

A paleo-neurologic investigation of the social brain hypothesis in frontotemporal dementia

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The social brain hypothesis posits that a disproportionate encephalization in primates enabled to adapt behavior to a social context. Also, it has been proposed that phylogenetically recent brain areas are disproportionately affected by neurodegeneration. Using structural and functional magnetic resonance imaging, the present study investigates brain-behavior associations and neural integrity of hyperspecialized and domain-general cortical social brain areas in behavioral variant frontotemporal dementia (bvFTD). The results revealed that both structure and function of hyperspecialized social areas in the middle portion of the superior temporal sulcus (STS) are compromised in bvFTD, while no deterioration was observed in domain general social areas in the posterior STS. While the structural findings adhered to an anterior–posterior gradient, the functional group differences only occurred in the hyperspecialized locations. Activity in specialized regions was associated with structural integrity of the amygdala and with social deficits in bvFTD. In conclusion, the results are in line with the paleo-neurology hypothesis positing that neurodegeneration primarily hits cortical areas showing increased specialization, but also with the compatible alternative explanation that anterior STS regions degenerate earlier, based on stronger connections to and trans-neuronal spreading from regions affected early in bvFTD.

Key words: neurodegeneration; social cognition; nonhuman primates; face processing; empathy.

Introduction

The primate brain is one of the most complex products of evolution. Its characteristic size and shape results from morphogenetic mechanisms like cell proliferation, migration, and neuritic elaboration. Particularly in large brains, the cerebral cortex shows a gyrencephalic macroscopic organization, while subcortical structures have a nuclear architecture, possibly driven by anisotropic and isotropic mechanical tension, respectively (Van Essen et al. 2018). Interestingly, as brain size increases across a wide range of mammals, a disproportionately large growth can be observed in phylogenetically younger structures (Finlay and Darlington 1995). Furthermore, there is evidence that the phylogenetic trajectory is paralleled during ontogeny (Hill et al. 2010).

Primate cerebral cortical organization has been extensively studied in humans and macaques. The human cerebral cortical surface exceeds the macaque cortical

surface by a factor of 10 (about 1,900 and 190 cm² per hemisphere, respectively) (Donahue et al. 2018). Furthermore, the relative expansion in humans is particularly evident in prefrontal and lateral temporal cortex (Van Essen and Dierker 2007). This gives rise to fundamental questions related to species-specific properties of the cerebral cortex and the behavioral correlates, with the issue of uniquely human areas at the forefront.

The regional disproportionate cortical surface in humans has been linked to the social brain hypothesis, stating that encephalization paralleled the behavioral ability to communicate with conspecifics and to adapt behavior to social signals within contemporary society (Dunbar 1998). In line with this, there is evidence that social species like humans and macaques have developed specialized brain regions to process signals from conspecifics (Patel et al. 2019). For instance, the human temporal cortex contains areas that respond to social

and emotional signals like facial expressions (Haxby and Gobbini 2011). The right superior temporal sulcus (rSTS) is considered a key structure in a specialized pathway for social and emotional processing (Pitcher and Ungerleider 2021). It shows functional specialization for multiple social and emotional functions along the anterior to posterior axis (Deen et al. 2015).

We have previously taken a comparative approach to investigate whether the primate brain comprises regions that show specialization for conspecific social signals. In particular, we presented human and nonhuman primate (macaque) facial expressions to human and macaque observers in an functional magnetic resonance imaging (fMRI)-experiment. Particularly in the rSTS, the results speak to a species-specific perspective on the social brain hypothesis. In humans, a posterior region (rSTSp) responds more to emotional facial expressions than to neutral facial expressions. Of note, the differential emotional response in rSTSp towards human facial displays does not differ from the emotional response towards nonhuman primate facial expressions. In other words, the rSTSp shows a trans-species emotional response profile. Interestingly, a region in the human middle STS (rSTSm) shows a more specific emotional response, with a strong preference for human emotional expressions over neutral human expressions but also over emotional facial expressions displayed by nonhuman primates. Furthermore, this conspecific response profile observed in the human rSTSm is not observed in any region of the macaque brain (Zhu et al. 2013). The functional characteristics of the human rSTSm are thus compatible with the notion that it constitutes a phylogenetically more recent area, compared to rSTSp (Friedrich et al. 2021).

It has been proposed that phylogenetically younger cortical areas are more prone to premature aging and neurodegeneration. Increased plasticity of these areas as well as wider connections to other brain areas may render them more vulnerable for decline (Ghika 2008; Hill et al. 2010). Many neurodegenerative diseases are characterized by a decline in variable aspects of social cognition and studying these syndromes can provide insights into the key components of the social brain (Kumfor et al. 2017). Social cognition deficits are the phenotypic hallmark of behavioral variant frontotemporal dementia (bvFTD), typically presenting with an initial insidious deterioration of social behavior including loss of empathy and emotion recognition deficits (Van den Stock and Kumfor 2019). bvFTD thus is a suitable condition to test hypotheses on the impact of neurodegeneration on the social brain. Furthermore, at the cellular level, there is evidence that bvFTD differentially affects so-called Von Economo neurons, which are presumed phylogenetically recent (Seeley et al. 2006; Kim et al. 2012; Lin et al. 2019).

On the other hand, the amygdala, a phylogenetically older brain region plays an important role in social cognition as well (Bickart et al. 2014). The functional coupling between amygdala and temporal cortex during

emotional processing has been evidenced via functional neuroimaging, neuromodulation and neuropsychological studies (Vuilleumier et al. 2004; Herrington et al. 2011; De Winter et al. 2016; Pitcher et al. 2017; Sokolov et al. 2018, 2020; Van de Vliet et al. 2018). Furthermore, it has been suggested that the human amygdala coevolved with neo-cortical areas (Stephan 1972).

The present study addresses three aims. First, we test the hypothesis that rSTSm, an area specifically tuned to human emotions without homolog in macaques, is disproportionately affected in bvFTD compared to rSTSp, an area that is responsive to facial expression in general and links with a nonhuman primate homolog. To this end, we investigate group differences between bvFTD patients and healthy controls in each of both STS regions. The multimodal dependent variables consist of gray matter volume and BOLD-responses related to face (faces vs scrambled stimuli) and emotion (fearful faces vs neutral faces) processing. Furthermore, we explore an anterior-posterior gradient for each of these modalities in 8 evenly distributed locations along the entire STS.

Secondly, we hypothesize that phylogenetic hyperspecialization of rSTSm may partly be driven in concert with structures that are functionally related yet show more domain general functional properties. The amygdala is considered a key structure in emotion processing and the primate (human as well as nonhuman) amygdala respond to both human and nonhuman facial expressions (Zhu et al. 2013; Taubert et al. 2020). Furthermore, the primate STS is causally (Pitcher et al. 2017) and functionally (Sokolov et al. 2018, 2020) connected to the amygdala. We therefore test the hypothesis that neurodegenerative changes in rSTSm are specifically related to amygdalar integrity. We investigate this at the level of the amygdalar complex as well as at the level of its major subdivisions: the phylogenetically older central amygdala and phylogenetically younger superficial and basolateral groups of nuclei (Pabba 2013). To investigate the specificity of any significant findings, the hippocampus was used as a control region.

Finally, we investigate the association between clinical phenotype, i.e. behavioral performance on emotion recognition tasks, on the one hand, and social and emotion responses in rSTSp and rSTSm on the other hand. To investigate the specificity of any significant findings, a control task assessing facial identity recognition was used.

Materials and methods

The present study was conducted on data (De Winter et al. 2016) and results (Zhu et al. 2013) obtained in previous studies. The study was conducted in accordance with the Declaration of Helsinki and all participants gave written informed consent. The ethical committee of University Hospitals Leuven approved the studies.

Table 1. Demographics and neuropsychological data.

	bvFTD	Controls	P-value
Male/female	11/8	11/9	0.743
Age (years)	67.4 (8.6)	66.6 (6.1)	0.855
Disease duration (years)	2.42 (1.49)	n/a	n/a
Education (years)	11.8 (2.4)	12.9 (3.0)	0.19
MMSE (SD)	26.3 (2.1)	29.3 (0.6)	<0.001
AVF (SD)	15.0 (5.8)	22.2 (5.8)	<0.001
BNT (SD)	38.8 (12.7)	54.4 (2.9)	<0.001
AAT comprehension (SD) ^a	94.1 (12.8)	109.5 (5.4)	<0.001
RCPMT (SD) ^a	16.4 (4.1)	20.8 (2.8)	0.001
AVLT ^b			
A1–A5 (SD)	27.3 (9.9)	50.9 (7.3)	<0.001
Delayed recall (SD)	4.4 (3.4)	0.7 (3.2)	<0.001
Recognition (SD)	6.9 (6.8)	14.0 (1.3)	<0.001
TMT			
A (SD) ^b	87.2 (104.2)	32.5 (9.4)	<0.001
B (SD) ^c	193.1 (141.2)	89.8 (42.3)	0.001
BORB ^d			
Length matching (SD)	88.5 (7.2)	90.2 (4.5)	0.4
Size matching (SD)	86.5 (6.8)	88.9 (6.3)	0.27
Orientation matching (SD)	80.9 (10.1)	86.1 (6.0)	0.066

AAT = Aachen Aphasia Test; AVF = Animal Verbal Fluency; AVLT = Auditory Verbal Learning Test; BNT = Boston Naming Test; BORB = Birmingham Object Recognition Battery; RCPMT = Raven's Colored Progressive Matrices Test; MMSE = Mini-mental state examination; n/a: not applicable; TMT = Trail Making Test.

^aN_{bvFTD} = 17; ^bN_{bvFTD} = 18; ^cN_{bvFTD} = 15; ^dN_{bvFTD} = 16.

Participants

A total of 19 probable bvFTD patients, according to the most recent international consensus criteria (Rascovsky et al. 2011) and 20 healthy controls participated in the study. Detailed information is reported elsewhere (De Winter et al. 2016). Patients were recruited from the memory clinic of University Hospitals Leuven and the department of Geriatric Psychiatry—University Psychiatric Center KU Leuven (Leuven, Belgium) as well as from the Neurology Department of the regional Onze-Lieve-Vrouw Ziekenhuis Aalst-Asse-Ninove (Aalst, Belgium). Patients were diagnosed by experienced neurologists or geriatric psychiatrists after clinical assessment, medical history taking, cognitive neuropsychological testing, and atrophy patterns on structural MRI. In 17 patients, diagnosis was also based on a typical pattern of hypometabolism on [¹⁸F]Fluorodeoxyglucose PET scan. Patients initially presented with changes in behavior and personality displaying disinhibition, apathy and/or perseverative/compulsive behavior. At inclusion, mean symptom duration assessed by medical history taking equalled 2.42 years (SD = 1.49). Patients were included after clinical judgment deemed them able to successfully undergo an experimental scanning session.

14 out of 19 patients were prescribed psychoactive drugs at the time of the experiment (see De Winter et al. 2016 for details). 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 that might affect the central nervous system. 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 and clinical characteristics are presented in Table 1.

Behavioral assessment

Cognitive assessment included Mini-mental state examination (MMSE), Rey's Auditory Verbal Learning Test, Animal Verbal Fluency, Raven's Colored Progressive Matrices A and B, Trail Making Test A and B, Birmingham Object Recognition Battery subtests, Boston Naming Test and Aachen Aphasia Test (Lezak et al. 2012). The results are presented in Table 1.

Furthermore, face processing was assessed using 3 experiments, one focused on identity matching and 2 on emotion matching. Each task consisted of 2-alternative forced-choice simultaneous match-to-sample format. In short, participants were presented with stimuli consisting of 1 face picture/video on top, and 2 underneath. The instruction was to indicate which of the 2 faces at the bottom matched the one on top. In the identity experiment, faces were to be matched on identity, while in the emotion experiments, faces were to be matched on emotion. The emotion matching assessments consisted of a static and a dynamic variant. The experimental procedures are described in detail elsewhere (de Gelder et al. 2015; Van den Stock et al. 2015; De Winter et al. 2016). Stimulus examples are presented in Figure 1.

fMRI experiment

The procedure has been reported in detail elsewhere (De Winter et al. 2016). In short, movie clips displaying a fearful or neutral (chewing) facial expression or their spatio-temporally scrambled versions were presented in a factorial rapid event-related fMRI-design while participants performed an oddball detection task (a white square appearing on the stimulus) (Fig. 2). Functional runs were complemented by a structural T1-weighted scan.

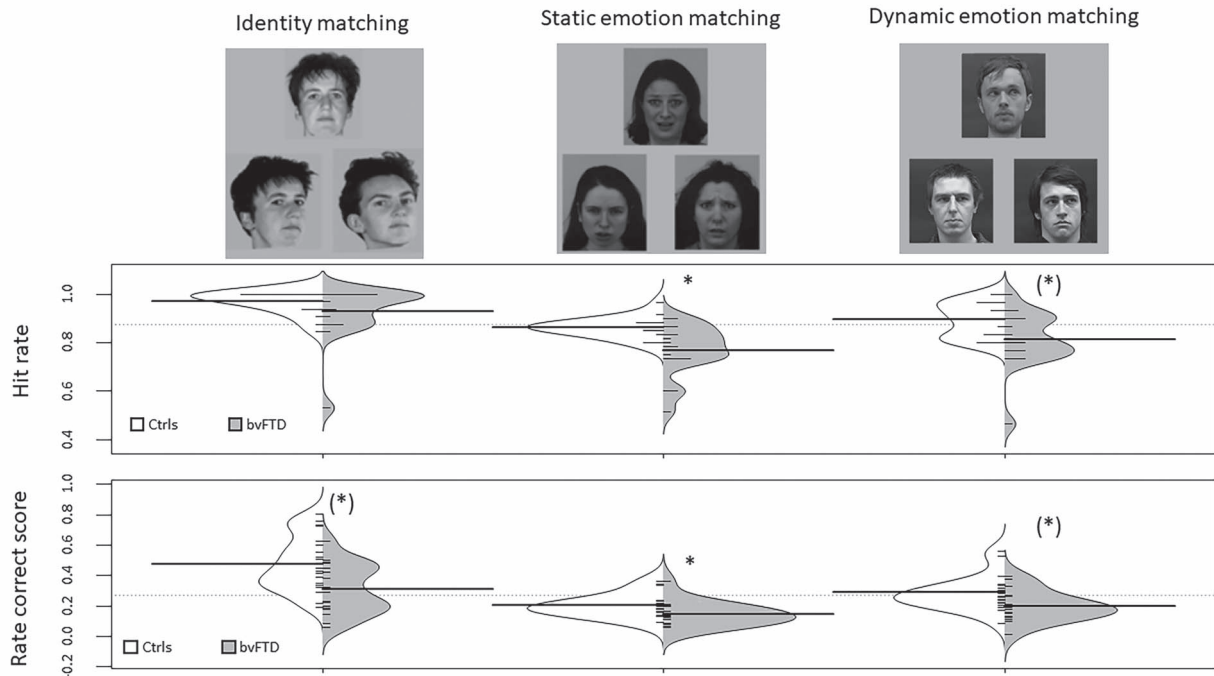


Fig. 1. Stimulus examples and results of behavioral experiments. The top row displays stimulus examples of identity matching (left), static (center), and dynamic (right) facial emotion matching experiments. The center and bottom row display split violin-plots with integrated rug-plots of the hit rate (center row) and rate correct score (RCS; bottom row) as a function of group and experiment. *: Significant ($P < 0.05$, Bonferroni-corrected) group differences following Mann-Whitney U tests. (*) significant ($P < 0.05$, uncorrected) group differences following Mann-Whitney U tests. Horizontal lines indicate group-specific median.

Image preprocessing

Preprocessing of structural data consisted of manually reorienting T1-weighted images to the AC-PC plane. T1 weighted-images were analyzed by means of the “Computational Anatomy Toolbox” (CAT12, <http://www.neuro.uni-jena.de/cat>) for SPM12 (Wellcome Trust Centre for Neuroimaging, UCL, London, United Kingdom) in order to obtain normalized gray matter volumes. One bvFTD patient was excluded based on suboptimal quality of the anatomical scan.

Preprocessing included normalization to MNI space, segmentation, and bias correction of intensity nonuniformities (default parameter settings). The amounts of volume changes, due to spatial registration, were scaled in order to retain the original local volumes (modulating the segmentations). All images were smoothed using an 8 mm isotropic Gaussian Kernel. Details on preprocessing of functional data are reported elsewhere (De Winter et al. 2016).

ROI definition

The main analyses were performed in two ROI's defined in a previous study with face stimuli of human and non-human primates. The human face stimuli in the dataset used for ROI-definition were the same as the stimuli in the dataset used for the ROI-analysis. The ROIs consisted of a region in the right posterior STS (rSTSp), responding to human fearful expressions as well as to monkey fearful expressions (versus their respective neutral displays)

and a region in the right middle STS (rSTSm), responding specifically to human facial expressions (Fig. 2) (Zhu et al. 2013).

Supplementary ROI analyses were performed in nonoverlapping regions in the right STS to investigate whether an anterior–posterior gradient effect was present. Using a previously reported STS mask (Deen et al. 2015), we created a series of 8 spherical ROIs along the anterior–posterior axis of the right STS. The ROIs had a 4 mm radius with gaps of 2 mm in between the spheres. For each y -coordinate, the STS mask coordinates were averaged across the x - and z -dimensions to obtain the centers of the spheres (Fig. 3).

In addition, ROIs of the right amygdala and hippocampus were defined using the Wake Forest University Pickatlas (Maldjian et al. 2003). Probabilistic cytoarchitectonic maps for right amygdalar subregions were derived from the SPM Anatomy toolbox (http://www.fz-juelich.de/inm/inm-1/DE/Forschung/_docs/SPMAnatomyToolbox/SPMAnatomyToolbox_node.html) (Eickhoff et al. 2005).

ROI analyses

Gray matter volume (GMV) of every ROI was derived from the modulated normalized GM images and percent signal change (PSC) was calculated for each of 2 contrasts investigating respectively social [(fearful faces + neutral faces) – (scrambled fearful faces + scrambled neutral faces)] and emotional responses (fearful faces – neutral

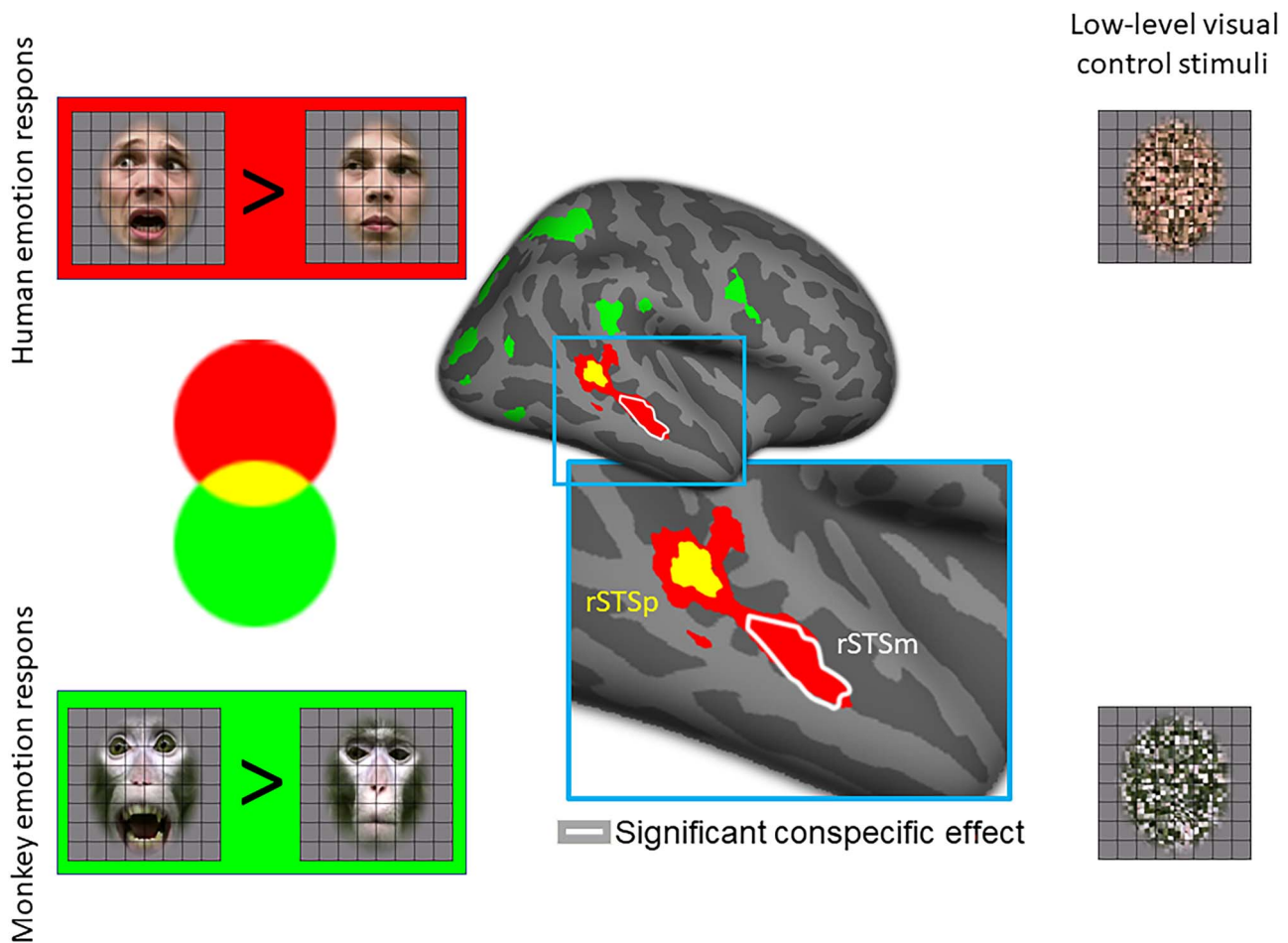


Fig. 2. Example stimuli used in the fMRI tasks and ROIs. Left column: Static frames of the dynamic stimuli displaying the intact fearful and neutral expressions of human (top) and monkey (bottom) faces from the fMRI task used to define the ROIs. In the fMRI task used in bvFTD patients and healthy elderly controls, only the intact human and scrambled human stimuli were used. The center image displays the topography of the human (red) and monkey (green) emotion responses and their overlap (yellow). The central bottom panel depicts rSTSp, activated by both human and monkey fear (vs neutral) and rSTSm, activated more by human fear than by monkey fear (vs neutral). The white outline marks the region showing a significant conspecific effect. The right column displays static frames of the dynamic stimuli used as low-level visual control.

faces). PSC for these contrasts was calculated in all 10 STS ROIs using Marsbar (Brett et al. 2002).

Data were analyzed in IBM SPSS Statistics version 24 and R (Team 2013). Linear mixed model (LMM) analyses with random intercept were performed to investigate regional and group differences in structure and function. In all LMMs, ROI, group, and ROI*group were included as fixed effects. All posthoc tests were performed using Bonferroni correction.

First, we investigated structural effects in rSTSp and rSTSm, followed by structural effects along the anterior–posterior STS-axis. In the LMM analyses on structural data, age was included as an additional variable of no interest. Subsequently, we investigated social and emotional responses in rSTSp and rSTSm, and finally along the anterior–posterior STS-axis.

Furthermore, we investigated the association of the neural characteristics (GMv, face response and emotion response) in the main STS ROIs (rSTSp, rSTSm) and GMv of the amygdala by means of partial correlation analyses within the bvFTD-group, controlled for TIV. In case of a

significant result, this was followed up with a partial correlation analysis with GMv of the amygdalar subregions (basolateral, medial, and superficial) as well as with GMv of the hippocampus to investigate the specificity of the association.

Whole brain analyses

To investigate a reduced face response or emotion response outside the predefined areas in the right STS, we performed 2 additional voxel-wise whole brain analyses, consisting of 2-sample t-tests (Ctrls > FTD) on the contrasts faces > scrambles and fearful faces > neutral faces. To benefit sensitivity, we valued the reduction of Type I errors over the reduction of Type II errors and used a liberal statistical threshold of $P < 0.001$ uncorrected.

Behavioral analyses

Performance on the psychophysical tasks focused on 2 constructs: ability and efficiency, respectively reflected in the hit rate and an adapted rate correct score (RCS)

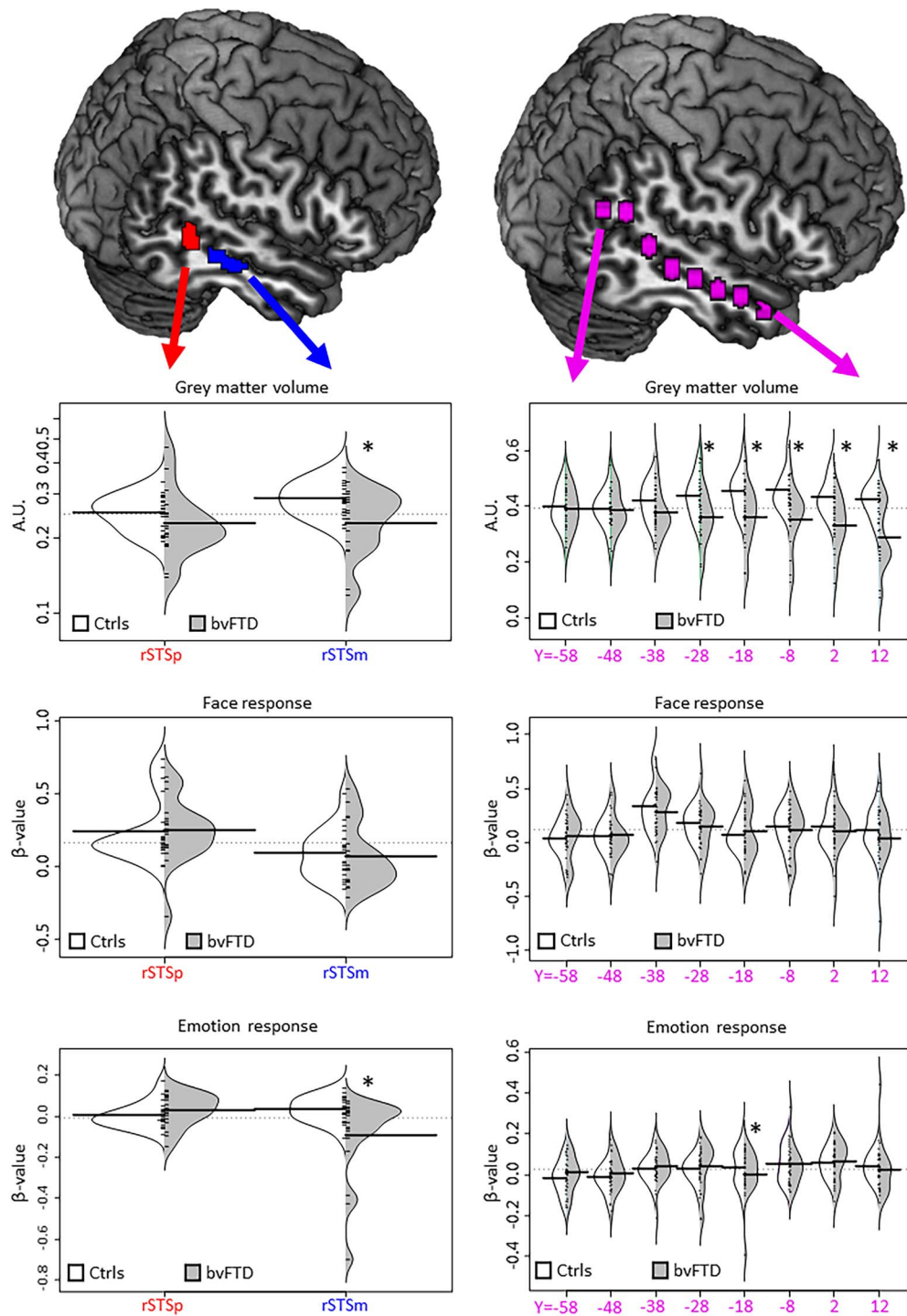


Fig. 3. ROI topography and ROI-analysis results. The left column displays the topography of rSTSp and rSTSm (top) and split violin with rug-plots of the ROI-analysis results on the 3 dependent variables, while in the right column the topography of the 8 ROIs along the anterior-posterior STS-axis is displayed (top) along with the split violin with rug-plots of the 3 dependent variables. *: Significant ($P < 0.05$, Bonferroni-corrected) group \times ROI interactions following linear mixed model analyses with random intercept and ROI, group, and ROI*group as fixed effects. Horizontal lines indicate group-specific mean.

(Woltz and Was 2006). We calculated RCS as the hit rate divided by the median response time (in seconds), reflecting the number of correct responses per second, corrected for outliers. RCS has been reported as more reliable and advantageous compared to the single measures of speed and accuracy as well as compared

to other measures that integrate speed and accuracy (Hughes et al. 2014; Vandierendonck 2017). Finally, we calculated Spearman correlation coefficients between the behavioral measures and PSC to faces and emotions in rSTSp and rSTSm to investigate brain-behavior associations.

Results

ROI analyses

Gray matter volume

A LMM analysis with random intercept on the gray matter volume estimates and group (bvFTD, ctrls), ROI (rSTSm, rSTSp), group x ROI and age (as a covariate of no interest) as fixed effects revealed a significant effect of group ($F(1,34.769)=4.216$, $P=0.048$), ROI ($F(1,36)=6.396$, $P=0.016$) and group*ROI interaction ($F(1,36)=5.862$, $P=0.021$). The effect of age was not significant ($F(1,35)=2.383$, $P=0.132$). Bonferroni-corrected posthoc tests revealed significantly less gray matter volume in the patient group in rSTSm ($P=0.004$, 95%CI [0.018, 0.090]) but not in rSTSp ($P=0.378$, 95%CI [-0.023, 0.060]; Fig. 3).

An analogous LMM focusing on the anterior–posterior gradient with 8 ROIs along the STS instead of rSTSm and rSTSp revealed a significant effect of ROI ($F(7,44.915)=3.188$, $P=0.008$), group ($F(1,33.571)=10.368$, $P=0.003$) and group*ROI ($F(7,44.915)=7.292$, $P<0.001$). Bonferroni-corrected posthoc tests revealed significantly lower gray matter volume in the patient group compared to the control group in the 5 most anterior ROIs ($y=12$: $P<0.001$, 95%CI [0.075, 0.206]; $y=2$: $P<0.001$, 95%CI [0.054, 0.163]; $y=-8$: $P<0.001$, 95%CI [0.057, 0.162]; $y=-18$: $P<0.001$, 95%CI [0.049, 0.149]; $y=-28$: $P=0.002$, 95%CI [0.031, 0.130]), but not in the three most posterior ROIs ($y=-38$: $P=0.143$; $y=-48$: $P=0.744$; $y=-58$: $P=0.664$; Fig. 3). The main effect of ROI qualified as a significant difference between the most anterior ROI ($y=12$) on the one hand and the third ($y=-8$, $P=0.033$, 95%CI [-0.092, -0.002]) and fourth ($y=-18$, $P=0.008$, 95%CI [-0.094, -0.008]) most anterior ROIs on the other hand.

Face response

A LMM analysis with random intercept on the face response (faces vs scrambled stimuli) and group (bvFTD, ctrls), ROI (rSTSm, rSTSp) and group x ROI as fixed effects revealed a significant effect of ROI ($F(1,36)=14.820$, $P<0.001$), but not of group ($F(1,36)=0.024$, $P=0.878$), nor of ROI*group ($F(1,36)=0.073$, $P=0.788$). A Bonferroni-corrected posthoc test showed that the percent signal change (PSC) for faces (vs scrambles) was significantly higher in rSTSp ($P<0.001$, 95%CI [0.078, 0.252]; Fig. 3).

An analogous LMM focusing on the anterior–posterior gradient revealed a significant effect of ROI ($F(7,53.420)=9.931$, $P<0.001$), but not of group ($F(1,36.478)=0.090$, $P=0.765$), nor of group*ROI ($F(7,53.420)=0.616$, $P=0.740$). Bonferroni-corrected posthoc tests revealed a higher PSC in the ROI at $y=-38$ compared to all other ROIs along the rSTS [$y=12$: $P<0.001$, 95%CI [0.088, 0.368]; $y=2$: $P<0.001$, 95%CI [0.055, 0.308]; $y=-8$: $P=0.017$, 95%CI [0.014, 0.281]; $y=-18$: $P<0.001$, 95%CI [0.099, 0.345]; $y=-28$: $P=0.004$, 95%CI [0.029, 0.262]; $y=-48$: $P<0.001$, 95%CI [0.130, 0.358]; $y=-58$: $P<0.001$, 95%CI [0.134, 0.379]; Fig. 3).

Emotion response

A LMM analysis with random intercept on the emotion response (fearful vs neutral stimuli) and group (bvFTD, ctrls), ROI (rSTSm, rSTSp) and group x ROI as fixed effects revealed a significant effect of ROI ($F(1,36)=4.501$, $P=0.041$) as well as a significant group*ROI interaction ($F(1,36)=11.665$, $P=0.002$). Bonferroni-corrected posthoc tests revealed a significantly higher PSC in healthy controls in rSTSm ($P=0.012$, 95%CI [0.029, 0.226]), but not in rSTSp ($P=0.276$). The main effect of ROI reflected a stronger emotional response in rSTSp ($P=0.041$, 95%CI [0.002, 0.093]). To investigate whether this was due to a decreased emotion response in the bvFTD group, we compared the emotion response between rSTSp and rSTSm for each group separately by means of paired-sample *t*-tests. This revealed a significant difference in the bvFTD group ($t(17)=2.838$, $P=0.011$, Cohen's $d=-0.669$), but not in the control group ($t(19)=1.787$, $P=0.090$). There was no significant effect of group ($F(1,36)=2.793$, $P=0.103$; Fig. 3). Three bvFTD patients showed negative outlier values for emotion response, partly due to negative responses to fearful faces (vs fixation baseline). We therefore reanalyzed the data without these outliers. The results again revealed a significant group*ROI interaction ($F(1,33)=10.039$, $P=0.003$) with a similar qualification, i.e. higher PSC in controls in rSTSm ($P=0.048$, 95%CI [0.000, 0.091]), but not in rSTSp ($P=0.148$).

The analogous LMM investigating an anterior–posterior gradient revealed a significant effect of ROI ($F(7,60.252)=4.135$, $P=0.001$), but not of group ($F(1,37.016)=0.013$, $P=0.909$), nor of group*ROI ($F(7,60.252)=0.503$, $P=0.829$). Bonferroni-corrected posthoc tests revealed a significantly higher PSC in the ROI at $y=2$ compared to the ROI at $y=-48$ ($P=0.003$, 95%CI [0.014, 0.118]) and compared to the ROI at $y=-58$ ($P=0.004$, 95%CI [0.013, 0.120]; Fig. 3).

Amygdala-STS associations

Partial correlation analyses, controlling for total intracranial volume (TIV), revealed a significant association between GMv of the amygdala and GMv of the rSTSm ($r=0.598$, $df=14$, $P=0.014$), but not with GMv of the rSTSp ($r=0.376$, $df=14$, $P=0.151$). A follow-up partial correlation analysis revealed that GMv in rSTSm correlated significantly with each amygdalar subregion, but also with hippocampal GMv (all r 's >0.562 , $df=14$, P 's <0.024).

Of all partial correlation analyses between STS responses and amygdalar volume, only the one with emotion response in rSTSm was significant ($r=0.555$, $df=14$, $P=0.026$; all other P 's >0.330 ; Fig. 4). The posthoc correlation analyses revealed significant partial correlations with each amygdalar nuclei grouping (all r 's >0.500 , $df=14$, P 's <0.049), but not with hippocampal volume ($r=0.396$, $df=14$, $P=0.129$).

rSTSm association with clinical phenotype

Group differences on both accuracy and efficiency measures for behavioral facial recognition tasks were

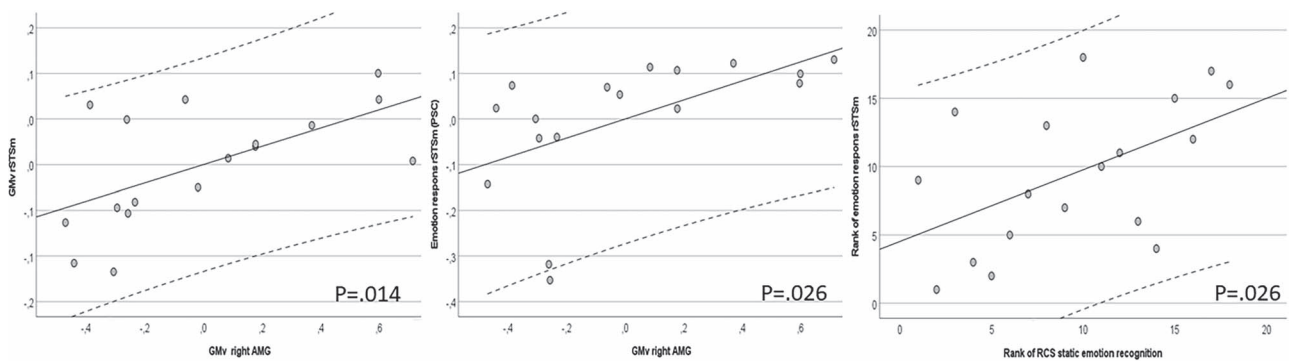


Fig. 4. Scatterplots displaying significant (partial) correlation results. Left: Significant partial correlation between gray matter volume (GMv) in rSTS_m and GMv in the right amygdala (left), controlling for TIV; Center: Significant partial correlation between emotion-related PSC in rSTS_m and GMv in the right amygdala, controlling for TIV; right: Significant Spearman correlation between PSC for emotions in rSTS_m and RCS for static emotion matching. Dashed lines represent the 95% individual confidence range.

statistically tested by means of Mann–Whitney *U*-tests. This revealed significant differences on all measures (all *P*'s < 0.024; η^2 's > 0.14), except on the accuracy score of facial identity recognition ($U=135.5$; $P=0.297$). However, only the group effect on accuracy and efficiency of static emotion recognition survived Bonferroni-correction (respectively $U=66.5/81.0$; corrected P -value = 0.006/0.018; $\eta^2 = 0.30/0.22$; Fig. 4).

Spearman correlation coefficients were calculated between the behavioral measures and PSC to faces and emotions in rSTS_{Sp} and rSTS_m. The only significant brain–behavior association was the one between emotion response in rSTS_m and efficiency of matching static emotional faces ($\rho = 0.523$, $n = 18$, $P = 0.026$; Fig. 4).

Whole brain analyses

None of the voxel-wise whole brain analyses revealed any significant results at the liberal threshold of $P < 0.001$, uncorrected.

Discussion

bvFTD is characterized by a deterioration of higher order social abilities presumed to differentiate humans from other species. It has been postulated that phylogenetically more recent cerebral areas underlying these skills might be more vulnerable to certain forms of neurodegeneration than other areas in the brain (Ghika 2008). We previously investigated neural responses to human and macaque facial displays in human as well as in macaque observers. The results revealed an area in humans that responds specifically to human emotions (rSTS_m), but the results did not reveal a region with a comparable conspecific response in the macaque sample. Here, we investigated whether this presumably recent area is structurally and functionally impaired in bvFTD and whether this impairment is selective compared to areas that respond to facial expressions in general (rSTS_{Sp}).

Our first aim was to investigate whether bvFTD selectively affects hyperspecialized regions (rSTS_m). The findings show reduced GMv in rSTS_m, but not in rSTS_{Sp}. Furthermore, we observed functional changes

in rSTS_m but not in rSTS_{Sp} and these changes are specifically related to responses to human emotions (vs neutral human facial displays) and not to social signals in general (face vs nonface stimuli). These findings indicate a stronger impact of bvFTD on the highly specialized rSTS_m, compared to the more domain-general face-responsive rSTS_{Sp}. This observation is in line with predictions from the paleo-neurology hypothesis. However, the results also adhere to the notion that anterior temporal regions degenerate earlier. Indeed, the analyses focusing on the anterior–posterior gradient revealed that the impact of bvFTD at the structural level follows an anterior–posterior pattern in the temporal lobe, with strongest degeneration of the most anterior areas, in line with previous findings (Seeley et al. 2008). Interestingly, both explanations are linked as there is evidence for a phylogenetic posterior–anterior specialization gradient along the temporal cortex (Valk et al. 2020). It has been suggested that the temporal pole shows hyper specialization by integrating complex and multimodal emotion cues at the conceptual level (Olson et al. 2007; Bertoux et al. 2020; Strikwerda-Brown et al. 2021). The functional results are less compatible with an anterior–posterior profile, as bvFTD affects emotional responses in the location of the rSTS_m, but not anterior to the rSTS_m. Then again, this observation may be explained by the local functional selectivity, i.e. processing of human expressions. While the main finding of the present study is in line with a paleo-neurology account, we are cautious to interpret this as strong paleo-neurology support. While our findings may provide a tentative indication, we are unable to report strong evidence to exclude alternative explanations. For instance, the findings may be explained by the notion that the rSTS_m is more affected based on stronger connections to and trans-neuronal spreading from regions affected early in bvFTD. Future studies may address these issues and compare anterior domain general regions with posterior hyperspecialized regions and/or focus on regions with strong vs weak connections to the structures that are early targeted by the disease.

With these caveats in mind, the present observations complement previous results at the cellular and molecular level. There is evidence that bvFTD disproportionately affects Von Economo neurons, which are presumed to be phylogenetically recent (Seeley et al. 2007; Seeley 2008; Kim et al. 2012). Von Economo neurons are primarily observed in the fronto-insula and anterior cingulate cortex (ACC), considered key nodes in the salience network, and associated with social cognition deficits in bvFTD (Zhou and Seeley 2014; Van den Stock and Kumfor 2019). Furthermore, converging histopathological evidence indicates that the earliest TDP-43 aggregates in bvFTD occur in anterior prefrontal cortices and amygdala, followed by anterior-to-posterior spreading of TDP-43 burden along the temporal cortex (Brettschneider et al. 2014; Jo et al. 2020). FTD-related tau pathology is typically observed in the insula and temporal pole (Lin et al. 2019; Tsai et al. 2019).

For our second aim, we related amygdalar volume to deterioration of hyperspecialized (rSTS_m) and domain-general (rSTS_p) social brain regions. The amygdala is phylogenetically older than the STS and has been associated with faster and more primitive emotional responses (LeDoux 1996) which interact with higher order cortical regions such as the STS in primates (Pitcher et al. 2017). Our results reveal an association between structural integrity of the amygdala and rSTS_m, but not rSTS_p.

Of note, the amygdala-rSTS_m GMv association was significant across all three amygdalar nuclei groupings, i.e. basolateral, centromedial, and superficial, but not amygdala-specific, as the association between GMv of the hippocampus and rSTS_m was also significant. While these structural cortico-subcortical associations are in line with an anterior-posterior gradient, this was not the case for structural subcortical-functional cortical associations. Indeed, amygdalar but not hippocampal GMv was associated with functional properties of the rSTS_m, but not of the rSTS_p. Furthermore, the link was not evident for the face response and thus specific for the emotional response. At the nuclear group level, the association was evident in each of the three subregions of the amygdala and thus generalized across phylogenetically older (i.e. centro-medial) and younger (basolateral and superficial) amygdalar nuclei groups. These combined findings are in line with the notion that deterioration of functional characteristics of rSTS_m in bvFTD goes hand in hand with structural degeneration of the amygdala. This bears the suggestion that functional specialization in the STS is at least partly driven through amygdalar connectivity.

The present findings further provide evidence for a link between the neuro-imaging results and the clinical phenotype of bvFTD. The present sample displayed deficits in the recognition of facial emotional expressions, and these were associated with the emotional response in rSTS_m, but not in rSTS_p. Of note, the bvFTD sample was primarily impaired at recognizing static expressions, rather than at recognition of ecologically more valid dynamic expressions, which are typically

easier to analyze (de Gelder and Van den Stock 2010). This pattern aligns with the “threshold”-hypothesis: if emotional deficits in bvFTD show a progression from subtle to manifest emotional cues, a deficit in recognizing emotional cues containing a critical level of ambiguity would precede a deficit in recognizing full-blown expressions. Support for this hypothesis comes from studies showing that bvFTD impairs recognition of low- but not high-intense emotional expressions (Kumfor et al. 2011; Jastorff et al. 2016). It has been hypothesized that deficits in facial emotional expression recognition underlie empathy symptoms in bvFTD (Rankin et al. 2005). Empathic deficits are a core feature of bvFTD (Rascovsky et al. 2011). Interestingly, empathy is typically considered a higher order process in social cognition, building on subordinate processes like emotional contagion (de Waal and Preston 2017) and self-other distinction (Schaafsma et al. 2015). The most evolved empathic behavioral manifestations have typically been reported in highly social animals and these species display a high degree of encephalization (de Waal and Preston 2017). Possibly, the empathic deficit that characterizes bvFTD reflects a primary emotional retrogenesis, analogous to the hypothesis that the functional decline that characterizes Alzheimer’s disease reverses Piaget’s developmental stages (Reisberg et al. 2002). One could speculate that species-specific brain areas, like rSTS_m are key regions in the neural circuitry underlying higher order processes like empathy.

Finally, the results of the present study expose a paradoxical finding related to the paleo-neurology hypothesis: on the one hand, presumably phylogenetically younger cortical areas (rSTS_m) are more vulnerable compared to older ones (rSTS_p), while on the other hand the older subcortical regions (amygdala) are affected earlier in the disease course compared to younger ones (e.g. lateral temporal cortex; Seeley et al. 2008). This might be related to the architectural differences between cortical and subcortical structures, i.e. a layered vs nuclear neural organization, with paleo-neurology principles primarily relevant for cortical structures. Indeed, the neo-cortical macroscopic gyral-sulcal and microscopic laminar organization contribute to the computational potential within a physically constrained environment. The layered cortical structure provides a framework for integration of sensory input, local and distant cortical and subcortical input, as well as cortical output, all while preserving topography. On the other hand, there is evidence that some subcortical structures, including the amygdala, have shown disproportionate phylogenetic development in humans. For instance, the lateral amygdala are 37% larger than predicted by ape volumetry (Barger et al. 2014). Because the lateral nucleus is the primary target of afferent connections arriving from higher order visual and auditory processing centers in the temporal lobe, it has been suggested that expansion of the lateral nucleus may be associated with the significant evolutionary expansion reported

for the human temporal (Barger et al. 2014). Moreover, the corticobasolateral portion of the amygdala scales with social group size across primates (Barton and Aggleton 2000) and amygdala volume predicts online and real-world social network sizes in humans (Bickart et al. 2011; Kanai et al. 2012). In other words, although the subcortical structures evolved earlier than cortical structures in phylogenetic perspective, they may have increased in structural complexity in humans, compared to nonhuman hominoids, in parallel with increasing social demands.

Several limitations of the present study and future directions need to be addressed. First, there is no direct evidence supporting that rSTSm is phylogenetically younger than rSTSp. We have proposed this assumption based on its increased specialization, but not on empirical evidence. Second, to investigate neural face-responses, we compared perception of faces with perception of scrambled stimuli, controlling for low-level visual features. While our previous findings have shown that this contrast revealed the well-known face-selective regions, the theoretical implication remains that this contrast dovetails with nonface object perception. Yet, our previous findings have documented the overlap of rSTSp and rSTSm with face-selective regions (Zhu et al. 2013).

Third, the present primary focus was limited to two macroscopic areas in the temporal cortex related to social and emotional processing of human facial expressions in a sample of bvFTD. Future studies may address additional levels of specificity and domain-generality of the present findings. For instance, it would be interesting to address whether similar patterns of results can be observed for language processing in FTD language variants and to include microscopic viewpoints. To critically compare the paleoneurology with the anterior–posterior gradient explanation, future studies could compare posterior hyperspecialized regions with anterior domain-general regions. Finally, longitudinal studies may investigate whether neurodegeneration progresses in the reverse direction of evolution, i.e. whether phylogenetically older structures are affected later in the course of the disease.

In conclusion, the present results indicate that hyperspecialized cortical areas of the social brain are more vulnerable to neurodegeneration in bvFTD, compared to domain-general areas, in line with the paleoneurology hypothesis that neurodegeneration disproportionately affects structures that are assumed to be phylogenetically more recent. These observations align with the notion of an anterior–posterior gradient in both functional specialization and presumed phylogenetic age. In addition, the findings suggest that degeneration of hyperspecialized regions is associated with structural degeneration of subcortical structures and that these changes link with clinical phenotype of bvFTD.

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