Modulatory Influences of Negative and Positive Emotion on the Acoustic Startle Eyeblink Reflex: An Examination of their Neural and Behavioral Correlates in Patients with Neurodegenerative Disease

by

Anita Anil Madan

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Psychology

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor Robert W. Levenson, Chair
Professor Stephen P. Hinshaw
Professor Ann M. Kring
Professor Arthur Shimamura
Professor William J. Jagust

Spring 2010

Abstract

Modulatory Influences of Negative and Positive Emotion on the Acoustic Startle Eyeblink Reflex: An Examination of their Neural and Behavioral Correlates in Patients with Neurodegenerative Disease

Anita Anil Madan

Doctor of Philosophy in Psychology

University of California, Berkeley

Professor Robert W. Levenson, Chair

The startle reflex is a primitive defensive response. Research has shown that the strength of its expression varies as a function of the organism's internal state. The startle response is enhanced in the context of negative emotions (negative-potentiation) and inhibited in the context of positive emotions (positive-attenuation). Based on animal studies, emotional influences on startle responding are thought to be mediated by subcortical systems in the brain (e.g., amygdala and nucleus accumbens). However, the neuroanatomical basis for the emotion modulated startle not been well-characterized in humans. Furthermore, researchers have not examined the consequences of impairments in the emotion modulated startle for functioning in everyday life. The present study attempted to clarify these issues.

The neuroanatomical and real-world behavioral correlates of the emotion modulated startle were examined in patients with neurodegenerative disease, who display a range of impairments in both the brain and behavior. The patient group primarily consisted of patients with frontotemporal lobar degeneration, a disease that causes profound changes in social and emotional functioning, and which selectively targets frontal, temporal, and subcortical systems in the brain – regions that have been implicated in the emotion modulated startle. A smaller group of patients with Alzheimer's disease was included to determine whether findings generalized to patients with more posterior neural atrophy. Finally, neurologically healthy controls were included to ensure that the typical emotion modulated startle pattern was obtained using the procedures applied in this study.

Participants viewed a series of negative, neutral, and positive pictures, and were intermittently exposed to a 105 dB acoustic startle stimulus while the magnitude of their startle eyeblink reflex was measured. Negative-potentiation and positive-attenuation scores were related to three brain regions of interest in the right- and left- hemisphere: the amygdala, nucleus accumbens, and orbitofrontal cortex (OFC). Finally, emotion modulation scores were related to caregiver-ratings of behavioral disturbance seen in patients' everyday lives.

The control group displayed the typical startle modulation pattern, with the largest startle eyeblink responses in the negative, followed by neutral, followed by positive condition. The patient group, as a whole, did not differ from the control group in terms of overall modulation pattern. However, among the patients, variability in startle modulation was related to neural loss in specific brain regions. Consistent with the animal literature, neural loss in the right amygdala

was associated with diminished negative-potentiation of the startle, but had no effect on positive-attenuation of the startle. Contrary to the animal literature, there was no association between the nucleus accumbens and positive-attenuation. However, neural loss in the left medial orbitofrontal cortex (OFC), a region that is functionally connected with the nucleus accumbens and involved in contextually-sensitive appraisals of positive/rewarding stimuli, was associated with enhanced positive-attenuation of the startle. Finally, when real-world behavioral correlates of the emotion-modulated startle were investigated, caregiver ratings of patients' day-to-day anxiety correlated with the level of negative-potentiation they displayed in the lab.

These findings support the idea that negative-potentiation and positive-attenuation of the startle response have distinct neuroanatomical bases. They also provide evidence of hemispheric specialization in the emotion modulated startle, with the right hemisphere supporting negative-potentiation, and the left-hemisphere supporting positive-attenuation. Finally, this study demonstrated that variation in the simple modulatory responses measured in the emotion modulated startle task can predict functional disturbances in real-world behavior.

Modulatory Influences of Negative and Positive Emotion on the Acoustic Startle Eyeblink Reflex: An Examination of their Neural and Behavioral Correlates in Patients with Neurodegenerative Disease

Introduction

The startle reflex is a defensive response to sudden and intense stimulation that is present in all mammals, reptiles, birds, and amphibians (Simons, 1996). It consists of a sequence of involuntary muscle contractions that serve to interrupt behavior and withdraw the body from imminent harm (Lang, Bradley & Cuthbert, 1990). These evolutionarily hard-wired behaviors are mediated by low-level brain stem circuitry (Davis, Walker, & Lee, 1999), which allows for rapid mobilization of a response prior to conscious awareness of the elicitor. Over the past thirty years, the simple startle response has gained prominence in psychological research (Grillon & Baas, 2003). Given its primitive nature this may seem surprising. However, an accumulating body of research has demonstrated that startle behavior is influenced by a number of contextual factors of interest to psychologists. The intensity of startle responding is particularly sensitive to variations in the organism's internal state, including factors of attentional engagement, emotion, and motivation (see Lang, 1995 for a review). By manipulating these factors under highly controlled experimental conditions, the startle reflex has proven to be a simple and powerful tool for probing ongoing affective and mental processes.

The Emotion Modulated Startle Response

The focus of this dissertation is on the well-established finding that emotional states, varying in valence, differentially modulate the magnitude of a concurrently elicited startle eyeblink reflex. Specifically, following the induction of a negative emotional state (usually by highly arousing picture stimuli), an independently evoked startle eyeblink response is increased in magnitude relative to its response in a neutral emotion condition. This is referred to as "negative-potentiation." Conversely, following the induction of a positive emotional state, the magnitude of an independently evoked startle eyeblink response is inhibited relative to its response in a neutral emotion condition. This is referred to as "positive-attenuation." These are highly replicable phenomena that have been demonstrated across startle probe modalities (acoustic: e.g. Vrana, et al., 1988; tactile: Hawk & Cook, 1997; visual: Bradley, Cuthbert, & Lang, 1990; Erickson, Levenston, Curtin, Goff, & Patrick, 1995), startle probe intensities (Cuthbert, Bradley, & Lang, 1996), and methods for eliciting emotion (films: Jansen & Frijda, 1994; odors: Miltner, Matjak, Braun, Diekmann, & Brody, 1994; Erlichman, Brown, Zhu, & Warrenburg, 1995; sounds: Bradley et al., 1994). Furthermore, alterations in the emotion modulated startle have been identified in a number of forms of psychopathology (e.g. fear and phobia: Hamm, Cuthbert, Globisch, & Vaitl, 1997; schizophrenia: Schlenker, Cohen, & Hopmann, 1995; psychopathy: Patrick, Bradley, & Lang, 1993), indicating the utility of this paradigm for clinical research.

Although the neural basis of the primary startle reflex is well understood, the neural bases of the emotional systems that exert modulatory influences on the startle reflex have not been well characterized in humans. Elucidating these neural systems will shed light on our understanding of normal and pathological emotion processing. In addition, although the emotion modulated startle paradigm has been useful in characterizing aberrations in emotion processing in a number

of forms of psychopathology, few studies have attempted to assess whether deficits in this laboratory-based measure are associated with measures of real-world functional impairment. This study attempts to address these gaps by studying the neural and real-world behavioral correlates of the emotion modulated startle response in a sample of patients with neurodegenerative disease.

In the sections that follow, I first present a theoretical account of the emotion modulated startle response that describes its psychological and clinical significance. Next, I review the characteristics of the basic startle response, focusing on its elicitation, behavioral profile, and neuroanatomy. Then I review the limited literature on the neural systems that modulate the basic startle. Finally, I present the rationale for using lesion patients as a model to examine (a) brain-behavior relationships and (b) real-world functional impairment, along with a description of the patients studied in the present research.

Psychological and Clinical Significance of the Emotion Modulated Startle

The basis of the emotion modulated startle pattern has been explained using a theoretical model that organizes emotional experience into two basic and opposing motivational systems (Lang, 1995). According to this model, emotions are conceptualized as action tendencies that are fundamentally rooted in an aversive or appetitive motivational system. These systems are thought to have evolved to mediate the organism's transactions with environmental stimuli that threaten or promote survival (Lang et al., 1990). The aversive motivational system evolved to respond to stimuli that signal threat; its general goal is to facilitate actions that remove the organism from potential harm. The appetitive motivational system evolved to respond to stimuli that signal reward or opportunities; its general goal is to facilitate actions that move the organism toward a desired stimulus. Each of these motivational systems is linked with its own set of action programs, associations, and mental representations, which have greater chance of access and greater strength of activation when that system is engaged. Consequently, when one system is engaged, associations linked to the non-engaged system have a lesser chance of access and reduced strength of activation (Lang, 1995). Thus, an individual who is in an unpleasant emotional state, and aversively motivated, will respond with greater likelihood and strength to other aversive cues, like a startle probe, because processing resources are engaged in noticing and responding to aversive events. On the other hand, an individual who is in a positive emotional state, and appetitively motivated, will respond with reduced likelihood and strength to an aversive cue, like a startle probe, because processing resources are engaged in orienting the individual toward a desirable event.

These modulatory responses are thought to reflect simple "motivational priming" phenomena that proceed without placing demands on high-level control processes (Bradley, Cuthbert, & Lang, 1999). Once the emotional stimulus is appraised, modulation of the startle response occurs automatically. Examples of motivational priming are ubiquitous in everyday life (e.g., Bargh, Gollwitzer, Lee-Chai, Barndollar & Troetschel, 2001). Indeed, emotions are commonly viewed as playing an important role in coloring people's thoughts, perceptions, and actions. It has been argued that the emotional modulated startle represents the most fundamental, and primitive, form of motivational priming (Lang, 1995).

Consistent with the "motivational priming" account, emotional stimuli that most directly activate aversive and appetitive systems, respectively, are those associated with the greatest modulation of startle responding. For instance, startle responding is most robustly and reliably potentiated in the context of threatening animal and human stimuli that elicit fearful and aversive states, and it is most robustly attenuated in the context of erotic stimuli that elicit positive and appetitive states (Bradley et al., 2001; Gard, Gard, Mehta, Kring, & Patrick, 2007). Studies examining startle modulation in the context of emotional stimuli that do not clearly engage the aversive or appetitive system have yielded less consistent modulatory responses. For instance, mutilated victim stimuli, which are often employed in startle studies because they are rated as highly negative and highly arousing, may produce a range of emotional responses – from disgust, to fear, to compassion – and subsequently tap into either the aversive (for fear or disgust) or appetitive (for compassion) system. Studies employing these stimuli have found both startle-potentiation and attenuation (see Grillon & Baas, 2003 for a review). Similarly, positive stimuli that are less arousing or motivationally salient (e.g. pleasant nature scenes) have yielded less robust attenuation of the startle (Bradley et al., 2001).

Individual differences in motivational system sensitivity also moderate the degree of startle modulation. A number of studies in nonclinical samples have demonstrated that individuals high on personality dimensions related to fear/threat sensitivity show enhanced negative-potentiation of the startle (Cook, Hawk, Davis, & Stevenson, 1991; Grillon, Ameli, Foot, & Davis, 1993; Corr, Wilson, Fotiadou, & Kumari, 1995). Complementary findings have been found in the clinical literature. Pathological fear in phobic patients has been associated with enhanced negative-potentiation of the startle (e.g., Hamm, Cuthbert, Globisch, & Vaitl, 1997). On the other hand, pathological *lack of fear* in psychopathy has been associated with a lack of negative-potentiation of the startle (e.g., Patrick, Bradley, & Lang, 1993). In both phobic participants and individuals with psychopathic traits, altered startle modulation is specific to threatening stimuli. Positive stimuli produce comparable levels of startle attenuation among both of these groups as they do among controls (Hamm et al., 1997; Patrick et al., 1993).

The relationship between individual differences in appetitive motivation sensitivity and inhibition of the startle has been studied less extensively. Only one study in a nonclinical sample directly tested whether individual differences in appetitive system sensitivity were associated with enhanced positive-attenuation of the startle. Hawk & Kowmas (2003) found that subjects high on a personality trait related to reward responsiveness showed enhanced positive-attenuation relative to controls. Reward responsiveness was unrelated to negative-potentiation.

In summary, these studies indicate that the emotion modulated startle probes the sensitivity of motivational systems governing responses to threatening and rewarding emotional stimuli. Furthermore, these studies indicate that individual differences in sensitivity to threatening and rewarding stimuli *selectively* moderate the degree of startle-potentiation and attenuation, respectively. This last point suggests that the aversive and appetitive systems driving the emotion modulated startle are dissociable and have differing neuroanatomical substrates. Before turning to an examination of the neuroanatomical systems that modulate the primary startle reflex, however, it is important to lay the foundation for such an analysis first by describing the systems involved in the elicitation of the startle reflex itself.

Startle Elicitation

Studies of human startle reflex modification have generally examined the acoustic startle reflex. The acoustic startle reflex is reliably elicited by brief (<50ms), intense (>90dB) sounds with near instantaneous rise times. Early research on human startle responding used a particularly aversive (>110dB) stimulus to elicit the prototypical whole-body startle. This response was originally characterized in the pioneering work of Landis and Hunt (1939) using a pistol shot and frame-by-frame analyses of high-speed motion pictures. They identified a sequence of stereotyped behaviors consisting of an immediate eyeblink followed by a series of protective movements to withdraw the head, neck, and torso from danger. Later research used a less noxious, lower intensity stimulus (90-105 dB) that, while insufficient to engage the prototypical whole-body response, was of strong enough intensity to elicit the eyeblink reflex: the fastest and most reliable element of the whole-body startle sequence (Lang, Bradley & Cuthbert, 1990). Compared to the high intensity acoustic startle stimulus, the lower intensity stimulus is less disruptive of ongoing behavior, is less likely to produce a secondary aversive reaction, and demonstrates more rapid recovery. Though the eyeblink response habituates quickly at short inter-stimulus intervals, it can dishabituate quickly, allowing for repeated presentations in a relatively brief experimental session (as many as 40-50 probes within a thirty minute session) (Lang & Bradley, 1990). As such, it has proved useful in repeated-measures designs, such as the emotion modulated startle, where startle probes are presented several times, under varying conditions.

Neuroanatomy of the Acoustic Eyeblink Reflex

The neuroanatomical basis of the acoustic startle reflex has been well-characterized. The startle response originates at the level of the brain stem. The eyeblink reflex, specifically, involves contraction of the obicularis oculi, a set of muscle fibers that encircle the eye. The obicularis oculi is innervated by the facial nerve, which emanates from the facial motor nucleus located at the pontine level of the brain stem (Berg & Balaban, 1999). In rodents, an acoustic startle stimulus activates this brain stem nucleus via a simple three-synapse pathway from (1) cochlear root neurons in the auditory canal onto (2) neurons in the nucleus reticularis pontis caudalis of the brain stem (believed to be the primary sensorimotor interface mediating the startle), onto the (3) motoneurons in the facial motor nucleus (Davis et al., 1982; Davis, Walker, & Lee, 1999). Selective ablations at any point along this pathway completely eliminate the startle response (see Davis et al., 1999, for a review). In humans, there is some debate about the intermediary connections that relay sensory input from the cochlear root neurons to the efferent neurons in the facial motor nucleus of the brainstem (Berg & Balaban, 1999). However, the critical role of the brainstem in the human startle eyeblink has been demonstrated in patients with neurodegenerative diseases. For example, the acoustic startle response is absent in patients with progressive supranuclear palsy, who display early atrophy in the nucleus reticularis pontis caudalis of the brain stem (Gironell et al., 2003).

Neuroanatomy of the Systems Modulating the Startle Response

Although the circuitry involved in the expression of the startle response is well-understood, the neural systems that *modulate* its expression are only partially understood. There is convincing evidence, however, that negative-potentiation of the startle response involves the

amygdala, a brain region that plays a well-established role in the processing of threat and the modulation of attention towards motivationally salient stimuli (see Phelps & LeDoux, 2005, for a review). Three lines of evidence from the animal literature in rodents support a critical role for the amygdala in enhancing responding to the defensive startle. First, there exist direct monosynaptic connections between the output nucleus in the amygdala and the reticular nuclei in the brain stem. Second, direct stimulation of the amygdala's output nucleus directly enhances the startle response. Third, selective ablation of this nucleus eliminates startle-potentiation in threatening contexts (see Davis et al., 1999; Lang, 1995 for a review).

Only recently have these findings been translated to humans using lesion patients (Angrilli, Mauri, Palomba, Flor, Birbaumer et al., 1996; Funayama, Grillon, Davis & Phelps, 2001; Buchanan, Tranel & Adolphs, 2004). Direct evidence for a critical role of the amygdala in human startle modulation has only been examined in one case study, which found impaired negative-potentiation in a lesion patient with damage primarily localized in the right-amygdala (Angrilli et al., 1996). This study did not assess positive-attenuation of the startle, however, leaving unanswered the question of the specificity of the amygdala in negative-potentiation. Two studies examined the emotion modulated startle response in a sample of patients with temporal lobe lesions, which included the amygdala. One study found impaired negative-potentiation following right- but not left-temporal lobe lesions (Funayama et al., 2001), whereas another found deficits following right, left, and bilateral temporal lobectomies (Buchanan et al., 2004). Notably, in each of these studies, temporal lobe damage selectively interfered with negative-potentiation while leaving positive-attenuation intact. These studies provide suggestive, but indirect, evidence for a role of the amygdala in negative-potentiation in humans. Interestingly, each of these lesion studies, including the one case study, implicates the right hemisphere in negative-potentiation, whereas the role of the left hemisphere in negative-potentiation has been demonstrated less reliably (see Buchanan et al, 2004 for a positive finding; Funayama et al., 2001 for a negative finding). Overall, evidence for the critical role of the amygdala in human negative-potentiation would be strengthened by a study that (1) directly quantified amygdala loss in a sample of lesion patients and related it to both negative-potentiation and positive-attenuation and (2) examined neural loss in other regions to demonstrate that the relation between amygdala damage and negative-potentiation was specific to amygdala loss.

The brain regions mediating the positive-attenuated startle have been studied less extensively. In one rodent study, ablation of the nucleus accumbens, a brain region involved in reward processing and appetitive behavior, selectively blocked the positive-attenuated startle while leaving negative-potentiation of the startle response intact (Koch, Schmid & Schnitzler, 1996). Like the amygdala, the nucleus accumbens has direct projections onto the nucleus reticularis pontis caudalis, the brainstem nucleus that is centrally involved in the initiation of the startle response (Koch et al., 1996), indicating that it is well-situated to modulate startle responding. However, because selective damage of the nucleus accumbens is rare in humans, no study has examined the role of this structure in the emotion modulated startle using a human sample.

It is assumed that subcortical regions that process threat and reward, such as the amygdala and nucleus accumbens, are directly involved in the modulation of brain stem-mediated reflex behavior. However, both the amygdala and nucleus accumbens are involved in

larger neural networks that may play indirect roles in startle modulation through their connections with these structures. One candidate region for such an indirect modulatory role is the orbitofrontal cortex (OFC). The OFC is intimately connected with both the amygdala and the nucleus accumbens (Kringelbach & Rolls, 2004). Like these regions, the OFC plays a role in assigning significance to incoming stimuli. However, unlike the amygdala and nucleus accumbens, neurons in the OFC adjust their responding as contingencies for stimulus reinforcement values change (Rolls, 2000). Thus, whereas the amygdala and nucleus accumbens are involved in simple threat/reward appraisals, the OFC appears to fine-tune these appraisals in a flexible, context-sensitive way.

Damage to the OFC results in a number of behavioral impairments suggestive of altered motivational processing including social disinhibition, impulsivity, euphoria, and binge eating (especially for sweets) (Viskontas, Possin, & Miller, 2007). This behavioral profile suggests that patients with OFC damage may be particularly sensitive to appetitive stimuli, and relatively insensitive to aversive stimuli. Although research has shown that OFC patients fail to use emotional reactions to guide their behavior (Bechara, Damasio & Damasio, 2000), surprisingly limited research has comprehensively assessed the integrity of these patients' reactions to emotional/motivational stimuli. Most of this work has been conducted on aversive stimuli, and the results have been equivocal. Laboratory tasks indicate that physiological responding to aversive stimuli is either intact (for loud noises: Roberts et al., 2004; Damasio, Tranel, & Damasio, 1990), enhanced (for loud noises and wrist-shock: Rule, Shimamura, & Knight, 2002), or slightly diminished (for monetary losses: Bechara, Tranel, Damasio, & Damasio, 1996). However, given the role of the OFC in appraising the motivational significance of stimuli and the observation of motivational deficits in OFC patients, it seems reasonable that OFC damage might alter responding on the emotion modulated startle.

The role of the OFC in the emotion modulated startle has not been examined directly. However, two human lesion studies have examined the emotion modulated startle in patients with traumatic brain injury, which often impacts the OFC. One study of frontal lesions due to traumatic brain injury or ischemic stroke found disrupted positive-attenuation and preserved negative-potentiation of the startle response (Sanchez-Navarro, Martinez-Selva, & Roman, 2005). However, another study of patients with traumatic brain injury found the opposite pattern of results – preserved positive-attenuation and impaired negative-potentiation (Saunders, McDonald, & Richardson, 2006). The lesion locations both within and across these studies were diverse, impacting cortical and subcortical structures extending beyond the OFC and including patients with both left- and right-sided injuries. The study that found impaired positive-attenuation included patients with lesions that, in some cases, impacted reward processing regions in the basal ganglia (Sanchez-Navarro et al., 2005). Thus, this study was unable to rule out the possibility that impaired positive-attenuation was due to damage extending to the nucleus accumbens. On the other hand, the study finding intact positive-attenuation primarily included patients with frontal and/or temporal lobe lesion locations (Saunders et al., 2006). Intact positive-attenuation in this sample is consistent with descriptions of preserved, and in some cases, enhanced reward processing in patients with OFC damage, whereas impaired negative-potentiation is consistent with prior findings of impaired negative-potentiation following lesions of the temporal lobe (Angrilli et al., 1996; Funayama et al., 2001; Buchanan et al., 2004). Though these studies did not examine the role of specific neural regions in the emotion

modulated startle, they do suggest that damage to fronto-temporal and frontal-striatal circuitry interferes with normal startle modulation. To date, no study has examined the independent contributions of frontal and subcortical neural injury to the emotion modulated startle response.

Summary of neural regions implicated in the emotion modulated startle

The most consistently implicated brain region in the emotion modulated startle is the amygdala. Animal and human lesion studies converge to implicate this region in the negative-potentiation of the startle response. However, direct evidence for the role of the amygdala in humans has only been demonstrated in one case study, and even in that patient, damage was not entirely confined to the amygdala. The role of the temporal lobes, more broadly, has been established in two studies that examined groups of lesion patients, but neither of these studies was able to establish a direct link between the amygdala and negative-potentiation of the startle.

Less is known about the neural regions underlying the positive-attenuated startle response. Although one animal study has implicated the nucleus accumbens, converging evidence from humans has not been examined. Anatomically, the amygdala and nucleus accumbens are well-situated to modulate startle responding directly, as each of these regions has direct projections to the central brain stem nucleus that mediates the startle response. However, other neural regions that are intimately connected with the amygdala and nucleus accumbens may indirectly modulate this circuitry. The OFC is a strong candidate for such a role. Anatomically, the OFC receives projections from both the amygdala and nucleus accumbens, and electrophysiological studies indicate that OFC neurons are responsive to both the punishing and rewarding consequences of stimuli. In addition, clinical evidence suggests that damage to the OFC results in deficits indicative of altered motivational processing, though the bases for these deficits remains unclear. Though no study has directly examined the role of the OFC in the emotion modulated startle, two studies of patients with traumatic brain injuries, which often impact the OFC, found impairments, suggesting a possible role for the OFC in this response.

A final question raised by the studies summarized here, is whether there are asymmetric contributions of the hemispheres to the emotion modulated startle. The studies reviewed above suggest that some aspects of the emotion-modulated startle may be lateralized. Across the studies that examined the role of the brain regions in negative-potentiation of the startle response, the right hemisphere was implicated most consistently. However, no study has examined the relative contributions of right and left hemisphere structures in the positive-attenuation of the startle. Laterality in emotion processing is an ongoing debate in the neuroscientific literature. Two competing hypotheses have been offered regarding the organization of emotion in the brain: (1) the “right hemisphere hypothesis”, which argues that the right hemisphere is preferentially involved in emotion processing (Borod, 1992), and (2) the “valence hypothesis”, which argues that the motivational component of emotion, specifically, is differentially represented in each hemisphere – particularly at the level of the frontal cortex (Davidson, 1984). Studies of resting frontal asymmetries, using EEG, have found greater relative left frontal activations in the context of positive/appetitive motivational states and greater relative right frontal activations in the context of negative/aversive motivational states (Davidson, 1984; 2000). Because EEG is limited to cortical measurements, however, it unknown whether these asymmetries extend to subcortical aspects of the motivational systems associated with these cortical activation patterns.

The Present Study

The present study aims to increase our understanding of the neural systems involved in the emotion modulated startle in humans by examining the contributions of the subcortical and cortical structures reviewed here as well as the roles of right-versus-left hemispheres in the emotion modulated startle.

Neurodegenerative Disease as a Model for Studying Emotion

Studies examining the neural bases of human emotion have used two general approaches. In one approach, functional imaging is used with neurologically intact volunteers to identify the neural systems activated in response to emotional tasks. In a second approach, performance on emotional tasks is examined in patients with brain damage. Whereas functional imaging approaches are useful for identifying the neural systems that are active during a given behavior, complementary data from lesion approaches, using patients with either focal or widespread neural pathology, are necessary for identifying which regions in those systems are critically involved (i.e., for establishing "necessity"). In general, research attempting to identify the neural regions critically involved in emotion is strengthened when the sample employed includes patients with varying lesion locations. Importantly, the effect of a given lesion on a behavior of interest may be due to the direct effect of the lesion or it may be due to the indirect effect of the lesion on processing in another structure with which it is functionally connected. Studies of patients with focal brain lesions can be limited by the range and type of lesion patients that are feasible to acquire. Neurodegenerative diseases, on the other hand, tend to be more common and they tend to impact entire neural systems selectively (Seeley et al., 2009). Moreover, the degree to which degenerative processes affect the integrity of specific structures within these systems is often variable. Thus, the substantial variation both within and across neural regions found in patients with neurodegenerative diseases offers a convenient way to study the relative contributions of a range of neural regions to a given behavior within a limited sample of patients. In the present study I examine patients with two types of neurodegenerative disease: frontotemporal lobar degeneration (FTLD) and Alzheimer's disease (AD). The neuropathology associated with these conditions has been implicated in emotion to varying degrees, and the disorders capture a range of socio-emotional deficits.

FTLD and AD are both common causes of dementia, occurring at approximately equal rates in individuals under the age of sixty (Ratnavalli et al., 2002). FTLD has received increased visibility in the past several years as a neurological condition that may provide insights into our understanding of human emotion (Levenson & Miller, 2007). Unlike AD, a disease that targets memory and results in profound cognitive decline, the core features of FTLD include social and emotional deficits that spare basic cognitive abilities in the initial stages of the disease. FTLD selectively atrophies anterior regions of the brain involved in emotion and social processing, including the frontal lobes, temporal lobes and amygdala. These are the same regions that have been implicated in the emotion modulated startle. Furthermore, the degree to which these regions are impacted in the disease is variable. FTLD is a heterogeneous syndrome that consists of three neuropathologically and clinically distinct subtypes (Neary et al., 1998). Frontotemporal dementia (FTD) is the most common subtype, which is characterized predominately by bilateral frontal disease that spreads subcortically as the disease progresses (Rosen et al., 2002). Semantic

dementia (SD) is characterized by asymmetric atrophy (primarily left- or right-sided) that begins subcortically in the amygdala and anterior temporal regions and later spreads to frontal regions (Neary et al., 1998, Rosen et al., 2002). Progressive non-fluent aphasia (PNFA), the least common subtype, is characterized by left-sided atrophy in frontotemporal regions (Fukui & Keretsz, 2000). The neuroanatomic variation in this disease makes it ideally suited for the study of the relative roles of cortical and subcortical regions, as well as left-versus-right hemispheres, in the emotion modulated startle. AD, on the other hand, tends to affect posterior brain regions involved in memory, language, and visuospatial navigation (e.g., medial temporal and parietal lobes; Braak & Braak, 1995). Though the neural systems impacted by AD have not been implicated in the emotion modulated startle, inclusion of this diagnosis offers the opportunity to examine whether neural atrophy in "non-emotional" brain systems contributes to dysfunction in the emotion modulated startle.

In addition to capturing a range of neuroanatomic variation, neurodegenerative diseases cause a range of behavioral impairments, which are particularly burdensome for caregivers (Ascher, Sturm, Seider, Holley, Miller & Levenson, in press). Behavioral deficits in FTLD are core features of the disease, and include a number of socio-emotional problems such as emotional blunting, loss of empathy, social disinhibition, euphoria, and compulsive behaviors (Neary et al., 1998). Though behavioral problems tend to emerge later in the course of AD, agitation and anxiety are often present. One question that has not yet been addressed in research employing the emotion modulated startle paradigm is how or whether alterations in the simple motivational priming response assessed on this laboratory task translate into clinically relevant behavioral problems seen in everyday life. Such an analysis would provide important insights into the down-stream consequences of this simple process for complex social and emotional functioning.

Summary of the Current Study

The primary aim of this study was to elucidate the neural regions involved in the emotion modulated startle by examining the contributions of clearly defined brain regions, which are atrophied in neurodegenerative diseases, to variations in startle modulation. Patients with FTLD were the primary focus of study, because their neurodegeneration targets the regions of interest in this study. A smaller number of AD patients was included to conduct preliminary analyses related to the generalizability of the findings. The patients in this study also displayed variable degrees of real-world behavioral problems. The secondary aim of the study was to examine whether variations in startle modulation are associated with ratings of social and emotional maladjustment observed in patients' everyday lives.

Hypotheses

Hypothesis 1: Task Validation (controls only)

The magnitude of participants' startle eyeblink responses will vary systematically as a function of emotion condition: negative > neutral > positive. Startle eyeblink magnitude will be largest when participants are viewing threatening picture stimuli (negative-potentiation) and smallest when participants are viewing positive picture stimuli (positive-attenuation).

Rationale: A number of prior studies have demonstrated this pattern of startle modulation during affective states (see Lang, 1995; 1998, for reviews). Establishing the typical modulation pattern for control subjects in the current study will provide validation of the task design and stimulus selection for the older adults presently under study.

Neural correlates of the emotion modulated startle (patients only)

Hypothesis 2: Amygdala

2a. Amygdala volume will be negatively correlated with negative-potentiation of the startle response. Patients with smaller amygdala volumes will display less negative-potentiation. This association will remain significant after controlling for intracranial volume (total head size), disease severity (assessed with the Clinical Dementia Rating scale (CDR)), age, and years of education.

Rationale: There is an extensive animal literature demonstrating that the amygdala is critical for the fear-potentiated startle in rodents (Davis et al., 1999). In humans, one previous case study, using a lesion patient with atrophy primarily confined to the right amygdala, found impaired negative-potentiation of the startle response (Angrilli et al., 1996).

2b. The role of the amygdala in the emotion modulated startle will be specific to negative-potentiation. There will be no association between amygdala volume and positive-attenuation.

Rationale: Negative-potentiation and positive-attenuation of the startle are theoretically driven by separate motivational systems with distinct neuroanatomical bases (e.g. Lang, 1995). Prior research has indicated that negative-potentiation, but not positive-attenuation, is impaired in lesion patients who have damage to the temporal lobes (Funayama et al., 2001; Buchanan et al., 2004).

2c. The association between the amygdala and negative-potentiation will be greater for the right-amygdala than it will be for the left-amygdala.

Rationale: Some researchers have suggested that the right hemisphere preferentially processes emotion (Borod et al., 2009), whereas other researchers have suggested that the right hemisphere is specialized for the processing of negative emotions (Heller, 1990), particularly for the motivational tendencies associated with negative emotions (Davidson, 2004). Both of these viewpoints support a greater role for the right hemisphere in negative-potentiation of the startle. Right-sided lesions in the temporal lobe or amygdala have been reliably associated with impaired negative potentiation of the startle (Angrilli et al., 1996; Funayama et al., 2001; Buchanan et al., 2004). Patients with left-sided lesions have only been assessed in two of these study, with one study finding no deficits (Funayama et al., 2001) and another finding deficits (Buchanan et al, 2004).

2d. The amygdala, but not the anterior temporal pole, will be associated with negative-potentiation.

Rationale. Previous studies that have examined the role of the human amygdala in negative-potentiation have used lesion patients whose damage extended beyond the amygdala (Angrilli et al., 1996; Funayama et al., 2001; Buchanan et al., 2004). These studies were unable to determine whether other regions in the temporal lobe, which are also involved in emotion processing, contributed to the impairment observed in negative-potentiation. The current study assesses the role of the anterior temporal pole in the emotion modulated startle. This region is involved in emotion processing, it is intimately connected with the amygdala, and it is often impacted among the patients under study. However, the anterior temporal pole appears to play a more complex, down-stream role in emotion processing than does the amygdala (Olson, Plotzker, & Ezzyat, 2007), and, thus, it is not expected to be involved in this simple defensive priming response.

Hypothesis 3: Nucleus Accumbens

3a. Patients with smaller nucleus accumbens volumes will display less positive-attenuation of the startle. This association will remain significant after controlling for intracranial volume (total head size), disease severity (assessed with the CDR), age, and years of education.

Rationale: The nucleus accumbens is involved in reward processing and appetitive motivation, and it directly synapses onto the brain stem nucleus that mediates the startle response. One animal study has shown that ablation of the nucleus accumbens disrupts positive-attenuation of the startle in the context of a conditioned cue for reward (Koch et al., 1996). However, the role of this region has not been explored in human lesion studies due to the rarity of isolated lesions to this region.

3b. The role of the nucleus accumbens in the emotion modulated startle will be specific to positive-attenuation. There will be no association between the nucleus accumbens and negative-potentiation.

Rationale: Though positive-attenuation of the startle was disrupted in nucleus accumbens-lesioned rodents, Koch et al. (1996) found that the fear-potentiated startle remained intact.

3c. Exploration of competing hypotheses: laterality:

1. Right hemisphere hypothesis: The association between the nucleus accumbens and positive-attenuation will be greater for the right-nucleus accumbens
2. Valence hypothesis: The association between the nucleus accumbens and positive-attenuation will be greater for the left-nucleus accumbens.

Rationale: Laterality in the positive-attenuation of the startle response has not been examined in previous studies. Evidence for the valence hypothesis largely comes from the EEG asymmetry literature, which implicates the left hemisphere in motivational processing associated with positive emotions (Davidson, 2004). However, these findings are related to asymmetries in the frontal lobes. Because EEG is unable to probe activation associated with subcortical structures, it is unclear whether these asymmetries extend to the subcortical aspects of these motivational systems.

Hypothesis 4: Orbitofrontal Cortex

4a. Patients with smaller OFC volumes will display enhanced positive-attenuation of the startle response. This association will remain significant after controlling for intracranial volume (total head size), disease severity (assessed with the CDR), age, and years of education.

Rationale: Enhanced positive-attenuation is presumably related to enhanced sensitivity of the appetitive motivational system. Clinically, damage to the OFC is associated with social disinhibition, euphoria, and impulsive behavior—deficits which are suggestive of increased sensitivity to appetitive stimuli.

4b. The association between the OFC and positive-attenuation will be greater for the left- than for the right-OFC.

Rationale: Research suggests that the motivational processing associated with emotions is lateralized at the level of the frontal lobes, and that left-frontal regions are specialized for positive/appetitive motivational processing (Davidson, 2004).

4c. Exploratory: OFC and negative-potentiation.

Disinhibited behaviors following OFC damage may also be indicative of reduced sensitivity of the aversive-motivational system. This would suggest that negative-potentiation would be diminished following OFC damage. However, research findings suggest that OFC patients' responses to aversive stimuli are either intact (Roberts et al., 2004; Damasio et al., 2000) or enhanced (Rule, Shimamura, & Knight, 2002). These findings would suggest that negative-potentiation would either be intact or enhanced following OFC damage.

4d. Within the frontal lobes, only the OFC will be associated with the emotion modulated startle.

Rationale: Although no prior study has specifically examined the role of the OFC in the emotion modulated startle, two studies have examined the emotion modulated startle in patients with traumatic brain injury (TBI) and found impairments. TBI results in heterogeneous lesions that often include the OFC, but can also affect other regions of the frontal lobes as well as subcortical regions. The current study assesses the role of the dorsolateral prefrontal cortex (DLPFC) in the emotion modulated startle. Like the OFC, this region of the frontal cortex is

involved in motivated processing. However, the DLPFC is involved in high-level control of cognitive processing (e.g., working memory), and, thus, it is not expected to be involved in the simple defensive priming response presently under study.

Behavioral correlates of the emotion modulated startle (patients only)

Hypothesis 5: Real world behavioral problems will be assessed using informant-based ratings from the Neuropsychiatric Inventory (NPI).

1. Behaviors expected to be related to variability in the emotion modulated startle response are: anxiety, disinhibition, euphoria, and eating behaviors. Specifically, negative-potentiation is expected to be correlated with anxiety, and positive-attenuation is expected to be correlated with disinhibition, euphoria, and eating behaviors.

    Rationale: Negative-potentiation is theoretically a measure of aversive motivational system sensitivity. Individuals who are more sensitive to aversive cues should display higher levels of anxious behavior in their day-to-day lives. Positive-attenuation is theoretically a measure of appetitive system sensitivity Individuals who are more sensitive to cues for reward should display higher levels of disinhibition, euphoria, and problematic eating behavior.

Method

Participants

Patients were recruited from the Memory and Aging Clinic at the University of California, San Francisco (UCSF). Controls were recruited through advertisements in the community. The study was approved by the University of California, Berkeley (UCB) Committee for the Protection of Human Subjects and the UCSF and San Francisco Veterans Affairs Medical Center (SFVAMC) Committee on Human Research. Written informed consent was obtained from all participants as well as from each patient's spouse or other caregiver. All patients underwent neuroimaging and medical, neurological and neuropsychological testing at UCSF and SFVAMC, and were then scheduled for a day-long testing session at the Berkeley Psychophysiology Laboratory at UCB.

Twenty-three patients were included in the study. Of these, 18 were diagnosed with FTLD (12 with frontotemporal dementia, 5 with semantic dementia, 2 with progressive aphasia) and 5 were diagnosed with possible or probable AD. FTLD patients were sampled more heavily, as the neuroanatomical and behavioral variation in these patients was of primary interest for the brain and behavior questions of this study. A smaller number of AD patients was included to conduct preliminary analyses related to the generalizability of the findings. Diagnoses for the FTLD and AD patients were made by an attending neurologist at UCSF using published research criteria (Neary et al., 1998; McKhann et al., 1984). The control group consisted of 14 participants who were free of psychiatric and neurological impairment.

Participants were paid $30 for participating in the 6-hour experiment.

Sample Demographics

Age. The mean age of the participants in the FTLD group was 64.8 years (standard deviation (SD) = 6.1), the mean age of participants in the AD group was 60 years (SD = 6.4), and the mean age of participants in the control group was 65 years (SD = 12.4). The groups did not differ significantly in age (F (3, 33) = .63, n.s.).

Sex. Seventy-two percent of the FTLD patients were male, 80% of the AD patients were male, and 43% of controls were male. The groups did not differ significantly in sex composition (χ^2 (3, N = 37) = 3.7, n.s.).

Education. The mean number of years of education completed was 15.0 years (SD = 3.4) in the FTLD group, 15.4 years in the AD group (SD = 3.5), and 18.3 years in the control group (SD = 2.0). Years of education differed significantly among the groups (F (3, 33) = 5.2, $p < .05$). Controls were significantly more educated than both FTLD (F (2, 29) = 9.4, $p < .01$) and AD patients (F (2, 16) = 4.9, $p < .05$). Education was included as a covariate in the analyses examining neuroanatomical correlates.

Clinical Characteristics of the Sample

Mini-Mental State Examination (MMSE). General cognitive status was assessed with the MMSE (Folstein, Folstein, & McHugh, 1975). The MMSE is a brief measure that assesses a number of domains of cognitive functioning including orientation, memory, attention, visuospatial processing, and language. Scores range from 0 to 30, with lower scores indicating greater cognitive impairment. The mean score for FTLD patients was 23.9 (SD = 5.6), which is in the mild range of impairment. The mean score for the AD patients was 18.8 (SD = 7.2), which is in the moderate range of impairment. Controls scored near ceiling, with average scores of 29.5 (SD = .7). The level of impairment found in the patient groups is typical of these populations; AD patients generally display lower MMSE scores due to the greater reliance of MMSE scores on memory and language, which are relatively spared early in the course of FTLD (Kramer et al., 2003). The groups differed significantly on this measure (F (3, 34) = 10.4, $p < .001$), with controls scoring higher than both FTLD patients (F (2, 29) = 5.5, $p < .01$) and AD patients (F (2, 16) = 10.7, $p < .001$). The difference between FTLD and AD patients approached significance (F (2, 20) = 2.9, $p = .10$). For the reason indicated in the section below, we controlled for Clinical Dementia Rating, rather than MMSE, as an indicator of disease severity in the analyses examining neuroanatomical correlates.

Clinical Dementia Rating (CDR). The CDR (Morris, 1997) is an informant-based semi-structured interview that assesses functional impairment on six domains of daily activities: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. It has been suggested that the CDR is a better indicator of disease severity across dementia types than is the MMSE, due its lesser emphasis on memory (e.g. Rosen, Narvaez,

Hallam, Kramer, Wyss-Coray et al., 2004). The CDR was administered to patients' caregivers, and total scores on each of the domains were summed ("sum of box scores") to provide an overall estimate of disease severity (greater scores indicated greater disease severity). The mean severity rating was 6.2 (SD = 4.4) for FTLD patients and 4.2 (SD = 1.9) for AD patients. The patient groups did not differ significantly in disease severity (F (2, 29) = .97, n.s.).

General Laboratory Procedure

Upon arrival to the laboratory, participants were given a brief overview of the testing procedures and were asked to read and sign consent forms explaining the tasks that they were to complete. Participants were then seated in a comfortable chair in a 3 x 6m room, and physiological sensors, used to measure cardiovascular activation and skin conductance, were attached. A video camera opposite the participant chair recorded participants' facial behavior continuously throughout the testing session. Participants were informed that separate video consent forms would be administered to them at the end of the day so that they could decide upon future uses of their videotapes (e.g., for research and/or educational purposes). A comprehensive battery of emotion tasks – including those assessing emotional reactivity, emotional understanding, social interaction, and various types of emotion regulation (Levenson, Ascher, Goodkind, McCarthy, Sturm et al., 2008) – was completed over the course of a 6-hour testing session that included a one-hour break for lunch. When participants returned from lunch, physiological sensors were reattached (with the addition of electromyography sensors for the emotion modulated startle task). The emotion modulated startle task was presented immediately following the lunch break.

Neuroimaging data were acquired at the SFVAMC within 3 months before or after the assessment for patients and within 1 year before or after the assessment for controls.

Measures and Design

Emotion modulated startle task

Negative-potentiation and positive-attenuation of the startle response were assessed with the emotion modulated startle task. Participants were fitted with headphones, and electromyography (EMG) sensors were attached below the left eye (see below). Participants were instructed that they would be viewing a series of emotionally evocative slides and that they would periodically hear noises over the headphones. They were instructed to simply ignore the sounds. In order to ensure comprehension of the task, several practice trials were administered prior to the start of the actual task. Following the practice trials, a series of 8 randomly spaced startle probes was delivered over the headphones to allow startle responding to habituate. The task took 22 minutes to complete.

EMG sensor placement. The startle eyeblink response was measured by recording electromyographic (EMG) activity from the obicularis oculi muscle below the left eye. Two miniature Ag/AgCl surface electrodes filled with Signa electrolytic gel were placed along the obicularis oculi in accordance with the placement guidelines recommended by Blumenthal et al. (2005). Prior to electrode placement, the skin was cleansed with alcohol and lightly abraded

using NuPrep, a grainy exfoliant gel. Skin preparation was repeated until impedance, measured using a Radio Shack multimeter, was below 10kOhms.

Startle Probe. The acoustic startle probe consisted of a digitally generated, 50-ms white noise burst with near-instant rise and fall times. It was amplified by a Mackie HM54 Headphone amplifier and delivered over Sennheiser HD-280 Pro headphones at 105dB. A Radio Shack sound level meter was used to calibrate the intensity of the startle probe prior to the start of each testing session.

Slide Stimuli. Sixty emotionally evocative images (20 positive, 20 neutral, and 20 negative) were selected from the International Affective Picture System (IAPS) based on published norms of self-reported ratings of emotional experience and arousal to the slides (Lang, Bradley & Cuthbert, 1999). Slides rated as both high on arousal and emotional valence (positive versus negative) have been demonstrated to elicit greatest startle attenuation (high arousal, high positive slides) and potentiation (high arousal, high negative slides) of the startle response (Bradley et al., 2000). Several considerations influenced the choice of specific slides within each emotion category. First, available normative ratings of self-reported experience and arousal to the slides have been acquired using young adult participants (Lang et al., 1999). Because a standard set of slides known to elicit the emotion modulation pattern in older adults was not available, we chose a range of slides within each emotion category that we thought would be most appropriate for eliciting the intended responses among the population under study. For instance, half of the slides within the positive and negative emotion categories consisted of human content and half consisted of non-human content. Bradley et al. (2001) posited that human emotional content elicits greatest modulation of the startle response because these slides are the most motivationally salient. Patients with FTLD have been clinically described as exhibiting decreased interest in social stimuli during the course of the disease (Snowden & Neary, 1999). Thus, in order to maximize the opportunity for observing emotional modulation of the startle response, we included both human and non-human arousing content in the emotion categories. Additional considerations, discussed below, were taken into account in choosing slide contents within each emotion category.

Positive Slides. Studies demonstrating positive-attenuation of the startle response typically use erotica and action slide contents because slides of these contents tend to be rated higher than slides of other contents on dimensions of arousal and positive valence in young adults. However our experience with dementia patients and older adults suggested to us that erotic stimuli may be perceived as offensive and may produce an aversive, rather than the intended positive, reaction among these groups. Research indicates that older adults derive positive emotion from the pursuit of enriching existing relationships (Carstensen, Pasupathi, Mayr, & Nesselroade, 2000). Thus, we chose positive slides that depicted happy couples/families, action/adventure, appetizing food, and pleasant landscapes. Equal numbers of slides were included within each of these categories.

Negative Slides. Negative slides were chosen based on normative ratings and use in past studies. Within the negative valence category, slides included images of threatening animals, threatening humans, mutilated victims, and contaminated objects. Equal numbers of slides were included within each of these content categories. Within

the negative valence category, some studies have found differences in startle modulation to pure threat (threatening humans and animals) and disgust (victim and contamination) contents (see Grillon & Baas, 2003, for a review). For the purpose of this study, blink responses to the pure threat contents were the focus of study because (1) theoretically, these contents most directly activate the aversive motivational system (Bradley et al., 2001), (2) empirically, these contents most reliably elicit negative-potentiation of the startle (Bradley et al., 2001; Gard et al., 2007; Grillon & Baas, 2003), and (3) the amygdala is most consistently implicated in threat, as opposed to disgust, processing (Phelps & LeDoux, 2005).

Neutral Slides. Neutral slides were chosen based on normative ratings and use in past studies. Neutral slides consisted of household objects. IAPS numbers for slides chosen in each valence category are listed below.[1]

Stimulus presentation. Slide stimuli were presented on a 20-inch widescreen LCD monitor located approximately .5 meters from the participant. The start of each trial was signaled by a white fixation "x" centered on a black screen for a duration of 1.5s, followed by one of the slide stimuli for a duration of 6s.

Stimuli were edited and recorded on Adobe Premier Pro software. The resulting videotaped stimulus tape was played on a Panasonic VCR located in a room adjacent to the participant's room. Slides were presented in a fixed order to ensure that the emotional content of slides was evenly distributed throughout the task. To prevent carry-over effects of slides of particular emotional contents, no more than two slides of the same emotion content were ever presented sequentially. Startle probes were presented on 80% of the trials (for 16 of the 20 slides within each emotion category). For trials on which the startle probe occurred, the probe was delivered between 2.5s and 5s following the onset of the slide (averaging 3.5s across all trials). This variability was built in to reduce the effects of habituation to the startle probe throughout the testing procedure. Finally, each trial was separated by a variable inter-trial interval ranging from 3-5s. Startle probes were presented for one quarter of the trials during the inter-trial interval, again to reduce the predictability of when the probes would occur.

Physiological recording of startle eyeblink response. Physiological data were acquired on two different polygraphs due to system upgrades that took place over the course of data collection. The majority of participants were tested on a Grass Model 7 polygraph (n = 29) prior to upgrading to a BIOPAC polygraph (n = 8). EMG data were simultaneously amplified and integrated. The EMG signal was filtered through a 13-1000Hz bandpass filter and amplified. The EMG signal was continuously sampled at a rate of 100Hz for 1.5s prior to the onset of each picture slide and for the entire 6s duration that the slide was displayed (total 7.5s).

The number of participants tested on the Grass and Biopac systems were: Controls: 10/4; FTLD: 14/4; AD: 5/0. The groups did not significantly differ from one another in terms of the

[1] The following IAPS slides were used: positive contents: 1710, 2070, 2340, 2530, 5000, 5660, 5760, 5780, 5830, 5891, 7230,7330, 7350, 7400, 7470, 8034, 8180, 8190, 8200, 8490; pure threat contents: 1050, 1070, 1120, 1300, 1930, 3530, 6230, 6260, 6350, 6510; neutral contents: 7002, 7004, 7006, 7009, 7010, 7025, 7030, 7034, 7035, 7040, 7041, 7050, 7060, 7080, 7090, 7150, 7175, 7217, 7233, 7235

proportion tested on each system (χ^2 (3, N = 37) = 1.8, n.s). In order to minimize variability in data acquired across the two polygraph systems, blink responses scored from raw EMG data were normalized to z-scores. Normalized blink responses in each of the emotion conditions (negative, neutral, positive) were compared for participants tested on each polygraph (Grass versus Biopac) using an Emotion (within: negative, neutral positive) x Polygraph (between: Grass, Biopac) mixed model, repeated measures ANOVA. No differences were found in the pattern of blink responses across the systems (F (2, 34) = .16, n.s.). Accordingly, data were pooled across the two polygraph systems.

EMG Data Reduction. The magnitude of the startle eyeblink response (peak minus onset values) was manually scored across each of the 48 probed trials (16 negative, 16 neutral, 16 positive). Blinks were scored in a 150ms window, 30ms following startle probe onset. Raw blink magnitudes were z-scored across each individual participant's trials. Standardized blink scores greater than 3 standard deviations above the participant's mean were considered outliers and not included in analyses. Within-subject standardized blink scores were averaged for each emotion condition (positive and negative) to create the positive-attenuation score and negative-potentiation score. The positive-attenuation score reflected the average within-subject standardized blink response across the 16 probed trials in the positive condition, with more negative values reflecting greater positive-attenuation. The negative-potentiation score reflected the average within-subject standardized blink response across the 8 probed threatening slides in the negative condition, with more positive scores reflecting greater negative-potentiation).

Neuroimaging

Image Acquisition. Structural MRIs were performed at the San Francisco Veterans Affairs Medical Center. 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; FOV=256 mm; matrix 256×256; voxel size 1.0×1.5×1.0 mm; TR=10 ms; TE=4 ms; flip angle=15°). Imaging data were missing on three of the patients due to either poor scan quality (1 FTLD patient, 1 AD patient) or imaging not being completed (1 AD patient). A summary of the number of participants who had usable data for each measure is listed in Table 1.

Selection of Regions of Interest. Right- and left-hemisphere volumes in three regions of interest (ROIs) – the amygdala, the nucleus accumbens, and the OFC – were selected based on previous studies of the neural correlates of the emotion modulated startle. Medial and lateral aspects of the OFC were separately quantified by the FreeSurfer program (described below), which allowed for the exploration of more localized brain-behavior associations within the OFC. For comparison purposes, two additional "control" regions were selected that are also involved in emotional or motivational processing but for which there was no strong reason to expect associations with emotion modulated startle. These two regions were the anterior temporal pole (ATP) and the rostral middle gyrus, which includes the dorsolateral prefrontal cortex (DLPFC). FTLD is often associated with degeneration in the ATP and DLPFC, in addition to the amygdala, nucleus accumbens, and OFC. As indicated in Table 2, the mean volume in nearly all of these regions was significantly smaller in the FTLD group compared to control group. Therefore, assessing ATP and DLPFC ROIs permitted examination of whether the hypothesized regions

(amygdala, nucleus accumbens, and OFC) alone impacted the emotion-modulated startle, or whether a more general pattern of degeneration associated with FTLD did so. The ATP is involved in emotional reactions to complex social stimuli that require access to knowledge about other people and their intentions. Whereas the amygdala and OFC, which are each richly connected with the ATP, are involved in the rapid formation of simple threat/reward appraisals, the ATP is involved in more complex appraisals of highly processed sensory stimuli (Olson, Plotzker, & Ezzyat, 2007). The DLPFC is involved in the high-level regulation of goal-directed behavior. Like the OFC, single-cell recording studies have shown that DLPFC neurons encode the motivational value of stimuli; however, DLPFC neurons selectively encode response selection when competing behavioral options exist (Hikosawa & Watanabe, 2000; Wallis & Miller, 2003). The emotion modulated startle is a simple regulatory phenomenon that proceeds automatically once the emotional stimulus is appraised and does not require high-level, or deliberate, response selection among competing options.

Quantification of Regions of Interest: FreeSurfer Software Package. ROIs were quantified using the FreeSurfer software package, a semi-automated tool that reconstructs cortical and subcortical volumes from MRI data (http://www.marinos.org/freesurfer). FreeSurfer automatically segments gray and white matter on the cortical surface of the brain, corrects for topological defects, and uses a deformation procedure to locate the pial (gray matter) surface of the brain (Desikan et al., 2006). The boundaries of cortical regions of interest are automatically delineated using a "sulcal" approach (see Desikan et al., 2006, for technical details and anatomical definitions). Subcortical regions are reconstructed using spatial probability information (see Fischl et al., 2002). The validity of this automated procedure has been established through comparison with manual tracing procedures (Desikan et al., 2006; Fischl et al., 2002).

Real-World Behavioral Assessment

Neuropsychiatric Inventory (NPI). The NPI (Cummings et al., 1994) was administered to patients' caregivers during their visit to UCSF. The NPI is an informant-based clinical interview that assesses behavioral disturbance seen in the everyday lives of dementia patients. The NPI reliably discriminates between the behavioral presentations of FTLD and AD (Levy et al., 1996). Several questions pertaining to 12 neuropsychiatric behaviors are scored. These are: delusions, hallucinations, depression, apathy, aggression, anxiety, disinhibition, aberrant motor behaviors, sleep, and appetite/dietary change. Each of the 12 scales has a maximum score of 12, with higher scores reflecting greater impairment. Of primary interest for the present study were the behaviors conceptually related to altered sensitivity to cues for threat and reward – specifically, anxiety, euphoria, disinhibition, and appetite/dietary change.

Data Analysis

To ensure that our implementation of the emotion modulated startle task was producing the expected results, a one-way repeated measures analysis of variance (ANOVA) with Emotion (negative, neutral, positive) as the within-subject factor and eyeblink magnitude as the dependent

variable, was conducted with control subjects. Planned comparisons using Bonferroni corrections were conducted to test contrasts that compared eyeblink magnitude in each of the emotion conditions. Linear trends were analyzed to confirm whether eyeblink magnitude exhibited the typical negative>neutral>positive pattern.

The emotion modulated startle pattern was also characterized in the sample as a whole. Between group analyses were conducted to determine if the patient groups differed from the controls. A mixed-model repeated measures ANOVA with Group (control, FTLD, AD) as the between-subjects factor, Emotion (negative, neutral, positive) as the within-subjects factor, and eyeblink magnitude as the dependent variable was conducted. Following Bradley et al. (2001), for all repeated measures ANOVAs, the multivariate test statistic (Wilks' Lambda) was used to avoid potential issues of sphericity (Vasey & Thayer, 1987). Partial eta squared (η_p^2) is reported as a measure of effect size for each ANOVA.

Next, the neuroanatomical correlates of the emotion modulated startle were examined. These analyses were first conducted with the FTLD group, which was the primary patient group of interest, due its localized and variable atrophy within the regions of interest (ROIs) examined in this study. For each ROI, regional volume was correlated with the negative-potentiation score and the positive-attenuation score using Pearson correlation coefficients. To reduce family-wise Type I error risk from multiple comparisons, Bonferroni corrections were applied to the analyses correlating frontal regions with emotion modulated startle scores, as these analyses were less strongly based in the literature and included exploratory analyses. A stricter significance level of ($p < .005$) was set for these analyses. Significant correlations were followed up with multiple regression analyses to determine whether the ROI still predicted the emotion modulation score after controlling for intracranial volume, age, education, and disease severity.

In cases where the ROI's regional volume significantly predicted emotion modulated startle among FTLD patients, a second set of multiple regression analyses was conducted that also included the AD patients. These analyses were performed to determine whether the effect existed among the combined patient sample, and to test whether the effect varied across FTLD and AD patients. To test whether an effect of regional volume on emotion modulated startle existed for the combined patient sample, emotion modulation score was regressed on regional volume, the control variables described above, and a dummy coded variable representing the effect of FTLD (=1) vs. AD (=0). To determine whether an effect of regional volume on emotion-modulated startle varied across FTLDs and ADs, the above analysis was repeated with the addition of the FTLD vs. AD X Regional Volume interaction term.

Finally, real-world behaviors assessed on the NPI were correlated with negative-potentiation and positive-attenuation using Pearson correlation coefficients.

RESULTS

Emotion Modulated Startle Pattern

Task Validation (controls only). Because the emotion modulated startle task is typically used in young adult samples and with different slide stimuli from those used presently, it was important to determine whether the expected startle modulation pattern was found in the present

study. As expected, there was a main effect of emotion, $F(2, 12) = 9.45$, $p < .01$, $\eta_p^2 = .61$, indicating that eyeblink magnitude differed across the emotion conditions. Significantly larger eyeblink responses were elicited in the negative compared to the positive condition, $F(1,13) = 17.58$, $p = .001$, $\eta_p^2 = .58$, and a significant linear trend, $F(1,13) = 17.58$, $p = .001$, $\eta_p^2 = .58$, indicated that eyeblink magnitude decreased steadily from the negative to neutral to positive condition. Thus, as displayed in Figure 1, the emotion modulated startle pattern found in previous studies replicated with our sample of older adults and our use of somewhat different slide stimuli.

The typical startle modulation pattern was also present in the sample as a whole, including control, FTLD, and AD participants (main effect of emotion: $F(2, 33) = 6.13$, $p = .005$, $\eta_p^2 = .27$; linear trend, $F(1,34) = 11.40$, $p = .002$, $\eta_p^2 = .25$). However, there was no Emotion X Group interaction, $F(4, 68) = .06$, n.s., $\eta_p^2 = .004$, indicating that effect of emotion on eyeblink magnitude did not differ across the groups. Thus, at the level of clinical diagnosis, we were unable to detect differences in the typical emotion modulated startle pattern. Table 3 displays the means and standard deviations of eyeblink magnitude for each group across each of the emotion conditions.

Neuroanatomical Correlates of the Emotion Modulated Startle

Amygdala

As expected, within the FTLD group, there was an association between amygdala volume and negative-potentiation. Specifically, smaller right-amygdala volumes were associated with diminished potentiation of the startle in the negative condition, $r = .50$, $p < .05$. Furthermore, as depicted in Figure 2, negative-potentiation was absent in patients with the smallest right-amygdalae (i.e., those with right-amygdala volumes below the median), indicating that the right amygdala is critical for this response. There was no association between the left-amygdala and negative-potentiation, and neither the left- nor right-amygdala was associated with positive-attenuation of the startle. These results support the predictions that amygdala loss would be associated with diminished negative-potentiation, that the effect would be lateralized to the right hemisphere, and that the association between the amygdala and emotion modulated startle would be specific to negative-potentiation. Further specificity regarding the role of the amygdala, but not other aspects of the temporal lobes, in negative-potentiation of the startle was also obtained. As predicted, there was no association between anterior temporal pole volumes and negative-potentiation. Table 4 displays the relevant correlations and their associated p-values.

The association between the right-amygdala and negative-potentiation remained significant after controlling for total brain volume, age, education, and disease severity in a multiple regression analysis, $\beta = .69$, $p = .047$. This relation also held after including the 3 AD patients on whom there were imaging data, $\beta = .77$, $p = .025$. Thus the effect existed among the combined patient sample. Finally, adding the FTLD vs. AD X right-amygdala interaction term did not yield a significant interaction effect. Thus, we were not able to detect differences in the effect of right amygdala loss on negative-potentiation across the diagnostic groups.

Nucleus Accumbens

Contrary to predictions nucleus-accumbens volume was not correlated with positive-attenuation. The correlation was r = -.08, n.s, for the right-nucleus accumbens and r = .10, n.s., for the left-nucleus accumbens.

Orbitofrontal Cortex

As predicted, within the FTLD group, there was an association between the OFC and positive-attenuation of the startle. Specifically, atrophy in the left-medial OFC was strongly associated with greater positive-attenuation, r = .69, p =.002. The relationship between the OFC and positive-attenuation was specific to the left-hemisphere and to the medial aspect of the OFC; atrophy in the lateral OFC was not related to positive-attenuation. These findings provide support for the "valence hypothesis," according to which the left-hemisphere is preferentially involved in positive emotion and appetitive motivation. The findings also provide support for the idea that there is functional specialization among the medial and lateral aspects of the OFC. Further support for a specific role of the medial OFC, and not other regions in the frontal lobes, in positive-attenuation was obtained. Consistent with predictions, there was no association between the rostral middle frontal gyrus, which includes the DLPFC, and positive-attenuation. None of the frontal variables was associated with negative-potentiation. Notably, that the medial OFC was associated with positive-attenuation and not negative-potentiation provides further support for the idea that the neural substrates of each of these priming responses are dissociable. Table 5 displays a summary of the relevant correlations and their associated p-values.

The association between the left-medial OFC and positive-attenuation remained significant after controlling for total brain volume, age, education, and disease severity in a multiple regression analysis, β = .71, p = .004. This relation remained significant in an analysis that also included the AD patients, β = .73, p = .004. Finally, adding the FTLD vs. AD X left-medial OFC interaction term did not yield a significant interaction effect. Thus we were unable to detect differences in the effect of left-medial OFC loss on positive-attenuation across the patient groups.

Follow-up analyses. Left-medial OFC loss was associated with *greater* positive-attenuation within the FTLD sample. However, this finding alone does not indicate whether positive-attenuation was *abnormally high* following left medial OFC loss. Thus, follow-up analyses were conducted, in which positive-attenuation was compared between patients with left medial OFC loss and healthy controls. For these analyses, "loss" was defined as less medial OFC volume relative to the volumes in the control group. A median split on left medial OFC volume (0 = "low", 1 = "high") was conducted after combining patients and controls together, such that patients with relatively small medial OFCs (FTLDs labeled "low") could be compared to healthy with relatively larger medial OFCs (controls labeled "high"). A mixed model repeated measures ANOVA was conducted with Emotion (neutral, positive) within, Group ("low" medial OFC patients, "high" medial OFC controls) between, and eyeblink magnitude as the dependent variable. Both groups had significantly smaller eyeblink responses in the positive compared to neutral condition (main effect of emotion: F (1, 13) = 54.17, p < .001, η_p^2 = .81), but the extent of attenuation was significantly greater for the patients with relatively smaller left-medial OFCs (Emotion X Group interaction: F (1, 13) = 10.19, p =.007, η_p^2 = .44). These findings, depicted in Figure 3, provide support for the prediction that OFC loss would be associated with *exaggerated*

positive-attenuation, an indication that sensitivity to appetitive stimulation is disinhibited in these patients.

Behavioral correlates of the emotion modulated startle

Consistent with predictions, negative-potentiation was associated with care-giver reported anxiety such that those who demonstrated greater negative-potentiation were rated as displaying more anxious behaviors, according to their caregivers. However, none of the variables expected to correlate with positive-attenuation – disinhibition, euphoria, and eating behaviors – displayed significant correlations. Table 6 displays a summary of the relevant correlations and their associated p-values.

Summary of findings

As predicted, amygdala loss was associated with diminished negative-potentiation (hypothesis 2a), the role of the amygdala in the emotion modulated startle was specific to negative-potentiation (hypothesis 2b), and the relation between amygdala loss and negative-potentiation was lateralized to the right-hemisphere (hypothesis 2c). Contrary to predictions based on the animal literature, there was no association between the nucleus accumbens and positive-attenuation (hypothesis 3). However, neural loss in the left- medial OFC was associated with an exaggeration of the positive-attenuated startle, supporting the hypothesis that OFC loss would disinhibit sensitivity to appetitive stimuli (hypothesis 4a). The laterality of this finding provided support for the "valence hypothesis," according to which *left* frontal regions are specialized for the processing of positive or appetitive motivational stimuli (hypothesis 4b). On the other hand, atrophy in the OFC was not related to negative-potentiation (exploratory questions 4c and 4d). Real-world behavioral problems that were hypothesized to relate to altered sensitivity to appetitive stimuli did not correlate with positive-attenuation. However, as predicted, the level of anxiety, reported by caregivers, in the patients' day-to-day lives was positively correlated with the degree of negative-potentiation that the patients displayed (hypothesis 5).

Discussion

In this study I examined the neural and behavioral correlates of the emotion modulated startle response in patients with neurodegenerative disease. The emotion modulated startle response represents a very basic means by which emotions come to influence subsequent behavioral responding. In this paradigm, the magnitude of the defensive startle response is measured in the context of ongoing negative and positive emotional states. The startle response is enhanced in the context of negative states (negative-potentiation) and inhibited in the context of positive states (positive-attenuation) (e.g., Lang & Bradley, 1990). These modulatory responses are thought to reflect "motivational priming" phenomena whereby emotional states activate one of two underlying and opposing motivational systems – "aversive" or "appetitive" – that tune the organism toward or away from motivationally salient events. When the aversive motivational system is activated, defensive responding, including the startle response, is enhanced. When the appetitive motivational system is activated, defensive responding, including the startle response, is inhibited. The neural bases of these fundamental modulatory influences of emotion have not been well-characterized in humans. Nor have researchers examined the

consequences of impairments in the emotion-modulated startle for functioning in everyday life. The present study attempted to clarify these issues.

First, this study established the utility and validity of the emotion modulated startle paradigm in a sample of older adults, using visual stimuli selected specifically for this population. The basic negative-potentiation and positive-attenuation findings found in younger populations (e.g. Vrana et al., 1988) were replicated within this sample. More importantly, this study provided evidence that negative-potentiation and positive-attenuation of the startle response have distinct neural correlates. Amygdala loss was associated with diminished negative-potentiation but had no effect on positive-attenuation. Orbitofrontal loss was associated with enhanced positive-attenuation but had no effect on negative-potentiation. In addition, the findings provided evidence that the neural systems supporting the emotion modulated startle response are lateralized. The finding linking amygdala loss with diminished negative-potentiation was specific to the right-hemisphere, and the finding linking OFC loss with enhanced positive-attenuation was specific to the left-hemisphere. Contrary to predictions, there was no association between the nucleus accumbens and the positive-attenuated startle. Finally, this study examined real-world functional correlates of the emotion-modulated startle. Reduced negative-potentiation was found to be associated with lower informant-based ratings of patients' anxiety. None of the real-world behavioral problems assessed was associated with positive-attenuation. These findings are discussed in detail below.

Neuroanatomical findings

Amygdala

This was the first study to quantify amygdala loss in a sample of human lesion patients and relate it to negative-potentiation of the startle response. Though a handful of lesion-mapping studies in humans have compared the emotion modulated startle among lesion patients with that among controls (Funayama et al., 2001; Buchanan et al., 2004; Sanchez-Navarro et al., 2005; Saunders et al., 2006), group-based comparisons provide less sensitivity and specificity than do approaches relating continuous measurements of clearly defined brain regions with continuous measurements of behavioral performance (Bates, Wilson, Saygin, Dick, Sereno et al., 2003). Findings indicated that amygdala volume was negatively correlated with negative-potentiation such that patients with smaller amygdala volumes displayed less negative-potentiation. Patients with the smallest amygdala volumes (those falling below the median) failed to show the negative-potentiated response altogether, indicating that the amygdala is critical for this response. These findings converge with animal studies, using rodents, demonstrating that removal of the amygdala completely abolishes the fear-potentiated startle (Davis at al., 1999), and they replicate the one prior human case study that found impaired negative-potentiation in a single patient with damage to the right amygdala (Angrilli et al., 1996).

Findings also indicated that the role of the amygdala in the emotion modulated startle response is specific to negative-potentiation. There was no association between amygdala size and positive-attenuation of the startle. The selective association of the amygdala with negative-potentiation is consistent with the idea that distinct neuroanatomically based motivational systems support negative-potentiation and positive-attenuation of the startle. Indeed, two prior studies using patients with damage to the temporal lobes, which included the amygdala, found

impaired negative-potentiation, but not impaired positive-attenuation, relative to controls (Funayama et al., 2001; Buchanan et al., 2004). The current findings also provide greater specificity about the role of temporal lobes in the negative-potentiated startle. The role of the anterior temporal pole was also assessed, as this region is also involved in emotional processing, is tightly connected with the amygdala, and is often affected in FTLD (Olson et al., 2007; Rosen et al., 2002). There was no association between anterior temporal pole volume and either negative-potentiation or positive-attenuation of the startle, indicating that temporal lobe damage per se was not the basis of impairment of negative-potentiation found in this sample.

Taken together, these findings support the contention that the amygdala is a key structure in the human aversive motivational system (Lang, Bradley & Cuthbert, 1990; Lang, 1995). The findings indicate that damage to the amygdala disrupts the ability of threatening stimuli to prime, or mobilize, the defensive response system. These findings also fit with a large body of prior research suggesting that the amygdala plays a broad role in modulating behavioral, attentional, perceptual, and memory systems in the service of facilitating the organism's ability to respond to dangerous circumstances (Phelps & Ledoux, 2005).

Orbitofrontal Cortex

This was the first study that directly examined the role of the OFC in the emotion modulated startle. Findings indicated that medial OFC loss, specifically, was correlated with positive-attenuation such that patients with more loss in this region displayed more attenuation. In order to determine whether this enhancement was within or above the normal range of responding, positive-attenuation was compared between patients with the smallest medial OFC's and healthy controls. Patients with the most medial OFC loss showed greater positive-attenuation than did healthy controls, indicating that damage to this region is associated with an exaggeration of this response. Enhanced positive-attenuation is theoretically related to enhanced sensitivity of the appetitive motivational system, which is typically activated by rewarding stimuli. Consistent with this idea, Hawk and Komas (2003) found that individuals who were high on a personality measure of reward responsiveness displayed enhanced positive-attenuation relative to controls. Greater reward responsiveness following OFC damage would be consistent with behavioral descriptions of disinhibition and inappropriate euphoria in these patients. In FTLD patients, specifically, OFC damage has also been related to profound changes in eating behavior, particularly an increased consumption of sweet foods, despite reports of satiety (Woolley et al., 2009), suggesting alterations in the appetitive motivational system that are consistent with the present findings.

The specificity of the finding within the OFC, showing that the medial OFC, in particular, was associated with positive-attenuation, is consistent with research indicating that medial and lateral aspects of the OFC have specialized functions (Elliot, Dolan, & Frith, 2007). In particular, one prior study suggested that these regions may be differentially specialized to deal with appetitive and aversive stimuli. Using positron emission tomography (PET), Small et al. (2001) examined the neural correlates of appetitive and aversive motivation in volunteers who were instructed to eat chocolate to beyond satiety. The medial and lateral OFC showed opposite patterns of activity, with the medial OFC responding most when participants were highly motivated to eat more chocolate and the lateral OFC responding most when participants

continued to eat despite being satiated. The authors concluded that the medial OFC may be part of a system that evaluates the positive/appetitive value of stimuli whereas the lateral OFC is a part of a separate system that evaluates the negative/aversive value of stimuli. The current findings are consistent with the idea that the medial OFC is involved in the appetitive motivational system.

The findings also suggested that the role of the OFC in the emotion modulated startle is specific to positive-attenuation. There was no association between OFC loss (either medially or laterally) and negative-potentiation. This finding provides further support for the idea that dissociable systems are involved in negative-potentiation and positive-attenuation of the startle. It also suggests that the simple motivational priming phenomena assessed in the emotion modulated startle paradigm differentially involve frontal cortical systems. Aversive stimuli, because of their importance for survival, may be preferentially processed in subcortical, evolutionarily old systems that promote rapid, hard-wired or learned, responses. On the other hand, appetitive stimuli, which do not require immediacy or stereotyped responding, may additionally recruit cortical systems that allow for flexible, adaptive, and novel responding. In addition, the evaluation of appetitive stimuli may be more complex than that of aversive stimuli. According to Bradley et al. (2001, p.280), "the study of appetitive motivation is often complicated by the fact that the attractiveness of a specific stimulus (e.g., food or drug) depends, to some extent, on a co-occurring aversive state (e.g., hunger or deprivation)." The reward value of appetitive stimuli increases as a function of hunger/deprivation and decreases as a function of satiety. Neuron firing rates in the OFC are responsive to precisely these shifts (Rolls, 2000). Thus, frontal regions may be particularly important for the evaluation of appetitive stimuli. Subcortical reward processing in the nucleus accumbens, by contrast, is mainly responsive to the presence or absence of reward – and not its relative value (Elliott, Newman, Longe, & Deakin, 2003). There is some evidence that evaluation of pleasant, but not unpleasant, stimuli draws on frontal cortical regions. Paradiso et al. (1999) used PET to examine neural responses to pleasant and unpleasant stimuli, using positive, negative, and neutral IAPS slides. They found greater frontal activations (in medial orbital and dorsolateral prefrontal cortices) to positive, but not negative, slides and greater subcortical activations (in the amygdala) to negative, but not positive, slides. This distinction between cortical and subcortical regions in the processing of pleasant and unpleasant stimuli, respectively, is consistent with the current findings.

It should be noted, however, that other studies have found common activations in frontal regions to both pleasant and unpleasant stimuli (Lane, Reiman, Ahern, Schwartz, & Davidson, 1997; Lane, Reiman, Bradley et al., 1997). It should also be noted that the specificity of the OFC in enhancing the sensitivity of the appetitive motivation system may appear inconsistent with clinical observations of emotional behavior following OFC damage that suggest that at least some aspects of aversively motivated behavior become sensitized. For instance, overt aggressive behavior is commonly described in human and monkey subjects with OFC lesions. One possible explanation for this discrepancy is that the emotion of anger, which underlies aggressive behavior, is a unique negative emotion in terms of its motivational pull. Though many theorists argue that the valence – positive versus negative – of emotional states drives the activation of the appetitive versus aversive motivational systems, respectively (Lang, 1995; Davidson, 1998; Tomarken & Keener, 1998), others have argued that the motivational direction – approach versus withdrawal – of emotional states determines which system will be activated (Carver & Harmon-

Jones, 2009). Specifically, according to the latter view, approach-related emotions will activate the appetitive system and withdrawal-related emotions will activate the aversive motivational system. Based on this view, the clinical observations of disinhibited aggressive behavior – which are, by definition, approach-related – in OFC patients are consistent with this study's finding of enhanced appetitive motivation in the context of OFC loss. In summary, there is some evidence, from both the laboratory and clinical observation, that the OFC plays a special role in appetitive motivation and that damage to this region disinhibits aspects of appetitive-motivated behavior.

Finally, the fact that the emotion modulated startle was intact, albeit enhanced with regard to positive-attenuation, in patients with medial OFC loss indicates that the medial OFC is not critically involved in the general capacity for positive-attenuation of the startle. Rather, the findings suggest that the medial OFC plays a modulatory role in the neural system that directly mediates this response. The precise mechanism through which the OFC modulates this system remains to be determined. This modulatory role may take place during stimulus appraisal. As described previously, neurons in the OFC are involved in appraising the reward value of stimuli, in a context-sensitive manner (Rolls, 2000). These nuanced appraisals may lead to adjustments in the sensitivity of subcortical response systems that promote appetitive behavior, and, consequently, inhibit defensive behavior. This is purely speculative, however, and future studies should clarify the nature of the interactions between the OFC and subcortical regions involved in reward appraisals and appetitive motivation. Whatever the mechanism, these findings indicate that when there is damage to the OFC, it is particularly difficult to activate the defensive response system in the context of ongoing positive states. There has been limited systematic study of emotional activation in the context of OFC damage. Because this is the first study to examine the role of the OFC in the emotion modulated startle, these findings should be considered preliminary.

Laterality

This study found evidence of laterality in both the negative-potentiated startle and the positive-attenuated startle. The relation of amygdala loss to diminished negative-potentiation was lateralized to the right hemisphere, suggesting a greater role for the right hemisphere in aversive priming of the startle reflex. This is consistent with findings of impaired negative-potentiation following right hemisphere damage, which are consistently obtained in lesion studies examining the role of the temporal lobes in the emotion modulated startle (Angrilli et al., 1996; Funayama et al., 2001; Buchanan et al., 2004).

Of these studies, only two compared patients with right and left temporal lobe damage. Whereas patients with right-sided damage displayed impaired negative-potentiation in both studies, the results were inconsistent for patients with left-sided damage: Funayama et al. (2001) found no impairment, whereas Buchanan et al. (2004) found impairment. In addition, indirect evidence for a preferential role of the right hemisphere in the emotion modulated startle has been found in studies using monaural startle probe presentations. In three experiments using healthy volunteers, Bradley et al. (1991; 1996) found significant emotion modulation of the startle when acoustic startle probes were presented to the left ear, but not when they were presented to the right ear. Because projections from the auditory nerve primarily run to the contralateral hemisphere, startle probes presented to the left ear are primarily processed in the right

hemisphere. Thus, the findings of Bradley et al. (1991; 1996) indicated that startle probes processed in the right hemisphere were more susceptible to motivational priming influences. It should be noted, however, that the index for emotion modulation used in these studies was based on the magnitude of the difference between startle responses to the negative and positive slide stimuli. Such an index provides information about the degree to which blinks are different in negative and positive conditions, but makes it impossible to determine whether differences in these conditions are due to enhanced negative-potentiation, enhanced positive-attenuation, or both. Regardless, there is accumulating evidence that the right hemisphere plays a special role in at least some aspect of the emotion modulated startle, and, based on the current study and past lesion studies, that negative-potentiation is implemented more robustly in the right hemisphere.

This was the first study to examine whether left- or right-hemisphere structures are differentially involved in positive-attenuation of the startle response. Findings indicated that damage to the *left* medial OFC was associated with an exaggeration of the positive-attenuation response. Prior research has suggested that the motivational systems involved in positive and negative emotion are differentially lateralized in the left and right hemispheres. Empirical support for this "valence hypothesis" largely comes from studies of resting frontal electroencephalographic (EEG) asymmetries, showing that greater relative left-frontal activation is associated with positive emotionality and approach-motivational tendencies, whereas greater relative right-frontal activation is associated with negative emotionality and avoidance-motivational tendencies (Davidson, 2004). Though source localization studies eventually traced these resting frontal asymmetries to the dorsolateral prefrontal cortex, later localization studies found that asymmetries in other regions of the prefrontal cortex were related to specific aspects of motivational processing. In particular, one source localization study examining the relationship between frontal EEG asymmetries and reward sensitivity found that individuals with greater relative resting activation in the left medial OFC, specifically, showed a bias to respond to reward-related cues (Pizzagalli, Sherwood, Henriques, & Davidson, 2005). The present findings provide further support for the role of the medial OFC, particularly in the left hemisphere, in a system that mediates responding to rewarding/appetitive stimuli.

Taken together, these findings demonstrate that aspects of the systems involved in the emotion modulated startle are lateralized. In particular, the findings appear to support the "valence hypothesis," which suggests that the right hemisphere supports motivational processing related to negative emotion and the left hemisphere supports motivational processing related to positive emotion.

Nucleus Accumbens

Contrary to predictions, this study failed to find an association between the nucleus accumbens and positive-attenuation of the startle response. It was expected that damage to the nucleus accumbens would impair positive-attenuation. This prediction was based on a study by Koch et al. (1996), which demonstrated that lesions of the nucleus accumbens in rodents abolished the positive-attenuated startle in the context of conditioned cues for reward.

Several factors may account for the current study's failure to replicate this finding. First, the current study may not have adequately sampled patients with a sufficient range of atrophy in the nucleus accumbens. Though the mean nucleus accumbens volume in the patient group was

smaller than that of the control group, the range of atrophy may have been too constricted to yield correlations. Alternatively, though smaller volumes were observed in the patients, the extent of their lesions may not have encompassed the precise subregions that putatively mediate inhibitory influences on the brain stem. Indeed, based on clinical observations, Viskontas, Possin, and Miller (2007) argued that the natural reward system remains relatively intact in frontotemporal dementia (e.g., patients directly seek out primary rewards such as food and sex).Consistent with this contention, localized atrophy in this sample was related to an exaggeration of the positive-attenuation response. Thus, several issues related to the sample may have contributed to this null finding.

A second factor that may account for this study's failure to replicate Koch et al.'s (1996) findings has to do with differences between the animal and human models of the positive-attenuation of the startle response. In the animal model, startle attenuation is assessed in the context of conditioned cues for food, among food deprived rodents. Food is a primary reinforcer that is necessary for survival; its motivational value is particularly high in the context of deprivation (an aversive state). In the human model, on the other hand, startle attenuation is assessed in the context of pleasant picture stimuli, only some of which include representations of primary reinforcers (e.g., food in the current study and sexual/erotic stimuli in other studies), but these stimuli are never presented in the context of deprivation. It may be the case that differing neural regions in the appetitive motivational system mediate startle attenuation across these differing contexts. Indeed, Josselyn et al. (2005) demonstrated that not all forms of startle-attenuation in appetitive contexts are dependent on the nucleus accumbens. The authors demonstrated that startle-attenuation can occur in the context of cues for safety (a noise signaling the absence of shock), and the level of attenuation observed is not diminished following lesions of the nucleus accumbens. Safety signals may not appear to be clear appetitive cues. However, by signaling that the environment is safe, the defensive system can be inhibited and, consequently, appetitive behaviors can be supported. Both cues for reward and cues for safety have been shown, in animal models, to support appetitive behaviors (Josselyn et al., 2005). Josselyn et al. (2005) argued that the neural structures that respond to cues for safety and reward may overlap, but their study also showed that dissociable neural structures likely mediate "safety-attenuation" and "reward-attenuation" of the startle.

The positive stimuli used in the present study included happy couples/families and pleasant landscapes that, while potentially rewarding, may also provide cues that tap into the safety system. This may account for the absence of an association between the nucleus accumbens and attenuation of the startle in response to these stimuli. The study of the neural substrates of the positive-attenuated startle is in its infancy. Further research, using both animal and human models, is needed to clarify the types of positive contexts (e.g., those signaling reward, those signaling safety) that do and do not inhibit the defensive response system and the underlying neural systems that mediate these responses.

Behavioral findings

In addition to examining the neural correlates of the emotion modulated startle response, this study explored the question of whether the subtle motivational priming processes assessed on this laboratory task are associated with meaningful functional consequences in everyday life.

Informant-based ratings of behavioral problems were obtained using the NPI. These ratings provide a window into whether a functional impairment is significant enough to be seen by others. The only significant relationship found was that between negative-potentiation and anxiety. Diminished negative-potentiation was associated with lower anxiety scores. This finding makes theoretical sense, as deficits in aversive motivation should be associated with a diminished likelihood of tuning into and responding to threatening situations behaviorally. It may be the case that the simple circuit that mediates the negative-potentiated startle has fairly direct downstream consequences for behavior. This is rather striking as negative-potentiation of the startle taps into a very primitive and basic defensive priming response. Because the threat system is built to respond quickly and efficiently, low-level circuitry may have particularly close ties to behavior. In addition, negative-potentiation of the startle may be a marker, more broadly, of an individual's proclivity to activate defensive responses across a range of systems beyond the primitive startle (e.g., perceptual, cognitive) that give rise to the behaviors assessed on the NPI Anxiety scale.

There were no associations between positive-attenuation and any of the NPI scales that were expected to relate to alterations in appetitive system sensitivity (e.g. disinhibition, euphoria, eating). Unlike the aversive system, the appetitive system may have more complex downstream links with real-world behavior. It has been suggested that whereas negative emotions lead to a narrowing of the behavioral repertoire, positive emotions lead to a broadening of behavioral options (Fredrickson, 1998). It may, thus, be more difficult to find behavioral correlates of a marker for positive/appetitive motivational system sensitivity, because the behaviors that result from such states are functionally more diverse. In general, behaviors are multi-determined. This is more so the case outside the constraints of controlled laboratory situations. Thus, finding any link between a simple laboratory phenomenon and real world behavior is difficult. This makes the finding with negative-potentiation and anxiety especially interesting.

Implications for Frontotemporal Lobar Degeneration

Patients with FTLD were chosen for this study because the disease syndrome targets the frontal and temporal lobes, regions that have been implicated in the emotion-modulated startle response. In addition patterns of atrophy vary across patients, in terms of the relative involvement of frontal and anterior temporal regions and the relative involvement of the left versus right sides of the brain. Thus, the neuropathological heterogeneity provided a good source of variability to examine brain-behavior relationships in a fairly small sample.

Though not the central question of this study, I examined whether patients with FTLD, as a group, showed abnormal patterns of startle modulation relative to controls. Findings indicated that there were no differences between FTLD patients and controls. The effect size estimates for differences between the groups were negligible, arguing against the idea that the sample was too small to detect the effect. As a group, FTLD patients showed the normal startle modulation pattern, with the largest startles in the negative condition and the smallest startles in the positive condition. The group level finding begs the question of what the correlations between discrete brain regions and the emotion modulated startle mean, particularly for patients with FTLD. In general, the finding highlights the heterogeneity of the disease. For instance, the overall level of negative-potentiation was similar in patients and controls because only patients with significant

atrophy in the right amygdala were impaired. Similarly, the level of positive-attenuation was similar in patients and controls, because only patients with significant left OFC atrophy displayed exaggerated positive-attenuation.

In general, laboratory studies that have examined the integrity of the emotion system in FTLD have found several areas of preserved functioning when comparing the performance of patients and controls. For instance, compared to controls, FTLD patients show similar levels of physiological reactivity to simple emotional stimuli (like loud sounds and simply themed amusing and sad film clips). Deficits tend to be found on aspects of emotional functioning that involve greater cognitive complexity, such as emotion recognition, self conscious emotion responding, and some aspects of emotion regulation (Levenson & Miller, 2007; Goodkind, Gyurak, McCarthy, Miller & Levenson, in press). In general, findings have indicated that while the basic infrastructure of the emotion response system is intact, emotional processing that requires reflection, use of context, picking up on subtleties, and high-level emotion regulation is impaired. The current findings are consistent with the idea that the basic infrastructure of the emotion system is intact in most patients with FTLD. In general, complex emotion abilities which are found to be impaired in this group tap into frontal lobe systems which are most susceptible to atrophy across patients with FTLD. The systems that drive the more low-level aspects of emotion, however, may be less consistently impacted across patients, making group-level differences more difficult to come by. Rather, these low-level aspects of emotion appear to vary meaningfully as a function of deficiencies in particular brain regions which vary across individuals diagnosed with FTLD. One implication of this suggestion is that group-level comparisons between controls and patients, which are based on clinical diagnosis, may under-estimate impairments in some of the more basic aspects of emotion processing.

Generalizability of Findings

Patients with AD were included in analyses to perform a preliminary assessment of whether damage to brain regions outside those affected by FTLD, particularly posterior brain regions, affected the results. The addition of these patients had little effect on any of the findings. It would be important, however, in future studies, to sample brain regions more broadly, with a larger sample, and across different patient groups, to determine whether these results replicate.

Although patients with neurodegenerative disease afford the advantage of providing variability in relatively small samples, studies are also needed that contrast patients with localized lesions with patients with more widespread pathology. In particular, in order to interpret better the finding linking the OFC with exaggerated positive-attenuation, it would be important to examine this response in patients with localized OFC damage, who do not also have damage in subcortical systems.

Strengths, Limitations, and Future Directions

The main strength of this study was that it examined the contributions of multiple brain regions to both the negative-potentiation and positive-attenuation aspects of the emotion modulated startle response within a single sample. In addition, unlike previous human lesion studies, which compared control groups to patient groups with lesions to broadly defined (e.g. temporal lobes) or heterogeneous areas (e.g. studies of TBI patients), neural loss in specific

regions was directly quantified in this study and related to startle modulation. Thus, the findings from this study provide greater specificity about the roles of specific regions in the emotion modulated startle.

A main limitation of the present study was its limited sample size. Null findings are difficult to interpret in small samples because they may be due to issues of low power as opposed to the effect being truly absent. This study did not provide an exhaustive assessment of all of the brain regions that might contribute to the emotion modulated startle. Given the small sample size and risk of producing Type I errors with increasing numbers of exploratory analyses, only a limited number of brain regions were selected that had some basis for examination in the prior literature. Having said this, it is important to note that sample sizes in studies with neurological patients are typically even smaller than this one. For example, the sample sizes in studies examining the role of the temporal lobes in the emotion modulated startle have ranged from one lesion patient (Angrilli et al., 1996) to groups of six (6 right temporal lobe versus 6 left temporal lobe lesion patients in Buchanan et al., 2004 and Funayama et al., 2001). Future studies might employ whole-brain statistical approaches, such as voxel-based morphometry, which provide a comprehensive assessment of anatomical differences throughout the brain. The advantage of such an approach is that it is not constrained by the specification of a priori regions of interest. Because the neural systems involved in positive-attenuation are not well-understood, and they appear to be more complicated than those involved in negative-potentiation, a whole-brain statistical approach may be particularly fruitful for future studies that seek to clarify the neural basis of this basic appetitive priming process.

The use of two different physiological data acquisition systems (occasioned by laboratory upgrades that occurred while this study was being conducted) may have contributed to error variance in the measurement of startle eyeblink magnitude. To address this measurement variability issue, within subject blink scores were standardized to control for differences in the absolute magnitude of eyeblinks (which may vary according to different sensitivities of the two systems), and the resulting scores reflected relative eyeblink sizes for each subject, within each emotion condition. The use of standardized scores is commonly used in emotion modulated startle paradigms, to control for individual differences in the absolute level of startle eyeblink reactivity. However, absolute startle eyeblink magnitude may be a meaningful and important individual difference measure. For instance, although the findings indicated that the FTLD patient group, as a whole, did not differ from controls in terms of relative blink sizes to negative, neutral, and positive stimuli, using z-scores precludes knowing whether they were overall more or less reactive to the startle probes than were the controls. Evidence from our laboratory has indicated that startle reactivity in FTLD patients is commensurate with that in controls in motoric, facial behavioral, and physiological channels, when elicited with the high intensity 110dB acoustic startle (Sturm et al., 2006). It is not known, however, whether this finding would translate to the eyeblink channel, using a much less intense startle elicitor. In summary, it remains to be determined whether the overall level of defensive activation was affected by brain injury in this sample.

A final issue is the generalizability beyond patients with FTLD. The fact that the amygdala predictions, which had a solid basis in the prior animal and human literatures, were supported in this sample provides some evidence that this finding is generalizable. This finding

also validates the use of neurodegenerative disease to model brain-behavior relationships. Specifically, it indicates that one can localize brain-behavior relationships even in a sample with widespread atrophy. This was also supported by the "control region" analyses. Nonetheless, in mapping brain-behavior relationships, it is important to find converging evidence from studies of patients with localized lesions. The medial OFC finding in particular awaits replication in future studies.

Summary and Conclusions

This study examined the neural and real-world behavioral correlates of the emotion modulated startle response in patients with neurodegenerative disease. Findings indicated that the right amygdala plays a selective role in negative-potentiation (but not positive-attenuation) and that the left medial OFC plays a selective role in positive-attenuation (but not negative-potentiation). Together, these findings support the contention that at least some aspects of the aversive and appetitive motivational systems are dissociable.

The amygdala findings are consistent with a large animal literature that has delineated the precise neural pathways involved in the fear-potentiated startle. This was the first study to demonstrate a specific association between the amygdala and negative-potentiation in a sample of human patients. Furthermore, because there was a strong basis for suspecting an association between the amygdala and negative-potentiation, these findings, using patients with neurodegenerative disease, provide a measure of validation for the use of these patients in modeling brain-behavior relationships.

There has been less extensive research on the neural basis of the positive-attenuated startle, and the current study was unable to replicate the animal finding that the nucleus accumbens is critical for this response. Failure to sample adequate variability in the nucleus accumbens, the content of the positive visual stimuli, or differences between the animal and human paradigms may have accounted for this discrepancy.

The finding that medial OFC damage was associated with exaggerated positive-attenuation suggests that cortical systems play an indirect and modulatory role in this simple priming response. The medial OFC finding has not been reported in previous work, however, and it should be considered preliminary pending replication. Future studies should also examine the emotion modulated startle in patients with localized damage to the OFC to determine whether these results generalize and replicate using other samples.

Finally, this study examined whether alterations in the emotion modulated startle were associated with real-world behavioral problems as viewed by caregivers. Diminished negative-potentiation was associated with lower anxiety ratings by caregivers, indicating that the negative-potentiated startle taps into a functional capacity associated with observable and meaningful real-world behavior. To my knowledge, this was the first study to examine whether the psychological processes assessed on this laboratory task have meaningful functional correlates in everyday life. Future studies should employ other measures of real-world functioning that hone in on specific emotional behaviors that may be relevant to the emotion-modulated startle.

Table 1

Number of Participants with Usable Data on each Measure.

	Controls	FTLD	AD	Total
Emotion Modulated Startle	14	18	5	37
Neuroimaging	n/a	17	3	20
Behavioral Ratings	n/a	18	5	23

Table 2.

Mean Volumes in Regions of Interest among Controls and FTLD Patients

	Controls (n=10)	FTLD (n=17)
	Mean (SD)	Mean (SD)
Amygdala		
Left	1569 (404)	1011 (408) ***
Right	1653 (285)	1328 (239) **
Nucleus Accumbens		
Left	497 (116)	380 (121) **
Right	595 (107)	423 (123) ***
Medial OFC		
Left	4375 (807)	3847 (662) *
Right	4588 (796)	4059 (760) *
Lateral OFC		
Left	7345 (1095)	6227 (1307) *
Right	7233 (1003)	6145 (1235) *
Rostral Middle Gyrus		
Left	14562(1624)	14125 (2382)
Right	16193 (3093)	13918 (3057) *
Temporal Pole		
Left	2404 (353)	1547 (319) ***
Right	2180 (504)	1702 (477) **

Mean volumes were compared between controls and FTLD patients with one-tailed t-tests , *p < .05, ** p < .01, ***p <.001

Table 3

Eyeblink Magnitude (within-subject z-scores) within each Emotion Condition for each Group

	Controls (n = 14)	FTLD (n = 18)	AD (n = 5)
Condition	Mean (SD)	Mean (SD)	Mean (SD)
Negative	.20 (.18)[a]	.26 (.57)[b]	.26 (.72)
Neutral	.10 (.58)	.10 (.23)[c]	.12 (.19)
Positive	-.18 (.25)[a]	-.22 (.27)[b,c]	-.11 (.40)

Superscripts indicate paired contrasts that were significantly different (at Bonferroni corrected $p < .008$)

Table 4

Correlations of Temporal Lobe Regions with Negative-Potentiation and Positive-Attenuation Scores among FTLD Patients (n= 17)

	Negative-Potentiation		Positive-Attenuation	
	r =	*p* =	r =	*p* =
Amygdala				
Right	**.50**	**.047**	-.25	.34
Left	.17	.52	-.37	.14
Temporal Pole				
Right	.39	.12	-.30	.25
Left	-.33	.20	.31	.22

Table 5

Correlations of Frontal Lobe Regions with Negative-Potentiation and Positive-Attenuation Scores among FTLD Patients (n= 17)

	Negative-Potentiation		Positive-Attenuation	
	r =	*p* =	r =	*p* =
Medial OFC				
Left	.00	.99	**.69**	**.002**
Right	.18	.50	.24	.36
Lateral OFC				
Left	-.12	.66	.41	.10
Right	.38	.14	.15	.58
Rostral middle gyrus				
Left	-.07	.79	.13	.63
Right	.06	.83	-.06	.83

Table 6

Real-World Behavioral Correlates of the Emotion Modulated Startle among FTLD and AD Patients (n=20)

	Anxiety	Disinhibition	Euphoria	Eating
Negative-potentiation	**.50***	.29	.06	.02
Positive-attenuation	-.15	.07	.27	-.08

Pearson correlation coefficients, *$p < .05$

Figure 1

Task Validation: Emotion Modulated Startle Pattern among controls (n = 14)

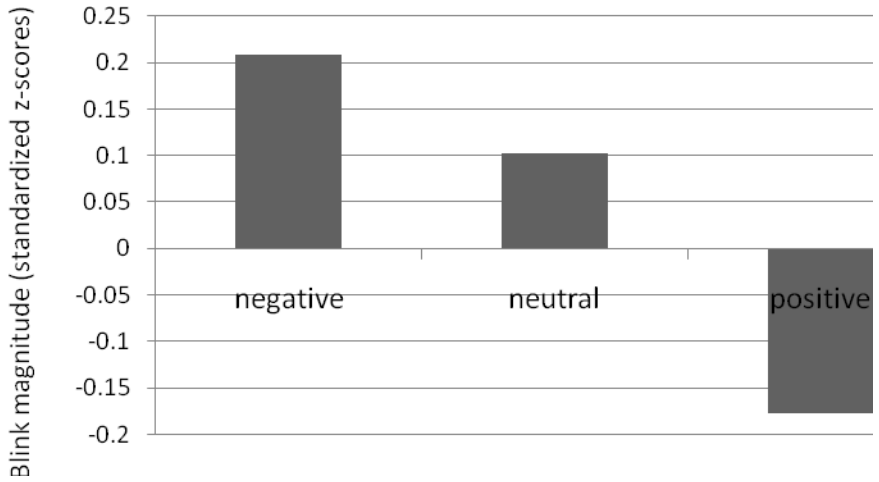
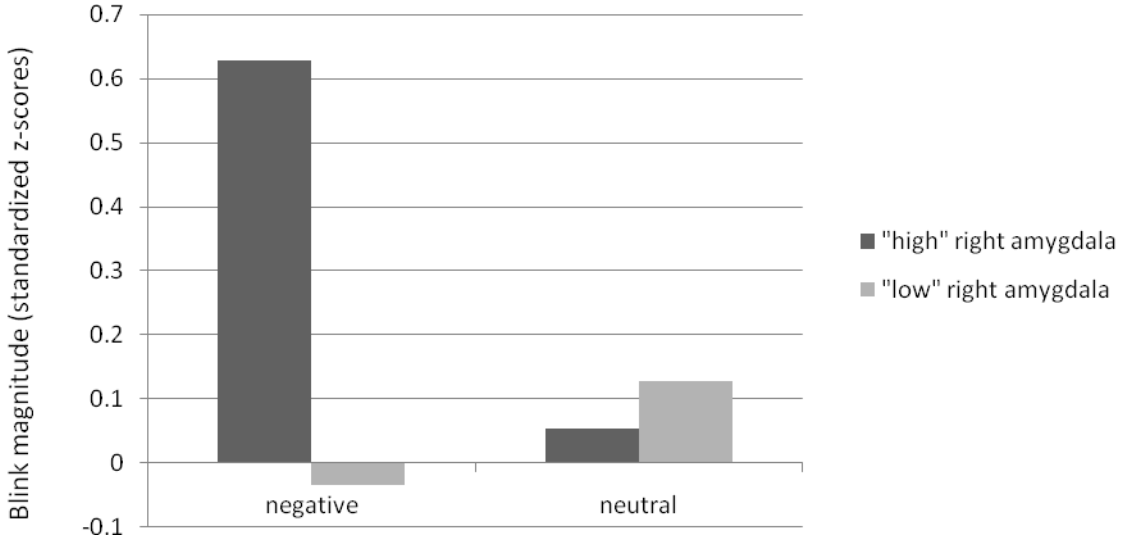


Figure 2.

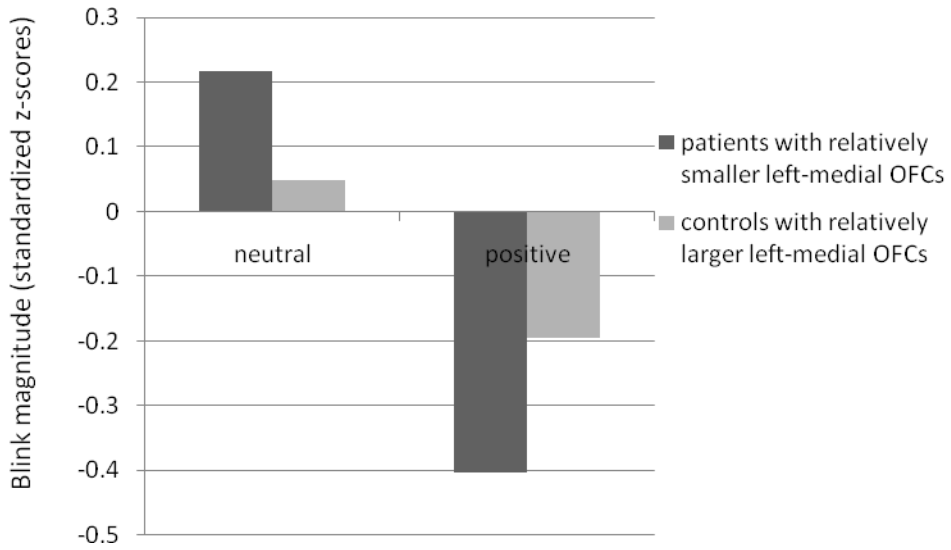
Absence of Negative-Potentiation in Patients with Smallest Right-Amygdalae (n = 17)



A median split was performed on the patients' right amygdala scores, and negative-potentiation was compared between patients with "high" and "low" scores, using repeated measures ANOVA. There was an Emotion X Right Amygdala interaction F (1, 15) = 7.54, p = .015, η_p^2 = .34. Only the patients with "high" right amygdala scores displayed negative-potentiation.

Figure 3

Exaggerated positive-attenuation in patients with relatively smaller left-medial OFCs compared to controls



References

Angrilli, A., Mauri, A., Palomba, D., Flor, H., Birnbaumer, et. al (1996). Startle reflex and emotion modulation impairment after a right amygdala lesion. *Brain*, 119 (6), 1991-2000.

Ascher, E. A., Sturm, V. E., Seider, B. H., Holley, S. R., Miller, B. L., & Levenson, R. W. (in press). Relationship satisfaction and emotional language in frontotemporal dementia and Alzheimer's disease patients and spousal caregivers. *Alzheimer Disease and Associated Disorders*.

Bargh, J. A., Gollwitzer, P. M., Lee-Chai, A. Y., Barndollar, K., & Troetschel, R. (2001). The automated will: Nonconscious activation and pursuit of behavioral goals. *Journal of Personality and Social Psychology*, 81, 1014-1027.

Bates, E., Wilson, D. P., Saygin, A. P., Dick, R., Sereno, M.I., Knight, R. T. et al. (2003). Voxel-based lesion-symptom mapping. *Nature Neuroscience*, 6, 448-450.

Bechara, A., Damasio, H. & Damasio, A. R. (2000). Emotion, decision making and the orbitofrontal cortex. *Cerebral Cortex*, 10, 295-307.

Bechara, A., Tranel, D., Damasio, H., & Damasio, A. R. (1996). Failure to respond autonomically to anticipated future outcomes following damage to the prefrontal cortex. *Cerebral Cortex*, 6, 215-225.

Berg, K. W. & Balaban, M. T. (1999). Startle elicitation: Stimulus parameters, recording techniques, and quantification. In M. E. Dawson, A. M. Schell, and A. H. Bohmelt (Eds.), *Startle modification: Implications for neuroscience, cognitive science, and clinical science* (pp. 95-113). New York: Cambridge University Press.

Blumenthal, T. D., Cuthbert, B. N., Filion, D. L., Hackley, S., Lipp, O. V., & vanBoxtel, A. (2005). Committee report: guidelines for human startle eyeblink electromyographic studies. *Psychophysiology*, 42, 1-15.

Borod, J. (1992). Interhemispheric and intrahemispheric control of emotion: A focus on unilateral brain damage. *Journal of Consulting and Clinical Psychology*, 60, 339-348.

Braak, H. & Braak, E. (1995). Staging of alzheimer's disease-related neurofibrillary changes. *Neurobiology of Aging*, 16, 271-278.

Bradley, M. M., Codispoti, M., Sabitinelli, D., & Lang, P. J. (2001). Emotion and motivation II: sex differences in picture processing. *Emotion*, 1 (3), 276-298.

Bradley, M. M., Cuthbert, B. N., & Lang, P. J. (1990). Startle reflex modulation: Emotion or attention? *Psychophysiology*, 27, 513-522.

Bradley, M. M., Cuthbert, B. N., & Lang, P.J. (1991). Startle and emotion: Lateral acoustic stimuli and the bilateral blink. *Psychophysiology*, 28, 285-295.

Bradley, M. M., Cuthbert, B. N., & Lang, P.J. (1996). Lateralized startle probes in the study of emotion. *Psychophysiology*, 33, 156-161.

Bradley, M. M., Cuthbert, B. N., & Lang, P.J. (1999). Affect and the startle reflex. In M. E. Dawson, A. M. Schell, and A. H. Bohmelt (Eds.), *Startle modification: Implications for neuroscience, cognitive science, and clinical science* (pp. 157-186). New York: Cambridge University Press.

Bradley, M. M., Zack, J., Lang, P. J. (1994). Cries, screams, and shouts of joy: Affective responses to environmental sounds. *Psychophysiology*, 31, S29.

Buchanan, T. W., Tranel, D., & Adolphs, R. (2004). Anteromedial temporal lobe damage blocks startle modulation by fear and disgust. *Behavioral Neuroscience*, 118 (2), 429-437.

Carstensen, L. L., Pasupathi, M., Mayr, U., Nesselroade, J. R. (2000). Emotional experience in everyday life across the adult life span. *Journal of Personality and Social Psychology*, 79, 644-655.

Carver, C. S. & Harmon-Jones, E. (2009). Anger is an approach-related affect: evidence and implications. *Psychological Bulletin*, 135, 183-204.

Cook, E. W., Hawk., L. W., Davis, T. L., & Stevenson, V. E. (1991). Affective individual differences and startle reflex modulation. *Journal of Abnormal Psychology*, 100, 5-13.

Corr, J. P., Wilson, G. D., Fotiadou, M., Kumari, V., Gray, N. S., Checkley, S. et al. (1995). Personality and affective modulation of the startle reflex. Personality and Individual Differences, 19, 543-553.

Cummings, J. L. (1997). The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology*, 48 (5 Suppl), S10-16.

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* , 44, 2308–2314.

Cuthbert, B.N., Bradley, M. M., & Lang, P. J. (1996). Affective imagery and startle modulation. Psychophysiology, 27, S24.

Damasio, A. R., Tranel, D. & Damasio, H. (1990). Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. *Behavioural Brain Research*, 41, 81-84.

Davidson, R. J. (1984). Affect, cognition, and hemispheric specialization. In C.E. Izard, J. Kagan, & R. Zajonc (Eds.) Emotions, cognition, and behavior (pp. 320-365). Cambridge, England: Cambridge University Press.

Davidson, R. J. (1998). Anterior electrophysiological asymmetries, emotion, and depression: Conceptual and methodological conundrums. *Psychophysiology*, 35, 607-614.

Davidson, R. J. (2000). Affective style, psychopathology, and resilience: brain mechanisms and plasticity. *American Psychologist*, 55, 1196-1214.

Davidson, R. J. (2004). What does the prefrontal cortex "do" in affect: perspectives from frontal EEG asymmetry research. Biological Psychology, 67, 219-233.

Davis, M., Gendelman, D.S., Tischler, M. D., Gendelman, P. M. (1982). A primary acoustic startle circuit: Lesion and stimulation studies. *Journal of Neuroscience*, 2, 791-805

Davis, M., Walker, D. L., & Lee, Y. (1999). Neurophysiology and neuropharmacology of startle and its affective modulation. In M. E. Dawson, A. M. Schell, and A. H. Bohmelt (Eds.), *Startle modification: Implications for neuroscience, cognitive science, and clinical science* (pp. 95-113). New York: Cambridge University Press.

Desikan, R. S., Segonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D. et al. (2006). An automatic labeling system for subdiving the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*, 31, 968-980.

Elliott, R., Dolan, R. J., & Frith, C. D. (2007). Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. *Cerebral Cortex*, 10, 308-317.

Elliott, R., Newman, J. L., Longe, O.A., & Deakin, J. F. (2003). Differential response patterns in the striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study. *Journal of Neuroscience*, 23, 303-307.

Erickson, L. M., Levenston, G. K., Curtin, J., Goff, A., & Patrick, C. J. (1995). Affect and attention in startle modulation: Picture perception and anticipation. *Psychophysiology*, 32 (Suppl. 1), S30.

Erlichman, H., Brown, S., Zhu, J., & Warrenburg, S. (1995). Startle reflex modulation during exposure to pleasant and unpleasant odors. *Psychophysiology*, 32, 150-154.

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C. et al. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, 33, 341-355.

Fukui, T. & Kertesz, A. (2000). Volumetric study of lobar atrophy in pick complex and alzheimer's disease. *Journal of Neuroscience*, 174, 111-121.

Funayama, E. S., Grillon, C., Davis, M., & Phelps, E. A. (2001). A double dissociation in the affective modulation of startle in humans: effects of unilateral temporal lobectomy. *Journal of Cognitive Neuroscience*, 13 (6), 721-729.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": A practical method for grading the cognitive state of patients for the clinical. *Journal of Psychiatric Research*, 12, 189-198.

Frederickson, B. L. (1998). What good are positive emotions? *Review of General Psychology*, 2, 300-319.

Gard, D. E., Germans Gard, M. K., Mehta, N., Kring, A. M., & Patrick, C. P. (2007). Impact of motivational salience on affect modulated startle at early and late probe times. *International Journal of Psychophysiology*, 66, 266-270.

Gironell, A., Kullisevsky, J., Roig, C., Pascual-Sedano, B., Rodriguez-Fornells, A., & Otermin, P. (2003). Diagnostic potential of the acoustic startle reflex, acoustic blink reflex, and electro-oculography in progressive supranuclear palsy: a prospective study. Movement *Disorders*, 11, 1273-1279.

Goodkind, M., Gyurak, A., McCarthy, M., Miller, B., & Levenson, R. W. (in press). Emotion regulation deficits in frontotemporal lobar degeneration and Alzheimer's disease. *Psychology and Aging*.

Grillon, C., Ameli, R., Foot, M., & Davis, M. (1993). Fear-potentiated startle: Relationships to the level of state/trait anxiety in healthy subjects. *Biological Psychiatry*, 32, 939-943.

Grillon, C. & Baas, J. (2003). A review of the modulation of the startle reflex by affective states and its application in psychiatry. *Clinical Neurophysiology,* 114, 1557-1579.

Hamm, A. O., Cuthbert, B. N., Globisch, J. & Vaitl, D. (1997). Fear and the startle: Blink modulation and autonomic response patterns in animal and mutilation fearful subjects, *Psychophysiology*, 34, 97-107.

Hawk, L. W. & Cook, E. W. (1997). Affective modulation of tactile startle. *Psychophysiology*, 34, 23-31.

Hawk, L. W. & Kowmas, A. D. (2003). Affective modulation and prepulse inhibition of startle among undergraduates high and low in behavioral inhibition and approach. *Psychophysiology*, 40, 131-138.

Hikosaka, K. & Watanabe, M. (2000). Delay activity of orbital and lateral prefrontal neurons of the monkey varying with different rewards. *Cerebral Cortex,* 10, 263-271.

Ikeda, M., Ishikawa, T., & Tanabe, H. (2004). Epidemiology of frontotemporal lobar degeneration. *Dement Geriatr Cogn Disord, 17*(4), 265-268.

Jansen, D. M. & Frijda, N. H. (1994). Modulation of the acoustic startle response by film-induced fear and sexual arousal. *Psychophysiology*, 31, 565-571.

Josselyn, S. A., Falls, W. A., Gewirtz, J. C., Pistell, P. & Davis, M. (2005). The nucleus accumbens is not critically involved in mediating the effects of safety signal on behavior. *Neuropsychopharmocology*, 30, 17-26.

Koch, M., Schmid, A., & Schnitzler, H. U. (1996). Pleasure-attenuation of startle is disrupted by lesions of the nucleus accumbens. *Neuroreport*, 7 (8), 1442-1446.

Kringelbach, M. L. & Rolls, E. T. (2004). The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Progress in Neurobiology*, 72, 341-372.

Landis, C. & Hunt, W. A. (1939). The startle pattern. New York: Farrar.

Lane, R.D., Reiman, E.M., Ahern, G.L., Schwartz, G.E. & Davidsion, R. J. (1997). Neuroanatomical correlates of happiness, sadness, and disgust. *American Journal of Psychiatry*, 154, 926-933.

Lane, R.D., Reiman, E.M., Bradley, M.M., Lang, P.J, Ahern, G.L, Davidson, R.J. et al. (1997). Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia*, 35, 1437-44.

Lang, P. J. (1995). The emotion probe. Studies of motivation and attention. *The American Psychologist*, 50 (5), 372-385.

Lang, P.J., Bradley, M.M, & Cuthbert, B.N. (1990) Emotion, attention, and the startle reflex. *Psychological Review*, 97, 377-395.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1999). *International affective picture system (IAPS): Technical manual and Affective Ratings.* Gainsville, FL: The Center for Research in Psychophysiology, University of Florida.

Levenson, R. W., Ascher, E., Goodkind, M., McCarthy, M., Sturm, V. & Werner, K. (2008). Laboratory testing of emotion and frontal cortex. In G. Goldenberg & B. Miller (Eds.) *Handbook of clinical neurology. Vol. 88: Neuropsychology and behavioral neurology* (pp. 489-498). Edinburgh, Scotland: Elsevier.

Levenson, R. W. & Miller, B. M. (2007). Loss of Cells—loss of self: Frontotemporal lobar degeneration and human emotion. *Current Directions in Psychological Science*, 16, 289-294.

Levy, M. L., Miller, B. L., Cummings, J. L., Fairbanks, L. A. & Craig, A. (1996). Alzheimer disease and frontotemporal dementias. Behavioral distinctions. *Archives of Neurology,* 53 (7), 687-690.

McKhann, G. M., Albert, M.S., Grossman, M., Miller, B. L., Dickson, D. & Trojanowski, J. (2001). Clinical and pathological diagnosis of frontotemporal dementia. *Archives of Neurology*, 58, 1803-1809.

Miltner, W., Matjak., M., Braun, C., Deikmann, H., & Brody, S. (1994). Emotional qualities of odours and their influence on the startle reflex in humans. *Psychophysiology,* 31, 107-110.

Morris, J.C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, 43 (11), 2412-2414.

Neary, D., Snowden, J. S., Gustafson, L., Passant, U., Stuss, D., Black, S., et al. (1998). Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology, 51*(6), 1546-1554.

Olson, I. R., Plotzker, A. & Ezzyat, Y. (2007). The enigmatic temporal pole: a review of findings on social and emotional processing. *Brain*, 130, 1718-1731.

Paradiso, S., Johnson, D. L., Andreasen, N.C., O'Leary, D. S., Watkins, G. L, Boles Ponto, L. L. et al. (1999). Cerebral blood flow changes associated with attribution of emotional valence to pleasant, unpleasant, and neutral visual stimuli. *American Journal of Psychiatry,* 156, 1618-1629.

Patrick, C. J., Bradley, M. M., & Lang, P. J. (1993). Emotion in the criminal psychopath: Startle reflex modulation. *Journal of Abnormal Psychology,* 102, 82-92.

Phelps, E. A. & LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron*, 48, 175-187.

Pizzagalli, D. A., Sherwood, R. J., Henriques, J. B. & Davidson, R. J. (2005). Frontal brain asymmetry and reward responsiveness: a source-localization study. *Psychological Science,* 16, 805-813.

Ratnavalli, E., Brayne, C., Dawson, K., & Hodges, J. R. (2002). The prevalence of frontotemporal dementia. *Neurology*, 58, 1615-1621.

Roberts, N. A., Beer, J. S., Werner, K. H., Scabini, D., Levens, S. M., Knight, R. T. et al. (2004). The impact of orbital prefrontal cortex damage on emotional activation to unanticipated and anticipated acoustic startle stimuli. *Cognitive, Affective, & Behavioral Neuroscience,* 4, 307-316.

Rolls, E. T. (2000). The orbitofrontal cortex and reward. *Cerebral Cortex*, 10, 284-294.

Rosen, H. J., Gorno-Tempini, M. L., Goldman, W. P., Perry, R. J., Schuff, N., Weiner, M. et al. (2002). Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology*, 67, 1752-1756.

Rosen, H. J., Narvaez, J. M., Hallam, B., Kramer, J. H., Wyss-Coray, C., et. al (2004). Neuropsychological and functional measures of severity in alzheimer's disease, frontotemporal degeneration, and semantic dementia. *Alzheimer's Disease and Associated Disorders,* 18 (4), 202-207.

Rule, R.R., Shimamura, A. P., Knight, R. T. (2002). Orbitofrontal cortex and dynamic filtering of emotional stimuli. *Cognitive, Affective, & Behavioral Neuroscience*, 2, 264-270.

Sanchez-Navarro, J. P., Martinez-Selva, J. M., & Roman, F. (2005). Emotional response in patients with frontal brain damage: effects of affective valence and information content. *Behavioral Neuroscience,* 119 (1), 87-97.

Saunders, J. C., McDonald, S., & Richardson, R. (2006). Loss of emotional experience after traumatic brain injury: findings with the startle probe procedure. *Neuropsychology*, 20 (2), 224-231.

Schlenker, R., Cohen, R., Hopmann, G. (1993). Affective modulation of the startle reflex in schizophrenia patients. *European Archives of Psychiatry and Clinical Neuroscience*, 245, 309-318.

Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L., & Greicius, M. D. (2009). Neurodegenerative disease targets large-scale human brain networks. *Neuron*, 62, 42-52.

Simons, R.C. (1996). Boo! Culture, experience and the startle reflex. New York: Oxford University Press.

Small, D. M., Zatorre, R. J., Dagher, A., Evans, A. C., & Jones-Gotman-M. (2001). Changes in brain activity related to eating chocolate: from pleasure to aversion. Brain, 124, 1720-1733.

Snowden, J. S. & Neary, D. (1999). Neuropsychiatric aspects of frontotemporal dementias. *Current Psychiatry Reports*, 1, 93-98.

Sturm, V. E., Rosen, H. J., Allison, S., Miller, B. L. & Levenson, R. W. (2006). Self-conscious emotion deficits in frontotemporal lobar degeneration. *Brain*, 129, 2508-2516.

Tomarken, A. J. & Keener, A. D. (1998). Frontal brain asymmetry and depression: A self-regulatory perspective. *Cognition and Emotion*, 12, 387-420.

Vasey, M. W. & Thayer, J. F. (1987). The continuing problem of false positives in repeated measures ANOVA in psychophysiology: A multivariate solution. *Psychophysiology*, 24, 479-486.

Viskontas, I. V., Possin, K. L. & Miller, B. L. (2007). Symptoms of frontotemporal dementia provide insights into orbitofrontal cortex function and social behavior. *Annals of New York Academy of Sciences*, 1121, 528-545.

Vrana, S. R., Spence, E. L., & Lang, P. J. (1988). The startle probe response: a new measure of emotion? Journal of Abnormal Psychology, 97, 487-491.

Wallis, J. D. & Miller, E. K. (2003). Neuronal activity in primate dorsolateral and orbital prefrontal cortex during performance of a reward task. *European Journal of Neuroscience*, 18, 2069-2081.

Woolley, J. D., Gorno-Tempini, M. L., Seeley, W. W., Rankin, K., Lee, S. S., Matthews, B. R. et al. (2007). Binge eating is associated with right orbitofrontal-insular-striatal atrophy in frontotemporal dementia. *Neurology*, 69, 1424-1433.