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First Symptoms and Neurocognitive Correlates of Behavioral Variant Frontotemporal Dementia

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Abstract.
Background: Previous works highlight the neurocognitive differences between apathetic and disinhibited clinical presentations of the behavioral variant frontotemporal dementia (bvFTD). However, little is known regarding how the early presentation (i.e., first symptom) is associated to the neurocognitive correlates of the disease's clinical presentation at future stages of disease.

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Objectives: We analyzed the neurocognitive correlates of patients with bvFTD who debuted with apathy or disinhibition as first symptom of disease.
Methods: We evaluated the neuropsychological, clinical, and neuroanatomical (3T structural images) correlates in a group of healthy controls ($n = 30$) and two groups of bvFTD patients (presented with apathy [AbvFTD, $n = 18$] or disinhibition [DbvFTD, $n = 16$]). To differentiate groups according to first symptoms, we used multivariate analyses.
Results: The first symptom in patients described the evolution of the disease. AbvFTD and DbvFTD patients showed increased brain atrophy and increased levels of disinhibition and apathy, respectively. Whole brain analyzes in AbvFTD revealed atrophy in the frontal, insular, and temporal areas. DbvFTD, in turn, presented atrophy in the prefrontal regions, temporoparietal junction, insula, and temporoparietal region. Increased atrophy in DbvFTD patients (compared to AbvFTD) was observed in frontotemporal regions. Multivariate analyses confirmed that a set of brain areas including right orbitofrontal, right dorsolateral prefrontal, and left caudate were enough to distinguish the patients' subgroups.
Conclusion: First symptom in bvFTD patients described the neurocognitive impairments after around three years of disease, playing an important role in the early detection, disease tracking, and neuroanatomical specification of bvFTD, as well as in future research on potential disease-modifying treatments.

Keywords: Apathy, behavioral variant frontotemporal dementia, disinhibition, apathy, first symptom, voxel-based morphometry

INTRODUCTION

The behavioral variant of frontotemporal dementia (bvFTD) is a neurodegenerative disease with early pervasive behavioral dysfunctions affecting social behavior, cognition, and personality [1–3]. Among the most frequent features at the early stages of bvFTD are apathy and disinhibition [4, 5]. Recent studies have focused on the early detection of bvFTD as it has implications for the differential diagnoses of psychiatric disorders [2], heritability [6], therapeutics [7], and the environmental management of patients [8]. Understanding how the first behavioral symptoms shape the neurocognitive profiles of bvFTD is fundamental to early detection.

Although behavioral symptoms in bvFTD can occur variably [9], two distinct presentations termed "apathetic" and "disinhibited" have been largely reported [9,10] and are considered the most prevalent behavioral symptoms of bvFTD [2]. Apathy is the quantitative reduction of self-generated voluntary and purposeful goal-directed behavior [10, 11] due to either a lack of motivation or the inability to elaborate a plan to achieve a goal [11]. The bvFTD apathetic presentation includes patients who have a lack of interest in their surroundings and difficulty initiating, planning, and self-motivating related to a specific goal [11]. In contrast, disinhibition involves a reduction of mechanisms of cognitive control, such as of inhibitory control [11, 12]. BvFTD disinhibited presentation predominantly exhibits with impulsiveness and hyperactivity, typically showing undue familiarity, disorganized behaviors, irritability, and sexual acting out [13]. Alterations in goal-directed behavior related to atrophy in frontal areas and basal ganglia are involved in apathetic bvFTD [11, 14, 15]. Conversely, impairment in inhibitory control related to atrophy in the orbitofrontal (OFC), frontal ventromedial and anterior temporal areas are implicated in disinhibited bvFTD [12, 14].

Despite the general importance of bvFTD behavioral symptoms [16], no study has specifically focused on how the early presentation of these symptoms shapes the neuropsychological correlates and the disease's pattern of atrophy. Whether the presence of apathetic or disinhibited first symptoms are involved in bvFTD neurocognitive characterization is relevant to the early detection of bvFTD, as well as potential disease-modifying treatments [14]. To our knowledge, this is the first study assessing whether first symptoms are associated to the future neurocognitive profile when patients debut with apathy or disinhibition.

Here, we evaluated the neuropsychological and neuroanatomical correlates (measured at an average of 3 years after the report of the first symptom) in a group of controls and two groups of bvFTD patients (debuting with apathy or disinhibition). We expected a different neurocognitive presentation between groups accordingly to the first symptom. We also expected that a differential pattern of neuropsychological scores in sensitive neuropsychological measures of apathy and disinhibition, as well as dissociable patterns of neuroanatomical signs between both groups, would be observed: specifically, the AbvFTD group's larger atrophy in goal-directed behavior areas (right frontal and basal ganglia regions) and the DbvFTD group's larger atrophy

in regions related to in inhibitory control process (ventromedial and OFC). Moreover, specific brain-behavior links within those neurocognitive correlates (sensitive neuropsychological measures and atrophy regions) in each group were anticipated. Finally, with a focus on practical differential diagnosis, we estimated which variables were better able to distinguish groups by conducting multivariate analyzes including a factorial discriminant analysis and applying a machine learning method.

METHODS AND MATERIALS

Participants

Thirty-four patients recruited from an ongoing protocol [17–19] met the revised criteria for probable bvFTD [4]. See Supplementary Material for a detailed description of patient assessment. Thirty control subjects were recruited from a larger pool of volunteers who did not have a history of drug abuse or a family history of neurodegenerative or psychiatric disorders. Controls were recruited and matched one by one with the bvFTD patients, controlling for sex, age, and years of education. All participants provided informed written consent, in agreement with the Helsinki declaration. The Ethics Committees of the Pontificia Universidad Javeriana and Institute of Cognitive Neurology approved this study.

First stage of evaluation-grouping strategy

First, we defined patient groups based on the debut symptom of disease. The debut symptom was established on the basis of family/caregiver reports and clinical history documents. To verify the presence and particularity of the debut symptoms, we only included patients who reported that the reason for the consultation was the discomfort associated to a defined and exclusive first symptom. This criterion was met by 34 out of a total of 41 patients. Seven patients were excluded as they reported that their consultation was not motivated by a main first symptom of apathy or disinhibition. Among those patients, four presented unspecified symptoms, including cognitive alterations. Two other patients were excluded because their consultation did not follow from discomfort associated to its first symptoms. The final samples included in the study comprised 18 patients who debuted with apathy (AbvFTD), and 16 who debuted with disinhibition (DbvFTD).

Ten external raters with clinical expertise (including five psychiatrists, three neurologists, and two neuropsychologists), blinded to diagnoses, assessed descriptions of first symptoms taking into account a group of clinical categories related to apathy or disinhibition in each case. Similar retrospective approaches have been used in studies exploring the lifetime prevalence of symptoms of mental disorders (see [1–3]). To be classified as apathetic, patients had to predominantly present the following symptoms: (a) changes in affectivity, in particular reduced or flattened affect; (b) changes in volition, including difficulty in initiating activities, reduced ability to plan or loss of motivation; or (c) changes in emotional responses, in particular indifference or reduced emotional responses to external events. Instead, to be labeled as disinhibited, patients had to predominantly present with these symptoms: (a) changes in affectivity, including irritability, euphoria, or inappropriate affect; (b) changes in social behavior, including undue familiarity, or breaching of social norms; or (c) changes in motor behavior, including impulsiveness, hyperactivity, disorganized behavior or sexual acting out. These criteria were based on previous studies of clinical signs of apathetic and disinhibited bvFTDs [4–6].

Based on the assessment of raters, patients were assigned to either the AbvFTD or the DbvFTD group. The reliability of the raters' assessments was measured using Cohen's kappa (κ) scores [7, 8]. Inter-rater reliability for was $k = 0.93$ for AbvFTD and $k = 0.87$ for DbvFTD; all (κ) scores were significant at $p < 0.001$.

Second stage of evaluation

Patient groups initially formed following a clinical criterion (namely first-consultation symptom) were studied around three years after disease debut (DbvFTD mean = 3.3 years SD = 4.1 versus AbvFTD mean = 3.1 years SD = 4.8). Neurocognitive and neuroanatomical correlates of each group were assessed at this stage. Neurocognitive processes were evaluated with a standardized neuropsychological measures typically used in patients with neurodegenerative diseases. VBM scores were used to assess brain atrophy correlates of patients in each group.

Neuropsychological assessment

Global cognitive performance was assessed through a comprehensive set of measures, namely, the Frontal Behavioral Inventory (FBI) [30], the INECO

Frontal Screening (IFS) Battery [31], the Montreal Cognitive Assessment (MoCA) [32], and the Mini-Mental State Examination (MMSE) [33].

Neuropsychiatric manifestations including apathy and disinhibition were assessed with the subjective subscales of apathy, executive functions, and disinhibition of the Frontal System Behavioral Scale (FrSBe) [34]. As an additional measure of disinhibition, we also administered the Hayling Test [35]. Other cognitive domains, including attention skills, verbal memory, attentional control, and cognitive control, were assessed with the Digit Symbol task [36], the Boston Naming Test [37], and the Wisconsin Card Sorting Task [38].

The Clinical Dementia Rating was used to determine the stage of dementia, as in previous research (see [26, 28, 29]).

Imaging recordings and voxel-based morphometry (VBM)

Images for this study were obtained from a Philips Achieva 3T scanner with a 16-channel SENSE antenna. The anatomical and 3D T1-weighted images had the following parameters: TR = 7.9, TE = 3.8, ACQ matrix 220×220 pixels, voxel size $0.5 \times 0.5 \times 0.5$ mm, 310 sections.

Neuroanatomical correlates were analyzed using VBM method. Data processing and analysis were performed with VBM8 in the Statistical Parametric Mapping 8 package (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) running under Matlab 2012b (The Mathworks, Natick, MA, USA). Each image was inspected for artifacts. All imaging analysis processes were conducted as described in the VBM pipeline (http://www.fil.ion.ucl.ac.uk/∼john/misc/VBM) and are briefly summarized as follows. The T1-weighted images were normalized to the same stereotaxic space generated from the complete data set using the DARTEL algorithm that significantly reduces the imprecision of inter-subject registration. Then, the images were segmented into WM and GM and non-brain voxels (CSF, skull). Subsequently, all images were modulated to correct volume changes by Jacobian determinants. Finally, images were smoothed by convolution with an isotropic Gaussian kernel of 8-mm full-width at half maximum for statistical analyses.

Assessment of neuroanatomical markers: whole-brain and regions of interest (ROI) analyses: To assess atrophy regions as predictors of groups, we have used two procedures: (a) we compared neuroanatomical differences between groups using whole-brain analyses; and (b) we restricted the multidimensionality of data using critical bilateral ROIs involved in bvFTD behavioral symptoms [14, 20, 21]. All VBM analyses between groups were corrected using FDR at 0.05. VBM procedure for ROIs analyses were conducted using a mask centered in a group of bilateral ROIs reported to be involved in neuropsychiatric symptoms (apathy and disinhibition) of bvFTD. Apathy as symptom of bvFTD is associated with atrophy in prefrontal regions—including bilateral dorso lateral prefrontal cortex (R-L DLPFC), and bilateral Orbito Frontal Cortex (R-L OFC), bilateral anterior cingulate cortex (R-L ACC)—and basal ganglia, in particular, caudate (Caud) and putamen (Put) [14, 20, 21]. In contrast, disinhibition in bvFTD is associated with gray matter loss in right medial temporal structures such as right amygdala (R amyg), bilateral hippocampus (R-L Hipp), R-L OFC and R-L ACC [14, 20, 21].

Assessment of anatomic-clinical relationship

To detect distinctive neurocognitive profiles in each group, we calculated correlations between sensitive neuropsychological measures and atrophy regions in each group via Pearson's correlation coefficient and Sidak correction. VBM scores in ROIs (see Table 2) and standardized scores of neuropsychological measures such as the MMSE, the MoCA, the FBI, the FrSBe, and the Hayling test, among others (see Table 1), were entered as factors. We assumed that an increase in severity of the neuropsychological scores would be associated with decreased tissue density.

Multivariate analyses

To evaluate which neuropsychological and neuroanatomical variables better determine group membership (groups created by first-consultation symptom), we used two methods of binary classification: a factorial discriminant analyses (FDA) and a support vector machine (SVM). Both analyzes provide convergent and confirmatory information that allowed us to (a) specify the contribution of neuropsychological and morphometric measures in differentiating between the apathetic group and the disinhibited group; and (b) look for a possible decision rule for the differential classification between groups based on the minimum relevant neuropsychological and VBM variables. To introduce variables in both methods, we selected only those that reached significant differences between groups after statistical corrections. In each method we used two models.

Table 1
Demographic and neuropsychological assessments in patients according to first symptoms AbvFTD versus DbvFTD

	Controls ($n=30$) Mean /SD	AbvFTD ($n=18$) Mean /SD	DbvFTD ($n=16$) Mean /SD	p value Controls versus bvFTD	p value AbvFTD versus DbvFTD
Demographics					
Age (years)	60.1 (6.55)	58.0 (7.43)	57.0 (8.64)	N.S.	N.S.
Gender (F/M)	14/16	8/10	8/8	N.S.	N.S.
Education (years)	13.22 (4.8)	13.68 (4.3)	14.67 (3.7)	N.S.	N.S.
Age of disease progression	NE	3.1 (4.8)	3.3 (4.1)	NE	N.S.
Mini-Mental State Examination	27.4 (2.1)	22.7 (6.5)**	23.7 (4.5)**	<0.01	N.S.
Montreal Cognitive Assessment	26.2 (3.1)	17.2 (6.7)**	17.1 (6.1)**	<0.01	N.S.
Clinical Dementia Rating	NE	1.5 (0.8)	1.5 (0.6)	NE	N.S
Neuropsychological assessment					
IFS Total Score	27.2 (1.9)	13.4 (5.8)	12.6 (5.8)	N.S	N.S.
Phonological Fluency	NE	9.39 (6,3)	9.5 (5.3)	NE	N.S.
Hayling Test	NE	13.4 (5.8)	26.2 (2.8)	NE	<0.01
Frontal Behavior Inventory	NE	23.3 (9.6)	23.1 (13.9)	NE	N.S.
FrSBe total*	NE	48.4 (31.4)	47.8 (27.7)	NE	N.S.
FrSBe apathy score*	NE	23.3 (9.5)	17.8 (9.6)	NE	<0.01
FrSBe disinhibition score*	NE	7.6 (7.5)	9.7 (8.2)	NE	<0.01
FrSBe executive functions score	NE	25.5 (13.7)	27.2 (9.7)	NE	N.S.
Wisconsin Card Sorting Test	NE	22.9 (9.6)	22.9 (8.9)	NE	N.S.

*To obtain an index of progression of FrSBe scores, we calculated the actual score subtracting the present score from the previous score.
**Significant differences compared to controls. IFS, INECO Frontal Screening; FrSBe, Frontal System Behavioral Scale; N.S., differences were not significant; NE, not assessed.

Table 2
VBM differences between DbvFTD > AbvFTD groups in selected ROIs

Brain region	X	Y	Z	Cluster k	Peak p (FDR-cor)	Peak t	Peak z
R Frontal Sup Medial (R Dlpfc)	52.5	9.9	24.3	547	<0.01	283.65	6.67
R Middle Frontal Gyrus (R Dlpfc)	49.4	12.9	17.6	938	0.02	229.31	6.82
R Frontal Sup (R Dlpfc)	62.5	19.9	14.3	699	0.03	244.76	6.00
R Frontal Sup Orb (R Ofc)	39.6	61.2	0.8	449	<0.01	400.52	7.05
R Frontal Mid Orb (R Ofc)	29.6	69.3	0.9	263	<0.01	531.48	6.60
L Anterior Cingulate (L Acc)	–1.8	30.6	24.3	388	0.04	209.10	5.62
L Caudate (L Caud)	–8.1	12.6	–1.5	780	<0.0	380.97	6.45
L Superior Temporal Gyrus (L Stg)	–34.2	9.9	–24.3	377	0.04	191.87	5.22
L Temporal Mid (L Stg)	–37.8	10.8	–24.2	241	0.02	200.87	5.81

The first model included both the neuropsychological and anatomical variables that yielded significant differences between groups. A second model included only anatomical variables to avoid considering factors related to apathy and disinhibition, which are directly related to the criteria used to create groups.

Factorial discriminant analysis: FDA is a multivariate statistical procedure that uses a set of explanatory variables to classify patients into different subgroups and allows for the construction of a new variable—namely, the predictive score. This technique was chosen because it is used for classifying subjects into groups on the basis of a battery of measurements, as well as on its parsimonious interpretation [22, 23]. Two FDA analyses were performed. In the first FDA we included significant neuropsychological measures and neuroanatomical variables reached significance differences between groups. In a second model we only included significant neuroanatomical variables. The individual predictive score of each significant VBM score (in ROIs) and each significant neuropsychological measure was examined by t-test. This score maximizes the ratio of the variability between the groups to the variability within the groups and therefore patients of different groups have score values as different as possible. The score was used to determine a rule of prediction. Subsequently, to select a best subset of predictor variables, a final stepwise discriminant analysis was performed (at the 5% level and with the "stepwise" option, which is a forward selection allowing elimination; this procedure was applied following previous studies [22]).

Support vector machine: SVM models [24–26] were used to evaluate the neuropsychological and anatomical correlates that allow us to determine the

group of each patient (AbvFTD and DbvFTD). SVM is a supervised classification algorithm rooted in statistical learning theory [27], where input data are classified into two classes (in this case, AbvFTD and DbvFTD). Conceptually, input vectors are mapped to a higher-dimensional feature space using kernel special functions. Classification is performed by constructing a hyperplane in the feature space based on a training of data that optimally discriminates between the two groups by maximizing the margin between the two data clusters [27]. We determined the optimal values of two constants: γ, width of the radial basis function, and C, an input parameter for the SVM algorithm, which represents the error/trade-off parameter that adjusts the importance of the separation error in the creation of the separation surface [26].

We implemented different methods to select the variables for the model. First, we entered into the model the same variables used in the FDA analyses, i.e., neuropsychological measures and ROIs that yielded significant differences between groups (AbvFTD versus DbvFTD) after multiple corrections. Second, to avoid a possible bias mediated by the inclusion of ROIs involved in behavioral symptoms, we performed a SVM model using anatomical variables extracted from whole brain analyses of the contrast AbvFTD versus healthy controls and those extracted from the contrast DbvFTD versus healthy controls. Third, we implemented a SVM model using only ROI variables involved in behavioral symptoms (apathy and disinhibition). To perform SVM models the recursive feature elimination method [28], implemented by the selection of attributes in Weka (toolbox InfoGainAttributeEval) was used. This method of classification evaluates the worth of an attribute by measuring the information gain to discriminate information between groups [26, 28]. SVM models were implemented by defining a 10-fold cross validation. All experiments were conducted using the Waikato Environment for Knowledge Analysis (WEKA) http://www.cs.waikato.ac.nz/ml/weka suite of ML software [18, 28].

Statistical analyses at second stage measures

Neuropsychological measures

Demographic and neuropsychological data were compared between two groups of patients (AbvFTD, DbvFTD) and a control group using one-way ANOVA and chi square tests for the categorical variables. A one-way ANOVA was used to assess differences in neuropsychological measures between groups of patients (AbvFTD and DbvFTD). Bonferroni *post-hoc* tests were used (when appropriate) to examine group differences within the neuropsychological measures.

Regions of interest analyses

First, we performed a whole brain analysis using VBM to analyze differences in brain atrophy between the group of patients with AbvFTD and the group of patients with DbvFTD, as well as healthy controls (controlling for global intracranial volume, age, gender and length of disease duration, corrected with FDR at 0.001). In assessing atrophy regions as predictors of groups, we restricted the multidimensionality of data using the critical bilateral ROIs involved in bvFTD behavioral symptoms [14, 21, 29] (see above "Assessment of neuroanatomical markers"). Thus, VBM analyses (corrected using FDR at 0.05) between groups were conducted using a mask centered in these reported ROIs.

Assessment of anatomic-clinical relationship

Multiple correlations (Pearson coefficient and Sidak correction) were performed to identify how brain atrophy (VBM scores) correlated with the neuropsychological measures in each group. VBM scores in ROIs (see Table 2) and standardized scores of neuropsychological measures such as the MMSE, the MoCA, the FBI, the FrSBe, and the Hayling test, among others (see Table 1), were entered as factors. We assumed that an increase in severity of the neuropsychological scores would be associated with decreased tissue density.

RESULTS

Clinical, demographic, and neuropsychological results

The three groups (AbvFTD, DbvFTD, and Controls) were matched for age [$F(2, 63) = 1.58$, $p = 0.21$], gender [$\chi^2(1) = 1.11$, $p = 0.33$], education [$F(2, 63) = 1.57$, $p = 0.21$]. Differences between three groups were observed in MMSE scores [$F(2, 63) = 13.54$, $p = 0.001$]. AbvFTD (Bonferroni $p < 0.001$) and DbvFTD (Bonferroni $p < 0.001$) patients were outperformed on the MMSE by healthy controls, there being no differences between bvFTD groups (Bonferroni $p > 0.71$). Moreover, differences among the groups were also observed in MoCA scores [$F(2, 63) = 13.54$, $p = 0.001$] and in IFS [$F(2, 63) = 23.04$, $p = 0.0001$]. AbvFTD patients and

DbvFTD showed lower MoCA and IFS scores than healthy controls (*post hoc* analyses for AbvFTD versus Controls and DbvFTD versus Controls contrasts reached significant values: Bonferroni tests in both contrasts yielded $p < 0.001$ for MoCA and $p < 0.0001$ for IFS). No differences were found between bvFTD groups (Bonferroni tests showed $p > 0.52$ for MoCA and $p > 0.89$ for IFS) (see Table 1).

We found significant differences between AbvFTD and DbvFTD in disinhibition measures of FrSBe scale (DbvFTD = 9.7 SD = 4.2 versus AbvFTD = 7.6 SD = 3.5; [F(1, 33) = 3.42, $p < 0.06$]) and Hayling test (the number of errors) (DbvFTD = 26.2 SD = 2.8 versus AbvFTD = 13.4 SD = 5.8) [F(1, 33) = 7.54, $p < 0.01$]. The AbvFTD group showed worse scores than the DbvFTD group for only the apathy subscore in FrSBe (AbvFTD = 23.3 SD = 9.5 versus DbvFTD = 17.8 SD = 9.6) [F(1, 33) = 6.55, $p < 0.01$]. No other analyzes showed significant differences between the patient groups (for a further description of these analyses see Table 1).

Based on results from neuropsychological measures, and in order to facilitate further analyses, we generated a global score of disinhibition based on scores of both subjective and objective indexes used to assess disinhibition. FrSBe scores were used as a subjective measure of both apathy and disinhibition following previous procedures [14]. Hayling Test scores were used to objectively assess disinhibition, as this scale is sensitive to track response initiation and response suppression [12, 30] and it has been largely used to assess disinhibition in patients with neurodegenerative diseases (see [20, 21]). This global-score approach mirrors procedures used in previous reports of our group (see [18, 31]).

VBM Results

Whole brain analyses comparing each bvFTD group (AbvFTD and DbvFTD) with healthy controls showed widespread bilateral atrophy predominantly involving the mediofrontal, OFC, and anteromedial temporal areas, bilateral insula, and basal ganglia (all FDR 0.001). In particular, the AbvFTD group showed reduced VBM values in R DLPFC, R-L OFC, R-L ACC, and R-L Caud. DbvFTD showed reduced VBM values in more areas, including the R DLPFC, R OFC, R-L ACC, L STG, R-L Caud, medial frontal regions (R-L FM), and bilateral insula (R-L Ins). Distribution of atrophy in both groups was consistent with previous VBM studies [14, 21, 29, 32] (see Supplementary Figure 1 and Supplementary Table 1).

Whole brain analyses

Whole brain analyses comparing each bvFTD group (AbvFTD and DbvFTD) with healthy controls showed widespread bilateral atrophy predominantly involving the mediofrontal, OFC, and anteromedial temporal areas, bilateral insula, and basal ganglia (all FDR 0.001). In particular, the AbvFTD group showed reduced VBM values in R DLPFC, R-L OFC, R-L ACC, R-L Caud. DbvFTD showed reduced VBM values in more areas, including the R DLPFC, R OFC, R-L ACC, L STG, R-L Caud, medial frontal regions (R-L FM), and bilateral insula (R-L Ins). Distribution of atrophy in both groups was consistent with previous VBM studies[14, 21, 29, 32] (see Supplementary Figure 1 and Supplementary Table 1).

Additional whole-brain analyses comparing AbvTFD and DbvFTD groups showed differences in the brain atrophy pattern according to type of contrast. The AbvFTD > DbvFTD contrast showed major atrophy for the apathetic group in a collection of areas including the R DLPFC, Left precuneus, Right Angular Gyrus, and L Caudate (FDR 0.05). Instead, the DbvFTD > AbvFTD contrast reflected major brain atrophy for the disinhibited group in a set of areas including R-L OFC, R FM, R DLPFC, L STG, R-L ACC, and Left and Right Temporal Middle (R-L Temp M) (FDR 0.05) (see Supplementary Figure 1C).

ROIs differences between groups

Reduced VBM values in DbvFTD (DbvFTD> AbvFTD contrast) were found in the R OFC, right dorso lateral prefrontal cortex (R Dlpfc), left caudate (L Caud), left superior temporal gyrus (L STG), and left ACC (all $p < 0.01$) (see Table 2 and Fig. 1A). Using the opposite comparison (AbvFTD > DbvFTD), analyzes did not show significant differences.

To assess which areas were involved in generating both symptoms, VBM results were then reanalyzed covarying for the disinhibition score in AbvFTD and for apathy score in DbvFTD. In AbvFTD, reduced VBM values in R DLPFC and L Caud were preserved after covarying for the disinhibition score (FDR 0.01). In DbvFTD, reduced VBM scores in the L STG, R FM, and R OFC were preserved after covarying for the apathy score (FDR 0.01). VBM scores of R Caud, L ACC and bilateral insula were overlapped in both groups after covarying for apathy and disinhibition scores.

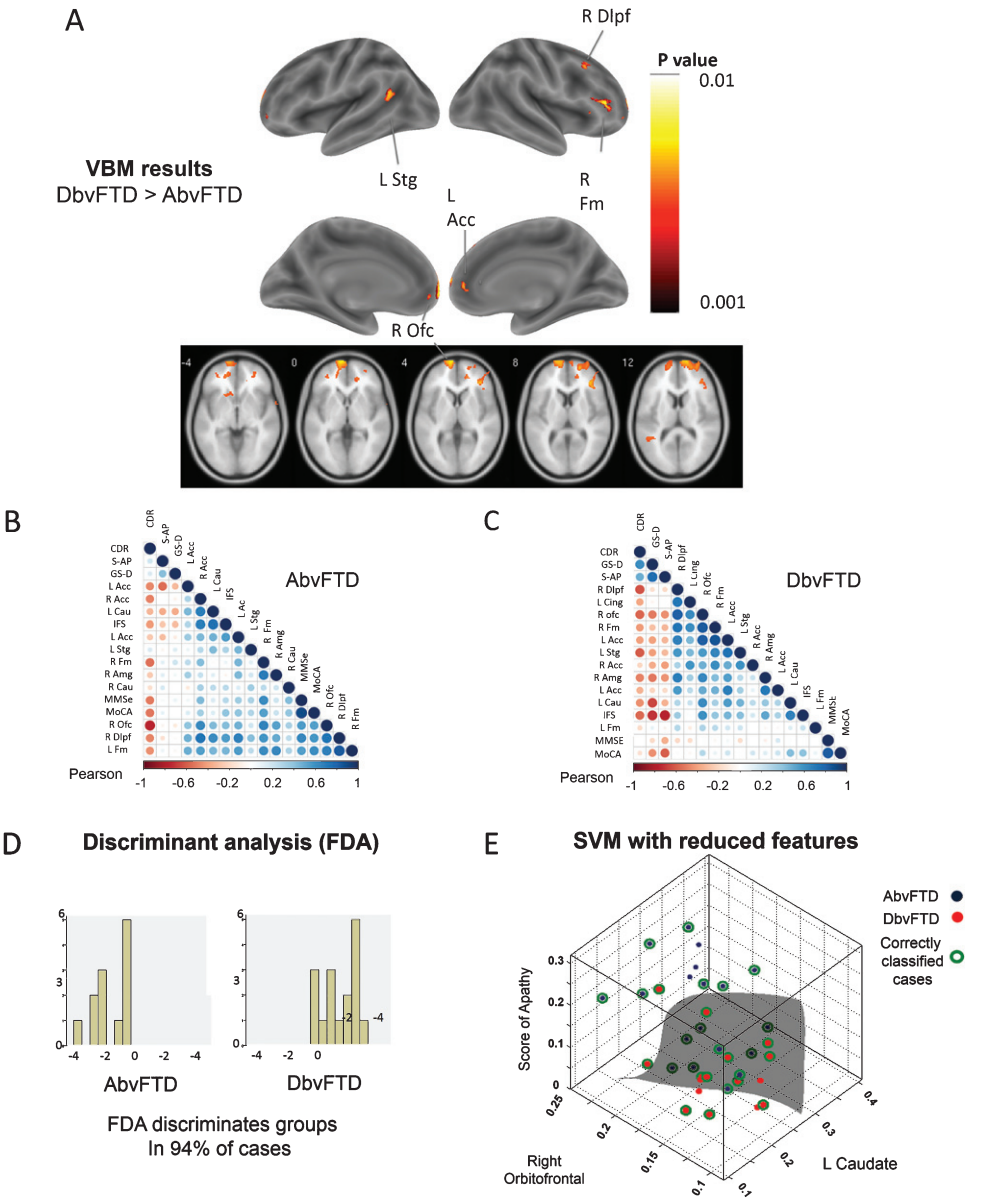

Fig. 1. Panel A depicts the significant areas that better discriminate between the apathetic (AbvFTD) and disinhibited groups (DbvFTD). Panel B and C show the matrices of correlations in each group: (A) apathetic group and (B) disinhibited group. We used significant variables between groups, including the neuropsychological measures and significant neuroanatomical scores as factors. Panel D shows the discriminant canonical function (FDA analysis) using six variables, including global score of disinhibition, score of apathy, R OFC, L Caud, R STG, and L ACC. This function is able to reach a discriminant power of 94.4%. Panel E shows a representation of classification using an SVM model with reduced features that was able to discriminate between groups with a precision index of 81%. The model postulated that R OFC, L Caud, score of apathy, and global score of disinhibition would be the better attributes to distinguish group membership. Here, we used a 3D-graph to facilitate the visualization, presenting the first three attributes selected by the SVM model (for a better visualization of SVM data, see Supplementary Figure 2).

Correlations between neuropsychological measures and ROIs in each group

Different patterns of correlations (Pearson, Sidak corrected) between neuropsychological measures and brain atrophy in each group (AbvFTD and DbvFTD) were detected (Fig. 1B,C). Among AbvFTD, we found a negative correlation between the score of apathy and voxel values of L Caud ($r^2 = -0.53$, $p < 0.01$) and R DLPFC ($r^2 = -0.48$, $p > 0.05$), as well as positive correlations among atrophy areas (R DLPFC and R ACC: $r^2 = 0.40$

$p < 0.05$; R OFC and R FM; $r^2 = 0.44$, $p < 0.05$). Among DbvFTD, the global score of disinhibition was inversely correlated with R OFC ($r^2 = –0.54$, $p < 0.01$), R DLPFC ($r^2 = –0.4$, $p > 0.05$), and L ACC ($r^2 = –0.51$, $p < 0.05$). In addition, a negative correlation between apathy score and L Caud ($r^2 = –0.49$, $p < 0.05$) was observed. Finally, in this group, positive correlations were also observed between R OFC and R DLPFC ($r^2 = 0.46$, $p < 0.05$) and between R DLPFC and L ACC ($r^2 = 0.51$, $p < 0.01$). No other correlations were significant.

Multivariate analyses

After identifying the neuropsychological variables and ROIs that showed a significant difference between groups, we included them as predictors in an FDA analysis and SVM model to assess the group classification of each patient. As neuropsychological measures, the global scores of disinhibition and apathy were included as predictors [33, 34]. Brain regions with significant differences between groups were: R OFC, R DLPFC, L Caud, L STG, and L ACC.

FDA

An FDA was performed on the reported variables (two neuropsychological measures and four ROIs). All variables showed a substantial separation between groups in terms of means of the discriminant score (r^2 ratio > 0.74). Among the 34 patients, 33 (97%) were correctly classified. To select a best subset of predictor variables, a final stepwise discriminant analysis was performed (at level 5%). After the stepwise discriminant analysis, the following five predictor-variables were retained: Global score of apathy and disinhibition, R OFC, DLPFC, and L caud. A second FDA was performed on these five remaining variables. Using this FDA among the 34 patients, 32 (94.1%) were correctly classified. The FDA used an individual predictive score of each significant VBM score and each significant neuropsychological measure based on the results of a *t*-test. We used this score to determine a prediction rule following a previous procedure [22]. The prediction rule was calculated as follows:

S = 2.68(Global score of disinhibition) – 2.78* (score of apathy) + 2.56*(R Ofc) + 2.08* (R Dlpfc) + 2.72*(L Caud)*

Following the S score, the next rule was derived: if S<0, then it belongs to the AbvFTD group. In contrast, if S>0, it belongs to the DbvFTD group. Using this decision rule, 100% (18/18) of the AbvFTD group and 88% (14/16) of the DbvFTD group were classified in the correct group (94.1%). Figure 1D shows that a subset of five variables seemed to be relevant in determining the group of each patient.

SVM

The SVM model included the global score of disinhibition and the score of apathy, and significant areas between groups, namely in the R OFC, R DLPFC, and L Caud, reached a sensitivity of 84.8%, an index of specificity of 80% and a precision index of 81.6% for differentiating between the groups.

To control the multidimensionality of analyses, we used an SVM model examining reduced features (measures) with the method of recursive feature elimination (RFE) using the selection of attributes in Weka [28]. This method assesses the worth of an attribute using an SVM classifier, and the features are ranked by the square of the weight assigned by the SVM. Following the rank proposed by this method, the four initial variables were selected as predictors; the first two attributes were two atrophy regions (R OFC and L Caud), and the two-second scores of apathy and disinhibition. An SVM model with these four variables reached a sensitivity of 83%, an index of specificity of 84% and a precision index of 81% for differentiating between the groups (see Fig. 1E and Supplementary Figure 2).

We ran two additional SVM models. The first one included anatomical variables extracted from whole-brain analyses of two contrasts (i.e., AbvFTD versus healthy controls and DbvFTD versus healthy controls). Following the rank proposed by the recursive feature elimination (RFE) method, the first eight attributes (brain areas) obtained by the model were: R Temporal M, Left Precuneus, L Caudate, R ACC, R OFC, L ACC, L STG, R FM. The SVM model using these attributes reached a sensitivity of 70%, and index of specificity of 68%, and a precision index of 67%. The last SVM model was performed only with the VBM scores of ROI areas that yielded between-group differences (namely R OFC, R DLPFC, L Caud, L STG, and L ACC areas). Following the RFE method, the first three attributes (brain areas) were L Caud, R DLPFC and R OFC. An SVM model with these three brain areas reached a sensitivity of 72.9%, an index of specificity of 71.8%, and a precision index of 72.1% for differentiating between the groups (see Fig. 1E and Supplementary Figure 2).

DISCUSSION

In this study, we evaluated how the first symptoms determine clinical and neuroanatomical profiles of bvFTD. The first symptom (apathetic or disinhibited) was related to bvFTD's neurocognitive characterization. After an average of 3 years of presentation of the first symptom (DbvFTD mean = 3.3 years SD = 4.1 versus AbvFTD mean = 3.1 years SD = 4.8), the patients who debuted with apathy (AbvFTD) presented higher apathy scores and the patients in the DbvFTD group exhibited higher disinhibition scores. Neuroanatomical signs revealed increased atrophy of DbvFTD compared with AbvFTD in several frontal, striatal, and temporal regions (Fig. 1A). Convergent multivariate analyzes (FDA and SVM) confirmed that apathy, disinhibition and related brain structures were able to determine the group with high accuracy (Fig. 1D,E). These findings highlight the relevance of bvFTD's first symptoms to the neurocognitive characterization and clinical course.

The first symptom determined the disease presentation, as shown by the results in neuropsychological measures assessed after around three years from the onset of disease (DbvFTD mean = 3.3 years SD = 4.1 versus AbvFTD mean = 3.1 years SD = 4.8). Although the patient groups did not show differences in global cognitive performance, they differed in sensitive measures to detect symptoms of apathy and disinhibition in bvFTD, including FrSBe and Hayling test (considered objective measures of apathy and disinhibition [33–35]). Even if apathetic and disinhibited presentations can be simultaneously present in the course of FTD disease [16], in our sample, the groups seem to preserve the clinical profile with which they began, independent of duration of disease progression. Previous studies have suggested that behavioral symptoms might persist across time and may occur simultaneously in advanced stages of the disease [9, 16]. To our knowledge, this is the first report showing the persistence of an initial symptom and its relevance in shaping disease presentation.

Previous work has shown specific neural correlates for the apathetic and disinhibited presentations (regardless of which was the initial symptom). bvFTD clinical presentation of apathy has been linked to atrophy of the frontal lobes and striatum [14, 15]. More specifically, ACC has been associated with difficulty in initiating activities [36], DLPFC appears to contribute to the generation of higher-level planning and organization [37], and OFC has been implicated in motivation [38]. In contrast, disinhibited bvFTD presentation has been associated with alterations in cognitive and inhibitory control related to atrophy in OFC and ventromedial areas [14, 21, 29, 32]. Our findings corroborate these findings. Whole brain analyzes in AbvFTD revealed reduced VBM values in DLPFC, OFC, ACC, insular and superior temporal areas, among others. Whole brain analyzes in DbvFTD revealed brain atrophy in the OFC, DLPFC, FM regions, tempoparietal junction, bilateral ACC, insular and temporal parietal regions, among others (Supplementary Figure 1 and Supplementary Table 1).

To our knowledge, this is the first evidence (indexed with both whole brain and ROIs analysis) of the DbvFTD group exhibiting a larger pattern of brain atrophy (R OFC, R DLPFC, L Caud, L STG, and L ACC, Fig. 1A) than AbvFTD after 3 years of evolution (approximation to length of disease duration at time of second stage of evaluation in both groups). Neuropsychiatric symptoms (in particular apathy and disinhibition) tend to increase over the time [9, 16]. However, there are no studies reporting the extent to which the first behavioral symptom shapes the brain atrophy pattern and the clinical profile. Arguably, disinhibition symptoms occur as a consequence of brain atrophy in a large and more diversified set of brain areas, which are implicated in cognitive control and inhibitory processes [12, 21]. By contrast, a smaller group of brain areas are related to apathy [11, 14]. Thus, brain atrophy in some of these areas would be enough to produce and sustain symptoms of apathy. Future research should be conducted to assess the extent to which the course of neuropsychiatric symptoms and treatments used to control those symptoms might contribute to the brain atrophy process.

Importantly, the differential atrophy between groups mapped onto the behavioral symptoms is measured by neuropsychological scales. In the DbvFTD group, disinhibition measures were negatively correlated with higher brain atrophy in R DLPFC, L Cau, and R OFC, as previously reported [21]. In AbvFTD, apathy was negatively correlated with atrophy of R DLPF, also reported previously [14] (see Fig. 1B,C). Positive correlations in both groups between VBM scores of near brain areas were also observed, suggesting a consistent pattern of atrophy between near and structurally connected regions, as reported in Alzheimer's disease [39, 40]. Together, the pattern of correlations in each group supports the existence of an independent path of presentation of disease according to the first symptom.

Given the multidimensionality of the results, we used convergent multivariate analyses to determine which variables were more sensitive to distinguish differences between groups. An FDA including scores of apathy, disinhibition and relevant brain areas (R DLPFC, R OFC, and L Caud) yielded an accurate classification, confirmed by SVM classification. The usage of methods that prioritize features with a higher weight are timely in bvFTD research [9]. The SVM model, with reduced features and data training, allows us to improve the neurodegenerative diagnosis by identifying the most relevant features, usually blind to classical statistical analyzes [22, 41]. SVM results with reduced features yielded four variables in the following order: the R OFC, the L Caud, the score of apathy, and the global score of disinhibition. It is noteworthy that in our sample of patients, the brain atrophy variables presented a higher discriminant value than the neuropsychological variables. It is possible that the brain areas selected as attributes have more discriminant weight than other areas because they are more implicated in one of the two behavioral profiles (apathy or with disinhibition). In fact, R OFC has been more frequently related to the disinhibited profile [20, 42], and the atrophy in L Cau has been more frequently associated with the apathetic profile [11, 14, 15]. This result (together with the FDA data) confirms the influence of first symptoms, given that both measures track apathy and disinhibition with high reliability in bvFTD patients [41, 43]. Thus, classification results suggest that both patient groups presented a predominant (disinhibited or apathetic) pattern of brain-behavioral affectation rather than a mixed pattern.

Our results show that atrophy in R Caud, L ACC, and bilateral insula seem to be involved in both groups of patients. These areas have been implicated in both apathy and disinhibition [4, 18, 25]. Our findings add evidence on how first symptoms are associated to neurocognitive alterations involved in both symptoms. Although we have found evidence of a differential neurocognitive pattern between apathy and disinhibition, our results also support the view that both symptoms share neural mechanisms [17, 24].

FTD patients usually present a mixed pattern of neuropsychiatric symptoms throughout the course of disease [3, 4, 9, 16, 44]. However, no studies have shown that the initial symptom will necessarily remain the dominant symptom in later disease stages. This exploration is required to improve the comprehension of how neuropsychiatric symptoms are presented in FTD. In our study, some patients had a mixed presentation of clinical features (high scores in both subjective and objective apathy and disinhibition measures), together with an overlap in neuroanatomical markers of each group. Although our results are compatible with the presence of mixed clinical profiles in bvFTD, significant differences in measures used to track apathy and disinhibition and between-group differences in brain atrophy patterns support the idea of a persistence of the debut symptom and its relevance as the predominant clinical alteration around three years after disease onset –an effect unreported to date.

While recently revised diagnostic criteria for bvFTD indicate that patients with possible bvFTD may exhibit early presentation of at least three behavioral/cognitive symptoms including apathy, disinhibition, and empathy impairment, among others [2], in our sample 34 out of 41 patients reported that the reason for consultation was the discomfort associated to a defined and exclusive first symptom. In our sample, only four patients described the presence of combination of behavioral symptoms. Although our results suggest that those patients who debuted with an exclusive symptom might present this feature as dominant in another stages of disease, this does not preclude the existence of mixed clinical presentations of FTD. We acknowledge that our results do not allow exploring the neurocognitive correlates of patients who debuted with a combination of behavioral symptoms. This question should be explored in future research.

Furthermore, further research should be conducted to assess neuropsychological and anatomical correlates in the earliest stages. Given that behavioral symptoms in bvFTD seem to be manifestations of impairments in a large group of neurocognitive mechanisms, additional investigations should be conducted to explore which particular cognitive processes are impaired by each symptom and in each stage of the disease. Considering the particular case of apathy, we have assessed apathy via a subjective clinical approach which lacks the multidimensionality of cognitive-clinical frameworks following previous reports [14, 45]. Bearing in mind that the presence of apathy depends on alterations of different cognitive processes, including planning, motivation, and goal-directed behavior, among others, future studies should be conducted to assess more fine-grained aspects of apathy in FTD patients following multimodal approaches.

Prima facie, our results could seem affected by circularity. However, we would like to clarify that this is not the case. First, while clinical presentation of BvFTD is usually mixed, we show that first symptoms leave different long-lasting traces which trigger differences in disease presentation even three years after disease onset (approximation to length of disease duration at time of second stage of evaluation in both groups). Also, our analysis did not just consider neuropsychological indexes of apathy and disinhibition. Rather, we contemplated different levels of analysis, as we included the first clinical description debuting with apathy and disinhibition, then provided anatomical evidence, and finally offered neuropsychological confirmation of apathy and disinhibition. In brief, the anatomical patterns we observed discriminated patients with high scores of apathy in AbvFTD (apathy debut) and high scores of disinhibition in DbvFTD (disinhibition debut). This last result suggests that an early dominant symptom is concordant with the ulterior clinical presentation in bvFTD. Furthermore, our results go beyond the apathy/disinhibition dimensions by showing a distinctive pattern of brain atrophy. In fact, atrophy patterns on their own (without neuropsychological measures of apathy/disinhibition) afforded accurate classification of both groups (see Results). In addition, note that it was not our goal to assess whether clinical marks of apathy and disinhibition correlate with brain atrophy. Instead, we explored whether initial symptoms are associated to different atrophy patterns. All these arguments seem to dispel concerns about circularity.

Co-occurrence of behavioral symptoms and mixed presentations are typical in bvFTD [16–18]. Nevertheless, our results highlighted the importance of evaluating each symptom in particular. Specifically, they suggest that behavioral presentation in bvFTD might be heterogeneous and likely even characterized by the presence of one dominant behavioral symptom. Furthermore, the study of behavioral symptoms in FTD following a multidimensional/clinical approach is relevant and aligns with an emerging literature on the existence of subtypes of clinical phenotypes in different types of neuropsychiatric conditions [26] and neurodegenerative diseases [27], including bvFTD [10, 23, 28–32]. This approach allows exploring the behavioral symptoms in bvFTD looking for fine-grained profiles rather than considering general, unspecific clinical presentations. Moreover, this approach might have a translational impact, as clinicians might emphasize treatment for the dominant symptom. Thus, we call for further research using longitudinal approaches to better understand whether the course of disease changes when patients debut with a particular symptom, and whether such an initial profile impacts disease progression and treatment options.

Although our study showed a differential neurocognitive profile each patient group, it does not indicate to what extent these differences are due to how the disease started. That being said, we acknowledge that retrospective analyses have intrinsic limitations. How neurocognitive patterns in both groups could be related to additional factors is beyond the scope of this report. A different design would be needed to address this issue. In particular, longitudinal studies might provide evidence on the particular relationship between debut symptoms and disease trajectories and progression in bvFTD.

Conclusion

Together, the results suggest that clinical dimensions at early stages have a crucial impact in bvFTD neurocognitive presentation. The clinical subdivision of bvFTD based on the first symptom appears to be useful in tracking the predominant behavioral manifestations and their neurocognitive correlates. This is especially relevant given that current probable vbFTD criteria assign the same weight to the presence of apathy, disinhibition, and other symptoms (e.g., empathy or ritualistic behavior). Along this line, studies that explore the extent to which an early pharmacological intervention on first symptoms can modify the neurocognitive presentation and prognosis of bvFTD might provide crucial information to cope with the global impact of the disease.

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SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-160501.

REFERENCES

[1] Ibanez A, Manes F (2012) Contextual social cognition and the behavioral variant of frontotemporal dementia. *Neurology* **78**, 1354-1362.

[2] Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EGP, Onyike CU, Hillis AE, Josephs KA, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini M-L, Rosen H, Prioleau-Latham CE, Lee A, Kipps CM, Lillo P, Piguet O, Rohrer JD, Rossor MN, Warren JD, Fox NC, Galasko D, Salmon DP, Black SE, Mesulam M, Weintraub S, Dickerson BC, Diehl-Schmid J, Pasquier F, Deramecourt V, Lebert F, Pijnenburg Y, Chow TW, Manes F, Grafman J, Cappa SF, Freedman M, Grossman M, Miller BL (2011) Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* **134**, 2456-2477.

[3] Piguet O, Hornberger M, Mioshi E, Hodges JR (2011) Behavioural-variant frontotemporal dementia: Diagnosis, clinical staging, and management. *Lancet Neurol* **10**, 162-172.

[4] Rascovsky K, Hodges JR, Kipps CM, Johnson JK, Seeley WW, Mendez MF, Knopman D, Kertesz A, Mesulam M, Salmon DP, Galasko D, Chow TW, Decarli C, Hillis A, Josephs K, Kramer JH, Weintraub S, Grossman M, Gorno-Tempini M-L, Miller BM (2007) Diagnostic criteria for the behavioral variant of frontotemporal dementia (bvFTD): Current limitations and future directions. *Alzheimer Dis Assoc Disord* **21**, S14-S18.

[5] Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF (1998) Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. *Neurology* **51**, 1546-1554.

[6] Kumar-Singh S, Van Broeckhoven C (2007) Frontotemporal lobar degeneration: Current concepts in the light of recent advances. *Brain Pathol* **17**, 104-114.

[7] Hughes LE, Rittman T, Regenthal R, Robbins TW, Rowe JB (2015) Improving response inhibition systems in frontotemporal dementia with citalopram. *Brain* **138**, 1961-1975.

[8] Merrilees J (2007) A model for management of behavioral symptoms in frontotemporal lobar degeneration. *Alzheimer Dis Assoc Disord* **21**, S64-S69.

[9] Brodaty H, Connors MH, Xu J, Woodward M, Ames D (2015) The course of neuropsychiatric symptoms in dementia: A 3-year longitudinal study. *J Am Med Dir Assoc* **16**, 380-387.

[10] Massimo L, Evans LK (2014) Differentiating subtypes of apathy to improve person-centered care in frontotemporal degeneration. *J Gerontol Nurs* **40**, 58-65.

[11] Levy R, Dubois B (2006) Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex* **16**, 916-928.

[12] O'Callaghan C, Hodges JR, Hornberger M (2013) Inhibitory dysfunction in frontotemporal dementia: A review. *Alzheimer Dis Assoc Disord* **27**, 102-108.

[13] Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S (2004) The role of the medial frontal cortex in cognitive control. *Science* **306**, 443-447.

[14] Zamboni G, Huey ED, Krueger F, Nichelli PF, Grafman J (2008) Apathy and disinhibition in frontotemporal dementia: Insights into their neural correlates. *Neurology* **71**, 736-742.

[15] Eslinger PJ, Moore P, Antani S, Anderson C, Grossman M (2012) Apathy in frontotemporal dementia: Behavioral and neuroimaging correlates. *Behav Neurol* **25**, 127-136.

[16] Ismail Z, Smith EE, Geda Y, Sultzer D, Brodaty H, Smith G, Agüera-Ortiz L, Sweet R, Miller D, Lyketsos CG (2016) Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. *Alzheimers Dement* **12**, 195-202.

[17] Baez S, Couto B, Torralva T, Sposato LA, Huepe D, Montañes P, Reyes P, Matallana D, Vigliecca NS, Slachevsky A, Manes F, Ibanez A (2014) Comparing moral judgments of patients with frontotemporal dementia and frontal stroke. *JAMA Neurol* **71**, 1172-1176.

[18] Baez S, Manes F, Huepe D, Torralva T, Fiorentino N, Richter F, Huepe-Artigas D, Ferrari J, Montañes P, Reyes P, Matallana D, Vigliecca NS, Decety J, Ibanez A (2014) Primary empathy deficits in frontotemporal dementia. *Front Aging Neurosci* **6**, 262.

[19] Couto B, Manes F, Montañés P, Matallana D, Reyes P, Velasquez M, Yoris A, Baez S, Ibáñez A (2013) Structural neuroimaging of social cognition in progressive non-fluent aphasia and behavioral variant of frontotemporal dementia. *Front Hum Neurosci* **7**, 467.

[20] Hornberger M, Savage S, Hsieh S, Mioshi E, Piguet O, Hodges JR (2010) Orbitofrontal dysfunction discriminates behavioral variant frontotemporal dementia from Alzheimer's disease. *Dement Geriatr Cogn Disord* **30**, 547-552.

[21] Hornberger M, Geng J, Hodges JR (2011) Convergent grey and white matter evidence of orbitofrontal cortex changes related to disinhibition in behavioural variant frontotemporal dementia. *Brain* **134**, 2502-2512.

[22] Charpentier P, Lavenu I, Defebvre L, Duhamel A, Lecouffe P, Pasquier F, Steinling M (2000) Alzheimer's disease and frontotemporal dementia are differentiated by discriminant analysis applied to (99m)Tc HmPAO SPECT data. *J Neurol Neurosurg Psychiatry* **69**, 661-663.

[23] Williams DL, Goldstein G, Minshew NJ (2006) The profile of memory function in children with autism. *Neuropsychology* **20**, 21-29.

[24] Noble WS (2006) What is a support vector machine? *Nat Biotechnol* **24**, 1565-1567.

[25] Yang ZR (2004) Biological applications of support vector machines. *Brief Bioinform* **5**, 328-338.

[26] Ben-Hur A, Ong CS, Sonnenburg S, Schölkopf B, Rätsch G (2008) Support vector machines and kernels for computational biology. *PLoS Comput Biol* **4**, e1000173.

[27] Creel SC, Newport EL, Aslin RN (2004) Distant melodies: Statistical learning of nonadjacent dependencies in tone sequences. *J Exp Psychol Mem Cogn* **30**, 1119-1130.

[28] Bron E, Smits M, Niessen W, Klein S (2015) Feature selection based on the SVM weight vector for classification of dementia. *IEEE J Biomed Heal Inform* **19**, 1617-1626.

[29] Massimo L, Powers C, Moore P, Vesely L, Avants B, Gee J, Libon DJ, Grossman M (2009) Neuroanatomy of apathy and disinhibition in frontotemporal lobar degeneration. *Dement Geriatr Cogn Disord* **27**, 96-104.

[30] Burgess PW, Shallice T (1996) Response suppression, initiation and strategy use following frontal lobe lesions. *Neuropsychologia* **34**, 263-272.

[31] Baez S, Herrera E, Villarin L, Theil D, Gonzalez-Gadea ML, Gomez P, Mosquera M, Huepe D, Strejilevich S, Viglieca NS, Matthäus F, Decety J, Manes F, Ibañez AM (2013) Contextual social cognition impairments in schizophrenia and bipolar disorder. *PLoS One* **8**, e57664.

[32] Powers JP, Massimo L, McMillan CT, Yushkevich PA, Zhang H, Gee JC, Grossman M (2014) White matter disease contributes to apathy and disinhibition in behavioral variant frontotemporal dementia. *Cogn Behav Neurol* **27**, 206-214.

[33] Kipps CM, Nestor PJ, Acosta-Cabronero J, Arnold R, Hodges JR (2009) Understanding social dysfunction in the behavioural variant of frontotemporal dementia: The role of emotion and sarcasm processing. *Brain* **132**, 592-603.

[34] Torralva T, Roca M, Gleichgerrcht E, Bekinschtein T, Manes F (2009) A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia. *Brain* **132**, 1299-1309.

[35] Carvalho JO, Ready RE, Malloy P, Grace J (2013) Confirmatory factor analysis of the Frontal Systems Behavior Scale (FrSBe). *Assessment* **20**, 632-641.

[36] Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD (2001) Conflict monitoring and cognitive control. *Psychol Rev* **108**, 624-652.

[37] Kaller CP, Rahm B, Spreer J, Weiller C, Unterrainer JM (2011) Dissociable contributions of left and right dorsolateral prefrontal cortex in planning. *Cereb Cortex* **21**, 307-317.

[38] Hare TA, Camerer CF, Knoepfle DT, Rangel A (2010) Value computations in ventral medial prefrontal cortex during charitable decision making incorporate input from regions involved in social cognition. *J Neurosci* **30**, 583-590.

[39] Steffener J, Stern Y (2012) Exploring the neural basis of cognitive reserve in aging. *Biochim Biophys Acta* **1822**, 467-473.

[40] Steffener J, Brickman AM, Rakitin BC, Gazes Y, Stern Y (2009) The impact of age-related changes on working memory functional activity. *Brain Imaging Behav* **3**, 142-153.

[41] Abdi H, Williams LJ, Beaton D, Posamentier MT, Harris TS, Krishnan A, Devous MD (2012) Analysis of regional cerebral blood flow data to discriminate among Alzheimer's disease, frontotemporal dementia, and elderly controls: A multi-block barycentric discriminant analysis (MUBADA) methodology. *J Alzheimers Dis* **31**(Suppl 3), S189-S201.

[42] Peters F, Perani D, Herholz K, Holthoff V, Beuthien-Baumann B, Sorbi S, Pupi A, Degueldre C, Lemaire C, Collette F, Salmon E (2006) Orbitofrontal dysfunction related to both apathy and disinhibition in frontotemporal dementia. *Dement Geriatr Cogn Disord* **21**, 373-379.

[43] Stout JC, Ready RE, Grace J, Malloy PF, Paulsen JS (2003) Factor analysis of the frontal systems behavior scale (FrSBe). *Assessment* **10**, 79-85.

[44] Mendez MF (2006) What frontotemporal dementia reveals about the neurobiological basis of morality. *Med Hypotheses* **67**, 411-418.

[45] Malloy P, Tremont G, Grace J, Frakey L (2007) The Frontal Systems Behavior Scale discriminates frontotemporal dementia from Alzheimer's disease. *Alzheimers Dement* **3**, 200-203.