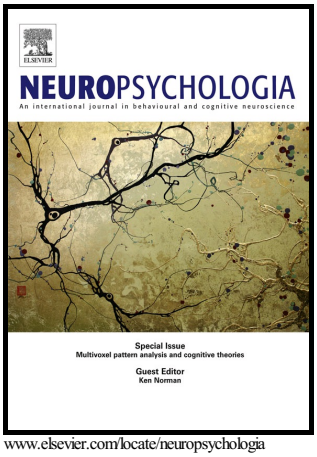

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Brain structural correlates of executive and social cognition profiles in behavioral variant frontotemporal dementia and elderly bipolar disorder

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Abstract

An early stage of behavioral variant frontotemporal dementia (bvFTD) often displays a mix of behavioral disturbances and personality changes hindering a differential diagnosis from elderly bipolar disorder (BD), making this process a big challenge. However, no studies have compared these pathologies from neuropsychological and neuroanatomical perspectives. The aim of the present study was to compare the executive functions (EF) and social cognition profiles as well as the structural neuroimaging of bvFTD and elderly patients with BD. First, we compared the executive and social cognition performances of 16 bvFTD patients, 13 BD patients and 22 healthy controls. Second, we compared grey matter volumes in both groups of patients and controls using voxel-based morphometry. Lastly, we examined the brain regions where atrophy might be associated with specific impairments in bvFTD and BD patients. Compared to controls, bvFTD patients showed deficits in working memory, abstraction capacity, inhibitory control, cognitive flexibility, verbal fluency and theory of mind (ToM). Patients with BD showed lower performance than controls in terms of abstraction capacity and verbal inhibitory control. In bvFTD patients, atrophy of frontal, temporal and insular cortices was related to executive functions deficits. Atrophy of the amygdala, the hippocampus, the parahippocampal gyrus, the putamen, the insula, the precuneus, the right temporo-parietal junction and superior temporal pole was associated to ToM impairments. No significant associations between atrophy and EF performance were observed in BD patients. BvFTD patients showed greater EF and ToM deficits than BD patients. Moreover, compared to BD, bvFTD patients exhibited a significant decrease in GM volume in frontal, temporal and parietal regions. Our results provide the first comparison of EF, social cognition and

neuroanatomical profiles of bvFTD and elderly BD patients. These findings shed light on differential diagnosis of these disorders and may have important clinical implications.

Keywords
behavioral variant frontotemporal dementia, late-life bipolar disorder, executive functions, theory of mind, structural neuroimaging.

1. Introduction

Behavioral variant frontotemporal dementia (bvFTD) is a neurodegenerative disorder associated with the progressive degeneration of frontal, insular and anterior temporal cortices, and its clinical manifestations are a direct reflection of these pathological changes. The mean age of onset of bvFTD is approximately 58 years, although cases presenting as early as the second decade of life and as late as aged in their nineties have been reported (Pressman & Miller, 2014). However, disease onset is difficult to identify. Since insight is limited, or absent, it is vital that close family members are interviewed alone, and sensitively, to elicit the nature of the early symptoms and their progression. (Piguet, Hornberger, Mioshi, & Hodges, 2011). BvFTD typically presents with marked changes in executive functions (EF), emotion processing, interpersonal relationships, and decision making. These deficits occur early in the disease with focal degeneration of the anterior cingulate cortex, frontoinsular and temporal cortices, as well as the dorsomedial prefrontal cortex, the striatum, and the thalamus (Rosen, et al., 2002; Seeley, et al., 2008).

From a clinical perspective, the presence of bvFTD is most frequently evidenced by a rich constellation of psychiatric symptoms such as changes in personality or behavioral disorders. These changes include socially inappropriate behavior, loss of manners or decorum, impulsive actions, apathy, inertia, loss of empathy, compulsive behavior, increased consumption of alcohol or cigarettes and hyperorality (Rascovsky, et al., 2011). Some of these symptoms may mimic those found in affective disorders such as late-life bipolar disorder (BD). Depression is the most common psychiatric confusion, but lack of interest, social withdrawal, and hyperemotivity are also frequent in bvFTD patients (Liu, et al., 2004). Besides, talkativeness, irritability, disinhibition, euphoria, impulsivity, poor decision-making, and compulsive behaviors could prompt the idea of a hypomanic episode (Woolley, Khan, Murthy, Miller, & Rankin, 2011). In this regard, Woolley, et al. (2011) found that around 52.2% of bvFTD patients receive a prior psychiatric diagnosis and were more likely to receive diagnoses of BD than patients with other neurodegenerative diseases. Although there are important aspects to be taken into account to guide the diagnosis, this symptom overlap may sometimes turn the differential diagnosis of these diseases into a big challenge during a regular outpatient clinic visit.

Unlike bvFTD, BD disorder have a prominent origin in adolescence and young adulthood (Carlson & Meyer, 2006). BD follows a developmental path, and manifest a variable but observable trajectory (Berk, 2009). Depression precedes the onset of mania in many cases of bipolar disorder (Depp & Jeste, 2004). Age of onset of illness has a peak between 20 and 29 years. There is no convincing evidence for childhood cognitive, motor and language developmental impairments preceding BD (Depp & Jeste, 2004). However, children with family history of BD manifesting depression coupled with externalizing disorders in late childhood or may be considered at high risk for BD (Akiskal, 1995).

Regarding late-life BD, only 5% of people had bipolar illness onset after age 60 years (Depp, et al., 2004). Aging is associated with substantial changes in several areas that have great relevance to BD in younger adults. In particular, changes in normal adults such as reduced

sleep quality, higher risk of suicide, and increased medical morbidity negatively affect the functioning of older people with BD (Depp & Jeste, 2004).

Previous research has characterized bvFTD and late-life BD independently, but little comparisons of these pathologies have been made from neuropsychological and neuroanatomical perspectives. The aim of the present study was to compare the neuropsychological and social cognition profiles as well as the structural neuroimaging of bvFTD and elderly patients with BD in order to understand the way in which these tools can contribute to their discrimination as distinct clinical entities as well as their differential diagnosis.

From a neuropsychological perspective, early in the disease process, patients with bvFTD can exhibit a relatively normal performance on formal neuropsychological tests despite the presence of significant personality and behavioral changes (Piguet, et al., 2011). As the disease progresses, the cognitive profile of bvFTD patients is characterized by relative sparing of episodic memory, preservation of language and visuospatial/constructive abilities and an important impairment in EF (Rascovsky, et al., 2011). Deficits in theory of mind (ToM) and emotion detection are also present early in the disease (Gregory, et al., 2002; Torralva, et al., 2007). At a neuroanatomical level, in most cases, magnetic resonance imaging (MRI) showed atrophy in mesial frontal, orbitofrontal, anterior insular and right temporal cortices, as well as in white matter tracts including the anterior corpus callosum, uncinated, arcuate and anterior and inferior longitudinal fasiculi (Rosen, et al., 2002; Seeley, et al., 2008; Whitwell, et al., 2009). Brain atrophy is also present in subcortical brain regions such as the amygdala, the hippocampus, the caudate, the striatum, the putamen, the thalamus and the hypothalamus (Garibotto, et al., 2011; D. C. Perry, et al., 2014; Rosen, et al., 2002).

W With respect to BD, there is consensus that the disease involves cognitive deficits which persist between affective episodes (Robinson, et al., 2006; Torres, Boudreau, & Yatham, 2007) and account for a substantial portion of the disability associated with this illness (Depp, et al., 2009). Specifically, older euthymic BD cases are impaired in several cognitive domains including attention, memory and EF (Depp, et al., 2007; Gildengers, et al., 2007; Martino, et al., 2008; Martino, Strejilevich, & Manes, 2013). A longitudinal 2-year study did not reveal changes in cognition between late-life BD patients and controls supporting the notion that this disorder does not have a significant adverse impact on cognitive and brain aging (Delaloye, et al., 2011). Although ToM impairments have been reported in younger BD patients (Bora, et al., 2005; Kerr, Dunbar, & Bentall, 2003), no previous studies have assessed this domain in elderly BD. Regarding the neuroanatomical changes, MRI studies (Delaloye, et al., 2009; Delaloye, et al., 2011; Haller, et al., 2011) have shown no volumetric grey matter (GM) reduction in elderly BD individuals when compared to healthy controls, further suggesting the absence of an active neurodegenerative process in these patients.

To our knowledge, no study has compared bvFTD and elderly BD patients including neuropsychological and structural neuroimaging measures simultaneously. Here, we describe the differential patterns of brain atrophy that are associated with EF and ToM deficits in bvFTD patients and elderly BD patients in comparison to control subjects. First, we assessed the executive and social cognition profiles of each clinical group. Second, we used voxel-based morphomery (VBM) to compare the patterns of atrophy in both bvFTD and BD groups regarding controls. Third, we compared GM volumes between bvFTD and BD patients. Lastly, we examined the brain regions where atrophy might be associated with specific impairments in bvFTD and BD patients.

2. Materials and Methods

2.1. Participants

Sixteen patients met the revised criteria for probable bvFTD (Rascovsky, et al., 2011). As stated in previous reports by our group (e.g., Baez, Couto, et al., 2014; Baez, Kanske, et al., 2016; Baez, Manes, et al., 2014; Baez, Morales, et al., 2016; Torralva, et al., 2007; Torralva, Roca, Gleichgerrcht, Bekinschtein, & Manes, 2009), diagnosis was initially made by a group of experts in bvFTD. Each case was individually reviewed at a multidisciplinary clinical meeting involving cognitive neurologists, psychiatrists, and neuropsychologists. BvFTD patients were recruited as part of a broader ongoing study on frontotemporal dementia (Baez, Kanske, et al., 2016; Baez, Morales, et al., 2016; Couto, et al., 2013). Patients presented with functional impairment and prominent changes in personality and social behavior as verified by a caregiver during initial assessment. All patients underwent a standard examination battery including neurological, neuropsychiatric, and neuropsychological examinations and a clinical MRI scan. Patients were included only if they showed frontal or temporal atrophy on MRI. Patients with white matter abnormalities were excluded. All patients were in the early/mild stages of the disease and did not meet criteria for specific psychiatric disorders, as assessed by psychiatric examination. Patients presenting primarily with language deficits were excluded.

Thirteen elderly BD patients (≥ 60 years of age) with more than 10 years of illness duration were also recruited. These patients were diagnosed with Type-I/II BD according to the diagnostic and statistical manual of mental disorders (DSM-IV) criteria. In addition, this group of patients completed a series of psychiatric questionnaires in order to establish a profile of clinical symptoms. Depression and mania were rated using the Spanish version of the Beck Depression Inventory (BDI-II) (Beck, Steer, & Brown, 1966) and the Young Mania Rating Scale (YMRS) (Colom, et al., 2002), respectively. All BD patients were in euthymic state, defined by scores less than or equal to 13 points according to the BDI-II (mean = 9.0, standard deviation = 6.1) and less than or equal to 6 according to the YMRS (mean = 2.6, standard deviation = 2.8) for at least 8 weeks and with no changes in their medication type or dosage over 4 months. We excluded patients with other axis-I diagnoses, history of substance abuse/dependency, history of mental retardation, neurological disease, or any clinical condition that might affect cognitive performance.

The performance of bvFTD and BD patients was compared with that of 22 healthy controls. By using a group-wise matching criterion, control subjects were paired with bvFTD and BD patients (see Table 1). Matching criteria were gender, age and years of education. 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. All of the participants provided written informed consent in accordance with the Helsinki declaration. The Ethics Committee of the Institute of Cognitive Neurology approved this study.

2.2. Cognitive Assessment

2.2.1. General cognitive status

The general cognitive status of the participants (Table 1) was assessed using the Mini-Mental State Examination (Folstein, Robins, & Helzer, 1983).

2.2.2. Executive function tasks

The INECO Frontal Screening (IFS) (Torralva, Roca, Gleichgerrcht, Lopez, & Manes, 2009). The IFS is a brief test that has proven to successfully detect executive dysfunction in patients with bvFTD and BD (Baez, Ibanez, et al., 2014; Gleichgerrcht, Roca, Manes, & Torralva, 2011; Torralva, Roca, Gleichgerrcht, Lopez, et al., 2009). This test includes the following eight subtests: (1) motor programming (Luria series, "fist, edge, palm"); (2) conflicting instructions (subjects were asked to hit the table once when the administrator hit it twice, or to hit the table twice when the administrator hit it only once); (3) motor inhibitory control; (4) numerical working memory (backward digit span); (5) verbal working memory (months backwards); (6) spatial working memory (modified Corsi tapping test); (7) abstraction capacity (inferring the meaning of proverbs), and (8) verbal inhibitory control (modified Hayling test). The maximum possible score on the IFS is 30 points.

Backward Digit Span (Weschler, 1999).
Participants were presented with a series of digits ranging from two to eight in length, and were asked to immediately repeat them back to the examiner in the reverse order. This task was used to assess mental manipulation and verbal working memory.

Phonological Fluency Test.
In this test, participants were asked to say as many words as possible beginning with the letter "P" during one minute. Its purpose was to assess the spontaneous production of words beginning with a given letter in a limited period of time.

Trail Making Test (Partington, 1949).
The test consisted of two parts: in the first one, participants were asked to connect –by using a pencil and without lifting it– 25 randomly arranged numbers on a sheet of paper. In the second part, they were asked to connect numbers and letters in an alternating, ascending fashion (i.e, 1, A, 2, B, and so forth). These tests were designed to assess speed of attention, sequencing, mental flexibility, visual search, and set shifting. The score obtained after subtracting performance under Part A from Part B was achieved as a more specific measure of cognitive flexibility.

Modified Wisconsin Card Sorting Test (Nelson, 1976).
We used the Nelson's modified card-sorting version in which two sets of 24 cards are used and ambiguity is eliminated by removing those cards that share more than one attribute with the stimulus cards. This test measured abstraction ability and the capacity to shift cognitive strategies, considered one of the gold standards of classic tests of EF.

2.2.3. Theory of mind

Reading the Mind in the Eyes Test.
A computerized version of Reading the Mind in the Eyes Test (RMET) was used. Photographs of the ocular region of different human faces (Baron-Cohen, Jollife, Mortimore, & Robertson, 1997) were presented. Participants were asked to choose which of four words best described what the person in each photograph was thinking or feeling.

2.3. Imaging Recordings

Both groups of patients (bvFTD and BD) and controls were scanned in a 1.5T Phillips Intera scanner with a standard head coil. A T1weighted spin echo sequence was used to generate 120 contiguous axial slices (TR = 2300 ms; TE = 13 ms; flip angle = 68◦; FOV = rectangular 256 mm; matrix size = 256 × 240; slice thickness = 1 mm) covering all the brain's surface and tissue.

2.4. Data Analysis

2.4.1. Behavioral data

Demographic and neuropsychological data were compared for all three groups using one-way ANOVA with Tukey's HSD post hoc comparisons when appropriate. When analyzing categorical variables (e.g. gender), chi square tests were used in order to analyze categorical variables (e.g. gender). The statistical significance level was set at $p < 0.05$.

Multigroup discriminant function analyses (MDA) (Porebski, 1966; Stevens, 1996) with step inclusion method (Wilki's Lamba) were performed to determine which are the measures that best discriminate between (a) controls and bvFTD patients, (b) controls and BD patients, and (c) bvFTD and BD patients. All neuropsychological measures, with exception of the IFS total score, were included as predictors. The IFS total score was not considered since the inclusion of this measure together with all its subscales may affect the MDA results. For every significant discriminant function, the level of variables' prediction in every group was tested by means of the module of classification of MDA's cases, using Statistical Package for Social Sciences (SPSS) version 18.0.

MDA combines independent variables by selecting and assessing the discriminant power of combined measures (predictor variables) applied in each group. Once the best predictors were selected, a final model was run without the selection method in order to determine accuracy of the discriminant function. The MDA is based on a factor analytic method, which can classify the participants in different groups according to the discriminate ability of selected predictors, and the results can be used to visually represent the position of groups relative to each other in a discriminant space. This technique was chosen since it is used for classifying subjects into groups on the basis of a battery of measurements, as well as on its parsimonious interpretation (Stevens, 1996). Moreover, this method can be used in small or medium sample sizes (Porebski, 1966).

2.4.2. VBM analysis

Images were preprocessed using the DARTEL Toolbox, in accordance with previously described procedures (Ashburner & Friston, 2000). Then, modulated 12-mm full-width half-maximum kernel-smoothed (Good, et al., 2001) images were normalized to the MNI space and analyzed through general linear models for 2nd level analyses on SPM-8 software. To explore regional GM reduction in the (a) bvFTD group relative to controls, (b) BD group relative to controls, and (c) bvFTD patients compared to BD patients, we performed two-sample comparisons, including total intracranial volume as a confounding covariate ($p < 0.05$ FEW corrected, extent threshold = 100 voxels).

2.4.3. Relationship between atrophic brain regions and neuropsychological impairments

We performed multiple regression analyses in SPM-8 to identify atrophied brain regions that

were associated with impaired performance on EF and ToM tasks (one for each measure showing significant differences between patients and controls). These associations were studied in bvFTD and BD patients combined with controls. This procedure has been previously employed in studies including patients with neurodegenerative diseases and serves to increase statistical power to detect brain-behavior relationships by achieving greater variance in behavioral scores (Irish, Addis, Hodges, & Piguet, 2012; Irish, Piguet, Hodges, & Hornberger, 2014; Sollberger, et al., 2009). The measures included in regression analyses for the bvFTD group were: (1) IFS total score, (2) verbal working memory, (3) abstraction capacity, (4) verbal inhibitory control, (5) categories on the WCST, (6) phonological fluency, (7) the Trail Making Test B-A, and (8) the RMET total score. For the BD group, the measures included in regression analyses were abstraction capacity, and verbal inhibitory control. In order to explore the relationship between regional GM reduction and the deficits observed in groups of patients, these analyses were restricted to areas of significant GM atrophy in patients relative to controls. Total intracranial volume was included as a covariate of no interest in all analyses ($p < 0.05$ FWE corrected, extend threshold = 100 voxels).

3. Results

3.1. Demographical data and general cognitive status

Both groups of patients and controls were successfully matched for age ($F(2.48) = 0.37$, $p = 0.70$), gender ($\chi^2 = 0.93$, $df = 1$, $p = 0.40$), and years of education ($F(2.48) = 0.07$, $p = 0.90$). A significant difference was found for MMSE scores among the three groups ($F(2.48) = 7.3$, $p < 0.005$). Post-hoc analysis (Tukey HSD, MS = 5.68, df = 48) revealed that bvFTD patients showed a lower performance than BD patients ($p < 0.01$) and controls ($p < 0.01$).

3.2. Executive functions

Significant differences between groups are shown in Figure 1.

There were significant differences among the groups in the IFS total score ($F(2.48) = 9.11$, $p < 0.001$). A post-hoc analysis (Tukey HSD, MS = 23.44, df = 48) showed that bvFTD patients exhibited a lower score than BD patients ($p < 0.05$) and controls ($p < 0.01$). A detailed analysis of the IFS subtests showed differences among the groups regarding their verbal working memory ($F(2.48) = 4.1$, $p < 0.05$). A post-hoc analysis (Tukey HSD, MS = 0.21, df = 48) showed that bvFTD patients had a lower performance than BD patients ($p < 0.05$) and controls ($p < 0.05$). There were also significant differences regarding their abstraction capacity ($F(2.48) = 1.6$, $p < 0.001$). A post-hoc analysis (Tukey HSD, MS = 0.74, df = 48) revealed that both bvFTD ($p < 0.001$) and BD patients ($p < 0.05$) showed lower scores than controls. Likewise, significant differences were found in their verbal control inhibition ($F(2.48) = 16.7$, $p < 0.001$). A post-hoc analysis (Tukey HSD, MS = 3.09, df = 48) showed that bvFTD ($p < 0.001$) and BD ($p < 0.05$) patients exhibited a lower performance than controls.

There were also significant differences in the total categories score of the WCST ($F(2.48) = 12.7$, $p < 0.001$). A post-hoc analysis (Tukey HSD, MS = 2.46, df = 48) showed that bvFTD patients completed less categories than BD patients ($p < 0.05$) and controls ($p < 0.001$). Furthermore, differences among the groups were found in the phonological fluency scores ($F(2.48) = 5.7$, $p < 0.01$). A post-hoc analysis (Tukey HSD, MS = 21.75, df = 48) revealed that bvFTD patients exhibited a lower performance than controls ($p < 0.001$). In addition, bvFTD

patients showed a lower performance than BD patients in the TMT part B minus part A score ($F(1.27) = 16.98$, $p < 0.01$).

No differences were observed between groups in the subtests of motor programming, conflicting instructions, digits backward span and visual working memory.

3.3. Theory of mind

There were significant differences among groups in the RMET total score ($F(2.48) = 22.1$, $p < 0.001$). A post-hoc analysis (Tukey HSD, MS = 6.77, df = 48) revealed that bvFTD patients showed lower scores than BD patients ($p < 0.001$) and controls ($p < 0.001$) (See Figure 1).

3.4. Multigroup Discriminant Function Analysis (MDA)

All EF and ToM measures (except the IFS total score) were included into the MDA as independent variables. We performed a stepwise MDA for each patient group vs. controls, individually. Moreover, we conducted a MDA for bvFTD vs. BD patients. For bvFTD patients vs. controls, four variables (verbal inhibitory control, verbal working memory, abstraction capacity and RMET) were selected by their best contribution in differentiating the groups. One discriminant function was calculated from the predictors with a Wilkis's $\lambda = 0.33$, $X^2(4) = 61.21$, $p < 0.01$. This function accounted for 100% of the total variance. Abstraction capacity discriminated most reliably between controls and bvFTD patients, followed by the RMET. Employing this model, 97.4% of participants were correctly classified, 100% of bvFTD patients and 96% of control subjects.

Defining BD and control groups as dependent variables, one variable (verbal inhibitory control) was selected by the stepwise discriminant procedure. One discriminant function was calculated with a Wilkis's $\lambda = 0.52$, $X^2(1) = 15.28$, $p < 0.01$. This function accounted for 100% of the total variance. With this model, 80.5% of participants were correctly classified, 75% of BD patients and 84% of control subjects.

For bvFTD vs. BD patients, two variables (TMT part B minus part A and RMET) were selected by their best contribution in differentiating the groups. One discriminant function was calculated from the predictors with a Wilkis's $\lambda = 0.40$, $X^2(2) = 21.59$, $p < 0.01$. This function accounted for 100% of the total variance. The TMT part B minus part A score discriminated most reliably between bvFTD and BD patients, followed by the RMET. Employing this model, 89% of participants were correctly classified, 78.6% of bvFTD patients and 100% of BD patients. Standardized coefficients of the variables selected in each MDA are shown in Table 2.

3.5. VBM results

In comparison to controls, bvFTD showed atrophy predominantly in frontal and temporal lobe structures ($p < 0.05$, FWE corrected). This includes the insular cortex, the frontal inferior gyrus, the cingulate cortex, the supplementary motor area, the hippocampus, the amygdala, the temporal poles, the fusiform gyrus and the temporal middle gyrus. Atrophy was also observed in the superior parietal lobule (see Figure 2, Table 5).

The comparison between BD patients and controls showed no significant differences at a threshold of $p < 0.05$ FWE corrected. However, using a more lenient threshold ($p < 0.001$,

uncorrected), the comparison showed that BD patients exhibited GM reduction in frontal regions (including insular cortex), the left putamen and the occipital lobe (see Figure 2 and Table 5).

Relative to BD, bvFTD patients exhibited a significant decrease in GM volume in frontal, temporal and parietal lobes ($p < 0.05$, FWE correction, Figure 2 and Table 5). This involves frontal medial areas, the frontal inferior gyrus, the cingulate cortex, the supplementary motor area, the temporal inferior lobe, the fusiform gyrus and the superior parietal lobe. The inverse comparison of the BD versus the bvFTD group yielded no significant voxels.

3.6. Atrophied brain regions related to specific impairments in groups of patients

BvFTD patients.
Significant associations are shown in Figure 3. Lower IFS total score was positively associated with lower GM volumes in two clusters involving the right amygdala, the hippocampus, the parahippocampal gyrus, the fusiform gyrus and the left orbitofrontal cortex. Furthermore, lower verbal inhibitory control was positively associated with decreased GM volumes in four different clusters, involving the bilateral insula, fusiform and parahippocampal gyri, the left superior temporal gyrus and the left inferior frontal/orbitofrontal cortex.

The number of categories completed in the WCST was positively associated with GM volumes in one cluster including the left insula, putamen and superior temporal gyrus. Lower scores on the phonological fluency test were positively associated with lower GM volumes in the bilateral insula and putamen, the right amygdala, fusiform and inferior frontal gyri, and the left superior temporal gyrus and orbitofrontal cortex. The score on the TMT part B- part A was negatively correlated with lower GM volumes in the left inferior temporal gyrus.

Lower performance on the RMET was positively correlated with GM reduction in the bilateral amygdala, hippocampus, parahippocampal gyrus, putamen, insula and precuneus, and the right temporo-parietal junction and the superior temporal pole.

No significant associations were found among scores in verbal working memory, abstraction capacity, and atrophied brain regions.

BD patients.
No significant associations were found between abstraction capacity or verbal inhibitory control and regions with lower GM volume.

4. Discussion

This is the first study to compare the neuropsychological (i.e., executive functioning and ToM) and neuroanatomical profiles of bvFTD and older BD patients. Furthermore, we explored the relationship between regional GM reduction in these patients and their performance in EF and ToM tasks. Results of the neuropsychological assessment showed that although both groups of patients had EF impairments, bvFTD patients exhibited greater deficits than BD patients. Moreover, unlike BD, bvFTD patients showed impaired affective ToM. At the neuroanatomical level, compared to BD, bvFTD patients exhibited a significant decrease in GM volume in frontal, temporal and parietal regions. Besides, EF and ToM performances were associated with regional GM atrophy in bvFTD patients. Such

associations were not found in BD patients. The present results provide further evidence to discriminate bvFTD and late-life BD as distinct clinical entities, and support the usefulness of neuropsychological and structural imaging assessments for the differential diagnosis of these pathologies.

4.1. Neuropsychological performance of bvFTD and BD patients

As consistently reported in previous studies (e.g.,Hornberger, Piguet, Kipps, & Hodges, 2008; R. J. Perry & Hodges, 2000; Torralva, Roca, Gleichgerrcht, Bekinschtein, et al., 2009), we found that, compared to controls, bvFTD patients exhibited EF impairments involving verbal working memory, cognitive flexibility, abstraction capacity and verbal inhibitory control. BvFTD patients also performed lower than controls in the RMET, supporting the findings of previous studies (Gregory, et al., 2002; Torralva, et al., 2007). Consistent with these results, the MDA showed that abstraction capacity, verbal inhibitory control and the RMET were the measures that best discriminated between bvFTD patients and controls. A function including all these measures correctly classified 100% of bvFTD patients.

Regarding BD patients, our results showed that this group performed lower than controls in measures of abstraction capacity and verbal inhibitory control. These findings are consistent with previous studies in elderly euthymic BD patients showing EF impairments (Depp, et al., 2007; Martino, et al., 2008; Martino, et al., 2013). Moreover, in line with these results, the MDA revealed that verbal inhibitory control is the measure that best discriminated between euthymic BD patients and controls. However, it is worth mentioning that classification accuracy of this function was lower than that achieved for bvFTD patients vs. controls, since only 75% of BD were correctly classified. This is expected because EF deficits in euthymic BD patients are much less severe than those observed in bvFTD patients.

In addition, no differences in ToM were found between BD patients and controls. Although no previous studies have assessed ToM in elderly BD patients, our results are coherent with a previous report on younger patients (Kerr, et al., 2003) showing that ToM is preserved in euthymic phases. Moreover, our results support previous evidence in younger euthymic BD patients showing deficits in cognitive ToM, but preserving affective ToM (Montag, et al., 2010). Further studies should investigative affective and cognitive ToM in elderly BD patients.

Comparisons between clinical groups revealed that bvFTD patients showed a lower general cognitive state and executive functioning than BD patients. Specifically, bvFTD patients exhibited lower performance in measures of verbal working memory and cognitive flexibility. Even though no studies have previously compared the executive functioning of bvFTD and elderly BD patients, our results are consistent with previous evidence showing that verbal working memory (Giovagnoli, Erbetta, Reati, & Bugiani, 2008; Stopford, Thompson, Neary, Richardson, & Snowden, 2012) and cognitive flexibility (Torralva, Roca, Gleichgerrcht, Bekinschtein, et al., 2009; Wicklund, Johnson, & Weintraub, 2004) are consistently impaired in bvFTD patients. Furthermore, our results showed that bvFTD patients had a lower performance in the RMET than BD patients. Consistently with this result, deficits in affective ToM have been systematically described in bvFTD patients (Baez, Manes, et al., 2014; Gregory, et al., 2002; Torralva, et al., 2007).

According to the clinical group comparisons, the MDA results showed that the TMT part B minus part A and the RMET scores are the measures that best discriminated between bvFTD and BD patients. A model including these predictors, correctly classified 78.6% of bvFTD

patients and 100% of BD patients. Together, the current findings suggest that EF and ToM impairments are more severe in bvFTD than in late-life BD. From a clinical point of view, these neuropsychological measures may be useful to discriminate between bvFTD and BD subjects. Moreover, the current findings suggest that while affective ToM are consistently impaired in bvFTD, this domain seems to be preserved in late-life BD. These deficits in ToM may have a negative impact of daily-life social functioning of bvFTD patients. Further studies should compare other cognitive (e.g., memory) and social-cognitive (e.g., empathy and decision-making) domains in bvFTD and elderly BD patients.

4.2. The atrophy pattern of bvFTD and BD patients

The global atrophy pattern of bvFTD patients involved mainly frontal regions, the insula, the cingulate cortex, the amygdala, the hippocampus, the fusiform gyrus and the anterior temporal poles. This result supports the atrophy pattern previously reported in the bvFTD research (Kipps, Nestor, Acosta-Cabronero, Arnold, & Hodges, 2009; Rosen, et al., 2002; Seeley, Crawford, Zhou, Miller, & Greicius, 2009; Whitwell, et al., 2009). Consistently with previous studies showing different atrophy patterns in bvFTD (Seeley, et al., 2008; Whitwell, et al., 2009), the group of patients assessed here showed parietal atrophy.

The comparison of GM volumes between BD patients and controls showed no significant differences at a threshold of $p < 0.05$ FWE corrected. This result is consistent with previous studies on euthymic elderly BD patients (Delaloye, et al., 2009; Delaloye, et al., 2011; Haller, et al., 2011) showing no volumetric GM reduction in these individuals when compared to healthy controls. However, using a more lenient threshold of $p < 0.001$ uncorrected, BD patients exhibited GM reduction in frontal regions (including the insular cortex), the putamen and the occipital lobe. This finding is in line with those of a previous study on elderly BD (Haller, et al., 2011) reporting GM reduction in the insula and the putamen, by restricting the analysis to the fronto-basal cortex and basal ganglia. Moreover, our results align with previous studies on younger BD patients (Haldane, Cunningham, Androutsos, & Frangou, 2008; Nugent, et al., 2006) showing involvement of the brain areas mentioned above. Together, our results indicate that although BD seems to follow a developmental path (Berk, 2009), brain changes in late-life BD are not as severe as those observed in patients with neurodegenerative diseases such as bvFTD.

This is the first study to compare the GM atrophy pattern of bvFTD and elderly BD patients. Our results revealed that compared to BD, bvFTD patients exhibited a significant decrease in GM volume in frontal medial areas, the frontal inferior gyrus, the cingulate cortex, the supplementary motor area, the temporal inferior lobe, the fusiform gyrus and the parietal superior lobe. These regions agree with the atrophy pattern observed in bvFTD patients compared to controls. In addition, regarding bvFTD, BD patients did not exhibit significant GM atrophy. Thus, our results suggest that GM atrophy is significantly more pronounced in bvFTD than in elderly BD patients.

4.3. The relationship between GM atrophy and impairments in executive functions and social cognition

In bvFTD patients, lower IFS total scores were associated with atrophy in the amygdala, the hippocampus, the parahippocampal gyrus, the fusiform gyrus and the orbitofrontal cortex. Consistently with these results, the prefrontal cortex has systematically proven to be an important region for executive functioning (Fuster, 2008; Stuss & Knight, 2002). Moreover, although the role of medial temporal lobe structures in EF has not been extensively

considered, it has been suggested that such brain regions are important for these cognitive functions (Oosterman, et al., 2008; Takahashi, et al., 2007). Indeed, a neuroimaging study on healthy individuals (Oosterman, et al., 2008) reported significant associations between medial temporal lobe atrophy and EF such as cognitive flexibility, inhibitory control and set shifting. Connections between the medial temporal structures and the prefrontal cortex (Simons & Spiers, 2003) may play a key role in EF. This issue should be further explored in healthy and clinical populations.

Impairments in verbal inhibitory control of bvFTD patients were associated with decreased GM volumes in the insula, fusiform, parahippocampal and left superior temporal gyri and the inferior frontal/orbitofrontal cortex. Impaired performance in the WCST was associated with atrophy in the insula, putamen and superior temporal gyrus. Lower scores on the phonological fluency test were also related to atrophy in the insula, putamen and superior temporal gyrus, but also in the amygdala, the fusiform and the inferior frontal gyri, and the orbitofrontal cortex. Higher differences in the TMT B minus TMT A were correlated with lower GM volumes in the inferior temporal gyrus. In coherence with our results, previous studies on bvFTD patients have linked the atrophy of inferior frontal/orbitofrontal cortices with deficits in verbal inhibitory control (Hornberger, Geng, & Hodges, 2011) and phonological verbal fluency (Lagarde, et al., 2013). Furthermore, in bvFTD patients, the number of categories found in the WCST has previously been associated with atrophy in the superior temporal gyrus (Lagarde, et al., 2013). Regarding the impact of insular atrophy on executive functioning, and supporting our findings, previous studies on healthy individuals (Muller, Langner, Cieslik, Rottschy, & Eickhoff, 2015; Ruscheweyh, et al., 2013) reported a strong association between GM in the insula and several EF (i.e., cognitive flexibility, working memory and inhibitory control). Lesion studies have implicated the insula in response inhibition (Swick, Ashley, & Turken, 2008) and verbal fluency (Baldo, Schwartz, Wilkins, & Dronkers, 2006). Basal ganglia also play an important role in executive functioning (Graybiel, 2000; Monchi, Petrides, Strafella, Worsley, & Doyon, 2006). Specifically, supporting our results, previous studies on clinical populations have highlighted the role of the putamen in cognitive flexibility (Eslinger & Grattan, 1993; Kehagia, Murray, & Robbins, 2010) and phonological fluency (Baldo, et al., 2006; Thames, et al., 2012). Likewise, our results suggest that atrophy in frontal, temporal and insular cortices, as well as in medial temporal and basal ganglia structures, is associated with EF impairments in bvFTD patients.

Regarding ToM, our results showed that lower performance on the RMET was correlated with GM reduction in medial temporal lobe structures (i.e., amygdala, hippocampus, parahippocampal gyrus), the putamen, the insula, the precuneus, the temporo-parietal junction and the superior temporal pole. In coherence with this finding, a previous study assessing bvFTD patients (Irish, Hodges, & Piguet, 2014) reported association between ToM performance and GM volume in the hippocampus, the amygdala, the thalamus, the orbitofrontal cortex and the temporal pole. Our results are in line with current theoretical models (Ibanez & Manes, 2012; Kennedy & Adolphs, 2012) suggesting that high-level social processes, such as ToM, are not related with to a particular brain. This social-cognitive process may be better understood in terms of extended cortical-limbic networks. Consistently, studies in healthy subjects (Adolphs, 2001; Saxe & Baron-Cohen, 2006; Siegal & Varley, 2002) have identified a widely distributed neural system implicated in ToM. According to our findings, this system includes the amygdala circuit (Siegal & Varley, 2002), the temporo-parietal junction, the precuneus and the medial prefrontal cortex (Adolphs, 2001; Saxe & Baron-Cohen, 2006; Saxe & Kanwisher, 2003). The insula and basal ganglia have also been implicated in affective ToM (Bodden, et al., 2013; Carrington & Bailey, 2009).

In spite of specific brain structural correlates of EF and ToM profiles were identified in bvFTD patients, it is worth mentioning that these changes may be modulated by factors such as the cognitive reserve. Several studies in frontotemporal degeneration (Placek, et al., 2016; Premi, et al., 2013) and Alzheimer's disease (AD) (Serra, et al., 2015; Stevens, 1996) have shown that cognitive reserve modulates neuroimaging and cognitive changes. Specifically, higher cognitive reserve in bvFTD patients is associated with superior executive functioning and GM volume in the prefrontal cortex (Placek, et al., 2016). The identification of factors influencing cognitive and anatomic changes in bvFTD suggests that cognitive reserve should be considered in symptom detection, prognosis, and treatment.

Unlike bvFTD, the GM atrophy of elderly BD patients was not significantly associated with EF impairments. These results are consistent with a longitudinal 2-year study on elderly BD (Delaloye, et al., 2011) showing no differences between patients and healthy controls in MRI findings, thus supporting the notion that this BD does not have a significant adverse impact on cognitive and brain aging. Our results suggest that GM atrophy is significantly more pronounced and have a more severe impact on cognition in bvFTD than in elderly BD patients. Furthermore, our findings support the view that the deterioration in cognitive and social-cognitive functions as well as brain structure seems to be related with the severity and chronicity of illness, rather than with the specific diagnosis of BD (Murray, et al., 2004).

4.4. Implications and future directions

This is the first study to compare the neuropsychological and neuroanatomical profiles of bvFTD and elderly BD patients. Our results have important clinical implications and support the utility of neuropsychological and structural neuroimaging assessments for discriminating these two pathologies.

From a clinical perspective, our results suggest that neuropsychological and structural neuroimaging assessments may be useful for the differential diagnosis of bvFTD and late-life BD. However, it would be important to dig deeper into the differences between these two disorders and other psychiatric and neurodegenerative disorders, since there is evidence proving that many bvFTD patients are incorrectly diagnosed (Woolley, et al., 2011). Supporting the results of this study, previous research in other types of dementia (i.e., AD) have shown associations between morphological brain changes and impairments in specific cognitive domains (Dos Santos, et al., 2011; Du, et al., 2007; Duarte, et al., 2006). For instance, episodic memory deficits in AD patients have been associated with changes in several cortical and subcortical sites including the parahippocampal and posterior cingulate gyri, the thalamus, and the hippocampus (Dos Santos, et al., 2011; Duarte, et al., 2006). Moreover, EF deficits correlate with changes in frontal and temporal regions (Dos Santos, et al., 2011; Duarte, et al., 2006).

As neurologists and psychiatrists, we need more specific diagnostic tools to help us make the correct diagnosis during our daily clinical practice. While neuroimaging biomarkers of AD diagnosis and progression (i.e., MRI and FDG PET) (Cohen & Klunk, 2014; Dubois, et al., 2014) have been identified, further research is needed in bvFTD. Moreover, future studies in neurodegenerative diseases should develop a practical visual scale to measure GM atrophy, as well as practical neuropsychological tools to help us make a differential diagnosis between bvFTD and BD when overlapping symptoms are present.

In spite of its novelty, some limitations of this study should be acknowledged. First, although patients included in this study were not receiving antipsychotic medication, some of them were taking psychoactive drugs that could influence cognitive functioning. Second, our BD sample size was relatively small, which may have prevented us from detecting significantly atrophied areas in our correlation analyses due to lack of statistical power. Further studies with larger samples should compare bvFTD and elderly BD patients. Lastly, in the current study we included patients with type I and II BD. Future studies should assess the structural correlates of executive and social-cognitive functioning of samples of each type of BD independently.

4.5. Conclusion

The findings of this study showed that although both bvFTD and elderly BD patients presented EF impairments, deficits were greater in the first clinical group. Moreover, GM atrophy is more pronounced in bvFTD than in late-life BD. Compared to BD, bvFTD patients exhibited a significant decrease in GM volume in frontal, temporal and parietal regions. Atrophy in these brain regions was associated with the EF and ToM performances in bvFTD patients. These associations were not found in BD patients. Our results support the utility of neuropsychological and structural imaging assessments for the differential diagnosis of bvFTD and elderly BD.

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Figure 1. Significant differences between groups in executive functions and theory of mind measures.

Figure 2. Voxel-based morphometry for bvFTD patients compared to controls, group (top), BD patients compared to controls (middle), and BD compared to bvFTD patients (bottom). Color bars indicate t scores of whole brain grey matter atrophy.

Figure 3. Atrophied brain regions related to neuropsychological impairments in bvFTD patients.

Table 1. Demographic, executive functions and ToM profiles.

	Controls (n= 22)	bvFTD (n=16)	BD (n=13)	Controls vs. bvFTD	Controls vs. BD	bvFTD vs. BD
Demographical data						
Age	62.5 (7.1)	65.8 (7)	61.9 (9.1)	ns	ns	ns
Gender (M:F)	7:15	7:9	3:10	ns	ns	ns
Education (years)	14.2 (4.5)	14.8 (4.3)	14.6 (4.5)	ns	ns	ns
General cognitive state						
MMSE	29.2 (2.7)	25.8 (4.1)	29.4 (0.5)	<0.01	ns	<0.05
IFS scores						
Total score	27.4 (1.3)	15.8 (7.1)	19.6 (6.3)	<0.01	ns	<0.05
Motor Programming	2.7 (0.5)	2.3 (0.9)	2.6 (0.4)	ns	ns	ns
Interference	2.7 (0.4)	2.4 (1)	2.5 (0.6)	ns	ns	ns
Motor IC	2.3 (0.7)	1.3 (1.1)	2.4 (1)	ns	ns	ns
DS backwards	2.9 (0.9)	3.2 (1.1)	3.4 (1.5)	ns	ns	ns
.erbal WM	1.9 (0.9)	1.5 (0.7)	1.9 (0.2)	<0.05	ns	<0.05
Visual WM	3.3 (0.7)	1.8 (1)	1.9 (0.9)	ns	ns	ns
Abstraction	2.6 (0.7)	0.9 (0.5)	2.0 (1.2)	<0.001	<0.05	ns
Verbal IC	4.6 (1.5)	1.7 (1.4)	3.4 (2.0)	<0.001	<0.05	ns
Executive functions and theory of mind						
WCST -categories	5.3 (1)	2.6 (2)	4.5 (1.5)	<0.001	ns	<0.05
Perseverative errors	3.7 (3.6)	6.7 (6.6)	6.6 (6.7)	ns	ns	ns
Non-perseverative errors	4.9 (4.6)	8.4 (5.9)	6.0 (3.6)	ns	ns	ns
Verbal fluency	15 (4.4)	9.9 (4)	14 (5.5)	<0.01	ns	ns
TMT A (seconds)		70.2 (29)	39.0 (10)	-	-	<0.001
TMT B-A (seconds)		136.1 (71)	45.0 (17.5)	-	-	<0.001
RMET	13.5 (1.6)	7.4 (3.7)	12.0 (2.6)	<0.001	ns	<0.001

Values are shown as mean (SD). bvFTD = behavioural variant Frontotemporal Dementia; BD = Bipolar Disorder; MMSE = Mini-Mental State Examination; IFS = INECO Frontal Screening; WCST = Wisconsin Card Sorting Test; TMT- A = Trails Making A TMT B-A = Trails Making B minus A

Table 2. Standardized coefficients of discriminant functions.

Predictor Variables	BvFTD vs. controls	BD vs. controls	BvFTD vs. BD
Abstraction capacity	0.95	1.0	-------
Verbal inhibitory control	0.51	-------	-------
TMT A minus TMT B	-------	-------	-0.63
RMET	0.71	-------	0.59

Table 3. Regions (based on AAL) of significant atrophy (local maxima) in bvFTD patients compared with healthy controls

Cluster (n° voxels)	Regions	X	Y	Z	Peak t
8039	Fusiform Gyrus R	37.7	-19.5	-30	8.57
	Amygdala R	24	-6	-16.5	6.76
12149	Hippocampus L	-13.5	-36	3	7.64
	Insula L	-24	9	-19.5	6.93
4076	Temporal Superior Pole R	48	10.5	-19.5	6.91
	Temporal Mid R	66	-45	10.5	6.88
	Occipital Mid R	46.5	-79.5	7.5	6.59
2878	Supplementary Motor Area L	-4.5	-1.5	57	6.38
	Cingulum Mid R	6	0	43.5	6.27
	Paracentral L	-4.5	-34.5	49.5	5.76
166	Precentral L	-42	-4.5	54	6.06
122	Frontal Inferior Gyrus R (pars triangularis)	48	33	9	5.69
131	Parietal superior L	-24	-78	43.5	5.45
	Occipital Superior L	-24	-84	30	4.82
105	Temporal Superior R	60	-9	4.5	5.19
510	Calcarine L	-13.5	-72	12	5.15
351	Precuneus R	13.5	-57	28.5	4.98
	Cuneus R	15	-60	19.5	4.84
102	Superior Frontal Gyrus R (medial orbital)	1.5	37.5	-12	4.80

All $p < 0.05$ (FWE correction); AAL: Automated Anatomical Labeling Atlas; L: left; R: right

Table 4. Regions (based on AAL) of significant atrophy (local maxima) in BD patients compared with healthy controls

Cluster (n° voxels)	Regions	X	Y	Z	Peak t
122	Frontal Superior R	27	-9	63	4.59
3058	Putamen L	-28.5	3	7.5	4.52

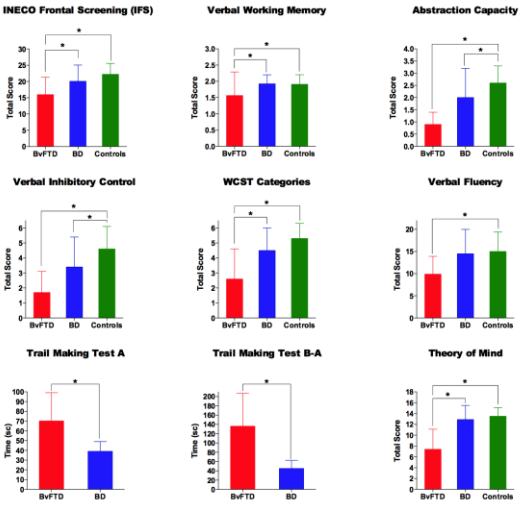
	Insula L	-42	-10.5	0	4.34
324	Calcarine L	-10.5	-72	15	3.81

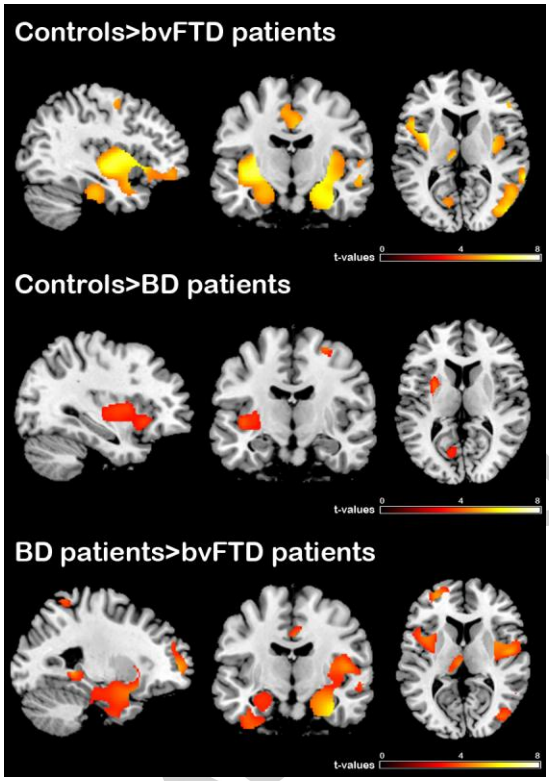
All p < 0.001 uncorrected; AAL: Automated Anatomical Labeling Atlas; L: left; R: right

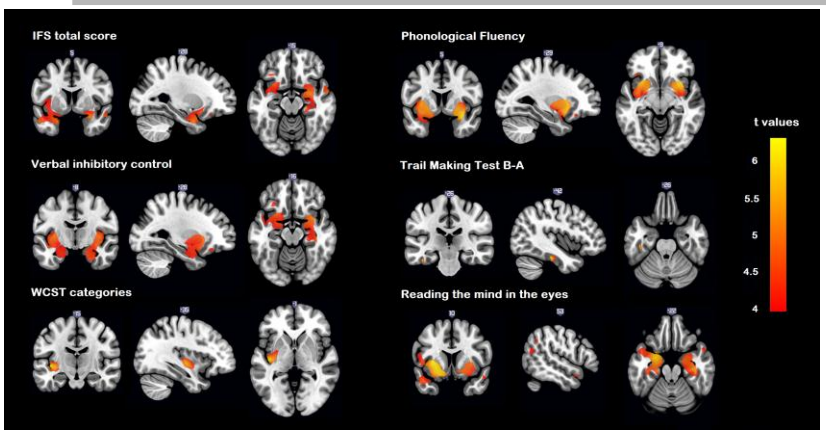
Table 5. Regions (based on AAL) of significant atrophy (local maxima) in bvFTD patients compared with BD patients

Cluster (n° voxels)	Regions	X	Y	Z	Peak t
13318	Fusiform Gyrus R	36	-28.5	-30	7.24
	Temporal Inferior R	57	-42	-9	6.08
10461	Temporal Inferior L	-40.5	-28.5	-28.5	6.25
	Thalamus L	-4.5	-19.5	10.5	5.08
1874	Cingulum Mid R	7.5	-39	33	6.14
	Supplementary Motor Area L	7.5	-1.5	45	4.24
2640	Frontal Mid L	-25.5	54	3	5.20
	Frontal Superior Medial	-10.5	49.5	31.5	4.58
392	Parietal Superior L	-21	-54	64.5	4.61
459	Frontal Inferior Gyrus L (pars triangularis)	-45	27	22.5	4.55
497	Precuneus L	-15	-70.5	37.5	4.36
	Occipital Superior L	-19.5	-78	42	4.10
437	Angular R	46.5	-57	37.5	3.93

All p < 0.05 FEW corrected; AAL: Automated Anatomical Labeling Atlas; L: left; R: right







Highlights

- BvFTD patients showed greater EF and ToM deficits than BD patients
- Compared to BD, bvFTD patients showed more frontal, temporal and parietal atrophy
- In bvFTD patients, gray matter atrophy was associated to EF and ToM deficits
- Atrophy was not associated with EF and ToM and performance in BD patients