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Disgust: Deficits in Behavioral Variant Frontotemporal Dementia and Correlates in the Brain

By

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Doctor of Philosophy

in

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University of California, Berkeley

Committee in charge:

Professor Robert Levenson, Chair

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Abstract

Disgust: Deficits in Behavioral Variant Frontotemporal Dementia and Correlates in the Brain

by

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Disgust is an emotion that is important for basic survival, in addition to having social and moral implications. Disgust reactivity appears to be significantly impaired in behavioral variant frontotemporal dementia (bvFTD), a neurodegenerative disease that selectively affects areas of the brain that are crucial for proper emotional functioning. Caregivers have reported that some bvFTD patients pick up garbage, drink beverages found on the street, and eat out of trashcans. Recent findings from our laboratory were consistent with these anecdotal reports, and demonstrated that patients with bvFTD showed deficits in their behavioral, physiological, and self-reported responses to a disgusting stimulus (Eckart, Sturm, Miller, & Levenson, 2012). The present study sought to build upon these findings. In this study, bvFTD patients and neurologically healthy control participants had their emotional facial behavior, physiology, and self-reported emotional experience measured while viewing a disgust-eliciting film. In order to determine whether disgust was potentially a uniquely compromised emotion in this population, participants' responses to a sadness-eliciting film were also examined. In addition, the present study utilized a neurologically varied sample of participants to explore (across diagnoses) the relationship between disgust reactivity and the insula, a region of the brain thought to be important for disgust responding (e.g., Adolphs, Tranel, & Damasio, 2003). The specificity of this disgust-insula relationship was examined by also testing the associations between the insula and participants' sad film responses and the associations between additional brain regions and participants' disgust film responses.

Results supported the hypothesis of a specific disgust deficit in bvFTD. BvFTD patients exhibited diminished disgust reactivity in behavioral, physiological, and experiential domains (with the most robust deficit found in physiology), yet these patients did not differ from healthy controls in their responses to sad stimuli, suggesting that the observed disgust deficit cannot be explained by a general blunting of negative emotions. In terms of brain-behavior relationships across the neurologically varied sample, results were overall in line with expectations. Lower insular volume significantly predicted smaller disgust film responses in behavioral and experiential domains, and predicted less somatic activity in response to disgusting stimuli. The present study also found that lower insular volume was partially related to diminished sad film responses, but no additional brain regions were associated with disgust film responses. These findings suggest that the insula may be important in some ways for all emotions (Craig, 2009), but may be particularly important in disgust. The present study expands on past work, sheds light

on the neural correlates of disgust, and provides additional information about areas of preserved and compromised functioning in bvFTD.

Introduction

Frontotemporal dementia (FTD) is the second most common neurodegenerative disease after Alzheimer's disease (Rosen et al., 2002a). FTD strikes 15 out of every 100,000 individuals in the 45-64 year-old age group, and is as common as Alzheimer's disease in individuals under the age of 65 (Ratnavalli, Brayne, Dawson, & Hodges, 2002). FTD is associated with a dramatic decline in social and emotional behavior. The symptoms of FTD include emotional blunting, lack of empathy, disinhibition, poor insight, and a loss of social interest (Neary, Snowden, & Mann, 2005). However, despite this dramatic socioemotional loss, in the early stages of the disease, many cognitive abilities remain relatively intact (e.g., memory and visuospatial processing seem to be uncompromised; Boxer & Miller, 2005).

FTD: Neuroanatomy

FTD selectively affects the frontal and anterior temporal lobes of the brain, regions that are crucial for proper social and emotional functioning (Kipps, Mioshi, & Hodges, 2009). The frontal lobes have been implicated in emotion recognition, emotion regulation, and insight (Rosen et al., 2005; Werner et al., 2007). Among frontal brain structures, the insula, located deep between the frontal and temporal lobes within the lateral fissure, is particularly important for visceral processing (Mutschler et al., 2009) as well as functions such as vestibular and motor integration and modulation (Flynn, Benson, & Ardila, 1999), and is highly vulnerable to the disease (Seeley, 2010). This region is of particular interest in the present study and is discussed below in greater detail. The temporal lobes are important for emotion recognition and empathy (Rosen et al., 2006; Werner et al., 2007), and among temporal brain structures, the amygdala has been implicated in fear conditioning and a wide range of other emotional processes (Phan, Wager, Taylor, & Liberzon, 2002). Because these frontal and temporal regions are so central to emotional functioning, neural loss in these areas would presumably result in dramatic social and emotional deficits, which is consistent with what is seen in patients with FTD (Neary et al., 2005).

The Insula

The insula has connections with many other areas of the brain (such as the premotor cortex, the somatosensory cortices, the amygdala, and the thalamic taste area; Augustine, 1996), and it appears to play a role in gastrointestinal, olfactory, gustatory, visual, somatosensory, and motor modulation (Flynn et al., 1999). The insula seems to be particularly important for visceral processing (Adolphs, 2002), and evidence suggests it is a critical part of a "salience network" that integrates external sensory stimuli with internal states (Seeley et al., 2007; Uddin & Menon, 2009). Although in the present study we examined volumes of the insula as a whole, this region can be divided anatomically into multiple subregions. The insular cortex is divided into two parts: the larger anterior insula and the smaller posterior insula. The posterior insula is involved in receiving visceral signals and may be important for encoding the duration of an interval or stimulus, playing a key role in our experience of time (Wittmann, Simmons, Aron, & Paulus, 2010). The anterior insula affects autonomic functions and is particularly involved in homeostatic regulation and interoceptive awareness (Mutschler et al., 2009). Seeley (2010) states that the anterior insula itself "can be divided into no less than two but more likely several distinct subregions" (p. 466). The two major subdivisions of the anterior insula are a ventral region and

dorsal region that may be involved in different processes. The ventral region (sometimes called the frontoinsula) may be more involved in the regulation of physiological changes related to emotional states, while the dorsal region may be more involved in speech and language fluency tasks (Mutschler et al., 2009; Seeley, 2010). The anterior insula is among the few brain regions containing a special class of neurons known as von Economo (VEN) or “spindle” neurons; these large neurons are thought to be unique to humans, apes, most cetaceans (the order of marine mammals including whales, dolphins, and porpoises), and elephants (Seeley, 2010). Although the exact functions of VENs remain unknown (Seeley et al., 2006), it has been proposed that VENs might enable highly integrated representations of emotional states (Craig, 2009).

FTD: Emotional Responding

Caregiver and Clinician Reports

A significant portion of existing knowledge about emotional functioning in FTD comes from caregiver reports and clinician observations. Caregivers of patients with FTD report major changes in the behavior and personality of these patients, including a pervasive “loss of emotions” (Bathgate, Snowden, Varma, Blackshaw, & Neary, 2001; Gregory, Serra-Mestres, & Hodges, 1999). For example, some caregivers have reported that patients with the behavioral subtype of FTD pick up garbage, drink beverages found on the street, eat out of trashcans, and sample food from strangers’ plates in restaurants; these behaviors suggest a compromised disgust response. Clinical reports regarding patients with FTD also point to disturbances such as disinhibition and emotional blunting (Grossman, 2002; Neary et al., 1998). Reports from caregivers and clinicians are incredibly important, because these individuals are the first-line detectors of emotional impairment and interact with patients in a natural environment for prolonged periods of time. However, if we rely solely on these reports, a picture of blanket emotional deficits emerges: FTD patients are presumed to be compromised in terms of all aspects of emotional functioning. Our laboratory believes that studying these patients in a controlled, standardized setting can provide a more differentiated view of areas of deficient and preserved emotional functioning in FTD.

Laboratory Studies

We have been using methods derived from contemporary affective science (Levenson et al., 2008) to explore emotional functioning in this population. These methods arguably allow us to examine preservation and loss of emotional functioning in FTD with greater specificity and precision than has been the case with the more informal home and bedside observations. Our laboratory assessment uses a model of emotion that delineates three types of processes: reactivity, empathy, and regulation. Reactivity is the degree to which a person experiences and expresses her emotions, for example, how intensely a person feels fear in the face of a threat. Empathy involves understanding and responding to the emotions of others. In our work with FTD patients, we have focused on the recognition component of empathy (i.e., accurately naming the emotion that another is feeling). Regulation involves controlling the expression or experience of emotions, for example, suppressing socially inappropriate laughter at a funeral. Our laboratory assesses each of these emotional processes in our patient work, as they may be differentially affected by FTD. The present study focused on emotional reactivity, because disgust reactivity was an area that necessitated further exploration; general findings from the areas of emotion recognition and emotion regulation will be reviewed shortly.

In addition to studying different emotional processes, our laboratory assesses different kinds of emotions: negative (e.g., fear), positive (e.g., happiness), and self-conscious (e.g., embarrassment). We also examine multiple emotions within these general types (e.g., within the negative emotion category we have studied sadness and disgust). All emotions help us orient ourselves in our physical and social environment, and have profound adaptive value (Levenson, 2003). Basic negative and positive emotions are considered to each have unique features such as a distinctive behavioral signal and antecedent event, and share characteristics with each other including a rapid onset, short duration, and unbidden occurrence (Ekman, 1992). Negative emotions signal threats in the environment and help us deal with these challenges, while positive emotions help with tasks such as forging social bonds and restoring physiological equilibrium (Fredrickson, 1998). Self-conscious emotions (e.g., shame, pride) represent a more complex level of processing, because they require an understanding of the social situation and an awareness of the self as viewed by others (Tangney, 1999). Embarrassment, the self-conscious emotion our laboratory has examined in FTD patients, occurs following transgressions of social norms (Keltner & Anderson, 2000) and serves an appeasement function, as it motivates reparation of the situation (Keltner & Anderson, 2000). Embarrassment and disgust are similar in some ways, as both emotions help to regulate social behavior (Keltner & Anderson, 2000; Rozin & Fallon, 1987). Our laboratory assesses many kinds of emotions in FTD, since not all emotions may be affected equally by the disease.

Recognition and Regulation

Experimental studies of emotional functioning in FTD conducted by other laboratories have primarily been in the category of emotion recognition. These studies tested the ability of patients to recognize emotional facial expressions presented in static pictures (Fernandez-Duque & Black, 2005; Lavenex, Pasquier, Lebert, Petit, & Van der Linden, 1999), though one study also tested the patients' ability to identify vocal emotional signals (e.g., laughing for happiness, retching for disgust; Keane, Calder, Hodges, & Young, 2002). These studies all demonstrated that FTD patients have difficulty identifying others' emotions.

We have examined emotion recognition in this population in our laboratory, and believe that our use of dynamic audiovisual stimuli (e.g., emotionally evocative scenes from movies or television) may allow for a more ecologically valid assessment of functioning than has been possible in these previous studies. Our work suggests there is some preservation of the ability of FTD patients to recognize emotions in films. Werner et al. (2007) found that FTD patients were comparable to controls in their recognition of happiness, and recent work has demonstrated that FTD patients do not differ from controls in their ability to recognize the emotions in negative films (Goodkind, Ascher, Sturm, Miller, & Levenson, in preparation). However, these patients do demonstrate deficits in the ability to recognize self-conscious emotions (Goodkind et al., in preparation).

In the area of emotion regulation in FTD, there is evidence for some preservation of the ability to down-regulate emotional responding when explicitly instructed to do so (Goodkind, Gyurak, McCarthy, Miller, & Levenson, 2010). Our laboratory is currently examining the connections between emotion recognition, emotion regulation, and specific brain region volumes.

Reactivity

In the realm of emotional reactivity, it appears that some low-level responses remain intact in the early stages of FTD. Our laboratory found that when presented with an aversive acoustic startle stimulus (a 115db, 100ms burst of white noise), FTD patients and controls did not significantly differ in their behavioral and physiological responses (Sturm, Rosen, Allison, Miller, & Levenson, 2006). This preservation of function likely reflects the fact that the brain stem circuitry that is responsible for the startle response (Davis, Gendelman, Tischler, & Gendelman, 1982) is typically preserved in FTD. In addition, in our laboratory Werner et al. (2007) found that responses to simply themed films of happiness, sadness, and fear were intact in patients with FTD. In response to these kinds of stimuli, FTD patients' emotional behavior, self-reported subjective experience, and physiology did not significantly differ from controls'.

In contrast, very high-level emotional reactivity appears to be severely compromised in this disease. Our laboratory examined FTD patients' emotional responses to two different stimuli that typically produce embarrassment in neurologically intact individuals. In one "karaoke" task, participants were instructed to sing along with a recorded popular song and afterwards watch the videotape of themselves singing. FTD patients were significantly less emotionally reactive to this task in both behavior and physiology than controls (Sturm, Ascher, Miller, & Levenson, 2008). In the second task, participants' secondary response to a high-intensity, aversive acoustic startle was examined. When startled in this manner, almost all people show an initial reflexive defensive response (e.g., hard eye closure, shoulder raise, neck tensing; Ekman, Friesen, & Simons, 1985). Following this response, there is often a secondary response such as laughing or showing signs of embarrassment as the person becomes aware of and processes their initial response. When our group examined FTD patients' secondary startle responses, we found that they showed significantly less embarrassment behavior than controls (even though their primary startle response did not differ; Sturm et al., 2006). This deficit in embarrassment likely reflects damage to frontal brain circuits necessary for the processing that leads to self-conscious emotional responding (Eslinger et al., 2005).

Given the evidence of intact emotional reactivity in FTD patients to some types of stimuli and impaired reactivity to others, it is important to continue to explore the conditions under which emotional reactivity is preserved and those under which it is compromised. Moreover, since different emotions serve different adaptive purposes, deficits in certain emotions will affect patients' behavior in unique and specific ways.

Disgust

We recently examined reactivity to disgust (Eckart, Sturm, Miller, & Levenson, 2012). Disgust has been recognized as an emotion since Darwin, and is important for directing us away from offensive objects. Aggregating descriptions across several investigators (Ekman, Friesen, & Ancoli, 1980; Rozin & Fallon, 1987; Rozin, Lowery, & Ebert, 1994), disgust has a characteristic facial expression (wrinkled nose, raised upper lip, tongue moves forward in mouth), an associated action tendency (distancing of the self from the offensive object), and a distinctive physiological manifestation (nausea). Disgust appears to have originally evolved with an oral/nasal focus; the origins of the facial muscle movements in the disgust facial expression may have served to reject offensive foods, smells, and other contaminated materials (Rozin, Haidt, & McCauley, 2008). In addition, disgust is a very visceral emotion, arguably much more so than emotions such as happiness or sadness. When we are presented with something disgusting, such

as rotten food or a noxious odor, we can feel ourselves gag or become nauseated. This internal visceral awareness is an important part of the disgust response (Rozin & Fallon, 1987), and aids us in avoiding potentially harmful food or other contaminated substances. From these evolutionary origins, which likely helped us to avoid ingesting dangerous substances, disgust has generalized into somewhat of a “moral” emotion, helping to guide us away from a wide range of offending and undesirable objects, situations, acts, and people (Rozin, Haidt, & Fincher, 2009). Lastly, disgust is unique as it is one of the few emotions that have been consistently linked with a particular brain region; in the case of disgust, this region is the insula (e.g., Wright, He, Shapira, Goodman, & Liu, 2004). Details concerning this connection will be described shortly.

In our recent work examining disgust responding in FTD, we focused on a particular subtype of the disorder, behavioral variant frontotemporal dementia (bvFTD). In this subtype, early and profound emotional and social deficits are common (e.g., impulsive and inappropriate behavior and a lack of insight into deficits; Kipps et al., 2009). Disgust was of particular interest given that anecdotal evidence suggests bvFTD patients may have a compromised disgust response. In this data collection wave we examined emotional responses to a film known to be effective in eliciting disgust. The film clip, from the movie “Trainspotting,” depicts a man defecating in a filthy toilet and then reaching his hand into the toilet to look for a package of drugs, sifting through his own feces. We compared emotional responses to this film in bvFTD patients and neurologically healthy controls, and assessed the integrity of the disgust response by measuring facial behavior, physiological reactivity, and subjective emotional experience. Results revealed that bvFTD patients were significantly less reactive than controls in all three domains.

Our laboratory assessment was recently modified to include a new, potentially more evocative disgusting film, and data were collected using a different set of neurological patients and healthy controls. The present study combined these two data collection waves with the goal of replicating our earlier bvFTD finding with a larger group of participants (half of whom viewed the newer disgusting film clip). The data were combined with adequate control for possible main effects and interactions involving the particular film viewed.

In addition, the present study sought to shed more light on the neural correlates of disgust. Given the evidence that the insula is involved in bodily awareness (e.g., Mutschler et al., 2009) along with the assumption that disgust is in general a highly visceral emotion (Rozin & Fallon, 1987), it is not surprising that disgust has been linked with this region. In fMRI studies, insula activation has been found when research participants are presented with disgusting stimuli. For example, insula involvement is found when participants view pictures of contamination or mutilation, view video clips showing the facial expression of disgust, and inhale noxious odorants producing a strong feeling of disgust, but not when they view pictures that elicit emotions other than disgust (Wicker et al., 2003; Wright et al., 2004). In lesion studies, patients with damage to the insula have demonstrated impairment in the ability to recognize and experience disgust. For example, Adolphs and colleagues reported that their patient’s impaired recognition of disgust was quite striking (Adolphs, Tranel, & Damasio, 2003). To illustrate, when the patient was told a story about a person vomiting, his descriptions of how the person would feel included “hungry” and “delighted.” Though this patient had lesions to additional brain areas, the authors hypothesized that the patient’s damaged insula accounted for his disgust deficits. Additionally, this patient was able to recognize basic emotions other than disgust. Indeed, a possible neural explanation for the previously observed disgust deficit in bvFTD patients may lie in the insula, which typically incurs significant loss in the early stages of the disease (Rosen et al., 2002b; Seeley, 2010). The present study utilized a neurologically varied

sample of participants (bvFTD patients and healthy controls in addition to patients with other neurodegenerative diseases) to explore the relationship between the integrity of the insula and disgust responding in our laboratory.

The Present Study

The present study had two primary aims: (1) To determine if emotional reactivity to disgust-eliciting films is compromised in patients with bvFTD. In order to determine whether disgust was uniquely compromised in this population, emotional reactivity to sadness-eliciting films was also examined. (2) To determine if disgust reactivity in general is associated with neural loss in the insula, a brain region thought to be crucial for proper disgust processing. In order to explore the specificity of this relationship, associations involving other brain regions (the pallidum, putamen, caudate, and amygdala) and other negative emotions (sadness) were also examined.

To address the first aim, we examined emotional responses to disgusting and sad films in bvFTD patients and neurologically healthy control participants. The emotional response to each film was assessed by measuring facial behavior, physiological activation, and subjective emotional experience. To address the second aim we utilized a neurologically varied sample of participants, which included a subset of the bvFTD patients and healthy controls as well as Alzheimer's disease (AD) patients and individuals with corticobasal degeneration or progressive supranuclear palsy (CBD/PSP). Within this sample, we examined links between regional brain volumes and emotional responses to the disgusting and sad films. Emotional responses were again assessed by measuring facial behavior, physiological activation, and subjective emotional experience. Regional brain volumes were quantified from structural magnetic resonance images (MRIs) using FreeSurfer (Desikan et al., 2006), a semi-automated program that generates volumes for cortical and subcortical regions of interest.

Hypotheses, Predictions, and Exploratory Analyses

Emotional Functioning in bvFTD

These hypotheses and predictions will be tested using a sample of bvFTD patients and healthy controls.

Hypotheses:

Disgust film response: facial behavior

BvFTD patients will behaviorally express a smaller amount of disgust than controls in response to a disgusting film.

Rationale. Previous research has shown that bvFTD patients exhibit less disgust behavior than controls in response to a disgusting film (Eckart et al., 2012).

Disgust film response: physiological reactivity

BvFTD patients will be less physiologically reactive than controls in response to a disgusting film.

Rationale. Past research has found that bvFTD patients exhibit less physiological responding than controls in response to a disgusting film (Eckart et al., 2012).

Disgust film response: self-reported emotional experience

BvFTD patients will report experiencing less disgust than controls in response to a disgusting film.

Rationale. Previous research has shown that bvFTD patients have a compromised experiential response to a disgust-eliciting film (Eckart et al., 2012).

Predictions:

Sad film response: facial behavior

BvFTD patients and controls will not differ from each other in the amount of sadness behaviorally expressed in response to a sad film.

Rationale. Past work with FTD patients has demonstrated an intact behavioral response to a sadness-eliciting film (Werner et al., 2007).

Sad film response: physiological reactivity

BvFTD patients and controls will not differ from each other in physiological activation in response to a sad film.

Rationale. Previous research has shown that FTD patients and controls do not differ from each other in their physiological responses to a sad film (Werner et al., 2007).

Sad film response: self-reported emotional experience

BvFTD patients and controls will not differ from each other in self-reported sadness in response to a sad film.

Rationale. Past work has demonstrated that FTD patients have an intact experiential response to a sadness-eliciting film (Werner et al., 2007).

Brain-Behavior Relationships

These hypotheses will be tested and these exploratory analyses will be performed using a neurologically varied sample consisting of bvFTD patients, AD patients, CBD/PSP patients, and healthy controls.

Hypotheses:

Insula and disgust film response: facial behavior

Lower insular volume will predict less disgust behavior in response to a disgusting film above and beyond other predictor variables (total intracranial volume, scanner type, Berkeley data collection wave, age, and sex).

Rationale. Although emotional responses are complex and likely involve multiple neural networks, disgust processing has consistently been linked with the insula (e.g., Wicker et al., 2003).

Insula and disgust film response: physiological reactivity

Lower insular volume will predict less general physiological activation in response to a disgusting film above and beyond other predictor variables (TIV, scanner type, Berkeley data collection wave, age, and sex).

Rationale. Disgust processing has consistently been linked with the insula (e.g., Murphy, Nimmo-Smith, & Lawrence, 2003), a region thought to be important for autonomic regulation (Mutschler et al., 2009).

Insula and disgust film response: self-reported emotional experience

Lower insular volume will predict less self-reported disgust experience in response to a disgusting film above and beyond other predictor variables (TIV, scanner type, Berkeley data collection wave, age, and sex).

Rationale. Disgust processing has consistently been linked with the insula (e.g., Wright et al., 2004), a region thought to be important for integrating internal experience (Uddin & Menon, 2009).

Exploratory analyses:

Insula and sad film responses

Although the literature suggests that disgust and the insula have a special relationship (e.g., Wicker et al., 2003), some researchers have proposed that the insula may be important for all subjective feelings (Craig, 2009).

Basal ganglia regions and disgust film responses

The literature suggests a special relationship between disgust responding and the insula; however, there is some evidence that disgust may also be linked to the pallidum, putamen, and caudate (Gray, Young, Barker, Curtis, & Gibson, 1997; Murphy et al., 2003; Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998).

Amygdala and disgust film responses

The amygdala, a highly studied region in the emotion literature (e.g., Ochsner, Bunge, Gross, & Gabrieli, 2002), is thought to be especially associated with the emotion of fear (e.g., Sprengelmeyer et al., 1998). The amygdala was included as a ‘control’ region and is not expected to be associated with responses to a disgusting film.

Methods

Participants

Overview: There were two samples of participants in this study. For the hypotheses and predictions involving emotional functioning in bvFTD, the sample consisted of bvFTD patients and neurologically healthy controls; group comparisons were conducted with this sample to examine deficits in emotional reactivity in bvFTD patients compared to healthy individuals. For the hypotheses and exploratory analyses involving brain-behavior relationships, the sample consisted of bvFTD patients, AD patients, CBD/PSP patients, and healthy controls. This anatomically varied group of participants was utilized to explore relationships (across diagnoses)

between regional brain volumes and emotional responses. There was some overlap between these two samples, as described below. Also important to note, the participants came from two waves of data collection. The major difference between these two waves was the particular disgust-eliciting film that was viewed. All participants were assessed at the Berkeley Psychophysiology Laboratory, and data from these two collection waves were combined. All participants were given the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) to assess their cognitive status (these scores are shown in Tables 1 and 3).

For the hypotheses and predictions involving emotional functioning in bvFTD, the sample consisted of 41 bvFTD patients and 50 controls. Of the 41 bvFTD patients, 20 were assessed in the first wave of data collection and 21 were assessed in the second. For the 50 control participants, 25 participants were assessed in each wave. Patients with bvFTD were recruited through the Memory and Aging Center at the University of California, San Francisco (UCSF). BvFTD was diagnosed using the Neary clinical criteria (Neary et al., 1998) by a group of neurologists, neuropsychologists, and nurses at UCSF using MRI brain images, neuropsychological measures, and clinical interviews. Neurologically healthy control participants were recruited by UCSF and by our laboratory through newspaper ads.

For the hypotheses and exploratory analyses linking regional brain volumes to emotional responses, the sample included bvFTD patients and healthy controls in addition to AD patients and individuals with CBD/PSP. These participants were recruited through the Memory and Aging Center at UCSF. The final sample consisted of 74 participants, made up of the following: 21 bvFTD patients (these participants were also in the group comparisons sample), 30 neurologically healthy controls (these participants were also in the group comparisons sample), 15 AD patients, and 8 CBD/PSP patients. 41 of the 74 participants were assessed in our laboratory during the first wave of data collection, with the remaining 33 participants assessed in the second. Below are brief descriptions of AD and CBD/PSP.

AD

Alzheimer's disease is a neurodegenerative disease in which brain atrophy typically begins in the medial temporal lobe, progresses to limbic regions such as the hippocampus, and eventually reaches the outer layers of the cortex (Braak & Braak, 1995). Evidence suggests that damage to the insula can occur early in the disease (Foundas, Leonard, Mahoney, Agee, & Heilman, 1997). In AD, the primary symptoms are cognitive. Most notable are deficits in memory, though other cognitive processes are also disrupted (e.g., visuospatial abilities; McKhann et al., 1984). In contrast, emotional functioning appears to be largely spared in the early stages of the disease (e.g., Fernandez-Duque & Black, 2005). These patients are an important addition to our sample, because they provide variety in terms of both insular degeneration and emotional functioning.

CBD/PSP

Corticobasal degeneration and progressive supranuclear palsy are neurodegenerative diseases with many common clinical features including eye movement abnormalities, motor difficulties, and executive dysfunction (Boeve, Lang, & Litvan, 2003; Houghton & Litvan, 2007). Anatomically, CBD has been associated primarily with asymmetric atrophy of the frontal and parietal lobes and striatum, while PSP has been associated with atrophy of the midbrain, pons, thalamus, and striatum (Boxer et al., 2006). Atrophy of the insula has been reported in both

diseases (Belfor et al., 2006; Padovani et al., 2006). CBD and PSP are clinically, pathologically, and genetically similar to FTD (Boeve et al., 2003). FTD-like social and emotional disturbances are common in CBD; patients with PSP often demonstrate these behavior changes as well, though they are typically not as severe as the changes seen in FTD. The anatomical characteristics and potential emotional deficits of the CBD and PSP patients make them a valuable addition to our sample.

Laboratory Assessment: Films and General Procedure

A six-hour laboratory session (with a one-hour break midway) designed to provide a comprehensive assessment of emotional functioning (Levenson et al., 2008) was conducted at our laboratory at the University of California, Berkeley. Data from the present study were collected in two waves; participants were assessed in our laboratory in either Wave 1 or 2. In Wave 1 and Wave 2, participants viewed emotion-eliciting film clips (in addition to completing other emotional tasks). The present study focuses on trials from Wave 1 and 2 in which participants viewed a disgust-eliciting film clip and a sadness-eliciting film clip.

After arriving at the laboratory, participants or their caregivers signed a consent form. Participants were then seated in a chair in a 3m x 6m room, where an experimenter applied physiological sensors. Participants were videotaped (with their consent) throughout the laboratory session. Stimuli were presented on a 21-inch television monitor placed directly in front of participants.

During the course of the laboratory session participants viewed a disgust-eliciting film clip and a sadness-eliciting film clip. The disgust-eliciting film clip in Wave 1 was 69 seconds long, preceded by a 60-second baseline. The film clip, from the movie “Trainspotting,” depicts a man defecating in a filthy toilet and then reaching his hand into the toilet to look for a package of drugs, sifting through his own feces. The disgust-eliciting film clip from Wave 2 was 105 seconds long, preceded by a 60-second baseline. The clip, from the television show “Fear Factor,” shows contestants biting into cow intestines, sucking out liquid, and drinking that liquid, all as fast as possible. The sad films in Wave 1 and 2 were both clips from the movie “The Champ.” The clips depict a young boy crying after learning that his boxer father has just died because of injuries sustained during a match. The clip from Wave 1 was 222 seconds long, preceded by a 60-second baseline. (This was the clip used by Werner and colleagues (2007) with a different set of participants.) The clip from Wave 2 was 92 seconds long, preceded by a 60-second baseline.

While watching the films, participants’ facial behavior was videotaped and their physiological activity was recorded. After each film clip, participants were asked how they felt while watching the clip. At the end of their participation in the laboratory session, participants were paid \$30 and permission was obtained for subsequent use of the video recordings.

Laboratory Assessment: Measures

Three aspects of emotional reactivity were measured while participants watched the films: facial behavior, physiological reactivity, and self-reported emotional experience.

Facial behavior. Each participant was videotaped using a partially concealed video camera that was embedded in a bookshelf and placed behind darkened glass. Facial behavior was later coded using the Emotional Expressive Behavior Coding System (Gross & Levenson, 1993) by trained coders blind to group membership. Ten emotions were coded on a 0 to 3 intensity scale: anger, contempt, confusion, disgust, fear, happiness/amusement, embarrassment, interest,

sadness, and surprise. Each type of emotion code was summed across the 30 most intense seconds of each film clip (previously determined by a panel of raters). The present study focused on the target emotion code for each type of film: sadness to a sad film and disgust to a disgusting film.

Physiological reactivity. Participants' physiological reactivity was recorded continuously using a system consisting of a Grass Model 7 polygraph and a computer or a BIOPAC polygraph and a computer. Physiological information was monitored and averaged on a second-by-second basis for each of the following measures: 1) Inter-beat interval: Electrodes with conductive paste were placed on opposite sides of the participant's chest to assess heart rate. Inter-beat interval was calculated as the interval between successive R waves. 2) Finger pulse amplitude: A photoplethysmograph recorded the amplitude of blood volume in the finger, using a photocell taped to the third finger of the participant's nondominant hand. 3) Ear pulse transmission time: A photoplethysmograph attached to the participant's right earlobe recorded the volume of blood in the ear. Transmission time was measured between the R wave of the EKG and the upstroke of pulse at the ear. 4) Skin conductance level: A constant-voltage device was used to pass a small voltage between electrodes attached to the first and third fingers of the participant's nondominant hand. 5) Finger temperature: A thermistor attached to the fourth finger of the participant's nondominant hand recorded temperature in degrees Fahrenheit. 6) Respiration period: A pneumatic bellows was stretched around the thoracic region, and the intercycle interval was measured between breaths. 7) General somatic activity: An electromechanical transducer attached to a platform under the participant's chair generated an electrical signal proportional to the amount of movement in any direction. 8) Systolic blood pressure and 9) diastolic blood pressure: A blood pressure cuff placed on the second finger of the participant's nondominant hand continuously recorded blood pressure using an Ohmeda Finapres 2300.

Change scores were computed for each measure (for each film of interest), subtracting the average of the 60-second pre-film baseline from the average level during the 30 most intense seconds of the film. The change scores were normalized to obtain Z-scores, using the mean and standard deviation from the sample of interest. (For group comparison analyses, change scores were normalized using the mean and standard deviation from the entire bvFTD and control sample. For brain-behavior regression analyses, change scores were normalized using the mean and standard deviation from the neurologically varied group sample.) Four measures (inter-beat interval, finger pulse amplitude, ear pulse transmission time, respiration period) were multiplied by -1 so that larger Z-scores always indicated greater activation. Finally, the average Z-score of all 9 measures was computed to provide a single composite score representing overall physiological activity for that film. Follow-up analyses of individual measures were conducted to ensure that any findings with a composite measure did not obscure important differences at the level of particular measures.

Self-reported emotional experience. After each film, participants were asked to rate how intensely they experienced each of eight (in Wave 1) or eleven (in Wave 2) emotions while watching the film. The following emotions were queried in both data collection waves: fear, anger, disgust, embarrassment, and sadness. Participants were given the response choices of "No," "A Little," or "A Lot," and these answers were later given a numerical score of 0, 1, or 2, respectively. Questions and response choices were presented both in text and aloud. The present study focused on the target response for each type of film: "disgusted" for a disgusting film and "sad" for a sad film.

Regional Brain Volumes: Image acquisition

Brain imaging was done at UCSF. Structural MRIs were obtained from each participant in the neurologically varied, brain-behavior sample described earlier; these scans were obtained on a 1.5 T, 3 T, or 4 T scanner (Boxer et al., 2010; Wilson et al., 2009). To ensure that results were not affected by scanner differences, scanner type was controlled for in all analyses (e.g., Wilson et al., 2009).

For 56 participants, T1 images were acquired on a 1.5 T Siemens Magnetom VISION system (Siemens, Iselin, NJ) equipped with a standard quadrature head coil, using a magnetization prepared rapid gradient echo (MPRAGE) sequence (164 coronal slices; slice thickness = 1.5 mm; field of view (FOV) = 256 mm; matrix 256 x 256; voxel size 1.0 x 1.5 x 1.0 mm; repetition time (TR) = 10 ms; echo time (TE) = 4 ms; flip angle = 15°).

For 12 participants, scans were obtained on a 3 T Trio Tim system (Siemens, Iselin, NJ) using high-resolution T1-weighted 3D MPRAGE sequences. The scan parameters were: TR/TE/T1, 2300/3/900 ms, flip angle 9°, 26 cm FOV, 256 x 256 in plane matrix, with a phase FOV of 0.94 and slice thickness of 1.0 mm.

For 6 participants, images were acquired on a 4 T Bruker MedSpec system with an 8 channel head coil controlled by a Siemens Trio console, using an MPRAGE sequence (176 sagittal slices; slice thickness = 1 mm; FOV = 256 x 256 mm; matrix = 256 x 256; voxel size = 1.0 x 1.0 x 1.0 mm; TR = 2300 ms; TE = 3 ms; flip angle = 7°).

Regional Brain Volumes: MRI analysis

FreeSurfer is a semi-automated program that can be used to generate volumes for cortical and subcortical regions of interest (Desikan et al., 2006). This procedure has been shown to be statistically indistinguishable from using manual tracing (Fischl et al., 2002). This approach was used to obtain regional brain volumes of the insula, caudate, putamen, pallidum, and amygdala. This approach was also used to obtain a measure of total intracranial volume, which was used as a covariate in analyses to control for head size. The FreeSurfer software authors request that the following explanatory paragraph be included in any study using this procedure:

Cortical reconstruction and volumetric segmentation was performed with the FreeSurfer image analysis suite, which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures are described in prior publications (Dale, Fischl, & Sereno, 1999; Dale & Sereno, 1993; Fischl & Dale, 2000; Fischl, Liu, & Dale, 2001; Fischl et al., 2002; Fischl, Salat et al., 2004; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999; Fischl, van der Kouwe et al., 2004; Han et al., 2006; Jovicich et al., 2006; Segonne et al., 2004). Briefly, this processing includes motion correction and averaging of multiple volumetric T1 weighted images (when more than one is available), removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) (Fischl et al., 2002; Fischl, Salat et al., 2004) intensity normalization (Sled, Zijdenbos, & Evans, 1998), tessellation of the gray matter white matter boundary, automated topology correction (Fischl et al., 2001; Segonne, Pacheco, & Fischl, 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Dale & Sereno, 1993; Fischl & Dale, 2000). Once the cortical models are complete, a number of deformable procedures can be performed for in further data processing and analysis including surface inflation (Fischl, Sereno, & Dale, 1999), registration to a spherical atlas which utilized individual cortical folding patterns to match cortical geometry across subjects (Fischl, Sereno, Tootell et al., 1999), parcellation of the cerebral cortex into units based on gyral

and sulcal structure (Desikan, Segonne et al., 2006; Desikan, Ségonne et al., 2006; Fischl, van der Kouwe et al., 2004), and creation of a variety of surface based data including maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl & Dale, 2000). The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data thus are capable of detecting submillimeter differences between groups. Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas, 2002) and manual measurements (Kuperberg, 2003; Salat et al., 2004). FreeSurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006).

Results

Overview of Analytic Approach

The present study had two primary aims: (1) to examine emotional reactivity to disgust in patients with bvFTD, and determine whether disgust was a uniquely compromised emotion in this population, and (2) to examine the relationship between disgust reactivity and the insula, and explore the specificity of that association in terms of emotion and brain region. To achieve the first aim, repeated measures analyses of variance (with follow-up analyses) were conducted to compare emotional responses to disgusting and sad films in bvFTD patients and neurologically healthy controls. To achieve the second aim, relationships between regional brain volumes and emotional responses to the disgusting and sad films were examined using linear multiple regressions with a sample of bvFTD patients, AD patients, CBD/PSP patients, and healthy controls.

Emotional Functioning in bvFTD

Analytic Approach

To examine participants' responses to the emotional films, a 2x2x2 repeated measures design was utilized. The within-subjects factor was type of emotional film, which had two levels (disgusting and sad). The between-subjects factors were diagnosis (bvFTD/control) and data collection wave (Wave 1/Wave 2), which was included to be sensitive to differences associated with the two waves of assessment.

Three repeated measures analyses of variance (ANOVAs) were conducted, one each for behavior, physiology, and self-report. For the behavioral analysis, the within-subjects variables were target behavior to the films (i.e., disgust behavior to a disgusting film and sadness behavior to a sad film). For the physiological analysis, the within-subjects variables were general physiological activation (i.e., the computed composite) to the films. For the subjective experience analysis, the within-subjects variables were target self-reported emotion to the films (i.e., "disgusted" for a disgusting film and "sad" for a sad film). We hypothesized that there would be a diagnosis x emotional film interaction for each of the three repeated measures ANOVAs, expecting bvFTD patients to show a deficit compared to controls in response to a disgusting film but not in response to a sad film. Given this a priori hypothesis, within each domain (behavior, physiology, self-report) separate ANOVAs were conducted for each type of

emotional film in order to look at simple effects and further examine diagnostic differences. For these follow-up analyses the factors were diagnosis and wave.

Age and sex were included as covariates in all analyses, as there were significant differences between the bvFTD and control groups in age ($F(1,89) = 23.44, p < .05$) and sex distribution (Chi-Square(1) = 16.47, $p < .05$). Means for the demographic variables are shown in Table 1.

Facial behavior

Repeated measures analysis: With target facial behavior to the films as the within-subjects variables, there was no significant interaction between emotional film and diagnosis, $F(1,85) = 1.70, ns$ (since this is the key interaction, the p value is reported here: $p = .196$). The analysis also revealed that there were no main effects for emotional film ($F(1,85) = .38, ns$) or diagnosis ($F(1,85) = 1.95, ns$), though there was a main effect for wave ($F(1,85) = 4.71, p < .05$), with Wave 2 films eliciting more target facial behavior than the films in Wave 1. None of the three remaining interactions were significant: emotional film by wave ($F(1,85) = .41, ns$), diagnosis by wave ($F(1,85) = .35, ns$), or emotional film by diagnosis by wave ($F(1,85) = .03, ns$).

Disgust film simple effects: In this analysis, disgust behavior to a disgusting film was the dependent variable. The analysis revealed a trend-level main effect for diagnostic group, $F(1,85) = 3.21, p < .1$, with bvFTD patients showing less disgust behavior than controls (means are shown in Table 2). There was also a trend-level main effect for wave, $F(1,85) = 3.86, p < .1$, with the Wave 2 disgust film eliciting more disgust behavior than the disgust film from Wave 1. Lastly, the interaction between diagnosis and wave was not significant, $F(1,85) = .11, ns$. Thus, the hypothesis that bvFTD patients would show less disgust behavior than controls in response to a disgusting film was supported at the trend level.

Sad film simple effects: In this analysis, sad behavior to a sad film was the dependent variable. There was no main effect for diagnostic group, $F(1,85) = .08, ns$ (means are shown in Table 2), and there was no main effect for wave, $F(1,85) = 1.88, ns$. The interaction between diagnosis and wave was also not significant, $F(1,85) = .38, ns$. Consistent with predictions, bvFTD patients and controls did not differ in the amount of sadness behaviorally expressed in response to a sad film.

Physiological reactivity

Repeated measures analysis: With physiological activation to the films as the within-subjects variables, there was a significant interaction between emotional film and diagnosis, $F(1,85) = 4.89, p < .05$. The analysis also revealed that there were no main effects for emotional film ($F(1,85) = .22, ns$) or diagnosis ($F(1,85) = .80, ns$), though there was a main effect for wave ($F(1,85) = 10.24, p < .05$), with Wave 2 films eliciting more physiological activation than the films in Wave 1. None of the three remaining interactions were significant: emotional film by wave ($F(1,85) = .15, ns$), diagnosis by wave ($F(1,85) = .62, ns$), or emotional film by diagnosis by wave ($F(1,85) = .91, ns$).

Disgust film simple effects: In this analysis, general physiological reactivity to a disgusting film was the dependent variable. The analysis revealed a main effect for diagnostic group, $F(1,85) = 4.22, p < .05$, with bvFTD patients demonstrating less physiological reactivity than controls (means are shown in Table 2). There was also a main effect for wave, $F(1,85) = 5.91, p < .05$,

with the Wave 2 disgust film eliciting more physiological activation than the disgust film from Wave 1. Lastly, the interaction between diagnosis and wave was not significant, $F(1,85) = .01$, *ns*. Thus, the hypothesis that bvFTD patients would be less physiologically reactive than controls in response to a disgusting film was supported. Follow-up analysis of individual physiological measures revealed diminished reactivity in bvFTD patients in respiration period ($F(1,74) = 7.39$, $p < .05$) but no significant differences in the other individual measures.

Sad film simple effects: In this analysis, general physiological reactivity to a sad film was the dependent variable. There was no main effect for diagnostic group, $F(1,85) = .30$, *ns* (means are shown in Table 2), though there was a main effect for wave, $F(1,85) = 7.70$, $p < .05$, with the Wave 2 sad film eliciting more physiological activation than the sad film from Wave 1. Lastly, the interaction between diagnosis and wave was not significant, $F(1,85) = 1.37$, *ns*. Consistent with predictions, bvFTD patients and controls did not differ from each other in physiological activation in response to a sad film.

Self-reported emotional experience

Repeated measures analysis: With target self-reported emotion to the films as the within-subjects variables, there was no significant interaction between emotional film and diagnosis, $F(1,85) = .001$, *ns* (since this is the key interaction, the p value is reported here: $p = .981$). The analysis also revealed that there were no main effects for emotional film ($F(1,85) = .21$, *ns*) or wave ($F(1,85) = .08$, *ns*), though there was a trend-level main effect for diagnosis ($F(1,85) = 3.88$, $p < .1$), with bvFTD patients reporting less target emotion than controls. None of the three remaining interactions were significant: emotional film by wave ($F(1,85) = .33$, *ns*), diagnosis by wave ($F(1,85) = .38$, *ns*), or emotional film by diagnosis by wave ($F(1,85) = .35$, *ns*).

Disgust film simple effects: In this analysis, self-reported disgust to a disgusting film was the dependent variable. The analysis revealed a trend-level main effect for diagnosis, $F(1,85) = 3.29$, $p < .1$, with bvFTD patients reporting less subjective experience of disgust to a disgusting film than controls (means are shown in Table 2). There was no main effect for wave, $F(1,85) = .01$, *ns*, and the interaction between diagnosis and wave was not significant, $F(1,85) = .89$, *ns*. Thus, the hypothesis that bvFTD patients would report experiencing less disgust than controls in response to a disgusting film was supported at the trend level.

Sad film simple effects: In this analysis, self-reported sadness to a sad film was the dependent variable. There was no main effect for diagnostic group, $F(1,85) = 2.22$, *ns* (means are shown in Table 2), and there was no main effect for wave, $F(1,85) = .25$, *ns*. The interaction between diagnosis and wave was also not significant, $F(1,85) = .03$, *ns*. Consistent with predictions, bvFTD patients and controls did not differ in self-reported sadness in response to a sad film.

Brain-Behavior Relationships

Analytic Approach

A series of multiple regression analyses were performed to examine the relationships between regional brain volumes and emotional responses in a neurologically varied sample. In each regression an emotion variable was designated as the dependent variable in order to determine whether a regional brain volume was a significant predictor of that emotion variable

above and beyond total head size and other variables that might explain a significant portion of the variance. Thus, in the first step of each regression analysis, total intracranial volume was entered, along with scanner type (2 dummy variables denoting 1.5T/3T/4T), wave (Wave 1/2), age, and sex. (Age and gender information for this sample is shown in Table 3). In the second step, the regional brain volume of interest was entered.

The primary relationships of interest were those between insular volume and emotional responses to one of the two disgusting films. Separate regression analyses were performed for behavioral, physiological, and experiential responses (using target emotional behavior, general physiological activation, and target emotional self-report respectively as the dependent variables).

To examine the specificity of the association between insular volume and disgust responding, regression analyses were also performed to test the relationships between participants' insular volume and responses to the sad films, as well as the relationships between participants' responses to the disgusting films and other selected brain regions.

Insula and disgust film responses

Smaller total insular volumes significantly predicted less disgust behavior to the disgusting films (standardized $\beta = .43$, R^2 change = .055, $p < .05$). In contrast, total insular volume did not predict general physiological activation to the disgusting films (standardized $\beta = .16$, R^2 change = .008, ns). Analyses of individual physiological measures revealed that lower total insular volume significantly predicted less general somatic activity in response to the disgusting films (standardized $\beta = .56$, R^2 change = .095, $p < .05$). Finally, lower total insular volume significantly predicted less self-reported disgust to the disgusting films (standardized $\beta = .44$, R^2 change = .059, $p < .05$). Thus, the hypotheses that lower insular volume would predict less disgust behavior as well as less self-reported disgust experience in response to a disgusting film were supported. The hypothesis that lower insular volume would predict less general physiological activation in response to a disgusting film was not supported, though lower insular volume did predict less general somatic activity in response to a disgusting film.

Insula and sad film responses

Total insular volume did not predict sad behavior to the sad films (standardized $\beta = .35$, R^2 change = .036, ns). In addition, total insular volume did not predict general physiological activation to the sad films (standardized $\beta = .01$, R^2 change = .000, ns). Examining the individual physiological measures, analyses revealed that lower total insular volume significantly predicted less general somatic activity in response to the sad films (standardized $\beta = .50$, R^2 change = .077, $p < .05$). And lastly, total insular volume did not predict self-reported sadness in response to the sad films (standardized $\beta = -.082$, R^2 change = .002, ns). Thus, the exploratory analyses revealed that insular volume and participants' behavioral and experiential responses to a sad film were not significantly related, but lower insular volume was associated with less general somatic activity in response to a sad film.

Additional brain regions and disgust film responses

Pallidum: Total pallidum volume did not predict disgust behavior to the disgusting films (standardized $\beta = -.03$, R^2 change = .001, ns), nor did it predict general physiological activation to the disgusting films (standardized $\beta = .00$, R^2 change = .000, ns). Individual physiological measures were examined, and analyses uncovered no significant relationships between the

pallidum and any of the individual channels. And finally, total pallidum volume did not predict self-reported disgust to the disgusting films (standardized $\beta = .01$, R^2 change = .000, *ns*). Thus, the exploratory analyses revealed that pallidum volume was not related to disgust film responses.

Putamen: Total putamen volume did not predict disgust behavior to the disgusting films (standardized $\beta = .19$, R^2 change = .033, *ns*). In addition, total putamen volume did not predict general physiological activation to the disgusting films (standardized $\beta = .09$, R^2 change = .007, *ns*). Individual physiological measures were examined, and analyses revealed no significant relationships between the putamen and any of the individual channels. And lastly, total putamen volume did not predict self-reported disgust to the disgusting films (standardized $\beta = .09$, R^2 change = .008, *ns*). Thus, the exploratory analyses revealed that putamen volume was not related to disgust film responses.

Caudate: Total caudate volume did not predict disgust behavior to the disgusting films (standardized $\beta = .11$, R^2 change = .010, *ns*). Total caudate volume also did not predict general physiological activation to the disgusting films (standardized $\beta = .19$, R^2 change = .030, *ns*). Individual physiological measures were examined, and analyses revealed no significant relationships between the caudate and any of the individual channels. And lastly, total caudate volume did not predict self-reported disgust to the disgusting films (standardized $\beta = .11$, R^2 change = .010, *ns*). Thus, the exploratory analyses revealed that caudate volume was not related to disgust film responses.

Amygdala: Total amygdala volume did not predict disgust behavior to the disgusting films (standardized $\beta = .12$, R^2 change = .012, *ns*). In addition, total amygdala volume did not predict general physiological activation to the disgusting films (standardized $\beta = .14$, R^2 change = .018, *ns*). Individual physiological measures were examined, and analyses uncovered no significant relationships between the amygdala and any of the individual channels. And finally, total amygdala volume did not predict self-reported disgust to the disgusting films (standardized $\beta = .22$, R^2 change = .040, *ns*). Thus, the exploratory analyses revealed that amygdala volume was not related to disgust film responses.

Discussion

Disgust is an emotion that plays an integral role in helping individuals avoid contaminated and other undesirable objects in the environment. This emotion, which is critically important for basic survival as well as for successful social and moral functioning, appears to be diminished in bvFTD. Consistent with this, caregivers have reported that some bvFTD patients pick up garbage, drink beverages found on the street, eat out of trashcans, and sample food off of strangers' plates, suggesting these patients may have a compromised disgust response. Recent findings from our laboratory have been consistent with these anecdotal reports, demonstrating that patients with bvFTD showed deficits in disgust reactivity in a controlled laboratory setting (Eckart et al., 2012). The present study sought to build upon these findings, extending them by including a more evocative disgusting film as well as evaluating the specificity of any bvFTD disgust deficit by also examining patients' emotional reactivity to a sad film. In addition, the present study utilized a neurologically varied sample of participants to explore the relationship

between disgust and the insula, a region of the brain thought to be particularly important for disgust processing (e.g., Adolphs et al., 2003). The specificity of this association was also examined. This two-pronged approach (conducting group comparisons as well as brain-behavior regressions) enabled both a detailed analysis of disgust reactivity in bvFTD and a broader investigation of the neural correlates of disgust across diagnoses. Using this approach, group differences in disgust reactivity emerged between bvFTD patients and neurologically healthy controls, the specificity of this deficit was confirmed, and some light was shed on the neural correlates of disgust.

Disgust Reactivity in bvFTD

In the present study, in response to a disgusting film bvFTD patients exhibited less disgust facial behavior, were less physiologically reactive, and reported experiencing less subjective disgust than controls. These group differences were most robust in the physiological domain, while differences in disgust facial behavior and self-reported disgust were significant at the trend level. And, though there was a trend-level group difference in self-reported disgust, we note that the self-reported domain produced the weakest result (e.g., the repeated measures film by diagnosis interaction reached a significance level of only .981). In our experience, assessing self-reported emotional experience reliably in patients with bvFTD is difficult.

All of these findings together are consistent with previous work (Eckart et al., 2012) and align with anecdotal reports that disgust responses seem to be greatly reduced in bvFTD. Disgust continues to be an important emotion to explore in this population, because deficits in disgust reactivity may shed light on the unusual and socially inappropriate behaviors engaged in by bvFTD patients outside of the laboratory. It is possible that loss of disgust may not only be related to patients' lack of aversion to physically contaminated objects, but could also play a role in the changes that occur in their moral decision-making and behavior (Mendez, Chen, Shapira, & Miller, 2005).

Responses to a sad film were also examined in the present study in order to determine whether disgust was a uniquely compromised emotion in this population. As expected, bvFTD patients and controls did not differ in their behavioral, physiological, or experiential responses to a sad film. This builds on a previous finding from our laboratory that documented intact sadness reactivity (though that finding was for a different group of participants and included additional FTD subtypes; Werner et al., 2007). Also, importantly, the sadness finding from the present study suggests that the disgust deficits observed in these bvFTD patients cannot be explained by a general blunting of all negative emotions.

Neural Correlates of Disgust

Emotional responses are complex and likely involve multiple neural networks. However, there are a few emotions that have been consistently linked in the literature with particular brain regions; disgust is one of these emotions, having been often associated with the insula (e.g., Wright et al., 2004). The present study examined the relationship between insular volume and disgust film responses within a neurologically varied sample, and examined the specificity of that connection.

In the present study, responses to a disgusting film were associated with insular volume. As hypothesized, lower insular volume predicted less disgust behavior and less self-reported

disgust in response to a disgusting film. These results are consistent with findings that insular damage is related to deficits in disgust responding (e.g., Adolphs et al., 2003) and lend support to the idea that a possible neural explanation for the disgust deficit in bvFTD may lie in the insula, which typically incurs significant loss in the early stages of the disease (Rosen et al., 2002b). Contrary to expectation, insular volume was not significantly associated with general physiological activation to a disgusting film. This was surprising, given suggestions that the insula plays an important role in autonomic regulation and bodily sensations in general (e.g., Mutschler et al., 2009). It is conceivable that this relationship would become apparent with a larger subject pool. It is also possible that our measures of physiological responding were not ideal for disgust. Our measures largely sample cardiovascular, electrodermal, and somatic activity, but disgust may be more closely associated with gastric activity. Thus, measures such as a gastroenterogram, which provides information about the electrical activity in the stomach and intestines, could potentially be useful in obtaining a more relevant measure of physiological activity in disgust. And finally, although the present study did not find a significant relationship between insular volume and a general physiological response to disgusting stimuli, insular volume did (positively) predict participants' physical movement in response to a disgusting film. This is consistent with the idea that the insula plays a role in motor modulation (Flynn et al., 1999).

In order to test the emotional specificity of the observed relationship between insular volume and disgust film responses, the present study examined the association between insular volume and sad film responses. These analyses revealed that the insula was not significantly related to participants' sad behavior or self-reported sadness in response to a sad film. The insula was also not related to general physiological activation in response to the film. However, the insula *was* significantly (and positively) related to participants' physical movement in response to a sad film. Overall, these findings suggest that the insula may be important in some ways for all emotions (Craig, 2009), but disgust and the insula might have a particularly close relationship (e.g., Wicker et al., 2003).

In order to test the anatomical specificity of the relationship between insular volume and disgust film responses, the present study examined the associations between responses to a disgust film and other brain regions. There is some evidence in the literature that disgust may also be linked to the pallidum, putamen, and caudate (Gray et al., 1997; Murphy et al., 2003; Sprengelmeyer et al., 1998), so the relationships between these regional volumes and disgust film responses were tested. No significant relationships were found. The present study also tested the connection between the amygdala and disgust film responses; the amygdala is thought to be especially associated with the emotion of fear (Phan et al., 2002), and was not expected to be associated with disgust film responses. Indeed, no significant relationships were found. These findings suggest that there may well be some degree of specificity in the relationship between the insula and disgust responding.

Implications

BvFTD is a rapidly progressing neurodegenerative disease that dramatically alters emotional and social behavior, and is often misdiagnosed early in the disease course (Pasquier, Lebert, Lavenex, & Guillaume, 1999). Our laboratory is working to provide a differentiated picture of the domains of emotional sparing and loss in bvFTD, with the ultimate hope that a solid understanding of the emotional landscape of this disease will help to improve its early

diagnosis. The present study builds on previous research from our laboratory (Eckart et al., 2012; Werner et al., 2007) and further refines our understanding of the emotional capabilities of patients with bvFTD. In addition, it contributes to the understanding of the anatomical substrates of emotional deficits by finding that, in a neurologically varied sample consisting of healthy controls and patients with bvFTD, AD, CBD, or PSP, regional brain volumes of the insula are related to participants' responses to disgusting stimuli. Importantly, this brain-behavior relationship is somewhat specific. This finding has implications for helping to understand the emotional changes that occur in disorders where insula loss is involved (including bvFTD, other FTD subtypes, AD, CBD, and PSP) and in improving our general understanding of how emotion is organized in the brain.

Strengths and Limitations

The present study had several strengths, including our use of objective laboratory measures (rather than relying on caregiver or clinician reports) as well as our measurement of multiple domains of emotional responding (behavioral expression, physiological reactivity, and self-reported emotional experience). In addition, the present study utilized two data analytic strategies in order to examine disgust reactivity in bvFTD patients (compared to healthy controls) and in the brain (across diagnoses). Using several different neurological patient populations in our brain-behavior sample provided a greater heterogeneity in both behavior and anatomy, arguably adding to our ability to detect associations between brain volumes and emotion variables.

Several limitations of the present study should also be taken into consideration. First, we did not assess disgust responding on repeated occasions within the same individuals, thus we cannot know exactly when in the course of bvFTD deficits in disgust reactivity first appear. Second, in our brain-behavior regressions we explored associations between emotional responses and regional volumes of the insula, basal ganglia, and amygdala. Although these regions were chosen because of their presumed roles in disgust and other negative emotions, this approach may have neglected to find additional brain regions that play important roles in disgust.

Conclusion

Disgust is an emotion that is important for basic survival, in addition to being important for effective social and moral functioning. Anecdotal reports and previous research from our laboratory have suggested that disgust reactivity is impaired in bvFTD (Eckart et al., 2012). The present study builds upon these results, finding that bvFTD patients exhibited diminished disgust reactivity in behavioral, physiological, and experiential domains. These patients did not differ from healthy controls in their responses to sad stimuli, suggesting that the observed disgust deficit cannot be explained by a general blunting of negative emotions. In terms of associated brain structures, the present study found that within a neurologically varied sample, insular volume was significantly related to disgust responding; results also indicated that this relationship is somewhat specific. The present study underscores the usefulness of applying techniques derived from basic affective science to the study of emotional functioning in patients with neurodegenerative disease (Levenson et al., 2008). These findings expand upon our previous work, shed light on the neural correlates of disgust, and provide additional information about areas of preserved and compromised functioning in bvFTD.

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Table 1: *Demographic variables of the group comparisons sample*

	bvFTD (n = 41)	Controls (n = 50)	Statistical test values
Age M (SD)	60.2 (6.8)	67.3 (7.2)	$F(1,89) = 23.44, p < .05$
Sex M/F	35/6	22/28	$\text{Chi-Square}(1) = 16.47, p < .05$
MMSE M (SD)	26.8 (3.6)	29.5 (.89)	$F(1,82) = 24.65, p < .05$

Note: Statistical test values for age and MMSE are from a one-way ANOVA comparing the two groups. Three patients with bvFTD and four controls did not have MMSE data. Statistical test values for sex are from a crosstabulation using a Pearson Chi-Square test. bvFTD = behavioral variant frontotemporal dementia; MMSE = Mini-Mental State Examination.

Table 2: *Facial behavior, physiological reactivity, and self-reported emotional experience of the group comparisons sample*

	bvFTD (n = 41)	Controls (n = 50)	Statistical test values
Disgust facial beh. to disgust film	10.02	20.37	$F(1,85) = 3.21, p < .1$
Sad facial beh. to sad film	8.47	10.74	$F(1,85) = .08, ns$
Physio. reactivity (composite) to disgust film	-.110	.103	$F(1,85) = 4.22, p < .05$
Physio. reactivity (composite) to sad film	.060	-.051	$F(1,85) = .30, ns$
Self-reported disgust to disgust film	1.37	1.80	$F(1,85) = 3.29, p < .1$
Self-reported sadness to sad film	1.10	1.46	$F(1,85) = 2.22, ns$

Note: Statistical test values are from GLM analyses with diagnosis and data collection wave as fixed factors and age and sex as covariates; main effects for diagnostic group are reported here. bvFTD = behavioral variant frontotemporal dementia.

Table 3: *Demographic variables of the neurologically varied sample*

	bvFTD (n = 21)	AD (n = 15)	CBD/PSP (n = 8)	Controls (n = 30)	Statistical test values
Age M (SD)	60.4 (5.7)	63.1 (8.2)	64.1 (4.7)	67.2 (7.1)	$F(3,70) = 4.32, p < .05$
Sex M/F	19/2	7/8	4/4	12/18	$\text{Chi-Square}(3) = 13.93, p < .05$
MMSE M (SD)	26.4 (3.3)	21.1 (5.5)	22.9 (6.4)	29.3 (1.0)	$F(3,67) = 18.60, p < .05$

Note: Statistical test values for age and MMSE are from a GLM analysis comparing the four groups. One patient with AD, one patient with PSP, and one control did not have MMSE data. Statistical test values for sex are from a crosstabulation using a Pearson Chi-Square test. bvFTD = behavioral variant frontotemporal dementia; AD = Alzheimer's disease; CBD/PSP = corticobasal degeneration/progressive supranuclear palsy; MMSE = Mini-Mental State Examination.