

## Neurobiology of Positive Emotion Disruption in Neurodegenerative Disease

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### Abstract and Keywords

Alterations in emotion are common in neurodegenerative disease. Although often associated with diminished functioning, neurodegeneration of emotion circuits can lead to both losses and gains in a range of emotional functions, including reactivity, regulation, appraisal, and empathy. Most previous research in this area has focused on the impact of neurodegeneration on negative emotions; however, there has recently been increasing interest in the degree to which neurodegenerative diseases may also alter positive emotions. This chapter reviews how different neurodegenerative diseases (e.g., frontotemporal dementia, amyotrophic lateral sclerosis, and Alzheimer's disease) impact positive emotions and the neural basis of positive emotion alterations. We will also discuss how decreases and increases in positive emotional reactivity can lead to specific behavioral symptoms in neurodegenerative disease and can impact patients' family members and caregivers.

Keywords: neurodegenerative diseases, dementia, salience network, visceromotor, emotion circuits, positive emotional reactivity

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### Introduction

Positive emotions play an essential role in everyday life. By imbuing life with pleasant feelings, positive emotions motivate and reinforce certain behaviors, foster well-being, and provide the necessary glue for creating and nurturing enduring social bonds (Fredrickson, 1998). Although early emotion researchers focused primarily on how negative emotions such as anger and fear help us cope with survival-related threats and opportunities by activating “fight-or-flight” behaviors, positive emotions and their associated neurobiological architecture have attracted increasing interest in recent years. Behaviorally, positive emotions share a common facial display, the smile, which led early theoretical models to view them as a single entity: happiness (Ekman, Davidson, & Friesen, 1990). Pioneering work on cognitive functions found that positive emotions broaden cognitive schemas, build intellectual resources, and encourage creative thinking and idea

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generation (Isen, 1990). Our early research on the physiology of positive emotions demonstrated that positive emotions help restore equilibrium after negative emotional events by reducing arousal and reestablishing homeostasis (Fredrickson, 1998; Levenson, 1988; Yuan, McCarthy, Holley, & Levenson, 2010). Later theories emphasized the influential role that positive emotions play in social behavior, such as expanding social networks and deepening kinship bonds (Fredrickson, 2004). Contemporary formulations build on these foundations and emphasize that there is a family of positive emotions in which each emotion differs in terms of expression (when also taking into account nonfacial expressive behavior), function, and underlying neural circuitry (Shiota et al., 2017). In sum, positive emotions play a critical role in human life by promoting opportunities and facilitating approach behavior, affiliation, resource building, and reward pursuit (Campos, Shiota, Keltner, Gonzaga, & Goetz, 2013; Gonzaga, Keltner, Londahl, & Smith, 2001; Lazarus, 1991).

Debates have long persisted about the conditions under which emotions are best viewed dimensionally or as discrete states (Ekman, 1992; Levenson et al., 2017; Russell, 1980; Russell & Barrett, 1999). Our discussion in this chapter largely views emotions as discrete states. Similar to negative emotions, positive emotions constitute a family of distinct affective states that serve adaptive functions; have different physiological, behavioral, and experiential profiles; and motivate specific thoughts and actions (Griskevicius, Shiota, & Neufeld, 2010; Shiota, Campos, & Keltner, 2003; Shiota et al., 2017; Shiota, Neufeld, Yeung, Moser, & Perea, 2011). Theorists differ in terms of how many positive emotions they envision, with arguments having been made for numerous discrete states, including amusement, attachment love, awe, contentment, enthusiasm, gratitude, interest, joy, liking/pleasure, nurturant love, relief, pride, and sexual desire (Campos et al., 2013; Shiota et al., 2017). Although empirical studies often attempt to differentiate the neuroanatomical substrates of various emotions, all emotions—both negative and positive—are the product of a common emotion-generating brain system known as the *salience network* (Benarroch, 1993; Critchley & Harrison, 2013; Dosenbach et al., 2007; Saper, 2002; Seeley et al., 2007). The salience network interacts with other brain networks that support appraisal and emotion regulation to produce the full spectrum of human emotion (Ochsner & Gross, 2005; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008).

Dysfunction in emotion-relevant brain systems is common in neurological and psychological disorders, and disruption of specific neural mechanisms may result in either increases or decreases in emotional behaviors (Levenson, Sturm, & Haase, 2014). Decline in appraisal systems may affect patients' emotional reactivity by altering their sensory thresholds, interfering with their judgment, or degrading their understanding of a stimulus' meaning. Impairment in emotion regulation networks, or enhanced activity in emotion generation networks, may lead to heightened emotional reactivity. Furthermore, disruptions in other emotion-processing circuits can result in deficits in the ability to recognize and respond appropriately to emotions in self and others. The location of the brain injury (or the scope of the network-level dysfunction), therefore, will determine which emotional aberrations arise in a given patient. Emotion system disruption can be quite widespread,

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affecting positive, negative, and self-conscious (e.g., pride, shame, or embarrassment) emotions, or quite selective, impacting certain emotions but sparing others.

Neurodegenerative diseases are progressive illnesses that may affect emotion-related brain networks and alter emotion generation and regulation (Levenson et al., 2014). Each neurodegenerative disease targets a specific distributed brain system, and insidious network decline leads to a unique constellation of cognitive, emotional, behavioral, and motor symptoms (Seeley, Crawford, Zhou, Miller, & Greicius, 2009). Gradual deterioration of the neural systems that support emotion may result in behavioral alterations (e.g., loss of empathy and disinhibition) as well as affective symptoms (e.g., apathy, irritability, and euphoria). These symptoms are difficult to treat and can have a profound impact on families and caregivers (de Vugt et al., 2006). Although mild changes in positive emotion may confer some advantages (e.g., greater positive emotional reactivity in patients making interactions more rewarding for caregivers), extreme changes in positive emotion, either losses or gains, may dramatically increase caregiver stress and burden.

For patients, reduced positive emotions may lead to depression and apathy, whereas elevated positive emotions may spur high-risk behaviors, such as approaching strangers and spending recklessly (Mendez, Chen, Shapira, Lu, & Miller, 2006; Woolley et al., 2007). Because neurodegenerative diseases are selective and progress through specific neural networks, they offer a novel window into the circuitry of positive emotion reactivity, regulation, appraisal, and empathy and can help to elucidate how disruption of specific neurobiological mechanisms can lead positive emotions to go awry.

## Neurobiology of Positive Emotions

The salience network is an emotion-generating and emotion-sensing brain network. Anchored by hubs in the anterior cingulate cortex and ventral anterior insula, the salience network is integral for efferent visceromotor emotion generation (i.e., triggering the patterned physiological and behavioral changes that accompany emotions) and afferent viscerosensory processing and integration (Craig, 2009; Critchley, 2005; Saper, 2002; Seeley, Zhou, & Kim, 2012). With projections to central pattern generators, including the central nucleus of the amygdala, hypothalamus, and periaqueductal gray, the salience network maintains homeostasis at rest and generates emotional reactions when an individual encounters stimuli with high personal relevance (Saper, 2002; Seeley et al., 2007).

The salience network not only initiates coordinated, multisystem efferent emotional reactions but also maps continuous afferent streams of interoceptive information via vagal afferents and the lamina I spinothalamocortical tract in the spinal cord. Interoceptive information from the body is relayed through the brainstem, thalamus, posterior insula, midinsula, and on to the ventral anterior insula, which represents the internal condition of the organs and viscera (Craig, 2002; Critchley & Harrison, 2013). This feedback loop enables rapid adjustments to be made to the outflow of the emotion generation systems and the employment of online emotion regulation strategies. Salience network activity is modulated by cognitive and behavioral control systems that include ventrolateral prefrontal cor-

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tex, orbitofrontal cortex (OFC), dorsomedial prefrontal cortex, and pre-/supplementary motor area as well as lateral and medial parietal areas (Aron, 2007; Koenigsberg et al., 2010; Ochsner & Gross, 2005; Parkinson, Liu, & Wheatley, 2014; Wager et al., 2008). These systems promote emotion regulation, allowing humans to modify their emotions to meet situational demands and personal goals.

The majority of neuroimaging and clinical studies on the salience network's role in emotion generation has focused on negative emotions (Hermans et al., 2011; Raz et al., 2016; Seeley et al., 2007). The salience network, however, also produces the changes in autonomic nervous system (ANS) activity, facial expression, and subjective experience that accompany positive emotions (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Touroutoglou, Lindquist, Dickerson, & Barrett, 2015). Although debate continues to surround the degree to which negative and positive emotions reflect similar or different patterns of brain activity (Clark-Polner, Johnson, & Barrett, 2017; Hamann, 2012; Kragel & Labar, 2013; Lindquist et al., 2012; Saarimaki et al., 2016; Vytal & Hamann, 2010), and some theoretical models propose that emotions lack unique neurobiological signatures (Barrett, 2006, 2012), we view emotions as being accompanied by distinct sequences of stereotyped behavioral and physiological changes (Levenson, 1994, 2003). According to this view, each positive emotion, like each negative emotion, is associated with a characteristic physiological and behavioral pattern that colors subjective experience and motivates specific thoughts and actions (Shiota et al., 2017). Thus, positive emotions, which are also products of the salience network, may have patterns of associated activity that make them distinct. We next review the neurobiological systems that appear to be particularly important for positive emotion generation.

### Recruitment of Reward Systems

Reward systems overlap with the salience network and may be particularly important for eliciting the pleasant feelings that accompany positive emotions. Numerous animal and human studies have outlined the neural circuitry of reward in exquisite detail (Berridge & Kringelbach, 2015; Carelli, 2002; Ferenczi et al., 2016). The ventral striatum (i.e., nucleus accumbens, olfactory tubercle, and parts of ventral caudate and putamen) is a key reward circuit hub (Berridge & Kringelbach, 2015; Haber & Knutson, 2010; Knutson, Adams, Fong, & Hommer, 2001) that is active during the anticipation and receipt of rewarding stimuli, including money, pleasant odors, attractive people, smiling faces, and appetitive cues (Kuhn & Gallinat, 2012; Sescousse, Caldu, Segura, & Dreher, 2013). The ventral striatum also responds to vicarious rewards: when individuals do not directly receive a reward themselves but observe others obtaining rewards (Morelli, Sacchet, & Zaki, 2015). Prosocial behaviors that generate positive emotions and strengthen social bonds, such as altruistic actions (e.g., spending money on others and donating to charities), empathic validation, and cooperation, among others (Batson et al., 1995; Decety & Jackson, 2004; Mobbs et al., 2009; Zaki & Mitchell, 2013), also activate the ventral striatum (Declerck, Boone, & Emonds, 2013; Dunn, Aknin, & Norton, 2008; Harbaugh, Mayr, & Burghart, 2007; Izuma, Saito, & Sadato, 2008, 2010; Morelli, Torre, & Eisenberger, 2014).

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The OFC, a region that is in close communication with the ventral striatum, also activates in response to rewarding affective cues (Berridge & Kringelbach, 2015; Haber & Knutson, 2010). The medial OFC, which has connections with reward systems and emotion generators, including the anterior cingulate cortex, amygdala, hypothalamus, and periaqueductal gray, plays a critical role in processing reward value, whereas the lateral OFC may be more essential for tracking punishment (Ongur & Price, 2000; Rolls, 2000). The OFC (p. 468) responds to numerous types of stimuli, including olfactory, gustatory, visual, auditory, and somatosensory cues (Blood, Zatorre, Bermudez, & Evans, 1999; O'Doherty, Rolls, Francis, Bowtell, & McGlone, 2001; O'Doherty et al., 2003; Rolls, Kringelbach, & de Araujo, 2003; Rolls, O'Doherty, et al., 2003) that evoke pleasant feelings and are inherently rewarding (Perry & Kramer, 2015). Both primary rewards (e.g., food) and more abstract stimuli (e.g., economic decisions) activate the OFC, which gauges the relative value of a stimulus in relation to an individual's current metabolic and motivational demands (Padoa-Schioppa & Assad, 2006). As stimuli lose their relative reward value (due to satiety, habituation, or goal attainment), the medial OFC tracks this diminution, and attendant activity in this region decreases (Kringelbach, O'Doherty, Rolls, & Andrews, 2003).

The ventral striatum and OFC have tight projections to other salience network structures that generate the emotional responses that accompany reward processing. The pregenual anterior cingulate cortex is a primary hub in emotion generation (Critchley, Mathias, & Dolan, 2001; Grabenhorst & Rolls, 2011) and has tight connections with the central nucleus of the amygdala (Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003; Price & Amaral, 1981), a region that also helps to decode the magnitude of reward value and triggers rapid visceromotor reactions (Bermudez & Schultz, 2010; Morrison & Salzman, 2010). During certain positive emotions, the salience network also engages the septal area, a region that plays an important role in primary reward processing and is associated with the positive emotional feelings that emerge during moments of social connection, unconditional trust, and empathy (Francis, Champagne, & Meaney, 2000; Inagaki & Eisenberger, 2012; Krueger et al., 2007; Morelli, Rameson, & Lieberman, 2014). Because the ventral anterior insula is a sensory integration site that processes the visceral changes that accompany emotions, it is also essential for reward processing and is integral for mapping the internal states that emerge during positive emotional experiences (Craig, 2003, 2005).

### Parasympathetic Engagement

In our view, each positive emotion is accompanied by a unique constellation of physiological changes that influence cognition and behavior (Griskevicius et al., 2010; Shiota et al., 2011, 2017). During an emotion, the parasympathetic and sympathetic branches of the ANS work in concert to produce stereotyped activity patterns across the body's cardiovascular, respiratory, electrodermal, and somatic systems (Levenson, 1994, 2003; Levenson et al., 2017). Whereas sympathetic activity generally increases arousal and mobilizes defensive behaviors, parasympathetic activity generally decreases arousal and promotes restorative functions (i.e., "rest and digest"). Via the influence of the vagus nerve on the sinoatrial node, the parasympathetic nervous system reduces heart rate to a pace that is

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slower than the rate set by intrinsic pacemaker cells (Carlson et al., 1992; Levy, Yang, & Wallick, 1993); this inhibitory influence is linked to the breathing cycle. During expiration, the vagus is active and causes heart rate to decelerate, but during inspiration, the influence of the vagus is blocked and heart rate accelerates (Rybak et al., 2004). This oscillating influence of the vagus on the heart creates respiratory-linked variability in heart rate, or respiratory sinus arrhythmia (Berntson et al., 1997), a downregulatory physiological process that is associated with numerous physical and socioemotional advantages (Graziano & Derefinko, 2013; Porges, 2003).

Parasympathetic activity restores homeostatic equilibrium after negative emotional events by reducing arousal, slowing physiological rhythms, and promoting a calm internal state (Fredrickson & Levenson, 1998). In mammals, higher parasympathetic activity is thought to confer social benefits by fostering interpersonal engagement and other-oriented positive emotions. According to the polyvagal theory, a phylogenetically newer branch of the vagus nerve emerges from the nucleus ambiguus, a brainstem nucleus that is an important ANS control center, and slows the heart and fosters social communication (Porges, 2001). This newer branch of the vagus stands in contrast to the older branch that originates in the dorsal motor nucleus of the vagus and primarily projects to subdiaphragmatic organs such as the gut. This older vagal system supports processes such as digestion and freezing behaviors and is thought to be less important for socioemotional functioning. We consider the question of relative importance to be unsettled but agree that these different vagal pathways clearly play different roles in social behavior and specific positive emotions.

Parasympathetic activity may be especially important for low arousal positive emotions (e.g., compassion, love, and affection) that are integral for enduring kinship bonds (Goetz, Keltner, & Simon-Thomas, 2010; Oveis et al., 2009). A moderate (p. 469) level of parasympathetic activity may actually be most advantageous given that very high and very low levels of parasympathetic activity are related to low empathy and may actually hinder emotional interest and understanding (Kogan et al., 2014). High parasympathetic activity is also associated with positive emotion dysregulation, including symptoms of euphoria and mania (Gruber, Johnson, Oveis, & Keltner, 2008; Martinez, Garakani, Aaronson, & Gorman, 2015; Thayer, Friedman, & Borkovec, 1996), whereas low parasympathetic activity is associated with negative emotion dysregulation, including symptoms of anxiety and panic (Martinez et al., 2015; Thayer et al., 1996). Taken together, these findings suggest that although the vagus downregulates arousal and facilitates a quiet internal milieu, there may be an optimal level of parasympathetic engagement for social attunement and positive emotional responsiveness.

### Left Hemisphere Predominance

Although the salience network generates all types of emotions, lateralized hubs within the network may be critical for positive emotion production. The relationship between brain asymmetry and emotion has been a long-standing topic of debate (Davidson & Fox, 1982). Although some models maintain that the right hemisphere plays an essential role

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in the perception and expression of all emotions (Tucker & Saper, 1985), others propose that there are lateralized neural representations of emotional valence such that the left (or nondominant) hemisphere plays a key role in positive emotions, whereas the right (or dominant) hemisphere plays a critical role in negative emotions (Davidson, 1992).

Patient studies offer abundant evidence for asymmetric positive and negative emotion systems in the brain. In Wada studies (which temporarily silence one hemisphere of the brain via a unilateral intracarotid injection of sodium amytal), when the right hemisphere is silenced, patients often exhibit optimism, smiling, and laughter (Perria, Rosadini, & Rossi, 1961; Sackeim et al., 1982). Similarly, right hemisphere lesions typically result in laughing and smiling (Gainotti, 1972; Sackeim et al., 1982). The opposite pattern tends to be true for left hemisphere dysfunction. In general, left hemisphere dysfunction is associated with reduced positive emotions, and patients with left hemisphere deficits often display increased negative emotions, including sadness and crying. An opposing relationship between the left and right hemispheres may cause right hemisphere dysfunction to “release” the left hemisphere, thereby facilitating positive emotion elicitation (and vice versa: left hemisphere dysfunction may release the right hemisphere, which facilitates negative emotion generation). Taken together, these studies suggest that when right hemisphere systems are disrupted, intact left hemisphere systems can still generate positive emotions.

Electrophysiological studies in healthy individuals have found that the left hemisphere plays a prominent role in positive emotion generation. Electroencephalography (EEG) studies of prefrontal activation suggest that asymmetric activity levels in the left and right frontal lobes is associated with distinct affective response patterns and that the left frontal lobe is more active during positive than negative emotions (Davidson, 1992; Davidson & Fox, 1982; Sackeim et al., 1982). Individuals with greater left than right prefrontal activity at baseline report higher levels of positive emotional experience, optimism, and approach behavior, whereas the opposite pattern is true for those with greater activity in the right prefrontal cortex than the left (De Pascalis, Cozzuto, Caprara, & Alessandri, 2013; Jacobs & Snyder, 1996; Urry et al., 2004). Those with left prefrontal hypoactivity, in contrast, have higher levels of negative emotions and symptoms, including depression (Henriques & Davidson, 1991; Schaffer, Davidson, & Saron, 1983). Even in infants, positive emotional stimuli elicit greater left than right frontal lobe activity (Davidson & Fox, 1982; Fox & Davidson, 1986). These studies offer an additional line of evidence that the left hemisphere, and the left frontal lobe in particular, is critical for positive emotion generation. Because frontal asymmetry indices are typically based on dorsolateral prefrontal cortex activity, however, these studies are not equipped to elucidate how lateralized ventral frontal and subcortical structures participate in positive emotion generation (Davidson & Irwin, 1999).

As described, positive emotions often involve high levels of parasympathetic activity. The cortical representations of the ANS's two branches also reflect left hemisphere dominance in parasympathetic activity. In patients undergoing surgery for epilepsy, stimulation of the left insula produces bradycardia and blood pressure decreases, a pattern that

is consistent with elevated parasympathetic tone (Oppenheimer, Gelb, Girvin, & Hachinski, 1992). Patients who have had left hemisphere strokes also exhibit diminished parasympathetic activity and heightened sympathetic activity (Oppenheimer, Kedem, & Martin, 1996; Robinson, James, Youde, Panerai, & Potter, 1997). While right-lateralized neural pathways promote sympathetic arousal, left-lateralized systems facilitate parasympathetic activity (Craig, 2005; Yoon, Morillo, Cechetto, & Hachinski, 1997). Key salience network hubs, including the anterior cingulate cortex and ventral anterior insula, exhibit asymmetry in promoting parasympathetic tone, such that left-lateralized structures play a dominant role in vagal outflow (Guo et al., 2012; Wittling, Block, Genzel, & Schweiger, 1998). Left hemisphere predominance in parasympathetic control, therefore, may also underlie the leftward representation of positive emotion-generating systems.

## Neurodegenerative Diseases Can Alter Positive Emotions

The salience network produces rapid, patterned emotional reactions that motivate adaptive behaviors. Although emotions typically have an onset that is automatic, emotion regulation systems enable individuals to modulate their emotions, a skill that generally improves over the life span (Carstensen et al., 2011; Gross et al., 1997; Shiota & Levenson, 2009). Emotion systems with this type of “two-core” structure facilitate the generation of time-tested visceromotor responses as well as controlled responses that are flexible, context appropriate, and commensurate with one’s goals (Levenson, 1999).

Neurodegenerative diseases often impact emotion-relevant circuits and may alter positive emotions in different ways. Disruption of emotion-generating or -inhibiting systems may result in a number of diverse, observable states and lead to problematic affective symptoms (Levenson et al., 2014). To illustrate the outcome of such disruption, we review several neurodegenerative diseases and the distinct effects that each has on positive emotions.

### Frontotemporal Dementia

Frontotemporal dementia (FTD) is a family of neurodegenerative diseases that are characterized by gradual degeneration of the frontal and anterior temporal lobes. FTD includes three clinical syndromes: behavioral variant FTD (bvFTD), semantic variant primary progressive aphasia, and progressive nonfluent variant primary progressive aphasia (Boxer & Miller, 2005). Each clinical syndrome is characterized by a specific constellation of behavioral, language, speech, and motor symptoms that emerge as neuropathological changes progress throughout frontal, temporal, and subcortical brain systems (Seeley et al., 2009). In bvFTD, degeneration of the salience network and associated neural systems that support emotion regulation (Agosta et al., 2013; Zhou et al., 2010) leads to prominent social and emotional symptoms (Seeley et al., 2008). Although early in the disease course each FTD syndrome is focal, affecting specific brain structures but sparing others,



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with disease progression atrophy becomes more widespread, and changes in emotion are increasingly common.

Patients with bvFTD exhibit profound changes in social behavior and emotion, and each patient's symptoms are a reflection of his or her unique pattern of brain atrophy (Rascovsky et al., 2007). In general, patients with bvFTD have impairment in empathy and social responsivity, deficits that have a negative impact on their close relationships (Goodkind et al., 2015; Rankin, Kramer, & Miller, 2005). Laboratory studies that utilize objective measures of socioemotional functioning have proven useful in identifying areas of emotional preservation and loss in FTD (Levenson et al., 2008). These studies have indicated that certain negative (i.e., disgust) and self-conscious (i.e., embarrassment) emotions are especially impaired in bvFTD (Eckart, Sturm, Miller, & Levenson, 2012; Sturm, Allison, Rosen, Miller, & Levenson, 2006; Sturm, Ascher, Miller, & Levenson, 2008), while other emotions (i.e., happiness) are relatively preserved (Werner et al., 2007).

Whether FTD also disrupts certain positive emotions but spares others is a question that has received relatively little attention to date. Clinically, patients with bvFTD often show reduced affiliative behavior, fun-seeking, humor detection, and prosociality (Clark et al., 2015; Moll et al., 2011; Sollberger et al., 2009), positive emotional behaviors that are critical for interpersonal relationships. Tests of baseline ANS physiology have revealed that patients with bvFTD have low resting parasympathetic tone, and that this impairment is associated with atrophy and functional connectivity deficits in the left ventral anterior insula (Guo et al., 2016). The study by Guo et al. (2016) also found that diminished heart rate variability was associated with lower agreeableness in patients with bvFTD, a personality trait that fosters social connection through positive emotions and warmth. Given that lower parasympathetic tone has been associated with lower socioemotional engagement and empathy (Porges, 2001), these findings suggest that deficient baseline parasympathetic activity in bvFTD may interfere with patients' ability to experience positive emotions that foster meaningful social bonds.

**(p. 471)** Although certain positive emotions appear to be deficient in bvFTD, other positive emotions seem to be amplified. For example, it is common for patients to become increasingly overfamiliar, jocular, creative, and elated (Mendez et al., 2006; Woolley et al., 2007), behaviors that suggest that some positive emotions may be dysregulated in bvFTD. To examine whether patterns of brain atrophy were associated with variability in positive emotional responsiveness, we measured happiness facial behavior (i.e., smiling and laughing) and physiological reactivity in patients with FTD while they watched an amusing video clip in a laboratory setting (Sturm et al., 2015). We used voxel-based morphometry, a structural neuroimaging technique, to identify brain regions in which smaller volume was associated with greater happiness facial behavior. Our results indicated that smaller volume in predominantly left hemisphere emotion regulation systems (e.g., dorsal anterior insula, caudate, and ventrolateral prefrontal cortex) was associated with greater happiness behavior while watching the film clip. Smaller volume in certain parts of this system was also associated with greater physiological reactivity while patients watched the film.

Contrary to long-standing models of emotional valence that posit that left-sided injuries always reduce positive emotions, our results pointed to a more nuanced model in which the hemisphere of the injury, in addition to the degree to which emotion generators or emotion regulators were involved, together determined whether there was gain or loss of positive emotion. Selective damage to left hemisphere emotion regulatory systems therefore may actually accentuate positive emotional reactivity by weakening ipsilateral connections between left hemisphere emotion regulation and generation systems (Barbas, Hilgetag, Saha, Dermon, & Suski, 2005). The findings from our study are consistent with previous research that has linked damage in left-lateralized reward structures (e.g., ventral striatum and OFC) to positive emotional enhancements, including excessive generosity (Ferreira-Garcia, Fontenelle, Moll, & de Oliveira-Souza, 2014) and heightened agreeableness (Rankin et al., 2004).

Studies of reward processing have offered convergent evidence that certain types of positive emotional responding may be enhanced in bvFTD. It is common for patients with bvFTD to overeat and to acquire a strong preference for sweet foods (Ahmed et al., 2016; Perry et al., 2014; Woolley et al., 2007). Patients also increase their consumption of alcohol and cigarettes (Perry et al., 2014) and have heightened interest in other primary rewards, such as music (Fletcher et al., 2015). Increased reward-seeking behavior in bvFTD has been associated with atrophy in reward-relevant regions, including the ventral striatum, OFC, and anterior insula (Ahmed et al., 2016; Whitwell et al., 2007; Woolley et al., 2007). While it is possible that patients with bvFTD have altered sensory processing or reduced sensitivity to punishment, there is accumulating evidence that reward systems may be dysregulated in bvFTD, leading to enhanced positive emotional experience (Perry et al., 2014).

### Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) affects the upper and lower motor neurons and results in progressive weakness, muscular wasting, and spasticity (Lomen-Hoerth et al., 2003). There is an increasing awareness that ALS and FTD are on opposite ends of a neurodegenerative disease continuum. Many patients have comorbid ALS and FTD symptoms, which arise due to shared neuropathological features and genetic risk factors (Weishaupt, Hyman, & Dikic, 2016).

Patients with ALS alone do not typically exhibit profound changes in behavior or emotion. They may, however, experience pseudobulbar affect: episodes of pathological laughing or crying. Although it was long held that pathological laughter and crying in ALS emerged in the absence of a clear eliciting stimulus and without attendant feelings of mirth or sadness (Gallagher, 1989; Minden & Schiffer, 1990), a more recent laboratory study found that pseudobulbar moments typically occurred in response to appropriate triggers and were accompanied by strong emotional feelings as well as changes in physiological activity and facial expression (Olney et al., 2011). While watching amusing film clips, patients with ALS were not hyperreactive; however, they demonstrated poor emotion regulation when instructed to control their emotional expressions (Olney et al., 2011). These find-

ings suggest that deficits in emotion regulation may contribute to positive emotion dysregulation in some patients with ALS. One possibility is that frontal connections that interact with emotion generators in the brainstem (e.g., periaqueductal gray) are disrupted in ALS and impede patients' ability to modulate their positive emotional reactions once they are under way.

### Alzheimer's Disease

Alzheimer's disease (AD) is characterized by progressive decline in episodic memory and other cognitive domains (McKhann et al., 2011). AD affects the (p. 472) default mode network, a distributed neural system that supports episodic memory and mental time travel (Buckner et al., 2005; Greicius, Srivastava, Reiss, & Menon, 2004). The default mode network is anchored by hubs in the medial temporal lobes and has tight connections with the precuneus, posterior cingulate cortex, lateral temporoparietal cortex, and medial prefrontal cortex (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle, MacLeod, Snyder, Powers, & Gusnard, 2001). As this system deteriorates in AD, there is gradual enhancement of the salience network, an opposing network that exhibits reciprocal activation patterns (Zhou et al., 2010). Whereas the default mode network is active during tasks involving autobiographical memory recall, self-focused attention, and mind wandering, it deactivates during tasks that shift attention away from the self and onto external demands in the environment (Buckner & Carroll, 2007; Gusnard & Raichle, 2001). Although heightened salience network connectivity in AD may enhance patients' sensitivity to negative affective cues (Hermans et al., 2011), it is unclear whether emotion system alterations also affect positive emotional responsivity in these patients.

Unlike cognition, which declines early in AD, emotional functioning and social behavior are typically preserved until the late stages of disease. In laboratory studies, patients with AD display intact social graces during a variety of social and emotional tasks. During conflictive emotional conversations, patients with AD use eye contact (Sturm et al., 2011) and emotional language (Ascher et al., 2010) in ways that are comparable to healthy controls. Previous studies on empathy in AD have found inconsistent results (Burnham & Hogervorst, 2004; Shimokawa et al., 2003), but it appears that empathy deficits in AD, when detected, can usually be accounted for by task difficulty and disease severity (Spolletini et al., 2008). We have shown that patients with AD can recognize positive, negative, and self-conscious emotions in other people as well as healthy controls when they are presented with naturalistic film clips in which a target character clearly displays a discrete emotion (Goodkind et al., 2015). Moreover, despite making errors on complex cognitive empathy (i.e., emotion recognition) tasks, patients with AD may exhibit accentuated emotional empathy (Sturm et al., 2013), a rudimentary form of empathy in which emotions are "contagious," traveling across individuals via automatic autonomic and behavioral mirroring mechanisms (Batson, Duncan, Ackerman, Buckley, & Birch, 1981; Decety, 2011). Whether patients with AD display particularly heightened sensitivity to the positive emotional states of others has not yet been well investigated.

Other aspects of positive emotional responsivity, such as reward processing, have received relatively little attention to date in AD. In contrast to FTD, there is some evidence that reward seeking may actually decrease in AD and that sensitivity to punishment may increase. On decision-making tasks, patients with AD have faster reaction times on social punishment (i.e., frowning faces) than on social reward (i.e., smiling faces) trials (Perry, Sturm, Wood, Miller, & Kramer, 2015). The findings are mixed, however, as to whether patients with AD show a diminished preference for positive stimuli (Mather & Carstensen, 2005) compared to healthy older adults, with some evidence for preservation of the “positivity effect” in AD (Sava, Krolak-Salmon, Delphin-Combe, Cloarec, & Chainay, 2017). As the disease begins to affect the anterior cingulate cortex and medial prefrontal cortex, however, regions important for reward processing, patients with AD may become apathetic (Lanctot et al., 2008; Rosen et al., 2005). Although apathy may account for decreased reward-seeking behavior in AD, atrophy in default mode network structures, including the medial prefrontal cortex, which supports social cue evaluation and emotion regulation (Xie et al., 2016), and the posterior cingulate cortex, which plays a role in reward valuation (Kable & Glimcher, 2007), may also disrupt reward processing.

### Parkinson’s Disease

Parkinson’s disease (PD) is associated with dysfunction in motor systems mediated by the basal ganglia. Patients with PD typically exhibit resting tremor, rigidity, bradykinesia, akinesia, and postural instability; cognitive deficits, most notably executive impairment, are also common (Zgaljardic, Borod, Foldi, & Mattis, 2003). In PD, progressive dysfunction in dopaminergic pathways within the substantia nigra (a midbrain region that is important for both fine motor control and behavioral guidance), ventral tegmental area, nucleus accumbens, caudate, and putamen (Farley, Price, & Hornykiewicz, 1977; Kish, Shannak, & Hornykiewicz, 1988) impacts both motor functioning and emotion. Given that dopamine plays a critical role in pleasure and reward processing, positive emotional responsivity may also change as the disease disrupts these critical circuits.

Decline in dopaminergic systems in PD may affect patients’ expression and experience of positive emotions in certain contexts. Masked facies (i.e., reduced facial expressivity) is a common (p. 473) symptom of PD (Bologna et al., 2013; Jankovic, 2008) and hinders positive emotional behavior, including smiling (Marsili et al., 2014). Despite impoverished facial expressivity, however, patients with PD report levels of positive (and negative) emotional experience comparable to those of healthy controls (Enrici et al., 2015; Ricciardi et al., 2015). Because facial mimicry aids emotion recognition (Niedenthal, Mermillod, Maringer, & Hess, 2010), facial motor deficits may have a negative impact on cognitive empathy in PD. Consistent with this model, laboratory studies of emotional empathy have shown that patients with PD have delayed and reduced mimicry of emotional faces—and positive faces in particular—compared to healthy controls, and that these impairments hinder emotion recognition (Livingstone, Vezer, McGarry, Lang, & Russo, 2016; Marneweck & Hammond, 2014).

Dysfunction in reward systems may also alter positive emotional experience in PD. In healthy individuals, the ventral striatum and nucleus accumbens activate in response to positive cues, including smiling faces (Vrticka, Andersson, Grandjean, Sander, & Vuilleumier, 2008). Altered reward circuitry in PD, therefore, may impact the value of positive affective cues. Some studies suggest that the anticipation and receipt of rewarding stimuli are behaviorally and anatomically dissociable processes, with the ventral striatum playing a key role in the anticipation of reward and the OFC being predominant in the receipt of reward (Knutson, Fong, Adams, Varner, & Hommer, 2001; Miller, Shankar, Knutson, & McClure, 2014). Patients with PD have diminished ventral striatum activity during reward anticipation but increased activity in the anterior cingulate cortex and medial prefrontal cortex during reward receipt (Keitz et al., 2008; Rowe et al., 2008; Schott et al., 2007). These findings suggest that patients with PD may underestimate anticipated reward values and be less motivated to engage in activities that they previously found enjoyable (Pluck & Brown, 2002). Despite this deficit, some decision-making tasks (Ibarretxe-Bilbao et al., 2009; Kobayakawa, Tsuruya, & Kawamura, 2010), but not all (Czernecki et al., 2002; Poletti et al., 2010), have found that patients with PD may have enhanced sensitivity to rewarding cues, suggesting that there may be multiple ways that reward-processing is disrupted in PD.

## Implications for Psychiatric Disorders

Emotional dysfunction is a central feature of many psychiatric disorders. Within the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* (American Psychiatric Association, 2013), problems with “mood” and “affect” are defining symptoms of most Axis I and many Axis II disorders. As with neurodegenerative disorders, early studies of emotion and psychopathology were more likely to deal with negative emotions (e.g., sadness in depressive disorders and fear in phobias) than with positive emotions. Nonetheless, positive emotions (in both scarcity and surfeit) play an important role in a range of *DSM* disorders (e.g., outbursts of positive emotion in the manic phase of bipolar disorder; anhedonia or inability to experience positive emotion in depression and schizophrenia). Consistent with this, contemporary psychopathology research has revealed new subtleties concerning the role that positive emotion and associated reward systems play in depression, bipolar disorder, and other disorders (Berenbaum & Oltmanns, 1992; Bylsma, Morris, & Rottenberg, 2008; Gruber, 2011; Gruber et al., 2008; Rottenberg, Kasch, Gross, & Gotlib, 2002). Positive emotion also plays an important role in the new Research Domain Criteria (RDoC) (Cuthbert & Insel, 2013), which moves away from syndromes and embraces smaller units of function and dysfunction that are grounded in associated neural circuits. In RDoC, positive valence systems (approach, reward, etc.) constitute one of the core domains of functioning, afforded equal footing with negative valence systems (threat, loss, etc.).

We have argued previously (Levenson, Sturm, & Haase, 2014) that neurodegenerative diseases that produce symptoms similar to those seen in psychiatric disorders can provide useful information concerning the likely neural substrates of psychopathology. This

promise resides in research that links well-characterized patterns of neurodegeneration derived from neuroimaging data with similarly well-characterized behavioral deficits in individuals with neurodegenerative diseases. Although modern neuroscience has greatly improved our ability to measure and quantify neurodegeneration (e.g., more powerful imaging devices, more accurate computerized quantification of degeneration, and new statistical approaches), there remains the challenge of determining the similarity of behavioral phenotypes associated with neuropathology and psychopathology.

Positive emotion in bipolar disorder and FTD provides a good example of this challenge. In the *DSM*, a diagnosis of bipolar disorder requires at least one episode of mania, which includes a period of elevated mood (Johnson, Edge, Holmes, & Carver, 2012). In FTD, euphoric mood is quite (p. 474) common, appearing in up to 40 percent of cases (Hirono et al., 1999; Liu et al., 2004). Given this, it is probably not surprising that individuals with FTD are often misdiagnosed as having bipolar disorder (Woolley, Khan, Murthy, Miller, & Rankin, 2011; Woolley et al., 2007). But, how similar is “elevated mood” in bipolar disorder to “euphoria” in FTD? Answering this kind of question requires a careful and sensitive behavioral assay of many individuals with the two kinds of disorders. Unfortunately, this kind of research has been quite rare. Nonetheless, we see great promise in this approach for both positive and negative (e.g., anhedonia in major depressive disorders and apathy in FTD) emotional behaviors. When behavioral phenotypes in psychopathology and neuropathology are similar, the associated areas of tissue loss in individuals with neurodegenerative disorders may provide useful clues into the neural circuitry that underlies behaviorally similar psychopathologies. Measuring the structural integrity and functional activity of these circuits in patients with psychiatric disorders may provide useful biomarkers for measuring risk for psychopathology, understanding etiology, and evaluating the effectiveness of behavioral and pharmacological treatments.

## Summary and Conclusion

To date, empirical studies of neurodegenerative diseases have focused predominantly on the integrity of negative emotions and have largely overlooked positive emotions. Positive emotions serve important physiological functions (slowing bodily rhythms and reducing arousal) and social functions (solidifying interpersonal bonds). Disruption of positive emotion systems can result in either gains or losses of specific types of positive emotions, alterations that can lead to socioemotional impairment, affective symptoms, and distress for families and caregivers. A better understanding of the neurobiological circuits underlying positive emotion generation and regulation will be imperative for advancing models of positive emotion dysfunction in neurological disorders and other clinical disorders in which positive emotions change during the course of the illness.

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