Right temporal lobe and socioemotional semantics: semantic behavioural variant frontotemporal dementia

Supplementary Material

Methods

Functional, Cognitive, and Behavioral Assessments:

In the main text we focus on the neuropsychological and socioemotional tests most relevant to rATL neurodegeneration. Here we present some of the more general and commonly used neuropsychological tests. A functional assessment was done through a semi-structural interview with the patient`s co-participant using the Clinical Dementia Rating Scale (CDR).[1] General cognition was assessed with the Mini-Mental State Examination (MMSE).[2] Verbal and visual episodic memory were tested with the California Verbal Learning Test (CVLT) and a 10-minute delayed free recall of the Benson complex figure recall, respectively.[3] Visuospatial processing was evaluated with the Benson complex figure copy, and the Visual Object Space Perception (VOSP).[4] Executive functioning was evaluated with backward digit span, Trails sequencing, Stroop color-naming test, and design fluency.[5,6] Language production and repetition were evaluated with the Western Aphasia Battery (WAB) subtests for Spontaneous Speech and Repetition. Lexical retrieval and access were evaluated with phonemic verbal fluency and the WAB Auditory Word Recognition subtest. Sentence comprehension was tested with the WAB Sequential Commands subtest and a syntactic comprehension task.[7,8] In the famous faces battery, the famous faces came from a pool of 200 black-and-white photographs of celebrities in different professional categories. Their familiarity was determined by a behavioral study conducted on 20 normal male subjects (age range 18–33 years) who were shown each face on a computer screen for 5 seconds and had to name the person.[9] Only those faces that were named within the 5 seconds by at least 19 subjects were included. The non-famous faces were matched to the famous ones for mean age, sex, and facial expression. All faces were matched for mean luminance. This battery has been used in cohorts that included healthy controls, Alzheimer's disease, behavioral variant frontotemporal dementia, semantic variant primary progressive aphasia, logopenic variant primary progressive aphasia, and nonfluent variant primary progressive aphasia.[10]

Emotional Theory of Mind (eToM):

The eToM test measures the examinee’s ability to conduct theory of mind reasoning and perspective taking with emotional material. Examinees are asked to watch videos of characters interacting in an emotional state, and then make first- and second-order ToM inferences about the characters’ knowledge and beliefs

about the others' emotional states. Importantly, this test is designed to measure emotional ToM in a manner that is distinct from concurrent emotion reading deficits; the emotions of the characters are always explicitly named by the narrator, thus the examinee does not need to be able to read emotions while performing the task, only to understand the perspective of the characters on the other's named emotional state. In this task, 8 video clips are shown, displaying two characters in a realistic setting expressing an emotion, with a voice-over narration describing the scene. When one character leaves the scene, a specific event changes the emotion of the other character, and then the first individual returns. After the video clip, the participant is asked three questions. The first is a control question asking what was the event that occurred when one of the characters was gone, and can be used to ascertain that the examinee had a basic level of understanding of the video. The second question measures the examinee's ability to correctly assign a first-order theory of mind belief by asking what the last emotional state was of the individual who constantly stayed in the scene. The third question measures the examinee's ability to correctly assign a second-order theory of mind belief by asking them to identify what one character thinks the other character feels. Half of the scenarios involve a "cheat" condition, in which one of the characters is unwittingly observed by the other, making eToM deductions more complex.

Statistical Analysis:

Receiver operating characteristic curves were generated to differentiate sbvFTD from bvFTD and sbvFTD from svPPA based on socioemotional and neuropsychiatric batteries. Cut-offs for sensitivity and specificity for the six values with best performance differentiating sbvFTD from bvFTD are shown in Supplementary Table 9. Values were chosen based on the highest specificity at a sensitivity over 88% for differentiating sbvFTD from bvFTD.

Imaging Analysis:

We ran a voxel-based morphometry (VBM) analysis to compare the brain MRIs of the rATL-predominant pathology proven group to the rATL-predominant group without pathological data. As these two groups were included based on the same imaging-based index. Although we did not expect any difference between the two groups; we ran this VBM analysis for quality check purposes. VBM preprocessing and analysis were performed using the VBM8 toolbox (dbm.neuro.uni-jena.de/vbm/) and SPM8 software (fil.ion.uc.ac.uk/spm/software/spm8). Following bias correction and tissue classifications, segmented images were normalized to the Montreal Neurological Institute (MNI) coordinate system space with a 1.0 mm cubic resolution using affine and nonlinear transformations via the Diffeomorphic Anatomical Registration using the Exponentiated Lie Algebra (DARTEL) method.[11] Default measures of the VBM8 toolbox were used in all preprocessing steps, except for the addition of a light clean-up procedure in the

morphologic filtering step. The spatially normalized, segmented, and modulated gray matter images were smoothed with an 8-mm full width at half maximum isotropic Gaussian kernel.

To determine whether there was a right or left laterality in the frontal-predominant group, we calculated the frontal laterality index based on the W-score of the right and left frontal lobes using the formula: Right Frontal / (Right Frontal + Left Frontal). Index value over 50% indicates right frontal predominant atrophy, index value less than 50% indicated left frontal predominant atrophy.

Results:

Quality Assurance Imaging Analysis Results:

The VBM analysis comparing the brain MRIs of the rATL-predominant pathology proven group to the rATL-predominant group without pathological data did not show any statistically significant differences at corrected $p < 0.05$.

Frontal Atrophy Laterality in the Frontal-Predominant Group:

Averaging the laterality index values of all the frontal-predominant cases, the mean was 50%, median 51%, and standard deviation 27%. Despite this finding, we want to point out that the focus of greatest atrophy was nevertheless located in the right frontal insula in this group. The area with maximum atrophy when considering only the frontal lobe regions was the right anterior insula (W-score = -2.29), followed by the left frontal operculum (W-score = -2.22), then left anterior insula (W-score = -2.20), and right frontal operculum (W-score = -2.15).

Supplementary Table.1: Region of interests (ROI)s included in calculating the atrophy indices based on the Desikan atlas.

Frontal ROI	Temporal ROI
Anterior cingulate gyrus	Amygdala
Anterior insula	Central operculum
Anterior orbital gyrus	Entorhinal area
Basal Forebrain	Fusiform gyrus
Frontal operculum	Hippocampus
Frontal pole	Inferior temporal gyrus
Gyrus rectus	Middle temporal gyrus
Lateral orbital gyrus	Parahippocampal gyrus
Middle cingulate gyrus	Planum polare
Medial frontal cortex	Planum temporale
Middle frontal gyrus	Superior temporal gyrus
Medial orbital gyrus	Temporal pole
Precentral gyrus medial segment	Transverse temporal gyrus
Superior frontal gyrus medial segment	
Opercular part of the inferior frontal gyrus	
Orbital part of the inferior frontal gyrus	
Posterior insula	
Posterior orbital gyrus	
Precentral gyrus	
Subcallosal area	
Superior frontal gyrus	
Supplementary motor cortex	
Triangular part of the inferior frontal gyrus	

Supplementary Table 2: Sensitivity of current and previous diagnostic criteria in the rATL-predominant patients: Based on medical record review, this table shows the percentage of the rATL-predominant patients who met previous and current diagnostic criteria during three different time points: The first three years after illness onset, by the time of the first evaluation, and by the time of the last evaluation. T-test showed no statistically significant differences between the autopsy and the living groups:

Criteria	Time point	rATL Autopsy Group % (n)	rATL Living Group % (n)	rATL Total % (n)
Neary FTD (1998)[12]	First three years of symptoms	16 (3)	12 (3)	13 (6)
	Initial evaluation	47 (9)	56 (15)	52 (24)
	Total illness duration	47 (9)	63 (17)	56 (26)
Neary Semantic (1998)[12]	First three years of symptoms	5 (1)	12 (3)	9 (4)
	Initial evaluation	6 (1)	15 (4)	11 (5)
	All illness	16 (3)	15 (4)	16 (7)
bv-FTD (2011)[13]	First three years of symptoms	26 (5)	27 (7)	27 (12)
	Initial evaluation	74 (14)	78 (21)	76 (35)
	Total illness duration	74 (14)	89 (24)	83 (38)
PPA (2011)[14]	First three years of symptoms	16 (3)	12 (3)	13 (6)
	Initial evaluation	16 (3)	15 (4)	16 (7)
	All illness	16 (3)	15 (4)	16 (7)
svPPA (2011)[14]*	First three years of symptoms	26 (5)	42 (11)	36 (16)
	Initial evaluation	68 (13)	85 (23)	78 (36)
	Total illness duration	68 (13)	92 (25)	83 (38)

* Meet semantic variant criteria but not general PPA criteria.

Supplementary Table 3: The sequence of the first two symptoms in the rATL-predominant group.

Sequence of the first two symptoms		
First symptoms (n)	**Second symptoms**	**Number of patients with specific sequence (first and second symptoms) (%)**
Loss of empath (19)	➔ person-specific knowledge	8 (42)
	➔ compulsions	8 (42)
	➔ verbal semantics	3 (16)
Person-specific knowledge (12)	➔ loss of verbal semantics	8 (66)
	➔ loss of empathy	3 (25)
	➔ apathy	1 (8)
Verbal semantic loss (5)	➔ person-specific knowledge	3 (60)
	➔ loss of empathy	1 (15)
	➔ Impaired judgment	1 (15)
Compulsions (4)	➔ loss of empathy	2 (50)
	➔ person-specific knowledge	2 (50)
Apathy (2)	➔ loss of empathy	1 (50)
	➔ Person-specific knowledge	1 (50)
Disinhibition (2)	➔ loss of empathy	2 (100)
Impaired judgment (1)	➔ compulsions	1 (100)
Episodic memory loss (1)	➔ compulsions	1 (100)

Supplementary Table 4: Statistical comparison of the early clinical symptoms.

Symptoms present in the first three symptoms	rATL vs frontal		rATLl vs lATL		lATL vs frontal	
	χ^2	*p*	χ^2	*p*	χ^2	*p*
Loss of empathy	22.04	**<.001**	11.2	**<.001**	1.54	0.214
Verbal semantic	17.86	**<.002**	32.62	**<.001**	90.1	**<.001**
Person-specific knowledge	56.16	**<.001**	3.32	0.68	36.6	**<.001**
Complex compulsions/rigid thought process	19.54	**<.001**	1.03	0.308	12.3	**< .001**
Repetitive motor behavior, hoarding, obsessions	8.49	**0.004**	0.03	0.863	8.7	**0.003**
Apathy	11.56	**<.001**	1.54	0.213	21.7	**< 0.001**
Disinhibition	5.22	**0.022**	0.814	0.367	10.78	**0.001**
Lack of judgment/dysexecutive	18.86	**<.001**	0	0.99	21.1	**< .001**
Episodic memory	4.03	**0.045**	3.2	0.072	**0.003**	0.955
Altered food preference	0.904	0.342	3.63	0.057	1.56	0.21
Motor neuron disease	0.051	0.821	0.013	0.909	0.13	0.718
Problems Navigation	0.66	0.416	0	0	0.778	0.378

Bold represents statistically significant results.

Supplementary Table 5: Apathy and Disinhibition in the Neuropsychiatric Inventory.

	rATL*	Frontal*	lATL*
Apathy			
Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or lack motivation for starting new activities? Is he/she more difficult to engage in conversation or in doing chores? Is the patient apathetic or indifferent?	32 (37)[g]	44 (48)[m]	12 (25)[g, m]
Does the patient seem less spontaneous and less active than usual?	28 (30)	37 (42)	9 (11)
Is the patient less likely to initiate a conversation?	17 (29)[g]	31 (42)	10 (11)[g]
Is the patient less affectionate or lacking in emotions when compared to his/her usual self?	22 (27)	32 (41)	5 (11)
Does the patient contribute less to household chores?	18 (30)[e]	36 (41)[e]	6 (11)
Does the patient seem less interested in the activities and plans of others?	22 (30)	35 (43)	5 (11)
Has the patient lost interest in friends and family members?	18 (30)	33 (42)	5 (10)
Is the patient less enthusiastic about his/her usual interests?	22 (30)	34 (40)	7 (11)
Does the patient show any other signs that he/she doesn't care about new things?	10 (29)[g]	15 (41)[m]	5 (11)[g,m]
Disinhibition			
Does the patient seem to act impulsively without thinking? Does he/she do/say things that are not usually done or said in public? Does he/she do things that are embarrassing to you or others?	32 (37)	40 (48)	10 (25)
Does the patient act impulsively without appearing to consider the consequences?	27 (29)	37 (39)	8 (10)
Does the patient talk to total strangers as if he/she knew them?	16 (30)[g]	20 (38)[m]	7 (10)[g,m]
Does the patient say things to people that are insensitive or hurt their feelings?	15 (29)	23 (39)	4 (10)
Does the patient say crude things or make sexual remarks that they would not usually have said?	3 (30)[e,g]	13 (38)[e]	1 (10)[g]
Does the patient talk openly about very personal or private matters not usually discussed in public?	6 (29)	15 (38)	1 (10)
Does the patient take liberties or touch or hug others in way that is out of character for him/her?	8 (30)[g]	8 (37)[m]	3 (10)[g,m]
Does the patient show any other signs of loss of control of his/her impulses?	17 (29)	22 (39)	6 (10)

*The first number represents the number of patients who had a positive answer to the question, the number between parentheses is the number of patients whose data on the question is available.
Right temporal different from frontal at <.05: e
Right temporal different from left temporal at <.05: g
Frontal different from left temporal at <.05: m

Supplementary Table 6: Neuropathological results of the right temporal autopsy group.

rATL case	Primary Diagnoses	Contributing Diagnoses	Incidental Diagnoses	AD Thal Phase	AD Braak Stage	AD CERAD NP Score
P1	FTLD-TDP Type C		1.Areriolosclerosis 2. Microinfarct 3. CAA 4. ADNC	1	1	0
P2	FTLD-TDP Type C		1. Vascular brain injury 2.Areriolosclerosis 3. LBD 4. ADNC	1	1	1
P3	FTLD-TDP Type C		1. AGD 2. Arteriolosclerosis 3. CAA 4. LBD 5.ARTAG 6. ADNC	2	2	2
P4	FTLD-TDP Type C	Traumatic brain injury; Traumatic tauopathy	1. AGD. 2. Microinfarcts. 3.Areriolosclerosis 4. ADNC	1	3	0
P5	FTLD-TDP Type C		1. ADNC 2.Vascular malformation	2	1	0
P6	FTLD-TDP Type C	AD	1. AGD 2. Arteriolosclerosis 3. CAA	5	6	3
P7	FTLD-TDP Type C	FTLD-tau PSP	ADNC	1	0	0
P8	FTLD-TDP Type C	AD	1. CAA 2.Hemorrhagic infarct 3. Arteriolosclerosis	4	6	3
P9	FTLD-TDP Type C		ADNC	Incomplete	2	3
P10	FTLD-TDP Type C		1. ADNC 2. CAA 3. Meningioma	1	2	0
P11	FTLD-TDP Type C		ADNC	Incomplete	2	0
P12	FTLD-TDP Type C			1	2	0
P13	1. FTLD-TDP Type C 2. Primary lateral sclerosis PLS-TDP		1.Areriolosclerosis 2.ADNC	1	0	0
P14	1. FTLD-TDP Type B 2. MND, lower motor neuron only MND-TDP		1. Arteriolosclerosis 2. ADNC	1	1	0
P15	FTLD-TDP type A		ADNC	NA	2	NA
P16	1.FTLD-TDP Unclassifiable 2. MND, lower motor neuron only MND-TDP	1. Lacunar infarct 2. Microinfatct	1. AGD 2. Arteriolosclerosis 3. CAA 4. ADNC	4	1	3
P17	FTLD-tau Pick`s type			0	0	0
P18	FTLD-tau Pick`s type		1. Arteriolosclerosis 2. ADNC	1	1	0
P19	FTLD-tau unclassifiable 4R tauopathy		1. ADNC 2. Vascular brain injury	Incomplete	0	0

Abbreviations: AD = Alzheimer`s disease; ADNC = Alzheimer`s disease neuropathological changes; AGD = Argyrophilic grain disease, ARTAG = Age-related tau astrogliopathy, CAA = Cerebral amyloid angiopathy. PSP = Progressive supranuclear palsy. FTLD = Frontotemporal lobar degeneration. TDP-43 = TAR DNA-binding protein 43.

Supplementary Table 7: APOE4 prevalence.

	Frontal n (%)	Healthy Control n (%)	Left Temporal n (%)	Right Temporal n (%)
E2E2	1 (1.3)			
E2E3	12 (16)	7 (12)	7 (11)	7.2 (18)
E2E4	1 (1.3)			
E3E3	42 (56)	40 (69)	36 (58)	22 (55)
E3E4	19 (25.3)	11 (19)	19 (30)	8.8 (22)

Supplementary Table 8: Sensitivity and specificity of the proposed diagnostic criteria.

Sample = sbvFTD and bvFTD patients	First Three Years	First Visit	All Visits
Sensitivity	81.39	86.04	93.02
Specificity	84.28	82.86	81.43

Supplementary Table 9: Area under the curve and sensitivity and specificity of certain cutoff points of the main socioemotional and neuropsychiatric tests in differentiating sbvFTD from bvFTD and svPPA.

sbvFTD-bvFTD	**AUC**	**Cutoff**	**Sensitivity**	**Specificity**
FF-Recognition	98	12.5	100	88
TASIT - sarcasm	90	6.5	88	67
TOM - Cognitive	76	10.5	93	56
BNT	75	6.50	93	57
PPVT	72	7.5	92	70
IAS - Dominance	71	25	92	63
sbvFTD-svPPA	**AUC**	**Cutoff**	**Sensitivity**	**Specificity**
FF-Recognition	82	10.5	84	50
TASIT - sarcasm	74	5.5	73	59
TOM - emotional	65	11.5	82	66
BNT	73	2.5	85	56
IAS - cold	75	21.5	84	58
CATS - affect matching	78	9.5	90	57

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