Facial expressiveness and physiological arousal in frontotemporal dementia: Phenotypic clinical profiles and neural correlates

Fiona Kumfor^{1,2,3} · Jessica L. Hazelton^{1,2} · Jacqueline A. Rushby⁴ · John R. Hodges^{2,3,5} · Olivier Piguet^{1,2,3}

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Abstract

Early theories of emotion processing propose an interplay between autonomic function and cognitive appraisal of emotions. Patients with frontotemporal dementia show profound social cognition deficits and atrophy in regions implicated in autonomic emotional responses (insula, amygdala, prefrontal cortex), yet objective measures of facial expressiveness and physiological arousal have been relatively unexplored. We investigated psychophysiological responses (surface facial electromyography (EMG); skin conductance level (SCL)) to emotional stimuli in 25 behavioural-variant frontotemporal dementia (bvFTD) patients, 14 semantic dementia (SD) patients, and 24 healthy older controls, while viewing emotionally positive, neutral, or negative video clips. Voxel-based morphometry was conducted to identify neural correlates of responses. Unlike controls, patients with bvFTD did not show differential facial EMG responses according to emotion condition, whereas SD patients showed increased zygomaticus responses to both positive and neutral videos. Controls showed greater arousal (SCL) when viewing positive and negative videos; however, both bvFTD and SD groups showed no change in SCL across conditions. Regardless of group membership, right insula damage was associated with dampened zygomaticus responses to positive film stimuli. Change in arousal (SCL) was associated with lower integrity of the caudate, amygdala, and temporal pole. Our results demonstrate that while bvFTD patients show an overall dampening of responses, SD patients appear to show incongruous facial emotional expressions. Abnormal responding is related to cortical and subcortical brain atrophy. These results identify potential mechanisms for the abnormal social behaviour in bvFTD and SD and demonstrate that psychophysiological responses are an important mechanism underpinning normal socioemotional functioning.

Keywords Electromyography · Skin conductance · Semantic dementia · Imaging

Introduction

Early theories of emotion processing proposed that autonomic functioning and cognitive appraisal of emotions are

closely interlinked (James, 1884; Lange, 1922). Specifically, perception of one's own emotional state and recognition of emotion in others is thought to occur secondary to the experience of somatic sensations. Contemporary theories have built on these accounts (Damasio et al., 1996; Schachter & Singer, 1962) and explored the neurobiological basis for this convergence of internal physiology and the external milieu (Ibañez & Manes, 2012; Singer, Critchley, & Preuschoff, 2009). The insula has emerged as a central structure for substantiating subjective feelings from the body (Craig, 2002, 2009). Specifically, the insula is critically involved in interoception, that is, the capacity to perceive “feelings” from the body, which indicate one's physical condition, and emotional and mood state (Craig, 2003). Predominantly, these internal physiological signals provide an index of one's level of arousal (and are less sensitive to the valence or specific emotion experienced) (Bradley & Lang, 2000; Damasio et al., 2000; Levenson, 1988). From a network perspective, the insula, together with the anterior cingulate cortex and orbitofrontal cortex, has been recognised as an important hub of the Salience Network,

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✉ Fiona Kumfor
fiona.kumfor@sydney.edu.au

- ¹ School of Psychology, The University of Sydney, Sydney, Australia
- ² Brain and Mind Centre, The University of Sydney, 94 Mallett St, Level 3 M02F, Camperdown, Sydney, NSW 2050, Australia
- ³ ARC Centre of Excellence in Cognition and its Disorders, Sydney, Australia
- ⁴ School of Psychology, The University of New South Wales, Sydney, Australia
- ⁵ Sydney Medical School, Faculty of Health Sciences, The University of Sydney, Sydney, Australia

which activates in response to emotionally relevant cues in the environment (Seeley et al., 2007).

Individuals diagnosed with frontotemporal dementia (FTD) have profound deficits in their ability to understand social and emotional cues and behave inappropriately when placed in social situations (Hutchings, Hodges, Piguet, & Kumfor, 2015; Kumfor & Piguet, 2012). Mounting evidence has demonstrated that this impairment occurs both in patients presenting with the behavioural variant of FTD (bvFTD), which is characterised by early changes in behaviour and personality (Piguet, Hornberger, Mioshi, & Hodges, 2011; Rascovsky et al., 2011) and with the semantic variant (semantic dementia; SD), which is characterized by early deficits in language and progressive loss of semantic knowledge (Gorno-Tempini et al., 2011; Hodges, Patterson, Oxbury, & Funnell, 1992). Despite this evidence, the mechanisms that give rise to these impairments in emotion processing and social behaviour are not well understood. This lack of knowledge has hampered the development of intervention strategies targeting these distressing symptoms (Hsieh, Irish, Daveson, Hodges, & Piguet, 2013a; Kumfor, Hodges, & Piguet, 2014a).

Of relevance, brain atrophy in bvFTD is present in the anterior insula and ventromedial prefrontal cortices (Seeley et al., 2008), which extends into subcortical regions, including the striatum, with disease progression (Landin-Romero et al., 2017). In contrast, patients with SD show early atrophy in the anterior temporal lobe, which tends to be asymmetrical (Mion et al., 2010; Rosen et al., 2002) and extends into the contralateral temporal lobe and orbitofrontal regions with disease progression (Kumfor et al., 2016). Given these divergent patterns of brain atrophy early on, one would predict that distinct mechanisms give rise to emotion processing deficits in bvFTD and SD. While bvFTD patients may show changes reflective of emotional blunting, deficits in SD patients may be more reflective of semantic or conceptual knowledge loss.

To date, few studies have employed psychophysiological techniques to objectively measure emotion processing in FTD, with mixed results. Some studies have reported attenuated skin conductance levels in response to aversive stimuli (loud noise) in bvFTD compared with Alzheimer's disease patients and healthy controls (Hoefer et al., 2008; Joshi et al., 2014). However, others have found no difference in physiological responses to complex emotional film stimuli between healthy controls and a mixed group of bvFTD and SD patients, despite impaired explicit emotion recognition performance in these syndromes (Werner et al., 2007). Interestingly, lower skin conductance levels in bvFTD patients during a baseline rest period also have been reported in some studies (Joshi et al., 2014) but not others (Balconi et al., 2015; Guo et al., 2016). Notably, physiological signatures are likely to differ between bvFTD and SD considering their differences

in clinical presentation and patterns of atrophy. Thus, mixed FTD samples may, in part, account for these varied findings. Moreover, some studies have used a composite score to assess physiological changes (including heart-rate, skin conductance, finger temperature, pulse amplitude, pulse transmission time, respiration, and blood pressure) (Werner et al., 2007), which may map onto different psychological processes.

In healthy adults, skin conductance has been shown to be a surrogate marker of emotion processing, with viewing of emotional facial expressions associated with larger changes in skin conductance (Williams et al., 2005). Moreover, greater changes in skin conductance are observed in people who show greater prosocial behaviours (Hein, Lamm, Brodbeck, & Singer, 2011). Of note, a recent study that examined skin conductance in bvFTD, while viewing emotional images, found significantly lower skin conductance in bvFTD patients than in healthy controls. Furthermore, the skin conductance response was not related to subjective ratings of valence and arousal, as observed in healthy controls and Alzheimer's disease patients (Balconi et al., 2015). Thus, the limited evidence available suggests that skin conductance responses may indeed be reduced in bvFTD. To our knowledge, no study has investigated skin conductance and emotion processing in SD. Thus, while concurrent measurement of skin conductance may provide insights into the changes in emotional behaviour in bvFTD and SD, few studies have examined this type of response systematically.

Facial surface electromyography is another way to objectively measure individuals' responses to emotional situations and has been successfully used in some clinical populations (e.g., traumatic brain injury) (McDonald et al., 2010; Rushby et al., 2013). Emotional blunting is one of the six core diagnostic criteria for bvFTD (Rascovsky et al., 2011); however, this technique has not been employed in FTD to date. Studies that have videotaped or photographed patients with FTD have reported mixed results in the range of facial expressions (Perry et al., 2001; Sturm, Rosen, Allison, Miller, & Levenson, 2006; Werner et al., 2007), with high variability in patient facial behaviour also reported (Sturm et al., 2013). Importantly, EMG recordings can detect minute changes in facial expressions and do not employ subjective ratings and thus are reliable measures of facial expressions in response to emotional stimuli in clinical syndromes.

This study was designed to determine changes in arousal and facial expressiveness in patients with bvFTD and SD when exposed to emotional stimuli compared to healthy older control participants using psychophysiological measures of emotion processing. We hypothesised that skin conductance and facial EMG would be abnormal in both patient groups compared with controls when viewing emotional but not neutral stimuli. In addition, we investigated the neural correlates

underlying changes in these objective physiological measures of emotion processing.

Methods

Participants

Twenty-five bvFTD patients, 14 SD patients and 24 healthy controls were recruited from FRONTIER, the younger onset dementia clinic located in Sydney, Australia. All participants underwent neuropsychological assessment, had an MRI scan, and were assessed by an experienced behavioural neurologist. Diagnosis of bvFTD and SD was reached by the multidisciplinary team, based on current consensus diagnostic criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011).¹ All controls scored greater than 88/100 on the Addenbrooke's Cognitive Examination-III (ACE-III) (Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013b). Patients and controls were excluded based on the presence of the following: current or prior history of psychiatric illness; significant head injury; alcohol or substance abuse; presence of neurological disorder; or limited proficiency in English.

Based on a study investigating individuals with FTD, AD, and controls, effect size for the difference in arousal (i.e., skin conductance) between groups was $f = 0.45$ (Joshi et al., 2014). No studies have investigated facial EMG in FTD; however, studies in traumatic brain injury, have reported effect sizes between $f = 0.48$ and $f = 0.54$ (de Sousa et al., 2011). An a priori power analysis conducted in G*Power for an ANOVA in three groups indicated that a total sample size of 54 participants would provide 90% power to detect an effect size of $f = 0.45$.

Approval for this study was granted by the South Eastern Sydney Local Health District ethics committee. Participants or their Person Responsible provided informed written consent in accordance with the Declaration of Helsinki. Participation was voluntary, and participants were reimbursed for travel costs.

Neuropsychological assessment

All participants completed the ACE (Revised or ACE-III) as a general screener of cognitive function (Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013b; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006). All patients were assessed using the Frontotemporal Dementia Rating Scale (FRS), a dementia staging tool that assesses changes in everyday functioning and behaviours (Mioshi, Hsieh, Savage, Hornberger, & Hodges, 2010). The FRS provides an index of disease severity and an associated Rasch score, with higher Rasch scores reflecting less severe disease stage.

¹ Five of the SD patients had greater right > left anterior temporal lobe atrophy at presentation (Chan et al., 2009; Kumfor et al., 2016).

To assess overt emotion recognition, we employed the Facial Affect Selection Test (Kumfor, Sapey-Triomphe et al., 2014b; Miller et al., 2012). Participants view an array of seven faces, each expressing a different emotion (anger, disgust, fear, sadness, surprise, happiness, or neutral) across 42 trials and are asked to "Point to the _____ face." Responses are untimed, and no feedback is provided. Images were selected from the NimStim database (www.mac-brain.org), were cropped to remove nonfacial information (e.g., hair), and were converted to greyscale.

Experimental procedure

Participants were seated in a small room facing a computer screen. EMG and skin conductance electrodes were placed on the participant as detailed below. Participants were then asked to relax for 2 minutes, during which time the baseline physiological recordings were acquired.

Next, participants viewed six excerpts from six movies (120 sec each), with two positive (*When Harry met Sally* and *Mr. Bean's Christmas*), two neutral (*Birds* and *Stream* documentaries), and two negative (*My Bodyguard* and *Cry Freedom*) films, which have been previously employed in traumatic brain injury (de Sousa, McDonald, & Rushby, 2012; Rushby et al., 2013). Movie clips were presented on a PC using Presentation software in a random order. Physiological measurements were recorded for the duration of the stimulus presentations. Following each excerpt, participants rated valence and arousal of the film clip via the computerised version of the *Self-Assessment Manikin* (SAM; Lang, 1980).

Physiological recording

Facial electromyography (EMG) and skin conductance level (SCL) were measured using an 8/35 Powerlab Data Acquisition System (ADInstruments, Castle Hill, Australia). The raw data were recorded using LabChart Pro for Windows (v. 7.3.7).

EMG activity of the zygomaticus major (cheek, smiling), and the corrugator supercilii (left brow, frowning) were measured using the Fridlund and Cacioppo (1986) method. To reduce inter-electrode impedance, target sites of the skin were cleaned and abraded with NuPrep gel (Weaver & Co., Aurora, CO). Shielded 9-mm diameter, gold-plated surface electrodes were then filled with Ten 20 conductive paste (Weaver & Co., Aurora, CO) and placed bipolarly. An additional ground electrode was positioned on the upper portion of the forehead. Facial EMG signals were digitized at a sampling rate of 2,000 Hz/s and stored off-line for later quantification.

SCL was measured using an ADInstruments Model GSR Amp (FE116), using two dry, bright-plated bipolar electrodes placed on the distal volar surface of digits II and IV of the left

hand. Before each session, the signal was calibrated to detect activity in the range of 0–40 microsiemens (μ S).

Data reduction

For SCL, outliers were identified using boxplots and participants were removed from subsequent analyses (2 controls, 2 bvFTD). For EMG, eight participants were excluded due to equipment errors (channel saturation during recording) or excessive talking/movement during the task (4 controls, 1 bvFTD, 3 left-SD). Participants were monitored during data acquisition to ensure that they were attending to the stimuli throughout the task.

Mean EMG responses (zygomaticus and corrugator) and SCL signals were derived for the 2-minute baseline and from four time intervals during each of the six film clips presented (Time interval 1: 0–30s, Time interval 2: 31–60s, Time interval 3: 61–90s, and Time interval 4: 91–120s). Data for each time interval were then averaged across films for each condition (i.e., positive, neutral, negative). This approach was taken given the different time courses of EMG and SCL responses. While SCL tends to increase or decrease linearly over time, EMG tends to measure faster changes, which may be considered as individual “events,” although task demands and context also may lead to more tonic changes (de Sousa et al., 2011; Dimberg & Thunberg, 1998). In order to analyse the entire period of measurement (rather than focusing on the end of the clip for SCL or the “most emotional” part of the video for EMG), we also included time as an independent variable in the relevant analyses. Bandpass filtering was applied to the raw EMG signals to reduce the amplitude of low- and high-frequency noise (20–400 Hz) and a 50-Hz notch filter was used to decrease electrical interference. EMG signals were then rectified and smoothed using a triangular window of 500 ms. Data were expressed in microvolts/second. For both corrugator and zygomaticus muscles, EMG response magnitudes to the stimuli were expressed as a proportion of the individual’s baseline value. This method is preferred, because it considers individual differences in EMG activity, ensuring that EMG responses are comparable both at an individual level across different muscle groups and at a group level across different individuals (Van Boxtel, 2010). The difference between baseline and average SCL for each time interval was calculated for each condition (positive, neutral, negative).

Statistical analyses

Data were analysed using SPSS V. 24 (IBM, Inc., Chicago, IL). One-way analyses of variance (ANOVAs) were conducted to investigate demographics and background neuropsychological performance according to group. Where appropriate, chi-square analyses were conducted to investigate differences in categorical variables. To investigate differences in facial

expressiveness during viewing the film clips, a repeated measures ANOVA was conducted with diagnosis (bvFTD, SD, controls) as the between-subjects measure and EMG (zygomaticus, corrugator), emotion (positive, neutral, negative), and time interval (30 sec, 60 sec, 90 sec, 120 sec) as the within-subjects variables. For the SCL analyses, a separate repeated measures ANOVA was conducted with diagnosis (bvFTD, SD, controls) as the between-subjects variable and emotional film type (positive, neutral, negative) and time interval (30 sec, 60 sec, 90 sec, 120 sec) as the within-subjects variables.

SAM scores were averaged according to emotional film type (positive, neutral, negative), and separate repeated measures ANOVAs were conducted to investigate differences in film ratings for valence and arousal. All analyses were considered significant at $p < 0.05$. Sidak post-hoc corrections for multiple comparisons were employed where appropriate.

Neuroimaging

Participants underwent whole-brain structural magnetic resonance imaging (MRI) on a 3 T Phillips scanner. High-resolution T1 images were obtained using the following protocol: 256 x 256, 200 slices, 1-mm² in-plane resolution, 1-mm slice thickness, echo time/repetition time = 2.6/5.8 ms, flip angle = 8°. Brain scans were available for 16 bvFTD, 11 SD (6 left-SD, 5 right-SD), and 20 controls.

FSL voxel-based morphometry (VBM), part of the FMRIB software library package <http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html> (Smith et al., 2004) was used to analyse the MRI data (Ashburner & Friston, 2000; Mechelli, Price, Friston, & Ashburner, 2005; Woolrich et al., 2009). First, structural images were brain-extracted using BET and tissue segmentation was undertaken using automatic segmentation (FAST) (Zhang, Brady, & Smith, 2001). Then, grey matter partial volume maps were aligned to Montreal Neurological Institute standard space (MNI152) using nonlinear registration (FNIRT), which uses a *b*-spline representation of the registration warp field (Rueckert et al., 1999). A study-specific template was created and the native grey matter images were nonlinearly re-registered. Modulation of the registered partial volume maps was performed by dividing them by the Jacobian of the warp field. The modulated, segmented images were smoothed with an isotropic Gaussian kernel (sigma = 3 mm, full-width at half maximum (FWHM) = 8 mm).

A voxel-wise general linear model (GLM) was applied to investigate grey matter intensity differences using permutation-based, nonparametric statistics with 5,000 permutations per contrast (Nichols & Holmes, 2002). In the first set of analyses, differences in grey matter integrity between patient groups and controls were investigated using *t*-tests. Next, to examine neural correlates associated with facial EMG and SCL, irrespective of group membership, we created separate

GLMs. For EMG, separate GLMs were created for positive, neutral, and negative films. Here, the difference between mean zygomaticus and mean corrugator response at Time Interval 4 was computed and entered as covariates into the respective GLMs. For SCL, two GLMs were created: positive videos and negative videos. We subtracted the mean SCL at Time Interval 4 for positive and negative videos from the mean SCL when viewing neutral videos, as an index of emotional increase in SCL, which were entered into the respective GLMs. For atrophy analyses, we report threshold-free cluster enhanced results at $p < 0.05$, corrected for multiple comparisons. The analyses correlating grey matter integrity with physiological measures analyses are reported voxel-wise at $p < 0.001$ uncorrected for multiple comparisons. In addition, to control for Type 1 error, we employed a conservative cluster extent threshold of 50 contiguous voxels.

Results

Demographic and cognitive characteristics

Study groups did not differ in age or sex distribution (Table 1). Controls had more years of education than the bvFTD group ($p = 0.003$), but the two patient groups did not differ ($p = 0.552$). No difference in disease stage on the FRS was observed between patient groups ($p = 0.245$), but disease duration was shorter in the bvFTD than in the SD group ($p = 0.007$). Consistent with previous findings, both patient groups performed worse than controls on a measure of overall cognitive function (ACE: both p values < 0.001), and both groups showed worse facial emotion recognition than controls (bvFTD $p < 0.001$; SD $p = 0.001$).

Psychophysiological data

At baseline, no difference in EMG recordings of the zygomaticus or corrugator was observed across groups, and SCL was similar across groups (Table 2).

Table 2 Baseline physiological measures

	bvFTD	SD	Controls	F	p
EMG – Zygomaticus	11.7 ±14.0	8.4 ±10.7	6.6±4.2	1.31	.28
EMG – Corrugator	9.8±3.6	11.0±7.3	7.3±3.8	2.78	.07
SCL	0.6±0.8	0.4±0.6	0.1±0.6	2.08	.14

Note, values are mean ± standard deviation. Scores available for: EMG data 20 controls, 24 bvFTD, 11 SD; SCL data 22 controls, 23 bvFTD, 14 SD. EMG = electromyography; SCL = skin conductance level.

Electromyography

Analyses of EMG recordings of emotional facial expressions during the film clips revealed significant main effects of EMG location ($F(1,52) = 18.677$, $p < 0.001$, $\eta_p^2 = 0.264$), Emotion ($F(2,104) = 20.467$, $p < 0.001$, $\eta_p^2 = 0.282$) and Time ($F(3,156) = 12.166$, $p < 0.001$, $\eta_p^2 = 0.190$), but not of Diagnosis ($F(2,52) = 1.143$, $p = 0.327$, $\eta_p^2 = 0.042$; Fig. 1). Significant two-way interactions were observed between EMG and Emotion ($F(2,104) = 26.976$, $p < 0.001$, $\eta_p^2 = 0.342$), Emotion and Time ($F(6,312) = 11.821$, $p < 0.001$, $\eta_p^2 = 0.185$), but not EMG and Time ($F(3,156) = 1.839$, $p = 0.164$, $\eta_p^2 = 0.034$). In addition, a significant three-way interaction between EMG x Emotion x Time ($F(6,312) = 14.537$, $p < 0.001$, $\eta_p^2 = 0.218$) and a trend level interaction between EMG x Emotion x Diagnosis ($F(4,312) = 5.922$, $p = 0.062$, $\eta_p^2 = 0.098$) was present. Finally, the four-way interaction between EMG x Emotion x Time x Diagnosis approached significance ($F(12,312) = 2.251$, $p = 0.067$, $\eta_p^2 = 0.080$).

These interactions were further examined using within-group pairwise comparisons. Controls showed significant differences between zygomaticus and corrugator responses across all time intervals when viewing positive films (p -values < 0.001). For neutral videos, controls showed a trend for greater zygomaticus response at Time interval 1 ($p = 0.068$); however, these attenuated for the remainder of

Table 1 Demographic characteristics of the study groups

	bvFTD n = 25	SD n = 14	Controls n = 24	F	p	Post hoc
Sex (M:F)	13:12	8:6	12:12	0.18	.912	-
Age (years)	60.7±6.6	64.7±7.1	65.2±6.8	3.06	.054	-
Education (years)	11.2±2.5	12.3±3.2	13.8±2.6	5.88	.005	bvFTD < controls
Disease duration (months)	55.7±31.6	85.9±30.4	-	8.09	.007	bvFTD < SD
FRS Rasch Score	-0.45±1.5	0.19±1.66	-	1.40	.245	-
ACE Total (/100)	71.8±17.9	60.0±21.4	95.5±2.4	28.03	<.001	Patients < controls
Facial Affect Selection Test (/42)	29.5±7.7	30.6±3.7	38.8±2.5	18.78	<.001	Patients < controls

Note, values are mean ± standard deviation. ACE = Addenbrooke's Cognitive Examination; FRS = Frontotemporal dementia Rating Scale.

Fig. 1 EMG responses in bvFTD, SD, and controls when viewing emotional films. Scores are corrected for baseline EMG response. Dots represent mean values and error bars represent standard error of the mean.

* $p < 0.05$, comparing zygomaticus and corrugator response within groups at each time interval (Sidak corrected for multiple comparisons). Note, SD, positive videos, Time interval 4: $p = .054$

time (Time interval 2: $p = 0.236$; Time interval 3: $p = 0.338$; Time interval 4: $p = 0.475$). For negative films, differentiation in EMG responses in controls was observed at Time interval 4 only, with significantly greater corrugator than zygomaticus activity present ($p = 0.014$). In bvFTD, patients showed no difference between zygomaticus and corrugator activity when viewing positive films (Time interval 1: $p = 0.096$; Time interval 2: $p = 0.110$; Time interval 3: $p = 0.060$; Time interval 4: $p = 0.110$). Similarly, in both the neutral and negative conditions, no significant differences in zygomaticus vs. corrugator activity was observed at any time interval (Neutral, all p values > 0.2 ; Negative, all p values > 0.05). For the SD group, significantly greater

zygomaticus than corrugator activity was evident on all time intervals of the positive films (Time interval 1: $p = 0.006$; Time interval 2: $p = 0.007$; Time interval 3: $p = 0.016$; Time interval 4: $p = 0.054$). Unlike controls, SD also showed significantly greater zygomaticus than corrugator activity for neutral films across all time intervals (all p values ≤ 0.001). Surprisingly, greater zygomaticus activity also was observed during Time interval 1 of the negative films ($p = 0.029$), but no significant differences were found for the subsequent time intervals (Time interval 2: $p = 0.693$; Time interval 3: $p = 0.461$; Time interval 4: $p = 0.496$). Means and standard deviations are provided in the *Supplementary Materials*.

Fig. 2 Skin conductance levels during positive, negative, and neutral film stimuli over time. Scores are corrected for baseline skin conductance level. Dots represent mean values. * $p < 0.05$, comparing positive vs.

neutral and negative vs. neutral at each time interval (Sidak corrected for multiple comparisons)

Skin conductance level (difference between baseline and task)

Analyses of SCL across groups revealed no main effect of Diagnosis ($F(2,56) = 0.714$, $p = 0.494$, $\eta_p^2 = 0.025$), or Time ($F(3,168) = 0.625$, $p = 0.505$, $\eta_p^2 = 0.011$) or Emotion ($F(2,112) = 2.021$, $p = 0.137$, $\eta_p^2 = 0.035$; Fig. 2). However, the interaction between Emotion and Time was significant ($F(6,336) = 14.142$, $p < 0.001$, $\eta_p^2 = 0.202$), and the interaction between Emotion, Time, and Diagnosis approached significance ($F(12,336) = 1.889$, $p = 0.035$ (sphericity assumed; Greenhouse-Geisser correction $p = 0.099$), $\eta_p^2 = 0.063$). These interactions were explored further using within-subjects pairwise comparisons, comparing SCL for positive and negative films with neutral films at each time interval. For controls, SCL was significantly higher at both Time interval 3 and 4 for the positive compared with the neutral film (Time interval 3: $p = 0.017$; Time interval 4: $p < 0.001$) and for the negative compared to the neutral conditions (Time interval 3: $p = 0.042$; Time interval 4: $p = 0.011$). No significant differences in SCL between the positive and neutral or negative and neutral condition at any of the time intervals in the bvFTD or SD groups were observed (all p values > 0.05). No between group pairwise comparisons reached significance.

Valence and arousal SAM ratings

For valence ratings, a significant main effect of video condition was present ($F(2,118) = 290.970$, $p < 0.001$) but not of diagnosis ($F(2,59) = 1.686$, $p = 0.194$; Fig. 3). A significant interaction between video condition and diagnosis was also observed ($F(4,118) = 5.932$, $p < 0.001$). Post-hoc tests revealed that all groups rated the positive and neutral videos as more positive than negative videos (controls: positive vs. negative: $p < 0.001$; neutral vs. negative: $p < 0.001$; positive vs. neutral: $p = 0.119$; bvFTD: positive vs. negative: $p < 0.001$; neutral vs. negative: $p < 0.001$; positive vs. neutral: $p = 1.000$; SD: positive vs. negative: $p < 0.001$; neutral vs. negative: $p < 0.001$; positive vs. neutral: $p = 0.697$). Post-hoc tests also revealed significant between-group differences in ratings. Specifically, both patient groups rated positive videos as less positive than controls (bvFTD: $p = 0.034$; SD: $p = 0.001$) and negative videos as less negative than controls (bvFTD: $p = 0.034$; SD: $p = 0.053$). Ratings were similar across groups for neutral videos (bvFTD: $p = 0.902$; SD: $p = 0.524$).

For arousal ratings, a significant main effect of video condition ($F(2,118) = 145.855$, $p < 0.001$), and a significant interaction between diagnosis and video condition was observed ($F(4,118) = 2.747$, $p = 0.035$), reflecting a trend for bvFTD

Fig. 3 Valence and arousal ratings across conditions in bvFTD, SD and controls. Bars represent mean SAM ratings. Error bars represent standard error of the mean. * $p < 0.05$ compared with controls, Sidak correction for multiple comparisons.

patients to rate neutral videos as more arousing than controls ($p = 0.052$). None of the other post hoc comparisons approached significance and no main effect of diagnosis was observed ($F(2,59) = 0.012$, $p = 0.998$).

These results suggest that although the bvFTD and SD groups can categorise the video types as positive, neutral, or negative, the perceived emotional content of these video conditions is less intense than controls.

Neuroimaging

Group-wise comparisons

The clinical groups showed the typical patterns of atrophy observed in these diseases (Supplementary Fig. 1; Supplementary Table 1). Compared with controls, bvFTD showed grey matter intensity decreases in frontal and temporal regions, including the orbitofrontal and medial prefrontal cortex, frontal pole, and anterior cingulate gyrus, together with the insular cortex, temporal fusiform, inferior temporal gyrus, and temporal pole, as well as subcortical regions, including the hippocampus and amygdala. In contrast, pronounced reduction was observed in SD in the temporal regions (but $L > R$), including the temporal fusiform cortex, inferior temporal gyrus, middle temporal gyrus, and temporal pole, as well as the insular cortex, hippocampus, and amygdala. Between patient group comparisons showed greater decrease in grey matter intensity in SD than in bvFTD in the parahippocampal gyrus, extending into the temporal fusiform cortex, temporal pole, and lingual gyrus. In contrast, bvFTD showed comparatively greater grey matter intensity decrease in the frontal pole extending into the orbitofrontal and medial prefrontal cortex than the SD group.

Neural correlates of EMG

VBM analyses revealed associations between EMG activity and brain integrity that were specific to the emotional valence of the films, regardless of group membership (Fig. 4; Table 3). For positive films, zygomaticus activity was associated with grey matter integrity of the right insula. In contrast, for negative films, corrugator activity was associated with grey matter integrity of the left subcallosal/orbitofrontal cortex, left middle frontal gyrus and left temporal fusiform. Finally, for neutral films, a reverse association was observed, whereby increased zygomaticus activity was associated with lower integrity of the left parahippocampal gyrus.

Neural correlates of skin conductance levels

With regards to skin conductance, response amplitude to positive films was associated exclusively with integrity of the left temporal pole, whereas response level to negative films was

associated with integrity of the left amygdala extending into the left putamen, the left caudate, and the right superior frontal gyrus (Fig. 5; Table 4).

Discussion

Our systematic investigation demonstrated syndrome specific abnormal physiological responses to emotional film clips in the two most common presentations of FTD. Compared with healthy older adults, bvFTD patients showed an overall dampening of physiological responding, whereas SD patients showed abnormal facial expressiveness, which was discordant with the emotional content of the stimuli. In the following sections, we discuss how these results inform our understanding of these FTD syndromes in the context of contemporary theories of emotion processing.

Profiles of facial expressiveness in bvFTD and SD

Impaired ability to recognise emotions is well established in bvFTD (Bora, Velakoulis, & Walterfang, 2016; Kumfor & Piguet, 2012; Shany-Ur & Rankin, 2011); however, the mechanisms underpinning these deficits remain unresolved. We demonstrated that patients with bvFTD have blunted facial expressions in response to emotional film stimuli. While this concurs with clinical diagnostic criteria (Rascovsky et al., 2011), to our knowledge, this is the first time this symptom has been demonstrated objectively using EMG. In contrast, while SD patients also demonstrate limited changes in skin conductance, they tended to show increased zygomaticus activity in response to film stimuli, irrespective of the emotional content of the situation. Interestingly, early studies have suggested that decreased facial expressions is a hallmark of right but not left SD (Edwards-Lee et al., 1997; Perry et al., 2001).

Indeed, our neuroimaging data analyses revealed that, regardless of group membership, damage to the right insula is associated with dampened zygomaticus responses to positive film stimuli, whereas increased zygomaticus activity to neutral films was associated with lower integrity of the left parahippocampal gyrus. Some theories have suggested that the right hemisphere may be specialised for “survival-related”/energy-expenditure emotions, whereas the left hemisphere may be involved in “affiliative”/energy-enrichment emotions (Craig, 2005). In contrast, others have proposed a general right hemisphere specialisation for emotion (Schwartz, Davidson, & Maer, 1975). Our results suggest a degree of lateralisation of function for facial expressiveness. Specifically, the right hemisphere damage led to a loss of emotional expression, and left hemisphere damage resulted in reduced facial emotion modulation leading to an increase in incongruous facial expressions. Indeed, this profile is

Fig. 4 Clusters which significantly correlate with facial EMG responses to positive (MNI coordinates: $x = 38$, $y = -16$, $z = 8$), neutral (MNI coordinates: $x = -30$, $y = -28$, $z = -12$) and negative films (MNI

coordinates: $x = -22$, $y = 14$, $z = 48$) in all participants combined. VBM analyses are voxel-wise reported at $p < 0.001$ uncorrected for family-wise error. Cluster extent threshold > 50 contiguous voxels.

Table 3 Clusters associated with EMG responses to positive, neutral and negative films

Regions	Side	MNI			Voxels	
		X	Y	Z		
Positive Films (Zygomaticus – Corrugator)						
Insula cortex, extending into Heschls' gyrus	Right	36	-10	4	384	
Neutral Films (Zygomaticus – Corrugator)						
Parahippocampal gyrus (posterior division), hippocampus, extending into lingual gyrus, temporal fusiform cortex	Left	-22	-32	-32	447	
Postcentral gyrus	Left	-70	-12	14	62	
Middle temporal gyrus, anterior division	Left	-54	2	-24	55	
Negative Films (Corrugator – Zygomaticus)						
Middle frontal gyrus, extending into superior frontal gyrus	Left	-38	32	42	306	
Temporal fusiform cortex (posterior division), extending into parahippocampal gyrus (anterior division)	Left	-28	-14	-48	130	
Subcallosal cortex, orbitofrontal cortex	Left	-12	12	-18	97	

Note. All clusters reported are voxelwise $p < .001$; cluster extent threshold 50 voxels.

Fig. 5 Clusters that significantly correlate with skin conductance levels when viewing positive compared with neutral films (MNI coordinates: $x = -53$, $y = 13$, $z = -18$) and negative compared with neutral films (MNI

coordinates: $x = -18$, $y = 4$, $z = 26$) in all participants combined. VBM analyses are voxel-wise reported at $p < 0.001$ uncorrected for family wise error. Cluster extent threshold > 50 contiguous voxels.

consistent with historical reports of decreased emotional expression and emotional indifference, together with emotional flattening of emotion and anosognosia in individuals with right-sided cerebral damage (Babinski, 1914; Mills, 1912). Notably, the posterior region of the insula, which was associated with zygomaticus activity in response to positive films, is highly interconnected with the primary and secondary somatosensory-motor cortices (Deen, Pitskel, &

Pelphrey, 2010), likely reflecting a somatosensory/interoceptive role of this subregion of the insula (Craig, 2002; Deen et al., 2010).

Conversely, the increased zygomaticus activity in SD patients may reflect a loss of understanding of the emotional context, leading to inappropriate facial emotional displays. The parahippocampal cortex is proposed to play an important role in processing contextual associations (Aminoff, Kveraga, & Bar, 2013). Specifically, this region plays an important role in forming associations between conditions that have been linked over repeated exposures. Of relevance, these associations may be temporal, behavioural, or emotional (Aminoff et al., 2013). Thus, the disintegration of these contextual associations may explain the inappropriate emotional responses observed in the left SD group. Studies that examine the role of context in emotion processing in these patient groups will be essential to explore this hypothesis further (Kumfor et al., 2018).

Dampened physiological arousal in bvFTD and SD

Our skin conductance data revealed that, unlike healthy older adults, both bvFTD and SD patients show dampened autonomic responses to emotional situations. While previously

Table 4 Clusters associated with skin conductance level responses to positive and negative films

Regions	Side	MNI		Voxels	
		X	Y	Z	
Positive Films (SCL Positive – SCL Neutral)					
Temporal pole	Left	-52	14	-24	179
Negative Films (SCL Negative – SCL Neutral)					
Caudate	Left	-20	-12	22	163
Amygdala, extending into putamen	Left	-18	0	-12	104
Superior frontal gyrus	Right	24	26	48	61

Note. All clusters reported are voxelwise $p < .001$; cluster extent threshold 50 voxels.

reported in bvFTD (Joshi et al., 2014), to our knowledge, this study is the first to demonstrate reduced autonomic arousal to emotional stimuli in a pure SD group. These results contrast with a previous study, which found change in skin conductance levels in SD patients during discussion of conflict with their partner (Sturm et al., 2011). It is possible that our standardised exposure to the emotional stimuli enabled the detection of these previously unrecognised abnormalities. Autonomic arousal and emotional experience are intimately linked (Damasio et al., 1996; James, 1884; Lange, 1922; Schachter & Singer, 1962). Our data demonstrate that the impaired performance on emotion recognition tests found in bvFTD and SD is compounded by a dampening of emotional experience and arousal when exposed to situations, which typically provoke increased skin conductance in healthy adults.

Importantly, this reduced arousal in response to emotional stimuli is associated with divergent neural correlates, depending on the emotional valence of the stimuli. For negative films, reduced autonomic arousal was associated with loss of integrity of predominantly subcortical brain regions including the caudate and amygdala, as well as a small region in the right superior frontal gyrus. In healthy adults, changes in skin conductance levels during affective tasks have been associated with increased activity in a number of cortical (insula, somatosensory, cingulate, prefrontal, and parietal cortices) and subcortical (thalamus, amygdala, thalamus, putamen) brain regions (Beissner, Meissner, Bär, & Napadow, 2013). We saw some degree of overlap with our results, suggesting that the reduction in sympathetic responses to emotional stimuli as measured via skin conductance reflects a pathological disturbance in the autonomic brain in bvFTD and SD. The relationship between abnormal skin conductance and integrity of the caudate was somewhat unexpected, as previous studies have suggested that the caudate is predominantly (but not always) involved in parasympathetic as opposed to sympathetic regulation (Beissner et al., 2013). Atrophy of the caudate is found in bvFTD (and to a lesser degree in SD) and has been associated with increased apathy, disinhibition, and aberrant motor behaviours (Halabi et al., 2013). Thus, our neuroimaging results indicate that subcortical striatal atrophy in FTD is associated with abnormal arousal responses to emotionally evocative stimuli. Whether reduced arousal is a mediating factor in the emergence of abnormal behaviours, such as disinhibition and apathy, in these clinical syndromes is an avenue which warrants future investigation.

In contrast, reduced skin conductance in response to positive films was associated with integrity of the left temporal pole. The regions associated with abnormal skin conductance response in our study were largely left-lateralised (except for the right superior frontal gyrus). Craig (2005) has proposed that the right forebrain is predominantly associated with sympathetic activity, i.e., withdrawal behaviour, arousal, danger,

and negative affect. Conversely, the left forebrain is thought to be predominantly associated with parasympathetic activity, i.e., affiliative emotions such as approach, nourishment, safety, and positive affect (Craig, 2005). Thus, the finding that lower skin conductance in response to negative videos was associated with integrity of the right superior frontal gyrus, largely concurs with this theory. However, associations between the left temporal pole and response to positive videos, are more difficult to reconcile. The temporal pole is known to be the hub for semantic processing (Patterson, Nestor, & Rogers, 2007) and is one of the earliest regions undergoing atrophy in SD (Kumfor et al., 2016; Mion et al., 2010). Our neuroimaging results suggest that while abnormal arousal to negative films reflects a disturbance of the autonomic brain, disrupted autonomic responses to positive films appears to reflect a degree of semantic knowledge loss. Importantly, much of the previous work investigating lateralisation of function has been based on functional imaging studies and patterns of activation in healthy adults. Here, the use of a lesion model demonstrates that damage beyond regions typically associated with emotional arousal can lead to inappropriate physiological responding. That is, if an individual is no longer able to understand the semantic meaning of emotional information, then the associated physiological response appears to be compromised. These results demonstrate the multifactorial aetiology of disrupted emotion processing in FTD. From a broader perspective, our results demonstrate the complementary nature of lesion models and functional imaging in healthy adults to uncover the implications of damage to components of this complex brain network. Future studies which directly compare right- and left-lateralised SD (e.g., Kumfor et al., 2016) will be important to shed further light on the potential lateralisation of function, with respect to emotion processing.

Decoupling between cognitive appraisal and emotional experience

Finally, our investigations revealed that bvFTD and SD patients subjectively interpret emotional stimuli as less intense than healthy older adults, although their ability to determine whether stimuli are generally positive or negative is maintained, which concurs with our previous research (Kumfor, Irish, Hodges, & Piguet, 2013). We suggest that in patients with bvFTD and SD, a decoupling between the emotional (physiological) experience and cognitive appraisal of a stimulus occurs. That is, while patients may retain the capacity to cognitively appraise that a person being shot is “negative” and “arousing,” they do not seem to experience the equivalent increase in physiological arousal. Considering the dampening of arousal demonstrated, it is plausible that this reduction in emotional intensity reflects a change in the emotional experience of these patients. We propose that this decoupling underpins the social symptoms observed in bvFTD and SD.

Limitations and future directions

One of the strengths of this study was that we examined bvFTD and SD as separate groups and examined our physiological measures of interest independently. However, it is now well recognised that the clinical syndrome of semantic dementia—due to anterior temporal lobe atrophy—can present differently depending on whether the atrophy is more left or right lateralised (Chan et al., 2009; Kumfor et al., 2016), with patients with more right lateralised atrophy showing more behavioural and social changes, as well as prosopagnosia (Irish, Kumfor, Hodges, & Piguet, 2013; Josephs et al., 2009; Kamminga et al., 2015). It will be interesting for future studies to examine the physiological profile of these different SD subtypes to better understand the potential role of hemispheric lateralisation of the autonomic brain. In addition, the stimuli used here, while emotionally provocative, have relatively little social demands (Schilbach et al., 2013). Future studies that measure physiological arousal while these patients engage in social situations will help to enhance our understanding of how changes in physiological arousal contribute to the social and behavioural changes observed in these clinical syndromes. It should be noted that disease duration differed between bvFTD and SD, reflecting the differences in survival in these clinical syndromes (which is almost twice as long in SD as in bvFTD) (Hodges, Davies, Xuereb, Kril, & Halliday, 2003; Hodges et al., 2010). Importantly, no differences were seen on the FRS, indicating that both bvFTD and SD groups were at a similar disease stage. Thus, we are confident that the different profiles seen in bvFTD and SD are unlikely to be accounted for by differences in disease severity.

Conclusions

This study demonstrates that the emotion processing impairments that are now well recognised in bvFTD and SD also can be detected using objective, noninvasive, psychophysiological measures, which are not confounded by cognitive impairments or task demands. This represents an important advancement in the capacity to detect emotion processing impairments early in the disease process and potentially before onset of obvious clinical symptoms (Borroni et al., 2017). In addition, our results provide support for the integration between internal body states, the autonomic brain, and emotion processing, which will help to refine theoretical models of human emotion and behaviour.

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Compliance with ethical standards

Conflicts of interest None to declare.

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