

# Self-conscious emotion deficits in frontotemporal lobar degeneration

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**Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disease associated with dramatic changes in emotion. The precise nature of these changes is not fully understood; however, we believe that the most salient losses relate to self-relevant processing. Thus, FTLD patients exhibit emotional changes that are consistent with a reduction in self-monitoring, self-awareness and the ability to place the self in a social context. In contrast, other more primitive aspects of the emotional system may remain relatively intact. The startle response is a useful way to examine the precise nature of emotional deficits in neurological patients. In addition to a stereotyped defensive response (characterized by negative emotional facial behaviour and physiological activation), in many individuals it also evokes embarrassment, a self-conscious emotional response. Embarrassment seems to occur as the person becomes aware that the reaction to the startle was excessive and was observed by others. Because the self-conscious response depends on certain regions in frontal cortex, we expected that FTLD patients would have specific deficits in their self-conscious response. To test this notion, we examined the response of 30 FTLD patients and 23 cognitively normal controls to a loud, unexpected acoustic startle stimulus (115-dB burst of white noise). Emotional behaviours were measured along with an assessment of somatic, electrodermal, cardiovascular and respiratory responses. Results indicated that FTLD patients and controls were similar in terms of physiological responses and negative emotional facial behaviour to the startle, indicating that the defensive aspect of the startle was preserved. However, there were profound differences in the self-conscious response. FTLD patients showed significantly fewer facial signs of embarrassment than controls. This deficit in self-conscious response could not be explained by sex, cognitive status, age, education, medication, or differences in the negative emotional behaviour or physiological response. Thus, the emotional deficit in FTLD patients' response to the startle suggests a reduction in self-consciousness. These findings suggest that the emotional deficit in FTLD may be most profound in higher-order processes akin to those involved in the generation of embarrassment. These deficits are consistent with neural loss in the medial prefrontal cortex, which may play an important role in the production of self-conscious emotions. Disrupted self-conscious emotions in FTLD patients may have clinical importance because these deficits may underlie some of the socially inappropriate behaviours that are common in these patients.**

**Keywords:** FTLD; autonomic nervous system; emotion; frontal lobe; behaviour

**Abbreviations:** FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration; MMSE = Mini-Mental State Examination; mPFC = medial prefrontal cortex

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## Introduction

Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disease that selectively affects the anterior portions (i.e. frontal lobes, temporal lobes and amygdala) of the brain (Neary *et al.*, 1998), regions that are thought to be important for our navigation of the social and emotional world (Stuss

and Levine, 2002). FTLD typically has its onset in mid-adulthood, is estimated to account for up to 20% of all cases of pre-senile dementia (Miller *et al.*, 1998) and has a prevalence similar to that of early-onset Alzheimer's disease (Ratnavalli *et al.*, 2002). The histological features of FTLD

are varied (Stevens *et al.*, 1998; McKhann *et al.*, 2001; Lipton *et al.*, 2004; Davies *et al.*, 2005; Johnson *et al.*, 2005). FTLD is a diagnostic category that includes three clinical subtypes: frontotemporal dementia (FTD), semantic dementia and progressive aphasia (Neary *et al.*, 1998). Although each subtype has a distinct pattern of cognitive, behavioural and emotional symptoms, there is also much overlap in the clinical presentation and neuroanatomical profile.

FTLD ravages social functioning. In other dementias, such as Alzheimer's disease, the initial symptoms involve primarily cognitive processes including memory and visuospatial abilities while social and emotional processes may remain relatively preserved (Swartz *et al.*, 1997; Mendez *et al.*, 1998). In FTLD, in contrast, memory and visuospatial abilities are often relatively spared until even quite late in the disease when patients require nursing home care (Gregory *et al.*, 1999); however, deficits in social behaviour typically are seen throughout the disease progression and can be quite profound (Gregory *et al.*, 1999; Williams *et al.*, 2005). FTLD patients often behave inappropriately and with disregard for social rules (Miller *et al.*, 1997) and have trouble comprehending other people's perspectives (Gregory *et al.*, 2002) and emotions (Lavenu *et al.*, 1999; Rosen *et al.*, 2002; Rankin *et al.*, 2005*b*). FTLD patients also have difficulty with self-awareness, showing an inability to recognize even dramatic changes in their own personality (Rankin *et al.*, 2005*a*) and identity (Miller *et al.*, 2001).

Emotions can be reflex-like and require minimal cognitive processing (e.g. the fear one feels when awakened by an unfamiliar sound at night), or complex, requiring higher-order processing of context, self, others and social rules (e.g. the embarrassment one feels after greeting a colleague by the wrong name at a conference). Although it is well documented that FTLD disrupts emotional functioning, the precise nature of this disruption is not known. Most existing research on emotional functioning in FTLD has focused on a particular emotional process, the ability to identify another person's emotions from photographs (Lavenu *et al.*, 1999; Rosen *et al.*, 2002). Only one previous study from our laboratory by KHW Werner *et al.* (in review) evaluated the emotional responses of FTLD patients *in vivo*. This study confirmed that FTLD patients had trouble identifying the emotions being experienced by characters in films, but found that simple emotional reactivity (i.e. self-report, facial and autonomic nervous system responses) to the films remained intact. Thus, these findings suggest that there may be certain areas of emotional functioning that are disrupted in FTLD and others that are preserved.

### Self-conscious emotion disruption?

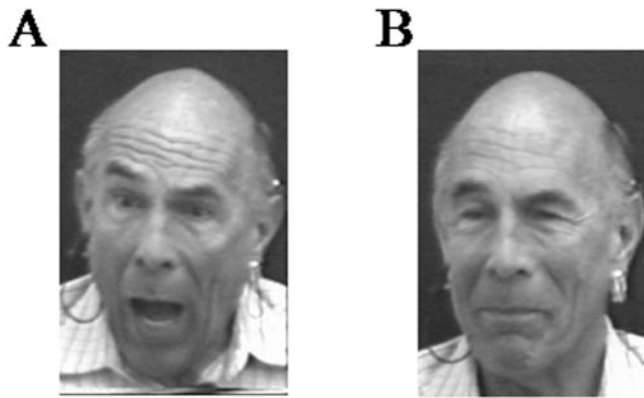
Self-consciousness is thought to be unique to humans and certain great apes (Gallup, 1982). Self-conscious emotions (e.g. embarrassment, pride, guilt, shame) probably evolved to preserve social networks (Parker, 1998) by facilitating the reparation of disrupted social bonds (Keltner and Buswell,

1997; Tangney, 1999). For example, embarrassment occurs as one reflects on the self through the eyes of others in the face of possible negative evaluation (Lewis, 1995) and promotes appeasement behaviour in other group members (Keltner and Buswell, 1997; Keltner and Anderson, 2000). Self-conscious emotions appear relatively late in ontogeny, not emerging until the requisite social cognitive abilities, such as the ability to form mental representations of self, others and social norms have developed (Lewis *et al.*, 1989).

Self-conscious emotions rely on complicated, distributed brain networks. Self-awareness, an integral component of self-conscious emotion, activates medial prefrontal cortex (mPFC) (Kircher *et al.*, 2000; Berthoz *et al.*, 2002; Johnson *et al.*, 2002; Kelley *et al.*, 2002; Zysset *et al.*, 2002; Fossati *et al.*, 2004; Takahashi *et al.*, 2004; Ochsner *et al.*, 2005). Self-awareness involves the mPFC during 'active' recollection of one's past (Fink *et al.*, 1996; Maddock *et al.*, 2001) as well as during 'passive' self-reflection that occurs when the mind is free to wander (Gusnard and Raichle, 2001; Raichle *et al.*, 2001). The mPFC has many reciprocal connections with brain regions that are important for gauging physiological states (Allman *et al.*, 2001) and is thought to play a critical role in linking internal feeling states with environmental contexts (Bechara *et al.*, 2000). Deficits in self-awareness have been reported in several psychopathological disorders that putatively involve frontal lobe dysfunction including autism (Frith and Frith, 1999; Carper and Courchesne, 2000; Toichi *et al.*, 2002) and schizophrenia (Pini *et al.*, 2001; Medalia and Lim, 2004; Suzuki *et al.*, 2005). Therefore, neural loss in the frontal lobes caused by neurodegenerative disease may also have deleterious effects on self-awareness and, thus, self-conscious emotions.

### Acoustic startle: elicitor of two types of emotional responses

In the present study, we used a single stimulus, the acoustic startle, to examine both negative and self-conscious emotional responding in FTLD patients. Early studies that utilized the acoustic startle administered it at a sufficiently aversive volume so as to produce a defensive, reflexive response (Sokolov, 1963). In more recent years, a less noxious version of the startle stimulus (a lower amplitude, repeatedly administered 'probe' stimulus) has gained popularity in studies of how emotional states modulate certain aspects of the startle reflex such as the eye-blink (Lang *et al.*, 1990). In the present study, we returned to the older tradition, using a 115-dB aversive acoustic stimulus that is ~15 times louder than those typically used in startle probe studies. This enabled us to examine both (i) the negative emotional response, a fairly stereotypical defensive reaction (Ekman *et al.*, 1985) and (ii) the self-conscious response, a reaction that unfolds as one becomes aware of, appraises and reacts to one's defensive response (Ekman *et al.*, 1985). This appraisal process is somewhat idiosyncratic;



**Fig. 1** Behavioural examples of a control participant's startle response. **(A)** Negative emotional behaviour (e.g. eyes widened, jaw dropped, shoulders raised). **(B)** Self-conscious emotional behaviour (e.g. smile suppression, as indexed by lip tightening). (Informed consent for the publication of these images was obtained from the participant.)

some individuals display anger or disgust, but most show self-conscious emotional behaviour (e.g. embarrassed smiling, nervous laughter; *see* Fig. 1 for examples).

The defensive reaction to the startle stimulus is thought to have evolved to protect an organism's physical integrity when faced with a potential threat (Ekman *et al.*, 1985). This response is phylogenetically old, as evidenced by its existence in quite simple organisms (Kandel, 1997), vertebrates (Cohen, 1974) and mammals (LeDoux and Phelps, 2000). In humans, the startle response is typically elicited in the laboratory with a loud, aversive noise that occurs without warning. It is characterized by a behavioural display that includes lip stretches, eye closures, neck stretches, shoulder raises, forward lunges, head jerks and torso movements (Ekman *et al.*, 1985). Facial expressions and subjective experience of negative emotions such as fear and surprise are also typical (Roberts *et al.*, 2004). Although neurophysiologists often view the startle response as a reflex, detailed analysis of its timing, duration and behavioural displays reveal that it shares characteristics of emotions as well (Ekman *et al.*, 1985).

The basic startle response has been associated with sub-cortical brainstem networks. The origin of the startle response is thought to be in the nucleus reticularis pontis caudalis of the brainstem (Davis *et al.*, 1982), a region that relays signals both down the spinal cord via the reticulospinal tract and up to the cortex (Brown *et al.*, 1991; Kofler *et al.*, 2001). Bilateral lesions of this region abolish the reflexive startle response in animals (Davis *et al.*, 1982). Humans with neurodegenerative diseases that affect the brainstem (e.g. parkinsonian disorders such as progressive supranuclear palsy) have abnormal startle responses, which may result from interrupted cortical projections to the nuclei of the reticular formation in addition to disturbances in the brainstem (Valdeoriola *et al.*, 1997).

Differences between the brain regions associated with basic aspects of the startle response and the regions associated with self-consciousness (reviewed earlier) open the possibility that in diseases such as FTLD certain aspects of the startle could be disrupted while others could be preserved. Specifically, we predicted that the physiological and negative emotional aspects of the startle response would remain intact in FTLD patients, while the self-conscious aspects would be diminished. Previous startle research with patients has not distinguished between the different aspects of the startle response; however, our reading of these studies suggests that the basic aspects of the startle response remain intact in patients with brain damage in the orbitofrontal cortex (Roberts *et al.*, 2004) and amygdala (Tranel and Hyman, 1990; Bechara *et al.*, 1995; LaBar *et al.*, 1995), regions that are also affected in FTLD. In the realm of self-conscious emotional responding, there has been one study showing inappropriate self-conscious emotions in orbitofrontal patients (Beer *et al.*, 2003), but no studies of FTLD patients. However, semi-structured interviews with informants (e.g. spouses, caregivers) have found a lack of self-conscious emotions (i.e. embarrassment) to be ubiquitous in FTLD (Snowden *et al.*, 2001). These observations, combined with the vulnerability of brain regions thought to be important for self-awareness, led to our hypothesis that the self-conscious aspects of the startle response would be selectively disrupted in FTLD.

## Methods

### Participants

Thirty patients diagnosed with FTLD and 23 cognitively normal control participants were studied. Patients and controls were extensively evaluated (neurological testing, neuropsychological testing, blood, structural magnetic resonance imaging) at the University of California, San Francisco Memory and Aging Center. Brain imaging was done at the San Francisco Veterans' Administration Hospital. All patients met diagnostic criteria (Neary *et al.*, 1998) for FTLD [FTD ( $N = 20$ ) or semantic dementia ( $N = 10$ ) subtypes]. No controls had a previous history of neurological or psychiatric disorder. The mean age of the patients was 61.5 years [standard deviation (SD) = 7.3 years], and the mean age of the controls was 66.0 years (SD = 7.9 years). The patient group consisted of 83.3% males, and the control group, 47.8% males. All participants were European American except for one patient and one control who were Chinese American. Mean education levels were 16.7 years (SD = 2.4) for the patient group and 17.1 (SD = 2.0) for the control group.

All participants were paid \$30 for an ~6-h laboratory session.

### Clinical descriptions of the participants

Clinical evaluations and neuropsychological testing were completed for FTLD patients and controls in close proximity to the time of emotional assessment (within 3 months for patients, 1 year for controls).

*Mini-Mental State Examination (MMSE)*. Cognitive abilities were preliminarily assessed with the MMSE (Folstein *et al.*, 1975). Patients' mean score was 25.4 (SD = 3.8), which places

them in the mild range of impairment. Controls scored near ceiling with a mean of 29.7 (SD = 0.5).

**Clinical Dementia Rating Scale (CDR).** Caregivers were interviewed in order to obtain a CDR score for each participant. The CDR requires a semi-structured interview with an informant to be conducted by a trained evaluator to rate the participant's day-to-day functioning. FTLD patients' scores placed them in the mild range of functional impairment ( $M = 0.92$ ,  $SD = 0.55$ ). Controls were within the normal range ( $M = 0.04$ ,  $SD = 0.14$ ).

**Neuropsychiatric Inventory (NPI).** The NPI is an informant-based scale that assesses the frequency and severity of psychopathological symptoms in dementia patients (Cummins *et al.*, 1994). Controls were in the normal range on all measures; thus, only data for the FTLD patients ( $n = 25$ ) will be reported here. FTLD patients' mean total NPI score was 32.8 (SD = 18.9), which indicates a moderate level of psychopathological symptoms. Approximately half of FTLD patients were reported to exhibit emotional deficits and decreased social interest: 44% of patients were described as lacking affection and emotion, 48% were described as having lost interest in the activities and plans of others, 44% were described as having lost interest in family members or friends and 48% were described as losing their enthusiasm for their usual interests.

**Medications.** Medications that participants were taking on the day of emotional testing were determined. Those that were thought to have a possible effect on emotional responding [serotonin reuptake inhibitors (SSRIs), tricyclics, miscellaneous anti-depressants, monoamine oxidase inhibitors, lithium, anti-psychotics, atypical anti-psychotics, acetylcholinesterase inhibitors, glutamate agonists, benzodiazepines, dopamine agonists, barbituates, antiepileptics, psychostimulants, anticholinergics, beta blockers] were tallied. This revealed that 13% of controls and 83% of patients were on one or more of these medications. The most common type for the FTLD patients was SSRIs.

**Bilateral lobar volumes.** Volumes for the frontal, parietal, temporal and occipital lobes were obtained using the BRAINS2 software package (University of Iowa Image Processing Lab). BRAINS2 also provides a validated method for automated detection of lobar volumes based on registration of images in standardized space (Magnotta *et al.*, 2002). Lobar volumes were corrected for head size using the total intracranial volume (brain plus CSF volumes). A comparison of these standardized lobar volumes between FTLD patients ( $N = 27$ ) and controls ( $N = 16$ ) revealed that, as expected, FTLD patients had significantly less left frontal [ $t(41) = -2.46$ ,  $P < 0.05$ ], right frontal [ $t(41) = -1.87$ ,  $P = 0.07$ ], left temporal [ $t(40.7) = -1.99$ ,  $P = 0.053$ ] and right temporal [ $t(39.1) = -1.80$ ,  $P = 0.08$ ] lobe tissue than controls. There were no differences between FTLD patients and controls in bilateral parietal [right:  $t(41) = -0.26$ , ns; left:  $t(41) = -0.21$ , ns] or occipital [right:  $t(41) = -0.63$ , ns; left:  $t(41) = 0.95$ , ns] tissue volumes. An analysis of FTLD subtypes (18 FTD, 8 semantic dementia) revealed that FTD patients had less right frontal lobe tissue than semantic dementia patients [ $t(24) = -2.16$ ,  $P < 0.05$ ], and semantic dementia patients had less left temporal lobe tissue than FTD patients [ $t(24) = 2.44$ ,  $P < 0.05$ ].

## General procedure

Participants were assessed at the University of California, Berkeley. Upon arrival, participants signed consent forms (approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley) that delineated the experimental tasks (including 'hearing a loud noise'). For FTLD participants, both

patients and caregivers signed the consent forms. An additional consent form regarding the future use of the videotapes was also presented but was not signed until the end of testing so that all participants would know exactly what had been recorded. Participants completed a health checklist regarding information about their medications, caffeine and alcohol intake, and recent sleep patterns to ensure that they had not taken substances or engaged in activities that would disrupt their normal physiological responses. Participants were seated in a comfortable chair in a well-lit, 3 × 6 m experiment room where an experimenter attached physiological sensors and briefly oriented them to the procedures.

## Experimental task: unanticipated acoustic startle

All stimuli were shown on a 21-in colour television monitor at a distance of 1.75 m from the participant. Participants were told to relax and watch the television screen but were not told what the task would consist of. An 'X' appeared on the television screen when the pre-trial baseline began and remained in view for 60 s. After 60 s, the startle stimulus (115-dB, 100-ms burst of white noise, akin to a gunshot) was presented without warning using hidden speakers located directly behind each participant's head.

## Measures

### Physiological responding

Physiological measures were monitored continuously using a Grass Model 7 polygraph, a computer with analogue-to-digital capability, and an online data acquisition software package written by one of the authors (R.W.L.). The software computed second-by-second averages for each measure: (i) heart rate (Beckman miniature electrodes with Redux paste were placed in a bipolar configuration on opposite sides of the participant's chest; the inter-beat interval was calculated as the interval, in milliseconds, between successive R waves), (ii) finger pulse amplitude (a UFI photoplethysmograph recorded the amplitude of blood volume in the finger using a photocell taped to the distal phalange of the index finger of the non-dominant hand), (iii) finger pulse transmission time (the time interval in milliseconds was measured between the R wave of the electrocardiogram (EKG) and the upstroke of the peripheral pulse at the finger site, recorded from the distal phalanx of the index finger of the non-dominant hand), (iv) ear pulse transmission time (a UFI photoplethysmograph attached to the right earlobe recorded the volume of blood in the ear, and the time interval in milliseconds was measured between the R wave of the EKG and the upstroke of peripheral pulse at the ear site), (v) systolic blood pressure (a blood pressure cuff was placed on the distal phalange of the non-dominant hand and continuously recorded the systolic blood pressure using an Ohmeda Finapres 2300), (vi) diastolic blood pressure (a blood pressure cuff was placed on the distal phalange of the non-dominant hand and continuously recorded the diastolic blood pressure), (vii) skin conductance [a constant-voltage device was used to pass a small voltage between Beckman regular electrodes (using an electrolyte of sodium chloride in unibase) attached to the palmar surface of the middle phalanges of the ring and index fingers of the non-dominant hand], (viii) general somatic activity (an electromechanical transducer attached to the platform under the participant's chair generated an electrical signal proportional to the amount of movement in any direction), (ix) respiration period (a pneumatic bellows was stretched around the thoracic region, and

the inter-cycle interval was measured in milliseconds between successive inspirations), (x) respiration depth (the point of the maximum inspiration minus the point of maximum expiration was determined from respiratory tracing), (xi) respiratory sinus arrhythmia (the rhythmic oscillation in heart period that accompanies breathing, which is an index of vagal control of the heart, was measured) and (xii) finger temperature (a thermistor attached to the distal phalange of the little finger of the non-dominant hand recorded temperature in degrees Fahrenheit).

These 12 measures were selected to provide a broad index of the activity of physiological systems important to emotional responding: cardiac, vascular, electrodermal, respiratory and striate muscle.

### Facial behaviour

All participants were videotaped continuously with a remotely controlled, high-resolution video camera that was partially concealed in the experiment room. Videotape timing was synchronized to the physiological measures using a system that inserted an invisible time-stamp on each video frame. Videotapes were later coded by a team of trained undergraduate coders with a modified version of the Expressive Emotional Behavior Coding (Gross and Levenson, 1993), which is based on the Facial Action Coding System (Ekman and Friesen, 1978). Coders, blind to participant diagnosis and to the nature of the trial, coded each second for nine emotional behaviours (anger, disgust, happiness, contempt, sadness, disgust, embarrassment, fear, surprise) on a 0–3 intensity scale. The code for embarrassment was based on Keltner and Buswell's (1997) description (i.e. gaze aversion, smiling and laughter, smile suppression, blushing, face-touches). For each participant, a total of 41 s was coded, which included a 20-s pre-startle period, the second in which the startle occurred, and a 20-s post-startle period. Inter-coder reliability was high (intra-class correlation coefficient = 0.76). As noted below, only the coding of the 17-s period starting with the startle was used for the analyses in this paper. This enabled us to examine behaviour during the startle (which lasted ~2 s) and immediately after (15 s).

### Data reduction

Physiological and behavioural data were analysed during a 17-s period starting with the 1-s period in which the startle occurred and continuing for the next sixteen 1-s periods. On the basis of our past experience, this time period is adequate to capture the entire startle response including any self-conscious reactions. Physiological data during the 60 s before the startle were also analysed to enable correction for pre-startle baseline levels.

### Physiological responding

Physiological reactivity scores were computed for each measure by subtracting the average level for the 60-s pre-startle baseline period from the averaged level during the 17-s startle period. To provide a single, more reliable measure of overall peripheral physiological responding, a composite score was calculated that comprised all physiological measures. To calculate this composite, standardized scores were computed for each physiological measure and reverse-scored as needed (i.e. cardiac inter-beat interval, finger pulse amplitude, finger pulse transmission time, ear pulse transmission time, respiration period) so that larger values reflected greater physiological arousal. The standardized scores were then averaged,

which resulted in a single physiological reactivity score for each participant.

### Facial behaviour

For each emotional facial behaviour, the intensity scores for each occurrence during the 17-s startle period were summed. A composite score for negative emotional behaviour was computed by summing the scores for fear, surprise, sadness, disgust and anger. The score for the embarrassment code was used to indicate self-conscious emotional responding. Thus, we ended up with two behavioural scores for each participant: negative emotional behaviour and self-conscious behaviour. An analysis of outliers revealed that there were four instances (all FTLD patients) where scores were >3 SD from the group mean for that score. These four data points were not included in further analyses.

## Results

Because our patient and control groups had different proportions of males and females, we computed 2 (FTLD versus control)  $\times$  2 (men versus women) analyses of covariance (ANCOVA), which enabled us to evaluate main effects of diagnosis and sex, and their interaction. Unless otherwise indicated, in all of our analyses the covariates were age, MMSE scores and years of education.

### Physiological responding

We predicted that FTLD patients would have an intact physiological response to the startle. On using 2 (FTLD versus control)  $\times$  2 (men versus women) ANCOVA, we found that our results were consistent with this prediction. On using the physiological composite score, we found no differences between the physiological responses of FTLD patients and controls [ $F(1, 43) = 0.62$ , ns]. Moreover, we found no indication of sex differences insofar as both the main effect for sex [ $F(1, 43) = 0.87$ , ns] and the sex  $\times$  diagnosis interaction [ $F(1, 43) = 1.82$ , ns] were not significant. Among the covariates, education [ $F(1, 45) = 4.23$ ,  $P < 0.05$ ] and age [ $F(1, 45) = 5.78$ ,  $P < 0.05$ ] both explained significant amounts of the variance in physiological responding with greater education and greater age associated with smaller physiological responses. Although the primary analysis focused on the physiological composite score, an analysis of the individual physiological measures also revealed no differences between FTLD patients and controls. In Table 1 non-standardized group means are presented for each physiological measure.

### Negative emotional behaviour

We predicted that FTLD patients would show a negative behavioural response to the startle that was similar to that of controls. On using a 2 (FTLD versus control)  $\times$  2 (men versus women) ANCOVA, we found that our results were consistent with this prediction. On using the negative emotional behavioural composite, we found that there

**Table 1** Group means of physiological responding in individual channels (corrected for pre-startle baseline levels)

	Controls		FTLD	
	Mean	SE	Mean	SE
Cardiac inter-beat interval (ms)	924.2	35.6	823.7	30.5
Somatic activity (units)	3.5	0.6	4.7	0.7
Skin conductance ( $\mu$ mhos)	3.6	0.4	2.3	0.4
Finger pulse transit time (ms)	279.4	7.4	269.2	6.5
Finger pulse amplitude (units)	6.3	1.0	5.2	0.9
Ear pulse transit time (ms)	211.1	7.6	188.1	5.0
Temperature (degrees Fahrenheit)	85.0	1.4	86.2	1.2
Respiration period (ms)	3447.9	517.5	2894.4	335.8
Respiration depth (units)	294.0	48.1	251.7	45.3
Respiratory sinus arrhythmia (ms)	47.4	15.8	25.8	9.2
Systolic blood pressure (mmHg)	136.2	0.3	139.3	3.3
Diastolic blood pressure (mmHg)	78.0	1.9	87.1	2.2

were no differences between FTLD patients and controls [ $F(1, 43) = 0.49$ , ns]. Moreover, we found no significant sex differences; both the main effect of sex [ $F(1, 43) = 3.25$ ,  $P = 0.08$ ] and the sex  $\times$  diagnosis interaction [ $F(1, 43) = 1.27$ , ns] were not significant. Analysis of the specific emotion codes revealed no differences in sadness [ $F(1, 44) = 0.13$ , ns], surprise [ $F(1, 44) = 0.00$ , ns] or disgust [ $F(1, 44) = 0.01$ , ns]. However, controls showed more fear behaviour than FTLD patients [ $F(1, 44) = 7.71$ ,  $P < 0.01$ ], and FTLD patients showed more anger [ $F(1, 44) = 4.29$ ,  $P < 0.05$ ] than controls.

### Self-conscious emotional behaviour

We predicted that FTLD patients would show deficits in self-conscious behaviour compared with controls. On using a non-parametric test of proportions, we found that the 6.7% of FTLD patients who showed a self-conscious response was significantly smaller than the 34.8% of controls who showed this response ( $z = 2.2$ ,  $P < 0.05$ ). Our 2 (FTLD versus control)  $\times$  2 (men versus women) ANCOVA was also consistent with this finding, revealing that FTLD patients showed significantly less self-conscious behaviour than controls [ $F(1, 43) = 5.41$ ,  $P < 0.05$ ]. There was no indication of sex differences; both the main effect for sex [ $F(1, 43) = 0.03$ , ns] and the sex  $\times$  diagnosis interaction [ $F(1, 43) = 0.06$ , ns] were not significant.

### Additional covariates: medications and negative emotions

We conducted several additional analyses to ensure that the deficit in self-conscious emotional behaviour we found in FTLD patients could not be accounted for by other factors.

Many FTLD patients and some of the controls in our sample were taking medications that might have affected their emotional responding; thus, we determined whether medication usage could have explained the found differences

between FTLD patients and controls in self-conscious behaviour. We computed a one-way ANCOVA (FTLD versus control) in which the number of relevant medications that were being taken by each participant was used as a covariate. Even after controlling for number of medications, FTLD patients still showed less self-conscious behaviour than controls [ $F(1, 47) = 5.91$ ,  $P < 0.05$ ].

As noted earlier, there was a difference between FTLD patients and controls in their discrete negative emotional behaviour (FTLD showed less fear and more anger than controls). To ensure that deficits in self-conscious emotion did not result from differences in other aspects of their emotional response, we computed a one-way ANCOVA (FTLD versus control) using negative emotional behaviour and physiological response as covariates. FTLD patients still showed less self-conscious behaviour than controls [ $F(1, 45) = 13.43$ ,  $P < 0.01$ ].

### Post hoc analyses of FTLD subtypes

We conducted *post hoc* analyses to explore whether there were subtype differences (FTD versus semantic dementia) within our FTLD group. We computed a 2 (FTD versus semantic dementia)  $\times$  2 (men versus women) ANCOVA with our original covariates of age, MMSE and years of education. FTD and semantic dementia patients did not differ in their physiological responding [ $F(1, 21) = 0.30$ , ns]; negative emotional behaviour [ $F(1, 20) = 1.18$ , ns]; or self-conscious behaviour [ $F(1, 20) = 1.69$ , ns].

### Discussion

Emotion encompasses a spectrum of responses ranging from simple to complex. Although it has been well documented that FTLD is a disease that disrupts emotional functioning, the precise nature of this disruption has not been well documented. Previous studies of emotional functioning in FTLD patients have primarily assessed the ability to recognize emotions in photographs of facial expressions. Deficits in self-conscious emotions, arguably an important contributor to the inappropriate social behaviour seen in the clinical syndrome, have not been assessed at all. Thus, the present study is unique in several ways including measuring multiple aspects of emotional responding *in vivo* in a controlled laboratory setting, assessing multiple indices of emotion (i.e. physiology and behaviour) and evaluating multiple types of emotion (i.e. negative and self-conscious emotions). This study reflects our view that the emotion system has multiple components that are differentially vulnerable to disease processes (Levenson *et al.*, 2006). In the present study, we expected that the frontal neural loss in FTLD would produce significant loss in the realm of self-conscious emotions while sparing simple emotional responding.

Our results confirmed these expectations. Using an acoustic startle stimulus that produces both negative

emotional and self-conscious emotional response, we found preserved peripheral physiological response and negative emotional behaviour, but diminished self-conscious emotional behavioural in FTLD patients compared with controls. These findings could not be explained by sex, cognitive status, age, education, medication or differences in the negative emotional behaviour or physiological response.

We believe that the deficit in self-conscious emotional behaviour results from loss of higher-order social cognitive processes that are involved in self-monitoring, viewing oneself from an observer's perspective and evaluating oneself in relation to social standards. Existing research suggests that FTLD patients do have impairments in related realms including (i) inability to self-reflect and to have insight into their personalities (Eslinger *et al.*, 2005; Rankin *et al.*, 2005a), (ii) difficulty intuiting other people's perspectives (Gregory *et al.*, 2002) and (iii) difficulty recognizing other people's emotions (Lavenex *et al.*, 1999; Rosen *et al.*, 2002; Rankin *et al.*, 2005b).

The nature of the neural loss typically seen in FTLD provides clues for the likely basis of these deficits. The complex social and emotional processing involved in self-conscious emotions probably activates a network of brain regions that integrates relevant information including appraisals of the stimulus (which invoke memories, beliefs and feelings), evaluations of the surrounding environment and modifications of responding based on social rules. Critical to these processes are neural pathways linking higher-order cognitive processes (e.g. mPFC) with those that monitor internal physiological states (e.g. anterior cingulate cortex, anterior insula). Self-conscious emotions such as embarrassment require the ability to process representations of self, others and social rules, which probably engage extensive neural networks including the mPFC, an area that typically incurs significant loss in FTLD. The anterior cingulate (Critchley *et al.*, 2005) and anterior insula (Craig, 2002) cortices play important roles in the generation of subjective feeling states and in the integration of cognitive and affective information. Our finding that FTLD patients' physiological responding to the startle stimulus was intact suggests that efferent brainstem pathways are intact. However, input regarding this elevated physiological state, which would be critical to self-conscious behaviour, may not be available owing to disease-related losses in afferent pathways involving anterior cingulate and anterior insula.

Some indirect support for this speculation derives from recent findings concerning self-conscious emotional behaviour in patients with a different kind of frontal lobe damage—selective injury to the orbitofrontal cortex. In contrast to our findings with FTLD patients, orbitofrontal patients express heightened self-conscious emotions (Beer *et al.*, 2003). Orbitofrontal patients typically have intact anterior cingulate and anterior insula cortices, and thus, in keeping with our model, should be able to produce self-conscious emotions. Moreover, the damage to orbitofrontal cortex may damage neural circuits necessary for

emotion downregulation, thus resulting in inappropriate levels of self-conscious (and other) emotions.

Although we have been focusing on the loss of self-conscious emotional behaviour in FTLD patients, our findings that the negative emotional behaviour and physiological aspects of the startle response are intact in these patients are also worthy of comment. We recently found similar evidence for the preservation of behavioural and physiological responses to emotion-eliciting films in FTLD patients. Thus, it appears that despite significant amounts of neural loss, FTLD patients are still capable of generating emotional responses when confronted with stimuli such as unexpected loud noises and films with simple emotional themes. Thus, the emotional deficits in FTLD may be more specific than originally thought. Whereas some of the evolutionarily 'older machinery' of emotion is still functioning properly in FTLD, higher-order emotional processes such as those involved in generating self-conscious emotional behaviour or in detecting the emotions being experienced by others may be significantly impaired.

### Clinical implications

Selective deficiency in self-conscious emotions may help elucidate some of the prominent clinical features of FTLD such as inappropriate social behaviour. Embarrassment is an emotion that normally provides cues that socially unsuitable behaviour has occurred, behaviour should be modified and amends should be made. Thus, lack of embarrassment in FTLD may be associated with the persistence of inappropriate behaviour, oblivion to social norms, and lack of social reparation. The patients in this study were in the mild-to-moderate range of impairment on most clinical ratings, which suggests that disruption of self-conscious emotion may occur even at early stages of disease progression. This finding is consistent with clinical observations that behavioural disturbances are typically an early marker of this disease.

These findings have implications for the paradoxical role of the self in FTLD. Whereas many FTLD patients become exceedingly self-centred over the course of their illness, their self-awareness decreases (e.g. they are unable to track changes in their personality and behaviour accurately). FTLD patients also have deficits in understanding other people and their emotional reactions. Thus, they seem to lose acuity in their mental representations of self and others and in their ability to track the self, especially in dynamic social contexts.

### Limitations

There were two characteristics of this study that need to be considered in interpreting findings. First, among the various kinds of emotional behaviours we coded, only embarrassment was considered as being self-conscious. Although we consider embarrassment to be the quintessential self-conscious emotion, it could be argued that other emotional

behaviours such as happiness also grow out of self-consciousness. We chose not to treat happiness behaviours as self-conscious because of the difficulty of distinguishing between smiles of genuine amusement or relief (which probably would not be self-conscious) and ‘nervous’ smiles (which probably would be self-conscious). Secondly, we speculated about particular brain areas where neural degeneration might have explained our findings, but could not confirm these with objective measures of tissue loss in these patients. Future work would benefit from quantifying loss in areas thought to be critical for self-conscious emotion such as mPFC, anterior insula and anterior cingulate cortex.

## Conclusion

We studied the impact of FTLT on negative emotional behaviour, peripheral physiology and self-conscious emotional behaviour (embarrassment) in response to an aversive acoustic startle stimulus. Results indicated that the effects of FTLT on emotional responding may be more selective than commonly thought. Negative emotional behaviour and physiological responding to the startle stimulus were similar in FTLT patients and controls; however, FTLT patients showed much less self-conscious emotional behaviour. These findings suggest that simple emotional responding is preserved in FTLT patients, probably reflecting the fact that the disease spares brainstem regions critical for generating these responses. However, self-conscious emotions require higher-order social cognitive operations that utilize neural circuitry in regions of frontal cortex that are damaged in FTLT.

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