Supplementary Material

Disentangling Clinical Profiles of Apathy in Behavioral Variant Frontotemporal Dementia

Supplementary Material 1

A. ECOCAPTURE protocol overview

The recruitment period of the ECOCAPTURE protocol started in September 2017. Within the ECOCAPTURE protocol, an ecological setting was used to observe and record participants' behavior during a predetermined 45-min multiple-phase script (described below). This setting reproduced a close-to-real-life situation in a functional exploration platform (PRISME, ICM core facility, Salpêtrière hospital, Paris, France) transformed into a fully furnished waiting room and equipped with video and a sensor-based data acquisition system (including an accelerometer) that tracked the participant's behavior. Participants were told that they had to wait in a room that serves as a staff lounge before doing further tests and they were left alone in the room (except during a few interventions of the experimenter between the phases of the script). At the time of initial consent, participants had been informed that their behavior would be recorded by video cameras located in the room. Apart from undergoing the 45-min scenario for ecological behavioral recording, all participants of the ECOCAPTURE protocol carried out extensive neuropsychological and clinical assessments and a brain MRI protocol.

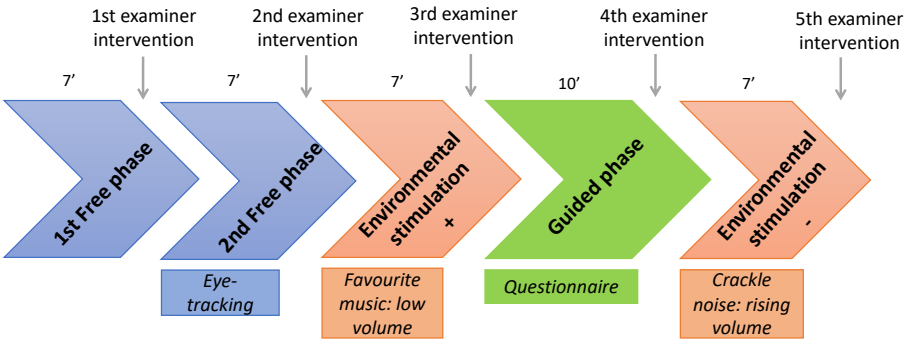
B. Description of the ECOCAPTURE scenario

The ECOCAPTURE paradigm mimics a naturalistic situation (i.e., waiting time in a comfortable waiting room) with a structured scenario designed to obtain objective measures of behavioral syndromes such as apathy or disinhibition.

Prior to the experimental session, the examiner asked the participant (and/or caregiver) to indicate his/her preferences for food, drinks, types of magazines, and music. The room and the scenario (type of music displayed as positive environmental stimulation) were customized accordingly.

Outside of the room (in the adjacent monitoring room), the examiner told the participant that he/she was going to wait a little in a staff lounge before doing more tests. The participant was then equipped with the device used to record the acceleration signal: a ®Movisens triaxial accelerometer worn on the hip during the whole ECOCAPTURE scenario.

As described below, the ECOCAPTURE scenario lasted for a total of about 45 min and was divided into 5 phases interrupted by short examiner interventions.



For our research, we focused specifically on the first free phase and on the guided phase detailed hereafter.

Details on the first free phase (FP-7 minutes)

The examiner invited the participant to enter the room, to make himself/herself comfortable in the room. Video coding of behaviors for FP was started when the observer left the room, leaving the participant alone in the waiting room.

This first phase was self-guided: subjects were simply invited to make themselves at ease in the room and to use the provided objects at their own convenience. They could use the space (e.g., sit on a chair around a table or on a sofa) and use provided foods, drinks, magazines, books, games, etc… For instance, some subjects used the kettle to boil water and prepared a cup of coffee or tea.

Details on the guided phase (GP-10 minutes)

After knocking the door, the examiner entered and brought the questionnaire to the participant, asking him/her to fill it out. The subject often asked for pens. The examiner simply said that everything needed to fill the questionnaire was in the room and no indication was given about the location of pens. Video coding of behaviors for GP was started when the participant was once again alone in the waiting room.

The questionnaire handled by the examiner was divided into five parts and the first written instruction was to complete the questionnaire in the following order and with the required pen:

QUESTIONNAIRES	PEN
QUESTIONNAIRE « FOOD ITEMS IN THE ROOM »	Blue pen
QUESTIONNAIRE « DEMOGRAPHIC » QUESTIONNAIRE TAILLE ET POIDS	Black pen
QUESTIONNAIRE « SLEEP »	Blue pen
QUESTIONNAIRE « MEALS »	Green pen
QUESTIONNAIRE « FURNITURE IN THE ROOM »	Red pen

All questionnaires contained very easy questions: either personal questions on age, job, marital status, height, weight, quality of sleep, preferences for meals… or questions requiring exploration of the room like selecting food items present in the room from a series of pictures of foods.

The most challenging aspect of the questionnaire was to fill it out with the correct pens. For instance, one part of the questionnaire had to be filled using a green pen. Finding the green pen in the room implied firstly, to find the box in which it was hidden, and secondly, to find the key to open the box.

C. Coding of observed behaviors and acceleration measures

Using the six videos covering the different viewpoints of the waiting room, behaviors were coded according to a predetermined ethogram for the FP and GP. For this study, we were specifically interested in two categories of behaviors: activity and walking. The video-based behavior coding was generated by using a manual video annotation tool (The Observer XT®, Noldus, Wageningen, The Netherlands). Inter-coder reliability was calculated in a subsample representing more than 20% of the participants (n = 8; 4 bvFTD and 4 HC). For this subsample, two different examiners coded the videos; one of them was blinded to the group identities of the subjects. All calculated Cohen's kappa coefficients were superior to 0.98, indicating close-to-perfect agreement between raters and therefore excellent interrater reliability.

We also used the values of movement acceleration (in g) automatically extracted at each second by the ®Movisens DataAnalyzer application. Through a saturation of the acceleration signal at the end of the ECOCAPTURE protocol (intense movement made by the experimenter with the accelerometer), we were able to calculate, for each participant, the offset between video and acceleration signal and thus to match coded behaviors with the corresponding acceleration signal.

Supplementary Material 2

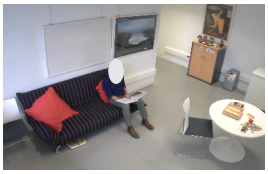
A. Extracted objective behavioral metrics and results of validity tests

Relying on previous observations [1], we assumed that in the specific ecological situation of the ECOCAPTURE protocol, a reduction of goal-directed behaviors would be manifested in the combination of: 1) a decreased time dedicated to the completion of "overt" goal-directed behaviors and 2) a tendency to wander in the room without being able to initiate and focus on any specific activity. As described in the figure below, we were therefore interested in two kinds of behavioral metrics in the free and guided phases:

1) *the activity time ratio***,** i.e., the ratio of time spent in sustained goal-directed actions, visibly organized towards a coherent purpose (e.g., reading a magazine, playing a game, any action visibly contributing to the filling of the questionnaire in the guided phase), which directly quantifies the *reduction of time spent in goal-directed behaviors*;

2) some *characteristics of walking episodes (occurrences, acceleration and duration)* which quantify *the tendency to wander (with frequent, long-lasting walking episodes of low acceleration)* and presumably *the lack of "goal-directedness" of movements in the room*.

Summarized methodology of extraction of behavioral metrics

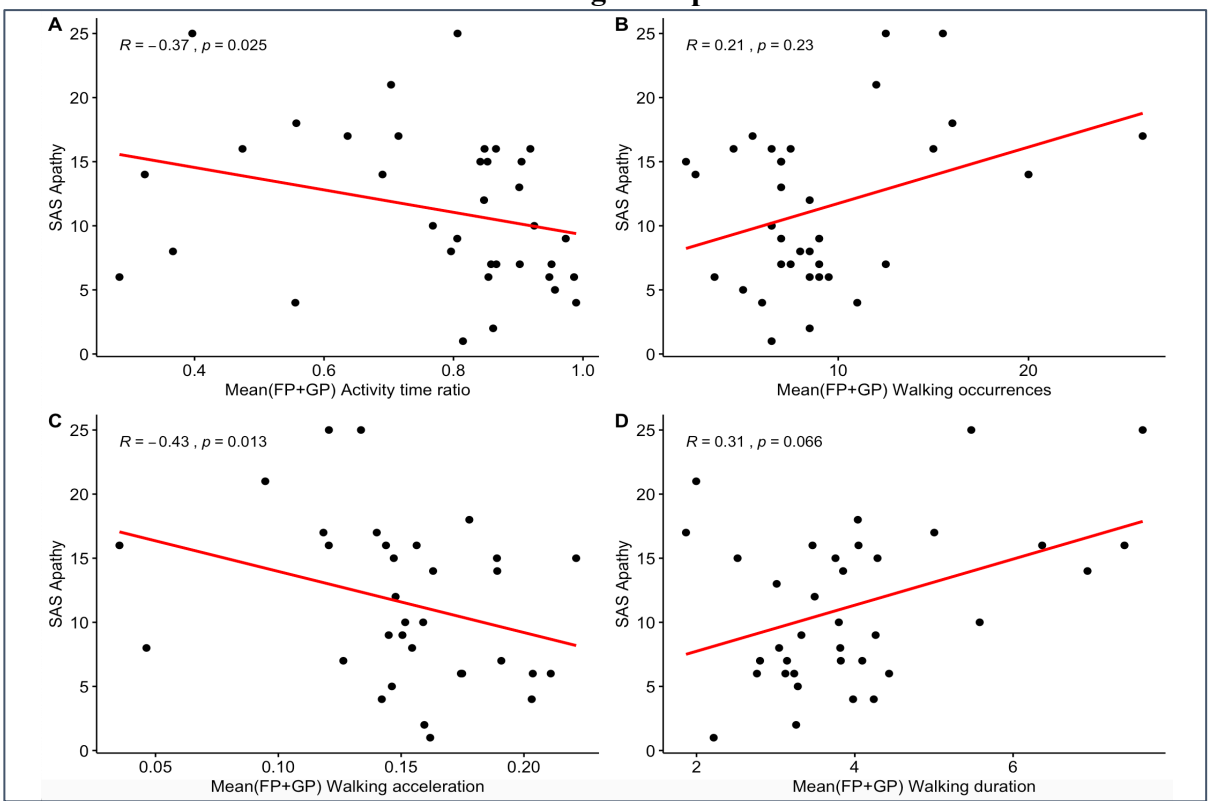


A1, A2, and A3 figure an example of a possible distribution across time of activity episodes for a participant, A1 and A2 being activity episodes in the free phase and A3 an activity episode in the guided phase. In this specific case, the computation of activity time ratio is described, for instance for the free phase, as the sum of the durations of A1 and A2 activity episodes divided by the total duration of the free phase. Similarly, W1 to W8 figure a possible distribution across

time of walking episodes for a participant. In this specific case, walking metrics, for instance for the free phase, are computed as follows: walking occurrences is the total number of walking episodes in the free phase (W1 to W4), walking acceleration is the mean acceleration of walking episodes W1 to W4, walking duration is the mean duration of walking episodes W1 to W4.

We investigated the validity of these extracted metrics through: 1) Comparisons between bvFTD patients (supposed to be highly apathetic) and controls; 2) Correlations with a validated clinical measure apathy by the Starkstein Apathy Scale (SAS). Comparisons confirmed that bvFTD patients and controls behaved differently on the four extracted metrics. Patients had lower activity time ratio, lower walking acceleration, higher walking duration than controls and contrary to controls, patients did not show an increase in walking occurrences in the guided phase compared to free phase. Correlations with SAS score (see figure below) further supported that the extracted behavioral metrics could be used as markers of reduced goal-directed behaviors: with higher SAS, the activity time ratio and walking acceleration decreased while walking duration and walking occurrences increased (especially in the free phase for walking occurrences ($R = 0.43$; $p < 0.01$)).

Correlations between apathy assessed by SAS and the four behavioral metrics averaged on free and guided phases



N=36 (bvFTD: N=20 / HC: N=16). $Mean_{(FP+GP)}$: mean calculated on the total of FP and GP ((FP+GP)/2)

B. Results of the Exploratory Factor Analysis (EFA) leading to the extraction of *F1* and *F2* [1]

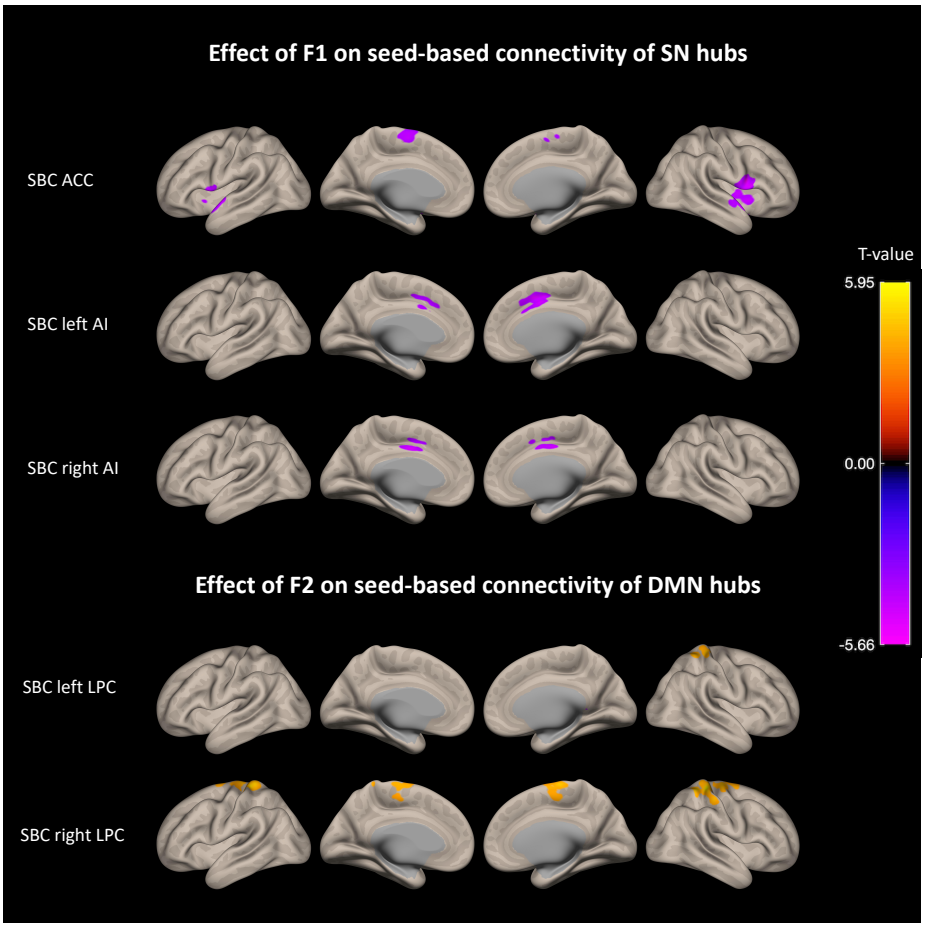
Observed variables	Factor loadings	
	F1	F2
SAS score	**0.85**	0.27
DAS-Executive score	**0.66**	0.11
$Mean_{(FP+GP)}$ Activity time ratio	**-0.48**	0.21
$Mean_{(FP+GP)}$ Walking acceleration	**-0.36**	0.02
$Mean_{(FP+GP)}$ Walking duration	**0.34**	0.12
$Mean_{(FP+GP)}$ Walking occurrences	**0.33**	-0.05
DAS-Initiation score	0.21	**0.67**
$Delta_{(FP-GP)}$ Walking duration	-0.12	**0.63**
DAS-Emotional score	0.14	**0.60**
$Delta_{(FP-GP)}$ Walking acceleration	0.12	**-0.53**

[1] Values indicate the factor loadings of the EFA. Coefficients in bold represent the highest loading (among the two factors) for each item. The calculation of individual scores on *F1* and *F2* takes into account all the factor loadings onto *F1* and *F2* respectively. N=36 (bvFTD: N=20 / HC: N=16). $Mean_{(FP+GP)}$, mean calculated on the total of FP and GP ((FP+GP)/2); $Delta_{(FP-GP)}$, delta calculated as the difference between FP and GP (FP-GP); Activity time ratio, ratio of time spent in goal-directed activity; Walking occurrences, occurrences of walking episodes; Walking acceleration, mean acceleration of walking episodes; Walking duration, mean duration of walking episodes. *N.B.*, $Delta_{(FP-GP)}$ Activity time ratio and $Delta_{(FP-GP)}$ Walking occurrences were removed from the analysis for both statistical and theoretical reasons (e.g., they were not supposed to be comparable enough in the free and guided phase in terms of their ability to quantify individual differences in the quantity of goal-directed behaviors);

C. Summary of results supporting the validity of *F1* and *F2* dimensions

- All the means of extracted behavioral metrics loaded on *F1* as well as the SAS and DAS-Executive scores. Therefore, ***F1* was assumed to correspond to the expected dimension of global reduction of goal-directed behaviors (or global apathy).** All the deltas of behavioral metrics loaded on *F2* along with DAS-Initiation and DAS-Emotional scores. Thus, ***F2* was supposed to correspond to the expected dimension assessing the specific deficit of self-initiation of goal-directed behaviors.**
- Between-group comparisons on extracted scores confirmed that both *F1* ($T = 6.86$; $p < 0.001$) and *F2* ($T = 2.37$; $p < 0.05$) dimensions were significantly higher in bvFTD compared to controls.
- Moreover, *F1* showed a high negative correlation ($R = -0.60$; $p < 0.001$) with executive function (i.e., cognitive processes allowing to select and monitor behaviors facilitating the attainment of chosen goals) measured by the FAB, in accordance with the assumption that *F1* measures a global reduction of goal-directed behaviors. In contrast, *F2* was not related to FAB total score ($R = -0.05$; $p = 0.78$).

- *F1* dimension was related to lower low-frequency signal power within several distinct regions of the PFC: the right OFC, the bilateral DLPFC and DMPFC. These regions correspond to the frontal part of the three frontostriatal circuits associated with apathy in the model proposed by Levy and colleagues [2–4]. As shown in the figure below, we also found that, across bvFTD and controls, *F1* was associated with a decreased connectivity between the three salience network (SN) hubs (i.e., from ACC seed to left/right frontoinsular regions and from left/right AI seeds to ACC), a decreased connectivity between the ACC and the ventral striatum, and a decreased connectivity between the ACC and the dorsomedial frontal cortex (i.e., supplementary motor area - SMA). These results were consistent with a model of connectivity changes explaining the severity of clinical symptoms (such as apathy) in bvFTD [5,6].
- *F2* was found to increase with the connectivity between left and right lateral parietal cortex (i.e., default-mode network (DMN) hubs) and medial frontal/parietal cortex. This was in agreement with a revised model of apathy in which impaired internal initiation of behavior mediated by a dysfunction of the lateral parietal lobule may be sufficient (although not necessary) to reduce goal-directed behavior, and would constitute a volitional subtype of apathy [7].



We observed a negative association between F1 and the seed-based connectivity of salience network (SN) hubs and on the opposite, a positive association between F2 and the seed-based connectivity of two default-mode network (DMN) hubs. N=34 (bvFTD: N=18 / controls: N=16). Effects are corrected for age and sex, and for family-wise error at the level of individual clusters at $p < 0.05$. SBC, seed-based connectivity; F1, global reduction of goal-directed behaviors; F2, specific deficit of self-initiation.

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Supplementary Material 3

Detail of clinical characteristics of bvFTD patients in the three subgroups

Study ID	bvFTD subgroup	Sex	Age	MMSE	DRS	FAB	SAS	DAS Executive	DAS Emotional	DAS Initiation
8	bvFTD-G1	F	45	25	123	13	**15**	8	**17**	13
9	bvFTD-G1	F	58	24	132	16	**25**	13	10	**22**
20	bvFTD-G1	M	64	21	125	14	**18**	9	13	13
28	bvFTD-G1	M	71	26	135	15	**25**	**15**	**16**	**19**
29	bvFTD-G1	M	67	29	113	14	**15**	5	9	**17**
30	bvFTD-G1	M	67	27	124	13	9	10	**15**	9
32	bvFTD-G1	M	74	23	108	16	**16**	5	**18**	15
35	bvFTD-G1	M	64	25	127	15	**21**	**16**	14	15
6	bvFTD-G2	M	50	23	123	14	13	1	8	7
7	bvFTD-G2	M	57	23	127	13	7	3	10	3
11	bvFTD-G2	M	72	25	117	13	**16**	8	3	0
19	bvFTD-G2	F	73	27	136	15	8	3	7	9
31	bvFTD-G2	M	61	21	104	12	**16**	4	11	5
2	bvFTD-G3	F	70	21	119	8	**15**	13	8	4
3	bvFTD-G3	F	64	20	110	6	**14**	**18**	9	3
14	bvFTD-G3	F	82	22	115	7	**17**	10	9	6
17	bvFTD-G3	M	73	28	114	14	10	12	8	11
22	bvFTD-G3	F	61	20	113	5	**16**	**16**	7	13
33	bvFTD-G3	M	70	23	106	10	**14**	13	14	6
36	bvFTD-G3	M	73	28	119	16	**17**	12	11	7

Values in bold are scores above the clinical cut-offs for SAS (≥14), DAS-Executive (≥14), DAS-Emotional (≥15) and DAS-Initiation (≥16).

Supplementary Material 4

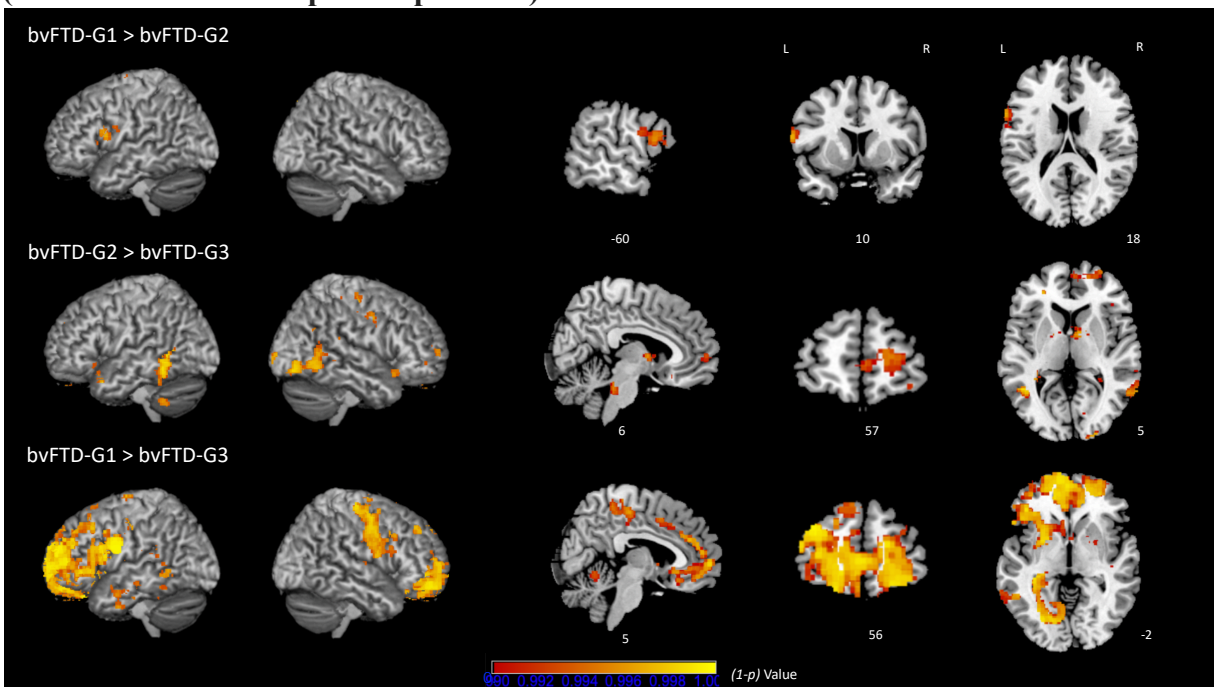
List of MNI coordinates of local maximum grey matter atrophy in frontal, insular, temporal, and subcortical regions for each subgroup of bvFTD patients

Regions for each subgroup	Hemisphere	MNI coordinates			T score
		x	y	z	
bvFTD-G1					
Middle Frontal gyrus	R	28	24	47	5.24
Cingulate gyrus (anterior)	R	5	-9	41	5.20
Insular cortex (anterior)	R	37	22	2	4.10
Frontal Orbital cortex	L	-38	23	2	3.91
Frontal Orbital cortex	R	36	19	-19	3.78
Middle Temporal gyrus (posterior)	R	57	-22	-19	5.13
Temporal pole	R	33	19	-29	4.03
Putamen	R	28	18	2	3.95
Caudate	R	18	20	5	3.09
bvFTD-G2					
Frontal Operculum cortex	L	-38	24	3	6.31
Insular cortex (anterior)	L	-27	24	-3	5.63
Inferior Frontal gyrus	L	-52	19	19	5.09
Precentral gyrus	R	9	-17	47	4.54
Cingulate gyrus (anterior)	R	8	32	-7	4.40
Inferior Frontal gyrus	R	46	16	21	4.34
Middle Frontal gyrus	R	45	18	48	4.29
Frontal Orbital cortex	R	30	23	-7	3.47
Temporal pole	R	38	18	-37	3.99
Inferior Temporal gyrus (anterior)	L	-52	-8	-31	3.97
Caudate	L	-14	21	1	3.78
Putamen	L	-22	21	-3	3.63
Caudate	R	14	22	3	3.62
Putamen	R	23	17	-3	3.52
bvFTD-G3					
Frontal Orbital cortex	L	-24	23	-9	6.87
Central Opercular cortex	L	-35	-1	17	6.11
Cingulate gyrus (anterior)	L	-12	44	7	5.99
Frontal pole	L	-23	56	1	5.90
Frontal Medial cortex	L	-4	31	-20	5.72
Frontal Operculum cortex	R	37	24	2	5.53
Inferior Frontal gyrus	L	-51	22	20	5.45
Frontal pole	R	26	54	-2	5.41
Central Opercular cortex	R	38	0	17	5.31
Precentral gyrus	R	42	-3	45	5.11
Superior Frontal gyrus	R	21	15	51	5.00
Cingulate gyrus (middle)	L	-8	0	41	4.86
Inferior Frontal gyrus	R	45	14	22	4.73
Middle Temporal gyrus (anterior)	L	-51	-3	-21	5.54
Superior Temporal gyrus (posterior)	L	-53	-24	-6	4.77
Middle Temporal gyrus (posterior)	R	56	-15	-14	4.52

Superior Temporal gyrus (anterior)	R	48	0	-20	4.43
Amygdala	R	32	-5	-21	5.03
Hippocampus	R	28	-5	-26	4.80
Amygdala	L	-31	-5	-21	4.73
Hippocampus	L	-28	-6	-26	4.24
Thalamus	R	20	-29	-4	4.03
Putamen	R	24	6	-5	5.12
Putamen	L	-25	18	-2	5.52
Caudate	R	11	13	-2	4.09
Caudate	L	-17	17	2	4.40
Thalamus	L	-23	-30	-4	3.00

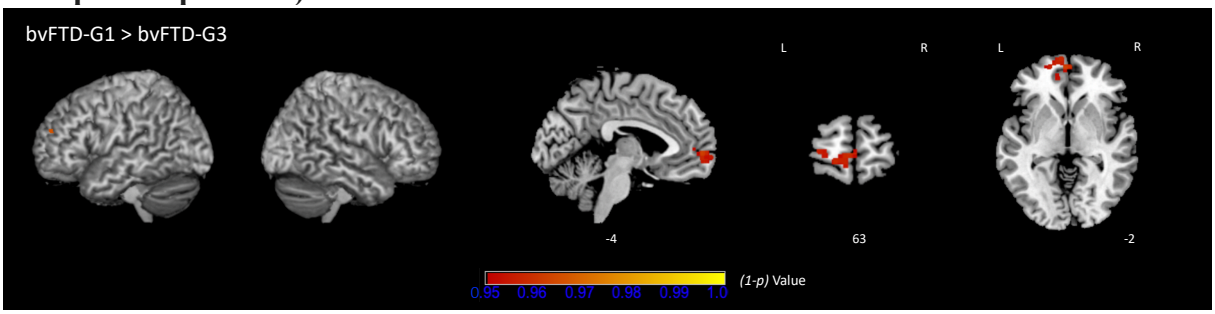
Supplementary Material 5

A. Comparisons between bvFTD subgroups on their global atrophy pattern (uncorrected for multiple comparisons)



BvFTD-G1 (N=8), bvFTD-G2 (N=5) and bvFTD-G3 (N=7). The (1-p) value maps show the distribution of higher grey matter density (or lower atrophy) in: 1. bvFTD-G1 compared to bvFTD-G2 (bvFTD-G1 > bvFTD-G2); 2. bvFTD-G2 compared to bvFTD-G3 (bvFTD-G2 > bvFTD-G3); 3. bvFTD-G1 compared to bvFTD-G3 (bvFTD-G1 > bvFTD-G3). They are superimposed onto a whole-brain MNI template. Effects were corrected for age and sex, and statistical significance was set at $p < 0.01$ uncorrected for multiple comparisons.

B. Comparisons between bvFTD subgroups on their global atrophy pattern (corrected for multiple comparisons)



BvFTD-G1 (N=8) and bvFTD-G3 (N=7). The (1-p) value map shows the distribution of higher grey matter density (or lower atrophy) in bvFTD-G1 compared to bvFTD-G3 (bvFTD-G1 > bvFTD-G3). It is superimposed onto a whole-brain MNI template. Effects were corrected for age and sex, and statistical significance was set at $p < 0.05$ FWE-corrected for multiple comparisons. There was no significant cluster for the comparison of bvFTD-G1 versus bvFTD-G2 and for the comparison of bvFTD-G2 versus bvFTD-G3.