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# Emotion perception and electrophysiological correlates in Huntington's disease

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# Emotion perception and electrophysiological correlates in Huntington's disease

## Abstract

**Objective** This study aimed to characterise, emotion perception deficits in symptomatic Huntington's disease (HD) via the use of event-related potentials (ERPs). **Methods** ERP data were recorded during a computerised facial expression task in 11 HD participants and 11 matched controls. Expression (scrambled, neutral, happy, angry, disgust) classification accuracy and intensity were assessed. Relationships between ERP indices and clinical disease characteristics were also examined. **Results** Accuracy was significantly lower for HD relative to controls, due to reduced performance for neutral, angry and disgust (but not happy) faces. Intensity ratings did not differ between groups. HD participants displayed significantly reduced visual processing amplitudes extending across pre-face (P100) and face-specific (N170) processing periods, whereas subsequent emotion processing amplitudes (N250) were similar across groups. Face-specific and emotion-specific derivations of the N170 and N250 ('neutral minus scrambled' and 'each emotion minus neutral', respectively) did not differ between groups. **Conclusions** Our data suggest that the facial emotion recognition performance deficits in HD are primarily related to neural degeneration underlying 'generalised' visual processing, rather than face or emotional specific processing. **Significance** ERPs are a useful tool to separate functionally discreet impairments in HD, and provide an important avenue for biomarker application that could more-selectively track disease progression.

## Keywords

Huntington's disease, emotion perception, electroencephalography (EEG), event related potential (ERP)

## Disciplines

Medicine and Health Sciences

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## **Emotion Perception and Electrophysiological Correlates in Huntington's Disease**

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**Key Words:** Huntington's disease, emotion perception, electroencephalography (EEG), event related potential (ERP).

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### **Highlights:**

- This study confirms an emotional face processing deficit in Huntington's disease (HD)
- This study demonstrates the electrophysiological underpinnings of the emotional processing deficit in HD

- This study suggests that the emotional processing deficit in HD is caused by a generic visual processing deficit

**Word Counts:** Abstract 200, Article body 4,494

## **Abstract**

**Objective:** This study aimed to characterise, emotion perception deficits in symptomatic Huntington's disease (HD) via the use of event-related potentials (ERPs).

**Methods:** ERP data were recorded during a computerised facial expression task in 11 HD participants and 11 matched controls. Expression (scrambled, neutral, happy, angry, disgust) classification accuracy and intensity were assessed. Relationships between ERP indices and clinical disease characteristics were also examined.

**Results:** Accuracy was significantly lower for HD relative to controls, due to reduced performance for neutral, angry and disgust (but not happy) faces. Intensity ratings did not differ between groups. HD participants displayed significantly reduced visual processing amplitudes extending across pre-face (P100) and face-specific (N170) processing periods, whereas subsequent emotion processing amplitudes (N250) were similar across groups. Face-specific and emotion-specific derivations of the N170 and N250 ('neutral minus scrambled' and 'each emotion minus neutral', respectively) did not differ between groups.

**Conclusions:** Our data suggest that the facial emotion recognition performance deficits in HD are primarily related to neural degeneration underlying 'generalised' visual processing, rather than face or emotional specific processing.

**Significance:** ERP's are a useful tool to separate functionally discreet impairments in HD, and provide an important avenue for biomarker application that could more-selectively track disease progression.

## Introduction

With the development of up and coming drug trials in Huntington's disease (HD), there is an urgent need to identify potential biomarkers that can sensitively track disease progression and importantly that are functionally relevant (Georgiou-Karistianis et al., 2013a, Georgiou-Karistianis et al., 2013b, Georgiou-Karistianis et al., 2013c). Previous studies have identified emotion perception deficits in premanifest HD (pre-HD) individuals 15 years prior to estimated onset (and in the absence of cognitive change), suggesting that emotion alterations may be one of the earliest quantifiable behavioural changes observed preclinically (Gray et al., 1997, Stout et al., 2011). To this end further investigation of emotion perception in HD may offer new insights regarding early functional changes, which could provide an important avenue for biomarker development.

Specific emotion perception deficits in HD were initially documented by Sprengelmeyer et al., (1996), who used six basic emotions (happiness, sadness, surprise, anger, disgust, fear) and showed that of these, perception of disgust was the most severely impaired. Other published studies have reported similar findings in HD (Hennenlotter et al., 2004, Montagne et al., 2006). However, studies with differing findings questioned the degree of impairment for disgust and implicated a universal deficit across basic negative emotions, primarily anger and fear (Calder et al., 2010, Henley et al., 2008, Milders et al., 2003, Snowden et al., 2008). Negative behavioural symptoms include apathy, irritability and an increased incidence of depression, whilst there is an additional decrease in self-care and personal hygiene (Rosenblatt, 2007, Snowden et al., 2008). These types of behavioural changes are likely the result of basal ganglia dysfunction together with alterations in prefrontal function (Georgiou-Karistianis et al., 2013a, Georgiou-Karistianis et al., 2013c, Gray et al., 2013). Conversely their origins may lie in the neural structures underlying perceptual and emotional processing of facial expression stimuli (Gray et al., 2007, Henson et al., 2003). Self-report questionnaires provide insight

into self-assessed emotional responsiveness, which in some HD studies have shown trends and significance for lower self-assessed emotion (Sprengelmeyer et al., 1996). Ratings of emotion intensities and perceived emotionality have not been previously investigated in HD and may further substantiate a broader emotional effect that is not specifically a perceptual problem.

Further understanding of the neural substrates and circuitry involved in emotion perception may provide insight into the behavioural and psychiatric symptoms of HD. A sensitive technique that can examine emotion perception in HD is event related potential (ERP) methodology, a derivation of the electroencephalography (EEG). To our knowledge there are currently no published ERP emotion perception studies in HD. The use of ERPs has however been implemented in other areas of HD research (for review see Nguyen et al., 2010), where attenuated amplitudes (reduced coherent neural firing rates) across a range of ERP indices have been reported (e.g., Antal et al., 2003, Beste et al., 2008, Munte et al., 1997). Emotional faces can similarly be studied using ERPs. Of particular relevance is that following more generic visual processing (0-100ms), specific structural encoding of the face occurs at circa 170ms (termed the N170), followed by valance-dependent processing of the face at circa 250ms (termed the N250). The N170 is primarily contributed to by fusiform area (FFA) and superior temporal gyrus (STG), whereas the N250 has less discrete sources (Bentin et al., 1996, Campanella et al., 2002, Henson et al., 2003). Assessment of the ERPs underlying emotional face processing can thus help delineate the disparate processes involved in this ecologically relevant function, and in particular can separate them from the motor-related functions required in performance measures such as reaction time and accuracy.

This study aimed to investigate for the first time the relationship between emotion perception deficits and underlying neurophysiological indices in symptomatic HD participants. We adopted a similar behavioural paradigm to that used previously (see

Johnson et al., 2007), with negative (disgust and anger), neutral and positive (happy) emotion types to further substantiate whether deficits in emotion perception are disgust-specific or generalise to another negative emotion (anger). Moreover, by measuring ERPs, this study also characterised the nature of the reported neurophysiological modulation in HD in response to emotional faces. Consistent with previous research it was hypothesised that HD participants would display decreased *accuracy* of facial expression identification, particularly for negative emotions (anger and disgust), compared with controls. Further, and based on the assumption that the poorer accuracy would correspond to 'less' emotional processing, it was hypothesised that the (subjective) emotional *intensities* of these expressions would be reduced in HD compared to controls, particularly for negative expressions. Finally, given that the literature suggests that the emotional face processing deficit in HD is specific to negative expressions, it was hypothesised that HD participants would display attenuated *ERP amplitudes* relative to controls for the emotional decoding index (N250) but not the structural encoding index (N170), particularly for negative expressions.

## **Method**

### *Participants*

Twenty-two right handed [Edinburgh Handedness Inventory, EHI (Oldfield, 1970)], individuals aged 40 to 70 participated in the study. There were 11 HD participants (eight male, three female), all clinically diagnosed by a qualified neurologist (A.C). Disease progression was assessed via the Unified Huntington's Disease Rating Scale (UHDRS) motor examination (Huntington Study Group, 1996). Symptomatic HD participants<sup>1</sup> had a UHDRS motor score of >5. HD participants had previously undertaken genetic testing and

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<sup>1</sup> UHDRS motor scores for two HD participants were not available.



CAG repeat length ranged from 40-47<sup>2</sup>. The HD sample was age, gender and IQ [National Adult Reading Test 2<sup>nd</sup> edition, NART-2 (Nelson et al., 1992)] matched to control participants.

In order to characterise the groups, participants completed a battery of neurocognitive scales and questionnaires, which were compared using independent samples Mann-Whitney U tests [Beck Depression Inventory – 2<sup>nd</sup> Edition, BDI-II (Beck et al., 1961), with HD participants scoring higher than control ( $p < 0.001$ ); Hospital Anxiety and Depression Scale, HADS (Zigmond et al., 1983), with HD participants scoring higher than control on depression ( $p=0.036$ ) but not the anxiety ( $p=0.17$ ) subscale; Positive and Negative Affect Schedule, PANAS (Watson et al., 1988), with reduced Positive (PA.;  $p=0.03$ ) and a trend to increased Negative Affect (NA;  $p=0.07$  in the HD group); Olatunji et al. (2007) modification of the Disgust Scale-Revised (DS-R), with HD scoring higher on ‘animal’ ( $p=0.03$ ) and a trend towards higher scores on ‘contamination’ ( $p=0.060$ ) subsets, but no difference on ‘core’ ( $p=0.188$ ) compared to controls; Emotion Regulation Questionnaire, ERQ (Gross et al., 2003), where no group differences were found; and Orientations to Happiness Measure, OTH (Peterson et al., 2005), where no group differences were found]. See Table 1 for demographic, clinical data, and scores on all scales.

The current study was approved by the Monash University Human Ethics Board and each participant gave informed, written consent.

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Table 1 about here

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### *Procedure*

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<sup>2</sup> CAG repeat length for one HD participant could not be confirmed.

Participants were prepped for the EEG and then moved into the EEG recording facility, where they rested for 5 minutes and then completed the facial expression task followed by the questionnaires and scales. For the facial expression task participants were provided with a thorough explanation, including familiarisation with each of the questions and response choices available, followed by a 5-minute practice period during which care was taken to ensure understanding, and then the main task was given.

### *Materials and Apparatus*

#### *Facial Expression Task*

The emotional face perception task utilised three basic emotions, *happiness*, *anger* and *disgust*, and also included *neutral* as an emotion type (Ekman, 1999). These facial expressions were adapted from the Karolinska Directed Emotional Faces (KDEF) set (Lundqvist et al., 1998). The set consisted of 63 vivid faces, both male and female, with each face depicting all four facial expressions (see Figure 1). The KDEF has been validated as a reliable facial set and used in a number of emotion studies (Goeleven et al., 2008). Additionally, 63 scrambled versions of the KDEF faces were used in the task as non-facial controls (Henson et al., 2003). Overall, the task consisted of 315 trials, substantially more than previous emotion perception studies, but a necessary requirement for ERP analyses, divided into 3 blocks of 105 trials each, with a brief break in between blocks. Given the requirement for extra stimuli, we did not use other typically-employed negative emotion types (i.e., fear and sadness) since this would have significantly increased the duration of the experiment. Therefore our results, concerning negative emotions, are restricted to emotion processing of disgust and anger, and do not necessarily generalise to all negative emotion types. The task was run through Cogent (Wellcome Laboratory of Neurobiology, Queen Square, London; <http://www.vislab.ucl.ac.uk/cogent.php>) and Matlab 2006b software (Mathworks,

Massachusetts, USA; <http://www.mathworks.com.au/products/matlab/index.html>) and displayed on a 17" computer monitor that was approximately 45cm in front of the participant, with stimuli 17 x 13 cm. There were two pseudo-random orders of task stimuli, with the order counterbalanced across participant (and matched across groups). Each trial was initiated by a fixation cross presented for 500ms, followed by a KDEF stimulus (expressive or scrambled face) for 750ms, followed by a second fixation cross for 500ms. After cessation of the second fixation cross, participants were required to respond to two questions that were presented following the fixation cross. Each question was displayed for 1300ms, during which time participants were required to respond. Question one was "Which Emotion?", where response options were, Happy, Neutral, Angry or Disgust. Question two was "How Emotional?" did participants find the stimulus, where participants had to respond on a Likert scale, from 1 (not very emotional) to 5 (very emotional); points 2-4 were not labelled. Responses were made via computer keyboard. For scrambled faces participants were required to "Press Any Key".

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Figure 1 about here

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### *EEG Acquisition*

A 64-electrode silver-silver chloride (Ag-AgCl) electroencephalography (EEG) elasticised Quik-cap (Compumedics) was used, configured in accordance with the international 10-20 system. Electrodes were also placed above and below the left eye, and on the other canthus of each eye (for oculographic recordings), on each mastoid process and with ground on the forehead. Data were digitised at 1000Hz and impedances were below 10k $\Omega$  at the start of the recording. Data were collected and analysed offline by Compumedics Neuroscan 4.5 software (Melbourne, Australia).

## *Data Analysis*

*Behavioural:* Accuracy was defined for each emotion type as correct, incorrect or no response, and in line with previous literature (Johnson et al., 2007) calculated as a percentage of the total number of stimuli for each emotion type. Intensity was defined as the average Likert response per emotion type.

*ERP:* EEG data were digitally filtered with a band-pass zero phase-shift filter of 0.5-30Hz (24 dB roll-off), re-referenced to the digitally calculated mean of the mastoid processes, EOG corrected (Semlitsch et al., 1986), epoched -200ms pre-stimulus to 800ms post-stimulus, baseline corrected, artefact rejected (EEG channels;  $> \pm 75\mu\text{V}$ ), and averaged for each face type separately. Data were then converted to common average reference, and grand mean waveforms created across subjects for scrambled faces and face-specific types combined ('Faces'; which omitted the scrambled ERPs), to establish the time range of the general visual processing (90-150 ms) and face-specific processing (136-216 ms) ERP peaks respectively, for the combined groups.

*Peak Picking:* The P100 latency for each participant's scrambled face ERP was then defined as the most positive point within the range of the grand mean P100 latency  $\pm 15$  ms, at POZ. N170 latency was similar defined, differing in that the grand mean N170 latency was used from the Faces ERP, and that neutral, happy, angry and disgust faces were then scored for the individuals separately. The P100 amplitude for each subject and face type was then calculated as the difference between the amplitudes at PO7, POZ and PO8 (positive) and F7, FZ and F8 (negative), respectively, and for the N170 amplitude as the difference between the amplitudes at PO7, POZ and PO8 (negative) and F7, FZ and F8 (positive), respectively. To reduce the influence of latency variation on the P200 and N250 peak picking, for each individual and face (excluding scrambled) ERP separately; 1/ P200 latency was defined relative to the preceding N170 peak (as the most positive peak in the range of the 'N170 latency + 70 ms' to 'N170 latency + 130 ms', at POZ), with the

peak calculated as the difference between the amplitudes at PO7, POZ and PO8 (positive) and F7, FZ and F8 (negative) respectively<sup>3</sup>; and 2/ N250 latency was defined relative to the preceding P200 peak (as the most negative peak in the range of the 'P200 latency + 0 ms' to 'P200 latency + 60 ms', at POZ), with peak calculated as the difference between the amplitudes at PO7, POZ and PO8 (negative) and F7, FZ and F8 (positive), respectively.

### Statistical Analysis

As sample sizes were small (N=11 per group), planned non-parametric comparisons were performed. These do not have the degree of flexibility that parametric tests have, and so the following simplified variables were computed to allow relevant hypotheses to be tested. For each participant: For the P100 index, peak amplitude data for Scrambled stimuli were averaged across the 3 levels of laterality (left, midline, right), creating the variable 'S'. For the N170 index, peak amplitude data for each of the Scrambled and Neutral stimuli separately, were averaged across the 3 levels of laterality (left, midline, right), creating 'S' and 'N' respectively, and an index of 'face specific processing' was created by subtracting peak amplitude results for 'S' from 'N' (Face Effect) . For the N250 peak amplitude, data for each of the Neutral, Angry, Disgust and Happy stimuli separately, were averaged across the 3 levels of laterality (left, midline, right), creating 'N', 'A', 'D' and 'H' respectively, and indices of 'emotion specific processing' were created by subtracting peak amplitude results from each of 'A', 'D' and 'H', from 'N', creating 'Angry Effect', 'Disgust Effect' and 'Happy Effect' respectively. The parallel derivation was computed for each of the behavioural measures (Accuracy and Intensity). Further, average behavioural measures were created across all face emotion types (N, A, D, H), for each of Accuracy and Intensity ('Faces'), and for P100, averages across all face types were created (S, N,

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<sup>3</sup> Note that the P200 peak was defined in order to determine the N250 latency, but was not further analysed.

A, D, H; All Faces). For each such variable, subscripts denote the dependent variable of interest (e.g., 'Angry Effect<sub>P100</sub>' for the P100 Angry Effect derivation). Due to the small sample size and exploratory nature of this study, no adjustment for Type I error was conducted. Statistics were conducted using SPSS v19.

### Behavioural

A Wilcoxon's Rank Sum test was used to test for differences in each of Accuracy (percentage correct) and Intensity, for each of Faces, neutral, happy, angry and disgust faces separately, as well as for Angry Effect, Disgust Effect and Happy Effect.

### Electrophysiological

#### *Role of Visual Processing (Prior to Face-Specific Processing) in HD*

To determine whether general visual processing differed between the groups, a Wilcoxon's Rank Sum test compared HD and control 'All Faces<sub>P100</sub>' values.

#### *Role of Facial Processing in HD*

1/ To verify that structural encoding of the faces resulted in enhanced processing of the N170, a Wilcoxon's Sign Rank test was used to compare 'S<sub>N170</sub>' to 'N<sub>N170</sub>' for the whole sample; 2/ To determine whether the N170 to faces differed between the groups, a Wilcoxon's Rank Sum test compared Control to HD 'N<sub>N170</sub>' amplitudes; 3/ To determine whether any enhanced N170 processing to 'N' (relative to 'S') differed between groups, a Wilcoxon's Rank Sum test compared Control to HD 'Face Effect<sub>N170</sub>' values; 4/ To determine whether enhanced face ('N') processing occurred relative to 'S', within each group separately, a Wilcoxon's Sign Rank test was used to compare 'S<sub>N170</sub>' to 'N<sub>N170</sub>'<sup>4</sup>.

#### *Role of Emotional Processing in HD*

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<sup>4</sup> Note that although analyses 3 and 4 are very similar, analysis 4 was added because although it has the limitation of not being able to compare the groups directly, it has the advantage of being fully within subject and thus more sensitive than Analysis 3 to face-related processing changes.

1/ To determine whether emotional modulation of the N250 was achieved, Wilcoxon's Sign Rank tests were used to compare 'N<sub>N250</sub>' to each of 'A<sub>N250</sub>', 'D<sub>N250</sub>' and 'H<sub>N250</sub>', for the whole sample; 2/ To determine whether N250 processing differed between groups, a Wilcoxon's Rank Sum test compared Control to HD 'N<sub>N250</sub>' values. 3/ To determine whether any enhanced N250 processing to the emotional faces differed between groups, Wilcoxon's Rank Sum tests compared Control to HD 'Angry Effect<sub>N250</sub>', 'Disgust Effect<sub>N250</sub>' and 'Happy Effect<sub>N250</sub>' values. 4/ To determine whether emotional modulation of the N250 were achieved, within each group separately, Wilcoxon's Sign Rank tests were used to compare 'N<sub>N250</sub>' to each of 'A<sub>N250</sub>', 'D<sub>N250</sub>' and 'H<sub>N250</sub>'<sup>4</sup>.

### Associations with Clinical Measures

'Spearman's measure of association' analyses were performed within the HD group to investigate possible relationships between clinical characteristics (CAG repeat length, years since diagnosis and UHDRS motor score), and any dependent variables that significantly differed between groups. Moreover, for HD participants, of the other scales/questionnaires that significantly differed between groups (i.e., BDI-II, PANAS-PA and Disgust-An) none correlated with the significant dependant variables in this study.

## **Results**

### Behavioural

As can be seen in Table 2, accuracy (percentage) scores were lower in HD than controls for the combined Faces ( $p=0.006$ ), with subsequent analyses showing that this was due to reductions in each of neutral ( $p=0.020$ ), angry ( $p=0.006$ ) and disgust ( $p<0.001$ ) faces, with no difference for happy faces ( $p=0.792$ ). There was a trend towards reduced Happy Effect ( $p=0.094$ ) and greater Angry Effect ( $p=0.130$ ) and Disgust Effect ( $p=0.063$ ) in HD

participants. As can be seen in Table 3, intensity scores did not differ between the groups for any face nor emotion-effect type ( $p > 0.341$ ).

### Electrophysiological

ERP waveforms for each of the five face types are shown for each group separately, in Figure 2.

#### *Role of Visual Processing (Prior to Face-Specific Processing) in HD*

As indexed by the All Faces<sub>P100</sub> amplitude, HD patients (mean=1.94, SD=2.16, median=1.28) had smaller visual processing responses (prior to face-specific processing) than Controls (mean=4.06, SD=2.30, median=4.22;  $p=0.045$ ).

#### *Role of Facial Processing in HD*

1/ Verifying that structural encoding of the faces resulted in enhanced N170 processing, for the combined group, Faces<sub>N170</sub> (mean=-4.96, SD=3.39, median=-4.17) had larger amplitudes than scrambled faces (mean=-3.29, SD=4.37, median=-2.65;  $p=0.003$ ). 2/ Demonstrating an impairment in facial processing, 'Face<sub>N170</sub>' was reduced in HD (mean=-3.31, SD=2.75, median=-2.59) relative to controls (mean=-6.61, SD=3.25, median=-7.48;  $p=0.017$ ). 3/ No difference in face-specific processing ('Face Effect<sub>N170</sub>') was found between HD (mean=-1.09, SD=2.68, median=-2.66) and controls (mean=-2.26, SD=2.65, median=-1.51;  $p=0.491$ ). 4/ However, suggesting that this lack of difference in face-specific processing may have been affected by the small sample size, 'S<sub>N170</sub>' and 'Face<sub>N170</sub>' differed in controls (Faces: see above; Scrambled: mean=-4.35, SD=3.88, median=-3.33;  $p=0.010$ ), but not HD patients (Faces: see above; Scrambled: mean=-2.23, SD=4.75, median=-0.16;  $p=0.182$ ), using the more sensitive within-subjects comparison.

#### *Role of Emotional Processing in HD*



1/ For the combined sample, relative to Neutral (mean=0.94, SD=2.79, median=0.79), there were reduced N250 amplitudes to Disgust (mean=0.37, SD=2.48, median=0.71;  $p=0.024$ ) and a trend to reduced N250 amplitudes to Angry (mean=0.56, SD=2.63, median=0.63;  $p=0.082$ ) faces, but no effect on Happy faces (mean=1.02, SD=2.76, median=1.43;  $p=0.884$ ). 2/ No evidence of an 'N<sub>N250</sub>' amplitude group difference was found (i.e. independent of emotion;  $p=0.818$ ). 3/ No difference in emotion-specific processing was found between HD and control groups for either 'Angry Effect<sub>N250</sub>' ( $p=0.768$ ), 'Disgust Effect<sub>N250</sub>' ( $p=0.412$ ) or 'Happy Effect<sub>N250</sub>' ( $p=0.577$ ). 4/ However, suggesting that that the lack of group differences for the above Angry and Disgust emotion effects may have been related to the small sample size, for controls, 'A<sub>N250</sub>' ( $p=0.050$ ) and 'D<sub>N250</sub>' ( $p=0.050$ ) but not 'H<sub>N250</sub>' ( $p=0.722$ ) were larger than 'N<sub>P250</sub>' amplitudes, whereas no differences were seen relative to 'N<sub>P250</sub>' for HD ('A<sub>N250</sub>',  $p=0.534$ ; 'D<sub>N250</sub>',  $p=0.213$ ; 'H<sub>N250</sub>',  $p=0.859$ ).

#### Associations with Clinical Measures

The only significant ( $p<0.05$ ) association between the significant dependent variables described above and either CAG repeat length, years since diagnosis and UHDRS motor score, was between CAG repeat length and P100 amplitude to all faces (i.e., general visual processing;  $r=-0.67$ ,  $p=0.031$ ), with a further trend to a similar inverse relation between CAG repeat length and accuracy to neutral faces ( $r=-0.59$ ,  $p=0.072$ ); see Table 4.

#### **Discussion**

The present study found that recognition of emotional faces was less accurate in HD patients relative to controls, an effect driven by poorer accuracy to each of neutral,

angry and disgust faces. This provides a replication of previous research reporting poorer recognition accuracy for disgust in HD (e.g., Hennenlotter et al., 2004, Montagne et al., 2006, Sprengelmeyer et al., 1996). However, as impairment to angry faces was also observed, the present study does not support the notion that disgust (or the neural processes subserving its recognition) is qualitatively different to other negative emotions, but accords well with recent studies reporting deficits in other negative emotion processing (specifically anger). This suggests a more universal deficit in negative emotion processing (Calder et al., 2010, Dogan et al., 2013, Henley et al., 2008, Johnson et al., 2007, Snowden et al., 2008). It should be noted however that as the present study did not use sad or fearful faces, it was not able to determine the degree of generalizability. It is difficult to determine how this conclusion is affected by the neutral face impairment found in the present study. Snowden et al., (2008) failed to find impairments in neutral facial discrimination in HD. Moreover, impairments were not found in premanifest HD (Johnson et al., 2007) or in symptomatic HD using neutral video clips (Dogan et al., 2013). It is unclear what may be driving the difference in results between this study and that by Snowden et al., (2008) since there is limited information on the neutral face performance results provided by Snowden et al., (2008). However, given that the control group in the Snowden et al., (2008) study were 10 years older than the manifest HD group (with the former similar in age to both the control and HD group of the present study), it is possible that age related decline may have obscured impairments in that study. However, should the present result be replicated, it would suggest that the impairment in HD is present in all non-positive valenced stimuli, or alternatively that neutral stimuli are viewed as negatively valenced (with the latter perhaps due to a difficulty in delineating neutral from negatively valenced faces).

Early visual processing (as indexed by the P100 amplitude) was reduced in HD compared to controls, regardless of face or emotion type. This finding is consistent with a

number of studies reporting impairments in early visual processing in HD (Antal et al., 2003, Ellenberger et al., 1978, Josiassen et al., 1984, Oepen et al., 1981), although others have failed to identify such an impairment (Ehle et al., 1984, Munte et al., 1997, Rosenberg et al., 1985, Scott et al., 1972). Such an impairment provides another explanation for the results; it is possible that prior to face and facial emotion processing, there is a visual processing deficit in HD that makes subsequent processing more difficult. This is consistent with the reduced N170 measure of structural decoding of the faces that was also found in HD, as it was independent of whether the faces were real or scrambled (and thus not face-specific), and also the lack of N250 group difference, which indexes the valence-specific emotional decoding of the faces. That is, there was nothing specific about the emotional content of the faces that differentiated the groups. This interpretation is consistent with a recent study assessing emotional response to auditory sounds in HD participants (Robotham et al., 2011), which reported performance decrements in HD across all emotion types, including positive valence sounds. However, given the use of a different modality (auditory as opposed to visual), and the lack of comparison between emotional and non-emotional sounds, it is difficult to translate the relevance to emotional face processing.

The difficulty with this hypothesis is that it does not appear to explain the differential accuracy of happy compared with neutral, angry and disgust faces. However, given that healthy controls are more accurate for neutral than angry faces, and angry than disgust faces (with the same pattern found in the present sample), the differential impairment within these face types in HD may merely be due to the relative difficulty. That is, given the impairment in visual processing, such faces may be somewhat difficult to process, and given the 'normal' hierarchy of difficulty for the faces (e.g., Harmer et al., 2004), in HD the impairment may merely be exaggerated for disgust relative to anger, and anger relative to neutral.

However, 'happy' faces did not fit this pattern, as they are typically more difficult than neutral stimuli to identify (as was the case in the present control group), and were not impaired in the present HD sample. This suggests that in addition to the general visual impairment in HD, emotional processing is also impaired but not observed in the present study. Particularly given the small sample size (11 versus 11), and the corresponding possibility of Type II error, we further explored this by comparing the N250 index of valance processing between neutral and each of happy, angry and sad faces, within each group separately. This represents a far more sensitive test as it is entirely 'within-subject' and thus less affected by between-subject variability. Here we found significant reductions in both angry and disgust (but not happy) faces relative to neutral, but only for controls. Similarly, the N170 index of structural encoding of the faces was larger for real than scrambled faces for controls, but not for HD. Thus the small sample size may have precluded the identification of differential emotional modulation for the groups, and the possibility of independent impairments in visual, facial and emotional processing cannot be ruled out.

This sample size limitation argues strongly for the use of substantially larger samples in future investigations. However, it should be noted that the small sample size will not increase Type I error (but rather require larger effect sizes to detect significant differences), and so the positive findings in the present study are not susceptible to this limitation. Instead, this means that the significant impairments reported here (accuracy and general visual processing) are associated with larger effect sizes than, for instance, the above speculated emotional processing deficits (N250 for anger and disgust). This is an important outcome to inform the search for functional biomarkers, which suggest that behavioural measures of emotional processing were more robust than the electrophysiological (N250). However, whether this will correspond to greater biomarker

utility remains to be seen, as it would depend on the relative expression of these functions pre-symptomatically, and which of the measurements are more functionally relevant.

In support of a visual processing deficit in HD (independent of facial or emotional processing), there was a strong inverse association between CAG repeat length and P100 amplitude ( $r=-0.68$ ), as well as a trend toward an association with overall accuracy ( $r=-0.48$ ; non-significant). This is an interesting finding in that it was independent of 'Years Since Diagnosis', and the associated 'UHDRS' motor scores, and thus may represent a core visual processing deficit that may have a different trajectory to the development of motor signs. Further exploration of this relationship is clearly warranted.

Contrary to our hypothesis, intensity ratings did not differ between groups for any emotion type, nor for any emotion-effect. Further, this does not appear to be due to Type II error, as algebraic means were almost identical for the groups. However, it is difficult to determine what this in fact means for the experiential intensity of the HD participants, as the subjectivity of the rating makes comparisons difficult to interpret. For example, it may be that HD and control participants experienced the emotional faces similarly, or alternatively it may be that HD participants experience a generally flatter emotional landscape, and that they scored the emotion of the faces relative to their less intense emotional experiences more generally. The lack of objectivity of this metric questions its utility in the current search for HD biomarkers.

It should be noted that the present ERP methodology differs from the behavioural research on emotional face processing HD. For example, the current method used shorter inter-stimulus intervals (ISI's), as well as shorter periods allocated for evaluation and behavioural responses to the stimuli (1300ms each). This difference was due to the large number of stimuli required to obtain adequate ERP signals, but may have altered the task when compared to performance-based research by making it somewhat more difficult. However, the briefer ISI's are sufficient to generate emotion-based differences in face

ERPs. Moreover, and as evidenced by the current performance data, all participants performed with a high degree of accuracy (neutral: >75% correct, compared to the chance level of 25%) and group differences were found as a function of emotion type, in spite of the shorter evaluation and behavioural response periods in the present study. Another issue to consider is that, as per standard behavioural and ERP protocols, fixation was not required for the presentation of face stimuli. This raises the possibility that the visual processing deficits observed in the HD group were not due to poorer neural processing per se, but rather less visual stimulation reaching the brain. However, as both groups performed with a high degree of accuracy for happy faces, this suggests that fixation was adequate for successful discrimination in both groups. This therefore does not explain the reduced visual processing responses in the HD group.

In summary the present study has replicated previous reports of impairments in behavioural measures of negative (but not positive) emotion processing in HD, as well as demonstrated impairments in neutral face processing. We also reported impaired visual processing in HD (P100; prior to face or emotion processing), without clear evidence of differences in face-specific (N170) or emotion-specific (N250) processing. This suggests that the reduced emotion recognition performance in HD reported in the literature (and here) is likely to represent a number of discreet impairments, and that electrophysiological methods offer new avenues for delineating such impairments. Further longitudinal investigation of such methods is required to assess their utility as sensitive biomarkers of disease progression for therapeutic trials.

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## Figure Legends

Figure 1. Examples of the Karolinska Directed Emotional Faces set depicting the four emotional expressions (angry, neutral, happy and disgust) and a scrambled face (Lundqvist et al., 1998).



Figure 2. Event-related potentials are displayed for Control (left hand column) and HD (right hand column) groups separately, for Fz (top row) and POz (bottom row) derivations separately, for each of the five face types (including 'scrambled').

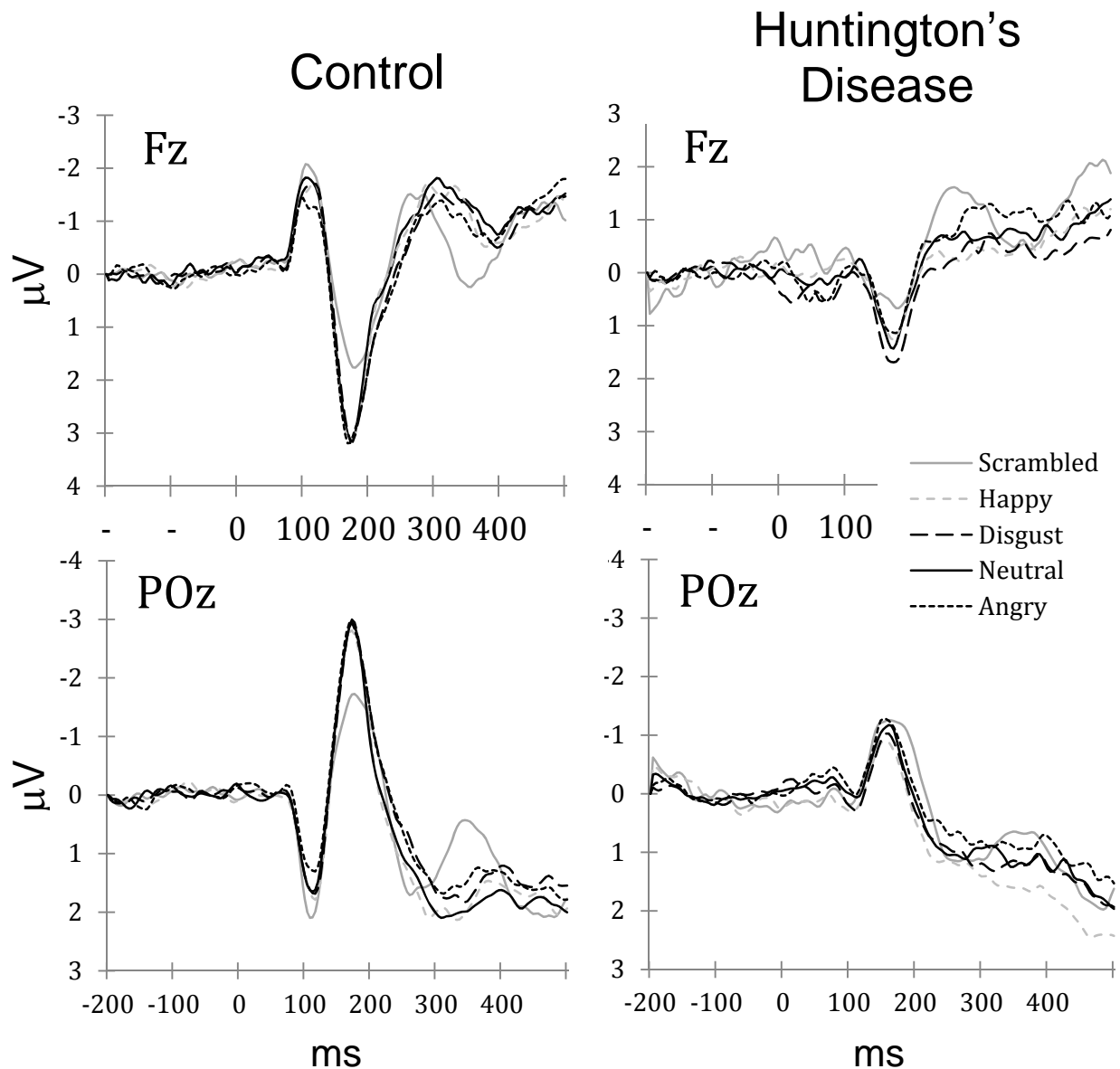


Table 1.

*Means (M), Standard Deviations (SD) and Ranges of Participant Demographic, Clinical Data and Questionnaire Scores.*

	Control (n=11)			HD (n=11)		
	M	SD	Range	M	SD	Range
Age	55.64	7.06	40-65	56.82	9.81	42-70
Disease duration <sup>#</sup>	-	-	-	5.30	4.42	0-14
CAG repeats <sup>#</sup>	-	-	-	42.30	2.00	40-47
UHDRS <sup>^</sup>	-	-	-	16.67	9.31	7-30
BDI-II	2.73*	2.10	0-7	13.09*	8.17	0-30
NART-R	17.91	5.70	8-27	21.10	7.22	9-33
HADS-A	3.55	2.50	1-7	5.55	3.70	0-13
PANAS-PA	36.27*	3.17	31-41	29.73*	8.80	12-40
PANAS-NA	14.64	7.88	10-36	17.27	4.67	10-2
ERQ-R	30.64	5.10	24-37	27.55	4.82	21-36
ERQ-S	14.36	4.41	7-18	17.36	5.85	8-25
OTHS-M	17.09	3.67	12-24	18.91	5.91	8-26
OTHS-E	18.00	3.49	14-23	16.91	5.77	7-24
OTHS-P	18.81	2.40	14-22	17.18	4.40	10-26
Disgust-Core	1.59	.52	2.67-.83	2.07	.71	1.08-3.08
Disgust-An	1.18*	.68	.63-2.75	2.12*	1.02	.5-4
Disgust-Cont	.84	.71	0-2.6	1.56	.96	0-3.2

*Note.* Each group comprised 8 males and 3 females. Disease characteristics (CAG repeat length and disease duration) for one HD participant and UHDRS scores for two HD participants were not available, reducing n to 10 and 9 for rows designated with # and ^ respectively. Dashes represent where descriptive information was not applicable. Age and Disease duration = years. CAG repeat length of the IT15 gene. UHDRS = Unified Huntington Disease Rating Scale, scores increase with motor symptoms severity. BDI-II = Beck Depression Inventory, 2<sup>nd</sup> Edition (score 0-13 minimal, 14-19 mild, 20-28 moderate, 29-63 severe). NART-R = National Adult Reading Test- Revised (maximum score 50). HADS-A = Hospital Anxiety and Depression Scale, Anxiety subscale (maximum score 21). PANAS = Positive Affect (PA) and Negative Affect (NA) Scale (both maximum score 50). ERQ = Emotional Regulation Questionnaire, R = Reappraisal (maximum score 42), S = Suppression (maximum score 28). SWLS = Satisfaction With Life Scale (maximum score 35). OTHS = Orientations To Happiness Scale, M = Meaning, E = Engagement, P = Pleasure, (each subscale maximum score 30). Disgust scale, Core, Animal and Contamination subscale (each subscale maximum score 4).

\* Significant ( $p < .05$ ) difference between groups.

Table 2.  
*Means (M), Standard Deviations (SD) and Percentages (%) for Correct, Errors and No Response Scores for HD and Control Participants During the Facial Expression Task.*

	Control			HD		
	M	SD	%	M	SD	%
<b>Happy</b>						
Correct	53.45	13.16	84.84	52.73	10.18	83.70
Errors	1.55	1.21	2.46	7.73	10.57	12.27
No Response	8.00	12.96	12.70	2.45	2.84	3.89
<b>Neutral</b>						
Correct	54.18	12.33	86.00	47.64	10.41	75.62
Errors	3.45	6.65	5.48	10.91	8.56	17.32
No Response	5.36	11.99	8.51	4.36	4.82	6.92
<b>Anger</b>						
Correct	50.45	10.39	80.08	38.64	12.75	61.33
Errors	7.55	4.25	11.98	20.18	9.39	32.03
No Response	5.09	11.18	8.08	4.36	5.63	6.92
<b>Disgust</b>						
Correct	48.18	13.10	76.48	24.73	15.58	39.25
Errors	8.64	7.12	13.56	34.45	15.76	54.68
No Response	6.18	10.97	9.81	3.73	4.88	5.92

Table 3

*Means (M) and Standard Deviations (SD) of Emotionality Intensity Scores for Control and HD groups.*

	Control	HD
Happy	3.35 (0.46)	3.54 (0.71)
Neutral	2.11 (0.77)	2.30 (0.87)
Angry	3.11 (0.55)	3.30 (0.65)
Disgust	3.56 (0.40)	3.69 (0.49)

Table 4

*Associations between Disease Characteristics and both Accuracy Scores and ERP Amplitudes in the HD group.*

	CAG Repeat		UHDRS		Disease Duration	
	<i>r</i>	<i>p</i> -value	<i>r</i>	<i>p</i> -value	<i>r</i>	<i>p</i> -value
<b>Accuracy Scores (%)</b>						
All Faces	-0.48	0.162	-0.37	0.362	-0.27	0.455
Neutral	-0.59	0.072	0.22	0.606	-0.22	0.544
Anger	-0.23	0.522	-0.63	0.094	-0.18	0.619
Disgust	-0.32	0.372	-0.34	0.414	-0.13	0.713
<b>ERP (Amplitude)</b>						
All Faces (P100)	-0.68	0.031	-0.31	0.450	0.16	0.650
All Faces (N170)	-0.03	0.932	-0.39	0.346	-0.10	0.776
Face Effect (N170)	0.03	0.932	0.63	0.096	0.26	0.476
Anger Effect (N250)	0.22	0.546	-0.36	0.379	-0.16	0.663
Disgust Effect (N250)	-0.18	0.618	-0.45	0.268	0.28	0.434

*Note.* CAG length = CAG repeat length on chromosome 4; Disease Duration measured in years; 'r' is Spearman's measure of association.