Received: 10 December 2024 | Accepted: 19 May 2025

DOI: 10.1111/jnp.70000

the british psychological society
promoting excellence in psychology

RESEARCH ARTICLE

Mini social cognition and emotional assessment: Diagnostic performance and neural correlates in behavioural-variant frontotemporal dementia

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Funding information
iBehave Network: Sponsored by the Ministry of Culture and Science of the State of North Rhine-Westphalia, Grant/Award Number: NW21-049 A-F; Deutsche Forschungsgemeinschaft (DFG)-funded Cluster of Excellence ImmunoSensation2 (—EXC2151—390873048)

Abstract

We aimed at validating the Mini Social Cognition and Emotional Assessment (Mini-SEA) in a German cohort of mildly impaired behavioural-variant frontotemporal dementia (bvFTD) patients and healthy controls. The Mini-SEA comprises the Facial Emotion Recognition Test (FERT) and the Faux Pas Test (FPT) measuring Theory of Mind (ToM) abilities in social norm-related real-life stories. We examined the diagnostic performance of the Mini-SEA alongside other neuropsychological assessments and investigated its structural neural correlates. We included 32 bvFTD patients and 54 controls in logistic regression models with forward-stepwise selection containing demographics, standard neuropsychological battery (CERAD-NAB+) and the Mini-SEA scores to identify the most relevant variables. Demographic, neuropsychological and daily-life

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activity associations were explored. Voxel-based morphometry analysis was conducted in a subsample (14 bvFTD and 14 controls) on regions previously linked to emotion processing and ToM functions. The Mini-SEA yielded a very good performance, being in the best-fitting model with a high odds ratio alongside the executive-language and memory measures. Specifically, the FERT indicated the strongest effect in the group differentiation. Mini-SEA showed significant associations with executive-language tests and daily-life activities. In canonical emotion processing brain regions, we found associations of the Mini-SEA composite and the FERT with grey matter volumes in the left insula and lentiform nucleus of putamen. Within ToM regions, associations were found for the Mini-SEA composite and the FPT in cerebellar regions. The German Mini-SEA discriminates well between mildly impaired bvFTD patients and controls. We also demonstrated its significant value for neuropsychological assessment and neuro-behavioural associations in regions underlying emotion processing and ToM.

KEYWORDS

emotions, frontotemporal dementia, neurodegeneration, neuroimaging, social cognition, theory of mind

INTRODUCTION

Social cognition is one of the core domains providing harmonious social interactions by understanding mental states (i.e. mentalizing) and emotions of others and adjusting behaviours within socio-cultural norms (Happé et al., 2017). Social cognition and emotional assessments perform as well as established standard neuropsychological measures in the diagnosis of several neuropsychiatric patient groups suggesting the routine implementation in neuropsychological practice and evaluation of the socio-emotional factors in clinical interventions (McDonald et al., 2023). For the wide-spread use of these assessments, test validation and consensus on the social cognition assessments (see review, Dodich et al., 2021) as well as the training of clinicians in application is crucial (Quesque et al., 2024). Considering the recent developments and expert initiatives on social cognition in the clinical context (e.g. Social Cognition work group in the Neuropsychiatric International Consortium Frontotemporal dementia (scNIC-FTD), Van den Stock et al., 2023; Signature Initiative, Dodich & Cerami, 2023), we aimed to investigate social cognition measurement specifically in behavioural-variant Frontotemporal Dementia (bvFTD) which is the most prevalent subtype of frontotemporal dementias (Hogan et al., 2016).

Patients with bvFTD diagnosis show early deficits in social cognition and interaction characterized by loss of sympathy or empathy, alongside other prominent symptoms such as behavioural disinhibition, apathy and stereotypic behaviours (Rascovsky et al., 2011). In fact, emotion recognition and mentalizing problems play a central role in the early symptoms of bvFTD (Rascovsky et al., 2011; Rascovsky & Grossman, 2013). Recently Barker et al. (2022) from the ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) study developed research criteria for prodromal bvFTD with loss of empathy or sympathy being core features (i.e. low socioemotional sensitivity, reduced empathic concern or impaired cognitive empathy perspective taking). Also, deficits in awareness of social expectations are supportive features of a diagnosis of mild behavioural and/or cognitive impairment in bvFTD (MBCI-FTD). Therefore, a sensitive and feasible

clinical assessment of social cognitive dysfunctions is a prerequisite for early/differential diagnosis of bvFTD.

Several neuropsychological tests have been developed to support the diagnosis and to foster further research into social cognition and empathy deficits in the neuropsychiatric population (e.g. Story-Based Empathy Task, Dodich et al., 2015; The Awareness of Social Inference Test, McDonald et al., 2003; Jarsch et al., 2022, 2023). Early changes in social cognition in bvFTD were previously investigated mainly with two paradigms: emotion recognition and Theory of Mind (ToM) (see review Henry et al., 2014). The Facial Emotion Recognition Tasks (e.g. Ekman 60 – based on the Pictures of Facial Affect Series; Diehl-Schmid et al., 2007; Ekman & Friesen, 1976) and several similar emotion recognition paradigms (e.g. body expressions; Van den Stock et al., 2015) indicated significant deficits in mildly impaired bvFTD compared to healthy controls (HC), Alzheimer's disease (AD) (see review Bora et al., 2016) and other neuropsychiatric diseases such as major depressive disorder (MDD) (e.g. Chiu et al., 2018). Specifically, emotion recognition dysfunctions are associated with the perfusion in dorsal regions of the medial prefrontal cortex (mPFC) in bvFTD (Bertoux et al., 2014). Reduced BOLD signal during facial emotional processing is also detected in the inferior frontal & fusiform gyrus, medial frontal gyrus, amygdala, insula and anterior cingulate cortex (ACC) (Virani et al., 2013). Moreover, grey matter (GM) volume correlates of the emotion recognition dysfunctions in bvFTD are also evident specifically for the bilateral ACC, medial prefrontal cortex, bilateral amygdala (Bertoux, Volle, et al., 2012; de Souza et al., 2022), insula and basal ganglia (Garcia-Cordero et al., 2021; Russell et al., 2020).

Early-stage ToM deficits are prominent in bvFTD compared to HC and AD samples and they can be measured by ToM paradigms such as Faux Pas Test (FPT), sarcasm recognition tasks (see review Bora et al., 2015) and false-belief paradigms (Le Bouc et al., 2012). Specifically, the high diagnostic value of the FPT (Stone et al., 1998) in bvFTD was replicated by several studies (e.g. Giovagnoli et al., 2019; Torralva et al., 2015). The FPT performance shows a significant relation to the perfusion in rostral left mPFC (Bertoux et al., 2014) and the GM structural correlates of the FPT are evident in the frontal poles, temporal poles, cingulate cortex and left temporoparietal region (de Souza et al., 2022), orbitofrontal and medial prefrontal cortex (Bertoux, Volle, et al., 2012) as well as the left basal ganglia (Russell et al., 2020) and cerebellum (i.e. in other neuropsychiatric groups: autism spectrum disorder, bipolar disorder II; Olivito et al., 2023).

Considering the potentially decisive role and neural correlates of the emotion recognition and ToM dysfunctions in the diagnosis of bvFTD, the Social Cognition & Emotional Assessment (SEA) and a shorter version (i.e. Mini-SEA) were developed specifically for the early diagnosis and its differentiation from AD and MDD (Bertoux, de Souza, et al., 2016; Bertoux, Delavest, et al., 2012; Funkiewiez et al., 2012). Apart from the initial French version (Bertoux et al., 2013, 2014; Bertoux, de Souza, et al., 2016; Tanguy et al., 2022), it was established in several languages in a multinational study (i.e. Genetic Frontotemporal Dementia Initiative—GENFI—Russell et al., 2020), and other studies in Portuguese (Barbosa et al., 2023; de Souza et al., 2022; Moura et al., 2021; Resende et al., 2021), Spanish (Custodio et al., 2021; Ibañez et al., 2021), Chinese (Wang et al., 2022) and English (Russell et al., 2021) showing good performance when discriminating bvFTD from AD, even after controlling for memory disorders (Bertoux et al., 2013; Bertoux, de Souza, et al., 2016) and apathy (Mariano et al., 2020). Therefore, this practical social cognition test can be proposed as a potential clinical standard.

Critically, the emotional processing and mentalizing skills should be evaluated within the country norms as the performance on social cognition tasks can be particularly susceptible to language and cultural differences (e.g. Dodell-Feder et al., 2020; Quesque et al., 2022). We therefore tested the Mini-SEA for the first time in a German sample as a composite score containing both the FERT and the FPT subtests. We leveraged data from a multicenter cohort to provide further proof of the validity of this test. We aimed at exploring the discrimination performance of the Mini-SEA between mildly impaired bvFTD patients and healthy controls alongside the routinely used neuropsychological assessments. Furthermore, we examined its structural neural correlates.

MATERIALS AND METHODS

Participants

We included 44 bvFTD patients from the multicentric DZNE Clinical Registry Study of Neurodegenerative Diseases – FTD (DESCRIBE-FTD) cohort according to current criteria (Rascovsky et al., 2011). The diagnosis was ascertained by a multidisciplinary group of clinicians, considering several domains of assessments (e.g. blood samples, MRI, neuroimaging, CSF biomarkers) containing medical history and psychiatric/neurological examination, family history, sensory testing, the Mini Mental State Examination (MMSE) (Folstein et al., 1975), the Global Clinical Dementia Rating scale (CDR; Berg, 1988; Morris, 1993, Morris et al., 1997) and the Dementia Rating Instrument PLUS National Alzheimer's Coordinating Center Behaviour and Language Domains (CDRplus NACC FTLD; Knopman et al., 2008, 2011; Miyagawa et al., 2019). Informants were interviewed with the Functional Activities Questionnaire (FAQ; Pfeffer et al., 1982). PET examinations were performed in cases with an unclear diagnosis to measure cerebral glucose metabolism and cerebral amyloid load either on PET-CT or PET-MRI devices.

Healthy controls (HCs) ($n = 58$) from the DZNE Degeneration Controls and Relatives (DANCER) cohort were initially recruited via media advertisement or represented relatives of patients. The telephone or in-house interviews ensured the study criteria were met. The main exclusion criteria were conditions of significant sensory impairment, neurodegenerative disorders, a history of stroke with residual clinical symptoms, a severe or unstable medical condition, current or previous major psychiatric disorders and usage of prohibited drugs. All human data included in this study was obtained in compliance with the ethical regulations (i.e. informed consent; University of Bonn Ethics Board statement 311/14).

The first mild bvFTD group was obtained ($n = 35$ bvFTD) after the exclusion of 9 patients either with a CDR global score over 1.0, sum of the additional two behavioural and language subscores of the CDR plus NACC FTLD over 3.0 or FPT Control Questions total score below 16 out of 20 (i.e. minimum value of the HC group) to create a subsample with mild cognitive dysfunctions without a significant impairment in story comprehension. Genetic examination was conducted in 24 of the 35 patients and 55 of the 58 controls. Two of the patients were C9orf72 mutation carriers. Two of the controls were excluded as one of them was a C9orf72 mutation carrier and another was a carrier of the MAPT gene mutation ($n = 54$ HC). Finally, age, sex and education level matched groups ($n = 30$ for both groups) were created from the complete to calculate Youden Index-based cut-off definitions of the Mini-SEA scores.

For the logistic regression analyses, 3 bvFTDs and 2 HCs without any score on the German version of the Consortium to Establish a Registry for Alzheimer's Disease—Neuropsychological Assessment Battery—Plus (CERAD-NAB+; Morris et al., 1989; Schmid et al., 2014) were excluded from the complete sample. Participants with a low number of missing values on CERAD-NAB+ variables were kept for further data imputation ($n = 32$ bvFTD, $n = 54$ HC) (see Supplementary Material S1 for the data imputation procedure description). This way we obtained the largest possible sample to identify the most relevant set of neuropsychological variables.

Instruments

The Mini-SEA consists of two parts: the Facial Emotion Recognition Test (FERT) and the Faux Pas Test (FPT). In the FERT, 35 black-and-white emotional face photos are presented (i.e. Ekman & Friesen, 1976) and the participants are expected to verbalize the best fitting emotional category which is presented under the face pictures with or without emotional expressions (i.e. Happiness, Surprise, Sadness, Fear, Disgust, Anger and Neutral).

The FPT consists of 10 short stories, 5 of them containing a faux pas. For each story with a faux pas, six questions are asked to measure patients' ability to attribute mental states of others (ToM) and to detect the violation of accepted social rules, social blunders or inappropriate actions of others (maximum

score of 30). For the 5 stories without any faux pas, 2 points are given if the participant is able to explain the absence of a faux pas (maximum score of 10). In total, 40 total points are summed. In addition, two control questions (i.e. 1 point for each correct answer) are asked for each story to measure general story comprehension ability (maximum score of 20). In our analyses, if the patient's total FPT control questions score was within the range of healthy controls, they were considered to be eligible for the analyses signalling no prominent problem with story comprehension. Finally, the raw scores of the FERT and the FPT are transformed to a scale from 0 to 15 and then the Mini-SEA Composite score (i.e. max 30) is calculated as the sum of these two scaled scores (Bertoux, Delavest, et al., 2012).

The CERAD-NAB+ battery (Schmid et al., 2014) contains the measurements: Semantic Fluency 'Animals' (Isaacs & Kennie, 1973), Boston Naming Test (15 Items) (Kaplan et al., 1978), Phonemic Fluency 'S-Words' (Benton et al., 1989; Spreen, 1977), Figure Drawing (Rosen et al., 1984), Figure Recall, Word Lists (i.e. recall, discriminability, learning scores; Atkinson & Shiffrin, 1971; Morris et al., 1989; Rosen et al., 1984; Welsh et al., 1994), the Trail Making Test (i.e. TMT-A, TMT-B, TMT--B/A; Reitan, 1979) and the MMSE (Folstein et al., 1975).

Statistical analyses

We first derived logistic regression-based cut-offs for the differentiation between the demographically matched bvFTD patients and healthy controls ($n = 30$ bvFTD, $n = 30$ HC) for application in clinical settings. The score with the highest Youden Index was chosen as the best cut-off. In addition, the matched group comparisons were conducted with the Mini-SEA scores via non-parametric Wilcoxon rank-sum tests with Bonferroni adjustment.

We then conducted logistic regression analyses for binary group classification for each Mini-SEA and CERAD-NAB+ battery variable controlling for age, sex and education levels ($n = 32$ bvFTD, $n = 54$ HC). This way we aimed to detect single variables that significantly distinguish mildlyimpaired bvFTD patients from the HCs. Single missing data imputation were conducted using the mice package (version 3.16.0; van Buuren & Groothuis-Oudshoorn, 2011) in R statistical software (R Core Team, 2022; version 4.2.2) with predictive mean matching method (Ho et al., 2011) on both groups (see S1 for the missing rates).

Finally, we implemented forward stepwise selection on a model containing significantly distinguishing variables of the CERAD-NAB+ battery, Mini-SEA sub-scores and the demographical variables. This model contained the pre-selected CERAD-NAB+ variables: TMT-A, TMT-B (executive functions); Semantic Fluency 'Animals', Boston Naming Test, Phonemic Fluency 'S-Words' (language); Word List—Recall, Learning (memory); Figure Recall (visual memory) and the global cognition screening measure (i.e. MMSE) alongside age, sex, education and the Mini-SEA sub-scores. In addition, we conducted a separate model with the same pre-selected variables of the CERAD-NAB+ and demographics but only with Mini-SEA composite score to investigate the overall performance of the test. This way we aimed to detect most relevant neuropsychological variables in the group differentiation and tested the diagnostic relevance of the Mini-SEA scores. Moreover, we calculated odds ratios for each variable in the final models.

Furthermore, demographic, neuropsychological and activities of daily living correlates of the Mini-SEA were calculated in the complete samples via Spearman rank-order and point-biserial correlation analyses with Benjamini–Hochberg false-discovery rate adjustment.

MRI acquisition and analysis

Participants were scanned for MRI using 3 Tesla Siemens scanners at several study locations by implementing a harmonized protocol across sites (two TrioTim, three Verio, two Skyra and one Prisma). Only two of the scanners had 20 channels and the majority had 32-channel head coils with synchronized

sequence parameters. T1-weighted magnetization-prepared rapid gradient echo images were acquired with the following sequence parameters: TR: 2500 ms, TE: 4.37 ms, TI: 1100 ms, flip angle: 7°, GRAPPA = 2, FOV: 256 × 256 mm^2, slice thickness: 1 mm, 192 sagittal sections, no gap. All of the scans were processed to implement voxel-based morphometry (VBM) analysis using the CAT12 toolbox (version 12.9 r2559; Gaser et al., 2022) on MATLAB R2020b. Details of the processing and obtaining of the GM maps are provided (S2). The GM maps were smoothed to reduce the background noise and normalized the GM volume using a 5-mm FWHM Gaussian smoothing.

Structural MRI data were available for 14 bvFTD patients and 36 controls. The nearest neighbour matching procedure on the age, sex and education variables was implemented fixing sex as the exact matching variable. With this procedure 14 demographically matched controls were selected with the sex ratio (5 females, 9 males) same as the bvFTD group ($n = 14$) (see S6). In these matched groups, we performed a VBM of the T1-weighted MRI data within the prespecified region of interest (ROI) grey matter (GM) masks 'Emotion' and 'Theory of Mind' (http://neurosynth.org; Yarkoni et al., 2011). This was done to increase statistical power and to possibly replicate the reported mini-SEA associations with these ROIs (see de Souza et al., 2022; Resende et al., 2021). The Emotion and Theory of Mind (ToM) masks covers several overlapping key regions such as the superior temporal gyrus, medial frontal gyrus and inferior frontal gyrus. Beyond the shared regions, the Emotion Mask uniquely includes regions such as the amygdala and insula, while the ToM Mask contains structures such as the precuneus and cerebellum (Figure S3 for the full lists). The smooth GM maps were inserted in a two-sample t-test to assess the within ROI's VBM differences between groups. A correction for the total intracranial volume was performed using a global scaling approach to overcome individual brain size differences. The 'Emotion' mask and the 'Theory of Mind' mask restricted the statistics by inserting these as an inclusion mask at the time of assessing the different contrasts. We then performed multiple regression analysis to assess the relationship between GM volume and the Mini-SEA composite and the subscores FERT and FPT. The significant clusters were obtained at $p < .001$ and results were reported at $p < .05$ after correcting for multiple comparisons using cluster-wise family-wise error (FWE) approach.

RESULTS

Demographics and clinical characteristics

Wilcoxon rank-sum tests indicated no significant age difference between the demographically matched groups (W = 393, $p = .404$) and, in the subsample with both Mini-SEA and CERAD-NAB+ variables (W = 948, $p = .655$) (Table 1). No significant education level difference was detected

TABLE 1 Age, sex and education characteristics of each subsample.

Subsample	Group	Age Mean (SD)	Age difference	Education mean (SD)	Education difference	N (f/m)	f %
Matched (1) $N = 60$	bvFTD	63.80 (11.90)	W = 393	14.50 (2.53)	W = 352	30 (9/21)	30.00
	HC	65.80 (11.00)	$p = .404$	15.40 (2.06)	$p = .143$	30 (9/21)	30.00
CERAD-NAB+ (2) $N = 86$	bvFTD	63.84 (11.62)	W = 948	14.03 (2.81)	W = 1208	32 (6/26)	18.80
	HC	63.42 (12.79)	$p = .655$	15.70 (2.53)	$p = .006$	54 (29/25)	53.70

Note: (1) Demographically matched sub-samples for the group comparisons and cut-off definitions; (2) Subsample for the analyses with the CERAD-NAB+ variables. 'age difference': non-parametric test result on age difference between groups. 'education difference': non-parametric test result on education (years) difference between groups. 'W': Wilcoxon rank-sum test statistics. 'N (f/m)': sample size and the female/male ratio. 'f %' percentage of females.

Abbreviations: f %, percentage of females; N (f/m), sample size and the female/male ratio; W, Wilcoxon rank-sum test statistics.

between the demographically matched groups (W = 352, $p = .143$). Healthy controls were more educated than bvFTD patients in the subsample with CERAD-NAB+ variables (W = 1208, $p = .006$). The female and male ratio in the demographically matched subsample was equal for both groups (30% female). The patients were predominantly male in the subsample with CERAD-NAB+ variables (18.80% female) and the ratio was balanced in the healthy controls (i.e. 53.60% female and 53.70% female, respectively).

In the demographically matched sample, dementia severity was rather mild with a mean CDR-global score of .75 (± .26), a CDR-FTLD behaviour score of 1.22 (±.6) and a CDR-FTLD language score of .43 (±0,42). The average age of disease onset in the demographically matched bvFTD group was 60.9 years (±11.6) and the average disease duration since onset of the first symptoms and first diagnosis was 2.66 years (±3.1) and .44 years (±.76) respectively. Similarly, mild clinical characteristics were also shown for the subsample with the CERAD-NAB+ variables (S4) and the subsample for the VBM analyses.

Mini-SEA cut-off values on the demographically matched subsamples ($n = 30$ bvFTDs, $n = 30$ HCs)

Using the Youden Index, optimal cut-offs were defined as 23.68 for the MiniSEA composite, 9.86 for the FERT and 12.00 for the FPT. The Mini-SEA composite score (AUC: .82 [.72, .93], sensitivity: .80, specificity: 73) and the FERT subscore (AUC: .82 [.71, .92], sensitivity: .63, specificity: 93) showed relatively higher discriminative power than the FPT (AUC: .76 [.64, .89], sensitivity: .73, specificity: .70).

The non-parametric demographically matched group comparisons indicated significant deficits in bvFTD on the Mini-SEA composite (HC: 24.58 ± 3.60; bvFTD: 19.43 ± 4.49; W = 161, $p < .0001$), the FERT (HC: 11,84 ± 1.47; bvFTD: 9.33 ± 2,23; W = 164, $p < .0001$) and the FPT (HC: 12.74 ± 2,64; bvFTD: 10.10 ± 2.92; W = 212, $p = .002$). No significant group difference was shown in the FPT control question scores indicating intact comprehension of the story content in the patients (HC: 19.60 ± 0.85; bvFTD: 19.06 ± 1,14; W = 319, $p = .111$).

Demographically controlled models for the Mini-SEA and CERAD-NAB+ variables and optimal model selection ($n = 32$ bvFTDs, $n = 54$ HCs)

Age-, sex- and education level-controlled binary logistic regression models with the Mini-SEA variables for the prediction of the bvFTD diagnosis indicated significant effects for the composite score ($p < .001$; AUC: .91 [.84: .98]), the FERT ($p = .001$; AUC: .90 [.83: .97]) and the FPT ($p = .006$; AUC: .87 [.79: .95]). Most of the CERAD-NAB+ variables also showed significant effects in these demographically controlled distinct models, except for the TMT-B/A, figure drawing and WL-discrimination (see Table 2).

The stepwise forward selection procedure on the model containing the FERT and the FPT subtests, pre-selected CERAD-NAB+ battery variables and demographic covariates indicated the best model fit with the FERT (OR: .52 [.30, .89]; $p = .018$), WL-learning (OR: .62 [.42: .95]; p = .018), phonemic fluency 'S-words' (OR: .70 [.52: .95]; $p = .022$) and TMT-A (OR: 1.09 [1.01:1.17]; $p = .020$) indicating the FERT provides the largest association on the group differentiation while the FPT score was not selected for the best fitting model.

In the model with the Mini-SEA composite score, the stepwise forward selection provided the same CERAD-NAB+ variables of WL-learning (OR: .67 [.46: .98]; $p = .037$), phonemic fluency 'S-words' (OR: .71 [.53: .95]; $p = .023$), TMT-A (OR: 1.09 [1.02:1.17]; $p = .016$) and the Mini-SEA composite score (OR: .74 [.58, .95]; $p = .017$).

Demographic, neuropsychological and activities of daily life correlates of the mini-SEA

Spearman rank-order correlation analyses on the complete HC sample ($n = 56$) yielded a significant negative correlation of age with the FERT ($rs = -.45$; $p = .003$), the FPT ($rs = -.31$; $p = .046$) as well as the Mini-SEA composite score ($rs = -.41$; $p = .006$) (see Table 3 and, Appendix A (Tables A1 and A2) for the demographic stratification). Sex showed a significant point-biserial correlation with the FERT ($rpb = .41$; $p = .006$) indicating better performance of females, while no significant relation was detected with the FPT ($rpb = .11$; $p = .512$). FERT and FPT scores were significantly correlated ($rs = .37$; $p = .012$). No significant relation was found between Mini-SEA scores and the years of education.

TABLE 2 Descriptives and demographically controlled logistic regression model results for each variable in the sample with CERAD-NAB+ variables.

	HC ($n = 54$)	bvFTD ($n = 32$)					
Variable	**M ± SD**	**M ± SD**	**Sens**	**Spec**	**AUC**	**CI**	***p***
Mini-SEA Composite	25.06 ± 3.11	19.42 ± 4.52	.94	.91	.91	[.84, .98]	<.001
FERT	12.07 ± 1.37	9.32 ± 2.31	.81	.85	.90	[.83, .97]	=.001
FPT	12.99 ± 2.39	10.1 ± 3.03	.84	.83	.87	[.79, .95]	=.006
TMT-A	35.83 ± 11.51	57.06 ± 32.88	.69	.91	.86	[.77, .94]	=.019
TMT-B	79.26 ± 29.55	138.22 ± 80.66	.75	.87	.87	[.80, .95]	=.009
TMT-B/A	2.29 ± 0.72	2.53 ± 1.05	.72	.81	.78	[.68, .88]	.999
MMSE	29.04 ± 1.2	26.75 ± 3.55	.88	.74	.84	[.75, .93]	=.040
Semantic fluency	24.67 ± 5.67	17.59 ± 6.93	.81	.85	.90	[.83, .97]	=.001
Boston naming test	14.74 ± 0.52	13.78 ± 1.52	.88	.76	.88	[.80, .95]	=.024
Phonemic fluency	15 ± 4.18	9.16 ± 3.49	.81	.85	.93	[.88, .99]	<.001
Figure drawing	10.59 ± 0.74	10.22 ± 1.21	.75	.69	.78	[.69, .88]	.999
Figure recall	9.94 ± 1.41	6.91 ± 3.75	.91	.72	.87	[.79, .94]	=.006
WL-discrimination	97.96 ± 4.29	92.19 ± 11.64	.84	.69	.84	[.75, .93]	.167
WL-recall	7.54 ± 1.93	5.16 ± 2.7	.78	.87	.86	[.78, .95]	=.008
WL-learning	21.93 ± 3.9	17.5 ± 5.19	.84	.83	.86	[.77, .95]	=.014

Note: *p* values are adjusted with the Bonferroni method.

Abbreviations: AUC, area under curve; CI, 95% confidence intervals of the AUC values; '*p*', *p* values represent the significance of the variable in the logistic regression models when age, sex and education (years) are held constant; Sens, sensitivity; Spec, specificity.

TABLE 3 Spearman rank-order correlation results of the mini-SEA and the demographic variables on the initial healthy control sample ($n = 54$) with Benjamini–Hochberg adjustment.

	1	2	3	4	5	6
1. Age	–					
2. Sex	−.29	–				
3. Education	−.09	−.25	–			
4. FERT	−.45**	.41**	.13	–		
5. FPT	−.31*	.11	.03	.37*	–	
6. Mini-SEA Composite	−.41**	.22	.10	.73****	.86****	–

Note: *p* values are adjusted with the Benjamini–Hochberg method; females are coded as 1 in the binary sex variable;

*$p < .05$. **$p < .01$. ****$p < .0001$.

Correlations between the Mini-SEA and the CERAD-NAB+ scores in the bvFTD subsample ($n = 32$) showed that the FERT has a significant positive relationship with the phonemic fluency 'S-words' ($rs = .45$; $p = .041$) and approached significance with the figure drawing score ($rs = .42$; $p = .059$) as a visuo-constructive ability assessment (Table 4).

The FPT indicated significant positive associations with the language variables semantic fluency 'animals' ($rs = .44$; $p = .049$), Boston naming test ($r = .50$; $p = .024$) and phonemic fluency 'S-words' ($rs = .39$; $p = .089$) approaching significance. Moreover, the FPT was significantly associated with the memory variables; figure recall ($rs = .49$; $p = .03$), word list recall ($r = .45$; $p = .042$), word list learning ($rs = .60$; $p = .004$) as well as the MMSE ($rs = .60$; $p = .004$).

Within the same line, Mini-SEA composite score showed significant positive associations with the language variables semantic fluency 'animals' ($rs = .44$; $p = .047$), Boston naming test ($rs = .51$; $p = .021$) and phonemic fluency 'S-words' ($rs = .51$; $p = .019$). It also showed a positive association with the visuo-constructive functions—figure drawing- ($rs = .38$; $p = .09$) approaching significance. The composite score had a very strong positive relationship with the global cognition MMSE ($rs = .61$; $p = .003$) and with the memory variables of visual memory—figure recall- ($rs = .47$; $p = .036$) and word list learning ($rs = .46$; $p = .036$).

The Mini-SEA composite score showed a negative association with the FAQ-Total score ($n = 29$) approaching significance ($rs = -.37$; $p = .074$) (S5). In the subscales, the FPT showed a strong negative association with the FAQ-total ($rs = -.41$; $p = .048$) whereas the FERT indicated no significant relationship ($rs = -.15$; $p = .480$).

Neural correlates of the bvFTD and mini-SEA performance

The demographically matched subsamples ($n = 14$ for each group) for the MRI analyses also showed mild clinical characteristics (S6). When compared to HCs, the bvFTD group showed significantly decreased GM volume in the bilateral ACC, left anterior and medial orbitofrontal cortex, right insula, bilateral inferior temporal gyrus, right middle and superior temporal gyrus (STG), right parahippocampal gyrus and left cerebellum crus I and II (see Figures 1 and S7 for all significant clusters). No significant GM volume increase was observed in the bvFTD group.

Applying the Theory of Mind (ToM)-related mask, we observed significantly decreased GM volume in the bvFTD group including bilateral middle temporal gyrus (MTG) and right STG. Applying the emotion processing mask, significantly decreased GM was observed in the clusters including bilateral amygdala, right hippocampus and left STG (Figure 2). The multiple regression analysis within the ToM mask revealed a positive association of GM volume with the Mini-SEA composite and FPT in left cerebellum crus II and bilateral cerebellum crus I & II, respectively. Within the emotion processing mask, we observed positive GM volume associations of the Mini-SEA composite in the cluster including left insula, lenticular nucleus of putamen and hippocampus, while for the FERT in left insula and lenticular nucleus of putamen.

DISCUSSION

In this study, we validated the German version of the Mini-SEA and investigated its neuro-behavioural correlates in a sample of mildly impaired bvFTD patients and healthy controls. The Mini-SEA discriminated well between mild bvFTD patients and healthy controls in the demographically matched groups as in the previous studies with other language versions (e.g. French, Bertoux, de Souza, et al., 2016; Bertoux, O'Callaghan, et al., 2016; Chinese, Wang et al., 2022; Portuguese, Barbosa et al., 2023). However, we note the differences in the mean scores and standard deviations between our study and the original French sample (Bertoux, Delavest, et al., 2012). These variations in the Mini-SEA scores can also be observed between studies from different languages (e.g. Custodio et al., 2021; de Souza

TABLE 4 Spearman rank-order correlation test results of the mini-SEA, demographic variables and CERAD-NAB+ variables in the bvFTD sample ($n = 32$).

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. Age	–																	
2. Sex	−.29	–																
3. Education	−.16	.03	–															
4. FERT	−.03	−.34	.13	–														
5. FPT	−.38†	−.10	.12	.40†	–													
6. Mini-SEA Composite	−.34	−.23	.13	.74***	.89***	–												
7. TMT-A	.29	.07	−.15	−.12	−.08	−.17	–											
8. TMT-B	.18	.19	.04	−.18	−.15	−.22	.77***	–										
9. TMT-B/A	−.13	.36	.09	−.13	−.19	−.18	−.01	.52*	–									
10. MMSE	−.24	−.08	.04	.27	.60**	.61*	−.15	−.11	−.09	–								
11. Semantic fluency	.01	−.29	−.14	.29	.44*	.44*	−.23	−.27	−.18	.56**	–							
12. Boston naming test	−.05	−.26	−.08	.35	.50*	.51*	−.09	−.15	−.21	.48*	.52*	–						
13. 'S-Words' fluency	.12	−.49*	−.07	.45*	.39†	.51*	−.38†	−.39†	−.19	.46*	.79***	.45*	–					
14. Figure drawing	−.03	−.42†	.23	.42†	.22	.38†	−.29	−.24	−.08	.34	.17	.30	.38†	–				
15. Figure recall	−.28	.14	−.14	.19	.49*	.47*	.00	.12	.22	.62**	.43†	.38†	.41†	.14	–			
16. WL-discrimination	−.14	−.07	−.05	.19	.31	.34	−.30	−.19	−.10	.67***	.50*	.44*	.33	.19	.42†	–		
17. WL-recall	−.35	.21	−.03	.05	.45*	.35	−.06	.03	.09	.56**	.58**	.52**	.35	.05	.78***	.48*	–	
18. WL-Learning	−.48*	.31	.12	.07	.60**	.46*	−.22	−.17	.03	.59**	.54*	.44*	.32	.12	.65**	.40†	.80***	–

Note: p values are adjusted with the Benjamini–Hochberg method; Females are coded as 1 in the binary sex variable.

†$p < .10$.

*$p < .05$. **$p < .01$. ***$p < .001$.

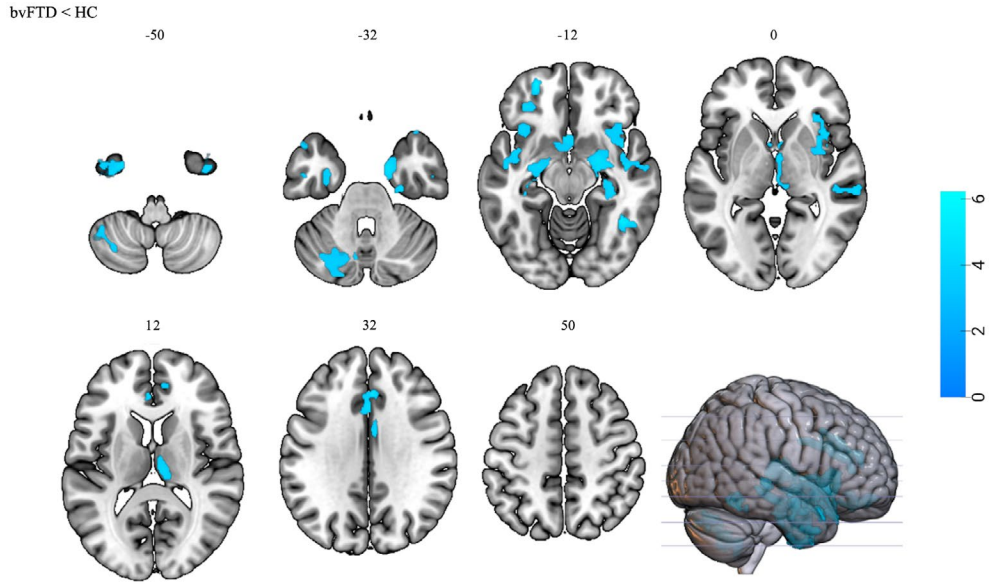

FIGURE 1 Group comparisons implementing the two-sample t-test showing decreased GM volume in bvFTD patients compared to healthy controls. The clusters are represented in sky blue colours at $p < .05$, correcting for cluster-level family-wise error at extent threshold ($k = 330$) for multiple comparisons. The sky blue colour bar shows the t-values.

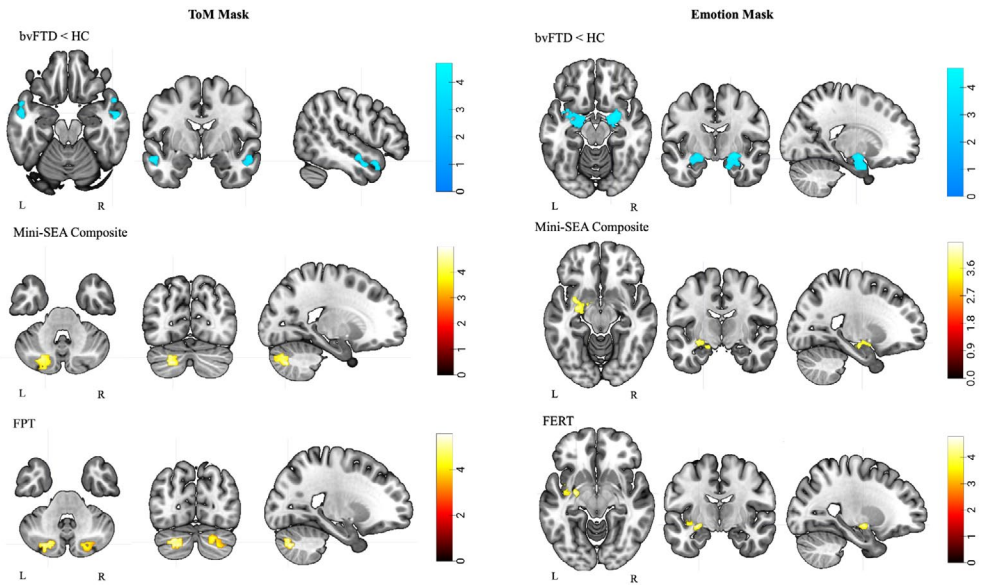

FIGURE 2 Multiple regression results in the ToM and emotion masks on the comparison between groups for the Mini-SEA scores. The significant clusters in the group comparison are represented in sky blue at $p < .05$ in the ToM (top left) and Emotion (top right) masks, indicated by sky blue colours showing t values. The GM correlates of the Mini-SEA composite (middle left) and FPT (bottom left) in the ToM mask and Mini-SEA composite (middle right) and FERT (bottom right) in the emotion recognition mask are represented at $p < .05$ in red and yellow colours.

et al., 2022; Wang et al., 2022) highlighting the importance of language and culture specific evaluation of social cognition tests (Dodell-Feder et al., 2020; Gendron et al., 2014; Russell et al., 2020).

Furthermore, the Mini-SEA composite score demonstrated a significant diagnostic value in the forward stepwise variable selection procedure of logistic regression models containing neuropsychological assessments of language, executive functions and memory functions. Specifically, the FERT demonstrated its significant relevance by being in the best fitting logistic regression models with the highest effect alongside the Phonemic Fluency "S-Words". bvFTD patients often show prominent semantic and lexical language impairments (see systematic review Geraudie et al., 2021) compared to healthy controls alongside the social cognitive and behavioural dysfunctions. We also found strong positive associations of the Mini-SEA with the Semantic Fluency, Phonemic Fluency (see also Moura et al., 2021) and confrontation naming (i.e. Boston Naming Test) indicating coinciding dysfunctions in these domains. Although the executive functions and ToM abilities are separate components (Bertoux, O'Callaghan, et al., 2016), overlapping frontal cortex disturbances could contribute to the early deficits in fluency tests (i.e. executive language tests) requiring mental flexibility and the ability to facilitate goal-directed behaviours under time pressure (e.g. Aita et al., 2018; Amunts et al., 2020).

Our variable selection procedure also indicated a significant contribution of the WL-learning memory score in the final best fitting models. This result replicated previous findings showing a prominently impaired memory performance in bvFTD patients compared to healthy individuals (see review, Poos et al., 2018). It is also critical to note that the memory performance showed strong associations with the semantic fluency ('Animals') ($r = .54, p < .05$) and Boston naming test ($r = .44, p < .05$) indicating a potential contribution of executive language dysfunctions on the relatively lower memory scores compared to healthy controls.

The FERT showed significant associations with age and sex in healthy controls and executive language functions in the bvFTD sample. Our results supported the evidence for an advantage of healthy females in emotion recognition tasks (see meta-analysis; Thompson & Voyer, 2014). A strong positive point-biserial correlation of the FERT and the sex variable indicated a trend for better emotion recognition performance in healthy female participants. Therefore, it is important to investigate potential causes of this result, such as stronger early emotional processing abilities in females (Bek et al., 2022). Moreover, a strong negative association between the FERT and age replicated previous results on the negative effects of aging on emotion recognition performance (see meta-analysis; Hayes et al., 2020). In this regard, it is crucial to consider the demographic confounds of the FERT in research and clinical practice (see Appendix A for the demographic stratification).

In the demographically matched groups, a high sensitivity and discriminatory power was demonstrated for the Mini-SEA composite score (AUC: 82) and the FERT sub-test (AUC: 82). The FPT had a slightly worse performance than the FERT (AUC: 76). Moreover, the forward selection procedure in the sample with CERAD-NAB+ variables did not include the FPT score in the best performing model, while the FERT subscale showed the strongest effect among routinely used neuropsychological scores of memory, verbal fluency and executive functions. Furthermore, the FERT showed significantly higher specificity, providing potentially fewer false positives than the FPT in the demographically matched group differentiations. Thus, this could be due to some of the healthy control participants who may have had problems with motivation or understanding the FPT task, which requires complex mentalizing and social norm evaluation abilities. In this regard, we detected two outliers with low FPT scores in the control group (i.e. 4.875 and 6), while they showed acceptable FPT control question scores (i.e. 20 and 19), FERT performance (i.e. 10.30 and 12.86), and intact functioning in other neuropsychological tests. After excluding these outliers, the FPT subscore reached the AUC value of .81, resulting in increased discriminatory power of the Mini-SEA composite score (AUC: .86). One of the potential reasons for these outliers could be due to the requirement of more complex linguistic processing in the FPT compared to other mentalizing tasks (e.g. story-based empathy task, Dodich et al., 2015). Moreover, variability in evaluators' experience may also lead to inconsistent measurement quality.

The between-group GM volume comparisons showed that the bvFTD group had an expected atrophy pattern consistent with the previous studies for bilateral anterior cingulate cortex, insula (see meta-analysis Buhour et al., 2017; Luo et al., 2020), orbitofrontal cortex (Dermody et al., 2016; Hornberger et al., 2011), right superior temporal gyrus and inferior temporal gyrus (Buhour et al., 2017), cerebellum (see meta-analyses and reviews Chen et al., 2018, 2019) and parahippocampal gyrus (Dermody et al., 2016). After restricting the GM volume comparisons to the emotion processing related regions, we detected similar amygdalar atrophy compared to controls as de Souza et al. (2022) reported. Using the ToM mask, similar temporal lobe atrophy was also demonstrated specifically on the bilateral MTG and right STG.

The positive association of the GM volume in the insula and the lenticular nucleus of putamen with the FERT could be related to the recent evidence of the associations between emotion recognition capacity and GM volume decrease in the insula and striatum which could simultaneously result in reduced introspective capacity in bvFTD (Hazelton et al., 2023; Russell et al., 2020). In other words, the emotion recognition problems of the bvFTD patients can be partly explained by the disruption in the processing of internal sensory information and their integration with the external signals. Thus, the insula could have a central role in the socioemotional deficits in bvFTD (Van den Stock & Kumfor, 2019).

Interestingly, the FPT performance was significantly associated only with the bilateral cerebellum crus I and II clusters in the ToM-related areas. The relation between cerebellar atrophy and cognition beyond motor functions in FTD was investigated rarely until recent years (see meta-analysis Chen et al., 2019). However, recent evidence suggested associations between the cerebellar volume and working memory, language, attention, executive and emotion processing dysfunctions (e.g. Chen et al., 2018; Tan et al., 2015) which could be due to the disruptions in the cerebro-cerebellar connections through the temporoparietal junction and PFC (Kelly & Strick, 2003; Van Overwalle et al., 2019). Previous results showed that the posterior cerebellar atrophy is specifically associated with the implicit ToM abilities in bvFTD patients (Synn et al., 2018; Van den Stock et al., 2019) when using a task with animated abstract shapes requiring goal-directed behaviour/intention attribution (i.e. Happé-Frith animation task; Abell et al., 2000). Moreover, a negative association of the cerebellar GM volume with the Mini-SEA composite and global cognitive test in bvFTD was reported (Ibañez et al., 2021). Therefore, this is the first study demonstrating this domain-specific relation of cerebellar atrophy using a ToM paradigm with realistic social interaction scenarios. Furthermore, our results supported recent evidence of the posterior cerebellar atrophy associations of the FPT in addition to other diagnostic groups (e.g. Autism Spectrum Disorder, Cerebellar Neurodegenerative Disorder & Bipolar Disorder (II); Olivito et al., 2023; Siciliano et al., 2023).

Our work is not without limitations. We did not compare bvFTD patients with other neuropsychiatric groups, as their successful differentiation using the Mini-SEA has already been demonstrated in studies conducted in other languages (e.g. Barbosa et al., 2023; Mariano et al., 2020). Another limitation of this study was the small sample size for the VBM analyses. Although the statistical power was increased by applying domain-specific masks, larger samples could provide the significant associations of the frontotemporal clusters.

CONCLUSIONS

The German version of the Mini-SEA provided initial evidence of its clinical utility by effectively distinguishing mildly impaired bvFTD patients from healthy controls, offering significant relevance alongside routinely used neuropsychological assessments. We critically demonstrate the importance of accounting for confounders of age and sex. Significant deficits in the executive language domain and its relation to the Mini-SEA scores emphasize the importance of a combined investigation of the executive language dysfunctions and social cognition in bvFTD patients. Further, we replicated the insular and striatal atrophy effects on emotion recognition performance and found novel associations of cerebellar atrophy with the FPT task. In sum, the German version of the Mini-SEA provides a compact

assessment of emotion recognition and ToM-related disturbances in bvFTD, useful for clinical practice and research. Critically, we showed the superior performance of the FERT over the FPT, offering an effective investigation of a social cognitive domain with much shorter test duration and less linguistic complexity.

AUTHOR CONTRIBUTIONS

Cem Doğdu: Methodology; conceptualization; software; writing – original draft; data curation; formal analysis; validation; investigation. **Neeraj Upadhyay:** Writing – original draft; formal analysis; visualization. **Ingo Frommann:** Validation; writing – original draft; writing – review and editing. **Luca Kleineidam:** Methodology; writing – review and editing. **Andreas Johnen:** Writing – review and editing; methodology. **Melina Stark:** Writing – review and editing. **Sandra Roeske:** Project administration. **Annika Spottke:** Project administration. **Anna Gamez:** Project administration. **Gabor C. Petzold:** Project administration. **Louise Droste zu Senden:** Project administration. **Julian Hellmann-Regen:** Project administration. **Stefan Hetzer:** Project administration. **Klaus Fliessbach:** Project administration. **Carolin Miklitz:** Project administration. **Emrah Düzel:** Project administration. **Falk Lüsebrink:** Project administration. **Wenzel Glanz:** Project administration. **Stefan Teipel:** Project administration. **Ingo Kilimann:** Project administration. **Josef Priller:** Project administration. **Eike Jakob Spruth:** Project administration. **Johannes Prudlo:** Project administration. **David Mengel:** Project administration. **Klaus Scheffler:** Project administration. **Matthis Synofzik:** Project administration. **Anja Schneider:** Project administration; supervision; funding acquisition. **Michael Wagner:** Supervision; conceptualization; writing – review and editing.

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ACKNOWLEDGEMENTS

We would like to thank the patients, their relatives and healthy volunteers who participated in the DESCRIBE-FTD and DANCER-FTD cohorts of the German Center for Neurodegenerative Diseases. We would like to thank Lisa Brandstetter for the cooperation in the translation process. This work was supported by the iBehave Network: Sponsored by the Ministry of Culture and Science of the State of North Rhine-Westphalia (C.D., and A.S. grant number NW21-049 A-F). A.S. is a member of the Deutsche Forschungsgemeinschaft (DFG)-funded Cluster of Excellence ImmunoSensation2 (grant number: EXC2151—390873048). Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets generated and analysed for this study are not publicly available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Data S1:

How to cite this article: Doğdu, C., Upadhyay, N., Frommann, I., Kleineidam, L., Johnen, A., Stark, M., Roeske, S., Spottke, A., Gamez, A., Petzold, G. C., Droste zu Senden, L., Hellmann-Regen, J., Hetzer, S., Fliessbach, K., Miklitz, C., Düzel, E., Lüsebrink, F., Glanz, W., Teipel, S., … Wagner, M. (2025). Mini social cognition and emotional assessment: Diagnostic performance and neural correlates in behavioural-variant frontotemporal dementia. *Journal of Neuropsychology*, *00*, 1–20. https://doi.org/10.1111/jnp.70000

APPENDIX A

TABLE A1 Mini-SEA scores stratified by demographics in the complete HC sample ($n = 56$).

					Mini-SEA composite	FERT	FPT
	Interval	***n***	**Min**	**Max**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age	24–55	10	24.7	52.7	26.5 (3.05)	13.1 (1.36)	13.4 (2.33)
	56–65	13	55.7	64.6	26.5 (2.13)	12.4 (1.36)	14 (1.44)
	66–75	27	65.1	75	23.9 (3.36)	11.6 (1.28)	12.3 (2.74)
	75+	6	75.5	82.8	24.5 (2.23)	11.6 (0.83)	12.8 (1.86)
Education	1–13	19	9	13	24.6 (3.13)	11.7 (1.23)	13.0 (2.17)
	14–17	26	14	17	25.3 (3.45)	12.4 (1.41)	12.9 (2.85)
	18+	13	18	20	25.1 (2.69)	12.0 (1.44)	13.1 (1.81)
Sex	–	30 females	–	–	25.7 (2.83)	12.6 (1.22)	13.1 (2.36)
	–	26 males	–	–	24.2 (3.36)	11.5 (1.31)	12.8 (2.47)

Note: Age and education variables indicate years. Interval column indicates the selected interval for the stratification of the Mini-SEA variables. '*n*' shows the number of participants in each interval. 'min' and 'max' indicate the minimum and maximum of age and education on the selected intervals.

TABLE A2 Mini-SEA scores stratified by demographics in the complete bvFTD sample ($n = 35$).

					Mini-SEA composite	FERT	FT
	Interval	***n***	**Min**	**Max**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age	35–55	5	35.4	53.9	22.2 (5.46)	10.4 (3.47)	11.8 (2.32)
	56–65	16	55.5	64.2	18.9 (4.75)	8.60 (2.20)	10.3 (3.35)
	66–75	6	65.8	72	19.5 (2.00)	9.64 (1.97)	9.88 (1.05)
	75+	8	75.5	84.9	17.8 (4.22)	9.59 (1.89)	8.25 (2.74)
Education	1–13	16	7	13	18.5 (4.14)	9.36 (2.10)	9.09 (2.88)
	14–17	16	14	17	19.7 (4.59)	8.87 (2.47)	10.8 (2.79)
	18+	3	18	19	20.9 (5.89)	10.8 (2.57)	10.1 (3.62)
Sex	–	9 females	–	–	17.2 (4.43)	7.95 (2.56)	9.29 (2.38)
	–	26 males	–	–	19.9 (4.29)	9.71 (2.07)	10.2 (3.10)

Note: Age and education variables indicate years. Interval column indicates the selected interval for the stratification of the Mini-SEA variables. '*n*' shows the number of patients in each interval. 'min' and 'max' indicate the minimum and maximum of age and education on the selected intervals.