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# I'M LOOKING THROUGH YOU: MENTALIZING IN FRONTOTEMPORAL DEMENTIA AND PROGRESSIVE SUPRANUCLEAR PALSY

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## **Abstract**

Mentalizing and emotion recognition are impaired in behavioral variant frontotemporal dementia (bvFTD). It is not clear whether these abilities are also disturbed in other conditions with prominent frontal lobe involvement, such as progressive supranuclear palsy (PSP). Our aim was to investigate social cognition (facial emotion recognition, recognition of social norms violation and mentalizing) in bvFTD and PSP. The neural basis of these functions in PSP and bvFTD groups, by analysis of structural neuroimaging, were also investigated. Twenty-three bvFTD patients, 21 PSP patients and 23 healthy controls were included. All participants underwent 3T brain MRI and a full cognitive exam including the short version of Social and Emotional Assessment (Mini-SEA), which is composed of a facial emotion recognition test (FERT) and the faux pas test. Two components of the faux pas test were distinguished: a score assessing the recognition of social norms violation and a score assessing mentalizing. Compared to controls, bvFTD and PSP patients had significantly reduced scores in all tests of social cognition but did not differ on these measures. PSP and bvFTD had cerebral atrophy in critical regions for social cognition processes, when compared to controls. The cortical correlates of emotion recognition partially overlapped in bvFTD and PSP, with correlations retrieved within the frontal medial cortex, cingulate, insula and limbic structures. PSP and bvFTD patients also displayed similar patterns of brain correlations for the composite score of social norms, with a significant cluster in anterior temporal lobes. Mentalizing scores were associated with frontal and temporal poles bilaterally, in both bvFTD and PSP. These findings support previous observations that PSP patients exhibit impairment in complex cognitive abilities, such as mentalizing. Moreover, these data extend previous findings showing that PSP and bvFTD share key clinical, cognitive and neuroimaging features.

**Keywords:** Progressive supranuclear palsy, Richardson' syndrome, frontotemporal dementia, theory of mind, emotion recognition

## Introduction

Social cognition refers to a set of different cognitive processes allowing inferring, storing and applying information about other people and adequately behaving in social situations. This domain is fundamental for interpersonal exchanges (Hutchings et al 2015) and encompasses variable abilities, such as emotion recognition, mentalizing (also called theory of mind-ToM) and social norms processing (Hutchings et al 2015, Van den Stock & Kumfor 2019). While these abilities rely on a widely distributed set of brain regions that is sometimes referred to as the “social brain” (Kumfor et al 2017), complex interactions between functional networks have been revealed for different dimensions of social cognition (Rankin 2020, Yang et al 2021). This is due in part to the increasing neuropsychological characterization of neurodegenerative diseases that constitute models of brain dysfunction.

Behavioral variant frontotemporal dementia (bvFTD) is the prototypical model of neurodegenerative disorder in which the “social brain” is affected. Indeed, patients with bvFTD exhibit early prominent social misconduct, such as social disinhibition and lack of empathy (Rascovsky et al 2011), some of which having been hypothesized (Johnen & Bertoux 2019) to lead to antisocial and even criminal behaviors (Liljegen et al 2015).

Tasks assessing social cognitive abilities, such as mentalizing (the ability to elaborate mental representations of others’ state of mind, such as feelings, thoughts and intentions) and emotion recognition, have been proven to be useful for the differential diagnosis of bvFTD, particularly with Alzheimer’s disease, the most frequent source of misdiagnosis (Bora et al 2015, Dodich et al 2021). The involvement of the medial prefrontal cortex has been pointed out when observing emotion recognition or mentalizing difficulties in bvFTD, alongside other key regions, such as the insula (Baez et al 2019, Bertoux et al 2012b, Van den Stock & Kumfor 2019). However, it is not clear whether social cognition has a clinical utility to distinguish bvFTD from other conditions with prominent involvement of frontal lobe structures and regions strongly connected to them (e.g. striatum), such as progressive supranuclear palsy (PSP).

PSP is a rare neurodegenerative disorder of insidious onset and progressive course. It has marked clinical heterogeneity, with Richardson’s syndrome (PSP-RS) being the most frequent

phenotype (Boxer et al 2017, Respondek et al 2014). PSP-RS presents with early postural instability, vertical supranuclear gaze palsy, slow and hypometric saccades, levodopa-resistant bradykinesia and axial rigidity (Boxer et al 2017, Respondek et al 2014). Similarly to bvFTD, PSP is pathologically classified as a frontotemporal lobe degeneration (FTLD) (Boxer et al 2017). There is a marked overlap between PSP and bvFTD on neuroimaging features, since PSP patients exhibit prefrontal and temporal atrophy (Agosta et al 2014, Caso et al 2016, Giordano et al 2013, Lagarde et al 2013).

Besides the motor aspects, patients with PSP can also manifest significant cognitive and behavioral dysfunctions, which has long been regarded as a “subcortical dementia”, traditionally characterized by bradyphrenia and executive dysfunction (Albert et al 1974). However, more recently, research has shown that PSP patients have wider cognitive deficits, such as conceptual thinking (Garcin et al 2018, Lagarde et al 2015) and social cognition impairments (Ghosh et al 2012, Ghosh et al 2009, Pontieri et al 2012, Shany-Ur et al 2012, Toller et al 2018). Regarding this last domain, studies have indeed shown that patients with PSP are impaired in visual and speech recognition of emotions (Ghosh et al 2012, Ghosh et al 2009), the latter having been related to the atrophy of the right inferior frontal gyrus. Deficits in sarcasm and lie detection have also been observed and associated to the atrophy of the rostral medial frontal cortex, left temporoparietal junction and right superior temporal gyrus (Ghosh et al 2012, Shany-Ur et al 2012, Strikwerda-Brown et al 2021).

Therefore, social cognition abilities seem impaired in both bvFTD and PSP, which tend toward reinforcing the pathological, cognitive and neuroimaging overlap between these disorders. However, beyond the shared deficit of emotion recognition, it is not clear whether mentalizing abilities are preserved in PSP or if difficulties in this domain could be due to the more subtle implicit language impairment that have been retrieved. In addition, if mentalizing impairment is indeed observed in PSP, it is still not clear whether quantitative or qualitative differences exist between PSP and bvFTD. This question should be addressed in both neuropsychological and neuroimaging domains, but has never been explored before. Exploring the performance and neural correlates of different subcomponents of the faux pas test, a gold standard evaluation of mentalizing abilities, could be an appropriate context to uncover qualitative differences. In this

test, mentalizing abilities as well as social norm understanding are both at stake, but no previous study delineated the performance at these two cognitive dimensions.

The aim of this study was to investigate two key aspects of social cognition in bvFTD and PSP. More specifically, we investigated patients' performance in facial emotion recognition and mentalizing through the mini Social Cognition and Emotional Assessment (mini-SEA) (Bertoux et al 2012a), and we explored the subcomponents of both tasks composing this short battery. The neural structural correlates of social cognition performance through voxel-based morphometry were also investigated. We hypothesized that greater social cognitive impairment as well as more severe atrophy in brain regions related to this domain would be identified in bvFTD. In particular, while we expect mentalizing difficulties in both diseases, we hypothesize to retrieve an impairment to recognize social norms violation only in bvFTD, due to the involvement of temporal regions that would not be expected in PSP.

## Material and methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

No part of the study procedures or analyses was pre-registered prior to the research being conducted.

### *Participants*

Sixty-seven individuals, including 23 with bvFTD, 21 with PSP and 23 age-, sex- and education-matched cognitively healthy controls were included in the study (see Table 1). All patients were recruited by an expert team of the Neurology Service of the University Hospital from the Federal University of Minas Gerais (Belo Horizonte, Brazil), except for one PSP patient recruited at the Neurology Service of the University of São Paulo (Ribeirão Preto, Brazil). The study was approved by local ethics committees. All participants gave written informed consent before participation.

Patients fulfilled the consensus diagnostic criteria for probable bvFTD (Rascovsky et al 2011) or PSP (Richardson' syndrome) (Hoglinger et al 2017). All patients underwent clinical follow-up during at least two years, in order to increase diagnostic reliability; the clinical progression of every patient agreeing with the initial diagnosis. Controls were recruited from the community, with no history of neurologic or psychiatric disorders, no cognitive complain, and normal cognitive screening.

Participants with severe psychiatric disorder (e.g., past diagnosis of bipolar disorder or schizophrenia) or with other neurological disease (e.g., history of stroke, epilepsy) were not included. Patients with bvFTD associated with motor neuron disease were not included. Participants with focal lesions or severe vascular lesions (e.g., Fazekas score  $\geq 2$ ) were also excluded. We did not include patients (from both bvFTD and PSP groups) scoring less than 20 on the Mini-Mental State Examination (MMSE), as severe cognitive impairment hampers comprehensive cognitive assessment.

## *Neuropsychological Assessment*

All participants underwent a neuropsychological assessment with the following tools: Brazilian version of the Mini-Mental State Examination (MMSE) (Brucki et al 2003), Frontal Assessment Battery (FAB) (Beato et al 2012), Figure Memory Tests (FMT) (naming, incidental memory, immediate memory, learning, delay recall and recognition) (Nitrini et al 2004), the Verbal Fluency Test ('FAS' and 'Animals'), Digit Span (Direct and Indirect orders), the Hayling Test (Burgess 1997) and the Apathy Scale (Guimaraes et al 2009). Materials are available at: [https://osf.io/742qt/?view\\_only=7072e6cc3162446d805914dd1b205617](https://osf.io/742qt/?view_only=7072e6cc3162446d805914dd1b205617). Legal copyright restrictions prevent public archiving of MMSE and Hayling tests which can be obtained from the copyright holders in the cited references.

The Brazilian version of the Mini-SEA (Bertoux et al 2012a, Mariano et al 2020) was used to assess social cognition. The Mini-SEA is composed of two tests: a short facial emotion recognition test and a modified and reduced version of the faux pas test.

The facial emotion recognition test (FERT) is composed of 35 images from Ekman's portfolio (Ekman 1975), with seven different emotions (happiness, sadness, fear, disgust, surprise, anger, and neutral). Each type of emotion is presented on a screen five times each (de Souza et al 2018). During all the procedure, the labels of emotions (happiness, sadness, fear, disgust, surprise, anger, and neutral) are shown to the participants, in order to avoid impaired performance due to memory disorder. Participants choose which emotion corresponds to the presented image. Besides the total score on the FERT, we also conducted a qualitative analysis to investigate participants' errors on the FERT. These analyses assessed two types of errors: 1) valence errors (i.e., when the participant mistakes an emotion by another with a different valence, such as happiness for sadness) (Bertoux et al 2020) and 2) perseveration errors, in which the participant repeat the same previously given response.

The modified and reduced version of the faux pas test (mFP) is composed of 10 short stories (please see Supplementary Material for examples) depicting a scene in which one-character either commits (in five stories) or does not commit (in five others) a social faux pas (an action that breaks social rules, regarding the context). The test thus involves the ability to decode



social rules and to infer others' knowledge, intention and feelings (i.e., mentalizing). The task of the participants is to read the story aloud and to detect the presence or absence of a faux pas. If a faux pas is detected (question 1), the participants have to answer to five other questions in order to assess their ability to understand who (question 2) committed the faux pas, what it was (question 3), the knowledge (question 4) and intention (question 5) of the person who committed the faux pas and the feeling experienced by the person who was victim of it (question 6). Two control questions assess the general understanding of the text for all stories, to rule out comprehension impairment. Participants were invited to read the stories as many times as necessary to answer the questions, in order to control for confounds, such as memory deficits. In this study, two components of the test were distinguished: a score assessing the recognition of social norms violation (the sum of scores for questions 1, 2 and 3); and a score assessing mentalizing (the sum of scores for questions 4, 5 and 6).

The raw scores on each mini-SEA subtest (FERT and mFP) are converted into weighted scores (out of 15), as previously described (Funkiewiez et al 2012). The total score of the Mini-SEA is the sum of the weighted scores on FERT (out of 15) and on the mFP (out of 15), and ranges from 0 to 30, with higher scores indicating better performance, as described elsewhere (Bertoux et al 2012a).

#### *MRI Procedure*

MRI was available for 20 bvFTD patients, 21 PSP patients and 20 healthy controls. Data were collected using a 3T Philips 32-channel system using an 8-channel head coil. The three-dimensional T1-weighted volumetric T1W.3D.TFE.ISO sequence involved the following parameters: TR: 8.125ms, TE: 3.72 ms, 256 x 256 matrix, coronal field of view, and 1 mm slice thickness. The delay between MRI and cognitive assessment was shorter than three months for all participants, except for one bvFTD patient (delay = 188 days). As this patient was not an outlier in terms of cognitive scores (MMSE, FAB, and social cognition tests) and brain atrophy, she was included in the VBM analysis.

#### *Statistical Analyses*

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 22 (IBM, USA). Descriptive statistics were performed to characterize the groups of participants. Chi-Square test was used for comparing categorical variables. Parametricity of data was determined with the Kolmogorov-Smirnov test and visual inspection of histograms, refuting the assumption of normality. Non-parametric tests (Kruskal-Wallis for continuous variables and Mann-Whitney U tests for two-by-two comparisons) were therefore used for the analyses. We adopted Bonferroni's correction for multiple comparisons and for multiple correlations and the level of significance ( $\alpha$ ) was set at 0.002. Effect sizes were computed and interpretations regarding their amplitude were based on Cohen (Cohen 1988). We characterized the types of errors (perseverations, valence) made during the FERT and compared the performance between groups, by a qualitative analysis associated to ANOVA. The graphics were prepared with GraphPad Prism 9.3.1.

### *MRI Analyses*

A voxel-based analysis with FSL software (version 5.0) (<http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html>) for "Voxel Based Morphometry" (VBM) (Smith et al 2004) was conducted. The procedure for preprocessing is described elsewhere (Goncalves et al 2020, Wong et al 2016). Briefly, tissue segmentation after brain extraction was performed and the resulting grey matter maps were aligned to the Montreal Neurological Institute standard space. Images were modulated and smoothed (FWHM: 3 mm). Quality checks were carried out after each step to ensure the accuracy of the procedure.

All analyses were performed with General Linear Model (GLM) in *a priori* regions of interest. Grey matter (GM) masks from Neurosynth database (<http://neurosynth.org/>) (Resende et al 2021, Yarkoni et al 2011) were used, by searching for the terms "emotion" (for correlations with FERT total score) and "theory of mind" (for correlations with the mFP scores). This approach aims to restrict the statistical analyses to voxels that are relevant to social cognition and increases the specificity of the findings, thus avoiding spurious results. The "emotion mask" includes limbic structures (amygdala, hippocampi), bilateral fusiform gyrus, temporal poles, anterior cingulate, orbitofrontal cortex and frontal poles. The "ToM mask" includes precuneus, bilateral temporoparietal junction, temporal poles, orbitofrontal cortex and frontal poles.

Please see Supplementary Material for figures of “emotion” and “ToM” masks. The neurosynth mask “theory of mind” was chosen instead of “mentalizing” as it involved more studies (N=181>151) while showing very similar regions involved given that these two terms are synonyms (Quesque & Rossetti 2020). As no mask was closely or remotely related to “social norms” (or “norms”), we kept the same “theory of mind” mask for all analyses involving the mFP scores.

Analyses were performed in three steps. First, we explored differences in GM intensities among groups with permutation-based non-parametric testing with 5000 permutations per contrast (Goncalves et al 2020, Wong et al 2016). The following contrasts were analyzed: controls>bvFTD; controls>PSP; PSP>bvFTD and bvFTD>PSP. Secondly, we explored correlations between GM density and social cognitive scores in PSP and bvFTD separately. In order to increase the variance and maximize statistical power, control participants were combined to each patients’ group, similarly to other studies in the field (e.g., (Bertoux et al 2020, Irish et al 2014, Strikwerda-Brown et al 2021)). Finally, overlap and subtraction (difference) analyses were performed between clinical groups to identify common and specific GM regions implicated in social cognition tasks respectively. Age and sex were considered as covariates in all analyses. For the correlation analyses, we also included the diagnosis and disease duration as nuisance variables. A threshold of 30 contiguous voxels (Yew et al 2013) was adopted, corrected at family-wise error (FWE) at the  $p<0.05$  threshold, for all analyses (Yew et al 2013). The Harvard-Oxford atlas was used for anatomical labelling.

#### *Data availability*

The conditions of our ethics approval do not permit public archiving of anonymised study data. Readers seeking access to the data should contact the corresponding author or the local ethics committee of the Universidade Federal de Minas Gerais (coep@prpq.ufmg.br); approval by the ethics committee is necessary for obtaining the data.

## Results

### *Demographics and clinical variables*

Table 1 presents demographic and general cognitive data for each group of participants. As expected, there was no difference among groups (bvFTD, PSP and controls) regarding demographics (age, educational level and sex distribution). Symptoms' duration was not different between bvFTD and PSP patients.

### *Neuropsychological data (Table 1)*

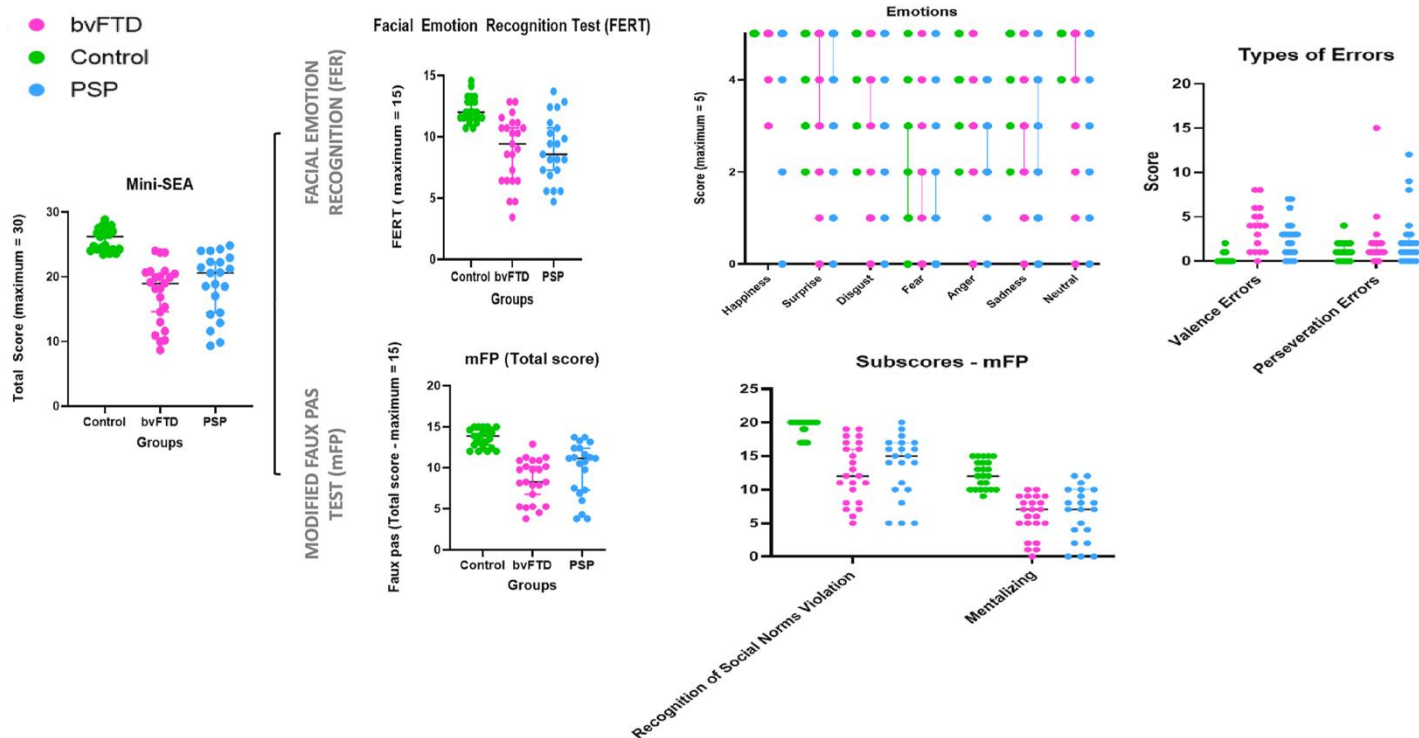
bvFTD and PSP patients performed significantly worse than controls in all cognitive measures, except in digit spans, Stroop and recognition (episodic memory test). There was a significant difference between groups on the Apathy scale, with patients (bvFTD and PSP) presenting higher scores than controls.

There were no significant differences between bvFTD and PSP regarding measures of global cognitive efficiency (MMSE), visual memory, working-memory/attention and executive functioning.

Regarding social cognition (Table 2 and Figure 1), patients with bvFTD and PSP underperformed at the FERT (total score) as compared to controls (bvFTD vs controls:  $p < 0.0001$ ;  $d = 1.61$ ; PSP vs controls:  $p < 0.0001$ ;  $d = 1.51$ ). Lower recognition of disgust, anger, sadness and neutral were observed among patients, regardless of their diagnostic group. Compared to controls (who obtained 2% of incorrect responses), patients with bvFTD committed more valence errors (e.g. negative emotions mistaken as positive or neutral), while clinical groups did not differ on valence errors (bvFTD = 7.35%; PSP = 11.29%). There was no difference among groups regarding the number of perseverative errors (controls = 3.29%, bvFTD = 7.35%, PSP = 6.14%,  $p = 0.25$ , ANOVA).

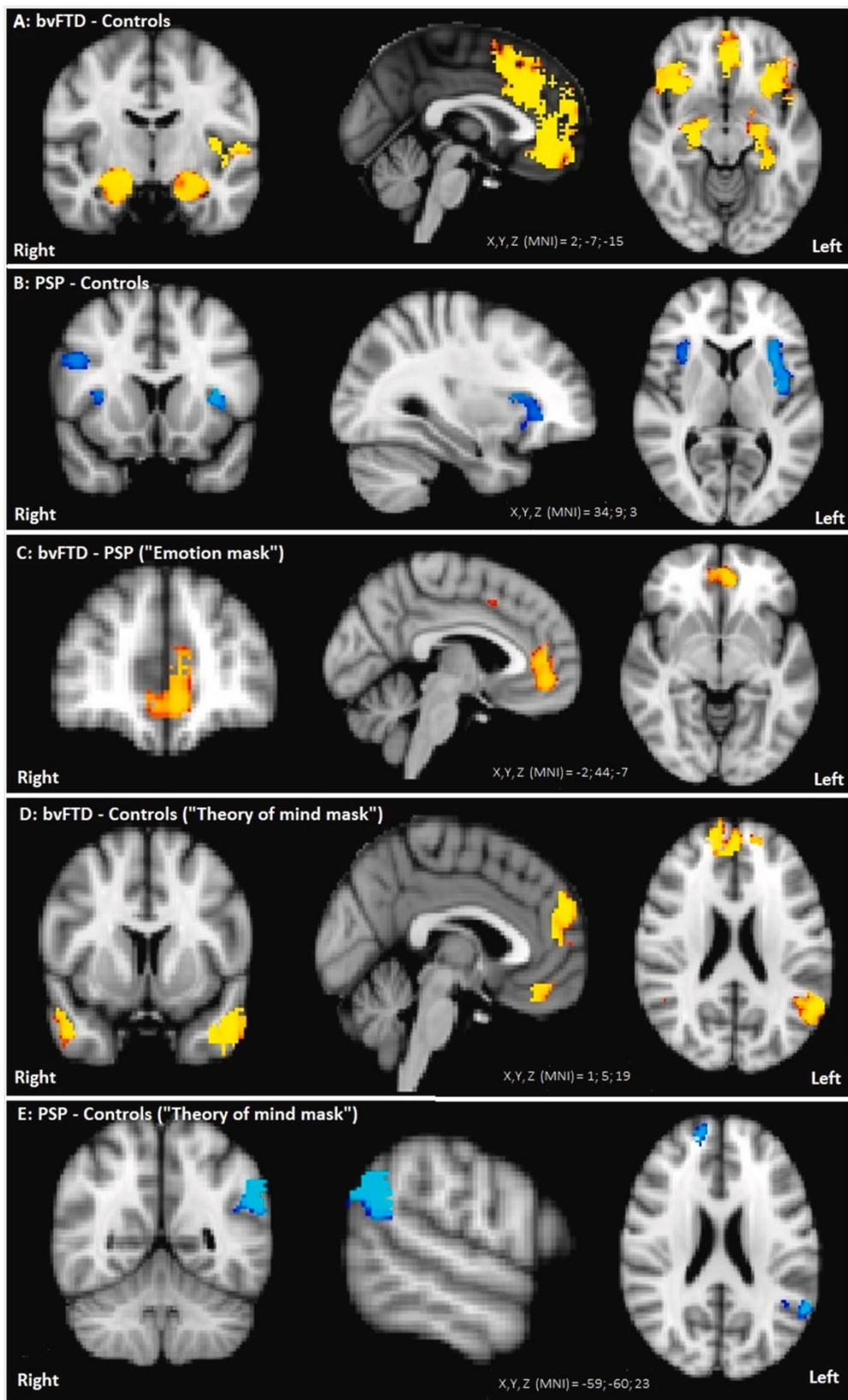
Compared to controls, patients with bvFTD and PSP also displayed significantly lower scores in the total score of the mFP (bvFTD vs controls:  $p < 0.0001$ ;  $d = 2.51$ ; PSP vs controls:  $p < 0.0001$ ;  $d = 1.86$ ), and regarding both the recognition of social norms violation (bvFTD vs controls:  $p < 0.0001$ ;  $d = 2.33$ ; PSP vs controls:  $p < 0.0001$ ;  $d = 1.93$ ) and mentalizing scores (bvFTD vs controls:  $p < 0.0001$ ;  $d = 2.49$ ; PSP vs controls:  $p < 0.0001$ ;  $d = 2.07$ ), despite a normal performance (no difference across groups) at the control questions.

No differences were observed between bvFTD and PSP groups in all measures of social cognition (FERT, mFP, mini-SEA total score). Moreover, there were no differences between bvFTD and PSP regarding the mFP subscores related to the recognition of social norms violation & the mentalizing performance. The mini-SEA total score differed significantly between patients (bvFTD and PSP) and controls (bvFTD vs controls:  $p < 0.0001$ ;  $d = 2.47$ ; PSP vs controls:  $p < 0.0001$ ;  $d = 1.76$ ), with lower scores for patient groups.



**Figure 1:** Social Cognition tests. Individual and group performance of controls and patients with behavioural variant frontotemporal dementia (bvFTD) and progressive supranuclear palsy (PSP) at the short version of Social and Emotional Assessment (Mini-SEA), which is composed of a facial emotion recognition test (FERT) and the modified faux pas (mFP) test.

*Neuroimaging*



**Figure 2** Contrasting the atrophy patterns of the groups. Panel A shows the significant clusters of less gray matter volume in behavioral frontotemporal dementia (bvFTD) compared with

healthy controls, using a mask ("emotion mask") to restrict the analyses only to brain regions previously associated with emotion processing from fMRI studies (Yarkoni et al., 2011). Panel B shows the significant clusters of less grey matter volume in progressive supranuclear palsy (PSP) patients compared with controls, with "emotion mask". Panel C shows the significant clusters of less grey matter volume in bvFTD patients compared with PSP, with "emotion mask". Panel D shows the significant clusters of less grey matter volume in bvFTD patients compared with controls, using a mask ("theory of mind [ToM] mask") to restrict the analyses only to brain regions previously associated with ToM from fMRI studies. Panel E shows the significant clusters of less grey matter volume in PSP patients compared with controls, with ToM mask. Yellow refers to the atrophy observed in bvFTD and blue to the atrophy observed in PSP. All analyses used Family Wise Error correction for multiple comparison analyses and a p value of .05, adding age, sex, diagnosis and disease duration as covariates. The images are displayed in radiological convention. The coordinates (X, Y, Z) were placed per the Montreal Institute Neuroimaging (MNI).

#### *Comparative analyses of GM atrophy patterns between groups*

The first step of analyses aimed to compare GM intensity across groups. Table 3 presents detailed data regarding significant clusters on comparative analyses ( $p_{FWE} < 0.05$ ).

Using the mask that limited these analyses to cerebral regions relevant to emotional processing ("emotion mask"), bvFTD patients had bilateral atrophy involving frontal poles, anterior cingulate, insula and limbic structures such as amygdala, when compared to controls, as shown in Figure 2A. The contrast controls < PSP showed bilateral insular atrophy in PSP patients (Figure 2B). Compared to PSP, bvFTD patients had bilateral anterior cingulate atrophy (Figure 1C). The contrast bvFTD < PSP did not disclose significant differences.

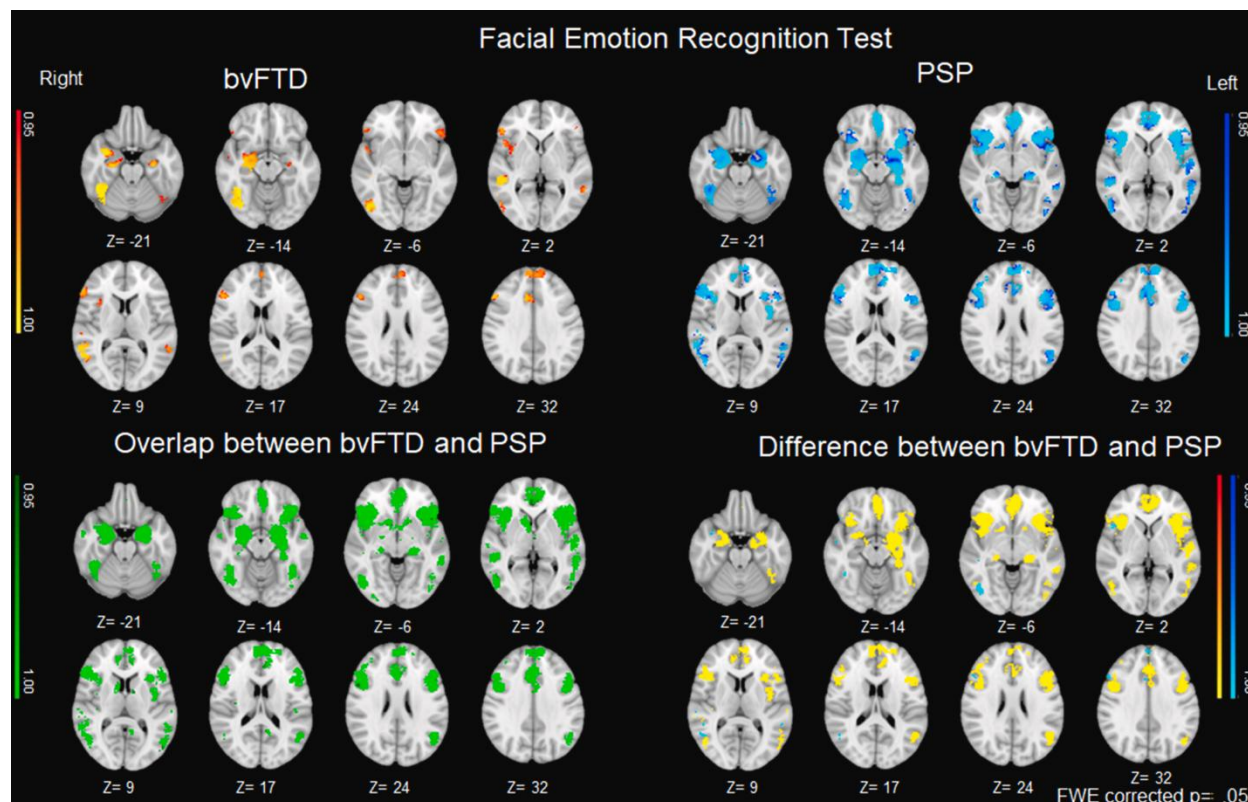
Using the "ToM mask", compared to controls, bvFTD patients had atrophy in bilateral temporal poles, frontal poles, anterior cingulate, and left temporoparietal region, involving both angular and supramarginal gyrus, as shown in Figure 1D. The contrast controls < PSP showed that PSP patients had atrophy in the right frontal pole and left temporoparietal region (Figure 1E). The contrasts bvFTD < PSP and PSP < bvFTD did not reveal significant differences.

#### *GM correlates of social cognition performance in clinical groups*



The second step of neuroimaging analyses was to correlate GM volumes to social cognition scores within groups (FWE,  $p < 0.05$ ). Table 4 shows detailed data regarding significant clusters from the correlation analyses within each group. In the bvFTD group, FERT total score correlated bilaterally to anterior cingulate, frontal medial cortex and bilateral amygdala GM (Figure 3A). The mFP test mentalizing score correlated with the GM in frontal poles, temporal poles, cingulate cortex and left temporoparietal region (Figure 4A), while the recognition of social norms violation score correlated bilaterally with the GM within the temporal and frontal poles (Figure 5A).

In the PSP group, FERT total score correlated with bilateral frontal medial cortex, amygdala, angular gyrus, supramarginal gyrus, striatum and insular cortex GM (Figure 3A). The mFP test mentalizing score correlated bilaterally to GM within the frontal pole, the cingulate cortex, the orbitofrontal cortex and the temporoparietal regions (Figure 4A). The score of recognition of social norms violation correlated to GM in the temporal poles, temporoparietal regions and frontal poles (Figure 5A).



**Figure 3:** Grey matter correlates of the facial emotion recognition test (FERT) in behavioral frontotemporal dementia (bvFTD) and progressive supranuclear palsy (PSP) patients. Panels A and B shows significant clusters that correlated with scores of facial emotion recognition in patients with bvFTD (Panel A) and PSP (Panel B), using a mask (“emotion mask”) to restrict the analyses only to brain regions previously associated with emotion processing from fMRI studies. Panel C shows significant overlapping clusters of GM correlates of the FERT in both bvFTD and PSP groups. Panel D shows significant clusters that correlated with the FERT exclusively in bvFTD patients (contrast bvFTD-PSP) and significant clusters that correlated with the FERT exclusively in PSP patients (contrast PSP-bvFTD). All analyses used Family Wise Error correction for multiple comparison analyses and a  $p$  value of 0.05, adding age, sex, diagnosis and disease duration as covariates. The color bar represents the  $p$  value. The images are displayed in radiological convention. The coordinates (X, Y, Z) were placed per the Montreal Institute Neuroimaging (MNI).

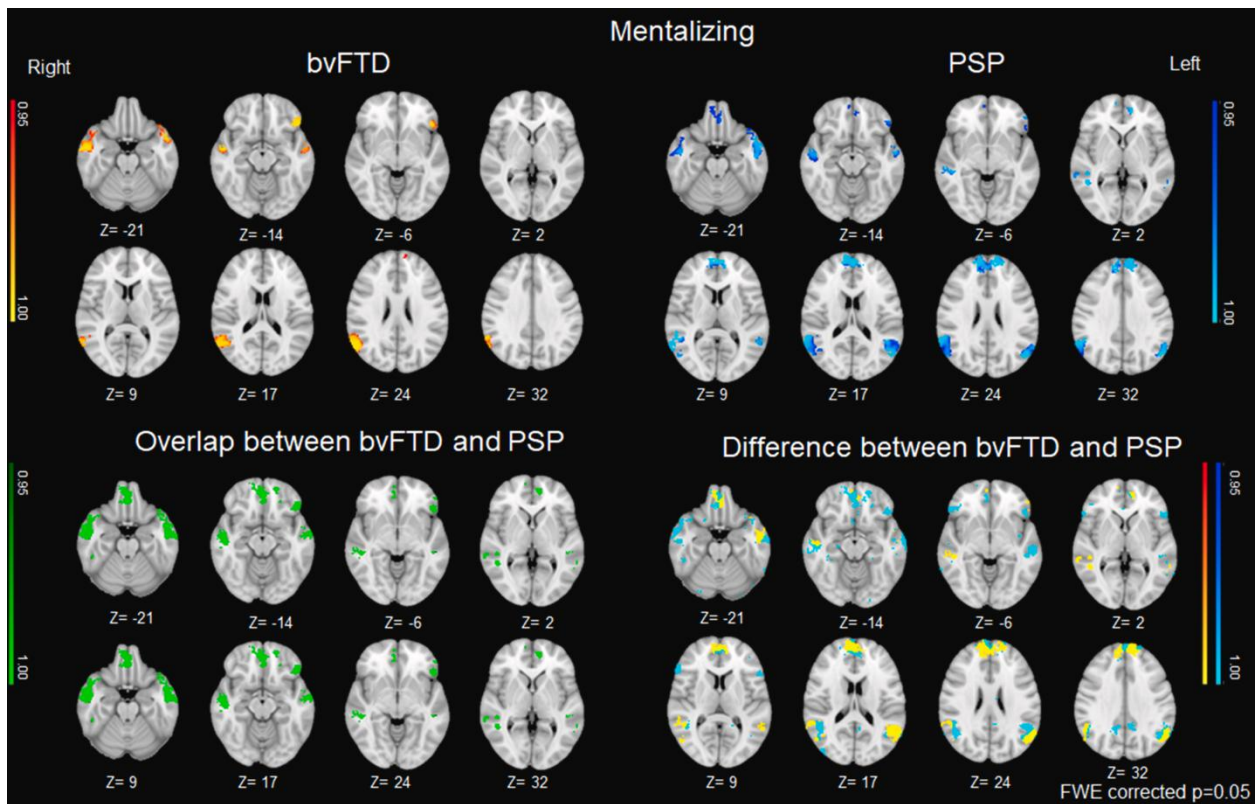
#### *Common correlates of social cognition performance between bvFTD and PSP*

In both bvFTD and PSP groups, the FERT total score positively correlated bilaterally to anterior cingulate, frontal medial cortex and bilateral amygdala (Figure 3C). Regarding correlations with the mentalizing score from the mFP test, both clinical groups displayed bilateral clusters within frontal and temporal poles (Figure 4C). The recognition of social norms violation score correlated with the GM within both temporal poles and bilateral frontal poles in clinical groups (Figure 5C).

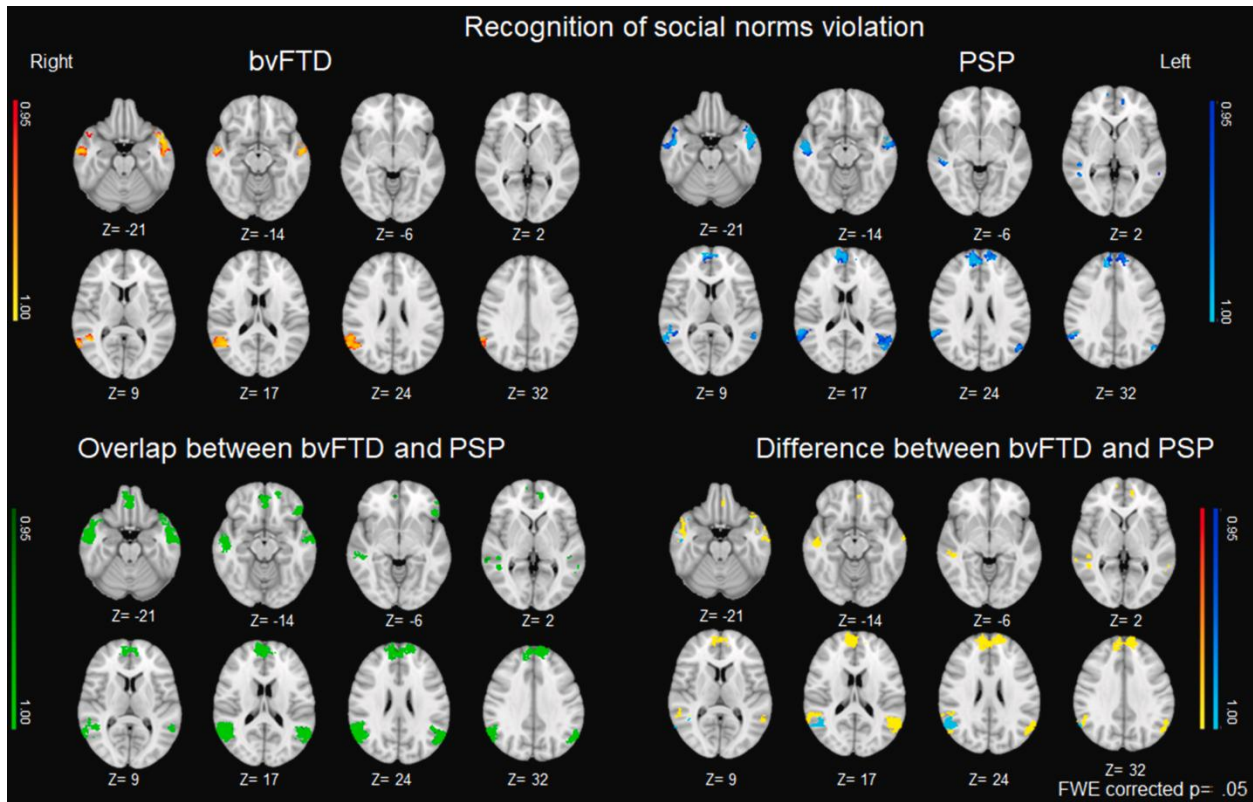
#### *Different patterns of correlations of social cognition performance between bvFTD and PSP*

For the FERT, we retrieved significant clusters in bilateral frontal medial cortex and bilateral fusiform GM (Figure 3D) in bvFTD patients, compared to PSP. The opposite contrast (PSP-bvFTD) yielded significant clusters in the bilateral caudate nuclei in PSP patients (Figure 2D).

For the mFP, specific clusters of GM within the bilateral orbitofrontal cortex and temporoparietal junction were retrieved in bvFTD (Figure 4A), while a specific cluster within the left frontal pole was observed in PSP (Figure 4B). Regarding correlations with the recognition of social norms violation, specific clusters within the bilateral orbitofrontal cortex and temporoparietal junction were retrieved in the bvFTD group (Figure 5D). Nospecific cluster was retrieved in PSP (Figure 5D).



**Figure 4:** Grey matter correlates of mentalizing (derived from the *faux-pas* test) in behavioral frontotemporal dementia (bvFTD) and progressive supranuclear palsy (PSP) patients. Panels A and B shows significant clusters that correlated with scores of mentalizing in patients with bvFTD (Panel A) and PSP (Panel B), using a mask (“theory of mind [ToM] mask”) to restrict the analyses only to brain regions previously associated with ToM processing from fMRI studies. Panel C shows significant overlapping clusters of GM correlates of the mentalizing in both bvFTD and PSP groups. Panel D shows significant clusters that correlated with the mentalizing exclusively in bvFTD patients (contrast bvFTD-PSP) and significant clusters that correlated with the mentalizing exclusively in PSP patients (contrast PSP-bvFTD). All analyses used Family Wise Error correction for multiple comparison analyses and a p value of 0.05, adding age, sex, diagnosis and disease duration as covariates. The color bar represents the  $p$  value. The images are displayed in radiological convention. The coordinates (X, Y, Z) were placed per the Montreal Institute Neuroimaging (MNI).



**Figure 5:** Grey matter correlates with the recognition of social norms violation (derived from the *faux-pas* test) in behavioral frontotemporal dementia (bvFTD) and progressive supranuclear palsy (PSP) patients. Panels A and B show significant clusters that correlated with scores of recognition of social norms violation in patients with bvFTD (Panel A) and PSP (Panel B), using a mask (“theory of mind [ToM] mask”) to restrict the analyses only to brain regions previously associated with ToM processing from fMRI studies. Panel C shows significant overlapping clusters of GM correlates of the recognition of social norms violation in both bvFTD and PSP groups. Panel D shows significant clusters that correlated with the recognition of social norms violation exclusively in bvFTD patients (contrast bvFTD-PSP) and significant clusters that correlated with the understanding of social norms exclusively in PSP patients (contrast PSP-bvFTD). All analyses used Family Wise Error correction for multiple comparison analyses and a  $p$  value of 0.05, adding age, sex, diagnosis and disease duration as covariates. The color bar represents the  $p$  value. The images are displayed in radiological convention. The coordinates (X, Y, Z) were placed per the Montreal Institute Neuroimaging (MNI).

## Discussion

This study investigated the performance and neural correlates of facial emotion recognition and mentalizing abilities in bvFTD and PSP. In order to confirm or infirm the existence of mentalizing difficulties in PSP, as well as to examine potential differences with bvFTD, we explored quantitative and qualitative neuropsychological as well as neuroimaging profiles in both diseases. To this aim, we studied two different dimensions of the mFP test, a gold-standard assessment of mentalizing abilities, in delineating the mentalizing and recognition of social norms violation components of this test. With the same goal in mind, we characterized the type of errors committed during the recognition of facial emotions, measured through another gold-standard test, the FERT. Overall, we observed that bvFTD and PSP do not differ in social cognition measures nor quantitatively, neither qualitatively. We also retrieved very similar neural correlates of social cognition impairment across both diseases.

Contrary to our hypothesis, PSP and bvFTD had similar impairment on all measures of social cognition. In the literature, the traditional cognitive profile of PSP is marked by executive dysfunction, with a wide range of deficits concerning processes such as cognitive slowing, conceptual thinking, cognitive flexibility and initiation (Aarsland et al 2003, Albert et al 1974, Caso et al 2016, Garcin et al 2018, Giordano et al 2013, Lagarde et al 2013). The focus on social cognition has only been put recently, with emotion recognition as well as sarcasms and lie detection abilities retrieved to be altered significantly in this disease (Ghosh et al 2012, Ghosh et al 2009, Shany-Ur et al 2012). Here, we confirm previous studies focused on emotion recognition and extended the findings in observing severe mentalizing difficulties and social norms misunderstanding in PSP. Taken together, this contrasts with what was considered as the prototypical model of “subcortical dementia”, with marked cognitive slowness and relative preservation of “higher cortical functions” (Albert et al 1974).

In our study, patients with PSP had a cognitive profile almost indistinct to the one presented by bvFTD individuals, with the same neuropsychological dimensions altered. Regarding social cognition, both groups showed lower abilities to recognize the same negative emotions (i.e., disgust & sadness), as well as to mentalize and recognize social norms violation. Beyond the absence of statistical differences, average performances and their range were very similar in

both patient groups, which could make them virtually indistinguishable on the basis of neuropsychological tests. When a qualitative (i.e., profiles of errors) exploration was performed, we again observed that both patient groups had a similar profile, with no differences regarding the types of errors committed during the FERT. In more details, PSP and bvFTD patients did not differ between each other in terms of perseverative or valence errors. These findings confirm that, in PSP, the recognition component of emotional processing is significantly disturbed. Given that only difficulties to recognize negative emotions were retrieved, one could point out a possible dissociation between non-negative (including neutral) and negative emotions. However, previous studies based on larger sample sizes in bvFTD have demonstrated that the recognition of all emotions could be compromised at group-level, although the recognition of happiness was preserved in most of patients (Bertoux et al 2015a). The effect observed here could be only due to the unbalanced ratio of negative/positive emotions to recognize, as suggested by other studies (Bertoux et al 2020) – a common limit regarding emotion recognition assessment methodology. Put in other words, with more negative emotions to recognize in the test, there are higher chances of failure.

To date, the explorations of the neural correlates of social cognition performance have been scarce in PSP, and no direct anatomical comparison with bvFTD has ever been performed, which motivated our neuroimaging investigations. On the anatomical level, PSP and bvFTD patients presented cerebral atrophy in critical regions for social cognition processes, when compared to controls. The structural correlates of emotion recognition performance significantly overlapped between bvFTD and PSP, with the involvement of the rostral medial prefrontal cortex, insula, striatum and limbic structures (e.g., amygdala) in both disorders, bilaterally. These findings are in line with the similar quantitative and qualitative profile in emotion recognition that we observed in both diseases. Altogether, these brain regions have been previously reported as the neural underpinnings of recognition of facial emotions in neurodegenerative disorders and FTL in particular (Bertoux et al 2012b, Kumfor et al 2018, Marshall et al 2019). They appear to be critical to facial emotion recognition given their role in value and affective processing, salience and interoception (Adolfi et al 2017, Garcia-Cordero et al 2016, Rolls 2019). Interestingly, while a combination of regions supporting both the salience network and semantic appraisal networks has been envisaged to support core socio-emotional

processing (Rankin 2020), our findings indicate that in bvFTD and PSP, dysfunctions of regions composing the salience network are mostly at stake regarding difficulties on facial emotion recognition. Because our imaging approach relied on a priori masks, our findings do not however discard the possibility that semantic appraisal network may as well be impaired in bvFTD or PSP (e.g. (Bertoux et al 2020, Rankin 2020)), but our study was not designed to explore this aspect. This should be investigated by whole-brain functional imaging analysis. Of note, when considering the specificities of the anatomical correlations with facial emotion recognition, we observed stronger and wider correlations in the prefrontal cortex in the bvFTD group, as well as the involvement of the fusiform gyrus. By contrast, in PSP, we retrieved a stronger involvement of the striatum. These specificities are not surprising given the pathophysiological bases of bvFTD and PSP. The fusiform gyrus, known to be critically involved in face processing (Tarr & Gauthier 2000), has been reliably retrieved among the neural correlates of facial emotion recognition in FTD (Kumfor et al 2018, Marshall et al 2019). Although striatal and prefrontal degeneration are observed in bvFTD and PSP respectively (Agosta et al 2018, Bertoux et al 2015b), the first is the hallmark of PSP and the second, of bvFTD (Perry et al 2017). It is therefore expected that these regions would preferentially modulate the cognitive dysfunctions in each disease. In addition, the strong structural and functional relationship existing between the prefrontal cortex and the striatum would explain why these relative anatomical specificities lead to the same deficit (O'Callaghan et al 2014, Tziortzi et al 2014).

Regarding the mentalizing performance, significant correlations within the bilateral rostral medial prefrontal cortex, temporal poles and the inferior parietal cortex were found in both disorders, consistently with what has been associated to mentalizing processing in bvFTD using the same task (Bertoux et al 2014) or sarcasms/lies detection in PSP (Ghosh et al 2012) patients. Remarkably, analyses of the specificities of the neural correlates indicate that the atrophy of the temporo-parietal junction is involved in mentalizing impairment in bvFTD. While a strong emphasis has been made on the medial prefrontal cortex in bvFTD, given its early and characteristic involvement, temporoparietal atrophy in bvFTD has been previously related to mentalizing difficulties (Baez et al 2019). Interestingly, the inferior parietal cortex has been described to play a key role in self-other distinction, a prior requisite for mental state

attributions (Quesque & Brass 2019). The focus on the prefrontal cortex also shows that medial regions are preferentially involved in bvFTD, while in PSP more lateral regions were retrieved. While this should be confirmed by future studies, one hypothesis to explain these relative discrepancies in the neural correlates of PSP and bvFTD is that, in both disorders, mentalizing abilities are altered, but in bvFTD, the ability for self-other distinction - carried by the temporoparietal region - could be impaired as well.

In our study, we chose to delineate the recognition of social norms violation from the mentalizing component of the task included in the mini-SEA. It should be pointed out that, even though the mentalizing and the recognition of social norms violation are partially interrelated, these two subcomponents of the mFP can be distinguished, as the detection of the faux pas precedes the inference about mental states. Although we expected that the temporal involvement that could drive the recognition of social norms violation aspect of the task would cause a decrease in performance for patients with bvFTD only, no differences were observed between our groups. PSP and bvFTD patients also had similar patterns of brain correlations for the composite score of social norms, with significant clusters on anterior temporal lobe. It has been previously shown that the right anterior temporal lobe plays a critical role in social semantics, and patients with damage in this region manifest violations of social norms (Panchal et al 2016). Although this association has been previously observed in bvFTD (Multani et al 2019, Panchal et al 2016), the current study is the first observation of this association in PSP patients. Interestingly, the scores of mFP and recognition of social norms violation correlated to GM in both temporal poles across bvFTD and PSP patients, with no marked right-left asymmetry. While some studies with semantic FTD suggested that right temporal pole is specialized in emotion and social cognition processes (Irish et al 2013, Josephs et al 2009, Kamminga et al 2015, Thompson et al 2003), other studies did not confirm these findings, and reported left or bilateral temporal involvement in social cognition tasks (Bertoux et al 2020, Downey et al 2015, Kumfor et al 2013, Kumfor et al 2016, Lindquist et al 2014).

Taken together, these findings reinforce the relevance of cortical involvement in PSP, with specific cognitive deficits due to the pathological distribution of neurodegeneration (Williams & Lees 2009). The involvement of the cortical regions retrieved to correlate with social cognitive



difficulties has also been previously reported in PSP patients in pure neuroimaging studies (Agosta et al 2018, Agosta et al 2014, Caso et al 2016, Josephs et al 2011, Lansdall et al 2018).

## **Limitations**

The present study has some limitations. First of all, the relatively small sample size limits the generalization of the present findings. However, our samples are similar to other studies in the field (Ghosh et al 2012, Kumfor et al 2018, Lagarde et al 2015). More studies, with larger number of patients, are warranted to confirm our results. The neuroimaging investigation was limited to GM correlates of cognitive deficits, but behavioral symptoms in PSP and bvFTD also depend on subcortical structures, such as on white matter integrity (Agosta et al 2014, Josephs et al 2011, Lansdall et al 2018). The analysis of functional connectivity was not performed in our study, although it may also help to understand the neural basis of social cognition deficits in neurodegenerative disorders (Marshall et al 2019, Multani et al 2019) and has the potential to shed light on the functional networks involved in such symptoms (Rankin 2020). However, neural correlations of social cognition in PSP have been scarcely performed in the past, and our study is therefore relevant. Another potential limit regards the diagnosis of PSP-RS and bvFTD, that were defined under clinical basis, without pathological confirmation. However, beyond the fact that this limit is common to most of the studies in the field, the diagnosis of patients was performed in expert clinics, and reliable in adopting consensual criteria and a follow-up of over 24 months. Finally, it would have been of value to include questionnaires assessing everyday social function. This point should be addressed in future studies in order to explore correlations between social function and social cognition tests, such as the FERT and the mFP.

## **Conclusion**

The findings of this study contribute to a broader understanding of cognitive impairment associated with PSP, expanding the original concept of “subcortical dementia”. Moreover, these

findings corroborate that PSP and bvFTD share many key clinical, cognitive and neuroimaging features, in agreement with pathological data showing that both disorders are associated to FTLD (Perry et al 2017). While other, more neurological (e.g. vertical gaze palsy, motor features...) dimensions could have more relevance than cognitive ones to help the differential diagnosis between PSP and bvFTD, we would like to emphasize that, in both diseases, future clinical interventions or symptoms management strategies aiming to increase the patients' well-being and alleviate their symptoms would have to consider, at some point, social cognition either as an outcome or as a leverage. Given the importance of social cognition in everyday functioning, from social interactions with family and friends to the social role or support one could have, this domain should be central to any novel therapeutic strategy. Future neuropsychological and molecular neuroimaging research might shed light on the neurobiological pathways underlying PSP and bvFTD and their symptoms (including "social" ones), allowing a better clinical diagnosis and follow-up of these conditions. It is our belief that social cognition or a neuropsychology that would focus on social functioning has a key role to play. In this perspective, our study may represent a stepping stone in that direction.

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## **Authors' contributions**

LCS designed the study, collected clinical and cognitive data, performed statistical and neuroimaging analyses and drafted the first version of the manuscript. MB designed the study, performed statistical analyses and critically reviewed the manuscript for intellectual content. RR designed the study and critically reviewed the manuscript for intellectual content. MH and EPFR performed neuroimaging analyses and critically reviewed the manuscript for intellectual content. FQ performed statistical analyses and critically reviewed the manuscript for intellectual content. LIM collected cognitive data and critically reviewed the manuscript for intellectual content. HCG, LBG, VT, and STC collected clinical data and critically reviewed the manuscript for intellectual content. FECC, ALT and PC designed the study, collected clinical data and critically reviewed the manuscript for intellectual content. All authors read and approved the final manuscript.

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**Table 1: Demographical, clinical, neuropsychological data (mean ± standard deviation (min-max))**

	Healthy Controls [n=23]	bvFTD [n=23]	PSP [n=21]	Kruskal-Wallis Test (all groups)	bvFTD vs PSP (Mann-Whitney test)	bvFTD vs controls (Mann-Whitney test)	PSP vs controls (Mann-Whitney test)
<b>Men:Women (numbers)</b>	8:15	13:10	9:12	Not applicable	Not applicable	Not applicable	Not applicable
<b>Age (years)</b>	64.7 ± 10 (48-81)	65.8± 9 (52-83)	67.7± 7.8 (55-81)	p < 0.72	p < 0.48 d = 0.50	p < 0.82 d = 0.36	p < 0.50 d = 0.06
<b>Education (years)</b>	12.7 ± 2.6 (8-17)	13± 3.3 (8-20)	13± 3.7 (6-20)	p < 0.92	p < 0.96 d = 0	p < 0.77 d = 0.19	p < 0.68 d = 0.13
<b>Disease duration (years)</b>	NA	3.7± 1.8 (1-7)	4.1± 1.9 (1-7)	Not applicable	p < 0.44 d = 0.05	Not applicable	Not applicable
<b>Mini-Mental State Exam ( / 30)</b>	29 ± 0.9 (27-30)	25.5± 2.7 (20-29)	26.1± 2.4 (20-29)	p < 0.0001	p < 0.45 d = 0.35	p < 0.0001* d = 1.74	p < 0.0001* d = 1.65
<b>Digit Span Forward</b>	7.7 ± 1.7 (5-12)	7± 1.5 (4-9)	7.6± 1.3 (5-10)	p < 0.33	p < 0.19 d = 0.28	p < 0.21 d = 0	p < 0.89 d = 0.25
<b>Digit Span Backward</b>	5 ± 1.4 (2-8)	3.8± 1.5 (0-7)	4± 1.2 (2-7)	p < 0.03	p < 0.96 d = 0.07	p < 0.019 d = 0.73	p < 0.028 d = 0.89
<b>Visual Memory Test</b>							
<b><i>Immediate Memory ( /10)</i></b>	8.8 ± 1.1 (6-10)	6.6± 2 (3-10)	6.7± 1.5 (3-9)	p < 0.0001	p < 0.75 d = 0.18	p < 0.0001* d = 1.41	p < 0.0001* d = 1.82
<b><i>Delayed Recall ( /10)</i></b>	9 ± 1 (7-10)	6.3± 2.8 (0-10)	6.7± 1.9 (1-10)	p < 0.0001	p < 0.65 d = 0.04	p < 0.0001* d = 1.11	p < 0.0001* d = 1.65

<b>Recognition ( /10)</b>	10 ± 0	9.3± 1.8 (3-10)	9.7± 1.1 (5-10)	p < 0.034	p < 0.008 d = 0.28	p < 0.37 d = 0.47	p < 0.11 d = 0.51
<b>Frontal Assessment Battery (/18)</b>	15.7 ± 1.7 (13-18)	11.3± 4.1 (4-18)	11.3± 3.4(6-17)	p < 0.0001	p < 0.84 d = 0.13	p < 0.0001* d = 1.48	p < 0.0001* d = 1.72
<b>Lexical Fluency (FAS)</b>	32.9 ± 9.1 (16-54)	18± 12.1 (2-41)	18.7± 11.4 (4-53)	p < 0.0001	p < 0.82 d = 0.22	p < 0.0001* d = 1.67	p < 0.0001* d = 1.43
<b>Fluency (Animals)</b>	18.5 ± 3.8 (11-27)	11.2± 5.6 (4-24)	10.3± 5.4 (3-21)	p < 0.0001	p = 1.0 d = 0.14	p < 0.0001* d = 1.72	p < 0.0001* d = 1.72
<b>Stroop Word/Colour – time (s)</b>	34.5 ± 10 (20-65)	48.3± 30 (18-151)	56.8± 24 (29-127)	p < 0.88	p < 0.81 d = 0.58	p < 0.029 d = 0.62	p < 0.11 d = 3.22
<b>Stroop Word/Colour – errors</b>	2.2 ± 2.7 (0-10)	8± 8.5 (0-24)	6± 4.9 (0-18)	p < 0.77	p < 0.35 d = 0.24	p < 0.039 d = 1.05	p < 0.12 d = 1.34
<b>Hayling Test</b>							
<b>part A–score ( /15)</b>	14.7 ± 0.5 (13-15)	14.3± 1 (12-15)	14.8± 0.5 (13-15)	p < 0.22	p < 0.27 d = 0.76	p < 0.092 d = 0.97	p < 0.72 d = 0.36
<b>part B–score ( /15)</b>	8.1 ± 0.5 (13-15)	4± 4.3 (0-12)	4.5± 3.9 (0-14)	p < 0.0001	p < 0.91 d = 0.48	p < 0.001* d = 1.66	p < 0.0001* d = 1.17
<b>part B–simple error ( /15)</b>	7 ± 0.5 (1-12)	11± 4.3 (3-15)	10± 4.5 (0-15)	p < 0.0001	p < 0.19 d = 0.59	p < 0.001* d = 1.66	p < 0.057 d = 0.88
<b>part B–qualified error ( /45)</b>	10.7 ± 5.6 (2-21)	25.4± 15 (3-45)	21.2± 11 (1-39)	p < 0.0001	p < 0.13 d = 0.69	p < 0.001* d = 1.77	p < 0.008 d = 1.45
<b>Apathy score ( /42)</b>	6.9 ± 3.4 (2-16)	26.7± 9 (5-41)	18.9± 7.9 (8-33)	p < 0.0001	p < 0.002* d = 1	p < 0.0001* d = 3.28	p < 0.0001* d = 2.24

## Legend

bvFTD: behavioural variant frontotemporal dementia; *d*: Cohen's *d*; PSP: Progressive Supranuclear Palsy.

\* Statistically significant ( $p < 0.002$ ; Mann-Whitney test, Bonferroni correction)

**Table 2: Social Cognition tests (mean ± standard deviation (min-max))**

	Healthy Controls [n=23]	bvFTD [n=23]	PSP [n=21]	Kruskal- Wallis Test (all groups)	bvFTD vs PSP (Mann- Whitney test)	bvFTD vs controls (Mann- Whitney test)	PSP vs controls (Mann- Whitney test)
<b>Facial Emotion Recognition Test</b>							
<i>Total Score ( /35)</i>	28.4± 2.4 (25-34)	20.9± 6.4 (8-30)	20.9± 6.1 (11-32)	p < 0.0001	p < 0.38 d = 0.15	p < 0.0001* d = 1.61	p < 0.0001* d = 1.51
<i>Happiness ( /5)</i>	5± 0 (5-5)	4.9± 0.5 (3-5)	4.5± 1.2 (0-5)	p < 0.13	p < 0.17 d = 0.22	p < 0.59 d = 0.40	p < 0.076 d = 0.51
<i>Surprise ( /5)</i>	4.3± 0.9 (2-5)	3.3± 1.6 (0-5)	3.8± 1.4 (0-5)	p < 0.18	p < 0.29 d = 0.47	p < 0.071 d = 1.48	p < 0.40 d = 1.0
<i>Disgust ( /5)</i>	4.4± 0.9 (2-5)	2.9± 1.8 (0-5)	2.8± 1.4 (0-5)	p < 0.0001	p < 0.68 d = 0.13	p < 0.003 d = 1.47	p < 0.0001* d = 1.87
<i>Fear ( /5)</i>	1.8± 1.5 (0-5)	1.3± 1.4 (0-5)	1.4± 1.5 (0-5)	p < 0.61	p < 0.81 d = 0.07	p < 0.35 d = 0.40	p < 0.48 d = 0.32
<i>Anger ( /5)</i>	3.7 ± 0.9 (2-5)	2.5±1.5 (0-5)	2.3±1.2 (0-4)	p < 0.0001	p < 0.62 d = 0.22	p < 0.02 d = 1.61	p < 0.003 d = 1.43
<i>Sadness ( /5)</i>	4.4 ± 0.8 (2-5)	2.3±1.6 (0-5)	2.4±1.7 (0-5)	p < 0.0001	p < 0.94 d = 0	p < 0.0001* d = 2.29	p < 0.0001* d = 1.99
<i>Neutral ( /5)</i>	4.8 ± 0.4 (4-5)	3.7 ±1.7 (0-5)	3.7 ±1.8 (0-5)	p < 0.11	p < 0.72 d = 0.05	p < 0.035 d = 1.18	p < 0.13 d = 1.17
<i>Valence Errors (frequency, %)</i>	2%	7.35%	11.29%	p < 0.001 <sup>‡</sup>	p < 0.66 <sup>‡</sup>	p < 0.001 <sup>‡*</sup>	p < 0.004 <sup>‡</sup>

<i>Perseverative Errors (frequency, %)</i>	3.29%	7.35%	6.14%	$p < 0.25^{\text{‡}}$	$p < 0.88^{\text{‡}}$	$p < 0.49^{\text{‡}}$	$p < 0.23^{\text{‡}}$
<b>Modified Faux-Pas Test</b>							
<i>Stories with Faux-Pas (/30)</i>	26.4± 2.9 (22-30)	14.3± 7.1 (0-24)	15.6± 8.6 (0-27)	$p < 0.0001$	$p < 0.38$ $d = 0.44$	$p < 0.0001^*$ $d = 2.51$	$p < 0.0001^*$ $d = 1.86$
<i>Stories without Faux-Pas (/10)</i>	10 ± 0.4 (8-10)	7.8 ± 2.1 (4-10)	9.1 ± 1.5 (6-10)	$p < 0.0001$	$p < 0.02$ $d = 0.11$	$p < 0.0001^*$ $d = 1.05$	$p < 0.027$ $d = 0.80$
<i>Total Score (/40)</i>	36.3± 3 (32-40)	22.1± 6.7 (10-30)	24.8± 8.6 (10-35)	$p < 0.0001$	$p < 0.13$ $d = 0.46$	$p < 0.0001^*$ $d = 2.76$	$p < 0.0001^*$ $d = 1.97$
<i>Mentalizing (/20)</i>	12.2±2 (9-15)	4.9±3.5(0-10)	6.1± 3.5 (0-12)	$p < 0.0001$	$p < 0.28$ $d = 0.34$	$p < 0.0001^*$ $d = 2.49$	$p < 0.0001^*$ $d = 2.07$
<i>Recognition of social norms violation (/20)</i>	19.3± 1.2 (17-20)	10.9± 5.4 (0-19)	12.6± 5.3 (0-20)	$p < 0.0001$	$p < 0.32$ $d = 0.32$	$p < 0.0001^*$ $d = 2.33$	$p < 0.0001^*$ $d = 1.93$
<b>Mini-SEA (Total Score / 30)</b>	25.8±1.7 (23.4-28.8)	17.4±4.7 (8.7-24)	18.7±4.7 (9.3-24.8)	$p < 0.0001$	$p < 0.25$ $d = 0.22$	$p < 0.0001^*$ $d = 2.47$	$p < 0.0001^*$ $d = 1.76$

## Legend

bvFTD: behavioural variant frontotemporal dementia;  $d$ : Cohen's  $d$ ; Mini-SEA: Short version of the Social and Emotional Assessment; PSP: Progressive Supranuclear Palsy. \* Statistically significant ( $p < 0.002$ ; Mann-Whitney test, Bonferroni correction) ‡ANOVA

<b>A. RESULTS FOR CONTRASTS BETWEEN GROUPS APPLYING THE "EMOTION MASK"</b>				
<b>A1. Contrast Controls &lt;bvFTD</b>				
<i>Regions</i>	<i>MNI Coordinates</i>			<i>Number of voxels</i>
	<i>X</i>	<i>Y</i>	<i>Z</i>	
Frontal medial cortex (L), paracingulate (L)	-2	36	-20	4012
Temporal pole (L), frontal orbital cortex (L), parahippocampal gyrus(L)	-26	6	-24	3832
Frontal orbital cortex (R), insular cortex (R)	38	20	-14	2431
Angular gyrus (L), supramarginal cortex (L)	-54	-58	30	165
<b>A2. Contrast Controls&lt; PSP</b>				
<i>Regions</i>	<i>MNI Coordinates</i>			<i>Number of voxels</i>
	<i>X</i>	<i>Y</i>	<i>Z</i>	
Frontal operculum cortex (L), insular cortex (L)	-32	16	10	552
Insular cortex (R), frontal operculum cortex (R)	32	14	10	204
Inferior frontal gyrus (R), precentral gyrus (R), middle frontal gyrus (R)	46	12	28	157
<b>A3. Contrast PSP&lt;bvFTD</b>				
<i>Regions</i>	<i>MNI Coordinates</i>			<i>Number of voxels</i>
	<i>X</i>	<i>Y</i>	<i>Z</i>	
Paracingulate gyrus (L), frontal medial cortex (L)	-4	46	-8	575
Thalamus (L)	-12	-6	4	99
Putamen (R), amygdala (R)	32	-8	-12	81
Thalamus (R)	14	-4	10	78
Temporal pole (L), parahippocampal gyrus (L), amygdala (L)	-30	2	-16	74

**B. RESULTS FOR CONTRASTS BETWEEN GROUPS APPLYING THE "THEORY OF MIND MASK"**

**B1. Contrast Controls < bvFTD**

<i>Regions</i>	<i>MNI Coordinates</i>			<i>Number of voxels</i>
	<i>X</i>	<i>Y</i>	<i>Z</i>	
Paracingulate gyrus (L), cingulate gyrus (L)	-10	46	2	1098
Angular gyrus (L), supramarginal cortex (L)	-56	-58	20	865
Temporal pole (R)	46	10	-32	743
Temporal pole (L)	-38	8	-36	687
Frontal medial cortex (R), subcallosal cortex (R)	0	34	-20	208
Frontal pole (R), frontal medial cortex (R)	4	54	-24	84

**B2. Contrast Controls< PSP**

<i>Regions</i>	<i>MNI Coordinates</i>			<i>Number of voxels</i>
	<i>X</i>	<i>Y</i>	<i>Z</i>	
Angular gyrus (L), supramarginal cortex (L)	-54	-58	26	407
Frontal pole (R)	12	68	16	100

## Legend

bvFTD: Behavioral variant of frontotemporal dementia; L: Left; MNI: Montreal Neuroimaging Institute; PSP: Progressive Supranuclear Palsy; R: Right



**Table 4: Coordinates of significant cluster maxima for cognitive correlations within groups**

<b>1. Positive Correlations with Facial Emotion Recognition Test - Total Score (bvFTD group)</b>				
<i>Regions</i>	<i>MNI Coordinates</i>			<i>Number of voxels</i>
	<i>X</i>	<i>Y</i>	<i>Z</i>	
Inferior temporal gyrus (R)	48	-46	-20	1288
Anterior Cingulate (R), paracingulate gyrus (R)	12	22	34	1040
Temporal pole (R)	36	0	-24	687
Middle temporal gyrus (R), inferior frontal gyrus (R)	52	24	32	374
Planum polare (perinsular region) (R)	50	2	-8	221
Frontal orbital cortex (L), inferior frontal gyrus (L)	-48	28	-4	166
Middle temporal gyrus (L)	-58	-48	0	127
Parahippocampal gyrus (L), hippocampus (L)	-28	-14	-22	112
Fusiform cortex (L)	-38	-64	-24	55
<b>2. Positive Correlations with Facial Emotion Recognition Test - Total Score (PSP group)</b>				
<i>Regions</i>	<i>MNI Coordinates</i>			<i>Number of voxels</i>

	X	Y	Z	
Parahippocampal gyrus (L), fusiform cortex (L)	-30	-36	-18	4446
Frontal pole (R), frontal medial cortex (R)	2	58	-16	4206
Parahippocampal gyrus (R), hippocampus (R)	26	-16	-24	3866
Middle temporal gyrus (R), angular gyrus (R), supramarginal gyrus (R)	62	-44	8	1420
Middle temporal gyrus (L), angular gyrus (L), supramarginal gyrus (L)	-60	-48	-2	1230
<b>3. Positive Correlations with Faux-Pas "Recognition of social norms violation" (bvFTD group)</b>				
<i>Regions</i>	<i>MNI Coordinates</i>			<i>Number of voxels</i>
	X	Y	Z	
Temporal pole (L)	-50	14	-30	771
Middle temporal gyrus (R), angular gyrus (R)	48	-56	14	719
Middle temporal gyrus (L)	60	-6	-30	388
<b>4. Positive Correlations with Faux-Pas "Recognition of social norms violation" (PSP group)</b>				
<i>Regions</i>	<i>MNI Coordinates</i>			<i>Number of voxels</i>

	X	Y	Z	
Frontal pole (R), paracingulate cortex (R)	10	60	10	1364
Middle temporal gyrus (R), superior temporal gyrus (R), temporal pole (R)	56	-10	-14	1156
Middle temporal gyrus (L), superior temporal gyrus (L), temporal pole (L)	-58	2	-28	998
Middle temporal gyrus (R), angular gyrus (R)	66	-54	6	783
Lateral occipital cortex (L)	-52	-68	30	591
Frontal medial cortex (L)	-4	36	-22	38
<b>5. Positive Correlations with Faux-Pas ""Mentalizing" " (bvFTD group)</b>				

<i>Regions</i>	<i>MNI Coordinates</i>			<i>Number of voxels</i>
	<i>X</i>	<i>Y</i>	<i>Z</i>	
Lateral occipital cortex (R), angular gyrus (R)	58	-64	26	757
Middle temporal gyrus (L)	60	-6	-30	721
Frontal orbital cortex (L), temporal pole (L), inferior frontal gyrus (L)	-48	26	-16	703
Frontal pole (L)	-12	62	28	35
<b>6. Positive Correlations with Faux-Pas "Mentalizing" (PSP group)</b>				
<i>Regions</i>	<i>MNI Coordinates</i>			<i>Number of voxels</i>
	<i>X</i>	<i>Y</i>	<i>Z</i>	
Frontal pole (R), paracingulate gyrus (R), superior frontal gyrus (R)	0	56	12	1489
Angular gyrus (R), supramarginal gyrus (R)	52	-46	30	1104
Temporal pole (L)	-38	10	-34	785
Lateral occipital cortex (L)	-50	-70	26	730
Middle temporal gyrus (R), superior temporal gyrus (R), supramarginal gyrus (R)	48	-36	0	718

Frontal pole (R)	6	58	-10	167
Frontal pole (L)	-50	42	-10	98

## Legend

bvFTD: Behavioral variant of frontotemporal dementia; L: Left; MNI: Montreal Neuroimaging Institute; PSP: Progressive Supranuclear Palsy; R: Right