Visual perception in prediagnostic and early stage Huntington’s disease

BRIAN F. O’DONNELL,1 TANYA M. BLEKHER,2 MARJORIE WEAVER,3 KERRY M. WHITE,3 JEANINE MARSHALL,3 XABIER BERISTAIN,4 JULIE C. STOUT,1 JACQUELINE GRAY,3 JOANNE M. WOJCIESZEK,4 AND TATIANA M. FOROUD3

1Department of Psychological and Brain Sciences, Indiana University, Bloomington, Indiana
2Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, Indiana
3Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana
4Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana

(Received June 18, 2007; Final Revision December 14, 2007; Accepted December 18, 2007)

Abstract

Disturbances of visual perception frequently accompany neurodegenerative disorders but have been little studied in Huntington’s disease (HD) gene carriers. We used psychophysical tests to assess visual perception among individuals in the prediagnostic and early stages of HD. The sample comprised four groups, which included 201 nongene carriers (NG), 32 prediagnostic gene carriers with minimal neurological abnormalities (PD1); 20 prediagnostic gene carriers with moderate neurological abnormalities (PD2), and 36 gene carriers with diagnosed HD. Contrast sensitivity for stationary and moving sinusoidal gratings, and tests of form and motion discrimination, were used to probe different visual pathways. Patients with HD showed impaired contrast sensitivity for moving gratings. For one of the three contrast sensitivity tests, the prediagnostic gene carriers with greater neurological abnormality (PD2) also had impaired performance as compared with NG. These findings suggest that early stage HD disrupts visual functions associated with the magnocellular pathway. However, these changes are only observed in individuals diagnosed with HD or who are in the more symptomatic stages of prediagnostic HD.

(JINS, 2008, 14, 446–453.)

Keywords: Huntington’s disease, Visual perception, Visual pathways, Neurodegenerative disease, Neuropsychology, Contrast sensitivity

INTRODUCTION

Huntington’s disease (HD) is an autosomal dominant disorder resulting from an increased number of triplet (CAG) repeats in the Huntington gene (Huntington’s Disease Collaborative Research Group, 1993). Whereas clinical and neuropsychological studies have documented marked dysfunction of motor and cognitive functions in HD (Ho et al., 2003), several lines of evidence suggest that visual pathways may also be affected in this disorder. Patients with HD exhibit visual evoked potential abnormalities (Ellenberger et al., 1978; Oepen et al., 1981) indicative of retinostriate dysfunction. Structural MRI assessment has shown reductions of grey matter (Fennema-Notestine et al., 2004; Mühlau et al., 2007; Rosas et al., 2002) and white matter in the occipital cortex (Beglinger et al., 2005; Fennema-Notestine et al., 2004). Post-mortem increases in gamma-aminobutyric acid (GABA) concentrations in the cortex, with the largest increases in the striate cortex, have also been reported (Storey et al., 1992). Visual perceptual impairments have been reported in other neurodegenerative disorders. For example, patients with Parkinson’s disease show deficits on tests of contrast sensitivity (Rodnitzky, 1998; Uc et al., 2005), color vision (Rodnitzky, 1998), and motion perception (Uc et al., 2005). In Alzheimer’s disease, deficits in contrast sensitivity (Gilmore et al., 2005; Rizzo et al., 2002) and motion perception (Rizzo et al., 2002) have been described. These findings suggest an evaluation of early stage vision in HD is warranted.

Disturbances in perception of visual cognition for stationary stimuli have frequently reported in this disorder...
Proximity to diagnosis, the sensitivity of these tests of visual perception to the neurodegenerative process was evaluated. Proximity to clinical onset was characterized by neurologic evaluation and by an algorithm based CAG length (Langbehn et al., 2004).

METHODS

Participants

Participants were recruited through the National Research Roster for Huntington’s disease patients and families, a registry of patients and families interested in participating in research. Inclusion criteria were: (1) a parent with HD; (2) either undiagnosed, or diagnosed with HD within the past 2 years; (3) between the ages of 19 and 65; and (4) absence of other neurological illness or a major psychiatric disorder. All participants had normal or corrected visual acuity (20/40 or better) on a Snellen Test of near vision. 87% of subjects had acuity values of 20/25 or better, and acuity not differ among groups (Fisher Exact Test p value = .53). This study was approved by the Indiana University School of Medicine Institutional Review Board (Protocol 0109-12), conformed to ethical standards of the 1964 Declaration of Helsinki, and all participants provided informed consent. Demographic and clinical information from the study participants (n = 289) are summarized in Table 1. There were no significant differences in age, education or gender distribution between the four groups.

All subjects were administered the Unified Huntington’s Disease Rating Scale (UHDRS), a standardized clinical evaluation (Huntington Study Group, 1996). The motor portion of the UHDRS was administered by an experienced movement disorder neurologist, who was aware that the participant was at-risk for HD but was blind to their gene status and results of other assessments during the visit. As part of the UHDRS, the neurologist assigned a confidence rating using a scale of 0 to 4 to indicate the extent of motor abnormalities and the neurologist’s confidence that the abnormalities represented symptoms of HD. A score of 0 indicated the evaluation was normal (no abnormalities). A score of 1 represented non-specific motor abnormalities with a confidence of less than 50% that these indicated a diagnosis of HD. A score of 2 indicated motor abnormalities that may be signs of HD with a confidence of 50–89%. A score of 3 suggested the motor abnormalities were likely signs of HD with a confidence of 90% to 98%. A score of 4 indicated the motor abnormalities were unequivocal signs of HD with a confidence in the diagnosis of ≥99%. In addition, UHDRS composite scores for overall motor impairment (motor assessment questions 1 to 15), chorea (question 12), and ocular motor impairment (questions 1 to 3) were separately evaluated. The Digit Symbol Test (Wechsler, 1981), a neuropsychological measure with demonstrated sensitivity to early cognitive changes in gene carriers (Foroud et al., 1995; Kirkwood et al., 2000), was also administered. Digit Symbol is a multifactorial test, which taps psychomotor speed, attention, and working memory mechanisms. The age scaled
equation: on the UHDRS of 4 were classified as manifest HD (HD). Those sub-
(groups) consisted of participants with an expanded HD allele and an overall rating on the UHDRS of 2 or 3. Those sub-
grades. In the stationary grating detection task, a sinusoidal grating with a spatial frequency of 9.9 cycles/degree of visual angle served as the target stimulus for a duration of 1000 ms. The grating was initially presented at 42% Michelson contrast. Tone pips signaled the onset and offset of the trial. Fifty percent of the trials presented a grating, and 50% were null trials. The subject indicated whether a grating was present or not.

In the moving grating discrimination task, a sinusoidal grating with a spatial frequency of 1.3 cycles/degree was temporally modulated to produce motion to the right or left at one of three temporal frequencies (2.1, 9.3, and 18.8 cycles/sec) for 480 ms. The grating was initially presented at 30% Michelson contrast. Tone pips signaled the onset and offset of each trial. After the offset of each stimulus, the subject responded whether the grating appeared to move to the right or to the left.

For the stationary and moving grating tasks, contrast was varied in steps of 0.05 log units and a staircase procedure was used to estimate 75% correct threshold level (O’Donnell et al., 2003; Tyler & McBride, 1995). For all tasks, Log10 contrast sensitivity was used for statistical analysis. Higher contrast sensitivity values indicated better performance.

Form and motion discrimination tests

Perception of form and dot motion properties were evaluated using psychophysical tests (Brenner et al., 2003; O’Donnell et al., 2006). In the form discrimination task, subjects were required to discriminate between two shapes (circle vs. square with rounded corners) at different levels of static visual noise. Stimuli were displayed with 75 × 75 pixel window, which subtended 2.9 degrees of visual angle. Each stimulus was presented for three seconds. Noise was added by randomly assigning a percentage of pixels within the display to black or white values. In order to quickly find the threshold range, the size of the noise increment was initially 13.3%. After the first error the increment was reduced to 6.7%, and after the further error the increment was reduced to 2.7%.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NG: N = 201</th>
<th>PD1: N = 32</th>
<th>PD2: N = 20</th>
<th>HD: N = 36</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>47 (10)</td>
<td>45 (10)</td>
<td>45 (12)</td>
<td>47 (11)</td>
<td>.60</td>
</tr>
<tr>
<td>Education (y)</td>
<td>15 (2)</td>
<td>16 (2)</td>
<td>16 (2)</td>
<td>16 (3)</td>
<td>.59</td>
</tr>
<tr>
<td>Gender</td>
<td>36 M/145 F</td>
<td>11 M/21 F</td>
<td>7 M/13 F</td>
<td>15 M/21 F</td>
<td>.34</td>
</tr>
<tr>
<td>CAG Repeats</td>
<td>N/A</td>
<td>42 (2)</td>
<td>42 (2)</td>
<td>43 (3)</td>
<td>.02</td>
</tr>
<tr>
<td>UHDRS Motor</td>
<td>4.8 (3.7)</td>
<td>5.2 (3.3)</td>
<td>14.4 (6.3)*</td>
<td>26.8 (10.2)*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>UHDRS Ocular Motor</td>
<td>1.3 (1.9)</td>
<td>1.2 (1.8)</td>
<td>4.9 (2.6)*</td>
<td>5.6 (2.8)*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>UHDRS Chorea</td>
<td>.2 (.7)</td>
<td>.3 (.9)</td>
<td>2.6 (2.8)*</td>
<td>8.2 (4.1)*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Digit Symbol</td>
<td>11.8 (2.4)</td>
<td>11.2 (2.9)*</td>
<td>10.5 (2.7)*</td>
<td>8.9 (2.5)*</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Note. Entries indicate mean values and SDs in parentheses for each group, with the exception of gender. ANOVAs were used to test for main effects of group for education, UHDRS scores, CAG repeats, and Digit Symbol. Gender was evaluated using Fisher’s exact test statistic. For ANOVAs, p values indicate an effect of group. Asterisks indicate differences between the non-gene carrier (NGC) group and gene carrier group (PD1, PD2, HD). The “+” symbol indicates that the HD group differed from the PD1 and PD2 groups (p < .02 in both cases). The Digit Symbol test score was age scaled.
The dot motion trajectory discrimination task consisted of a field of dots moving either right or left across the screen at a velocity of 3.5 degrees/second. One hundred dots were presented for 500 ms in a rectangular display subtending 8.1 degrees visual angle. Thresholds were obtained by varying the number of dots that were moving randomly (dynamic visual noise). As in the form discrimination condition, the size of the increment in noise was initially large at 10%. After an error trial, the increment was 5%, and after the fourth error, the increment was reduced to 2%.

Both tasks used an adaptive staircase method to estimate performance thresholds (Levitt, 1971; O’Donnell et al., 2006). The subject responded verbally to each trial. The subject’s performance gradually converged around a visual noise threshold value, which was the amount of noise required to obtain a 71% performance level. The visual noise threshold, calculated as the mean value of the final six trials of the staircase was the dependent measure used for analysis (O’Donnell et al., 2006). Higher visual noise thresholds indicate better performance.

**Statistical Analysis**

The distribution of each visual test variable was reviewed to assess normality and detect extreme outliers defined as greater than 4 standard deviations from the mean. These extreme values were assigned as missing values for the remaining analyses. One-way analysis of variance (ANOVA) was then performed to detect group effects (NG, PD1, PD2, HD) for the six tests of visual perception, and UHDRS scores. ANCOVA with gender and age as co-variates was used to compare Digit Symbol scores. For those measures demonstrating a significant group effect, one-sided t-tests were used in post-hoc analyses to evaluate which of the three gene carrier groups differed significantly from the NG group. Fisher Exact Test was used to evaluate categorical data. Pearson correlation coefficients were used to test relationships between clinical measures and visual perception tests. All subjects had complete neurological and genetic data. Subjects with missing data for a perceptual or neuropsychological measure were excluded from analysis including that measure.

**RESULTS**

**Visual Tests**

Significant group effects were observed for three of the six tests of visual perception (Table 2). Significant group effects were found with all three contrast sensitivity tests using moving gratings at the 2.1 Hz modulation rate ($F(3,278) = 14.8, p < .0001$), 9.3 Hz ($F(3,279) = 8.5, p ≤ .0001$) and 18.8 Hz ($F(3,279) = 3.4, p = .02$). Post-hoc analyses demonstrated that the individuals with manifest HD, even though they were in the very early stages of illness, performed significantly worse than the NG and PD1 groups on all three tests ($p < .01$), whereas the difference between the HD and PD2 groups was only significant for gratings at 2.1 Hz ($p = .001$). Post-hoc analyses to identify abnormalities among the two prediagnostic gene carrier groups and non-gene carriers only identified significant differences when comparing the PD2 and NG groups on gratings at 9.3 Hz ($p = .01$), whereas no significant differences were observed between the PD1 and NG groups. The PD2 group performed worse than the PD1 group for the 9.3 Hz ($p = .01$) moving gratings. Significant group effects were not observed for contrast sensitivity with the stationary grating. Noise thresholds for form discrimination and dot motion discrimination did not differ among groups.

**Clinical Measures**

UHDRS total motor ($p < .0001$), chorea ($p < .0001$), and oculomotor ($p < .0001$) scores all showed differences among groups. In all cases, HD and PD2 groups were impaired compared to the NG group, whereas the PD1 group did not differ from NG. ANCOVA employing the Digit Symbol Test detected a significant group effect ($F(5,278) = 13.3, p < .0001$). Post-hoc comparisons of each of the gene

<table>
<thead>
<tr>
<th>Test</th>
<th>NG</th>
<th>PD1</th>
<th>PD2</th>
<th>HD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 201</td>
<td>N = 32</td>
<td>N = 20</td>
<td>N = 36</td>
</tr>
<tr>
<td><strong>Contrast sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stationary</td>
<td>1.79 (.36)</td>
<td>1.68 (.33)</td>
<td>1.78 (.39)</td>
<td>1.73 (.42)</td>
</tr>
<tr>
<td>2.1 Hz modulation</td>
<td>2.09 (.13)</td>
<td>2.10 (.13)</td>
<td>2.05 (.14)</td>
<td>1.92 (.19)*</td>
</tr>
<tr>
<td>9.3 Hz modulation</td>
<td>2.13 (.13)</td>
<td>2.14 (.13)</td>
<td>2.05 (.18)*</td>
<td>2.02 (.19)*</td>
</tr>
<tr>
<td>18.8 Hz modulation</td>
<td>1.68 (.19)</td>
<td>1.73 (.15)</td>
<td>1.64 (.14)</td>
<td>1.59 (.25)*</td>
</tr>
<tr>
<td><strong>Discrimination thresholds</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dot motion</td>
<td>81.8 (9.2)</td>
<td>79.5 (12.1)</td>
<td>80.7 (9.1)</td>
<td>77.1 (10.6)</td>
</tr>
<tr>
<td>Form</td>
<td>71.9 (9.1)</td>
<td>74.3 (10.1)</td>
<td>73.1 (9.6)</td>
<td>69.1 (13.9)</td>
</tr>
</tbody>
</table>

**Table 2.** Mean scores for visual perception thresholds

*Note. Entries indicate mean values and SDs in parentheses for each group. Contrast sensitivity indicates the log10 contrast sensitivity (1/contrast threshold). Higher values indicate better performance. Form and motion thresholds indicate percent noise at threshold. Higher thresholds indicate better performance. *Post-hoc comparison with NG significant at $p < .05$.*
carrier groups with the NG group were performed, and all comparisons were significant (NG vs. PD1: \( p = 0.04 \); NG vs. PD2: \( p = 0.008 \); NG vs. HD: \( p < 0.0001 \)). These data are shown in Table 1.

**Correlation Analysis**

Estimated time to diagnosis, but not the number of CAG repeats, was correlated with the thresholds for moving gratings (Table 3). These results provide further evidence of the sensitivity of moving grating contrast sensitivity to proximity of onset of the disorder. Among the neuropsychological tests, Digit Symbol was correlated with a single visual test measure, contrast sensitivity at the 2.1 Hz modulation rate.

**DISCUSSION**

The present study indicated that patients with HD show a selective deficit in contrast sensitivity for moving gratings relatively early in the neurodegenerative process. This deficit was present in gene carriers who were closest to onset based on neurological examination and CAG repeats. This may represent a selective deficit in the symptomatic gene carriers compared to non-gene carriers, since other measures of visual function did not differ significantly among groups.

Contrast sensitivity for moving gratings was impaired for individuals with manifest HD. In addition, gene carriers in the PD2 group who showed non-specific motor abnormalities were also impaired on one of these tests. These specific abnormalities suggest selective dysfunction in the magnocellular (M) pathway, which is sensitive to low spatial frequencies, high temporal frequencies, and luminance (Livingstone & Hubel, 1988; Wandell, 1995). Stationary grating contrast sensitivity was unaffected in any of the gene carrier groups, suggesting that the parvocellular (P) pathway, which prefers medium to high spatial frequencies and low temporal frequencies, is less sensitive to the early effects of HD. Similarly, previous studies of HD patients have not detected deficits for contrast sensitivity utilizing stationary gratings (O’Donnell et al., 2003; Sprengelmeier et al., 1996). The spared high spatial frequency contrast sensitivity found in HD carriers differs from several other clinical conditions, suggesting that this deficit may be related to specific neuropathological changes in HD. For example, aging is associated with relatively spared low spatial frequency, and impaired high spatial frequency contrast sensitivity for stationary gratings (Spear, 1993). Contrast sensitivity deficits in Parkinson’s disease vary with stage of illness and severity but appear most pronounced at intermediate spatial frequencies (Rodnitzky, 1998). In a study of patients with schizophrenia, Slaghuis (1998) found that patients diagnosed with schizophrenia were impaired for moving and stationary gratings, with most consistent deficits at higher spatial frequencies. Unlike the present HD sample, patients diagnosed with Parkinson’s disease (Uc et al., 2005) and schizophrenia (O’Donnell et al., 2006) can show dot motion deficits as well as impaired stationary contrast sensitivity. Thus, in Parkinson’s disease, aging, and schizophrenia, the pattern of visual deficits frequently differs from that of HD gene carriers.

These disturbances in contrast sensitivity could be produced by a variety of neuropathological mechanisms. Magnocellular pathway abnormalities could occur in the retina, lateral geniculate nuclei of the thalamus, or occipital cortex. Whereas detailed neuropathology of the visual pathways is not yet available in HD, visual evoked potential abnormalities in HD have been described in diagnosed patients, suggestive of retinostriate or visual cortex dysfunction (Ellenberger et al., 1978; Oepen et al., 1981). Structural MRI findings have directly implicated abnormalities of gray and white matter in visual cortex. Several MRI reports indicate that white matter volume is reduced in the cerebral cortex (Beglinger et al., 2005), and that white matter volume reduction may be most severe in the occipital cortex in HD patients (Beglinger et al., 2005; Fennema-Notestine et al., 2004). With respect to gray matter volume, some reports indicate widespread reduction in volume, including the occipital cortex (Fennema-Notestine et al., 2004; Mühlau et al., 2007), although other investigators have reported no reduction in gray matter volumes (Beglinger et al., 2005). Rosas et al. (2002) reported MR measured thinning of the cortical ribbon, which was most severe in posterior brain regions, including dorsal visual cortex (Brodmann areas 17, 18, and 19). Storey et al. (1992) reported an increase in gamma-aminobutyric acid (GABA) concentrations in multiple cortical regions, with the largest increases in striate cortex (area 17). GABAergic neurons seem to play an important role in visual processing in ani-

**Table 3. Correlations among perceptual, genetic, and neuropsychological variables in gene carriers**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Visual test</th>
<th>Grating (Modulation rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Form Motion</td>
<td>(Static) (2.1) (9.3) (18.8)</td>
</tr>
<tr>
<td><em>CAG</em></td>
<td>.02 − .09</td>
<td>.06 − .11 .05 .07</td>
</tr>
<tr>
<td>Est. Time to Diagnosis</td>
<td>.20 .06</td>
<td>.18 .34** .24* .34**</td>
</tr>
<tr>
<td>Digit Symbol</td>
<td>.13 .04</td>
<td>− .06 .25* .14 .07</td>
</tr>
</tbody>
</table>

*Note: CAG refers to number of CAG repeats. Est. Time to Diagnosis refers to the estimated years to diagnosis based on number of CAG repeats and age at the time of testing. ** p < .01; * p < .05.*
Visual perception in Huntington’s disease

HD is associated with psychomotor slowing, the shorter ing tests was shorter than the stationary grating test. Because of difficulty. Secondly, the display time of the moving grat- Thus, thresholds were obtained within a very narrow range and form perception, thresholds were estimated at 72%. Sensitivity to behavioral deficits. In order to minimize this possibility, the psychophysical staircase method estimates possibility, the psychophysical staircase method estimates sensitivity for stationary gratings was unaffected in the early stages of HD. Disturbances in visual cognition for stationary stimuli in the absence of memory demands has been most consistently found in diagnosed HD patients, suggesting that these functions may be mildly affected in the earliest stages of the illness (Gómez-Tortosa et al., 1996; Jacobs et al., 1995; Mohr et al., 1991; Sprengelmeyer et al., 1996).

In summary, gene carriers late in the prediagnostic stage of HD and patients with diagnosed HD showed a deficit in contrast sensitivity for temporally modulated gratings. Among gene carriers, contrast sensitivity was correlated with estimated time to onset. With respect to the neuropathology of HD, these data implicate involvement of the prestriate visual pathways or cortical visual pathways relatively early in the disease process. Use of structural and functional neuroimaging in conjunction with behavioral testing could help identify the neural correlates of these abnormalities in visual perception. These data further suggest that the neurodegenerative process in HD does not proceed in a nonparallel fashion with respect to visual processing. During the prediagnostic period (PD1) when gene carriers show minimal neurological abnormality, deficits have been observed in some neuropsychological tests such as Digit Symbol (Foroud et al., 1995; Kirkwood et al., 2000), in quantitative saccades (Blekher et al., 2006), and in motor timing variability (Hinton et al., 2007). In contrast, the selective deficit for moving, low frequency gratings observed in this study was only detected in the more symptomatic pre-diagnostic gene carriers (PD2) and in individuals with manifest HD. The present study, and studies by O’Donnell et al. (2003) and Sprengelmeyer et al. (1996), found that contrast sensitivity for stationary gratings was unaffected in the early stages of HD. Disturbances in visual cognition for stationary stimuli in the absence of memory demands has been most consistently found in diagnosed HD patients, suggesting that these functions may be mildly affected in the earliest stages of the illness (Gómez-Tortosa et al., 1996; Jacobs et al., 1995; Mohr et al., 1991; Sprengelmeyer et al., 1996).

ACKNOWLEDGMENTS

The authors thank the participants in this study. Dr. Christopher W. Tyler of the Smith Kettlewell Eye Institute, San Francisco, CA assisted with the contrast sensitivity methods. This study was supported by NINDS RO1 NS42659 (Foroud), N01-NS-2326 (Foroud), and NIMH I RO1 MH62150-01 (O’Donnell).

REFERENCES


