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Research report

Amygdala atrophy affects emotion-related activity in face-responsive regions in frontotemporal degeneration

François-Laurent De Winter [a,b,1], Jan Van den Stock [a,b,1], Beatrice de Gelder [a,c], Ronald Peeters [d,e], Jan Jastorff [a], Stefan Sunaert [d,e], Wim Vanduffel [f,g,h], Rik Vandenberghe [i,j] and Mathieu Vandenbulcke [a,b,*]

[a] Laboratory for Translational Neuropsychiatry, Research Group Psychiatry, Department of Neurosciences, KU Leuven, Leuven, Belgium
[b] Department of Old Age Psychiatry, University Hospitals Leuven, Leuven, Belgium
[c] Department of Cognitive Neuroscience, Maastricht University, Maastricht, The Netherlands
[d] Department of Radiology, University Hospitals Leuven, Leuven, Belgium
[e] Department of Imaging and Pathology, KU Leuven, Leuven, Belgium
[f] Laboratory for Neuro- and Psychophysiology, Department of Neurosciences, KU Leuven, Leuven, Belgium
[g] Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, USA
[h] Department of Radiology, Harvard Medical School, Boston, MA, USA
[i] Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven, Leuven, Belgium
[j] Department of Neurology, University Hospitals Leuven, Leuven, Belgium

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ABSTRACT

In the healthy brain, modulatory influences from the amygdala commonly explain enhanced activation in face-responsive areas by emotional facial expressions relative to neutral expressions. In the behavioral variant frontotemporal dementia (bvFTD) facial emotion recognition is impaired and has been associated with atrophy of the amygdala. By combining structural and functional MRI in 19 patients with bvFTD and 20 controls we investigated the neural effects of emotion in face-responsive cortex and its relationship with amygdalar gray matter (GM) volume in neurodegeneration. Voxel-based morphometry revealed decreased GM volume in anterior medio-temporal regions including amygdala in patients compared to controls. During fMRI, we presented dynamic facial expressions (fear and chewing) and their spatiotemporally scrambled versions. We found enhanced activation for fearful compared to neutral faces in ventral temporal cortex and superior temporal sulcus in controls, but not in patients. In the bvFTD group left amygdalar GM volume correlated positively with emotion-related activity in left fusiform face area (FFA). This correlation was amygdala-specific and driven by GM in superficial and

* *Corresponding author*. Department of Old Age Psychiatry, University Hospitals Leuven, UZ Leuven, Herestraat 49, 3000 Leuven, Belgium.
E-mail address: mathieu.vandenbulcke@uzleuven.be (M. Vandenbulcke).
[1] FLDW and JVdS contributed equally to the work.
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basolateral (BLA) subnuclei, consistent with reported amygdalar-cortical networks. The data suggests that anterior medio-temporal atrophy in bvFTD affects emotion processing in distant posterior areas.

1. Introduction

Human emotions are complex constructs that consist of several processes subserving multiple behavioral functions like vigilance, subjective experience and action preparation (Damasio & Carvalho, 2013; Darwin, 1872; Frijda, 1986). Emotions have been neuro-anatomically linked to a distributed set of cortico-subcortical brain regions (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Vytal & Hamann, 2010) and studied most extensively by means of perception of facial expressions. Accurate recognition of facial expressions is crucial for adequate social communication. One of the most influential models of face perception proposes a distributed network consisting of a core system and an extended system (Haxby & Gobbini, 2011). The core system consists of occipito-temporal regions in extra-striate visual cortex and is associated with processing of the visual appearance of faces. The fusiform face area (FFA) (Kanwisher, McDermott, & Chun, 1997) and occipital face area (OFA) (Puce, Allison, Asgari, Gore, & McCarthy, 1996) mediate the representation of invariant features of faces for identification, whereas the posterior superior temporal sulcus (pSTS) mediates the representation of changeable aspects such as expression. The extended face processing system is comprised of other regions that interact with the regions in the core system depending on the cognitive operation at hand, e.g., the anterior temporal cortex for processing of familiarity and biographical knowledge (De Winter et al., 2016; Kriegeskorte, Formisano, Sorger, & Goebel, 2007). Regarding processing of emotions, a key role is proposed for the amygdala, exerting a modulatory influence on neural face processing (Bickart, Dickerson, & Barrett, 2014; de Gelder, Frissen, Barton, & Hadjikhani, 2003; Haxby & Gobbini, 2011). In particular, it is hypothesized that amygdalar responses to facial emotion perception influence activation in face-responsive regions like the pSTS and FFA. In addition, there is evidence that the modulatory influence on occipito-temporal areas originates primarily in the basolateral (BLA) section of the amygdala (Bickart, Hollenbeck, Barrett, & Dickerson, 2012; Van den Stock, Hortensius, Sinke, Goebel, & de Gelder, 2015).

Evidence from patients with amygdalar damage is in line with a modulatory influence from the amygdala on other areas of the face processing network (Benuzzi et al., 2004; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). For instance, Vuilleumier et al. (2004) reported decreased modulation of brain activation when perceiving fearful versus neutral faces in posterior face areas in epilepsy patients with amygdalar sclerosis. Furthermore, the decreased modulation was inversely proportional to the structural integrity of the amygdala. On the other hand, emotion effects in visual cortex associated with non-facial stimuli are unaffected by amygdala resection (Edmiston et al., 2013), suggesting that the amygdala modulation is face- or category-specific.

In behavioral variant frontotemporal dementia (bvFTD), facial emotion recognition deficits have been documented extensively (e.g., Kumfor & Piguet, 2012; Lavenu, Pasquier, Lebert, Petit, & Van der Linden, 1999; Omar, Rohrer, Hailstone, & Warren, 2011; Van den Stock, De Winter, et al., 2015; Van den Stock, Hortensius, et al., 2015) and have been clearly related to atrophy of the amygdala (Kumfor, Irish, Hodges, & Piguet, 2013; Rosen et al., 2002). Anterior medio-temporal (including the amygdala) gray matter (GM) volume changes, together with atrophy of medio-frontal and striatal regions, are present early in the disease (Diehl-Schmid, Onur, Kuhn, Gruppe, & Drzezga, 2014; Seeley et al., 2008; Whitwell et al., 2009). Furthermore, impaired facial emotion processing is considered to be a critical factor contributing to the characteristic social cognitive deficits in bvFTD (Rankin, Kramer, & Miller, 2005). However, it is unknown whether impaired facial emotion processing in bvFTD is caused exclusively by atrophy in anterior temporal or frontal areas, or whether distant activity changes in the so-called core face processing network contribute to the deficits. Insights in functional changes at different levels of emotion perception, including detection and recognition, are crucial to understand how patients perceive their social environment and to develop behavioral treatment strategies.

Specifically, in the present study, we combine structural and functional brain imaging to test the hypothesis that neurodegeneration of the amygdala influences the processing of emotional stimuli in posterior temporal face-responsive regions. In particular, we investigate the effect of amygdalar atrophy on brain activation in FFA and pSTS during processing of emotional versus neutral dynamic facial expressions in a sample of bvFTD and matched controls.

2. Material and methods

2.1. *Participants*

Nineteen patients diagnosed with bvFTD and twenty healthy controls participated in our study. Patients were recruited from the memory clinic and the Old Age Psychiatry Department of University Hospitals Leuven (Leuven, Belgium) as well as from the Neurology Department at the regional Onze-Lieve-Vrouw Ziekenhuis Aalst-Asse-Ninove (Aalst, Belgium). Diagnoses were made by experienced neurologists or old age psychiatrists after clinical assessment, hetero-anamnesis, cognitive neuropsychological testing and atrophy patterns on structural MRI. In 17 patients, diagnosis was also based on a typical pattern of hypo-metabolism on $^{[18F]}$Fluorodeoxyglucose PET scan. Genetic analysis for causative mutations

was performed in 8 patients: progranulin (GRN; $n = 3$), microtubule-associated protein tau (MAPT) + GRN ($n = 1$), chromosome 9 open reading frame 72 (C9orf72; $n = 1$) and GRN + C9orf72 ($n = 3$). One patient with a family history of ALS-FTD-fulfilled the revised diagnostic criteria of 'behavioral variant FTD with definite FTLD Pathology', based on a C9orf72 pathogenic mutation, while the other 18 patients fulfilled the criteria for 'Probable bvFTD' (Rascovsky et al., 2011). Patients initially presented with changes in behavior and personality displaying disinhibition, apathy and/or perseverative/compulsive behavior. At inclusion, mean symptom duration assessed by hetero-anamnesis equaled 2.42 years (SD = 1.49). Patients were included after clinical judgment deemed them able to successfully undergo an experimental scanning session. It has to be noted that six additional patients agreed to participate in the study, but could not be included since no experimental scanning data could be acquired due to a lack of cooperation and/or agitation. In total 14 out of 19 patients were prescribed psychoactive drugs at the time of the experiment. These included: a selective serotonin reuptake inhibitor (SSRI) ($n = 3$); an SSRI or a selective serotonin-noradrenalin reuptake inhibitor (SNRI) combined with trazodone ($n = 5$); a second-generation antipsychotic (SGA) combined with trazodone ($n = 2$); an SSRI or SNRI combined with an SGA ($n = 3$); an SGA and a benzodiazepine ($n = 1$).

Healthy control subjects were recruited through a database of elderly volunteers as well as through advertisements in a local newspaper. Exclusion criteria were present or past neurological or psychiatric disorders including substance abuse as well as significant systemic comorbidities or use of medication susceptible to affect the central nervous system.

This study was conducted according to the Declaration of Helsinki and approved by the ethical committee of University Hospitals Leuven, Belgium. All subjects gave written informed consent. All subjects had normal or corrected-to-normal visual acuity. All patients were right-handed as assessed through the Edinburgh Handedness Inventory (mean 97.6% in both patients and controls). Demographic data are presented in Table 1.

2.2. Behavioral assessment

2.2.1. Cognition

We included measurements assessing global cognitive ability (Mini Mental State Examination) (Folstein, Folstein, & McHugh, 1975), verbal memory (Rey's Auditory Verbal Learning Test) (Rey, 1958), categorical verbal fluency (animal verbal fluency) (Lezak, Howieson, & Loring, 2004), abstract reasoning ability (Raven's coloured progressive matrices A and B) (Raven, 1995), visual divided attention and task shifting (Trail Making Test A and B) (Reitan, 1958), low-level aspects of visual perception [Birmingham Object Recognition Battery (BORB) (Riddoch & Humphreys, 1993): length, size and orientation matching], confrontation naming (Boston Naming Test) (Kaplan, Goodglass, & Weintraub, 1983) and language comprehension (comprehension subsection of Aachen Aphasia Test) (Weniger, Willmes, Huber, & Poeck, 1981).

2.2.2. Psychophysics

As part of the assessment participants performed several behavioral tasks designed to examine different aspects of face and facial emotion processing. A brief description of the experiments is given in this section. A more detailed description of the stimuli and of task design can be found in the Supplementary materials.

Face processing was assessed by a face detection task and a face identity matching task. During face detection participants were asked which of two images showed the highest face-semblance. In the face identity matching task the instruction was to indicate which of two face pictures displayed the same identity as a third face picture viewed from a different angle.

Table 1 – Demographics and neuropsychological data.

	$N_{controls}/N_{bvFTD}$	bvFTD (SD)	Control (SD)	p-Value
Age in years	20/19	67.4 (8.6)	66.6 (6.1)	.743
Male/Female	20/19	11/8	11/9	.855[a]
Disease duration in years		2.42 (1.49)	n/a	n/a
Education in years	20/19	11.8 (2.4)	12.9 (3.0)	.190
MMSE	20/19	26.3 (2.1)	29.3 (.6)	<.001
AVF	20/19	15.0 (5.8)	22.2 (5.8)	<.001
BNT	20/19	38.8 (12.7)	54.4 (2.9)	<.001
AAT comprehension	20/17	94.1 (12.8)	109.5 (5.4)	<.001
Raven's CPM (A and B)	20/17	16.4 (4.1)	20.8 (2.8)	.001
Auditory verbal learning	20/18			
Total A1–A5		27.3 (9.9)	50.9 (7.3)	<.001
Delayed recall		4.4 (3.4)	10.7 (3.2)	<.001
Recognition		6.9 (6.8)	14.0 (1.3)	<.001
TMT A (s)	20/18	87.2 (104.2)	32.5 (9.4)	<.001
TMT B (s)	20/15	193.1 (141.2)	89.8 (42.3)	.001
BORB				
Length matching (%)	20/16	88.5 (7.2)	90.2 (4.5)	.400
Size matching (%)	20/16	86.5 (6.8)	88.9 (6.3)	.270
Orientation matching (%)	20/16	80.9 (10.1)	86.1 (6.0)	.066

AAT = Aachen Aphasia Test; AVF = Animal Verbal Fluency; BNT = Boston Naming Test; BORB = Birmingham Object Recognition Battery; CPM = Coloured Progressive Matrices; MMSE = Mini-mental state examination; n/a: not applicable; TMT = Trail Making Test.

[a] Chi-square test.

Facial emotion processing tasks examined detection of facial emotion, matching of static and dynamic facial expressions as well as discrimination, selection and categorization of facial emotional expressions. The detection task consisted of the simultaneous presentation of a neutral and an emotional face (with varying intensities of emotion) with the same identity while subjects were asked to indicate the emotional face. For the matching tasks participants were asked which of two emotional faces displayed the same emotional expression as a third face. The three faces on display had a different identity. Facial emotion discrimination, selection and categorization tasks were taken from the Florida Affect Battery (FAB) (Bowers, Blonder, & Heilman, 1999) (subtests 2, 4 and 3, respectively). The tests respectively consisted in judging whether two faces depict the same or a different emotion, deciding which of five faces depicts the emotion stated by the examiner and in categorizing the emotion of a single face using five alternative forced choices.

Stimuli of all these tasks except for those from the FAB were presented using Presentation® software.

2.3. *fMRI experiment*

2.3.1. *Stimuli (Fig. 1A)*

Stimulus materials consisted of six full-color movie clips of six male professional actors displaying a fearful facial expression and six full-color movie clips of the same actors displaying a chewing expression. All movie clips were frontal views with face contours removed and mean luminance equalized. Eye-gaze was averted but heads were fixed in frontal orientation. A mirror-reversed version of each clip was constructed to control for gaze direction, and movement asymmetries. Spatiotemporally scrambled versions of stimuli were created removing facial shape and dynamic expression but retaining low-level motion information from the original clips. Construction of stimuli has been described in more detail previously (Zhu et al., 2013).

2.3.2. *Experimental design and procedure (Fig. 1B)*

We used a two emotion (fearful, chewing) × two modality (intact, scrambled) factorial event-related fMRI-design. Stimuli had a duration of 2 sec and were presented with a grid overlaid, followed by an inter-stimulus interval of 2.5 sec–3.5 sec displaying only the grid. Twelve null-trials only presenting the grid were interspersed. Stimuli were presented at 5 × 5 visual degrees while a central fixation point (6′) was continuously present. Subjects were instructed to fixate on the fixation point. We made use of an orthogonal task by means of oddball detection. The oddball consisted of a white square appearing in one of the corners of the stimulus. Subjects were instructed to press a button whenever they detected the oddball. Every run included 12 oddball trials, equally divided over the four conditions and four locations. A run consisted of 12 events/condition and lasted for 360 sec. Four runs were obtained for every subject except for four patients and two controls in which only two runs were acquired and one patient in which three runs were acquired. Before scanning, the subjects were shown an image of the grid and fixation point as well as a static example of a scrambled stimulus with and without an additional white square.

Sixteen patients and all control subjects participated in three behavioral post-scanning experiments to assess the emotional significance of the facial stimuli (fear and chewing) of the fMRI experiment. In each experiment, a trial consisted of a fixation cross (1–3 sec) followed by a stimulus (2 sec) and a question mark (Zhu et al., 2013). In the first post-scanning experiment, subjects were instructed to categorize the expression given six alternatives (anger, disgust, fear, happiness, sadness or neutral). In the second and third post-scanning experiment, subjects were instructed to rate the arousal and valence contained in the stimuli using the Self-assessment Manikin (Bradley & Lang, 1994).

2.4. *Image acquisition*

All subjects were scanned on a 3 Tesla Philips Achieva scanner using a 32-channel head coil. A high resolution anatomical scan (TR 9.6 msec, TE 4.6 msec, flip angle 8°, 182 slices, matrix size 256 × 256 and .98 × .98 × 1.20 mm^3 voxel size) was acquired during each session. A standard EPI sequence (TR 2 sec, TE 30 msec, flip angle 90°, 38 slices, matrix size 80 × 80 and 2.75 × 2.75 × 3.50 mm voxel size) was used. Functional scans were preceded by four dummy scans to allow for magnetization to reach equilibrium state.

2.5. *Image analysis*

2.5.1. *Voxel-based morphometry*

First T1-weighted structural images were manually reoriented and centered on the anterior commissure. The VBM8 toolbox

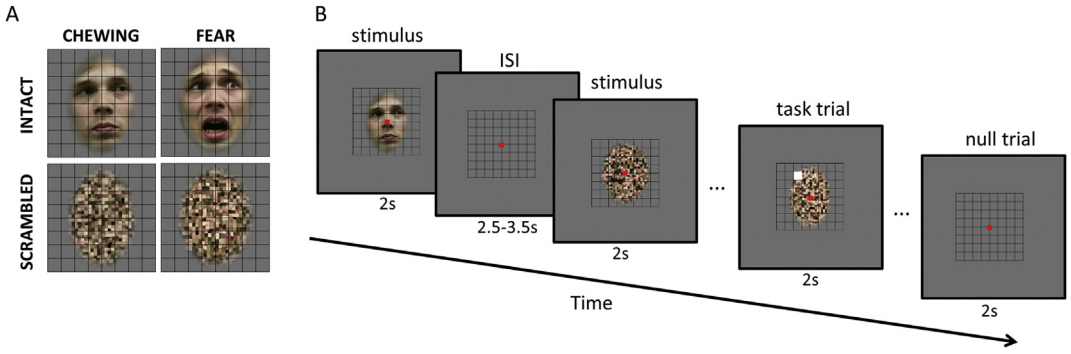

Fig. 1 – Stimuli and design of fMRI experiment. A. Stimuli: example of intact chewing and fearful facial expressions and their scrambled versions. B. Event-related experimental fMRI design. Trials consisted of 2 sec clips with an inter-stimulus interval between 2.5 and 3.5 sec. An example of the orthogonal oddball task is also given. ISI = inter-stimulus interval.

(http://dbm.neuro.uni-jena.de/vbm/) for SPM8 (Wellcome Trust Centre for Neuroimaging, UCL, London, United Kingdom) was used for structural image analysis. Preprocessing included bias correction, segmentation and normalization to MNI space within a unified model, including high-dimensional DARTEL-normalization. In order to compensate for the effect of normalization and preserve absolute tissue volumes the resulting normalized GM segmentations underwent Jacobian modulation. Modulated images were smoothed using a Gaussian kernel of 8 mm at FWHM. These processed GM images were then entered in a general linear model and a two sample *t*-test was performed for a whole-brain group comparison. Threshold was set at $p < .05$ (FWE-corrected) with cluster extent 50 voxels.

GM volumes in several regions-of-interest (ROI) were derived from the modulated normalized GM segmentations. Amygdala and hippocampus ROIs were defined using a commonly used atlas (http://fmri.wfubmc.edu/software/pickatlas). Probabilistic cytoarchitectonic maps for different amygdalar subregions were derived from the SPM Anatomy Toolbox (http://www.fzjuelich.de/inm/inm1/DE/Forschung/_docs/SPMAnatomyToolbox/SPMAnatomyToolbox_node.html). Additionally, we calculated GM volume within the conjunction of atlas-based amygdala and the region where a significant group difference was found.

2.5.2. *Processing of functional imaging data*

Data were analyzed using SPM8 within a Matlab environment (Mathworks, Inc.,Natick, Massachusetts, United States). Preprocessing of EPI images included realignment, slice-timing correction, coregistration to the subject's individual high-resolution anatomical image, unified segmentation and normalization to MNI space. Images were smoothed using a Gaussian kernel of 8 mm FWHM. All stimulus conditions with onsets and duration were entered into a general linear model; head movement parameters were entered as regressor-of-no-interest for each run. Single subject statistics were modeled by convolving each trial with the canonical hemodynamic response function. A random-effects group analysis was performed on parameter estimates of activity for each contrast across participants per group using a one-sample *t*-test. Similarly a group comparison was performed using a two sample *t*-test.

The mean percent signal change (PSC) for separate conditions relative to baseline was calculated in individual subjects by averaging the PSC within functionally defined face-responsive ROIs using a custom matlab script.

2.6. *Statistical analysis*

Normality testing was performed on all variables using a Shapiro–Wilk test (alpha set at .05). On normally distributed data two-sample *t*-tests were performed to investigate group effects. In case a normal distribution could not be assumed, Mann–Whitney U tests were performed instead. Paired *t*-tests were used to compare variables within each group for normally distributed data. For similar comparisons in non-normally distributed data a Wilcoxon-signed-rank-test was used. Pearson's correlations were calculated for correlations between normally distributed variables while Spearman's correlations were used for non-normally distributed variables.

3. Results

3.1. *Behavioral results*

3.1.1. *Cognition*

Compared to controls bvFTD-patients were moderately impaired on most cognitive tasks. No difference was found for perceptual tasks of the BORB. Results are presented in Table 1.

3.1.2. *Face processing*

We did not find significant group differences for the face detection ($U = 218.5$, $p = .428$) nor for the face identity matching ($U = 121.5$, $p = .141$) variables.

3.1.3. *Emotion processing*

One patient did not complete the emotion processing experiments. The results reveal significant group differences on all variables, i.e., emotion detection ($U = 94$, $p = .011$), static facial emotion matching ($U = 68.5$, $p < .001$), dynamic facial emotion matching ($U = 89.5$, $p = .012$), emotion selection ($U = 106$, $p = .030$), emotion categorization ($U = 107$, $p = .033$) and emotion discrimination [$t(36) = 2.387$, $p = .022$].

Results of face and emotion processing experiments are presented in Fig. 2.

3.1.4. *fMRI task (orthogonal odd ball detection task)*

Due to technical failure no responses could be recorded for one control subject during the experiment as well as for one patient during one run. In patients there was a mean of 10.7 (SD = 1.6) hits out of twelve targets per run versus 11.2 (SD = 1.1) for controls. We did not find a significant group difference [$t(36) = -.916$, $p = .366$].

3.1.5. *Post-scanning experiment (Fig. 3A and B)*

Both patients and controls perceived fearful expressions as more arousing [bvFTD [$t(15) = 5.338$, $p < .0001$]; controls [$t(19) = 9.493$, $p < .0001$]] and more negative [bvFTD [$t(15) = -11.148$, $p < .0001$]; controls ($Z = -3.923$, $p < .0001$)] than chewing expressions. When directly comparing groups we found that patients perceived fearful stimuli as less arousing [$t(34) = 2.454$, $p = .019$, 2-tailed] and less negative ($U = 87$, $p = .02$) than controls. We did not find such a difference for the perceived arousal [$t(34) = -.202$, $p = .841$, 2-tailed] or valence [$t(34) = .057$, $p = .955$, 2-tailed] of chewing stimuli.

Chewing and fearful faces were mostly accurately categorized (neutral: 72.9% in bvFTD and 77.5% in controls; fearful: 66.6% in bvFTD and 80% in controls). Fearful expressions were less often correctly categorized as such by patients than controls ($U = 98$, $p = .04$), no such difference was found for chewing faces ($U = 160$, $p > .9$).

3.2. *Imaging results*

3.2.1. *Structural MRI results (Fig. 4)*

Voxel-based morphometry results revealed significant atrophy in bilateral antero-medial fronto-temporal cortex including medial orbitofrontal cortex, ventral striatum, amygdala and hippocampus in the bvFTD group compared to

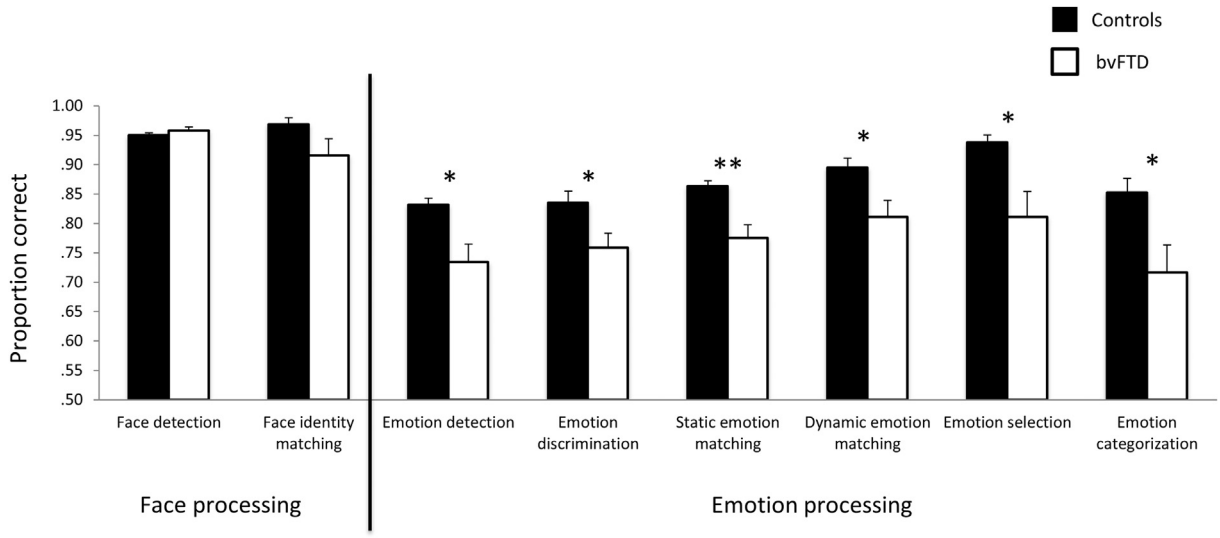

Fig. 2 – Results of the psychophysical experiments. Mean and standard error of the mean are plotted. *$p < .05$; **$p < .001$.

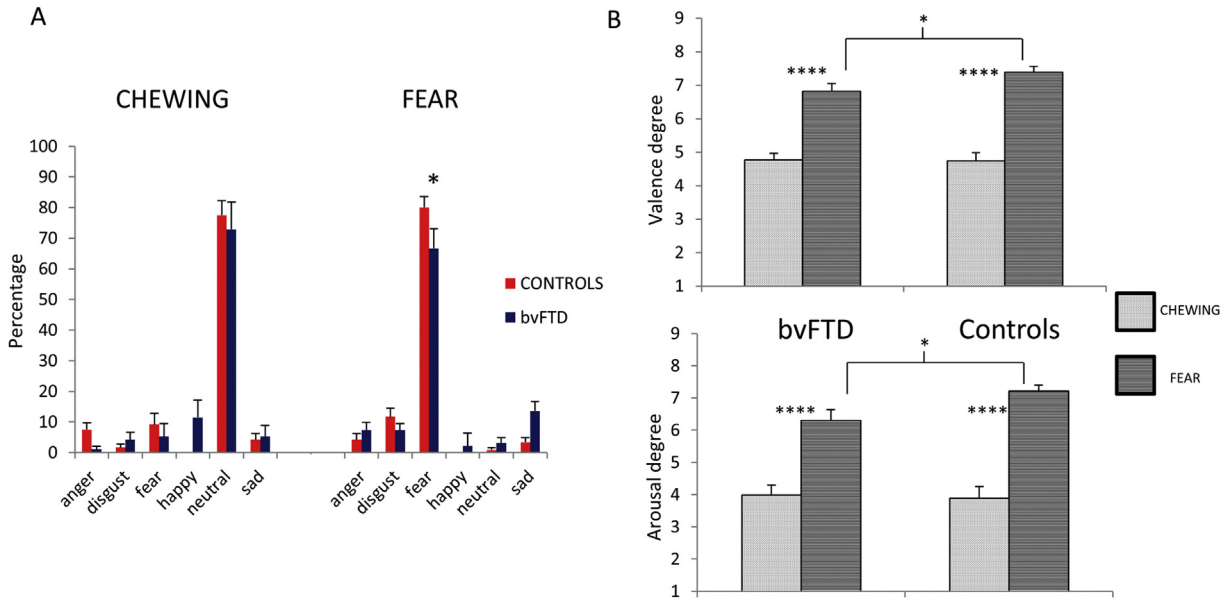

Fig. 3 – Behavioral results in post-scanning experiments. A. Forced categorization of chewing and fearful facial expressions. Percentage of choices for different categories are shown for each facial expression. B. Valence and arousal ratings of chewing and fearful facial expressions. Scores from 1 to 9 corresponding to highly positive to highly negative or lowest arousal to highest arousal. Mean and standard error of the mean are plotted. *$p < .05$, ****$p < .0001$.

controls. Threshold was set at $p < .05$ (FWE-corrected) with cluster extent 50 voxels.

3.2.2. *Functional MRI results*

3.2.2.1. Definition of face-responsive regions (ROI definition) (Fig. 5A). We combined fMRI data of both bvFTD-patients and healthy controls and entered them into a random-effects analysis. We then contrasted chewing and fearful expressions versus their scrambled versions. Threshold was set at $p < .05$ (FWE-corrected) with a cluster extent of 10 voxels. This yielded four clusters in left and right posterior temporal (i.e., pSTS) and fusiform cortices, the latter corresponding to the FFA.

3.2.2.2. Differential PSC for fear and chewing contrasted with their scrambled versions (Fig. 5B). In the control group we found a significantly higher PSC for fearful compared to chewing expressions when contrasted with their respective scrambled versions in three of the four defined face-responsive regions, i.e., in left FFA [$t(19) = -2.605$, $p = .009$, 1-tailed], left pSTS [$t(19) = -3.045$, $p = .003$, 1-tailed] and right pSTS [$t(19) = -2.910$, $p = .004$, 1-tailed] but not in right FFA [$t(19) = -1.470$, $p = .08$, 1-tailed].

In the bvFTD group we did not find a significant difference in any of these regions [left FFA [$t(18) = -1.240$, $p = .12$, 1-tailed], right FFA ($Z = -.765$, $p = .22$, 1-tailed), left pSTS

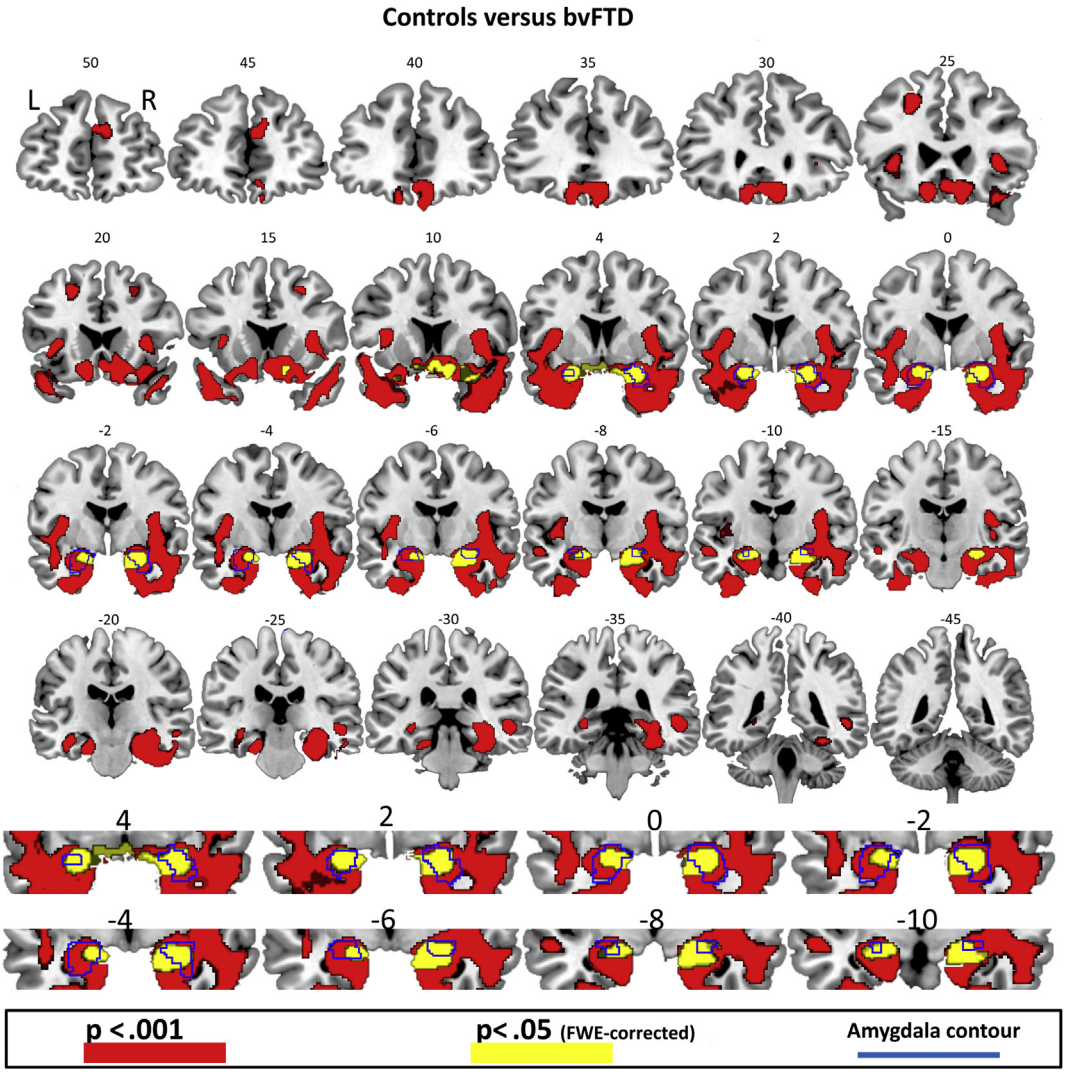

Fig. 4 – Structural imaging results (VBM results). Coronal slices illustrating GM atrophy in bvFTD patients compared to controls (whole brain). Areas in yellow: $p < .05$ after FWE-correction. Blue: delineation of atlas-derived amygdala. For illustrative purposes atrophic areas at a threshold of $p < .001$ uncorrected are shown in red. Y-coordinates in MNI space above coronal slices. Panels below show enlarged view of slices including the amygdala. L = Left; R = Right. Color key at the bottom.

($Z = -.604$, $p = .27$, 1-tailed), right pSTS [$t(18) = -1.521$, $p = .07$, 1-tailed]].

3.2.2.3. Correlation between GM volume and PSC (Fig. 6). The primary aim of our study was to explore whether amygdala volume in bvFTD patients correlated with emotional enhancement in face-responsive regions. To investigate this we correlated left and right amygdala GM volumes with the PSC for fearful contrasted with chewing faces (controlled for low level spatiotemporal features), i.e., with emotion-related PSC, in respectively left and right FFA and pSTS. Considering our a priori hypothesis regarding the direction of the association (Bickart, Dickerson, et al., 2014; Vuilleumier, et al., 2004), we calculated 1-tailed correlations. Furthermore, in order to correct for differences in brain size we performed partial correlations, controlling for total intracranial volume. Therefore, we first calculated unstandardized residuals of GM volumes and PSC following linear regression to Total Intracranial Volume. Subsequently, we performed Shapiro–Wilk tests on these residuals to test if they were normally distributed.

Within the bvFTD group we found a positive correlation between left amygdalar GM volume with emotion-related PSC in left FFA [$r = .513$, $N = 19$, $p = .012$ (1-tailed)]. We did not find a significant correlation with PSC in left pSTS [$r = -.031$, $N = 19$, $p = .450$ (1-tailed)] nor was there a significant correlation of right amygdala volume with PSC in right FFA [$r = -.179$, $N = 19$, $p = .231$ (1-tailed)] or right pSTS [$r = -.05$, $N = 19$, $p = .419$ (1-tailed)].

Subsequently, we performed several post-hoc tests to investigate the specificity of the correlation between atlas-defined amygdala volume and emotion-related PSC in FFA in bvFTD.

First, we calculated and correlated left hippocampal GM volume with the emotion-related PSC in the left FFA. This did not reveal a significant correlation [$r = .253$, $N = 19$, $p = .148$ (1-

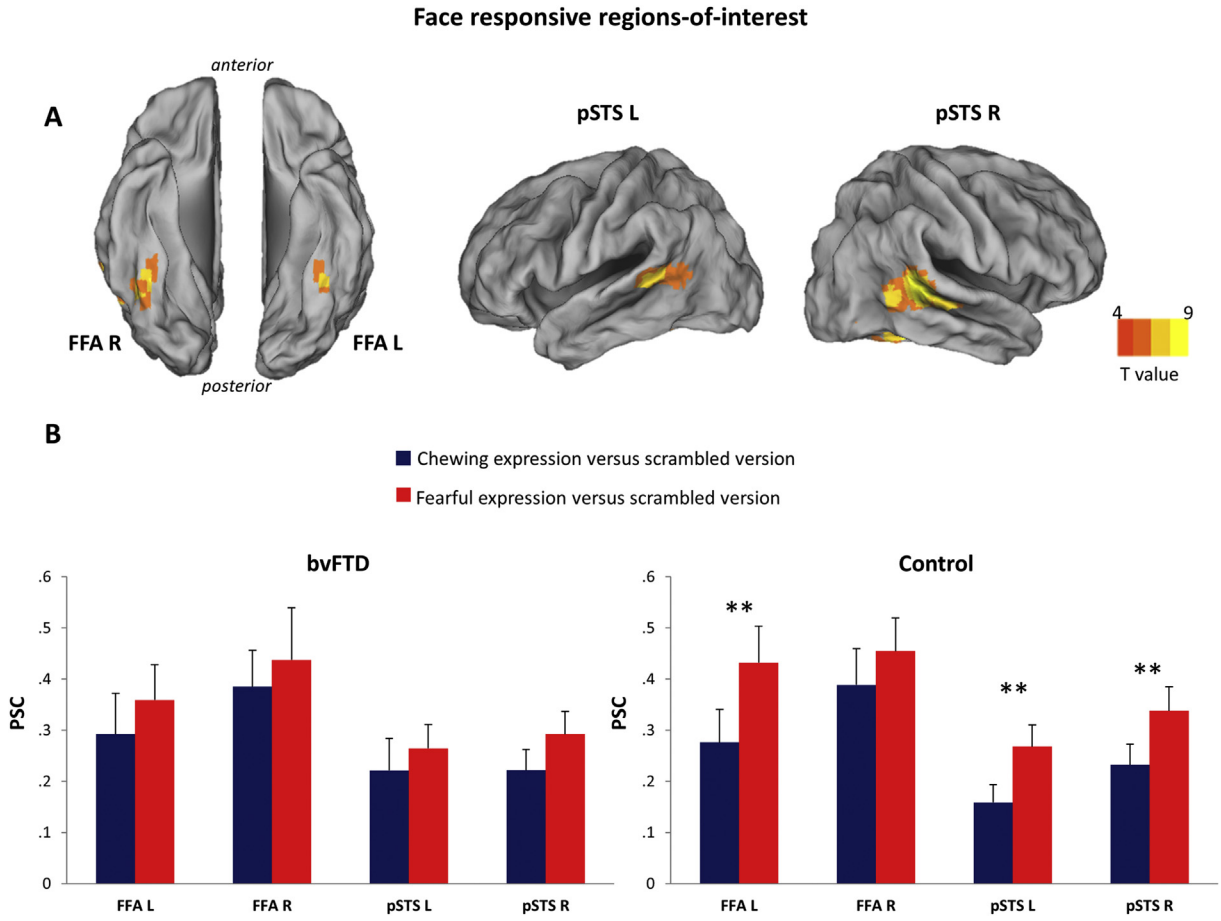

Fig. 5 – Face-responsive regions and differential activation of chewing and fearful expressions. A. Face-responsive regions defined by contrasting facial expressions (chewing and fearful faces) with their scrambled versions for bvFTD patients and control subjects combined displayed on fiducial brains from Caret. $p < .05$ after FWE-correction. L = Left, R = Right. B. PSC in face-responsive regions for chewing faces versus their scrambled versions compared to PSC for fearful faces versus their scrambled versions. bvFTD patients on the left, control subjects on the right. $^{**}p < .01$.

tailed)]. Furthermore, this volume did not correlate with emotion-related PSC in left pSTS [$r = .170$, $N = 19$, $p = .244$ (1-tailed)].

Secondly, we investigated whether the correlation was specifically associated with amygdalar atrophy. For this purpose, we calculated the GM volume in the overlap between atlas-based left amygdala and the significantly atrophic region derived from the structural group comparison. Correlating this volume with the emotion-related PSC in left FFA revealed a significant positive correlation [$r = .549$, $N = 19$, $p = .008$ (1-tailed)].

Finally, we calculated the volumes of the BLA, centromedial (CMA) and superficial amygdala (SA) to explore whether the correlation found for the left amygdala was specific to any of its subregions. We found a significant positive correlation of emotion-related PSC in left FFA with GM volume in BLA [$r = .450$, $N = 19$, $p = .027$ (1-tailed)] and SA [$r = .488$, $N = 19$, $p = .017$ (1-tailed)] but not with CMA [$r = .306$, $N = 19$, $p = .101$ (1-tailed)].

3.2.2.4. Comparing GM volumes in face responsive ROIs between groups. We found a significantly smaller volume in right pSTS [$U = 123$, $p = .031$ (1-tailed)] in bvFTD but no significant volume differences in the other ROIs [left FFA $t(37) = .339$, $p = 0369$ (1-tailed); right FFA $t(37) = -.584$, $p = .282$ (1-tailed); left pSTS $U = 189$, $p = .494$ (1-tailed)]. In addition, in the bvFTD group there was no significant correlation between GM volume in left amygdala and left FFA [$r = -.112$, $N = 19$, $p = .325$ (1-tailed)] or left pSTS [$\rho = -.067$, $N = 19$, $p = .393$ (1-tailed)], respectively.

3.2.2.5. Correlation of facial emotion psychophysics with emotion-related PSC and with amygdala volume. To investigate the association between facial emotion processing performance and emotion-related PSC in face responsive regions in bvFTD, we performed a Principal Component Analysis (PCA) on the total scores of the emotion processing experiments. The PCA was a priori restricted to a single component solution, maximizing the variability contained by the input variables. The single component result explained 66.5% of the total variance. There was no correlation between the corresponding component loadings and emotion-related PSC in any of the ROIs [left FFA [$r = .337$, $N = 18$, $p = .085$ (1-tailed)], right FFA [$\rho = .053$, $N = 18$, $p = .418$ (1-tailed)], left pSTS [$r = .377$, $N = 18$, $p = .061$ (1-tailed)], right pSTS [$r = .239$, $N = 18$,

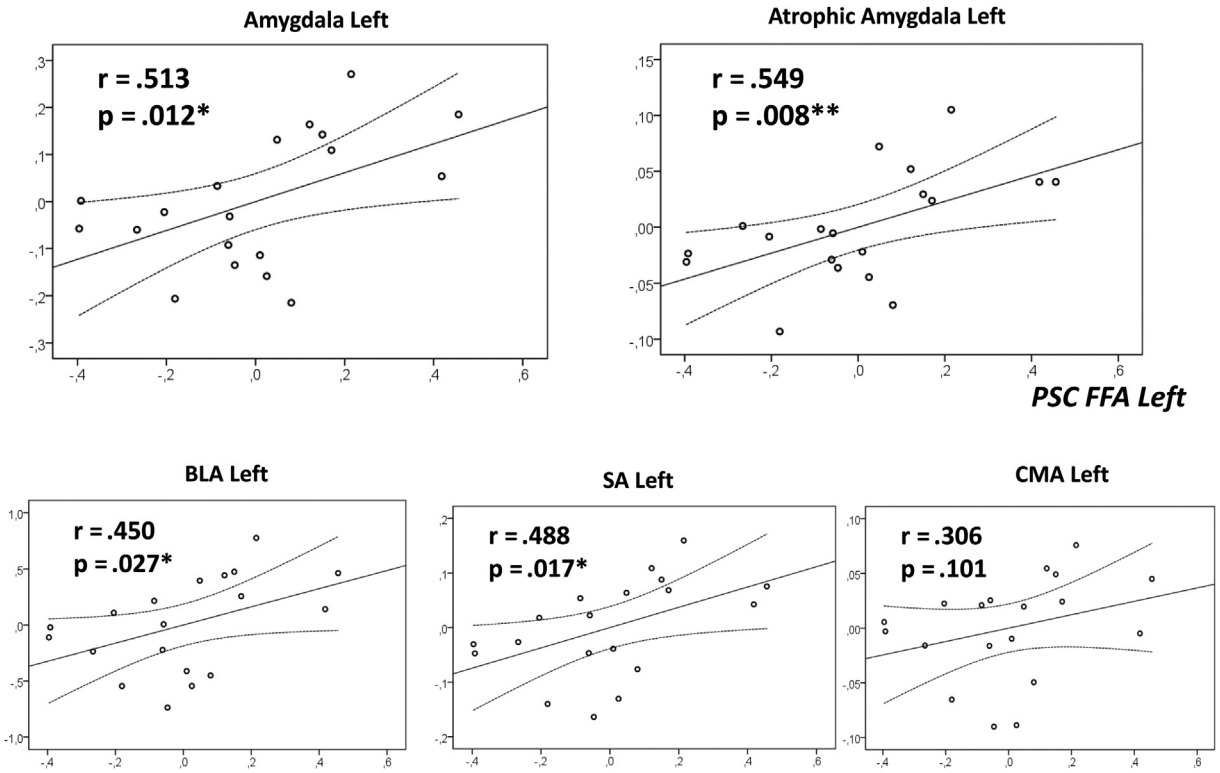

Fig. 6 – Partial regression plots. Correlation of GM volumes (*y*-axis) and emotion-related PSC in left FFA (*x*-axis) in bvFTD (corrected for total intracranial volume). **p* < .05; ***p* < .01.

$p = .169$ (1-tailed)]]. There was a significant correlation with left [$r = .420$, $N = 18$, $p = .041$ (1-tailed, uncorrected for multiple comparisons)] but not with right amygdala volume [$r = .215$, $N = 18$, $p = .196$ (1-tailed)].

3.2.2.6. Correlation of categorization of emotional stimuli and arousal ratings with emotion-related PSC and with amygdala volume. We did not find a correlation of performance on categorization of the fearful stimuli shown in the fMRI experiment (first postscanning experiment) with emotion-related PSC in any face responsive region in bvFTD [left FFA [$r = .082$, $N = 16$, $p = .381$ (1-tailed)], right FFA [$r = .061$, $N = 16$, $p = .412$ (1-tailed)], left pSTS [$r = 0030$, $N = 16$, $p = .455$ (1-tailed)], right pSTS [$r = .097$, $N = 16$, $p = .360$ (1-tailed)]]. Neither was there a significant correlation with left [$r = .153$, $N = 16$, $p = .286$ (1-tailed)] or right amygdala volume [$r = .113$, $N = 16$, $p = .339$ (1-tailed)].

We found a correlation between the arousal ratings for fearful minus chewing expressions (in the second post-scanning experiment) and emotion-related PSC in right FFA [$r = .432$, $N = 16$, $p = .048$ (1-tailed, uncorrected for multiple comparisons)] in bvFTD. This effect was close to significance in the left FFA [$r = .389$, $N = 16$, $p = .068$ (1-tailed)]. There was no significant correlation with the other face-responsive regions: left pSTS [$r = -.088$, $N = 16$, $p = .373$ (1-tailed)], right pSTS [$r = .150$, $N = 16$, $p = .289$ (1-tailed)]. Neither was there a significant correlation with left [$\rho = .162$, $N = 16$, $p = .275$ (1-tailed)] or right amygdala volume [$\rho = -.106$, $N = 16$, $p = .348$ (1-tailed)].

We also investigated whole brain functional activation in both the bvFTD and control group as well as group differences. This is reported in the Supplementary materials (also Fig. S1 and Table S1).

4. Discussion

The aim of the present study was to investigate how atrophy of the amygdala caused by neurodegeneration affects emotional modulation of activation in posterior face-responsive regions. We investigated a sample of bvFTD patients with mild general cognitive decline (as evidenced by an average MMSE-score of >26). Behaviorally, the study sample was impaired on all administered facial emotion recognition tasks which is consistent with the clinical phenotype of bvFTD. In contrast, there was no impairment for face shape recognition or unfamiliar face identity recognition. The functional imaging experiment contained face and non-face stimuli. These were contrasted to define face-responsive ROI, i.e., FFA and pSTS.

First we estimated differential activation in these areas for chewing and fearful faces versus their respective scrambled versions. In the elderly control group we found a significantly increased activation in pSTS and left FFA for fearful faces whereas the bvFTD group did not show such an increase in any of the face responsive areas. Although both groups rated the fearful expressions as more arousing and negative than the neutral ones, the bvFTD group perceived fearful

expressions as less arousing and less negative than the control group. Neutral expressions were however similarly perceived in both groups. These findings suggest an impairment specifically relating to the perception of socially relevant stimuli.

Subsequently, in the bvFTD group we estimated the emotional modulation in these areas by contrasting fearful with neutral faces and correlating these estimates with the GM volume of the amygdala. The results revealed a significant positive correlation between GM volume in the left amygdala and emotional modulation in left FFA. The correlation was specific for the amygdala as we did not observe it for the GM volume in the hippocampus. Furthermore, the significant correlation persisted when only the atrophic region of the amygdala was considered. These findings support the notion that increased activation in FFA for perceiving emotional compared to neutral faces, results from a modulatory influence originating in the amygdala (Vuilleumier, 2005; Vuilleumier & Pourtois, 2007). Presumably, the influence of the amygdala on distant face-responsive regions occurs through direct connections. Indeed, in the healthy brain, a white matter pathway between amygdala and fusiform cortex has been documented by means of diffusion weighted imaging and diffusion tensor tracking (Smith et al., 2009). Interestingly, this study also revealed a parallel pathway from the hippocampus to the fusiform cortex. The amygdalar selectivity of our findings, i.e., a correlation between amygdalar and not hippocampal volume on the one hand and emotional enhancement in FFA on the other hand, indicate that the emotional modulation of FFA originates in the amygdala rather than in the hippocampus, despite their mutual connection to the fusiform cortex.

Furthermore, we investigated differential contributions of amygdalar subregions on emotional enhancement in posterior face-responsive regions. This revealed that the correlation between amygdalar volume and this emotional enhancement was driven by the BLA and superficial subsections. Connectivity based parcellation studies of the amygdala have consistently revealed three subregions, grossly corresponding to the citoarchitectonically defined regions. The results revealed that the BLA (part of the ventrolateral section of the amygdala associated with a network subserving social perception) is primarily associated with projections to and from cortical areas particularly the fusiform gyrus (Bickart, Dickerson, et al., 2014; Bickart et al., 2012). It has been reported that FTD patients with the largest atrophy in this network, exhibit the most prominent lack of attention for social cues (Bickart, Brickhouse, et al., 2014; Bickart, Dickerson, et al., 2014). Furthermore, activation of the BLA during perception of social emotional expressions is modulated by trait empathy (Van den Stock, Hortensius, et al., 2015), a key deficit in bvFTD.

The correlation between amygdala volume and emotional modulation in the FFA was only found in the left hemisphere. This is in line with the absence of differential activation for chewing and fearful expressions in right FFA in both the bvFTD and control group. Recent findings of a left-lateralized amygdalo-fusiform fiber pathway in healthy subjects (Smith et al., 2009) could provide a possible explanation. Additionally, even though face and emotion processing have been considered to be right-lateralized, recent evidence suggests that perception of dynamic faces shows no clear lateralization in FFA (De Winter et al., 2015). In addition a recent study investigating emotional face processing in bvFTD (Virani, Jesso, Kertesz, Mitchell, & Finger, 2013) reported reduced functional activity compared to healthy controls in left but not right fusiform cortex.

In our study there was no significant correlation between amygdalar volume and emotion effects in other face-responsive regions, i.e., STS. This observation is in line with previously reported white matter connections between the FFA and anterior temporal regions, while the face responsive STS shows primarily structural connectivity with fronto-parietal areas (Gschwind, Pourtois, Schwartz, Van De Ville, & Vuilleumier, 2012).

By correlating behavioral data with imaging data, we found an association between facial emotion processing ability (PCA-score) and left amygdala integrity and between differential arousal judgments for emotional stimuli and emotional enhancement in right FFA as well as a trend in left FFA. The behavioral benefit of modulation of face-responsive regions by the amygdala is thought to entail prioritization of the processing of stimuli with emotional value (Vuilleumier & Pourtois, 2007). Our results support this view.

Functional neural effects associated with distant neurodegeneration have been evidenced previously e.g., contralateral activity changes using a semantic paradigm in primary progressive aphasia patients (Vandenbulcke, Peeters, Van Hecke, & Vandenberghe, 2005). Here, we demonstrate changes in emotion-related activity associated with atrophy in the amygdala. More specifically this study demonstrates an association between atrophy in the amygdala and diminished preferential activation for facial emotional expressions in face-responsive fusiform cortex. The fusiform gyrus as well as association areas in temporal and orbitofrontal cortex are part of a network linked with the ventrolateral amygdala supporting the detection of socially relevant stimuli (Bickart, Dickerson, et al., 2014; Bickart et al., 2012). Atrophy in this network in bvFTD is associated with lack of awareness and understanding of others' emotional behavior (Bickart, Brickhouse, et al., 2014). Regions in this network, including the fusiform gyrus are involved in processing featural and expressive aspects of faces (Haxby, Hoffman, & Gobbini, 2002). Here we provide evidence for disruption of this network in bvFTD due to anterior neurodegeneration affecting emotion-related activity changes in structurally unaffected posterior temporal face-responsive regions. These findings provide a plausible neural correlate contributing to altered perception of emotional signals through facial expression. This may in turn contribute to the social cognitive deficits in bvFTD patients.

5. Limitations

As we did not include a clinical control group, there is no evidence that the present results are specific for bvFTD. There is conflicting evidence regarding the degree of emotion recognition impairment in frontotemporal lobar degeneration compared to other neurodegenerative disorders like

Alzheimer's disease (AD). While some studies have reported a larger impairment in frontotemporal lobar degeneration (Lavenu et al., 1999), others have reported equally large deficits (Miller et al., 2012). Furthermore evidence for reduced neural activity during perception of emotional facial expressions has been demonstrated previously in AD within parts of the mirror neuron system (Lee, Sun, Leung, Chu, & Keysers, 2013).

The atrophy pattern in our sample indicates strong temporal atrophy rather than frontal. This may reflect the possibility that temporal dominant bvFTD patients (Whitwell et al., 2009) are more likely to comply with requirements related to imaging protocols. This limitation may have led to an inclusion bias with a higher proportion of temporal dominant bvFTD patients.

The use of psychoactive drugs in a part of the bvFTD patients, while absent in the control group, may have influenced the fMRI results.

6. Conclusions

Structural neurodegeneration of the BLA and SA, but not of the hippocampus and CMA amygdala is associated with reduced emotional modulation of a posterior temporal face-responsive area in a sample of bvFTD patients. This provides a plausible neural substrate for a lack of awareness for emotionally relevant stimuli which in turn may contribute to the socio-cognitive deficits typical of this population. These findings evidence functional emotion-related activity changes in structurally unaffected posterior temporal regions associated with anterior neurodegeneration.

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Supplementary material

Supplementary material related to this article can be found at http://dx.doi.org/10.1016/j.cortex.2016.06.001.

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