

Altered functional MRI responses in Huntington's disease

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This study examined the effects of Huntington's disease (HD) on neural activity during performance of the Porteus maze task. fMRI data were acquired from three HD patients and three controls. Reduced fMRI signal was observed in the patients relative to the controls in occipital, parietal and somato-motor cortex and in the

caudate, while increased signal was found in HD in the left postcentral and right middle frontal gyri. The altered fMRI responses in HD patients may result from neural, metabolic, neurovascular coupling and/or hemodynamic differences associated with this disorder. *NeuroReport* 13:703–706 © 2002 Lippincott Williams & Wilkins.

Key words: Brain mapping; Cerebral blood flow; Cognition; fMRI; Huntington's disease; Magnetic resonance imaging; Neuroimaging; Striatum; Visual cortex

INTRODUCTION

Huntington's disease (HD) is a fatal genetic disorder that causes neural degeneration via a poorly defined mechanism. Past work in presymptomatic or early-stage HD patients has consistently reported the presence of hypoperfusion and/or decreased glucose utilization during rest in striatal regions [1–11]. These changes correlate with cognitive test scores [1,2,10], suggesting that alterations in blood flow are related to the cognitive changes in HD. Using functional transcranial Doppler ultrasonography (fTCD), we previously reported decreased blood flow in the anterior cerebral artery, relative to a resting baseline, when HD patients performed the Porteus maze test [12,13]. In subsequent SPECT studies using the same Porteus maze test, we also found reduced rCBF in the caudate and orbitofrontal cortex of HD patients [2].

In the present study, we again examined the effect of the Porteus maze test on CBF in HD patients using fMRI. fMRI has a higher spatial and temporal resolution and provides more anatomical detail of brain activity than either Doppler or SPECT, thus providing a more detailed analysis of neural and hemodynamic differences between HD patients and controls. As described below, we found that patients with early-stage HD had reduced CBF relative to controls in the striatum and a variety of cortical regions, but increased flow in the right prefrontal cortex and cerebellum.

SUBJECTS AND METHODS

The UCHC IRB approved this study. All subjects signed informed consent forms. Three healthy control subjects and

three early-stage HD patients were tested. HD patients had a mean (\pm s.e.) of 39.0 ± 2.0 years, with 12.0 ± 0 years of education; controls were 43.7 ± 5.5 years old with an average of 14.7 ± 1.3 years of education. CAG repeats ranged between 42 and 47 for the three patients. All of the HD patients were rated as having no clearly defined motor symptoms associated with HD on the Unified Huntington's Disease Rating Scale [14]. Five additional HD patients were tested and were unable to perform this task without head movements.

Three stimulus conditions were used. In the maze task, mazes were taken directly from the Porteus maze set. The trace task served as a visual-motor control with a dotted line showing the route that exited the maze which subjects simply traced. Subjects solved the maze and trace tasks using a trackball. The fixation task served as a visual control which used maze-like stimuli altered to be unsolvable, with a fixation point which subjects foveated while the fixation stimuli were on the screen. Three maze and three trace stimuli were presented sequentially in random order interleaved with fixation stimuli for 11 min/run. Maze and trace stimuli were presented for 90s each with 20s for fixation. All subjects performed each test for the identical length of time. If subjects completed the maze or trace conditions before the end of the trial, the cursor was placed at the beginning of the maze and the test was repeated.

A Siemens Vision 1.5 T MRI system was used, with single-shot gradient echo, echo-planar imaging (EPI) with blood oxygen level dependent (BOLD) sensitivity, (TE = 40 ms, 4s/volume, 25.6 mm field of view, 36 oblique/axial slices, 4 mm³ resolution) imaging the whole neocortex and dorsal

cerebellum. High-resolution T1-weighted images were acquired to obtain anatomical information.

Movement correction and normalization were performed using SPM99 and were verified by visual inspection. Data were then spatially smoothed to 1 cm^3 FWHM resolution and multiple regression was performed upon individual voxels. Time series following the stimulus time course were modeled separately for the (1) maze and trace *vs* fixation for all subjects, (2) maze *vs* trace for all subjects, (3) difference between controls and patients in maze and trace *vs* fixation, and (4) difference between controls and patients in maze *vs* trace conditions. These four orthogonal models of neural metabolic response were then used to model the expected BOLD response by convolution with a Gaussian model of the hemodynamic response function (delay = 4.8 s, s.d. = 1.8 s) [15]. The resulting F and df for the effects of interest were adjusted for temporal overlap, and converted to Z statistic. A test of spatial contiguity [16] was then performed separately on regions with positive and negative direction of signal change (voxel-wise $|Z| > 12$ for maze and trace *vs* control, $|Z| > 5.0$ for the other three, all with region-wise $p < 0.001$) with identified regions of interest (ROIs). Average time series were then obtained for ROIs and compared across conditions and patient groups.

RESULTS

All subjects: The largest regions of significantly increased BOLD signal (average 0.70%, average $Z = 14.4$) during the

maze and trace tasks relative to fixation were found in areas involved in visual processing (cuneus, precuneus, lingual, fusiform, middle occipital and middle temporal gyri), spatial processing (bilateral inferior and superior parietal lobules), motor control (pre- and postcentral gyri, both with three times greater volume in the hemisphere contralateral to the responding hand, and cerebellum), and executive function (middle and medial frontal gyri) as shown in Fig. 1a. The maze task produced an average of 0.47% greater activation than the trace task (average $Z = 9.75$) in most of the same areas, including precuneus, cuneus, middle temporal, fusiform, lingual, and superior occipital gyri, superior parietal lobule and supramarginal gyrus, as well as portions of the cerebellum and thalamus. The trace task produced an average of 0.52% greater activation than the maze task (average $Z = 6.14$) in nearby visual regions (bilateral cuneus, middle occipital, inferior occipital, lingual and middle temporal gyri) and subcortical motor regions (caudate and lentiform nucleus).

Patients *vs* controls: Significantly reduced BOLD signal (averaging -0.78% , average $Z = -6.5$) was observed in the HD patients relative to controls for the maze and trace *vs* fixation in a wide range of areas, including those directly affected by HD (corpus striatum, especially the caudate), as well as visual processing areas (precuneus, cuneus, lingual gyrus, inferior and middle occipital gyri middle and superior temporal gyri) spatial processing areas (superior

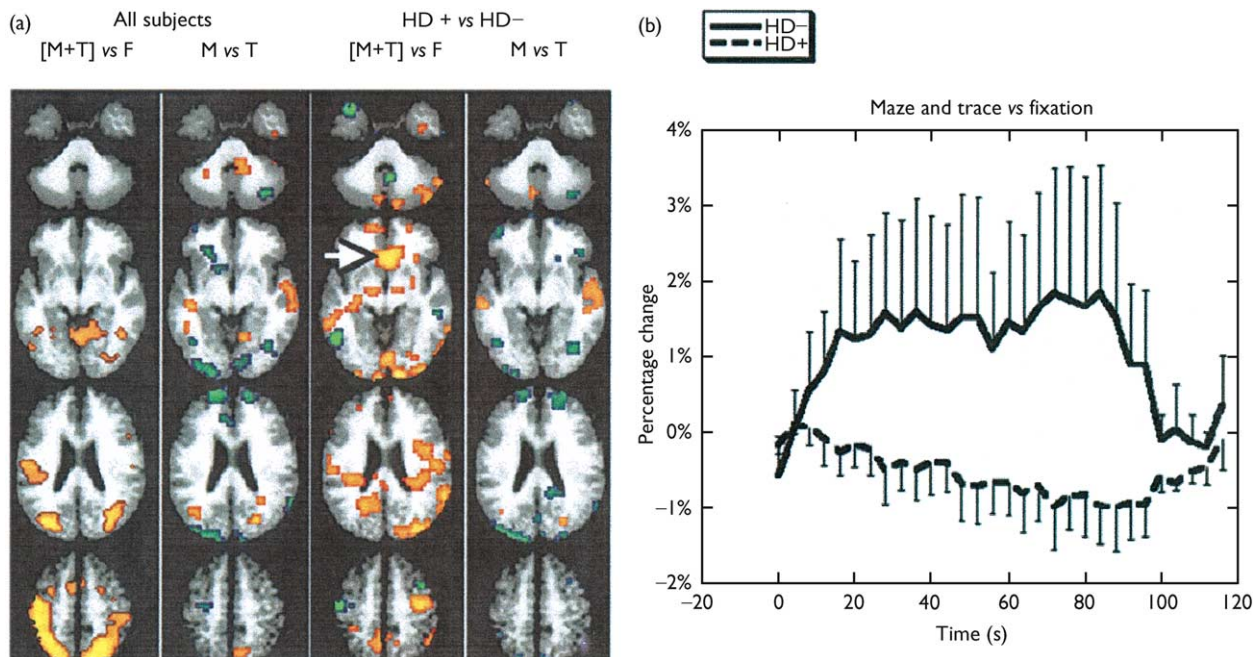


Fig. 1. (a) Spatially normalized Z-score statistical maps plotted onto a structural image averaged across all subjects. Red and yellow show positive values, blue and green show negative values. The right of the subject is displayed on the right of the figure. Axial slices are located at -32 mm , -8 mm , $+20\text{ mm}$, and $+48\text{ mm}$ relative to the plane passing through the anterior commissure. In order from left to right, columns 1 and 2 show the results of contrasts between maze and trace minus fixation ($[M+T]$ vs F) and maze minus trace (M vs T) for all subjects, and columns 3 and 4 show the results of contrasts between maze and trace minus fixation ($[M+T]$ vs F) and maze minus trace (M vs T) for controls minus HD patients. (b) Shows time series averaged over maze and trace stimulus blocks *vs* fixation, and further averaged across controls (solid line) and HD patients (dashed line) for the region of significant difference between groups including the caudate, indicated by arrow at -8 mm slice in column 3 of (a). The maze and trace tasks occurred from 0 to 90 s, fixation occurred from 90 to 110 s. s.e. are shown as vertical bars. Note the negative trend response for HD patients, while controls showed a large positive response during the same time period.

and inferior parietal lobules, supramarginal gyrus, medial temporal lobe), motor areas (pre- and postcentral gyri and cerebellum) and executive and affective processing areas (anterior and middle cingulate gyri, subcallosal gyrus, insula and inferior, superior, medial, and middle frontal gyri). A few regions were also found with significantly increased BOLD signal (averaging 0.64%, average $Z = 8.0$) in HD patients relative to controls in the right cerebellum (tonsil and culmen), left middle occipital, postcentral and middle temporal gyri, and right middle frontal gyrus. Significantly reduced BOLD signal (averaging -0.34% , average $Z = -5.34$) was observed in HD patients *vs* controls for the comparison of MAZE and TRACE conditions in the bilateral middle temporal gyri, left cerebellum and right fusiform and superior temporal gyri. HD subjects showed a more positive response (averaging 0.61%, average $Z = 5.98$) than controls bilaterally in the superior, medial and middle frontal gyri, right superior and middle temporal gyri, right middle occipital gyrus and posterior cingulate gyrus.

Time series were computed for ROIs from regions with significant differences between HD patients and controls and averaged within these groups (Fig. 1b). The examination of time series obtained from the region including the caudate nucleus revealed a negative trend for HD subjects, while controls showed a large positive response.

DISCUSSION

The current experiment replicates previous neuroimaging studies reporting a reduction in metabolism and rCBF in the caudate nucleus/cortex of HD patients at rest [1–5,7–13,17–20] and during Porteus maze testing [2,12,13]. All subjects responded during maze and trace tasks in a variety of areas supporting visual, motor, spatial and executive functions. However, the current findings demonstrate that the magnitude of BOLD activation is altered in many of these same regions in HD, and includes both increased and decreased magnitude of the BOLD response relative to unaffected volunteers, depending on the brain regions examined. The present results also replicate our previous finding of a negative trend response in HD patients during maze and trace tasks relative to fixation in the vasculature feeding the caudate [12,13]. This finding suggests that response differences in this region are not simply the result of reduced caudate volume, but that a change in response pattern may also occur.

To our knowledge, only one previous study has used fMRI to examine response differences associated with HD [21]. This study examined a single patient using a clock-reading task. As this task did not produce activation in the striatum, response differences associated with HD were not observed in this region. In agreement with the current study, a higher BOLD response magnitude was found in some brain regions for their HD patient relative to control subjects.

The mechanism accounting for the alteration of BOLD signal during maze testing is unclear. The current findings, together with earlier reports, suggest that the altered BOLD effect may result from altered cognitive, neural, neurovascular and/or metabolic activity in HD. This effect is complex and appears to vary depending on the stage of the disease and the brain region measured. For example,

resting metabolic activity in HD is reportedly normal [11,18] or below normal [5,8,11,17,18] in the striatum of presymptomatic HD patients, and below normal in early- to late-stage patients [1,4–8,10,11,20]. Patients (particularly those with more advanced disease) are reported to have decreased resting cortical metabolic activity [6,20] although some debate on this exists [5].

The results of the present study suggest that HD patients may have an enhanced level of activity within certain brain regions that assist in the performance of the maze tasks. The right hemisphere middle frontal gyrus, which is involved with working memory and is activated during performance of mazes [22], showed increased activation in our patients. Similarly the cerebellum, which in other species is associated with maze performance [23], also showed increased activation in HD. This suggests that the HD patients might have compensated for the loss of neurons in the caudate and reduced activity in visual and motor regions, by increased activity in other regions.

Alternatively, a dysregulation of the cerebral vasculature may exist in HD. Recent findings in HD transgenic mice indicate that nitric oxide (NO), one important regulator of vasomotor tone, is decreased in late-stage HD [24]. Manipulations of NO in late-stage HD mice increases resting CBF compared to control animals [25]. Further work to examine the relative contribution of altered metabolic activity *vs* impaired vasomotor regulation may help explain the pathophysiological underpinnings of these BOLD effects.

CONCLUSION

The current findings show that BOLD responses differ significantly between HD patients and controls during maze testing. This suggests that some aspect of BOLD signal generation is altered in HD, which might involve changes in cognitive, neurophysiological, neurovascular coupling or hemodynamic processes. Previous work, in conjunction with the present results, raises the possibility that disturbed regulation of blood flow may contribute to the oxidative stress believed to be important in HD. Mechanisms that could account for these findings potentially include altered production of the vasodilator nitric oxide, increased synthesis of the neurotoxic compound peroxynitrite, and changes in resting metabolic activity.

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