correlation), and education level (Spearman rank correlation).

Mean differences between patient groups and control participants on total number of correct TRACE items were analyzed with one-way analyses of covariance (ANCOVA) with resampling by means of bootstrapping (1000s repetitions) as the assumption of homoscedasticity and normality were violated. Age and education level (Duits & Kessels, 2006) were added as covariates. A separate ANCOVA including disease duration as covariate was performed to compare TRACE performance between patient groups. Bootstrapped 95% confidence intervals are reported. All post-hoc pairwise comparisons were Bonferroni corrected.

We performed logistic regression analyses and determined sensitivity and specificity by the area under the curve (AUC) by nonparametric ROC analyses to investigate classification abilities of the TRACE between patient groups and controls, and between patient groups. Optimal cut-off levels were given by the highest Youden's index (Youden, 1950).

To compare the TRACE with the SAT across the different patient groups, we performed a 2×4 repeated measures ANOVA with test (i.e., TRACE and SAT) as a within-subjects factor and patient group (i.e., bvFTD, nfvPPA, lvPPA, svPPA) as between-subjects factor. Post-hoc paired sample t-tests were performed to investigate the difference in TRACE and SAT performance in each group. Statistical assumptions for repeated measures ANOVA and paired sample t-tests were not violated (i.e., the difference score between the SAT and TRACE was normally distributed and there was no heteroscedasticity).

Due to small sample sizes we ran nonparametric equivalents for all ANOVAs in this study but results remained largely (>90%) similar. For reasons of clarity we present only the results from the parametric set of analyses.

Spearman rank correlations were performed to investigate the association between the TRACE total number of correct items and the other neuropsychological tests in each patient group. For the VAT, the percentage correct was calculated due to different

Table 1. Demographic and neuropsychological data

	bvFTD	nfvPPA	lvPPA	svPPA	Controls
Demographics					
n	16	10	10	9	59
Sex f:m	8:8	6:4	3:7	2:7	31:28
Age, y	56.8 ± 8.8	67.0 ± 8.9	72.8 ± 9.0	60.8 ± 7.4	54.0 ± 11.4
[Range]	[39–73]	[55–81]	[57–83]	[52–72]	[32–78]
Education level[a]	5.4 ± 0.8	4.7 ± 1.0	5.3 ± 1.3	5.2 ± 1.4	5.4 ± 1.0
Disease duration, y	5.1 ± 3.5	3.1 ± 1.6	3.3 ± 1.8	5.5 ± 2.8	-
[Range]	[1.5–13.3]	[1.1–6.2]	[0.5–6.7]	[2.2–8.9]	-
Neuropsychological data					
MMSE [max = 30]	26.8 ± 2.8	26.3 ± 3.4	25.7 ± 2.1	24.8 ± 4.4	28.9 ± 1.4
FAB [max = 18]	13.9 ± 2.6	13.2 ± 4.0	12.1 ± 3.6	14.8 ± 3.5	16.8 ± 1.7
BNT 60 [max = 60]	46.9 ± 7.6	51.9 ± 5.6	42.7 ± 10.0	12.6 ± 11.3	54.4 ± 5.2
Animal fluency	15.5 ± 5.6	14.9 ± 6.8	12.3 ± 4.1	7.1 ± 5.5	24.6 ± 4.7
Letter fluency	20.7 ± 12.9	17.9 ± 9.4	20.5 ± 12.1	19.2 ± 13.3	39.0 ± 12.2
TMT A [max = 300]	43.5 ± 17.2	73.3 ± 82.0	89.9 ± 57.4	41.4 ± 16.6	28.8 ± 15.1
TMT B [max = 300]	138.2 ± 80.3	167.6 ± 87.9	229.8 ± 88.1	155.4 ± 100.4	66.7 ± 43.2
ERT total [max = 96]	41.4 ± 12.0	39.8 ± 16.9	40.0 ± 8.4	40.5 ± 13.7	55.5 ± 9.1
SAT [max = 30]	24.0 ± 6.2	27.0 ± 2.3	26.6 ± 2.4	18.6 ± 7.8	-
VAT %[b]	92.3 ± 22.9	91.7 ± 13.7	73.8 ± 29.1	62.5 ± 31.8	100.0 ± 0.0
TRACE data					
TRACE total score	21.9 ± 4.7	22.1 ± 6.0	21.7 ± 3.1	13.9 ± 6.5	27.0 ± 2.3
Range	13–30	14–29	19–28	19–28	20–30
Skewness[c]	−0.04	−0.32	0.96	−0.18	−1.07

Values are: raw mean ± standard deviation or *n* unless otherwise specified. Abbreviations: bvFTD = behavioral variant frontotemporal dementia; nfvPPA = non-fluent variant primary progressive aphasia; lvPPA = logopenic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia; MMSE = Mini-Mental State Examination; FAB = Frontal Assessment Battery; BNT 60 = Boston Naming Test 60 items; TMT = Trail Making Test; ERT = Emotion Recognition Test; SAT = Semantic Association Test; VAT = Visual Association Test; TRACE = Test Relaties Abstracte Concepten. [a]Level of education was recorded using seven categories in accordance with the Dutch educational system (1 = less than 6 years of primary education to 7 = academic schooling) (Duits & Kessels, 2006). [b]For the VAT, the percentage correct was calculated due to different maximum scores depending on age (12-item for persons ≥65 years old vs. 24-item for persons <65 years old). [c]Skewness values are a representation of the extent to which a given distribution varies from a normal distribution, where a perfect normal distribution has a skew of zero (Upton & Cook, 2008).

versions and therefore different maximum scores depending on age (12-item for persons ≥65 years old vs. 24-item for persons <65 years old). The TMT scores were truncated to 300 s for patients that exceeded the time limit or were unable to complete the test due to cognitive disabilities ($n = 10$). In addition, we investigated the association between SAT and other language tests (i.e., BNT, animal, and letter fluency) with Spearman rank correlations in the PPA patient groups (as there were only two bvFTD patients with a SAT in combination with BNT or verbal fluency measures).

Results

Demographic Data

Demographic, clinical, and neuropsychological data are shown in Table 1. Patients with nfvPPA and lvPPA were older than control participants (nfvPPA: Beta = 13.0, 95%CI 2.9–23.1, $p < .01$; lvPPA: Beta = 18.8, 95%CI 8.7–28.9, $p < .01$), and patients with lvPPA were older than patients with bvFTD (Beta = 16.0, 95%CI 4.1–27.9, $p < .01$). There were no differences between patient groups in education level ($H(4) = 3.7$, $p = .5$), disease duration ($H(3) = 5.9$, $p = .1$) or sex ($X^2(4) = 4.8$, $p = .3$), but there was a significant main effect of group on MMSE ($H(4) = 30.6$, $p < .01$) and FAB ($H(4) = 37.9$. $p < .01$). Post-hoc pairwise comparisons revealed that all patient groups, except nfvPPA, performed worse on the MMSE than control participants (bvFTD: $z = 3.4$, $p < .01$; lvPPA: $z = 4.1$, $p < .01$; svPPA: $z = 3.2$, $p < .01$). All patient groups, except svPPA, performed worse on the FAB than control participants (bvFTD: $z = 4.4$, $p < .01$; nfvPPA: $z = 3.9$, $p < .01$; lvPPA: $z = 4.2$, $p < .01$).

Normative Data in the Control Population

Cumulative frequencies (Supplementary Table S1), percentile scores (Supplementary Table S2) and mean performance on the TRACE stratified by age group, sex, and education level for control participants (Supplementary Tables S3 and S4) can be

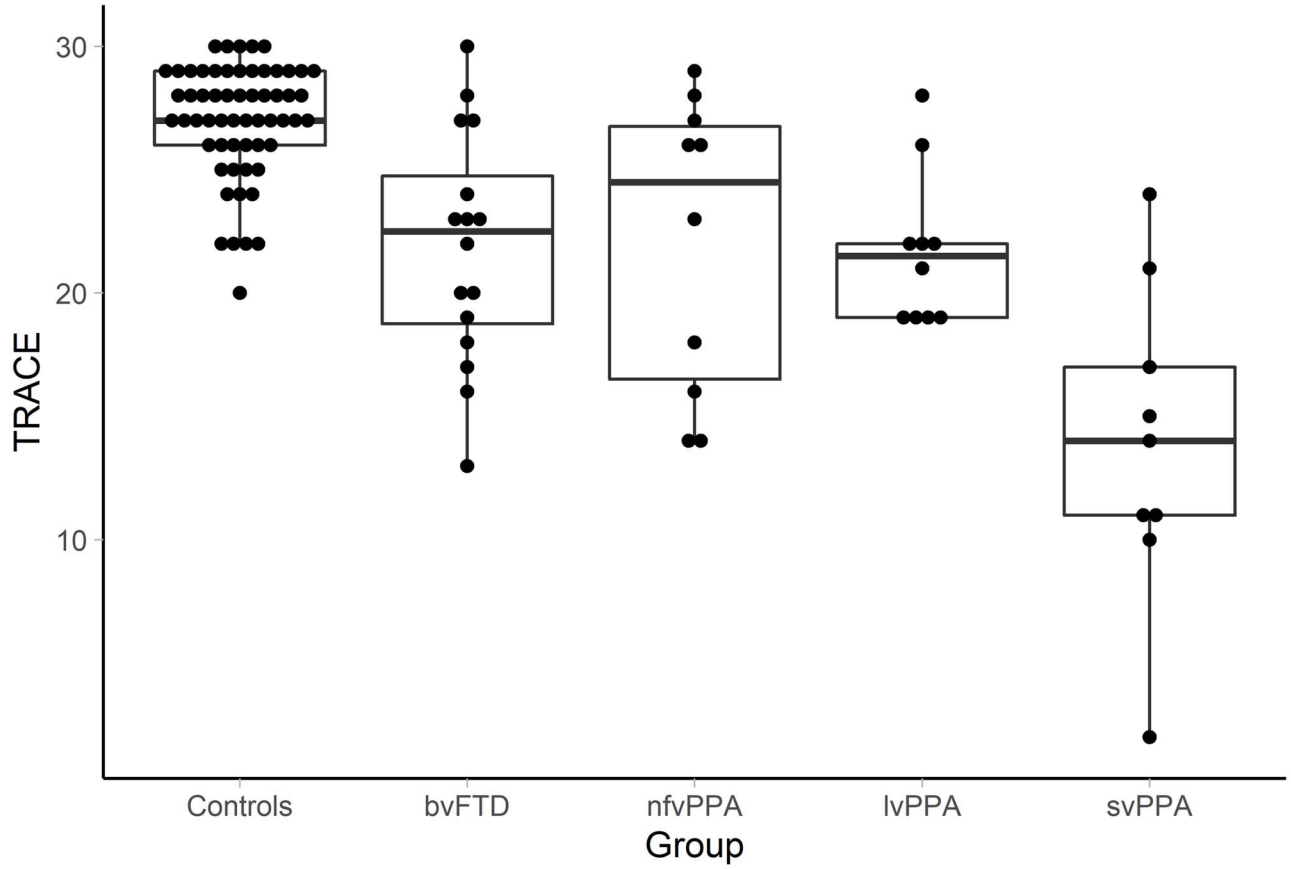

Fig. 3. TRACE total scores in each patient group. TRACE = Test Relaties Abstracte Concepten; bvFTD = behavioral variant frontotemporal dementia; nfvPPA = nonfluent variant primary progressive aphasia; lvPPA = logopenic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia.

found in the Supplementary data. Overall, control participants scored between 20 and 30 out of a total possible score of 30 and the 5th percentile score is 22. There was a weak negative correlation between TRACE performance and age ($\rho = -0.2$, $p = .03$), and a moderate positive correlation between TRACE performance and education level ($\rho = 0.5$, $p < .05$) in control participants. There was no significant difference between males and females on the TRACE ($z = -1.5$, $p = .14$).

Group Differences TRACE

Means, standard deviations and ranges of TRACE scores can be found in Table 1 and Figure 3. There was a significant main effect of group ($F(4, 97) = 22.8$, $p < .01$, $\eta^2 = 0.53$). All patient groups, except nfvPPA patients, performed worse on the TRACE than control participants (bvFTD: Beta = −5.1, 95%CI −8.4 to −1.9, $p < .01$; nfvPPA: Beta = −4.1, 95%CI −9.1 to 1.0, $p = .2$; lvPPA: Beta = −5.1, 95%CI −9.2 to −1.0, $p < .01$; svPPA: Beta = −12.9, 95%CI −19.4 to −6.4, $p < .01$). There was also a significant main effect of group in the analysis comparing patient groups with disease duration as covariate ($F(3, 38) = 3.2$, $p < .01$, $\eta^2 = 0.30$). Patients with svPPA performed worse than patients with bvFTD (Beta = −7.9, 95%CI −15.2 to −0.6, $p = .03$), nfvPPA (Beta = −8.6, 95%CI −16.4 to −0.8, $p = .02$) and lvPPA (Beta = −7.5, 95%CI −14.5 to −0.4, $p = .03$). After removing one outlier (total TRACE = 2/30, Fig. 3) from the group with svPPA, results remained largely similar. The difference between bvFTD and svPPA became nonsignificant, although a trend remained visible (Beta = −6.2, 95%CI −12.6 to 0.1, $p = .05$).

Classification Abilities of the TRACE

The classification abilities of the TRACE can be found in Table 2. The TRACE significantly differentiated between control participants and patients with bvFTD ($X^2(1) = 24.6$, $p < .01$), nfvPPA ($X^2(1) = 13.5$, $p < .01$), lvPPA ($X^2(1) = 24.4$, $p < .01$) and

Table 2. Classification abilities of the TRACE

	Odds ratio	Wald chi square	SE	AUC	95% CI AUC	Cutoff	Sensitivity (%)	Specificity (%)
bvFTD versus controls	1.54	3.91	0.17	0.83	0.68–0.87	24	75	86
nfvPPA versus controls	1.39	3.15	0.14	0.76	0.57–0.94	23	50	92
lvPPA versus controls	1.84	3.75	0.30	0.90	0.78–1.00	22	80	92
svPPA versus controls	2.11	2.57	0.61	0.96	0.96–1.00	24	100	86
bvFTD versus nfvPPA	0.99	-0.11	0.08	0.48	0.22–0.74	16	30	88
bvFTD versus lvPPA	1.01	0.11	0.10	0.54	0.31–0.77	23	80	31
bvFTD versus svPPA	1.33	2.42	0.16	0.84	0.66–1.00	15	67	94
nfvPPA versus lvPPA	1.02	0.84	0.10	0.54	0.23–0.84	22	80	60
nfvPPA versus svPPA	1.24	2.16	0.13	0.83	0.65–1.00	21	89	60
lvPPA versus svPPA	1.50	2.10	0.30	0.86	0.67–1.00	17	78	100

Abbreviations: bvFTD = behavioral variant frontotemporal dementia; nfvPPA = nonfluent variant primary progressive aphasia; lvPPA = logopenic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia; SE = standard error; AUC = area under the curve; CI = confidence interval.

Table 3. Spearman rank correlation coefficients between TRACE and other neuropsychological tests

Tests	bvFTD			nfvPPA			lvPPA			svPPA		
	n	*r*	*p*	*n*	*r*	*p*	*n*	*r*	*p*	*n*	*r*	*p*
BNT 60	14	**0.63**	0.02	10	**0.75**	0.01	10	0.38	0.28	9	0.48	0.19
Animal fluency	14	0.45	0.11	10	**0.85**	0.00	10	0.40	0.25	9	0.56	0.12
TMT A	12	-0.03	0.94	10	-0.30	0.40	10	0.08	0.82	8	-0.23	0.59
TMT B	12	-0.33	0.30	10	-0.60	0.07	10	0.19	0.61	8	-0.20	0.64
Letter fluency	14	**0.65**	0.01	10	**0.67**	0.04	10	0.58	0.08	9	0.45	0.22
ERT total score	14	**0.66**	0.01	8	**0.79**	0.02	5	0.72	0.17	6	0.66	0.16
SAT	4	0.50	0.50	8	0.45	0.26	9	0.14	0.71	7	0.56	0.19
VAT %[1]	13	0.29	0.33	9	0.41	0.27	10	-0.49	0.16	7	0.27	0.60

Abbreviations: bvFTD = behavioral variant frontotemporal dementia; nfvPPA = nonfluent variant primary progressive aphasia; lvPPA = logopenic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia; BNT 60 = Boston Naming Test 60 items; TMT = Trail Making Test; ERT = Emotion Recognition Test; SAT = Semantic Association Test; VAT = Visual Association Test. [1] For the VAT, the percentage correct was calculated due to different maximum scores depending on age (12-item for persons ≥65 years old vs. 24-item for persons <65 years old).

svPPA ($X^2(1) = 40.7$, $p < .01$). In addition, the TRACE had significant discriminative ability between patients with svPPA and bvFTD ($X^2(1) = 10.5$, $p < .01$), nfvPPA ($X^2(1) = 7.2$, $p < .01$) and lvPPA ($X^2(1) = 10.3$, $p < .01$).

Correlations with Other Neuropsychological Tests

Spearman rank correlation coefficients between TRACE and neuropsychological tests, and TRACE and language tests can be found in respectively Tables 3 and 4. In patients with bvFTD and nfvPPA, the TRACE had a significant positive correlation with the BNT ($\rho > 0.60$), letter fluency ($\rho \geq 0.65$) and ERT ($\rho \geq 0.66$), with the latter group also having a significant correlation with animal fluency ($\rho = 0.85$). There were no significant correlations between the TRACE and other neuropsychological tests in lvPPA and svPPA, though there was a trend between the TRACE and ERT ($\rho \geq 0.66$). Interestingly, in patients with nfvPPA there were no significant correlations between the SAT and other language tests ($\rho \leq 0.26$), whereas there were significant positive correlations between the SAT and other language tests (i.e., BNT, verbal fluency measures) in patients with svPPA ($\rho \geq 0.75$).

Differences between the TRACE and SAT

There were significant main effects of group ($F(1,35) = 11.4$, $p < .01$, $\eta^2 = 0.39$), and test ($F(1,35) = 7.7$, $p < .05$, $\eta^2 = 0.46$), but there was no significant interaction effect ($F(1,35) = 1.6$, $p = .2$) (Table 1), indicating that all patients performed worse on the TRACE than on the SAT. Additional paired sample t-tests showed that patients with bvFTD ($t(3) = -3.4$, $p = .02$, Cohen's $d = 1.70$), nfvPPA ($t(7) = -2.1$, $p = .04$, Cohen's $d = 0.74$) and lvPPA ($t(8) = -3.2$, $p < .01$, Cohen's $d = 1.07$) performed significantly worse on the TRACE than on the SAT, but patients with svPPA were equally impaired on the TRACE and SAT ($t(6) = -1.1$, $p = .2$).

Table 4. Spearman rank correlation coefficients between SAT-verbal, TRACE and other language tests

Tests	nfvPPA						lvPPA						svPPA					
	SAT			TRACE			SAT			TRACE			SAT			TRACE		
	n	*r*	*p*	*n*	*r*	*p*	*n*	*r*	*p*	*n*	*r*	p	*n*	*r*	*p*	*n*	*r*	*p*
BNT 60	8	0.17	0.70	10	**0.75**	0.01	9	−0.04	0.93	10	0.38	0.28	7	**0.96**	0.00	9	0.48	0.19
Animal fluency	8	0.26	0.54	10	**0.85**	0.00	9	0.54	0.14	10	0.40	0.25	7	**0.84**	0.02	9	0.66	0.12
Letter fluency	8	0.23	0.58	10	**0.67**	0.04	9	0.33	0.40	10	0.58	0.08	7	**0.75**	0.05	9	0.45	0.22

Abbreviations: bvFTD = behavioral variant frontotemporal dementia; nfvPPA = nonfluent variant primary progressive aphasia; lvPPA = logopenic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia; BNT 60 = Boston Naming Test 60 items; SAT = Semantic Association Test; TRACE = Test Relaties Abstracte Concepten.

Discussion

This study examined the diagnostic utility of the TRACE, a test for abstract semantic concept knowledge, in the FTD spectrum by comparing Dutch-speaking patients with bvFTD, PPA, and control participants. Patients with bvFTD, lvPPA, and svPPA, but not nfvPPA, had lower TRACE scores than control participants and patients with svPPA performed worse than the other patient groups. The TRACE discriminated well between patient groups, except nfvPPA, and controls and between svPPA and other patient groups with high sensitivity and specificity. Patients with bvFTD, nfvPPA and lvPPA performed worse on the TRACE than SAT, but patients with svPPA were equally impaired on the TRACE and SAT. There were strong correlations between the TRACE and language tests (i.e., BNT, verbal fluency) in patients with bvFTD and nfvPPA, whereas in patients with svPPA the SAT had strong correlations with other language tests. These results indicate that the TRACE is sensitive to detect subtle semantic deficits in bvFTD and lvPPA and can differentiate between FTD subtypes in Dutch-speaking patients, and therefore could be a valuable addition to the standard neuropsychological protocol in Dutch memory clinics.

Patients with bvFTD were significantly impaired on the TRACE and 75% of patients and controls were correctly classified. Furthermore, they had more difficulty with identifying abstract than concrete semantic concepts. Recent studies from Cousins et al. (2016, 2017) have indeed shown that patients with bvFTD are impaired on both the comprehension and production of abstract nouns. It is thought that due to the multiple meanings of abstract nouns, there are typically more competing interpretations than for concrete nouns, and abstract nouns therefore rely more on executive functioning to select the correct meaning and process the word efficiently (Cousins et al., 2016). This is further corroborated by neuroimaging studies that related abstract noun processing and production to atrophy of the left inferior frontal gyrus, an area known to be important in executive processes such as semantic control/selection (Moss et al., 2005; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Hoffman et al., 2010; Wang et al., 2010). In line with this, our results showed significant positive correlations with tests for executive functioning (i.e., letter fluency), social cognition (i.e., emotion recognition), and language (i.e., naming), which are cognitive constructs known to deteriorate progressively in bvFTD. Thus, this semantic deficit in bvFTD is likely due to the relative difficulty of abstract words, which is typically not observed with more traditional tests for semantic knowledge that use concrete stimuli such as Pyramids and Palm Trees test and SAT.

Patients with svPPA performed worse on the TRACE than the other patient groups and 100% of cases and controls were correctly classified. This is not a surprising finding given that atrophy in svPPA tends to be most severe in the left anterior and ventral temporal lobes, causing the clinical profile to be typically characterized by a global impairment in verbal and nonverbal semantic memory (Cousins et al., 2017). Several studies have indeed shown a superior performance on concrete as compared to abstract verbs, nouns, associates, and synonyms in patients with svPPA (Hoffman, Jones, & Ralph, 2013; Jefferies, Patterson, Jones, & Lambon Ralph, 2009). Yet, numerous other studies have demonstrated a reversal of the concreteness effect and relative sparing of abstract noun comprehension compared to concrete nouns in svPPA (Breedin, Saffran, & Coslett, 1994; Cousins et al., 2017; Cousins et al., 2016; Joubert et al., 2017; Macoir, 2009; Papagno, Capasso, & Miceli, 2009; Warrington, 1975; Yi, Moore, & Grossman, 2007). Additional analyses from our study demonstrate an equal impairment on the abstract and concrete task in patients with svPPA. Thus, the amplified concreteness effect that is usually seen in patients with bvFTD, lvPPA, and nfvPPA is not present in patients with svPPA. Furthermore, we found strong positive correlations in svPPA between the SAT and other language tests that call upon concrete knowledge (i.e., BNT and verbal fluency), but not between the TRACE and these language tests, suggesting that the SAT and TRACE have different underlying representations and measure different aspects of semantic memory that can be differentially affected. Together, these results imply that the combination of an abstract and concrete semantic test is most useful in differentiating svPPA from other clinical subtypes in a Dutch sample.

Possible factors that have been raised before and might also explain the discrepancy between prior study findings and our findings are differences between study population and more specifically variance in the trajectory, severity, and disease stage of study samples (Cousins et al., 2016; Joubert et al., 2017). For example, Cousins et al. (2016) argue that semantic impairment in svPPA might be initially nonspecific (and thus include impairment in both concrete and abstract concepts), but as the disease spreads through the ventrolateral temporal lobe, words with rich visual features (i.e., concrete) are becoming increasingly impaired. Vice versa it might be that early atrophy in the visual association cortex may lead to an initial impairment in the understanding of concrete words, but as the disease progresses toward other brain regions, a multimodal semantic deficit may arise (Agosta et al., 2009; Bonner & Price, 2013). Thus, individual variation in the extent and precise distribution of atrophy in the temporal lobe might determine how semantic impairment evolves in svPPA patients (Hodges & Patterson, 2007). Differences in characteristics of the experimental materials such as comprehension versus production or high versus low frequency words or the use of verbs/nouns/synonyms and variation in education/occupational experience might also explain, in part, the contradictory findings between studies (Hoffman et al., 2013). In addition, patients with svPPA often have difficulty reading and may exhibit surface dyslexia (Gorno-Tempini et al., 2011), which may have led to lower TRACE scores than for the other subtypes. Although patients are initially asked to read aloud the words themselves, instructions for test administration include reading the words to the patient if there are visual impairments or reading difficulties. The TRACE starts with two practice items to test whether the patient understood the instructions and check for possible visual or reading difficulties. The effect of possible surface dyslexia is therefore believed to be minimal.

Patients with lvPPA, but not nfvPPA, performed worse than control participants. For patients with lvPPA and controls 80% were correctly classified, but for nfvPPA and controls only 50% were correctly classified. The clinical profile of lvPPA is characterized by impaired lexical retrieval in conversational speech and impaired repetition of sentences, and that of nfvPPA by effortful, nonfluent speech that is associated with highly simplified grammatical structures and a deficit in understanding grammatically complex utterances (Grossman, 2018). Since semantic impairments are not considered as core features in lvPPA and nfvPPA, relatively few studies have focused on investigating semantic knowledge in these subtypes. The few studies that have been carried out showed that semantic knowledge is indeed relatively intact in patients with lvPPA and nfvPPA (Sebastian et al., 2018; Vonk et al., 2019), though there are studies that show atypical presentations of lvPPA with semantic memory deficits (Funayama et al., 2013; Giannini et al., 2017; Marshall et al., 2018). Furthermore, neuroimaging studies have demonstrated that, as the disease progresses, the anterior temporal lobe becomes more involved in lvPPA and thus semantic impairment, similar to svPPA, can be expected (Rohrer et al., 2013). Longitudinal studies confirm that semantic memory degrades over time in this group, though not as severe as in svPPA (Sebastian et al., 2018). The significant difference between the concrete and abstract task indicates that more traditional semantic tests with concrete stimuli are not sensitive enough to detect semantic impairment in the beginning stages of lvPPA whereas a test for abstract semantic concepts, such as the TRACE, is.

Strengths of the current study are the inclusion of and direct comparison between patients with bvFTD and all three forms of PPA, as they are rare diseases. The relatively small numbers of PPA patients that we included, may have influenced statistical power, but is inherent to the low-base rate of these disorders. Studies on the epidemiology of FTD syndromes have shown a range in prevalence between 10 and 22/100.000 and incidence between 1.6 and 4.1/100.000 (Coyle-Gilchrist et al., 2016; Knopman & Roberts, 2011). This underlines the uniqueness of a single-center study including 45 patients with different clinical subtypes, but warrants replication in other cohorts and in different languages. Furthermore, the use of a well-validated cognitive test to investigate abstract semantic knowledge rather than (new) experimental materials and/or designs, allows for the investigation of the utility of the TRACE as a clinical tool. However, as the TRACE is currently only available in Dutch, this may have repercussions for external validity. Another disadvantage of the study was that the neuropsychological assessment was part of the clinical evaluation with which diagnoses were determined. As such, the TRACE may have confounded the diagnostic classification of cases resulting in possible circular reasoning. However, diagnosis did not solely depend on the neuropsychological assessment as, in our multidisciplinary meeting, international consensus criteria for bvFTD (Rascovsky et al., 2011) and PPA (Gorno-Tempini et al., 2011) were followed using all available clinical information, including MR imaging of the brain, anamnestic and heteroanamnestic information as well as behavioral and neuropsychiatric questionnaires. Another limitation to consider is the heterogeneity within and between patient groups as it remains difficult to match groups on disease severity and duration. Furthermore, results from the correlational analysis should be interpreted cautiously as they are exploratory in nature rather than hypothesis driven and we did not statistically compare correlation coefficients due to small sample sizes. Directions for future research entail correlating TRACE performance with neuroimaging findings in a larger sample size, investigating decline over time with longitudinal follow-up and translating the test to English and other languages to investigate the psychometric properties of the TRACE in non–Dutch-speaking samples enabling replication of our results in other, larger FTD cohorts.

Our study demonstrates the presence of deficits in abstract semantic knowledge by means of the TRACE in Dutch-speaking patients with bvFTD, svPPA, and lvPPA, but not in patients with nfvPPA. Patients with svPPA performed worse than the other

groups. The TRACE proved a good classifier between patient groups, except nfvPPA, and controls as well as between svPPA and other FTD subtypes. We demonstrate a significant concreteness effect in patients with bvFTD, lvPPA, and nfvPPA, whereas this concreteness effect was not present in patients with svPPA—indicating equally impaired performance for both abstract and concrete words in those patients. The TRACE had strong associations with language tests in patients with bvFTD and nfvPPA, whereas the SAT had strong associations with language tests in patients with svPPA. Together, these results suggest that the degradation of abstract word knowledge is more specific to patients with bvFTD and lvPPA whereas a test for concrete semantic knowledge is more sensitive to identify svPPA. In conclusion, the TRACE is able to detect subtle semantic deficits, differentiate between FTD subtypes in Dutch-speaking patients and provides, in combination with tests for concrete semantic concepts, new relevant information that can significantly help in the differential diagnosis between FTD subtypes.

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Supplementary Material

Supplementary material is available at *Archives of Clinical Neuropsychology* online.

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