

Loss of Cells—Loss of Self

Frontotemporal Lobar Degeneration and Human Emotion

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ABSTRACT—Frontotemporal lobar degeneration (FTLD) is a devastating disease that profoundly changes emotion, self, and personality while initially sparing many aspects of cognitive functioning. This article reviews research that applies methods from basic affective science to obtain a more precise view of FTLD's impact on emotional functioning. This research indicates that simple forms of emotional reactivity are relatively preserved in the early stages of the disease. In contrast, more complex emotional processes, such as those involved with self-conscious emotions (e.g., embarrassment), emotion regulation, and recognizing emotions in others, are severely impaired. FTLD provides rich opportunities for increasing our understanding of the nature of emotion and of the emotional and social brain.

KEYWORDS—emotion; self; dementia; frontotemporal dementia; neurodegeneration

A warm, nurturing mother becomes increasingly indifferent to her family; her son comes to her with a serious injury and she shows no concern. A cultured professional begins to make embarrassing social gaffes and seems to neither notice nor care. A conservative businessman becomes increasingly vulnerable to “get rich quick” schemes and seems unaware of how his actions are contributing to his company's growing debt.

These scenarios are typical of those encountered in patients with frontotemporal lobar degeneration (FTLD). Devastating for the lives of patients and their families, FTLD is nonetheless one of the most informative neurological disorders for those interested in human emotion, personality, and the self. FTLD initially spares cognitive functions such as memory and spatial abilities, which are early targets of Alzheimer's disease (AD). Instead, FTLD hones in on those parts of the brain that determine how we feel, our sense of self, our personality, and how we interact with others. FTLD and AD are both neurodegenerative diseases, but

they travel different routes. AD has sometimes been described as a slow journey into darkness, with family members continuing to catch glimpses of the person they knew and loved along the way. In contrast, FTLD progresses much more rapidly, quickly erasing the person once known. The “new” person who emerges in FTLD can still remember, calculate, navigate, and conduct many of the activities of normal life, making the disease seem even more cruel.

FTLD: THE SYNDROME

FTLD causes 13% of all dementias and an even greater percentage of early onset dementias (Ikeda, Ishikawa, & Tanabe, 2004). Compared to AD, FTLD (a) sets in at an earlier age; (b) progresses more rapidly; (c) has more clear-cut anatomical markers; (d) presents initially with symptoms that are more behavioral, emotional, and social; and (e) is associated with neural degeneration affecting more anterior brain regions. In the early stages of AD, patients are often aware of and concerned about their memory loss and other symptoms. In contrast, FTLD patients are often quite unaware of, and without insight into, their changing behaviors and abilities.

FTLD typically appears before the age of 65, often becoming clinically apparent in a person's fifties. Thus, it afflicts people in the prime years of work and family life. Because it so radically alters social and emotional functioning, FTLD wreaks havoc with careers and families. The clinical course of FTLD is fast and relentless. Among patients at the Memory and Aging Center at UCSF, the average time from diagnosis to death is less than 5 years. The underlying pathology of FTLD consists of excessive accumulation of certain proteins (tau and TDP-43) in neuronal and glial cells, eventually leading to the death of cells mostly in the frontotemporal brain regions. In AD, in contrast, another protein (beta-amyloid) accumulates outside cells, adjacent to synapses and within small cerebral vessels. Additionally in AD, changes in the tau protein lead to the growth of fibrous tangles within cells.

FTLD affects a specific set of paralimbic (anterior cingulate, orbitofrontal, anterior insula) and limbic (amygdala and anterior hippocampus) anatomical structures. This anatomic selectivity

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is the neural basis for the emotional deficits that often herald the onset of the disease. Why the pathological process attacks these particular brain regions remains unknown. Recent work (Seeley et al., 2006) suggests that neurons called Von Economo cells are decimated in FTLT. These neurons are found mainly in a certain layer (5b) of the anterior cingulate, orbitofrontal, and anterior insula regions, and they have a 30% higher concentration in the right than the left frontal lobe. Von Economo cells are newly evolved, only being found in large-brained, highly social animals (including great apes and cetaceans), and they are greatly expanded in density in humans. Von Economo neurons may provide a critical connection between evolutionarily older emotion circuitry in paralimbic brain regions and evolutionarily newer emotion circuitry in prefrontal cortical regions. Although their exact functions remain unknown, Von Economo cells may be particularly important for linking emotional information to higher-order social observations and cognitive processes (e.g., inferring the intentions of others). Preliminary studies from our group suggest that these neurons may be the first site of neurodegeneration in FTLT.

The extent of tissue loss in magnetic resonance imaging (MRI) scans of FTLT patients can be quite dramatic even to the untrained eye, as illustrated in the coronal slices from structural MRI images in Figure 1. The FTLT patient's brain on the right shows profound volume loss in the amygdala region (circled) and enlarged ventricles (empty spaces in the brain through which the cerebrospinal fluid flows; arrows) compared to the normal brain on the left.

The rapidity with which FTLT progresses can be seen in Figure 2, which is based on two structural MRIs of a patient obtained 15 months apart. The red areas indicate regions where the patient's brain has significantly less volume than a normal brain. The onslaught of the neurodegenerative process over this 15-month period is vividly illustrated by the much more ex-

tensive red areas in the image on the right than in the one on the left.

FTLT: DIAGNOSIS AND SUBTYPES

Despite its dramatic symptoms and attendant neural changes, FTLT has been relatively understudied and is often misdiagnosed. Because many of the initial symptoms are behavioral, FTLT patients are typically taken to mental health professionals, where their symptoms lead to diagnoses such as depression, manic-depression, schizophrenia, obsessive-compulsive behavior, or antisocial personality disorder. Psychiatric treatments, whether involving drugs or therapy, are not likely to be effective and may even worsen symptoms, thus adding to the burden and frustration of patients' families. When referrals to neurologists occur, incorrect diagnoses are common unless the neurological team is experienced in diagnosing FTLT.

Accuracy in diagnosing FTLT benefited greatly from publication of the "Neary criteria" (Neary et al., 1998), which reflected an expert panel's consensus opinion on the symptoms of the three major FTLT subtypes: frontotemporal dementia (FTD), semantic dementia (SD), and progressive nonfluent aphasia (PNFA). Briefly, FTD is the prototypical "behavioral" variant, in which a patient presents with personality change, disruptions in social functioning, emotional blunting, and loss of insight and motivation. Memory typically remains intact, but deficits are seen in executive functions such as planning, attention, and problem solving. SD and PNFA are the "language" variants of FTLT. In SD there are severe problems with naming objects and comprehending the meaning of words, faces, and emotions. In contrast, speech remains fluent and grammatical, and memory and visuospatial functioning are similarly preserved. In PNFA, speech becomes nonfluent and effortful, with errors of grammar and pronunciation and problems with word retrieval. However,

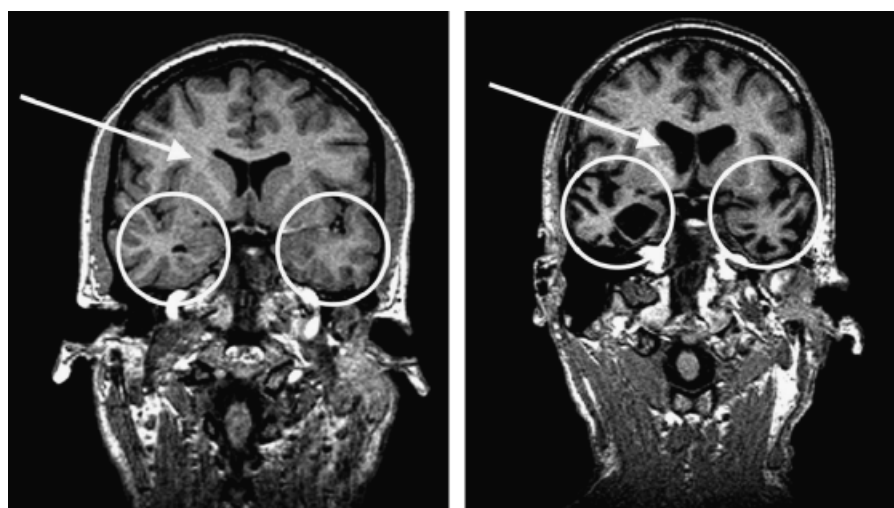


Fig. 1. Magnetic resonance imaging scan (coronal slice) of brains of a normal control (left) and of a frontotemporal lobar degeneration patient (right), with amygdala region (circled) and ventricles (arrows) marked.

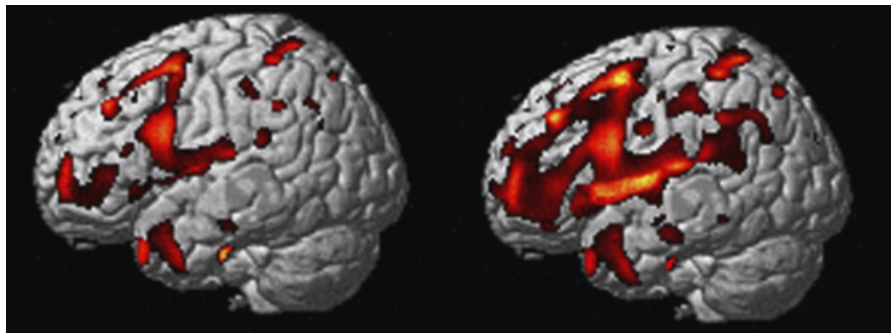


Fig. 2. Results of magnetic resonance imaging scans of a frontotemporal lobar degeneration patient obtained 15 months apart. Red areas indicate regions where the patient's brain has significantly less volume than a normal brain.

understanding of word meaning is preserved along with other cognitive functions.

The Neary criteria utilize information from multiple sources including clinical observations, case histories, informant reports, and neuropsychological testing. However, the neurodegeneration that produces these symptoms is neither “tidy” nor “static.” Thus, even early in the course of FTL D, a patient may not fall cleanly into only one diagnostic subtype. Also, over time, patients may show an increasingly wide array of symptoms as neuronal loss becomes more diffuse (although it still remains confined mainly in frontal and anterior regions).

FTLD AND EMOTION

Despite the important role that emotional changes play in FTL D, the descriptions of these alterations are relatively crude. The Neary criteria (Neary et al., 1998), for example, list “emotional blunting” and “impairment in regulation of personal conduct” (p. 1548) as symptoms of the FTD subtype, and “loss of sympathy and empathy” (p. 1549) as a symptom of the SD subtype. In contrast, symptoms involving speech, semantics, and executive function are described with much greater precision (e.g., “loss of word meaning, manifest by impaired naming and comprehension,” p. 1549).

We have argued (Levenson, 2007) that a comprehensive assessment of emotional functioning in patients (and those without the disorder) should at minimum encompass three emotional processes (*emotional reactivity*, *emotional regulation*, *emotional understanding*), three emotion types (*negative emotions*, *positive emotions*, *self-conscious emotions*), and four emotion response systems (*self-reported emotional experience*, *peripheral physiology*, *expressive behavior*, and *natural language*). Our hypothesis is that, rather than affecting emotion in an all-or-none fashion, FTL D (and other neurological and psychiatric disorders) result in areas of lost and preserved emotional functioning at specific intersections of emotion processes, emotion types, and emotion response systems.

EMOTIONAL PROCESSES IN FTL D

Emotional Reactivity

Emotional reactivity refers to the type, magnitude, and duration of responses to changes in the internal and external environment that have significance for one's goals and well-being (Levenson, 2007). Based on the Neary criterion of emotional blunting, we would expect to find profound diminishment of emotional reactivity in FTL D.

The existing research on emotional reactivity in FTL D has been primarily based on clinical and informant interviews. These studies do suggest that emotional reactivity is diminished in FTL D (Seeley, et al., 2005; Snowden, et al., 2001). However, as valuable as these descriptive studies are, their assessments of emotional functioning are often global and undifferentiated, representing summaries encompassing many emotions, contexts, and situations. A more precise assessment of emotional reactivity would consider patients' actual emotional responses to multiple elicitors under well-controlled conditions that enable sampling of a range of emotions and emotion response systems.

To our knowledge, the only data of this kind come from two recent studies from our group, both of which find evidence for some preservation of low-level emotional reactivity (for both positive and negative emotions) when using relatively simple emotion elicitors. In one study, we examined the emotional response to an aversive acoustic startle stimulus (Sturm, Rosen, Allison, Miller, & Levenson, 2006). The startle response is thought to exist on the boundary between reflex and emotion (Ekman, Friesen, & Simons, 1985); thus, it provides a good starting part for assaying emotional reactivity in FTL D. In our startle study, FTL D patients did not differ from controls in negative emotional behavior or autonomic response. In the other study (Werner, et al., 2007), emotional films with very simple themes were used to elicit happiness, sadness, and fear. No differences were found between FTL D patients and controls in self-reported emotional experience, expressive behavior, or autonomic response.

In contrast, when we examined other more complex forms of emotional reactivity in FTLN patients, there were clear signs of disruption. For example, in our study using acoustic startle, the self-conscious emotional response (i.e., embarrassment) that normal controls typically show when they have been startled was notably absent in FTLN patients (Sturm et al., 2006).

These studies point to important nuances in the impact of FTLN on emotional reactivity. Low-level emotional reactions such as the defensive response to sudden aversive stimuli or the happiness and sadness that occur in response to simply themed films that require minimal cognitive appraisal may be relatively preserved in the early stages of the disease. Arguably these kinds of simple emotional responses are subserved by brainstem circuits (e.g., startle circuits delineated in rodents, Davis, Gendelman, Tischler, & Gendelman, 1982) that are relatively spared in FTLN. In contrast, more complex self-conscious emotional reactivity (e.g., embarrassment) and emotions that arise in situations requiring more elaborate appraisals (e.g., responding to the subtleties of family and work life) may be sharply diminished. These latter emotional responses are likely subserved by frontal and anterior temporal regions that are highly vulnerable in FTLN.

In considering these findings, we realize that the evidence for preservation of low-level emotional reactivity in the early stages of FTLN is based on findings of “no differences” between groups of patients and controls. Such findings are always vulnerable to issues related to statistical power (i.e., would the differences be significant with larger sample sizes?). Nonetheless, we believe that different aspects of emotional reactivity deteriorate at different rates in FTLN, following the basic pattern: Simple, low-level forms of emotional reactivity deteriorate more slowly than complex, high-level forms. Fleshing this picture out more fully will clearly require additional cross-sectional and longitudinal studies.

Emotional Regulation

Emotional regulation refers to the adjustments in type, magnitude, and duration of emotional responses that are made to meet personal, situational, and interpersonal demands (Levenson, 2007). Clinical observations of FTLN often include reports of behavioral disinhibition including aggressiveness, poor impulse control, and irritability (Bozeat, Gregory, Ralph, & Hodges, 2000; Miller et al., 1991), which likely reflect problems in emotional regulation.

Separating emotional regulation from emotional reactivity in the laboratory is challenging. When a research participant shows an unusually large response to a standardized emotional stimulus, does this indicate heightened reactivity, diminished regulation, or both (Levenson, 2007)? This distinction is particularly important in neurodegenerative disease, because different brain regions are implicated in disturbances in reactivity (e.g., brain stem and limbic circuits) and disturbances in regu-

lation (e.g., prefrontal circuits). Another important distinction is between “instructed” regulation (ability to regulate emotion when told to do so) and “spontaneous” regulation (ability to regulate emotional responses on one’s own volition in situations where regulation is appropriate). Instructed regulation requires recruiting the necessary resources to follow explicit commands. Spontaneous regulation is more complex, additionally involving such processes as situational appraisal, strategy formulation, response inhibition, self-monitoring, and being aware of and concerned about what others think. Stated simply, in assessing emotional regulation, we need to determine both what individuals can do and what they do do.

We are aware of no published laboratory studies of emotion regulation in FTLN that make these important distinctions. Recently, we (Goodkind, McCarthy, & Levenson, 2005) studied responses to an aversive acoustic startle stimulus in FTLN patients, AD patients, and normal controls. The startle was presented under three experimental conditions designed to help separate reactivity (response when the startle occurred without warning), instructed regulation (response when a person was warned that the startle was coming and told explicitly to down-regulate), and spontaneous regulation (response when a person was warned that the startle was coming but not explicitly told to down-regulate). Findings revealed that all groups showed equivalent reactivity to the unwarned startle. For instructed regulation, both AD and FTLN patients were able to down-regulate, but not as well as controls. For spontaneous regulation, FTLN patients were much more impaired than AD patients. Thus, paralleling deficits we found earlier with self-conscious emotional reactivity (Sturm et al., 2006), FTLN patients’ deficits in emotion regulation emerged most vividly in situations that involved processing information about self, others, and the social context. Additional studies of different kinds of emotion regulation in FTLN patients are clearly needed and have great potential for expanding our understanding of the brain areas that are critical for emotion regulation.

Emotional Understanding

Emotional understanding refers to the recognition of emotions in self and others and the understanding of why they have occurred and what their potential consequences are (Levenson, 2007). This complex ability draws upon processes of perceiving, identifying, and labeling facial expressions, body movements, verbalizations, and social cues (Werner et al., 2007). Emotional understanding has been well studied in neurologically normal individuals in the psychological literature, where it has been termed empathic accuracy or cognitive empathy.

Clinician and caregiver descriptions suggest that FTLN patients have clear deficits in knowing and understanding the emotions of others (Rankin, Kramer, & Miller, 2005). These observations are confirmed by findings that FTLN patients have difficulties identifying the emotions of others in photographs of

static facial expressions (Rosen et al., 2004; Rosen et al., 2002) and in films (Werner et al., 2007). Across studies there are indications that deficits in emotion identification are more pronounced for negative emotions than for positive emotions¹ and are most strongly associated with neurodegeneration in the right temporal lobe (Rankin et al., 2006; Rosen et al., 2006; Werner et al., 2007). These deficits may lead to the losses of empathy and sympathy that characterize both the FTD and SD subtypes of FTLT (Neary et al., 1998) and that are so disturbing to families and loved ones.

SUMMARY AND CONCLUSIONS: WHAT HAVE WE LEARNED ABOUT FTLT AND EMOTION?

Applying methods and concepts derived from basic affective science to the study of FTLT has changed our views both about FTLT and about emotion.

In terms of FTLT, the emotional losses are clearly more selective than previously thought. In the early stages of the disease, low-level emotional reactivity (e.g., reactions to unexpected noises and to simply themed emotional films) is relatively preserved compared to more complex forms of emotional reactivity (e.g., becoming embarrassed when startled), the ability to down-regulate emotional responses (when instructed and spontaneously), and the ability to identify the emotions of others. We believe that this pattern of preservation and loss derives from the sparing of brainstem and limbic emotional circuits that subserve low-level emotional reactivity, and damage to frontal and anterior temporal circuits that are necessary for higher-level, more complex aspects of emotional functioning. Further refinement of these distinctions and development of more specific and sensitive tests of emotional functioning may help us improve the diagnosis of FTLT and its subtypes, track the course of the disease, assess the impact of candidate genes, and evaluate the efficacy of possible treatments.

In terms of emotion, studies of FTLT underscore the folly of treating the emotion system as a monolith. The evidence to date supports a more highly differentiated view of emotional functioning, indicating that different emotional processes (reactivity, regulation, understanding) and different types of emotion (positive, negative, self-conscious) are subserved by different neural circuits. These findings raise important caveats for contemporary affective neuroscience. For example, typical brain-activation paradigms (e.g., having participants identify the emotions in photographs of negative and positive facial expressions) are better viewed as studying particular emotional-processing circuits rather than as proxies for understanding the full complexities of the emotional brain.

¹Finding greater deficits for negative than positive emotions may also result from most studies having patients see more exemplars and choose from more terms for negative emotions than for positive emotions.

We expect that the marriage between methods and concepts derived from basic affective science and well-characterized neurological patients will be a long-lived and highly productive union. Studies that issue from this alliance afford a unique opportunity to obtain a deeper understanding of the complexities of emotional functioning and to derive a more precise understanding of the emotional impact of a wide range of neurological diseases.

Recommended Reading

- Seeley, W.W., Carlin, D.A., Allman, J.M., Macedo, M.N., Bush, C., Miller, B.L., & DeArmond, S.J. (2006). (See References). Describes a specialized cell that is an early target of neurodegeneration in FTLT and speculates about its role in processing social and emotional information.
- Sturm, V.E., Rosen, H.J., Allison, S., Miller, B.L., & Levenson, R.W. (2006). (See References). Illustrates the use of laboratory methods derived from basic affective science to refine our understanding of areas of preserved and lost emotional functioning in FTLT.
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