

## Neural bases of dysphoria in early Huntington's disease

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### Abstract

Psychiatric disorders, including disorders of emotion control, are common in Huntington's disease. The neurobiological mechanism of the increased rate of disorders of emotion control are not known. Emotion perception deficits have been reported in Huntington's disease, but studies of emotional experience have been limited. In the present study we aim to expand the research in emotion in Huntington's disease by examining the neural bases of induced dysphoria at an early stage of Huntington's disease. Ten Huntington's disease patients and 12 demographically matched healthy volunteers underwent [<sup>15</sup>O] water positron emission tomography while in a transient state of dysphoria induced by viewing negatively charged affect-laden stimuli. Both groups experienced dysphoric mood, but Huntington's disease patients responded to the stimuli with greater arousal, anger and fear than healthy controls. Induced dysphoric mood was associated with a widespread reduction of activity within the frontal and parietal lobes, thalamus, and cerebellum. These differences could not be explained based on the smaller gray matter volumes of the corresponding regions, although in Huntington's disease patients smaller caudate nucleus volumes predicted lower dorsal-lateral prefrontal activity. Areas of increased activity included the striate and extrastriate cortex, the left thalamus, the transverse temporal gyrus, and the posterior hippocampus. This study elucidates possible mechanisms contributing to psychiatric disturbances of emotion often found in patients with Huntington's disease.

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### 1. Introduction

Huntington's disease is an autosomal dominant, neurodegenerative disorder that results from an unstable expansion of the trinucleotide repeat cytosine–adenine–guanine (CAG) of the gene IT-15 that codes for the

protein huntingtin. Huntington's disease is relentless, leading to increasing functional disability and death over a period of 10–30 years (Paulsen et al., 2004). Clinical features of Huntington's disease usually arise in adulthood with the emergence of abnormal involuntary movements, psychiatric disturbance and cognitive impairment. Because functional decline often begins before overt clinical features, there has been a great emphasis on identifying preclinical manifestations of the disorder to allow for the possibility of early therapeutic interventions.

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Psychiatric morbidity in Huntington's disease is multifaceted and severe, with uniformly high prevalence estimates of over 90% (Folstein et al., 1983; Paulsen et al., 2001). Psychiatric aspects of Huntington's disease constitute a major burden to patients and families, and are associated with more rapid functional deterioration (Marder et al., 2000), greater disability (Hamilton et al., 2003; Nehl and Paulsen, 2004), and earlier nursing home placement (Mayeux et al., 1986). Emotional disorders, psychosis, and personality changes with behavioral and emotional dyscontrol are most common.

Clinicians who care for patients with Huntington's disease often observe exaggerated responses to emotional stimuli. Family members often describe temper outbursts in situations where annoyance might have been expected. Similarly, persons with Huntington's disease describe feelings of sadness becoming severe depression and the experience of "nervousness" converting to incapacitating anxiety (Paulsen et al., 2001). Depression is a significant component of the overall psychiatric morbidity in Huntington's disease (Guttman et al., 2003), and is reported to be responsible for the premature end of life by suicide at a rate six times that in the general population (Schoenfeld et al., 1984; Almqvist et al., 1999; Paulsen et al., 2005). Emotional dyscontrol may manifest as personality changes and include the DSM-IV subtypes labile and disinhibited (Leroi et al., 2002).

Contributions to the development of psychopathology in Huntington's disease are multifactorial and likely include psychosocial factors (i.e., adjustment to a fatal genetic illness and increased disability), but the neuropathology of Huntington's disease suggests a preeminent role for biological mechanisms. Biological mechanisms may include changes in the brain regions subserving emotion processing. Deficits of recognition of facial disgust (Sprengelmeyer et al., 1996; Gray et al., 1997; Halligan, 1998; Milders et al., 2003; Wang et al., 2003; Hennenlotter et al., 2004) are consistent with the general notion of emotional disturbance of Huntington's disease patients. However, the neurobiological mechanism of the increased rate for the disorders of emotion control are not yet known.

Death of the GABAergic medium spiny neurons in the caudate nucleus is often observed in Huntington's disease, with additional involvement of the putamen, globus pallidus, and cerebral cortex (Vonsattel et al., 1985). Anatomical neuroimaging studies have shown volume loss up to 57% in the caudate, 64% in the putamen, and 21–25% in the amygdala in persons with mild Huntington's disease (Rosas et al., 2001). Mechanistically, abnormal emotional responses in Huntington's disease would be expected based on the dysfunction of the basal

ganglia–thalamocortical circuitry (Alexander et al., 1990). Within this circuit, the ventral striatum (including the medial and ventral portions of the caudate nucleus and putamen, the nucleus accumbens and the striatal cells of the olfactory tubercle) receives projections from "limbic" structures, including the hippocampus, amygdala, entorhinal cortex and perirhinal cortex (Haber, 2003). Within this "limbic loop", several prefrontal regions including the anterior cingulate and the medial orbitofrontal cortex exert regulatory functions through excitatory glutamatergic projections to the ventral striatum (Nakano et al., 2000). Then the ventral striatum sends inhibitory, GABA-mediated projections on to the ventral pallidum. The ventral pallidum continues the inhibitory output to the medial dorsal nucleus of the thalamus. The final connection in the loop is excitatory feedback from the thalamus, returning back to the anterior cingulate and medial orbitofrontal cortex.

The motor (Alexander et al., 1990), cognitive (Aron et al., 2003), and emotional symptoms (Leroi et al., 2002) of Huntington's disease have been attributed to distant effects of basal ganglia damage to the thalamus and frontal lobes (Joel, 2001). Depending on the stage of the disease, frontal lobe dysfunction would directly or indirectly [via "release" of phylogenetic older structures—see Jackson's "theory of levels" (Jackson, 1876)] give way to "productive" or "positive" symptoms of Huntington's disease including chorea and ballism, hallucinations or mania, and emotional incontinence. The role of frontal lobe dysfunction in personality changes with labile mood and in depressive disorders is well established (Damasio et al., 2000; Rolls, 2004). In a parsimonious view, dysfunction of the frontal lobes would be the converging basis of the biological mechanisms for mood, personality and emotional psychopathology in Huntington's disease.

Whereas the frontal lobes are grossly affected later in the illness (Selemon et al., 2004), frontal lobe dysfunction is often observed in the early stages of the disease, even before motor symptom onset (Butters et al., 1978; Josiassen et al., 1982; Jason et al., 1988; Rothlind et al., 1993). Because functional and metabolic abnormalities are not consistently found in the early stages of the illness (Kuhl et al., 1982; Tanahashi et al., 1985; Young et al., 1986; Weinberger et al., 1988; Sax et al., 1996), subjects with Huntington's disease may need to be examined under specific mental conditions that elicit the frontal deficit.

Mood induction represents a valid method to probe neural structures subserving emotion in several neuropsychiatric disorders including depression, anxiety and schizophrenia (George et al., 1995; Morris et al., 1996; Lane et al., 1997; Paradiso et al., 2003a; Rauch et al.,

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