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Abnormal error-related antisaccade activation in premanifest and early manifest Huntington disease

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Abstract

Objective—Individuals with the trinucleotide CAG expansion (CAG+) that causes Huntington disease (HD) have impaired performance on antisaccade (AS) tasks that require directing gaze in the mirror opposite direction of visual targets. This study aimed to identify the neural substrates underlying altered antisaccadic performance.

Method—Three groups of participants were recruited: 1) Imminent and early manifest HD (early HD, n=8); 2) premanifest (presymptomatic) CAG+ (preHD, n=10); and 3) CAG unexpanded (CAG−) controls (n=12). All participants completed a uniform study visit that included a neurological evaluation, neuropsychological battery, molecular testing, and functional magnetic resonance imaging during an AS task. The blood oxygenation level dependent (BOLD) response was obtained during saccade preparation and saccade execution for both correct and incorrect responses using regression analysis.

Results—Significant group differences in BOLD response were observed when comparing incorrect AS to correct AS execution. Specifically, as the percentage of incorrect AS increased, BOLD responses in the CAG− group decreased progressively in a well-documented reward detection network that includes the pre-supplementary motor area and dorsal anterior cingulate cortex. In contrast, AS errors in the preHD and early HD groups lacked this relationship with BOLD signal in the error detection network, and BOLD responses to AS errors were smaller in the two CAG+ groups as compared with the CAG− group.

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Conclusions—These results are the first to suggest that abnormalities in an error-related response network may underlie early changes in AS eye movements in premanifest and early manifest HD.

Keywords

Huntington disease; premanifest; saccades; functional MRI; error monitoring

Introduction

Huntington disease (HD) is an autosomal dominant disorder caused by an expanded number of CAG repeats (CAG+) in the huntingtin gene (Huntington's Disease Collaborative Research Group, 1993). The disease is characterized by progressive worsening of motor, cognitive, and behavioral control. The Unified Huntington Disease Rating Scale (UHDRS) (Huntington Study Group, 1999), which emphasizes motor abnormalities, is often used to classify participants in research studies. However, many studies indicate that cognitive (Diamond et al., 1992; Hahn-Barma et al., 1998; Kirkwood et al., 2000b; Lawrence et al., 1998; Paulsen et al., 2006a; Rosenberg et al., 1995), psychomotor (Foroud et al., 1995; Kirkwood et al., 2000b; Kirkwood et al., 2000a; Paulsen et al., 2006a; Rosenberg et al., 1995; Siemers et al., 1996), and psychiatric signs (Cummings, 1995; De Marchi & Mennella, 2000; Duff et al., 2007; Hofmann, 1999; Kirkwood et al., 2002; Morris, 1995; Paulsen et al., 2001; Vecsei & Beal, 1996) can be detected during the premanifest (presymptomatic) period, before unequivocal motor signs are observed.

Abnormalities in saccades, rapid eye movements that shift gaze from one location to another, are widely observed in HD (Ali et al., 2006; Antoniadou et al., 2007; Blekher et al., 2006; Blekher et al., 2004; Golding et al., 2006; Hicks et al., 2008; Kirkwood et al., 2000b; Kirkwood et al., 2000a; Lasker & Zee, 1997; Peltsch et al., 2008; Penney, Jr. et al., 1990). However, a distinction between types of saccades is important. A prosaccade (PS) is a type of visually-guided saccade that shifts gaze toward a visual stimulus. A PS is often termed reflexive, though the accuracy of the term has been questioned (Hutton, 2008) because cognitive processes clearly influence PS initiation. Individuals with HD may have slowed PS or require blinks or head movements to facilitate saccade initiation (Kirkwood et al., 2000a; Lasker & Zee, 1997; Leigh et al., 1983). However, more recent studies suggest that these abnormalities are a feature of the later stages of HD progression (Blekher et al., 2006; Golding et al., 2006).

Unlike PS, a volitional saccade is an endogenously generated movement in response to a command. The ability to initiate these volitional saccades and to correctly perform volitional saccadic tasks is particularly affected in premanifest and early HD (Antoniades et al., 2007; Blekher et al., 2006; Blekher et al., 2004; Golding et al., 2006; Lasker & Zee, 1997).

An antisaccade (AS) is a type of volitional saccade that requires the suppression of a reflexive saccade toward a peripheral visual stimulus, and the voluntary generation of a saccade to the mirror opposite location of the stimulus. As compared to those who do not have the disease-causing expansion (CAG−), both premanifest and manifest HD subjects make more AS errors and have longer and more variable latencies of AS initiation (Blekher et al., 2006; Blekher et al., 2004; Lasker & Zee, 1997; Peltsch et al., 2008). The AS task is well-suited to studying neural abnormalities in premanifest and manifest HD because behavioral abnormalities are reliably detected and there is a substantial body of literature describing brain activity underlying AS performance in healthy controls (reviewed by McDowell and colleagues (2008)).

PS are generated by activity in known brain regions, including the visual cortex, parietal cortex, frontal and supplementary eye fields (FEF, SEF), striatum, and superior colliculus (reviewed by McDowell and colleagues (2008)). Based on functional magnetic resonance imaging (fMRI) studies, AS generation activates the same regions as does PS generation, albeit to a greater extent (McDowell et al., 2008), with the possible exception of the visual cortex (Dyckman et al., 2007; McDowell et al., 2005). In addition to regions activated by PS, AS also activate dorsolateral prefrontal cortex (DLPFC) (DeSouza et al., 2003; Ettinger et al., 2008; Matsuda et al., 2004; McDowell et al., 2002; McDowell et al., 2005; McDowell et al., 2008; Muri et al., 1998; Sweeney et al., 1996) and anterior cingulate cortex (ACC) (Brown et al., 2006; Doricchi et al., 1997; Gaymard et al., 1998; Matsuda et al., 2004; Milea et al., 2005; Polli et al., 2005). Lesions in the DLPFC lead to more AS errors, but do not affect PS (Pierrot-Deseilligny et al., 1991; Pierrot-Deseilligny & Rivaud-Pechoux, 2003; Pierrot-Deseilligny et al., 2003). The ACC plays a role in conflict monitoring generally (Braver et al., 2001; MacDonald, III et al., 2000; Miller & Cohen, 2001), and increased activity in the period preceding an AS is associated with better performance (Ford et al., 2005). On the other hand, increased ACC activity is associated with errant reflexive saccades during the response phase of an AS task (Ford et al., 2005; Polli et al., 2005), suggesting an error monitoring role for the ACC as well. These findings suggest that successful AS execution depends on multiple processes such as planning, reflex suppression, and error monitoring.

Separating the preparatory period leading to an AS (i.e. knowing the instruction to make an AS while awaiting the cue to execute it) and the response period (i.e. the presentation of the peripheral stimulus and the saccadic response) is one strategy to help disentangle planning and error. Using such an approach, Brown et al. (2007) identified the FEF, SEF, DLPFC, ACC, and intraparietal sulcus (IPS) as active during AS preparation, while FEF, SEF, and IPS regions were involved in the response period. Others have similarly identified the pre-supplementary motor area (pre-SMA), FEF, and SEF as important regions in maintaining the preparatory set necessary for correct AS performance (Amador et al., 2004; Schlag-Rey et al., 1997).

A number of studies have investigated neural abnormalities in HD using fMRI (Clark et al., 2002; Dierks et al., 1999; Georgiou-Karistianis et al., 2007; Hennenlotter et al., 2004; Kim et al., 2004; Kloppel et al., 2009; Paulsen et al., 2004; Reading et al., 2004; Saft et al., 2008; Thiruvady et al., 2007; Wolf et al., 2007; Wolf et al., 2008b; Wolf et al., 2008a; Zimbelman et al., 2007). Findings from these reports include both hypo- and hyperactivation of many different regions. However, the neural abnormalities underlying impaired AS in HD have not been investigated. We used an event-related AS paradigm to investigate whether performance of an AS task in a sample of CAG+ individuals was affected by: 1) abnormal brain activity while preparing for an AS response, or 2) abnormal activity while executing an AS.

Methods

Participants

All participants were recruited primarily from individuals who had taken part in previous studies. The inclusion criteria were: 1) parent diagnosed with HD; 2) age between 18 and 65; 3) no diagnosis of HD, or if diagnosed, having received the diagnosis within the past 2 years; and 4) self-reported right-handedness. No participants reported a concurrent neurologic illness, major psychiatric diagnosis (e.g. schizophrenia, bipolar disorder), or current alcohol or drug abuse at any visit. Participants were asked not to disclose their CAG status, if known, to study staff. This study was approved by the local institutional review board (IUPUI IRB Study No. 0109). All participants provided written informed consent.

Clinical Evaluation and Study Group Assignment

Molecular testing of the huntingtin gene was performed (Bond & Hodes, 1996) to determine the number of CAG repeats. Individuals in the CAG[−] group had 2 alleles with fewer than 28 CAG repeats (n=12). Individuals with at least 1 allele of more than 38 CAG repeats were considered CAG⁺ (n=19). One CAG⁺ participant was not included in the analysis due to excessive motion during imaging, resulting in a final sample size of 18 CAG⁺ individuals.

An experienced movement disorder neurologist (J.W.) administered the motor portion of the UHDRS (Huntington Study Group, 1999). The neurologist was aware that the participants were at-risk for HD, but was blind to the results of all other study assessments, including huntingtin gene testing. Total Motor Score (TMS) was calculated as the sum of the scores on items 1–15 of the UHDRS motor assessment. Additionally, on the basis of the motor examination only, the neurologist assigned an overall confidence rating (UHDRS diagnosis confidence level, item 17) that represented the likelihood of motor abnormalities attributable to HD. The ratings were defined as: (0) normal (no abnormalities); (1) nonspecific motor abnormalities (less than 50% confidence); (2) motor abnormalities that may be signs of HD (50% to 89% confidence); (3) motor abnormalities that are likely signs of HD (90% to 98% confidence); and (4) motor abnormalities that are unequivocal signs of HD ($\geq 99\%$ confidence). Those CAG⁺ participants with a confidence rating from 0–2 were considered premanifest (preHD, n=10), while those receiving a 3 or 4 were considered to have imminent or early HD (early HD, n=8).

Neuropsychological performance was evaluated using measures from: 1) The Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981): Arithmetic and Picture Arrangement subtests; 2) Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler, 1997): Letter-Number Sequencing; 3) UHDRS: Symbol Digit Modalities Test (Smith, 1982), and Verbal Fluency; 4) Stroop Color-Word Interference Task (Stroop, 1935): Word Reading, Color Naming, Interference; 5) H-scan system (Hochschild, 1983): Visual Reaction Time, Audio Reaction Time, Decision Reaction Time, Movement Time, Decision Movement Time, and Alternate Button Tapping; 6) California Verbal Learning Test (CVLT) (Delis et al., 1987): Immediate Free Recall, Semantic Clustering, Recognition Discriminability, Short Delay Free Recall, Short Delay Cued Recall, Long Delay Free Recall, and Long Delay Cued Recall; and 7) Trail Making Test (Reitan, 1958): Parts A and B. These tests were chosen based on their extensive use in evaluating premanifest and manifest HD (Paulsen et al., 2006a; Rupp et al., 2010; Stout et al., 2007; Witjes-Ane et al., 2007), and were administered as previously described (Stout et al., 2007). Analysis of covariance (ANCOVA) was used to test for group differences, with age, gender, and education included as covariates. A significant ANCOVA test was followed by post hoc one-sided t tests of all groupwise comparisons. Covariates were removed from the model when not significant to preserve statistical power.

Antisaccade Paradigm

A mixed event-related design was used to study brain activation elicited by PS and AS (Figure 1). Similar to Brown et al. (2006), participants were initially given a color-coded instruction to perform a PS or an AS (Figure 1, panel 1; 2 or 4 s). The instruction was then extinguished with the simultaneous appearance of a peripheral stimulus (1 s). Subjects were instructed to look at the stimulus (PS trials) or in the mirror-opposite location of the stimulus (AS trials; Figure 1, panel 2). The peripheral stimulus was then extinguished and a centrally-located white circle appeared, upon which participants fixated their gaze while awaiting the next instruction (Figure 1, panel 3; 3–15 s, mean 5.2 s). Sixteen PS and sixteen AS trials were presented in each 5:20 minute functional imaging scan in a pseudorandom order using E-prime (www.pstnet.com/eprime.cfm). All but two participants completed four functional

imaging scans; one terminated the protocol after the third scan due to loss of sensation in his arms, and eye movement data were not collected during one scan for another.

Eye Movement Recording and Analysis

An R-LRO 6.1 eye-tracking system designed for fMRI (Applied Science Laboratories, Bedford, MA) was used to track eye movements during imaging at a sampling rate frequency of 60 Hz. Eye movements were analyzed offline using a semi-automated, in-house software program written in Matlab (<http://www.mathworks.com>) as described previously (Blekher et al., 2004). For each trial, the saccade was determined to be either correct or incorrect. We also identified self-corrected AS errors, defined as an initial saccade made toward the stimulus that was corrected by making a saccade away from the stimulus. No external feedback was given to the participants regarding accuracy. The percentages of incorrect trials and of self-corrected AS errors were then determined, and ANCOVA was used to test for between-group differences (CAG-, preHD, early HD) with age, gender, and education included as covariates when appropriate. A significant ANCOVA ($p \leq 0.05$) was followed by one-tailed t -tests of all pairwise comparisons.

Image Acquisition and Analysis

Subjects were imaged using a Siemens (Erlangen, Germany) 3T Magnetom Trio-Tim scanner with a 12-channel head-coil array. A whole-brain, structural image volume (1.0 mm $\times$ 1.0 mm $\times$ 1.2 mm voxels) was acquired first using a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence to enable anatomic registration of the functional volumes (Jack, Jr. et al., 2008). Functional imaging was performed with a blood oxygenation level dependent (BOLD) contrast sensitive gradient echo, echo-planar imaging sequence (repetition time 2000 ms, echo time 29 ms, flip angle 76°, field of view 220 mm $\times$ 220 mm, 35 interleaved axial slices, 2.5 mm $\times$ 2.5 mm $\times$ 3.0 mm voxels) incorporating a 3D prospective acquisition correction algorithm, which adjusts the acquisition in real time to account for head movement.

Given that atrophy in the caudate and putamen have been consistently described (Aylward et al., 1994; Aylward et al., 1996; Brandt et al., 1995; Campodonico et al., 1998; Harris et al., 1992; Harris et al., 1999; Paulsen et al., 2006b; Rosas et al., 2001), an automated segmentation procedure in FreeSurfer V4 (Fischl et al., 2002) was used to extract caudate and putamen volumes from each individual's structural image. We then used ANCOVA with age, gender, and intracranial volume (ICV) as covariates to test for group differences. Post hoc analysis was carried out on all measures with a significant group effect using a two-tailed t -test for all pairwise comparisons.

Image analysis was performed using SPM5 (Wellcome Trust Centre for Neuroimaging, University College London, UK, <http://www.fil.ion.ucl.ac.uk/spm/>). Functional image volumes were corrected for slice acquisition timing differences and rigid-body realigned to the initial volume of the first functional imaging scan, which was also a reference volume for MPRAGE co-registration. The MPRAGE volume segmentation into tissue classes generated nonlinear spatial transformation parameters enabling a conversion of functional image volumes to a common coordinate system (Montreal Neurological Institute; MNI). The resulting functional image volumes were resampled to 2 mm isotropic voxels and smoothed by a 6 mm full-width at half-maximum isotropic Gaussian kernel (Friston et al., 2000).

Brain responses to eye movements in each participant were modeled in a general linear model using SPM's canonical hemodynamic response function. Six movement parameters (three translations and three rotations) obtained during realignment were included as regressors to account for residual movement-induced effects. Serial correlations in the fMRI

time series were accounted for using an autoregressive model implementing classical (restricted maximum likelihood) parameter estimation. A high-pass filter with a cut-off of 1/128 Hz was applied to each voxel's time series to remove low frequency noise.

A first level model yielded contrast images for each participant that represented the mean BOLD response to three eye movement conditions: [correct AS > correct PS], [correct AS > incorrect AS], [incorrect AS > correct AS]. Incorrect AS trials included both self-corrected and uncorrected AS errors. BOLD activity associated with PS error trials was not modeled due to the very small number of errors made by all participants on the PS trials. Event onsets were defined for: 1) the preparation phase, which included the times of the instructional stimulus presentations; and 2) the response phase, which included the times of the peripheral stimulus presentations. This second approach was feasible since all participant reaction times were less than 750 msec. A second level, random effects analysis within the CAG− group was then used to identify activated regions that achieved a corrected cluster level significance ($p_{\text{cluster}} < 0.05$) under a voxel-wise height threshold of $p_{\text{voxel}} < 0.001$. The correction for multiple comparisons was performed within a whole-brain search volume common across all CAG− participants, with implicit rejection of cerebrospinal fluid voxels and exclusion of predominantly white matter voxels (probability of white matter from SPM segmentation > 0.70). Functional regions of interest (ROI) were defined for each significant cluster in the CAG− group under each eye movement condition described above. These ROIs were then used as the criterion to define “normal” activation in an unaffected, healthy sample. Mean activity within each ROI was extracted in all participants using the MarsBaR toolbox (<http://marsbar.sourceforge.net/>).

To compare the mean activation among the groups, it is important to account for the frequency of incorrect responses (Polli et al., 2005). Thus, a multiple linear regression model implemented in SAS version 9.13 was used to examine the relationship between mean activation and group, percentage of incorrect AS, and the interaction between group and percentage of incorrect AS. The preHD group was treated as the reference group in the model so that comparisons could be made between the CAG− and preHD groups and between the preHD and early HD groups, and a significance threshold of $p \leq 0.01$ was used because of the number of statistical tests performed. Age, gender, and education were included as covariates in the model when they had a significant effect on the model ($p \leq 0.01$).

Results

The demographics, TMS, neuropsychological test performance, and caudate and putamen volumes of the groups are shown in Table 1. The groups did not differ significantly in age, education, or gender, and there was no significant difference in the number of CAG repeats in the larger allele for the two CAG+ groups.

For most cognitive and motor measures, the preHD group was insignificantly different from the CAG− subjects, indicating that the preHD individuals were largely intact cognitively. The exception was a significantly faster movement time in the CAG− when compared to the preHD ($p \leq 0.05$). While the group average performance was not of such an extent as to suggest profound cognitive impairment within the early HD subjects, performances were significantly lower than those of the controls on measures of declarative memory (CLVT short and long delay recall trials, recognition discriminability), semantic organizational strategies during declarative learning (semantic clustering), and working memory (WAIS-III Letter Number Sequencing). The early HD group was also significantly slower than controls on measures of audio and visual reaction time, movement time, and alternate button tapping, and had a significantly higher TMS.. HD subjects were not, however, significantly different

in other measures of psychomotor speed (Trail Making Test A, Symbol-Digit Modalities) or executive function (Picture Arrangement, Verbal Fluency, Trail Making Test B, Stroop). Although in the anticipated direction, working memory required for WAIS-R mental arithmetic was also insignificantly different from the controls. Except for CVLT recognition discriminability and H-Scan movement time, those measures that differentiated the early HD group from the CAG− group also differentiated the early HD group from the preHD group. Consistent with previous studies (Aylward et al., 1994; Aylward et al., 1996; Brandt et al., 1995; Campodonico et al., 1998; Harris et al., 1992; Harris et al., 1999; Paulsen et al., 2006b; Rosas et al., 2001), the groups differed in caudate and putamen volumes bilaterally, and all three pairwise group comparisons were highly significant ($p \leq 0.001$).

Antisaccade task performance

ANCOVA was used to test for group differences in the percentages of incorrect PS and AS. A significant group effect was found for both the percentages of incorrect PS and AS ($p \leq 0.02$) (Figure 2). For the PS task, *post hoc* testing revealed that the CAG− group made significantly fewer errors than both CAG+ groups ($p \leq 0.01$), although the error rates were low overall. For the AS task, the early HD group made significantly more errors than the CAG− ($p = 0.002$) and preHD groups ($p = 0.05$), and there was a trend toward a difference between the CAG− and preHD groups ($p = 0.08$). More than 85% of AS errors were self-corrected in all groups, with no statistical difference between the groups ($p = 0.6$).

BOLD responses during AS task (Table 2, Figure 3).

Preparation, [correct AS > correct PS]—Eleven functional ROIs emerged as significant within the CAG− group (Figure 3A): Left and right DLPFC; left and right FEF; right anterior insula/frontal operculum; pre-SMA/dorsal ACC (dACC); left and right parietal eye field (PEF); left and right middle occipital gyrus (MOG); and right calcarine cortex.

When testing extracted mean activations in a multiple linear regression model, there was a significant effect of the percentage of incorrect AS in the left and right PEF ($p \leq 0.01$). In both cases, the BOLD response decreased as the percentage of incorrect AS responses increased.

Response, [correct AS > correct PS]—One functional ROI emerged as significant within the CAG− group in the right PEF (Figure 3B). There were no significant effects of group, percentage of incorrect AS, or their interaction in this ROI ($p \geq 0.3$, Table 2).

Preparation and response, [correct AS > incorrect AS]—No functional ROIs were defined as there were no regions that met our criteria in the CAG− group during either preparation or response.

Preparation, [incorrect AS > correct AS]—Two functional ROIs were significant within CAG− group (Figure 3C): Left and right calcarine cortices. There were no significant effects of group, percentage of incorrect AS, or their interaction in this ROI ($p \geq 0.03$, Table 2).

Response, [incorrect AS > correct AS]—Six functional ROIs emerged as significant within the CAG− group (Figure 3D): Left inferior frontal gyrus (IFG); pre-SMA; dACC; posterior cingulate cortex (PCC); right inferior parietal lobule (IPL); and left middle temporal gyrus (MTG).

A significant interaction between group and percentage of incorrect AS ($p \leq 0.01$) was found for the pre-SMA, dACC, and left MTG, with the same general pattern across these ROIs

(Table 2). In all cases the slope of the regression line was significantly different between the CAG− and preHD groups ($p \leq 0.003$), but not significantly different between the preHD and early HD groups ($p \geq 0.3$). Specifically, the BOLD response decreased as the percentage of incorrect AS increased in the CAG− group, but not in either of the CAG+ groups (Figures 4A: pre-SMA, and 4B: dACC).

A significant main effect of group was found for all six ROIs ($p \leq 0.002$). In all cases there was a significant difference between the CAG− and preHD groups ($p \leq 0.002$), with the BOLD response being greater in the CAG− group. Additionally, there was a significant difference between the preHD and early HD groups in the right IPL ($p = 0.01$), with the BOLD response greater in the preHD group.

Discussion

This is the first study to explore the BOLD fMRI response during an AS task in CAG+ individuals. The brain regions activated by AS (with a baseline of PS) within the CAG− group (Figure 3A) closely resemble those from previous studies of other populations (Anderson et al., 2008; Brown et al., 2006; Brown et al., 2007). In particular, our healthy control CAG− participants activated the DLPFC, FEF, PEF, insula, ACC, pre-SMA. The increased activation in the visual cortex was consistent with some studies (DeSouza et al., 2003), though other studies have found the opposite pattern (Dyckman et al., 2007; McDowell et al., 2005). During the response phase, activation was limited to the right PEF.

Activation related to AS errors (with a baseline of correct AS) was limited to visual cortex during preparation, but was more widespread during the response phase as evidenced by activation in the IFG, pre-SMA, ACC, PCC, IPL, and MTG. Previous studies have typically identified the ACC as being activated by errant saccades (Ford et al., 2005; Polli et al., 2005), and Polli et al. (2005) also found increased activation in the IFG, pre-SMA, and anterior insula. Similar error-monitoring activity in the ACC and in a more dorsal pre-SMA area has been described in non-saccadic tasks as well (Braver et al., 2001; Carter et al., 1998; Garavan et al., 2002; Hester et al., 2004; Kiehl et al., 2000; Menon et al., 2001; Rubia et al., 2003; Ullsperger & von Cramon, 2001; Ullsperger & von Cramon, 2003), suggesting that these areas are critical to the monitoring of errant behavior more generally.

Abnormal Activation in CAG+ Groups

Abnormalities in AS performance are sensitive markers of the premanifest period of HD (Becker et al., 2009; Blekher et al., 2006; Blekher et al., 2009). Given these previous findings, it would be reasonable to hypothesize that activation abnormalities would be found either in the preparation or response phase of an AS task (compared to a PS baseline). Our analysis found that cortical activation did distinguish between the CAG− group and a preHD group with very subtle quantitative motor signs, no obvious cognitive impairments, and emerging degeneration in the basal ganglia. However, the activation that distinguished between the groups was related to AS errors in the response phase (with a baseline of correctly executed AS). Specifically, activity was inversely related to the percentage of incorrect AS in the CAG− controls, but not in the preHD or early HD patients. In the case of the preHD, restriction of range cannot explain this difference, as the distribution of error rates was similar across both the preHD and the CAG− groups.

Activity in the ACC and pre-SMA (two of the five areas in which group $\times$ error interaction emerged) is likely to be particularly important. Both of these regions are repeatedly noted as sites of error-related activation, even in studies that do not involve ocular motor responses (Braver et al., 2001; Carter et al., 1998; Garavan et al., 2002; Hester et al., 2004; Kiehl et al., 2000; Menon et al., 2001; Rubia et al., 2003; Ullsperger & von Cramon, 2001; Ullsperger &

von Cramon, 2003). Furthermore, an event related potential study of error processing showed decreased error-related negativity during a Flanker task in patients with manifest HD (Beste et al., 2006). That is, brain responses to provoked behavioral errors were less prominent in HD subjects than in healthy controls—a result that mirrors our findings with AS errors.

Detection of errant behavior, or of events that violate expectations, is a necessary function for executive control, and the failure to process such errors will lead to poor adaptive behavior. The dopaminergic mesocorticolimbic brain circuit has received much attention for its hypothesized roles in reward related processing (Berridge, 2007; Schultz, 2006). However, a key element in this processing is the learned anticipation of outcomes based on experience, and the detection of events that do not conform to these learned expectations. For example, seminal work by Schultz and his collaborators (Schultz et al., 1997; Fiorillo et al., 2003) has shown that dopaminergic midbrain neurons increase their firing to unanticipated events and decrease their firing when an anticipated (cued) reward fails to arrive. Holroyd and Coles (2002) elaborate on such findings and hypothesize that medial frontal (ACC, pre-SMA) areas are signaled by this midbrain activity, provoking their engagement in error (deviant event) processing. Moreover, midbrain dopaminergic neurons are smaller and have a loss of tyrosine hydroxylase mRNA in HD (Yohrling et al., 2003). Thus, one potential explanation of our findings is an early loss of midbrain signaling in preHD patients.

Although both the ACC and pre-SMA are consistently implicated in error-related activation, there are also questions about the exact nature of each region's role in saccadic pathways. Compelling evidence from a rare patient with a small focal lesion to the left SEF, posterior to the pre-SMA (Husain et al., 2003; Parton et al., 2007), suggests SEF involvement in resolving conflict both from internally generated saccadic plans and during rule switching, but not in saccade generation *per se*. Similarly, functional imaging data show that activity in caudal SMA is related to sudden changes in planned saccades, while SEF activity is related to successfully implemented plan changes (Nachev et al., 2005). In primates, Schall and Boucher (2007) localized different populations of neurons in the ACC, pre-SMA, and adjacent SEF, wherein one population of neurons accounted for conflict-related activation, one for reinforcement-related activation, and one for error-related activation; thus, one region may play a role in multiple functions.

The ACC also has connections to important regions in saccadic pathways. In a meta-analysis of cingulate cortex, Beckmann et al. (2009) characterized a cluster in the dACC (their “cluster 4”) that overlaps with the region activated in our study by AS error trials, and which appears to mediate conflict resolution and error detection. Through tractography, Beckmann et al. (2009) showed this dACC region has white matter projections to prefrontal and premotor areas, as well as to the dorsal striatal regions that are an early site of degeneration in HD. Picard and Strick (2001) similarly identified an overlapping rostral cingulate motor zone in their meta-analysis as governing conflict and action selection.

Reinforcing our findings in HD, other disorders with presumed frontal and dopaminergic involvement also show functional brain abnormalities linked to errors in AS. In particular, similar error-related activation in the ACC was significantly reduced in a sample of schizophrenic patients (Polli et al., 2008) at peak coordinates [8, 13, 25]/[−13, 17, 25] that were quite close to our own [0, 16, 24]. Conversely, Thakkar et al. (2008) reported that in autism spectrum disorders there is dACC *hyperactivation* in response to correct AS, which was in turn related to rigid and repetitive behavior.

While pre-SMA and cingulate cortex have received the most attention for their roles in error-related activation, there is evidence that the IPL and IFG have related roles. Although we did not find a statistically significant interaction between group and percentage of AS errors in these regions, there was a trend ($p \leq 0.03$) that was similar to the activation patterns in the pre-SMA and dACC. A number of studies identify the IPL as playing an important role in the inhibition of an unwanted response (Braver et al., 2001; Brown et al., 2006; Garavan et al., 2002; Menon et al., 2001), while others have found that the IPL is activated in response to error commission (Hester et al., 2004; Rubia et al., 2003; Ullsperger & von Cramon, 2003). Interestingly, most of these studies (Brown et al., 2006; Garavan et al., 2002; Menon et al., 2001; Ullsperger & von Cramon, 2003) found evidence for asymmetric activation of the right IPL. Findings in the IFG have been reported even more rarely than in the IPL, but Hodgson et al. (2007) showed that lesions in ventrolateral frontal cortex (including IFG) predict impaired AS performance. There is also evidence of error-related activation in the IFG (Polli et al., 2005; Ullsperger & von Cramon, 2001). These previous findings and the similarity of the activation patterns between the IPL and IFG and the pre-SMA and dACC suggest that these regions may play a role in the error-related network along with pre-SMA and cingulate cortex, although more study is necessary.

This study was limited by the inability to dichotomize the preHD group into groups estimated to be closer to or farther from onset. Similarly, we were unable to use estimated time to onset (Langbehn et al., 2004) in our analysis because of the limited number of participants in the preHD group. As we focused our group analysis on those regions with significant activation in the CAG- healthy control group, we cannot make conclusions regarding the recruitment of other brain regions in an attempt to compensate for pathology in regions normally involved in task performance. However, our method did permit detecting deviant activation in CAG+ individuals in regions usually involved in task performance (though only decreased activation was found). Unlike prior studies, and contrary to expectations, there was only a marginal difference in the percentage of incorrect AS between the CAG- and preHD groups ($p=0.08$). However, it is likely that a smaller sample size and adaptation of the task to a more difficult mixed event-related design contributed to this finding.

In summary, this is the first study to examine the underlying functional neuroanatomy associated with AS performance in HD. While future studies, including longitudinal ones, are necessary to determine the temporal appearance of abnormalities within the context of disease progression, our data suggest that impaired AS performance may be related to abnormal cortical activity during the processing of saccadic errors. Importantly, deficits in this error-related activity appear to occur early in the disease process (i.e., in premanifest individuals with normal AS performance), pointing to a prodromal decline in an important supervisory executive network.

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References

- Ali FR, Michell AW, Barker RA, Carpenter RH. The use of quantitative oculometry in the assessment of Huntington's disease. *Experimental Brain Research*. 2006; 169:237–245.

- Amador N, Schlag-Rey M, Schlag J. Primate antisaccade. II. Supplementary eye field neuronal activity predicts correct performance. *Journal of Neurophysiology*. 2004; 91:1672–1689. [PubMed: 14645374]
- Anderson EJ, Husain M, Sumner P. Human intraparietal sulcus (IPS) and competition between exogenous and endogenous saccade plans. *Neuroimage*. 2008; 40:838–851. [PubMed: 18222708]
- Antoniades CA, Altham PM, Mason SL, Barker RA, Carpenter R. Saccadometry: a new tool for evaluating presymptomatic Huntington patients. *Neuroreport*. 2007; 18:1133–1136. [PubMed: 17589313]
- 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]
- Aylward EH, Codori AM, Barta PE, Pearlson GD, Harris GJ, Brandt J. Basal ganglia volume and proximity to onset in presymptomatic Huntington disease. *Archives of Neurology*. 1996; 53:1293–1296. [PubMed: 8970459]
- Becker W, Jurgens R, Kassubek J, Ecker D, Kramer B, Landwehrmeyer B. Eye-head coordination in moderately affected Huntington's Disease patients: do head movements facilitate gaze shifts? *Experimental Brain Research*. 2009; 192:97–112.
- Beckmann M, Johansen-Berg H, Rushworth MF. Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *The Journal of Neuroscience*. 2009; 29:1175–1190. [PubMed: 19176826]
- Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology*. 2007; 191:391–431. [PubMed: 17072591]
- Beste C, Saft C, Andrich J, Gold R, Falkenstein M. Error processing in Huntington's disease. *PLoS One*. 2006; 1:e86. [PubMed: 17183717]
- Blekher TM, Yee RD, Kirkwood SC, Hake AM, Stout JC, Weaver MR, et al. Oculomotor control in asymptomatic and recently diagnosed individuals with the genetic marker for Huntington's disease. *Vision Research*. 2004; 44:2729–2736. [PubMed: 15358067]
- Blekher T, Johnson SA, Marshall J, White K, Hui S, Weaver M, et al. Saccades in presymptomatic and early stages of Huntington disease. *Neurology*. 2006; 67:394–399. [PubMed: 16855205]
- Blekher T, Weaver M, Rupp J, Nichols WC, Hui SL, Gray J, et al. Multiple step pattern as a biomarker in Parkinson disease. *Parkinsonism and Related Disorders*. 2009; 15:506–510. [PubMed: 19211293]
- Bond CE, Hodes ME. Direct amplification of the CAG repeat of huntingtin without amplification of CCG. *Clinical Chemistry*. 1996; 42:773–774. [PubMed: 8653908]
- Brandt J, Bylsma FW, Aylward EH, Rothlind J, Gow CA. Impaired source memory in Huntington's disease and its relation to basal ganglia atrophy. *Journal of Clinical and Experimental Neuropsychology*. 1995; 17:868–877. [PubMed: 8847393]
- Braver TS, Barch DM, Gray JR, Molfese DL, Snyder A. Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. *Cerebral Cortex*. 2001; 11:825–836. [PubMed: 11532888]
- Brown MR, Goltz HC, Vilis T, Ford KA, Everling S. Inhibition and generation of saccades: rapid event-related fMRI of prosaccades, antisaccades, and nogo trials. *Neuroimage*. 2006; 33:644–659. [PubMed: 16949303]
- Brown MR, Vilis T, Everling S. Frontoparietal activation with preparation for antisaccades. *Journal of Neurophysiology*. 2007; 98:1751–1762. [PubMed: 17596416]
- Campodonico JR, Aylward E, Codori AM, Young C, Krafft L, Magdalinski M, et al. When does Huntington's disease begin? *Journal of the International Neuropsychological Society*. 1998; 4:467–473. [PubMed: 9745236]
- Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*. 1998; 280:747–749. [PubMed: 9563953]
- Clark VP, Lai S, Deckel AW. Altered functional MRI responses in Huntington's disease. *Neuroreport*. 2002; 13:703–706. [PubMed: 11973474]

- Cummings JL. Behavioral and psychiatric symptoms associated with Huntington's disease. *Advances in Neurology*. 1995; 65:179–186. [PubMed: 7872139]
- De Marchi N, Mennella R. Huntington's disease and its association with psychopathology. *Harvard Review of Psychiatry*. 2000; 7:278–289. [PubMed: 10689592]
- Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. The California Verbal Learning Test. New York: Psychological Corporation; 1987.
- DeSouza JF, Menon RS, Everling S. Preparatory set associated with pro-saccades and anti-saccades in humans investigated with event-related fMRI. *Journal of Neurophysiology*. 2003; 89:1016–1023. [PubMed: 12574477]
- Diamond R, White RF, Myers RH, Mastromauro C, Koroshetz WJ, Butters N, et al. Evidence of presymptomatic cognitive decline in Huntington's disease. *Journal of Clinical and Experimental Neuropsychology*. 1992; 14:961–975. [PubMed: 1452640]
- Dierks T, Linden DE, Hertel A, Gunther T, Lanfermann H, Niesen A, et al. Multimodal imaging of residual function and compensatory resource allocation in cortical atrophy: a case study of parietal lobe function in a patient with Huntington's disease. *Psychiatry Research*. 1999; 90:67–75. [PubMed: 10320212]
- Doricchi F, Perani D, Incoccia C, Grassi F, Cappa SF, Bettinardi V, et al. Neural control of fast-regular saccades and antisaccades: an investigation using positron emission tomography. *Experimental Brain Research*. 1997; 116:50–62.
- Duff K, Paulsen JS, Beglinger LJ, Langbehn DR, Stout JC. Psychiatric symptoms in Huntington's disease before diagnosis: the predict-HD study. *Biological Psychiatry*. 2007; 62:1341–1346. [PubMed: 17481592]
- Dyckman KA, Camchong J, Clementz BA, McDowell JE. An effect of context on saccade-related behavior and brain activity. *Neuroimage*. 2007; 36:774–784. [PubMed: 17478104]
- Ettinger U, Ffytche DH, Kumari V, Kathmann N, Reuter B, Zelaya F, et al. Decomposing the neural correlates of antisaccade eye movements using event-related fMRI. *Cerebral Cortex*. 2008; 18:1148–1159. [PubMed: 17728263]
- Fiorillo CD, Tobler PN, Schultz W. Discrete coding of reward probability and uncertainty by dopamine neurons. *Science*. 2003; 299:1898–1902. [PubMed: 12649484]
- Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002; 33:341–355. [PubMed: 11832223]
- Ford KA, Goltz HC, Brown MR, Everling S. Neural processes associated with antisaccade task performance investigated with event-related fMRI. *Journal of Neurophysiology*. 2005; 94:429–440. [PubMed: 15728770]
- Foroud T, Siemers E, Kleindorfer D, Bill DJ, Hodes ME, Norton JA, et al. Cognitive scores in carriers of Huntington's disease gene compared to noncarriers. *Annals of Neurology*. 1995; 37:657–664. [PubMed: 7755361]
- Friston KJ, Josephs O, Zarahn E, Holmes AP, Rouquette S, Poline J. To smooth or not to smooth? Bias and efficiency in fMRI time-series analysis. *Neuroimage*. 2000; 12:196–208. [PubMed: 10913325]
- Garavan H, Ross TJ, Murphy K, Roche RA, Stein EA. Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. *Neuroimage*. 2002; 17:1820–1829. [PubMed: 12498755]
- Gaymard B, Ploner CJ, Rivaud S, Vermersch AI, Pierrot-Deseilligny C. Cortical control of saccades. *Experimental Brain Research*. 1998; 123:159–163.
- Georgiou-Karistianis N, Sriharan A, Farrow M, Cunnington R, Stout J, Bradshaw J, et al. Increased cortical recruitment in Huntington's disease using a Simon task. *Neuropsychologia*. 2007; 45:1791–1800. [PubMed: 17321554]
- Golding CV, Danchaivijitr C, Hodgson TL, Tabrizi SJ, Kennard C. Identification of an oculomotor biomarker of preclinical Huntington disease. *Neurology*. 2006; 67:485–487. [PubMed: 16625001]
- Hahn-Barma V, Deweer B, Durr A, Dode C, Feingold J, Pillon B, et al. Are cognitive changes the first symptoms of Huntington's disease? A study of gene carriers. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1998; 64:172–177.

- Harris GJ, Codori AM, Lewis RF, Schmidt E, Bedi A, Brandt J. Reduced basal ganglia blood flow and volume in pre-symptomatic, gene-tested persons at-risk for Huntington's disease. *Brain*. 1999; 122:1667–1678. [PubMed: 10468506]
- Harris GJ, Pearlson GD, Peyser CE, Aylward EH, Roberts J, Barta PE, et al. Putamen volume reduction on magnetic resonance imaging exceeds caudate changes in mild Huntington's disease. *Annals of Neurology*. 1992; 31:69–75. [PubMed: 1531910]
- Hennenlotter A, Schroeder U, Erhard P, Haslinger B, Stahl R, Weindl A, et al. Neural correlates associated with impaired disgust processing in pre-symptomatic Huntington's disease. *Brain*. 2004; 127:1446–1453. [PubMed: 15090475]
- Hester R, Fassbender C, Garavan H. Individual differences in error processing: a review and reanalysis of three event-related fMRI studies using the GO/NOGO task. *Cerebral Cortex*. 2004; 14:986–994.
- Hicks SL, Robert MP, Golding CV, Tabrizi SJ, Kennard C. Oculomotor deficits indicate the progression of Huntington's disease. *Progress in Brain Research*. 2008; 171:555–558. [PubMed: 18718352]
- Hochschild, R. Intervention in the Aging Process, Part A: Quantitation, Epidemiology and Clinical Research. New York: Alan R. Liss; 1983. The H-scan: An instrument for the automatic measurement of physiological markers of aging; p. 113-125.
- Hodgson T, Chamberlain M, Parris B, James M, Gutowski N, Husain M, et al. The role of the ventrolateral frontal cortex in inhibitory oculomotor control. *Brain*. 2007; 130:1525–1537. [PubMed: 17452376]
- Hofmann N. Understanding the neuropsychiatric symptoms of Huntington's disease. *The Journal of Neuroscience Nursing*. 1999; 31:309–313. [PubMed: 10633308]
- Holroyd CB, Coles MG. The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychological Review*. 2002; 109:679–709. [PubMed: 12374324]
- Huntington Study Group. Unified Huntington's Disease Rating Scale-99. Rochester NY: Huntington Study Group; 1999.
- Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 1993; 72:971–983. [PubMed: 8458085]
- Husain M, Parton A, Hodgson TL, Mort D, Rees G. Self-control during response conflict by human supplementary eye field. *Nature Neuroscience*. 2003; 6:117–118.
- Hutton SB. Cognitive control of saccadic eye movements. *Brain and Cognition*. 2008; 68:327–340. [PubMed: 19028265]
- Jack CR Jr, Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, et al. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. *Journal of Magnetic Resonance Imaging*. 2008; 27:685–691. [PubMed: 18302232]
- Kiehl KA, Liddle PF, Hopfinger JB. Error processing and the rostral anterior cingulate: an event-related fMRI study. *Psychophysiology*. 2000; 37:216–223. [PubMed: 10731771]
- Kim JS, Reading SA, Brashers-Krug T, Calhoun VD, Ross CA, Pearlson GD. Functional MRI study of a serial reaction time task in Huntington's disease. *Psychiatry Research*. 2004; 131:23–30. [PubMed: 15246452]
- Kirkwood SC, Siemers E, Bond C, Conneally PM, Christian JC, Foroud T. Confirmation of subtle motor changes among presymptomatic carriers of the Huntington disease gene. *Archives of Neurology*. 2000a; 57:1040–1044. [PubMed: 10891987]
- Kirkwood SC, Siemers E, Hodes ME, Conneally PM, Christian JC, Foroud T. Subtle changes among presymptomatic carriers of the Huntington's disease gene. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2000b; 69:773–779.
- Kirkwood SC, Siemers E, Viken R, Hodes ME, Conneally PM, Christian JC, et al. Longitudinal personality changes among presymptomatic Huntington disease gene carriers. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*. 2002; 15:192–197.

- Kloppel S, Draganski B, Siebner HR, Tabrizi SJ, Weiller C, Frackowiak RS. Functional compensation of motor function in pre-symptomatic Huntington's disease. *Brain*. 2009; 132:1624–1632. [PubMed: 19369489]
- Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clinical Genetics*. 2004; 65:267–277. [PubMed: 15025718]
- Lasker AG, Zee DS. Ocular motor abnormalities in Huntington's disease. *Vision Research*. 1997; 37:3639–3645. [PubMed: 9425536]
- Lawrence AD, Hodges JR, Rosser AE, Kershaw A, ffrench-Constant C, Rubinsztein DC, et al. Evidence for specific cognitive deficits in preclinical Huntington's disease. *Brain*. 1998; 121:1329–1341. [PubMed: 9679784]
- Leigh RJ, Newman SA, Folstein SE, Lasker AG, Jensen BA. Abnormal ocular motor control in Huntington's disease. *Neurology*. 1983; 33:1268–1275. [PubMed: 6225033]
- MacDonald AW III, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*. 2000; 288:1835–1838. [PubMed: 10846167]
- Matsuda T, Matsuura M, Ohkubo T, Ohkubo H, Matsushima E, Inoue K, et al. Functional MRI mapping of brain activation during visually guided saccades and antisaccades: cortical and subcortical networks. *Psychiatry Research*. 2004; 131:147–155. [PubMed: 15313521]
- McDowell JE, Brown GG, Paulus M, Martinez A, Stewart SE, Dubowitz DJ, et al. Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. *Biological Psychiatry*. 2002; 51:216–223. [PubMed: 11839364]
- McDowell JE, Dyckman KA, Austin BP, Clementz BA. Neurophysiology and neuroanatomy of reflexive and volitional saccades: evidence from studies of humans. *Brain and Cognition*. 2008; 68:255–270. [PubMed: 18835656]
- McDowell JE, Kissler JM, Berg P, Dyckman KA, Gao Y, Rockstroh B, et al. Electroencephalography/magnetoencephalography study of cortical activities preceding prosaccades and antisaccades. *Neuroreport*. 2005; 16:663–668. [PubMed: 15858402]
- Menon V, Adelman NE, White CD, Glover GH, Reiss AL. Error-related brain activation during a Go/NoGo response inhibition task. *Human Brain Mapping*. 2001; 12:131–143. [PubMed: 11170305]
- Milea D, Lobel E, Lehericy S, Pierrot-Deseilligny C, Berthoz A. Cortical mechanisms of saccade generation from execution to decision. *Annals of the New York Academy of Sciences*. 2005; 1039:232–238. [PubMed: 15826977]
- Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*. 2001; 24:167–202.
- Morris M. Dementia and cognitive changes in Huntington's disease. *Advances in Neurology*. 1995; 65:187–200. [PubMed: 7872140]
- Muri RM, Heid O, Nirkko AC, Ozdoba C, Felblinger J, Schroth G, et al. Functional organisation of saccades and antisaccades in the frontal lobe in humans: a study with echo planar functional magnetic resonance imaging. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1998; 65:374–377.
- Nachev P, Rees G, Parton A, Kennard C, Husain M. Volition and conflict in human medial frontal cortex. *Current Biology*. 2005; 15:122–128. [PubMed: 15668167]
- Parton A, Nachev P, Hodgson TL, Mort D, Thomas D, Ordidge R, et al. Role of the human supplementary eye field in the control of saccadic eye movements. *Neuropsychologia*. 2007; 45:997–1008. [PubMed: 17069864]
- Paulsen JS, Hayden M, Stout JC, Langbehn DR, Aylward E, Ross CA, et al. Preparing for preventive clinical trials: the Predict-HD study. *Archives of Neurology*. 2006a; 63:883–890. [PubMed: 16769871]
- Paulsen JS, Magnotta VA, Mikos AE, Paulson HL, Penziner E, Andreasen NC, et al. Brain structure in preclinical Huntington's disease. *Biological Psychiatry*. 2006b; 59:57–63. [PubMed: 16112655]
- 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.

- Paulsen JS, Zimbelman JL, Hinton SC, Langbehn DR, Leveroni CL, Benjamin ML, et al. fMRI biomarker of early neuronal dysfunction in presymptomatic Huntington's Disease. *American Journal of Neuroradiology*. 2004; 25:1715–1721. [PubMed: 15569736]
- Peltsch A, Hoffman A, Armstrong I, Pari G, Munoz DP. Saccadic impairments in Huntington's disease. *Experimental Brain Research*. 2008; 186:457–469.
- Penney JB Jr, Young AB, Shoulson I, Starosta-Rubenstein S, Snodgrass SR, Sanchez-Ramos J, et al. Huntington's disease in Venezuela: 7 years of follow-up on symptomatic and asymptomatic individuals. *Movement Disorders*. 1990; 5:93–99. [PubMed: 2139171]
- Picard N, Strick PL. Imaging the premotor areas. *Current Opinion in Neurobiology*. 2001; 11:663–672. [PubMed: 11741015]
- Pierrot-Deseilligny C, Muri RM, Ploner CJ, Gaymard B, Demeret S, Rivaud-Pechoux S. Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. *Brain*. 2003; 126:1460–1473. [PubMed: 12764065]
- Pierrot-Deseilligny C, Rivaud S, Gaymard B, Agid Y. Cortical control of reflexive visually-guided saccades. *Brain*. 1991; 114:1473–1485. [PubMed: 2065261]
- Pierrot-Deseilligny C, Rivaud-Pechoux S. Contribution of oculomotor examination for the etiological diagnosis of parkinsonian syndromes. *Revue Neurologique*. 2003; 159:3S75–3S81. [PubMed: 12773891]
- Polli FE, Barton JJ, Cain MS, Thakkar KN, Rauch SL, Manoach DS. Rostral and dorsal anterior cingulate cortex make dissociable contributions during antisaccade error commission. *Proceedings of the National Academy of Sciences of the United States of America*. 2005; 102:15700–15705. [PubMed: 16227444]
- Polli FE, Barton JJ, Thakkar KN, Greve DN, Goff DC, Rauch SL, et al. Reduced error-related activation in two anterior cingulate circuits is related to impaired performance in schizophrenia. *Brain*. 2008; 131:971–986. [PubMed: 18158315]
- Reading SA, Dziorny AC, Peroutka LA, Schreiber M, Gourley LM, Yallapragada V, et al. Functional brain changes in presymptomatic Huntington's disease. *Annals of Neurology*. 2004; 55:879–883. [PubMed: 15174024]
- Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual & Motor Skills*. 1958; 8:271–276.
- Rosas HD, Goodman J, Chen YI, Jenkins BG, Kennedy DN, Makris N, et al. Striatal volume loss in HD as measured by MRI and the influence of CAG repeat. *Neurology*. 2001; 57:1025–1028. [PubMed: 11571328]
- Rosenberg NK, Sorensen SA, Christensen AL. Neuropsychological characteristics of Huntington's disease carriers: a double blind study. *Journal of Medical Genetics*. 1995; 32:600–604. [PubMed: 7473650]
- Rubia K, Smith AB, Brammer MJ, Taylor E. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage*. 2003; 20:351–358. [PubMed: 14527595]
- Rupp J, Blekher TM, Jackson JG, Beristain X, Marshall J, Hui SL, et al. Progression in prediagnostic Huntington disease. *Journal of Neurology, Neurosurgery & Psychiatry*. 2010; 81:379–384.
- Saft C, Schuttkie A, Beste C, Andrich J, Heindel W, Pfeleiderer B. fMRI reveals altered auditory processing in manifest and premanifest Huntington's disease. *Neuropsychologia*. 2008; 46:1279–1289. [PubMed: 18221758]
- Schall JD, Boucher L. Executive control of gaze by the frontal lobes. *Cognitive, Affective, and Behavioral Neuroscience*. 2007; 7:396–412.
- Schlag-Rey M, Amador N, Sanchez H, Schlag J. Antisaccade performance predicted by neuronal activity in the supplementary eye field. *Nature*. 1997; 390:398–401. [PubMed: 9389478]
- Schultz W. Behavioral theories and the neurophysiology of reward. *Annual Review of Psychology*. 2006; 57:87–115.
- Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science*. 1997; 275:1593–1599. [PubMed: 9054347]

- Siemers E, Foroud T, Bill DJ, Sorbel J, Norton JA Jr, Hodes ME, et al. Motor changes in presymptomatic Huntington disease gene carriers. *Archives of Neurology*. 1996; 53:487–492. [PubMed: 8660148]
- Smith, A. Symbol-Digit Modalities Test (SDMT) manual. Los Angeles, CA: Western Psychological Services; 1982.
- Stout JC, Weaver M, Solomon AC, Queller S, Hui S, Johnson SA, et al. Are cognitive changes progressive in prediagnostic HD? *Cognitive & Behavioral Neurology*. 2007; 20:212–218. [PubMed: 18091069]
- Stroop JR. Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*. 1935; 18:643–662.
- Sweeney JA, Mintun MA, Kwee S, Wiseman MB, Brown DL, Rosenberg DR, et al. Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *Journal of Neurophysiology*. 1996; 75:454–468. [PubMed: 8822570]
- Thakkar KN, Polli FE, Joseph RM, Tuch DS, Hadjikhani N, Barton JJ, et al. Response monitoring, repetitive behaviour and anterior cingulate abnormalities in autism spectrum disorders (ASD). *Brain*. 2008; 131:2464–2478. [PubMed: 18550622]
- Thiruvady DR, Georgiou-Karistianis N, Egan GF, Ray S, Sritharan A, Farrow M, et al. Functional connectivity of the prefrontal cortex in Huntington's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2007; 78:127–133.
- Ullsperger M, von Cramon DY. Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *Neuroimage*. 2001; 14:1387–1401. [PubMed: 11707094]
- Ullsperger M, von Cramon DY. Error monitoring using external feedback: specific roles of the habenular complex, the reward system, and the cingulate motor area revealed by functional magnetic resonance imaging. *The Journal of Neuroscience*. 2003; 23:4308–4314. [PubMed: 12764119]
- Vecsei L, Beal MF. Huntington's disease, behavioral disturbances, and kynurenines: preclinical findings and therapeutic perspectives. *Biological Psychiatry*. 1996; 39:1061–1063. [PubMed: 8780845]
- Wechsler, D. Wechsler Adult Intelligence Scale. 3. San Antonio TX: Psychological Corporation; 1997.
- Wechsler, D. Wechsler Adult Intelligence Scale - Revised. New York: Psychological Corp; 1981.
- Witjes-Ane MN, Mertens B, van Vugt JP, Bachoud-Levi AC, van Ommen GJ, Roos RA. Longitudinal evaluation of "presymptomatic" carriers of Huntington's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*. 2007; 19:310–317. [PubMed: 17827417]
- Wolf RC, Sambataro F, Vasic N, Schonfeldt-Lecuona C, Ecker D, Landwehrmeyer B. Altered frontostriatal coupling in pre-manifest Huntington's disease: effects of increasing cognitive load. *European Journal of Neurology*. 2008a; 15:1180–1190. [PubMed: 18754766]
- Wolf RC, Sambataro F, Vasic N, Schonfeldt-Lecuona C, Ecker D, Landwehrmeyer B. Aberrant connectivity of lateral prefrontal networks in presymptomatic Huntington's disease. *Experimental Neurology*. 2008b; 213:137–144. [PubMed: 18588876]
- Wolf RC, Vasic N, Schonfeldt-Lecuona C, Landwehrmeyer GB, Ecker D. Dorsolateral prefrontal cortex dysfunction in presymptomatic Huntington's disease: evidence from event-related fMRI. *Brain*. 2007; 130:2845–2857. [PubMed: 17855375]
- Yohrling GJ, Jiang GC, DeJohn MM, Miller DW, Young AB, Vrana KE, et al. Analysis of cellular, transgenic and human models of Huntington's disease reveals tyrosine hydroxylase alterations and substantia nigra neuropathology. *Brain Research. Molecular Brain Research*. 2003; 119:28–36. [PubMed: 14597227]
- Zimelman JL, Paulsen JS, Mikos A, Reynolds NC, Hoffmann RG, Rao SM. fMRI detection of early neural dysfunction in preclinical Huntington's disease. *Journal of the International Neuropsychological Society*. 2007; 13:758–769. [PubMed: 17697407]

Figure 1. The fMRI task protocol

A central circle turns green (G) for a PS (**A**) and red (R) for an AS (**B**) (panel 1). The circle is extinguished as a horizontal peripheral square (stimulus) appears. For a PS, participants look at the square; for an AS, participants look directly opposite the square (panel 2). The central circle then reappears (panel 3), upon which participants fixate while awaiting the next instruction. Dotted circle indicates the correct eye position (shown here for illustration purposes, but not visible to participants during testing). s: seconds.

Figure 2. Performance on the PS and AS tasks

For the PS task, the CAG- group made significantly fewer errors than the preHD and early HD group. For the AS task, the early HD group made significantly more errors than the CAG- and preHD groups. Error bars indicate standard error. AS: antisaccade; PS: prosaccade.

Figure 3. Functional ROIs defined in CAG- participants for each saccade comparison

(A) Significant activation during preparation for the [correct AS > correct PS] comparison in the bilateral DLPFC, FEF, PEF, and MOG; the right insula and calcarine cortex; and the pre-SMA/dACC. (B) Significant response-related activation for [correct AS > correct PS] in the right PEF. (C) Significant activation during preparation for the [incorrect AS > correct AS] comparison in the bilateral calcarine cortices. (D) Significant activation during responses for [incorrect AS > correct AS] in the left IFG, pre-SMA, dACC, PCC, right IPL, and left MTG. AS: antisaccade; dACC: dorsal anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; FEF: frontal eye fields; IFG: inferior frontal gyrus; IPL: inferior parietal lobule; L: left; MOG: middle occipital gyrus; MTG: middle temporal gyrus; PCC: posterior cingulate cortex; PEF: parietal eye fields; pre-SMA: pre-supplementary motor area.

Figure 4. BOLD response as a function of the percentage of incorrect AS

In the pre-SMA (**A**) and dACC (**B**) [incorrect AS > correct AS] activation is dependent on the percentage of incorrect AS in the CAG- group but not in either CAG+ group; the CAG- group has greater overall activation. Furthermore, there are no differences in activation between the preHD and early HD groups. AS: antisaccade; BOLD: blood oxygenation level dependent; dACC: dorsal anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; MOG: middle occipital gyrus; pre-SMA: pre-supplementary motor area; PS: prosaccade.

Table 1

Participant Demographics and Neuropsychological Characterization

		CAG- (n=12)	PreHD (n=10)	Early HD (n=8)
Age (years)		46.4 ± 11.4	44.2 ± 15.2	42.8 ± 13.4
Education (years)		14.8 ± 2.1	15.7 ± 3.2	15.8 ± 4.4
Gender (M:F)		5:7	4:6	3:5
# of CAG repeats in larger allele		20.2 ± 3.3	42.2 ± 2.1	45.5 ± 5.1
Caudate (mm ³)	Left^{a,b,c}	3437 ± 400	3151 ± 251	2384 ± 463
	Right^{a,b,c}	3523 ± 439	3215 ± 343	2541 ± 368
Putamen (mm ³)	Left^{a,b,c}	5448 ± 885	4925 ± 785	3644 ± 720
	Right^{a,b,c}	5116 ± 701	4679 ± 893	3359 ± 616
UHDRS				
Symbol Digit Modalities Test (correct/90 s)		51.2 ± 8.8	48.8 ± 13.3	41.8 ± 9.0
Total Motor Score ^{b,c} (min, max)		4.25 ± 4.2 (0, 12)	7.4 ± 4.5 (3, 16)	28.4 ± 11.5 (15, 43)
Verbal Fluency		41.0 ± 16.5	41.5 ± 11.6	37.3 ± 17.4
H-Scan				
Audio Reaction Time (s) ^{b,c}		0.16 ± 0.02	0.16 ± 0.02	0.20 ± 0.03
Visual Reaction Time (s) ^{b,c}		0.22 ± 0.03	0.23 ± 0.03	0.27 ± 0.03
Decision Reaction Time (s)		0.26 ± 0.03	0.28 ± 0.06	0.32 ± 0.06
Movement Time (s) ^{a,b}		0.14 ± 0.03	0.16 ± 0.05	0.19 ± 0.05
Decision Movement Time (s)		0.11 ± 0.02	0.13 ± 0.05	0.13 ± 0.04
Alternate Button Tapping (s/30 round trips) ^{b,c}		17.3 ± 3.0	18.1 ± 3.0	21.9 ± 4.1
WAIS-R				
Arithmetic (total score, raw)		13.5 ± 3.8	12.9 ± 3.6	11.4 ± 4.0
Picture Arrangement (total score, raw)		14.7 ± 4.4	15.7 ± 2.7	13.4 ± 3.7
WAIS-III				
Letter-Number Sequencing (total score, raw) ^{b,c}		11.8 ± 1.5	11.9 ± 2.3	9.3 ± 3.1
CVLT				
Immediate Free Recall (number of words in 5 attempts)		62.3 ± 8.1	60.6 ± 9.0	52.8 ± 15.1
Semantic Clustering (raw score) ^{b,c}		3.9 ± 3.0	4.0 ± 2.6	2.0 ± 2.5
Recognition Discriminability (raw score) ^b		3.7 ± 0.3	3.4 ± 0.6	3.0 ± 0.5
Short Delay Free Recall (number of words) ^{b,c}		13.8 ± 1.8	13.1 ± 2.2	10.8 ± 3.5
Short Delay Cued Recall (number of words)		14.5 ± 1.4	13.2 ± 2.2	12.4 ± 2.6
Long Delay Free Recall (number of words) ^{b,c}		14.2 ± 1.5	13.3 ± 2.1	10.6 ± 2.6
Long Delay Cued Recall (number of words)		14.7 ± 1.1	13.5 ± 2.0	12.4 ± 2.3
Trail Making Test				
Part A (s)		28.2 ± 10.4	25.2 ± 6.7	32.9 ± 13.3
Part B (s)		58.4 ± 19.5	59.1 ± 15.7	69.6 ± 37.9
Stroop				
Color Naming (correct/45 s)		76.9 ± 16.7	85.3 ± 10.3	70.5 ± 14.6

	CAG- (n=12)	PreHD (n=10)	Early HD (n=8)
Word Reading (correct/45 s)	97.0 ± 23.9	103.9 ± 15.4	94.5 ± 14.2
Interference (correct/45 s)	47.2 ± 10.7	48.9 ± 9.2	43 ± 8.9

Mean ± SD shown unless otherwise stated. Post hoc testing indicates a significant difference ($p \leq 0.05$) between

^a CAG- and preHD,

^b CAG- and early HD, and

^c preHD and early HD.

CVLT: California Verbal Learning Test; mm: millimeters; s: seconds; UHDRS: Unified Huntington Disease Rating Scale; WAIS-III: Weschler Adult Intelligence Scale - Third Edition; WAIS-R: Weschler Adult Intelligence Scale - Revised.

Table 2

ROI locations and sizes as defined by CAG- controls, and non-zero linear regression parameter estimates and *p* values (with preHD as the reference group) from the modeling of ROI-extracted mean activations.

Contrast/ROI		Parameter Estimates (<i>p</i> values)			
Size (mm ³)	Peak MINI Location (x,y,z)	Group		Percentage of Incorrect AS	Group × Percentage of Incorrect AS
		PreHD vs CAG−	PreHD vs Early HD		
Correct AS > Correct PS					
Preparation					
Left DLPFC	464	−30, 44, 34			
Right DLPFC	1480	28, 44, 22			
Left FEF	3184	−18, 0, 66			
Right FEF	3696	18, 4, 62			
Right Anterior Insula/Frontal Operculum	640	38, 20, 4			
Pre-SMA/dACC	6776	−4, 10, 50			
Left PEF *	1584	−20, −58, 52		−0.03 (0.01)	
Right PEF *	4384	18, −66, 52		−0.03 (0.0008)	
Left MOG	480	−26, −80, 20			
Right MOG	1024	30, −80, 20			
Right Calcarine Gyrus	1240	12, −80, 6			
Stimulus-response					
Right PEF	1136	8, −60, 54			
Incorrect AS > Correct AS					
Preparation					
Left Calcarine Gyrus	2912	−14, −54, 8			
Right Calcarine Gyrus	1304	20, −54, 14			
Stimulus-response					
Left IFG	632	−42, 20, −18	5.40 (0.001)		
Pre-SMA	1704	16, 16, 58	4.93 (0.0001)		−0.13 (0.003)
dACC	1224	0, 16, 24	6.20 (0.0002)		−0.18 (0.003)

	Contrast/ROI	Parameter Estimates (<i>p</i> values)				
		Size (mm ³)	Peak MNI Location (x,y,z)	Group		Percentage of Incorrect AS
				PreHD vs CAG-	PreHD vs Early HD	
PCC		664	2, -14, 36	4.53 (0.002)		
Right IPL		456	50, -42, 38	2.68 (0.0007)	-2.37 (0.01)	
Left MTG		720	-60, -34, -4	4.56 (<0.0001)		
						-0.11 (0.001)

Covariates that remained in the model due to a significant effect (*p*<0.05) are indicated by superscripts:

* education; dACC: dorsal anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; FEF: frontal eye field; IFG: inferior frontal gyrus; IPL: inferior parietal lobule; mm: millimeters; MOG: middle occipital gyrus; MTG: middle temporal gyrus; PCC: posterior cingulate cortex; PEF: parietal eye field; pre-SMA: pre-supplementary motor area.