Published in final edited form as:

Psychiatry Res. 2008 January 15; 162(1): 73–87. doi:10.1016/j.psychres.2007.04.001.

Neural bases of dysphoria in early Huntington's disease

Sergio Paradiso^{*,a,d}, Beth M. Turner^{a,d}, Jane S. Paulsen^{a,b,d}, Ricardo Jorge^a, Laura L. Boles Ponto^c, and Robert G. Robinson^{a,d}

^aDepartment of Psychiatry, University of Iowa, Iowa City, IA

^bDepartment of Neurology, University of Iowa, Iowa City, IA

^cDepartment of Radiology, University of Iowa, Iowa City, IA

^dDepartment of Neurosciences, University of Iowa, Iowa City, IA

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 great emphasis in identifying these preclinical manifestations of the disorder in order to allow for the possibility of early therapeutic interventions.

Psychiatric morbidity in Huntington's disease is multifaceted and severe with uniformly high prevalence estimates of over ninety percent (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 response 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). Emotion dyscontrol may manifest as personality changes and include the DSM-IV subtypes labile and disinhibited (Leroi et al., 2002).

*Address correspondence and reprint requests to: Sergio Paradiso, MD, PhD, The University of Iowa Roy J. and Lucille A. Carver College of Medicine, Psychiatry Research T215 GH, Iowa City, IA 52242, Phone: (319) 384-9248, Fax: (319) 353-8656, sergio-paradiso@uiowa.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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(s) 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 are 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., 2003). With the exception of research on perception of disgust in facial expressions (Sprengelmeyer et al., 1996; Gray et al., 1997; Halligan, 1998; Milders et al., 2003; Wang et

al., 2003; Hennenlotter et al., 2004), studies on emotion processing in Huntington's disease have been limited. Because dysphoria has been found to be the most often endorsed psychiatric symptom in Huntington's disease (Paulsen et al., 2001), in the present study we aimed at expanding the research on the neural underpinnings of emotion processing in Huntington's disease by examining the functional neuroanatomy associated with an induced state of dysphoric mood in the early stages of the disease. We adopted a definition of dysphoria largely based on Andreasen and Black (Andreasen and Black, 2001). Dysphoria was defined as an altered state of emotion characterized by sadness, fear/anxiety, and/or tense irritability or anger.

Patients with established diagnosis of Huntington's disease (rather than pre-symptomatic gene carriers) were chosen for this study. Based on clinical observations and scientific reports (Paulsen et al., 2001), it was felt that this group of patients in the early stages of the disease would show the significant clinical phenomenon of exaggerated negative emotional response, including dysphoric mood (Paulsen et al., 2001). This study compared the brain activity elicited during a state of experimentally induced dysphoria recorded using [^{15}O]water and positron emission tomography (PET) in patients in the early stages of Huntington's disease and in healthy comparison subjects controlling for the brain activity generated during a neutral mood state. Based on the role of the prefrontal cortex in emotion control (Rolls, 2004) and on prefrontal dysfunction in early Huntington's disease (Butters et al., 1978; Josiassen et al., 1982; Jason et al., 1988; Rothlind et al., 1993), we expected, at a minimum, that patients would show lower functional activity in frontal lobe structures compared to controls. Because of the expected group differences in brain structure (especially in the caudate nucleus and the frontal lobe) we carried out focused analyses aimed at determining the extent to which structural neuroanatomical changes would explain differences in emotional response and functional neuroanatomy.

2. Methods

2.1 Participants

Twelve persons with Huntington's disease were recruited from the Huntington's disease registry at the University of Iowa. The registry consists of persons diagnosed with Huntington's disease through clinical evaluation and confirmed via genetic testing as well as persons at risk for Huntington's disease (by virtue of family history) who have or have not undergone genetic testing. Participants with a polymerase chain reaction (PCR) confirmed CAG expansion in the IT-15 gene coding for huntingtin were selected from the registry for a minimal amount of chorea to facilitate functional and structural imaging. Under a psychiatrist's supervision (RJ), participants were tapered off all psychotropic medications or medications that could alter cerebral perfusion over a two week period. One participant was unable to complete the medication taper and was withdrawn from the study. Due to movement artifacts, functional and structural imaging data from another participant could not be utilized.

Twelve healthy volunteers matched to the ten remaining Huntington's disease participants for sex and equated for age and education were used as comparison participants. Healthy volunteers were recruited from the community by newspaper advertising and screened to rule out psychiatric, neurologic, or serious medical illnesses. The University of Iowa Institutional Review Board approved the project. After complete description of the study, written informed consent was obtained from the participants. The healthy subjects used as control comparisons to the Huntington's disease patients were part of a larger group of healthy older individuals who participated in our mood induction studies (Paradiso et al., 2003b; Robinson et al., 2007).

Study participants underwent a comprehensive neuropsychological assessment to characterize general intelligence, memory, attention, visuospatial skills, and executive function. Huntington's disease participants also completed the Mattis Dementia Rating Scale (Mattis and Psychological Assessment Resources Inc., 1988). Anxiety and depression were measured using the Hamilton Depression (Hamilton, 1967) and Anxiety scales (Hamilton, 1969). Huntington's Disease participants also completed the Unified Huntington's Disease Rating Scale (Huntington's Study Group, 1996) to characterize disease progression. This scale is comprised of ratings of chorea, independent functioning, and total functional capacity. The total amount of chorea in the face, trunk, and upper and lower extremities was summed; possible scores range from 0, absent, to 28, maximum. Independent functioning was assessed on a scale of 0 to 100 with 0 requiring complete assistance and 100 requiring no assistance. Total functional capacity was calculated based on the sum of occupation, finances, domestic chores, activities of daily living and care level scores; possible scores range from 0, severe impairment, to 13, normal functional capacity. Based on the Total Functional Capacity score, the Shoulson-Fahn stage of illness (possible ranges of 0–5) was calculated (Shoulson and Fahn, 1979).

2.2 Activation Stimuli

The stimuli and study paradigm have previously been described by Paradiso and colleagues (Paradiso et al., 2003b). Briefly, “themed” sets of stimuli each containing 18 images were chosen from the International Affective Picture System (Lang et al., 1995) to visually induce a state of dysphoria and an affectively neutral state. These image sets were part of an emotion induction protocol aiming at inducing differing mood states. In one PET session of about 4 hours duration subjects were shown 8 image sets in pseudorandom order (six emotion and two neutral conditions). In this report we focus on brain activity elicited during a state of dysphoric mood using the neutral conditions as baseline. A state of dysphoric mood was induced by the presentation of pictorial stimuli including images of individuals and situations of extreme filth, squalor, desperation, malnourishment, disease and death. The emotionally neutral stimuli included objects, people, scenery, animals, or landscapes previously found to elicit a minimal emotional reaction (Lang et al., 1995). Emotional states were assessed following each set of images using Likert scales ranging from 0 (absence of feeling) to 10 (very intense feeling) using the following descriptors: general arousal intensity, happiness, amusement, surprise, sadness, fear, disgust, and anger. This broad spectrum of emotions was assessed to ensure participants' emotional responses were not inconsistent with the intended emotion (e.g., responding with happiness to upsetting stimuli). Pictures were displayed for six seconds each, with the total “theme” lasting 108 seconds. The order of picture set presentation was randomized. Sequences were viewed on a 12-inch color video monitor in full view 18 inches from the participants' eyes while they were lying in the PET camera. All participants had normal or corrected to normal vision. The room was darkened; eye movements were not restricted.

2.3 MRI Data Acquisition and Processing

Magnetic resonance (MR) imaging scans were obtained for each participant with a standard T1-weighted three-dimensional SPGR sequence on a 1.5-T GE scanner (echo time = 5 ms; repetition time = 24 ms; flip angle = 40 degrees; number of excitations = 2; field of view = 26 × 26 cm; matrix = 256 × 192; slice thickness = 1.5 mm). Two dimensional proton density (PD) and T2 sequences were also acquired (echo time = 36 ms for PD and 96 ms for T2; repetition time = 3000 ms, number of excitations = 1; field of view = 26 × 26 cm; matrix = 256 × 192; slice thickness = 3.0 mm for PD and 4.0 mm for T2). MR images were analyzed with locally developed software (BRAINS) (Andreasen et al., 1992). All brains were realigned parallel to the anterior commissure/posterior commissure (AC-PC) line and the interhemispheric fissure to ensure comparability of head position across participants.

Alignment also placed the images in standard Talairach space. Images from multiple participants were co-registered and resliced in three orthogonal planes to produce a three-dimensional data set that was used for visualization and localization of functional activity. Similar to previous methodology utilized in our laboratory, automated neural networks were used to identify brain structures including the left and right thalamus and caudate nuclei, frontal and parietal gray matter, and cerebellum (Andreasen et al., 1996; Corson et al., 1999; Spinks et al., 2002). After identification of the above structures by the automated neural network, visual inspection determined anatomic accuracy before volumes were measured.

2.4 PET Image Data Acquisition and Processing

PET images were obtained with a GE 4096 Plus whole-body tomography capable of producing 15 slices with an interslice separation of 6.5 mm. Images were acquired in 20 five-second frames. Imaging began at the time of injection ($t=0$) and continued for 100 seconds. Injections consisted of 50 mCi of [^{15}O] water. The time from injection to radiolabeled water bolus arrival in the brain was measured in each participant prior to the test protocol. Based upon this time, pictures from a specific theme were shown starting 15 seconds prior to bolus arrival. The PET data from frames reflecting forty seconds immediately after bolus transit were summed and these data reconstructed into a single image with 2-mm voxels in a 128×128 matrix using filtered backprojection and a Butterworth filter (order = 6, cutoff frequency = 0.35 Nyquist interval). Injections were repeated at approximately 15-minute intervals with the activation stimuli themes randomized across injections. Subjective emotional ratings were collected within 60 to 90 seconds following the end of each PET scan while participants remained lying in the scanner.

Images for each subject were normalized to values of one by dividing by the global count activity. Automated Image Registration (AIR) software was then utilized to co-register each individual's PET and MR images. AIR utilizes a two-stage process of an initial coarse fit based on surface matching of MRI and PET images and then a variance minimization program using surface fit data as input. Brain landmarks identified on MRI were used to place each co-registered image into standardized coordinate space. An 18-mm Hanning filter was applied to the PET images. In order to minimize motion artifacts, the filtered PET image was spatially transformed into the same standardized space as the MR image and was then clipped to a hand-edited outline of the brain drawn on each individual's MR scan. A threshold of 160 was chosen based on the normalized MR scan for each individual. This value was chosen to retain gray and white matter within the brain while eliminating motion artifacts outside of the brain and surrounding the ventricles.

2.5 Analysis

Emotional responses and neuropsychological performance—Within-group differences in responses to the emotionally evocative stimuli were evaluated with Wilcoxon Exact Ranked Sum Tests. Between-group differences in performance on neuropsychological tests and in response to emotionally evocative stimuli were evaluated using Mann-Whitney U tests. These tests were two-tailed; the P -value was set at 0.05.

Functional neuroanatomy—Group differences in regional brain activity were examined using a non-parametric statistical technique not affected by between-group differences in variance (Arndt et al., 1996a; Arndt et al., 1996b). In the within-group comparison (Worsley et al., 1992), the relative PET count activity for the neutral stimuli presentation was subtracted from activity during the dysphoria inducing stimuli on a subject by subject basis. The subtraction images were averaged across subjects and voxel-by-voxel t -tests of the relative count changes were performed. This work was based on the theory of Gaussian

fields developed by Worsley and colleagues (Worsley et al., 1992) which corrects for the large number of voxel-by-voxel t-tests performed, the lack of independence between voxels, and the resolution of the processed PET images. Significant regions of activation are calculated on the t-map images. A t-value of 3.61 was considered to be statistically significant ($P < 0.0005$, one-tailed, uncorrected) and a minimum size threshold was set at 50 contiguous voxels in order to omit isolated outlying values.

The randomization analysis was based on an initial subtraction of the dysphoria inducing and neutral conditions. That is, the normalized PET counts for the neutral stimuli were subtracted from the data for the dysphoria inducing stimuli for all individuals within the study. The randomization utilized a boot-strapping technique, repeatedly sampling two groups of 12 and 10 without regard for the diagnoses (Arndt et al., 1996a; Paradiso et al., 2003a). After each resampling, voxel-wise t-maps were generated. After 3000 randomizations the distributions of the voxel-wise t-values were stored to estimate the probabilities associated with the t. Regions of significant activation were identified on the t-map images and corrected for the large number of t-tests performed, the lack of independence between voxels, and the resolution of the processed images. There were about 300,000 gray matter voxels in our images representing approximately 242 resolution elements. The degrees of freedom were extremely large for the t-tests (2,178 for the within group analysis and 5,082 for the between group analysis = number of resolution elements * [number of subjects - 1]). Consistent with our previous studies, we used an uncorrected P -value of 0.0005 as the minimum significance threshold for defining a peak. Similar to the within-subjects analyses, only areas that exceeded 50 contiguous voxels were included in the results in order to omit isolated outlying values.

Structural neuroanatomy—Based on the expectation that patients with Huntington's disease would show reduced cortical gray matter and caudate volumes, correlation analyses were conducted to examine the extent to which these changes explained regional brain activity. The gray matter volumes of brain regions showing a significant difference in the between-group functional analyses were correlated with the corresponding functional activity (e.g., the gray matter volume of the frontal lobe with the normalized count values in the frontal lobe) identified by the Talairach coordinates containing the maximum t-value from the between-group comparisons (Zeki et al., 1991; Horwitz, 1994; Silbersweig et al., 1994). In addition, the gray matter volumes of brain regions showing a significant group effect in the between-group comparison were correlated with the emotional responses to the experimental stimuli in patients and controls. Based on its central role in Huntington's disease the volume of the caudate nuclei were correlated with all brain regions showing a significant difference in the between-group functional analyses and with the emotional responses to the experimental stimuli in patients and controls. Analyses were conducted using Spearman's rho using intracranial volume as a covariate. The P -level of these tests was set at a conservative significance of $P < 0.01$.

3. Results

3.1 Demographics and neurocognitive assessment

Demographic characteristics, anxiety and depression scores for participants who completed the study are shown in Table 1. Consistent with our clinical experience, patients with Huntington's disease showed greater anxiety and depression, but no subject met criteria for major depressive or generalized anxiety disorder. There was a statistically significant difference between the Huntington's disease and the control participants on the Hamilton Depression Scale. Two participants with Huntington's disease scored 17 or more on the Hamilton Depression Scale (range 1–28). There was a nonsignificant trend toward increased anxiety in the Huntington's disease group measured with the Hamilton Anxiety Scale (range

1–24) and no participant scored above 17 (Beck and Coppen, 1990). Independence scale, functional capacity, and stage and duration of illness data are summarized in Table 2. All participants included in the functional imaging analyses scored 120 or above on the Mattis Dementia Rating Scale. Severity of illness scores indicated that participants were in the very early stages of the disease.

Neuropsychological test results are shown in Table 3. Patients with Huntington's disease showed significantly lower general intelligence (FSIQ) scores, verbal (VIQ) and performance (PIQ) measures (Wechsler, 1981). One of the patients with Huntington's disease was in the borderline mentally retarded range (FSIQ=72) (American Psychiatric Association, 1994), while all others had intelligence scores of 82 or greater. There were no group differences in visuospatial constructional abilities as assessed by the Rey-Osterrieth Complex Figure Test – copy condition (Meyers and Meyers, 1995), Judgment of Line Orientation (Benton, 1994), Benton Visual Retention Test (Benton, 1994), or Benton Facial Recognition Test (Benton, 1994). No deficits in visual memory were found on the Rey-Osterrieth Complex Figure Test – immediate or delay conditions (Meyers and Meyers, 1995). Consistent with previous studies (Josiassen et al., 1982), Huntington's disease participants showed poorer attention as measured by WAIS-R Digit Span (age corrected scaled scores) (Wechsler, 1981). As shown in previous studies (Amos, 2000), Huntington's disease patients had a tendency as a group to make more perseverative errors on the Wisconsin Card Sort Test (Heaton et al., 1981), although this difference did not reach statistical significance.

3.2 Emotional responses

Within-group Wilcoxon Ranked Sum tests showed that healthy volunteers were in a state of dysphoria (greater arousal, sadness, anger, disgust and less happiness) after exposure to the stimuli. There were no changes in feelings of amusement, fear or surprise in healthy volunteers. Participants with Huntington's disease also showed a dysphoric reaction that included decreased happiness and amusement, and increased ratings of sadness, disgust, anger, and arousal. The results are presented in Table 4.

Mean participant emotional responses following stimuli presentation and effect sizes are shown in Table 5. Between-group analyses showed that Huntington's disease patients responded with greater fear (two-tailed Mann Whitney-U = 32.5, $P = 0.03$), anger (two-tailed Mann Whitney-U = 32.5, $P = 0.04$), and arousal (two-tailed Mann Whitney-U = 28.5, $P = 0.02$) compared to healthy volunteers. There were no significant group differences on reaction to neutral stimuli. Change scores between sad and neutral conditions were consistent with the results from individual stimuli comparisons: Huntington's disease patients' emotional response was significantly angrier than healthy controls (two-tailed Mann Whitney-U = 31.0, $P = 0.05$, effect size = 1.0), and fear response approached significance for fear (two-tailed Mann Whitney-U = 33.0, $P = 0.07$, effect size = 0.72). No other difference approached statistical significance.

3.3 Functional findings

In a within-group comparison, Huntington's disease patients experiencing an induced state of dysphoria showed decreased activity in the ventral frontal lobe and increased activity in primary and secondary visual cortices (see Table 6). Each individual's within-subject analyses were also viewed at this step and supported the within-group conclusions. In healthy volunteers, experience of dysphoria was associated with thalamic ($T_{\max} = 4.1$, volume = 0.1 cc; Talairach's $x = 15$, $y = -20$, $z = 9$) and secondary visual cortex ($T_{\max} = 4.9$, volume = 1.4 cc; Talairach's $x = 46$, $y = -66$, $z = 3$) activity, a pattern of brain activity consistent with our prior studies using larger samples of similar age (Paradiso et al., 2003b).

Between-group analysis confirmed relatively lower activity in dorsal and ventral sectors of the prefrontal lobe, and in addition evidenced relatively lower activity in the parietal lobe, right thalamus and cerebellum in Huntington's disease patients compared to healthy volunteers. Higher activity was appreciated in the left thalamus, transverse temporal gyrus, hippocampus, and primary and secondary visual cortices (see Table 7 and Figure 2).

3.4 Correlations between brain activity and structure

Because group differences in functional activity may have been related to gray matter differences between patients and the comparison group, areas identified as having significantly lower functional activity in Huntington's disease [i.e., right and left middle frontal gyri (Talairach's $x=40$, $y=27$, $z=30$ and Talairach's $x=-28$, $y=59$, $z=-7$), right superior frontal gyrus (Talairach's $x=21$, $y=39$, $z=9$), right inferior frontal gyrus (Talairach's $x=46$, $y=34$, $z=-13$), right parietal lobe (Talairach's $x=47$, $y=-43$, $z=38$ and Talairach's $x=49$, $y=-41$, $z=34$), thalamus (Talairach's $x=17$, $y=-14$, $z=10$) and the cerebellum (Talairach's $x=26$, $y=-38$, $z=-22$)] were correlated with the gray matter volume of the corresponding brain region (thalamus, cerebellum and frontal and parietal lobes).

Patients showed decreased volumes in the thalamus [Huntington's disease thalamus mean = 10.55 cc, SD = 1.81; controls mean = 12.42 cc, SD = 1.23, $F(2, 18) = 9.06$, $P < 0.002$], frontal lobe [Huntington's disease frontal lobes mean = 241.82 cc, SD = 17.06, controls mean = 245.45 cc, SD = 25.47, $F(2, 18) = 6.20$, $P < 0.009$] and cerebellum [Huntington's disease cerebellum mean = 125.04 cc, SD = 9.36; controls mean = 132.98 cc, SD = 22.47, $F(2, 18) = 5.74$, $P < 0.01$] compared to the healthy volunteers. No significant between-group differences were found in the volume of the parietal lobe [Huntington's disease parietal lobes mean = 134.20 cc, SD = 15.01, controls mean = 131.64 cc, SD = 18.10, $F(2, 18) = 5.64$, $P > 0.01$].

There were no significant correlations between frontal lobe volumes and frontal areas of lower activity in patients {right middle frontal gyrus [Spearman's $\rho(9) = -0.12$, $P = 0.75$], left middle frontal gyrus [Spearman's $\rho(9) = 0.12$, $P = 0.75$], right superior frontal gyrus [Spearman's $\rho(9) = 0.49$, $P = 0.13$], right inferior frontal gyrus [Spearman's $\rho(9) = 0.52$, $P = 0.12$]}. Similarly, volumes of the parietal lobe did not significantly correlate with parietal regions of lower activity in patients [both parietal regions, Spearman's $\rho(9) = -0.50$, $P = 0.12$]. Cerebellar volumes did not significantly correlate with the regions of interest in the cerebellum [Spearman's $\rho(9) = 0.45$, $P = 0.17$], and the volume of the thalamus did not significantly correlate with functional activity within the thalamus [Spearman's $\rho(9) = -0.34$, $P = 0.30$].

Because of the established importance of the caudate nuclei in the pathophysiology of Huntington's disease, group comparisons on the caudate size and correlations between its volume and decreased functional activity were computed. Consistent with the literature, the mean volume of the caudate nucleus was smaller and more variable in size across the patients' group compared to healthy controls [Huntington's disease caudate mean = 3.02 cc, SD = 1.44, controls mean = 5.30 cc, SD = 0.79, $F(2, 18) = 11.45$, $P < 0.001$]. The volume of the caudate was inversely correlated with two regions in the frontal lobe: the middle frontal gyrus [Talairach's $x=40$, $y=27$, $z=30$; Spearman's $\rho(9) = -0.76$, $P = 0.006$] and the superior frontal gyrus [Talairach's $x=46$, $y=34$, $z=-13$; Spearman's $\rho(9) = -0.72$, $P = 0.01$]. The caudate volume was not correlated with the parietal lobe locations [Talairach's $x=47$, $y=-43$, $z=38$, and $x=49$, $y=-41$, $z=34$; Spearman's $\rho(9) = -0.30$ and -0.31 , $P = 0.37$ and 0.35 , respectively], the thalamus [Spearman's $\rho(9) = 0.08$, $P = 0.81$] or cerebellum [Spearman's $\rho(9) = 0.45$, $P = 0.17$].

3.5 Correlations of emotional responses and brain structure

With this set of analyses, we examined the extent to which structural anatomy predicted emotional responses to the experimental stimuli. The areas of interest were those previously identified as having significantly lower activity in Huntington's disease (i.e., frontal and parietal lobes, thalamus and cerebellum) as well as the caudate nucleus which was included due to its central role in Huntington's disease. No correlations between gray matter volumes and emotional responses reached a significance level of $P < 0.01$.

3.6 Correlations of depression and brain activity

Because patients with Huntington's disease showed greater depressive symptoms than the comparison subjects, we carried out analyses to examine the extent to which group differences in brain activity were explained by depression severity. To this end, total scores from the Hamilton Depression Scale in patients were correlated with their regional brain activity. The functional areas of interest were identified as those showing significantly higher or lower activity in HD patients compared to controls for the randomization analyses (Table 7). No correlation between depressive scores and any brain location was found to be significant. These results suggest that severity of depressive symptoms did not explain the difference in brain activity between patients and comparison subjects.

4. Discussion

Dysphoria is a state of altered emotions characterized by fear, sadness, anger and mental discomfort. Dysphoric mood cuts across psychiatric diagnostic categories and is often observed in patients with Huntington's disease. In Huntington's disease, the behavioral counterpart of this altered mood state is often manifested by an elevated rate of temper outbursts in response to common daily events (Paulsen et al., 2001). The findings in this study offer the first neurobiological explanation of dysphoric mood in patients in the very early stages of Huntington's disease. This study revealed that, while both healthy volunteers and Huntington's disease patients responded with dysphoric mood, including less happiness, and increased arousal, sad, angry and disgusted feelings to our experimental stimuli, consistent with the emotional psychopathology observed in Huntington's disease, patients experienced more fear and anger and were overall more aroused in response to the stimuli than the comparison subjects. Patients with Huntington's disease showed lower activity in dorsal and ventral sectors of the prefrontal lobe, in the parietal lobe, right thalamus and the cerebellum relative to the healthy volunteers. In addition, patients showed higher activity in the left thalamus, transverse temporal gyrus, hippocampus, and primary and secondary visual cortices.

Before discussing these findings some caveats need to be discussed. First, consistent with the literature, patients showed lower general intelligence and attention scores compared to comparison subjects. All but one of the patients were in the low average or average intelligence range. The remaining patient fell in the "borderline" range (FSIQ = 72). Patients' performance on visual/spatial tasks was intact. This and the low cognitive demands of the experimental stimuli (essentially "observing the stimuli and taking them in") allow the parsimonious conclusion that perception of experimental stimuli did not account for group differences in emotional responses and brain activity.

Interpretation of the results of this study should be limited to patients in the early stages of Huntington's disease. This study was designed based on our group's interest in examining the neural underpinnings of exaggerated negative emotional responses in Huntington's disease, a clinical manifestation very common in the early stages of the disease (Paulsen et al. 2001). As expected, patients with Huntington's disease showed greater severity of

depressive symptoms with respect to comparison subjects. While the differing baseline mood may have played a role in the patients' emotional responses, our correlation analyses showed that depression did not explain the brain activity differences. An alternative approach could have been used to examine this issue, e.g., performing brain activity analysis using depression severity as a covariate. However, because depression severity tends to increase between Shoulson-Fahn stages 1 and 2 and then declines as the disease progresses, and because our study participants were in Shoulson-Fahn stages 1 and 2, performing analyses using depression severity as a covariate would remove disease stage-specific variance. Similarly, examination of non-depressed patients would be equivalent to not examining the typical population of Huntington's disease patients.

While patients showed significant structural differences, we were unable to explain either the relatively lower brain activity or the elevated emotional responses of Huntington's patients based on their smaller gray matter volumes. In addition, the lack of statistically significant correlations between regional gray matter volumes and the corresponding areas of relatively lower activation in Huntington's disease suggests that group differences in gray matter did not fully account for group differences in brain activity. Because some correlations approached statistical significance, these results require replication.

These findings have important implications on the use of functional neuroimaging in the examination of the early stages of Huntington's disease. For instance, while consistent with the literature (Aylward et al., 1994), patients had smaller caudate volumes, these (and all the other structural changes) did not predict the increased emotional reactivity in Huntington's disease as it may have been expected based on the association between mood disturbance and basal ganglia abnormality (Rabins et al., 1991; Krishnan et al., 1992; Starkstein and Mayberg, 1993; Koponen et al., 2002). It is possible that the caudate nucleus may have played an indirect role on the emotional reactivity of patients, as indicated by the significant relationship between caudate nucleus volume and frontal lobe activity. While it should be noted that examination of samples of patients with less homogeneous disease severity may yield different results, the present study highlights the utility of functional imaging methods to begin to uncover the mechanisms of altered emotionality in early Huntington's disease.

The analysis of the brain function data suggested that nodes known to be associated with sad and dysphoric mood in age comparable healthy volunteers showed reduction of activity in Huntington's disease subjects. Experiencing sad/dysphoric feelings has been associated with elevated activity of ventral medial prefrontal cortex both in young (Pardo et al., 1993; Phan et al., 2002) and in older healthy volunteers (Paradiso et al., 2003b). However, Huntington's disease patients responded with a pattern of decreased frontal activity more consistent with clinical depression (Martinot et al., 1990). The reduced activity in the frontal lobe parallels the decreased activity in the thalamus. Functional imaging studies have shown that the thalamus is one of the limbic regions associated with sad mood induced by visual stimuli and recall of a personal event (George et al., 1995; Hornak et al., 1996; Damasio et al., 2000) and has been posited to be a neural node subserving the experiential aspects of emotion (Reiman et al., 1997). Similar results were obtained studying emotional responses to negative visual stimuli in the elderly (Paradiso et al., 1997; Paradiso et al., 2003b). Another subcortical region found to have increased activity in response to sad stimuli in healthy volunteers (George et al., 1993; Paradiso et al., 1997; Paradiso et al., 1999), but showing relative reduction in Huntington's disease is the cerebellum. This finding is consistent with the growing body of evidence linking damage to the cerebellum to disturbed emotion (Schmahmann and Sherman, 1998; Marvel et al., 2004; Turner et al., 2007).

In addition to feelings of sadness, patients with Huntington's disease experienced significantly greater fear, anger and overall arousal. While greater emotionality in

Huntington's patients was expected based on the frontal hypoactivity elicited by our stimuli (Hariri et al., 2000), and on the evidence indicating that ventral and orbital lesions of the primate frontal cortex lead to alteration in the control of anger and aggressive behavior (Butter and Snyder, 1972; Kamback, 1973; Raleigh et al., 1979; Blair and Cipolotti, 2000; Blair, 2001; Brower and Price, 2001), patients' increased arousal may have additional explanations. The significant greater arousal in Huntington's disease patients may have functional counterparts in the increased activity of cortical and subcortical regions including striate and extra-striate visual cortex, and the thalamus. Traditionally the thalamus has been associated with the organization of wakeful behaviors attained linking arousal systems in the brainstem with cerebral cortex and basal ganglia (Steriade, 1997; Schiff and Plum, 2000; Llinas et al., 2002; Van der Werf et al., 2002). More recently, functional neuroimaging has demonstrated that the visual cortex increases its activity in response to arousing emotional stimuli irrespective of valence (Puce et al., 1995; Lane et al., 1997; Lang et al., 1998). To examine this hypothesis, we correlated the brain activity in the patients' thalamus and visual cortex with the change from baseline rating of arousal. We found that greater arousal scores correlated with greater activity in the thalamus [Talairach's $x=-7$, $y=-19$, $z=12$; Spearman's $\rho(9) = 0.78$, $P = 0.005$], primary visual cortex [Talairach's $x=12$, $y=-64$, $z=13$; Spearman's $\rho(9) = 0.74$, $P = 0.01$] and the secondary visual cortex [Talairach's $x=39$, $y=-68$, $z=22$; Spearman's $\rho(9) = 0.78$, $P = 0.005$]; thus supporting the role of thalamus and visual cortical structures in the greater arousal reported by Huntington's patients in response to our emotional stimuli.

The generalized affective response shown by Huntington's disease patients in our report is consistent with the model proposed by Litvan and colleagues (Litvan et al., 1998) suggesting that movement and psychiatric abnormalities may co-occur in disorders of the corticostriatal circuits. For instance, differential involvement of the direct and indirect striatal output pathways may account for concurrent abnormalities of hyperkinetic movements and hyperactive behaviors [e.g., greater agitation and irritability in Tourettes and Huntington's disease (Kulisevsky et al., 2001)] versus hypokinetic movement disorders and behaviors [e.g., greater apathy in progressive supranuclear palsy (Litvan et al., 1998)]. Feelings of dysphoria (general arousal, sadness, fear and anger) may occur with decreased brain activation in frontal nodes that are no longer capable of modulating the limbic striatal-pallidal-thalamic circuits. The relative reduction of ventral frontal, thalamic and cerebellar activity, and the reduced volumes of the basal ganglia (albeit apparently not directly affecting emotional responses) are consistent with a functional fronto-subcortical disconnection.

In summary, patients with early Huntington's disease did not show blunted emotional response to dysphoria evoking stimuli. Rather, consistent with the clinical presentation of the disease, they showed moderate increases in anger, fear and arousal compared to healthy volunteers. Reduced activity in frontal, parietal, thalamic, and cerebellar regions represents the functional bases for this phenomenon. No direct evidence of an association between caudate nucleus pathology and increased emotionality was found in this study, but smaller caudate volumes predicted lower frontal dorsal activity. Examination of individuals with the genetic mutation for Huntington's disease, but without basal ganglia changes, is necessary to determine the extent to which frontal lobe dysfunction is a primary component in the enhanced emotional reactivity in Huntington's disease independent from caudate degeneration.

The findings in this study suggest that a pattern of functional frontal-subcortical disconnection may be detected in Huntington's disease using positron emission tomography imaging and affective probes early in the illness (Gomez-Tortosa et al., 1996; Aylward et al., 1998; Selemon et al., 2004). The notion that frontal lobe white matter changes may

precede the gray matter reduction is consistent with this hypothesis (Aylward et al., 1998; Beglinger et al., 2005). Functional imaging (fMRI and PET) conducted in participants who have the gene mutation for Huntington's disease, but do not manifest symptoms may offer clues about early brain dysfunction in disease prior to detection of volume loss on morphologic magnetic resonance imaging. More research is clearly indicated to better understand early dysfunction of neuronal circuits associated with neurodegenerative diseases. Such functional imaging data may provide markers of pre-diagnostic disease that can serve as outcomes in experimental therapeutics.

Acknowledgments

Drs. Paradiso and Paulsen contributed equally to the conceptualization of this project. This study was supported by funds from the National Institutes of Health (NS40068, MH01579), the Roy J. Carver Charitable Trust and the Howard Hughes Medical Institute awarded to JS Paulsen, and from NIH MH00163 and MH52879 awarded to RG Robinson. Dr. Paradiso was supported by the Edward J. Mallinckrodt, Jr. Foundation and by an Institutional Mentored Career Development Award (K-12). Beth Turner was funded in part by an Innovative Imaging Technologies grant from the National Institutes of Health. The authors thank Michelle Benjamin, Elizabeth Penziner, Ania Mikos, Rebecca Reese, Alberto Abreu, Teresa Kopel, Todd Kosier, Gene Zeien, and Peggy Nopoulos for their assistance with this research.

REFERENCES

- Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Progress in Brain Research*. 1990; 85:119–146. [PubMed: 2094891]
- Almqvist EW, Bloch M, Brinkman R, Craufurd D, Hayden MR. A worldwide assessment of the frequency of suicide, suicide attempts, or psychiatric hospitalization after predictive testing for Huntington disease. *American Journal of Human Genetics*. 1999; 64:1293–1304. [PubMed: 10205260]
- American Psychiatric Association. *Diagnostic and statistical manual of mental disorders : DSM-IV*. 4th ed.. Washington, DC: 1994. Task Force on DSM-IV.
- Amos A. A computational model of information processing in the frontal cortex and basal ganglia. *Journal of Cognitive Neuroscience*. 2000; 12:505–519. [PubMed: 10931775]
- Andreasen, NC.; Black, DW. *Introductory textbook of psychiatry*. 3rd ed.. Washington, DC: American Psychiatric; 2001.
- Andreasen NC, Cohen G, Harris G, Cizadlo T, Parkkinen J, Rezai K, Swayze VW 2nd. Image processing for the study of brain structure and function: problems and programs. *Journal of Neuropsychiatry and Clinical Neurosciences*. 1992; 4:125–133. [PubMed: 1627972]
- Andreasen NC, Rajarethinam R, Cizadlo T, Arndt S, Swayze VW 2nd, Flashman LA, O'Leary DS, Ehrhardt JC, Yuh WT. Automatic atlas-based volume estimation of human brain regions from MR images. *Journal of Computer Assisted Tomography*. 1996; 20:98–106. [PubMed: 8576490]
- Arndt S, Cizadlo T, Andreasen NC, Heckel D, Gold S, O'Leary DS. Tests for comparing images based on randomization and permutation methods. *Journal of Cerebral Blood Flow and Metabolism*. 1996a; 16:1271–1279. [PubMed: 8898701]
- Arndt S, Cizadlo T, O'Leary D, Gold S, Andreasen NC. Normalizing counts and cerebral blood flow intensity in functional imaging studies of the human brain. *Neuroimage*. 1996b; 3:175–184. [PubMed: 9345488]
- Aron AR, Watkins L, Sahakian BJ, Monsell S, Barker RA, Robbins TW. Task-set switching deficits in early-stage Huntington's disease: implications for basal ganglia function. *Journal of Cognitive Neuroscience*. 2003; 15:629–642. [PubMed: 12965037]
- Aylward EH, Anderson NB, Bylsma FW, Wagster MV, Barta PE, Sherr M, Feeney J, Davis A, Rosenblatt A, Pearson GD, Ross CA. Frontal lobe volume in patients with Huntington's disease. *Neurology*. 1998; 50:252–258. [PubMed: 9443488]

- Aylward EH, Brandt J, Codori AM, Mangus RS, Barta PE, Harris GJ. Reduced basal ganglia volume associated with the gene for Huntington's disease in asymptomatic at-risk persons. *Neurology*. 1994; 44:823–828. [PubMed: 8190282]
- Beck, P.; Copen, A. *The Hamilton Scales*. New York: Springer-Verlag; 1990.
- Beglinger LJ, Nopoulos PC, Jorge RE, Langbehn DR, Mikos AE, Moser DJ, Duff K, Robinson RG, Paulsen JS. White matter volume and cognitive dysfunction in early Huntington's disease. *Cognitive and Behavioral Neurology*. 2005; 18:102–107. [PubMed: 15970729]
- Benton, AL. *Contributions to neuropsychological assessment : a clinical manual*. 2nd ed.. New York: Oxford University Press; 1994.
- Blair RJ. Neurocognitive models of aggression, the antisocial personality disorders, and psychopathy. *Journal of neurology, neurosurgery, and psychiatry*. 2001; 71:727–731.
- Blair RJ, Cipolotti L. Impaired social response reversal. A case of 'acquired sociopathy'. 2000; 123(Pt 6):1122–1141.
- Brower MC, Price BH. Neuropsychiatry of frontal lobe dysfunction in violent and criminal behaviour: a critical review. *Journal of neurology, neurosurgery, and psychiatry*. 2001; 71:720–726.
- Butter CM, Snyder DR. Alterations in aversive and aggressive behaviors following orbital frontal lesions in rhesus monkeys. *Acta Neurobiol Exp (Wars)*. 1972; 32:525–565. [PubMed: 4627622]
- Butters N, Sax D, Montgomery K, Tarlow S. Comparison of the neuropsychological deficits associated with early and advanced Huntington's disease. *Archives of Neurology*. 1978; 35:585–589. [PubMed: 150836]
- Corson PW, Nopoulos P, Andreasen NC, Heckel D, Arndt S. Caudate size in first-episode neuroleptic-naïve schizophrenic patients measured using an artificial neural network. *Biological Psychiatry*. 1999; 46:712–720. [PubMed: 10472424]
- Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J, Hichwa RD. Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neuroscience*. 2000; 3:1049–1056.
- Folstein S, Abbott MH, Chase GA, Jensen BA, Folstein MF. The association of affective disorder with Huntington's disease in a case series and in families. *Psychological Medicine*. 1983; 13:537–542. [PubMed: 6226055]
- George MS, Ketter TA, Gill DS, Haxby JV, Ungerleider LG, Herscovitch P, Post RM. Brain regions involved in recognizing facial emotion or identity: an oxygen-15 PET study. *Journal of Neuropsychiatry and Clinical Neurosciences*. 1993; 5:384–394. [PubMed: 8286936]
- George MS, Ketter TA, Parekh PI, Horwitz B, Herscovitch P, Post RM. Brain activity during transient sadness and happiness in healthy women. *American Journal of Psychiatry*. 1995; 152:341–351. [PubMed: 7864258]
- Gomez-Tortosa E, Arias Navalon JA, del Barrio Alba A, Barroso Fernandez T, Pardo Pardo C, Sanchez Martin JA, Garcia Yebenes J. Relation between frontal lobe blood flow and cognitive performance in Huntington's disease. *Neurologia*. 1996; 11:251–256. [PubMed: 8974425]
- Gray JM, Young AW, Barker WA, Curtis A, Gibson D. Impaired recognition of disgust in Huntington's disease gene carriers. *Brain*. 1997; 120(Pt 11):2029–2038. [PubMed: 9397019]
- Guttman, M.; Alpay, M.; Chouinard, S.; Como, P.; Feinstein, A.; Leroi, I. Clinical management of aggression and frontal symptoms in Huntington's disease. In: Bedard, MA.; Agrid, Y.; Chouinard, S.; Fahn, S.; Korczyn, AD.; Lesperance, P., editors. *Mental and Behavioral Dysfunction in Movement Disorders*. Totawa, New Jersey: Humana Press; 2003. p. 409–426.
- Haber SN. The primate basal ganglia: parallel and integrative networks. *J Chem Neuroanat*. 2003; 26:317–330. [PubMed: 14729134]
- Halligan PW. Inability to recognise disgust in Huntington's disease. *Lancet*. 1998; 351:464. [PubMed: 9482434]
- Hamilton JM, Salmon DP, Corey-Bloom J, Gamst A, Paulsen JS, Jerkins S, Jacobson MW, Peavy G. Behavioural abnormalities contribute to functional decline in Huntington's disease. *Journal of Neurology Neurosurgery and Psychiatry*. 2003; 74:120–122.
- Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967; 6:278–296. [PubMed: 6080235]
- Hamilton M. Diagnosis and rating of anxiety. *Br J Psychiatry Special Pub*. 1969; 3:76–79.

- Hariri AR, Bookheimer SY, Mazziotta JC. Modulating emotional responses: effects of a neocortical network on the limbic system. *Neuroreport*. 2000; 11:43–48. [PubMed: 10683827]
- Heaton, RK.; Chelune, GJ.; Talley, JL.; Kay, GG.; Curtiss, G. Wisconsin Card Sorting Test Manual: Revised and Expanded. Odessa, FL: Psychological Assessment Resources, Inc.; 1981.
- Hennenlotter A, Schroeder U, Erhard P, Haslinger B, Stahl R, Weindl A, von Einsiedel HG, Lange KW, Ceballos-Baumann AO. Neural correlates associated with impaired disgust processing in pre-symptomatic Huntington's disease. *Brain*. 2004; 127:1446–1453. [PubMed: 15090475]
- Hornak J, Rolls ET, Wade D. Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. *Neuropsychologia*. 1996; 34:247–261. [PubMed: 8657356]
- Horwitz B. Data analysis paradigms for metabolic-flow data: combining neural modeling and functional neuroimaging. *Human Brain Mapping*. 1994; 2:112–122.
- Huntington's Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group. *Movement Disorders*. 1996; 11:136–142. [PubMed: 8684382]
- Jackson, H. West Riding Asylum Reports. 1876.
- Jason GW, Pajurkova EM, Suchowersky O, Hewitt J, Hilbert C, Reed J, Hayden MR. Pre-symptomatic neuropsychological impairment in Huntington's disease. *Archives of Neurology*. 1988; 45:769–773. [PubMed: 2968784]
- Joel D. Open interconnected model of basal ganglia-thalamocortical circuitry and its relevance to the clinical syndrome of Huntington's disease. *Movement Disorders*. 2001; 16:407–423. [PubMed: 11391734]
- Josiassen RC, Curry L, Roemer RA, DeBease C, Mancall EL. Patterns of intellectual deficit in Huntington's disease. *Journal of Clinical Neuropsychology*. 1982; 4:173–183. [PubMed: 6213679]
- Kamback MC. The effects of orbital and dorsolateral frontal cortical ablations on ethanol self-selection and emotional behaviors in monkeys (*Macaca nemestrina*). *Neuropsychologia*. 1973; 11:331–335. [PubMed: 4209334]
- Koponen S, Taiminen T, Portin R, Himanen L, Isoniemi H, Heinonen H, Hinkka S, Tenovuo O. Axis I and II psychiatric disorders after traumatic brain injury: a 30-year follow-up study. *American Journal of Psychiatry*. 2002; 159:1315–1321. [PubMed: 12153823]
- Krishnan KR, McDonald WM, Escalona PR, Doraiswamy PM, Na C, Husain MM, Figiel GS, Boyko OB, Ellinwood EH, Nemeroff CB. Magnetic resonance imaging of the caudate nuclei in depression. Preliminary observations. *Archives of General Psychiatry*. 1992; 49:553–557. [PubMed: 1627046]
- Kuhl DE, Phelps ME, Markham CH, Metter EJ, Riege WH, Winter J. Cerebral metabolism and atrophy in Huntington's disease determined by 18FDG and computed tomographic scan. *Annals of Neurology*. 1982; 12:425–434. [PubMed: 6217782]
- Kulisevsky J, Litvan I, Berthier ML, Pascual-Sedano B, Paulsen JS, Cummings JL. Neuropsychiatric assessment of Gilles de la Tourette patients: comparative study with other hyperkinetic and hypokinetic movement disorders. *Movement Disorders*. 2001; 16:1098–1104. [PubMed: 11748741]
- Lane RD, Reiman EM, Bradley MM, Lang PJ, Ahern GL, Davidson RJ, Schwartz GE. Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia*. 1997; 35:1437–1444. [PubMed: 9352521]
- Lang, PJ.; Bradley, MA.; Cuthbert, BN. International affective picture system (IAPS): Technical manual on affective rating. Gainesville: University of Florida; 1995.
- Lang PJ, Bradley MM, Fitzsimmons JR, Cuthbert BN, Scott JD, Moulder B, Nangia V. Emotional arousal and activation of the visual cortex: an fMRI analysis. *Psychophysiology*. 1998; 35:199–210. [PubMed: 9529946]
- Leroi I, O'Hearn E, Marsh L, Lyketsos CG, Rosenblatt A, Ross CA, Brandt J, Margolis RL. Psychopathology in patients with degenerative cerebellar diseases: a comparison to Huntington's disease. *American Journal of Psychiatry*. 2002; 159:1306–1314. [PubMed: 12153822]
- Litvan I, Paulsen JS, Mega MS, Cummings JL. Neuropsychiatric assessment of patients with hyperkinetic and hypokinetic movement disorders. *Archives of Neurology*. 1998; 55:1313–1319. [PubMed: 9779658]

- Llinas RR, Leznik E, Urbano FJ. Temporal binding via cortical coincidence detection of specific and nonspecific thalamocortical inputs: a voltage-dependent dye-imaging study in mouse brain slices. *Proceedings of the National Academy of Sciences of the United States of America*. 2002; 99:449–454. [PubMed: 11773628]
- Marder K, Zhao H, Myers RH, Cudkowicz M, Kayson E, Kieburz K, Orme C, Paulsen J, Penney JB Jr, Siemers E, Shoulson I. Rate of functional decline in Huntington's disease. *Huntington Study Group. Neurology*. 2000; 54:452–458. [PubMed: 10668713]
- Martinot JL, Hardy P, Feline A, Huret JD, Mazoyer B, Attar-Levy D, Pappata S, Syrota A. Left prefrontal glucose hypometabolism in the depressed state: a confirmation. *American Journal of Psychiatry*. 1990; 147:1313–1317. [PubMed: 2399999]
- Marvel, CL.; Paradiso, S.; Andreasen, NC.; Ponto, LL.; Hichwa, RD.; Robinson, RG. Cerebral blood flow differences during visually-induced fear in patients with cerebellar lesions. Paper presented at the 10th International Conference on Human Brain Mapping; Budapest, Hungary. 2004 Jun 13–17.
- Mattis, S. Psychological Assessment Resources Inc.. DRS, Dementia rating scale. Odessa, FL: Psychological Assessment Resources Inc.; 1988.
- Mayeux R, Stern Y, Williams JB, Cote L, Frantz A, Dyrenfurth I. Clinical and biochemical features of depression in Parkinson's disease. *American Journal of Psychiatry*. 1986; 143:756–759. [PubMed: 2424323]
- Meyers JE, Meyers KR. Rey Complex Figure Test under four different administration procedures. *Clinical Neuropsychologist*. 1995; 9:63–67.
- Milders M, Crawford JR, Lamb A, Simpson SA. Differential deficits in expression recognition in gene-carriers and patients with Huntington's disease. *Neuropsychologia*. 2003; 41:1484–1492. [PubMed: 12849766]
- Morris JS, Frith CD, Perrett DI, Rowland D, Young AW, Calder AJ, Dolan RJ. A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature*. 1996; 383:812–815. [PubMed: 8893004]
- Nakano K, Kayahara T, Tsutsumi T, Ushiro H. Neural circuits and functional organization of the striatum. *J Neurol*. 2000; 247(Suppl 5):V1–V15. [PubMed: 11081799]
- Nehl C, Paulsen JS. Cognitive and psychiatric aspects of Huntington disease contribute to functional capacity. *Journal of Nervous and Mental Disorders*. 2004; 192:72–74.
- Paradiso S, Andreasen NC, Crespo-Facorro B, O'Leary DS, Watkins GL, Boles Ponto LL, Hichwa RD. Emotions in unmedicated patients with schizophrenia during evaluation with positron emission tomography. *American Journal of Psychiatry*. 2003a; 160:1775–1783. [PubMed: 14514490]
- Paradiso S, Johnson DL, Andreasen NC, O'Leary DS, Watkins GL, Ponto LL, Hichwa RD. Cerebral blood flow changes associated with attribution of emotional valence to pleasant, unpleasant, and neutral visual stimuli in a PET study of normal subjects. *American Journal of Psychiatry*. 1999; 156:1618–1629. [PubMed: 10518175]
- Paradiso S, Robinson RG, Andreasen NC, Downhill JE, Davidson RJ, Kirchner PT, Watkins GL, Ponto LL, Hichwa RD. Emotional activation of limbic circuitry in elderly normal subjects in a PET study. *American Journal of Psychiatry*. 1997; 154:384–389. [PubMed: 9054787]
- Paradiso S, Robinson RG, Boles Ponto LL, Watkins GL, Hichwa RD. Regional cerebral blood flow changes during visually induced subjective sadness in healthy elderly persons. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2003b; 15:35–44. [PubMed: 12556569]
- Pardo JV, Pardo PJ, Raichle ME. Neural correlates of self-induced dysphoria. *American Journal of Psychiatry*. 1993; 150:713–719. [PubMed: 8480815]
- Paulsen, J.; Nehl, C.; Guttman, M. Basal ganglia and movement disorders. In: Rizzo, M.; Eslinger, PJ., editors. *Principles and Practice of Behavioral Neurology and Neuropsychology*. Philadelphia, PA: W.B. Saunders; 2004. p. 525-550.
- Paulsen JS, Hoth KF, Nehl C, Stierman L. Critical periods of suicide risk in Huntington's disease. *American Journal of Psychiatry*. 2005; 162:725–731. [PubMed: 15800145]
- Paulsen JS, Ready RE, Hamilton JM, Mega MS, Cummings JL. Neuropsychiatric aspects of Huntington's disease. *Journal of Neurology Neurosurgery and Psychiatry*. 2001; 71:310–314.

- Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage*. 2002; 16:331–348. [PubMed: 12030820]
- Puce A, Allison T, Gore JC, McCarthy G. Face-sensitive regions in human extrastriate cortex studied by functional MRI. *Journal of Neurophysiology*. 1995; 74:1192–1199. [PubMed: 7500143]
- Rabins PV, Pearlson GD, Aylward E, Kumar AJ, Dowell K. Cortical magnetic resonance imaging changes in elderly inpatients with major depression. *American Journal of Psychiatry*. 1991; 148:617–620. [PubMed: 2018163]
- Raleigh MJ, Steklis HD, Ervin FR, Kling AS, McGuire MT. The effects of orbitofrontal lesions on the aggressive behavior of vervet monkeys (*Cercopithecus aethiops sabaeus*). *Experimental neurology*. 1979; 66:158–168. [PubMed: 113236]
- Rauch SL, Shin LM, Wright CI. Neuroimaging studies of amygdala function in anxiety disorders. *Annals of the New York Academy of Sciences*. 2003; 985:389–410. [PubMed: 12724173]
- Reiman EM, Lane RD, Ahern GL, Schwartz GE, Davidson RJ, Friston KJ, Yun LS, Chen K. Neuroanatomical correlates of externally and internally generated human emotion. *American Journal of Psychiatry*. 1997; 154:918–925. [PubMed: 9210741]
- Robinson RG, Paradiso S, Mizrahi R, Fiedorowicz JG, Kouzoukas DE, Moser DJ. Neuropsychological correlates of normal variation in emotional response to visual stimuli. *The Journal of nervous and mental disease*. 2007; 195:112–118. [PubMed: 17299297]
- Rolls ET. The functions of the orbitofrontal cortex. *Brain & Cognition*. 2004; 55:11–29. [PubMed: 15134840]
- Rosas HD, Goodman J, Chen YI, Jenkins BG, Kennedy DN, Makris N, Patti M, Seidman LJ, Beal MF, Koroshetz WJ. Striatal volume loss in HD as measured by MRI and the influence of CAG repeat. *Neurology*. 2001; 57:1025–1028. [PubMed: 11571328]
- Rothlind JC, Bylsma FW, Peyser C, Folstein SE, Brandt J. Cognitive and motor correlates of everyday functioning in early Huntington's disease. *Journal of Nervous and Mental Disorders*. 1993; 181:194–199.
- Sax DS, Powsner R, Kim A, Tilak S, Bhatia R, Cupples LA, Myers RH. Evidence of cortical metabolic dysfunction in early Huntington's disease by single-photon-emission computed tomography. *Movement Disorders*. 1996; 11:671–677. [PubMed: 8914093]
- Schiff ND, Plum F. The role of arousal and "gating" systems in the neurology of impaired consciousness. 2000; 17:438–452.
- Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. *Brain*. 1998; 121(Pt 4): 561–579. [PubMed: 9577385]
- Schoenfeld M, Myers RH, Cupples LA, Berkman B, Sax DS, Clark E. Increased rate of suicide among patients with Huntington's disease. *Journal of Neurology Neurosurgery and Psychiatry*. 1984; 47:1283–1287.
- Selemon LD, Rajkowska G, Goldman-Rakic PS. Evidence for progression in frontal cortical pathology in late-stage Huntington's disease. *Journal of Comparative Neurology*. 2004; 468:190–204. [PubMed: 14648679]
- Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. *Neurology*. 1979; 29:1–3. [PubMed: 154626]
- Silbersweig DA, Stern E, Schnorr L, Frith CD, Ashburner J, Cahill C, Frackowiak RS, Jones T. Imaging transient, randomly occurring neuropsychological events in single subjects with positron emission tomography: an event-related count rate correlational analysis. *Journal of Cerebral Blood Flow and Metabolism*. 1994; 14:771–782. [PubMed: 8063873]
- Spinks R, Magnotta VA, Andreasen NC, Albright KC, Ziebell S, Nopoulos P, Cassell M. Manual and automated measurement of the whole thalamus and mediodorsal nucleus using magnetic resonance imaging. *Neuroimage*. 2002; 17:631–642. [PubMed: 12377139]
- Sprengelmeyer R, Young AW, Calder AJ, Karnat A, Lange H, Homberg V, Perrett DI, Rowland D. Loss of disgust. Perception of faces and emotions in Huntington's disease. *Brain*. 1996; 119(Pt 5): 1647–1665. [PubMed: 8931587]

- Starkstein, SE.; Mayberg, HS. Depression in Parkinson disease. In: Starkstein, SE.; Robinson, RG., editors. Depression in Neurologic disease. Baltimore: The Johns Hopkins University Press; 1993. p. 97-116.
- Steriade, M. Thalamus. In: Steriade, M.; Jones, EG.; McCormick, DA., editors. Thalamus. Amsterdam: Elsevier; 1997. p. 721-742.
- Tanahashi N, Meyer JS, Ishikawa Y, Kandula P, Mortel KF, Rogers RL, Gandhi S, Walker M. Cerebral blood flow and cognitive testing correlate in Huntington's disease. Archives of Neurology. 1985; 42:1169–1175. [PubMed: 2933014]
- Turner BM, Paradiso S, Marvel CL, Pierson R, Boles Ponto LL, Hichwa RD, Robinson RG. The cerebellum and emotional experience. Neuropsychologia. 2007; 45:1331–1341. [PubMed: 17123557]
- Van der Werf YD, Witter MP, Groenewegen HJ. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. Brain Res. 2002; 39:107–140.
- Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP Jr. Neuropathological classification of Huntington's disease. Journal of Neuropathology and Experimental Neurology. 1985; 44:559–577. [PubMed: 2932539]
- Wang K, Hoosain R, Yang RM, Meng Y, Wang CQ. Impairment of recognition of disgust in Chinese with Huntington's or Wilson's disease. Neuropsychologia. 2003; 41:527–537. [PubMed: 12559147]
- Wechsler, D. Wechsler Adult Intelligence Scale - Revised. New York: Psychological Corp.; 1981.
- Weinberger DR, Berman KF, Iadarola M, Driesen N, Zec RF. Prefrontal cortical blood flow and cognitive function in Huntington's disease. Journal of Neurology Neurosurgery and Psychiatry. 1988; 51:94–104.
- Worsley KJ, Evans AC, Marrett S, Neelin P. A three-dimensional statistical analysis for CBF activation studies in human brain. Journal of Cerebral Blood Flow and Metabolism. 1992; 12:900–918. [PubMed: 1400644]
- Young AB, Penney JB, Starosta-Rubinstein S, Markel DS, Berent S, Giordani B, Ehrenkaufer R, Jewett D, Hichwa R. PET scan investigations of Huntington's disease: cerebral metabolic correlates of neurological features and functional decline. Annals of Neurology. 1986; 20:296–303. [PubMed: 2945510]
- Zeki S, Watson JD, Lueck CJ, Friston KJ, Kennard C, Frackowiak RS. A direct demonstration of functional specialization in human visual cortex. Journal of Neuroscience. 1991; 11:641–649. [PubMed: 2002358]

Figure 1.

Statistical maps of brain regions showing differences in functional activity based on within-group comparison of sadness versus neutral images in Huntington's disease. Two types of statistical maps of the positron emission tomographic data are shown: peak maps on the left and t-maps on the right. Regions that are significantly activated in the induced sadness condition are superimposed on a composite magnetic resonance image scan derived by averaging the MRI scans from the participants. The peak map shows areas where all contiguous voxels exceed the predefined threshold for statistical significance ($P < 0.0005$). The t-map shows the t-value for all voxels in the image and provides a general overview of the landscape of differences in functional activity between the two conditions. Only areas of relative change in activity with a $t > 3.61$ or $t < -3.61$ are shown. Green crosshairs are used to show the location of the slice. A large area of decreased functional activity is seen between the crosshairs in all 3 planes. Inspection of multiple planes in the

MRI scans indicates that the center of this area is in the frontal cortex. Within the images R indicates right, L, left, A, anterior, and P, posterior.

Figure 2.

Statistical maps of brain regions with differences in functional activity based on between-group randomization analysis comparing the sad minus neutral conditions in Huntington's disease participants and healthy volunteers

The randomization analysis is a nonparametric statistical test that indicates the significance of the differences between Huntington's disease participants and healthy volunteers. It is based on an initial within-group subtraction of the response to the sad scenes minus the neutral scenes, followed by a between-group difference in response to the two conditions. Two types of statistical maps of the positron emission tomographic data are shown: peak maps on the left and t-maps on the right. Regions that are significantly activated in the induced sadness condition are superimposed on a composite magnetic resonance image scan derived by averaging the MRI scans from the participants. The peak map shows the small areas where all contiguous voxels exceed the predefined threshold for statistical significance

($P < 0.0005$). The t-maps show the t-value for all voxels in the image and provide a general overview of the landscape of differences in functional activity between the two groups. Green crosshairs are used to show the location of the slice. An area of increased functional activity is seen between the crosshairs in all 3 planes. Inspection of multiple planes in the MRI scans indicates that the center of this area is in the frontal cortex. Within the images R indicates right, L, left, A, anterior, and P, posterior.

Table 1

Demographic Information of Participant Groups

	HNV (n=12)	HD (n=10)	U	P
Age	60.3 (7.9)	54.1 (8.3)	36.0	0.11
Education	15.0 (3.5)	12.2 (2.6)	31.5	0.06
Gender	50% male	50% male		
HAM-D	3.3 (3.0)	11.1 (8.1)	21.5	0.01
HAM-A	5.8 (3.2)	9.4 (5.1)	32.5	0.07

Legend: HNV=Healthy Normal Volunteers; HD=Huntington's disease participants. U = two-tailed Mann-Whitney U. HAM-D = Hamilton Depression Scale; HAM-A = Hamilton Anxiety Scale.

Table 2

Illness specific characteristics of Huntington's disease participants

Duration of illness (years)	3.2 (2.0)
Mattis Dementia Rating Total Score (possible range 0–144)	133.9 (7.2)
Chorea (possible range 0–28)	2.4 (2.6)
Independence Scale (possible range 0–100)	89.5 (9.0)
Total Functional Capacity (possible range 0–13)	10.2 (2.6)
Shoulson-Fahn Stage (possible range 0–5)	1.5 (0.5)

Table 3**Neuropsychological Functioning**

	HNV (n=12)	HD (n=10)	U	P
Intelligence:				
VIQ	111.7 (12.5)	89.1 (14.6)	13.0	0.01
PIQ	118.3 (18.7)	99.7 (15.9)	24.0	0.02
FIQ	116.7 (17.2)	93.1 (15.5)	18.0	0.01
Visuospatial functions:				
RCFT-Copy	28.4 (5.8)	27.5 (4.7)	48.0	0.43
Line Orientation	22.7 (3.8)	22.1 (7.7)	53.0	0.64
BVRT	29.2 (2.2)	27.0 (4.4)	41.0	0.35
BFRT	22.5 (2.0)	20.8 (2.9)	37.5	0.13
Visual Memory:				
RCFT-Immediate	15.3 (4.8)	14.5 (7.8)	46.5	0.37
RCFT-Delay	14.1 (4.0)	13.6 (5.9)	50.5	0.53
Attention:				
Digit Span	10.8 (1.9)	7.2 (2.6)	15.0	0.01
Executive functions:				
WCST – PE	7.3 (4.5)	14.4 (11.2)	34.5	0.09

Legend: HNV=Healthy Normal Volunteers; HD=Huntington's disease participants; U = Mann-Whitney U. VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; FIQ = Full Scale Intelligence Quotient; RCFT = Rey-Osterrieth Complex Figure Test; BVRT = Benton Visual Retention Test; BFR = Benton Facial Recognition Test; WCST – PE = Wisconsin Card Sort Test Perseverative Errors.

Table 4

Affective responses produced after viewing dysphoria inducing stimuli

	HNV (n=12)		HD (n=10)	
	Z	exact <i>P</i>	Z	exact <i>P</i>
Happy	-2.8	0.01	-2.9	0.01
Amused	-1.4	0.19	-2.2	0.03
Sad	-3.1	0.00	-2.8	0.01
Fear	-1.6	0.15	-1.9	0.06
Disgust	-3.0	0.01	-2.5	0.01
Angry	-2.5	0.01	-2.7	0.01
Surprise	-0.7	0.46	-1.5	0.16
Arousal	-2.4	0.02	-2.3	0.02

Legend: Change in affective state induced by dysphoria inducing stimuli from a neutral stimuli baseline in HNV and HD. HNV= Healthy Normal Volunteers; HD = Huntington's disease participants. Z = Wilcoxon Exact Ranked Sum Test.

Table 5
Affective responses produced after viewing dysphoria inducing and neutral stimuli

	Dysphoria inducing					Neutral				
	HNV (SD) (n=12)	HD (SD) (n=10)	U	P	ES	HNV (SD) (n=12)	HD (SD) (n=10)	U	P	ES
Happy	0.2 (0.4)	1.6 (3.1)	56	0.39	0.67	4.7 (3.1)	6.5 (2.0)	40.0	0.11	0.68
Amused	1.0 (2.9)	0.0 (0.0)	49.5	0.08	-0.46	2.0 (1.9)	3.3 (3.3)	51.5	0.36	0.50
Sad	7.5 (2.4)	7.5 (3.4)	56.5	0.55	0	1.5 (2.6)	1.5 (2.0)	62.5	0.81	0
Fear	1.6 (2.5)	5.3 (4.3)	32.5	0.03	1.08	0.8 (1.5)	1.5 (3.0)	63.5	0.86	0.30
Disgust	4.8 (2.7)	5.8 (3.2)	53.0	0.42	0.34	1.1 (2.4)	0.5 (1.8)	56.0	0.35	-0.28
Angry	3.0 (2.9)	6.0 (3.5)	32.5	0.04	0.94	0.3 (0.9)	0.2 (0.6)	61.0	0.60	-0.13
Surprise	2.2 (3.6)	4.4 (3.8)	40.5	0.10	0.60	1.3 (2.3)	2.5 (3.4)	51.0	0.27	0.42
Arousal	6.1 (2.7)	8.5 (1.8)	28.5	0.02	1.03	3.5 (2.2)	5.1 (2.8)	40.0	0.11	0.64

Legend: HNV=Healthy Normal Volunteers; HD=Huntington's disease participants. U = two-tailed Mann Whitney U; ES = effect size.

Brain regions showing relative changes in activity in Huntington's disease participants during exposure to dysphoria inducing compared with neutral stimuli: Within- subject analysis

Table 6

Location	T _{max}	Vol (cc)	Voxels	x	y	z
Left frontal lobe (BA 11)	-5.2	0.7	315	-30	59	-7
Primary visual cortex (BA 17)	4.0	0.1	52	8	-65	12
Secondary visual cortex (BA 18/19/37)						
Right occipital lobe	5.4	2.9	1383	47	-69	0
Left occipital lobe	4.6	0.9	425	-48	-71	0
Left fusiform gyrus	4.0	0.2	115	-42	-45	-13

Legend: Brain regions and Brodmann areas (in parentheses) with relative differences in regional cerebral blood flow after the subtraction are shown. T_{max} is the highest t-value identified in the peak. Volumes of the peaks in cc that exceed the t=3.61 (df = 2,178) threshold are shown. This threshold corresponds to an uncorrected significance level of $P < 0.0005$ per voxel. In order to omit isolated outlying values only areas that exceeded 50 contiguous voxels were included in the table. Talairach coordinates x, y, z are described in the text.

Brain regions showing relative changes in activity in Huntington's disease participants versus healthy volunteers in response to dysphoria inducing versus neutral stimuli

Table 7

Brain region (Brodmann Area - BA)	P*	Vol (cc)	Voxels**	x***	y***	z***	HD****	NHV****
<i>Relatively Lower Activity in HD patients</i>								
Prefrontal cortex (BA 8/9/10/47)								
Middle frontal gyrus (8/9)	<0.001	0.5	237	40	27	30	-0.060	0.036
Middle frontal gyrus (10)	<0.001	4.0	1860	-28	59	-7	-0.108	0.045
Superior frontal gyrus (10)	0.002	0.2	87	21	39	9	-0.048	0.033
Inferior frontal gyrus (47)	<0.001	0.3	143	46	34	-13	-0.055	0.051
Inferior parietal cortex (BA 7)	0.002	0.3	132	47	-43	38	-0.058	0.025
Inferior parietal cortex (BA 39/40)	0.002	0.1	54	49	-41	34	-0.050	0.031
Right Thalamus	0.002	0.2	109	17	-14	10	-0.023	0.059
Cerebellum	0.003	0.1	54	26	-38	-22	-0.060	0.019
<i>Relatively Higher Activity in HD patients</i>								
Left Thalamus	0.001	0.2	103	-7	-19	12	0.054	-0.035
Transverse temporal gyrus (BA 41)	0.001	0.2	88	49	-6	10	0.042	-0.048
Posterior hippocampus	<0.001	1.6	727	29	-48	2	0.063	-0.033
	0.002	0.1	54	-31	-53	2	0.049	-0.032
Primary visual cortex (BA 17)	<0.001	1.0	485	12	-64	13	0.072	-0.044
Secondary visual cortex (BA 18/19)								
	<0.001	0.7	342	8	-93	13	0.020	-0.075
	<0.001	0.5	216	47	-61	-7	0.099	0.000
	0.001	0.3	132	-19	-83	28	0.039	-0.049
	0.003	0.1	42	39	-68	22	0.049	-0.030

* Randomization (Significance of Peak) P-value

** Size of significant peak, Number of voxels

*** Talairach coordinates

**** Differences in normalized PET counts for dysphoria inducing and neutral conditions

Legend: The randomization analysis is a nonparametric statistical test that indicates the significance of the differences between Huntington's disease participants and healthy volunteers. It is based on an initial within-group subtraction of the response to the dysphoria inducing minus the neutral images, followed by a between-group difference in response to the two conditions. The P-values indicate the

magnitude of the significance level for each peak, indicating between-group differences in response. Brain regions and Brodmann areas (in parentheses) are shown. Volumes of the peaks in cc that exceed the $t(=3.61)$ ($df = 5,082$) threshold are shown. This threshold corresponds to an uncorrected significance level of $P < 0.0005$ per voxel. In order to omit isolated outlying values only areas that exceeded 50 contiguous voxels were included in the table. Talairach coordinates x, y, z are described in the text.