



## Research report

# Damage to left frontal regulatory circuits produces greater positive emotional reactivity in frontotemporal dementia

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## ABSTRACT

Positive emotions foster social relationships and motivate thought and action. Dysregulation of positive emotion may give rise to debilitating clinical symptomatology such as mania, risk-taking, and disinhibition. Neuroanatomically, there is extensive evidence that the left hemisphere of the brain, and the left frontal lobe in particular, plays an important role in positive emotion generation. Although prior studies have found that left frontal injury decreases positive emotion, it is not clear whether selective damage to left frontal emotion regulatory systems can actually increase positive emotion. We measured happiness reactivity in 96 patients with frontotemporal dementia (FTD), a neurodegenerative disease that targets emotion-relevant neural systems and causes alterations in positive emotion (i.e., euphoria and jocularity), and in 34 healthy controls. Participants watched a film clip designed to elicit happiness and a comparison film clip designed to elicit sadness while their facial behavior, physiological reactivity, and self-reported emotional experience were monitored. Whole-brain voxel-based morphometry (VBM) analyses revealed that atrophy in predominantly left hemisphere fronto-striatal emotion regulation systems including left ventrolateral prefrontal cortex, orbitofrontal cortex, anterior insula, and striatum was associated with greater happiness facial behavior during the film ( $p_{FWE} < .05$ ). Atrophy in left anterior insula and bilateral frontopolar cortex was also associated with higher cardiovascular reactivity (i.e., heart rate and blood pressure) but not self-reported positive emotional experience during the happy film ( $p < .005$ , uncorrected). No regions emerged as being associated with greater sadness reactivity, which suggests that left-lateralized fronto-striatal atrophy is selectively associated with happiness dysregulation. Whereas previous models have proposed that left frontal injury decreases positive emotional responding, we argue that selective disruption of left hemisphere emotion regulating systems can impair the ability to suppress positive emotions such as happiness.

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## 1. Introduction

Positive emotions refer to a family of emotions that includes happiness, amusement, attachment love, nurturant love, awe, and enthusiasm, among others (Shiota, Neufeld, Yeung, Moser, & Perea, 2011). These emotions serve important social functions, facilitating approach behavior, motivating social engagement, fostering new social connections (Fredrickson, 2004), and reversing the physiological activation caused by negative emotions (Fredrickson & Levenson, 1998). Certain levels of positive emotional reactivity are thought to be optimal; levels that are too low or too high can be problematic. For example, overly low levels of positive emotion underlie clinical symptoms such as anhedonia and depression whereas overly high levels can give rise to inappropriate interpersonal boundaries, risktaking, and mania (Gruber, Harvey, & Purcell, 2011).

Distributed brain systems involved in both emotion generation and emotion regulation act in concert to produce observed levels of a positive emotional response (typically measured in terms of changes in facial behavior, physiology, and subjective experience). While emotion generating systems (i.e., projections from pregenual anterior cingulate cortex to the central nucleus of the amygdala, hypothalamus, and brainstem) initiate rapid emotional responses to positive emotional cues (Saper, 2002), emotion regulating systems (i.e., ventrolateral prefrontal cortex, orbitofrontal cortex, dorso-medial prefrontal cortex, and pre/supplementary motor area), with connections to striatum, thalamus, and subthalamic nuclei, promote down-regulation of affective responding in ways that are commensurate with individual goals and the social context (Aron, 2007; Ochsner & Gross, 2005; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). Thus, whether an injury to neural systems that support positive emotion results in muted or intensified emotion should depend on the locus of the anatomical injury. In general, damage to emotion generating circuits should reduce positive emotional reactivity whereas damage to emotion regulating circuits should weaken inhibition and thus result in heightened positive emotion.

The extent to which positive emotion is lateralized in the brain has long been debated. While some argue that there is right hemisphere dominance for the perception and expression of both positive and negative emotion (Tucker, 1981), others propose that the left hemisphere plays a dominant role in positive emotion (Davidson & Fox, 1982). Previous studies have concluded that left-hemisphere damage typically diminishes positive emotion whereas right-hemisphere damage typically increases positive emotion. Two lines of evidence support this conclusion. In Wada studies that deactivate the right hemisphere (via unilateral intracarotid injection of sodium amytal) but preserve the left, patients frequently exhibit optimism and laughter (Perria, Rosadini, & Rossi, 1961; Sackeim et al., 1982). Similarly, numerous lesion studies, but not all (House, Dennis, Warlow, Hawton, & Molyneux, 1990), have found that right-hemisphere injury often results in laughing and smiling (Gainotti, 1972; Sackeim et al., 1982). Positive emotions are thought to persist in patients with right hemisphere damage or dysfunction because

of preservation (and even release) of left-hemisphere circuits that produce positive emotion. Positive emotions produced by these circuits may be more apparent when right hemisphere negative emotion generators are attenuated.

Despite the advances in understanding the laterality of positive emotion, the ways that left hemisphere neural systems support positive emotion generation and regulation remain poorly understood. The majority of previous clinical studies that related asymmetric brain injury to positive emotional change did not directly relate lesion size or location with positive emotional behavior. Thus, it is difficult to know whether all left hemisphere lesions diminish positive emotion or whether the effects depend on lesion location. Electrophysiological studies of prefrontal activation asymmetry offer more anatomical specificity, pointing to the left frontal lobe as an integral left hemisphere hub for positive emotion generation (Davidson, 1992). However, in these studies, frontal asymmetry indices have typically been based on dorsolateral prefrontal cortex activity. Thus, they are not well-suited to shed light on the role of ventral frontal and subcortical structures in positive emotion (Davidson & Irwin, 1999) nor to tease apart the roles of left-dominant frontal systems that support positive emotion generation from those that support emotion regulation. Determining whether greater left frontal activity during positive emotion reflects the involvement of positive emotion generators, regulators, or both, is critical to our understanding of the ways that left frontal systems mount positive emotional responses. Although focal lesion, Wada test, and asymmetry studies have provided invaluable information regarding the neural architecture of positive emotion, we believe that further explication of this architecture will benefit greatly from the application of additional approaches.

Neurodegenerative diseases, which selectively disrupt distributed neural networks (Seeley, Crawford, Zhou, Miller, & Greicius, 2009), offer a powerful lesion-based approach for determining how lateralized brain systems promote positive emotion. Frontotemporal dementia (FTD) is a neurodegenerative disease that targets neural systems that are integral for emotion generation and regulation. In FTD, gradual degeneration of the frontal, anterior temporal, and insular cortex, and subcortical structures (i.e., striatum, amygdala, and hypothalamus) is accompanied by parallel declines in social behavior, emotion, speech, and language (Boxer & Miller, 2005). Many patients with FTD have bilateral atrophy, affecting the left and right hemispheres similarly, while others have asymmetric atrophy. Predominantly right-sided atrophy is associated with socioemotional impairment (e.g., loss of empathy and disinhibition); predominantly left-sided atrophy is associated with progressive deterioration of speech and language. Given that patients vary in the degree to which they have atrophy in left and right emotion-relevant networks and in the extent to which they exhibit change in positive emotion, FTD is a particularly useful population in which to test theories of positive emotion lateralization.

Positive emotional alterations in FTD have received relatively little attention to date. Although many patients with FTD lose interest in people and activities that were previously enjoyable and rewarding, behaviors that suggest a decline in positive emotion, other patients exhibit euphoria, impulsivity,

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