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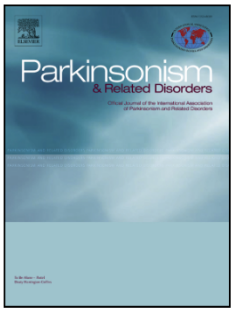

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H. Diana Rosas, Lydia Lewis, Natalie Connors, Nathaniel D. Mercaldo, Shahin Nasr

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Are you angry? Neural basis of Impaired Facial Expression Recognition in Pre-Manifest Huntington's

H. Diana Rosas MD[a,b,c,d], Lydia Lewis BS[a,b,c,d], Natalie Connors BS[a,b,c,d], Nathaniel D. Mercaldo PhD[a,b,d], Shahin Nasr PhD[b,d]

[a]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA 02129
[b] Department of Radiology, Harvard Medical School, Boston, MA 02115[cc] Department of Neurology, Harvard Medical School, Boston, MA 02115
[d]Center for Neuroimaging of Aging and Neurodegenerative Diseases, Massachusetts General Hospital, Charlestown, MA 02129

Corresponding author:

Dr. H. Diana Rosas
Massachusetts General Hospital, Dept of Neurology, Athinoula A. Martinos Center for Biomedical Imaging
149 13th Street, Room 10126
Charlestown, MA 02129
(617) 726-0658

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rosas@helix.mgh.harvard.edu

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Abstract

Introduction: Early non-motor symptoms in Huntington's disease (HD), including visual perceptual difficulties, can have profound negative impacts on quality of life. In particular, deficits in emotion recognition may contribute to misinterpretation of social cues, and may adversely affect interpersonal relationships, work relationships and/or general well-being. This may be particularly salient during the pre-manifest period, a period prior to the onset of motor symptoms. We sought to evaluate impairments in emotion recognition in gene-positive individuals who did not meet criterial for a diagnosis of HD; we also sought to determine associations between emotion recognition processing and altered cortico-striatal circuitry. *Methods:* We used a standardized battery to evaluate performance on a facial expression recognition task in a cohort of motor pre-manifest HD (Pre-HD) individuals (N=21). Functional MRI (fMRI) was then used to assess the face processing network in a subset (N=15). *Results:* We found significantly decreased response accuracy to certain facial expressions, particularly of negative emotions ($p<0.001$) in Pre-HDs. When Pre-HDs viewed faces with different emotions, activation within the Superior Temporal Sulcus (fSTS) was reduced compared to controls; in contrast, the level of evoked response within other face-selective cortical regions was comparable. *Conclusion:* Early deficits in emotion recognition in Pre-HD appear to be associated with alterations in the fSTS response, a distinctly different pathway from that involved in face perception and provide support for early cognitive and behavioral interventions.

Word count: 227

Keywords: Pre-manifest Huntington's disease, superior temporal sulcus, impaired emotion

1. Introduction

Huntington's disease (HD) is a neurodegenerative disease caused by the expansion of a polyglutamine (CAG) repeat in the huntingtin (htt) gene. Although HD has been historically classified primarily as a movement disorder, significant cognitive and behavioral symptoms can adversely impact quality of life. Early cognitive impairments, including deficits in working memory, attention, executive function, and in visual perception, can result in significant functional disability, including in social and occupational domains.

Visual perceptual deficits have received recent attention; early HD patients show visual perceptual impairments, including in: line-bisection[1], motion discrimination[2], object and pattern recognition[1], and scene perception[3]. Such deficits may adversely affect visually-guided activities (e.g., working with objects/tools, navigation, driving). By extension, visual perceptual dysfunction may have an independent and profound impact on an individual's functional independence especially early in disease. Deficits in visual perception could also translate into difficulties in discerning facial expressions, particularly those relating to negative emotions such as anger and sadness[4]. Deficits in emotion recognition may be particularly problematic for individuals who are motor pre-manifest (Pre-HD), when they could adversely influence social interactions or exacerbate early behavioral symptoms, including depression and anxiety, particularly given the importance of an intact emotion recognition in interpersonal interactions.

reflect neuronal dysfunction of limbic areas or the loss of non-motor cortical-striatal or cortical connections such as the visual cortico-striatal loop, an important projection between the dorsal striatum (the caudate more specifically) and high-level cortical areas, including the face-selective portion of the superior temporal sulcus (fSTS). The fSTS itself has been hypothesized to play an important role in social cognition[5]. Though the specific role of cortical face-responsive areas are still debated, the fusiform face area (FFA), involved in encoding the relationship between the parts of the face, is thought to contribute in face detection and recognition, while the occipital face area (OFA) is involved in encoding face parts and other low-level attributes and feeds relevant perceptual information to areas FFA and fSTS[6]. Disruption of any one of these regions or networks could have major clinical impact for individuals with HD.

Based on our prior work, we hypothesized that deficits in facial expression recognition during the HD prodrome were associated with dysfunction of the fSTS. We first used an Emotion Recognition Task (ERT) to confirm deficits in face emotion recognition in a cohort of Pre-HD subjects. We then assessed the spatial organization and activation of face-selective cortical areas in response to emotional face stimuli as part of a functional MRI (fMRI) experiment. Our findings suggest that face-selective cortical dysfunction in Pre-HD involves the fSTS. Our results also further support the hypothesis that fSTS dysfunction could contribute to psychiatric symptoms and/or difficulties with social functioning during the HD prodrome and may have profound implications for quality of life including affecting interpersonal and work relationships during the HD prodrome. As such, early interventions, including cognitive and or behavioral therapies, could have a major impact on patient's lives, prior to a formal diagnosis of HD.

2. Material and Methods

Participants

Twenty-one Pre-HDs (12 female) aged 54 ± 9 years (mean ± S.D.) and sixteen age-matched HCs (10 female) aged 56 ± 12 were recruited from our research database. “Pre-HD” implied that in the setting of a genetic expansion for HD, formal clinical criteria for a motor diagnosis of HD (Unified Huntington Disease Rating Score diagnostic confidence score) had not been met. PHD’s had a median CAG repeat of 42 (interquartile range 41-43) and a median Montreal cognitive assessment (MOCA) score of 28.5 (interquartile range 27-29). All Pre-HDs had a clinical diagnostic confidence score of two or lower. Controls had a median MOCA score of 29 (interquartile range 28-29). Twenty-one Pre-HDs. A subset of participants completed the fMRI experiments (N= 15 Pre-HDs; 11 HCs). Procedures were explained and written informed consent obtained before study activities were conducted, in accordance with the Code of Ethics of the World Medical Association and guidelines of the Institutional Review Board of Massachusetts General Hospital.

Stimuli and procedures

Emotion recognition task to evaluate emotion recognition in Pre-HDs

We used the ERT, a standardized selection of 70 expressions from the Ekman-Friesen faces, to assess emotion recognition response accuracy outside of the scanner. Participants practiced using seven gray-scaled images, each corresponding to one of the following: anger, sadness, happiness, fear, disgust, surprise, or neutral. Participants were then asked to select and verbally report the

practice, the experimenter provided feedback about their response accuracy. After the practice trials, participants evaluated emotions without feedback.

Neuroimaging

Scan Protocols:

fMRI emotion recognition paradigm:

Participants were scanned on a 3T Siemens scanner (Tim Trio) with 32-channel receive coil array. Anatomical data were acquired using a 3D T1-weighted MPRAGE sequence: TR=2530ms, T=3.39ms, T1=1100ms, flip angle 7°, voxel size 1x1x1.33, FOV=256x256x170 mm^3. Functional data were acquired using a single-shot gradient-echo EPI, 2.0mm isotropic voxels: TR=5000ms, TE=31ms, flip angle=90°, matrix=128x128, 69 axial slices covering the entire brain, without acceleration. Scans were visually inspected to ensure that they were of sufficiently high quality to not affect results.

Participants were presented with images of neutral, happy, and angry faces equally balanced across sexes (35 per facial expression), from the Karolinska Emotional Faces set. Each stimulus subtended approximately 20˚ × 20˚ of visual angle and were presented for one second in different blocks according to the facial expression and gender (i.e., 3×2 design), resulting in six different block-types, each of 20 unique images. To evaluate the specificity of responses, participants were also presented with a set of real-world scenes[3].

Functional and anatomical MRI data were pre-processed and analyzed using FreeSurfer and FS-FAST (Version 6.0; http://surfer.nmr.mgh.harvard.edu/). Functional images were corrected for motion artifacts, spatially smoothed (Gaussian, 3mm FWHM), and rigidly aligned (6 DOF) relative to the participant's structural scan using a Boundary-Based Registration. The mean BOLD signal time-course was measured for each ROI for each subject. Sources of variance were used as noise regressors and removed.

Statistical analyses:

Demographics:

Descriptive summaries were computed by group (HC and Pre-HD). Continuous variables were summarized as the median and IQR (interquartile range; 25-75 percentiles), categorical variables as frequencies (percentages). Differences in their distributions by cohort were assessed using either the chi-square test/Fisher's exact test or Mann-Whitney.

ERT Analysis:

The conditional probability of each emotion classification was computed for all emotion pairs. Probabilities were averaged across study participants by group and multiplied by 100 to reflect percentages. Separate logistic regression models were constructed to quantify the association between the correct classification of each emotion and cohort. We also developed models that accounted for potentially confounding participant covariates (age and sex). Exponentiated coefficients associated with the coefficient related to cohort, and their 95% confidence intervals, were computed. Estimates corresponded to the fold-change in the odds of correctly classifying an

fMRI analyses:

Functional data were resampled onto an independently generated averaged brain template (fsaverage – Freesurfer) to create group-averaged maps. Maps were corrected for multiple comparisons within each space using a Monte Carlo simulation with 10,000 iterations and Bonferroni correction(correction threshold set at $p<10^{-3)}$. All other statistical tests were done using either a t-test or a repeated measures ANOVA, with correction using the Greenhouse-Geisser method. A $p<0.05$ was considered significant. (MATLAB 2017a statistics and machine learning toolbox,MathWorks, Inc).

Results

Demographics:

We were unable to detect differences between HCs and Pre-HDs in the distribution of age (p=0.269) or sex (p=1.000) in the ERT or the fMRI experiments (age (p=0.138), sex (p=1.000), respectively.

Response Accuracy during the ERT:

The two groups did not differ significantly in their ability to identify expressions representing disgust, happiness, surprise or neutral (Supplementary Table 1). In comparison to HCs, Pre-HDs were significantly less likely to correctly identify anger (OR=2.02, 95%CI: 1.21-3.26, p=0.007), sadness (2.92, 1.76-4.85, $p<0.001$), or fear (1.57, 1.01-2.44, p=0.043). Similar results were

Presence and Spatial Organization of Face-Selective Areas in Pre-HD:

We evaluated the group-averaged activity maps generated by contrasting the responses evoked by faces versus scenes (**Figure1**) in order to identify face-selective areas in the two cohorts. Using a random-effects analysis, we found face-selective regions corresponding to the FFA and OFA in both. Given the small size of the fSTS, we used a fixed-effects analysis and were able to localize it.

Activation of Face-Selective Cortical Regions in Response to Emotional Faces:

We compared the level of response evoked by the facial expressions (happy, neutral and angry) between groups. **Figure 2** shows activity maps produced by facial expressions (relative to a blank screen) in the right hemisphere. In both groups, these stimuli evoked a significant response within early visual areas in the occipital lobe and higher-level, category-selective visual areas (such as the FFA and OFA); however, these stimuli demonstrated less activation of the fSTS in PreHDs than in HCs. These results suggest that while viewing facial expressions, functional activity in Pre-HDs was altered almost exclusively in the fSTS.

4. Discussion

Deficits in emotion processing have been reported to occur early in HD but little has been known about the neural underpinning of those deficits. In our study, we found that deficits in emotion recognition in pre-manifest individuals were associated with dysfunction of the fSTS and did not simply reflect a non-specific visual perceptual deficit or deficits related more generally to the

First, these results provide novel insights into the neural underpinnings of impaired socio-emotional functioning, during the HD pre-manifest period. Our findings suggest that disruption of a functional link between the caudate and fSTS may contributed to impaired face perception in pre-HD individuals. These findings are also consistent with the known contribution of the fSTS in facial expression and gaze direction encoding[6]. The fSTS is also known to be functionally connected to adjacent areas involved in theory of mind, or the ability to think about the thoughts and beliefs of others, and its dysfunction could provide at least a partial explanation for impairments in affective empathy[7], social interactions and social cognition[5], deficits that have been reported during the pre-manifest period.

Secondly, deficits in emotion recognition could have profound effects on the quality of life. For example, they have been found to be associated with a higher risk for depression, anxiety or interpersonal conflict; these are psychiatric symptoms which occur with a much higher incidence in the HD population, and which are often present during the HD prodrome. It is of interest that our Pre-HD cohort appeared to demonstrate greater difficulty identifying negatively charged emotions, such as anger, sadness or fear, as has been suggested previously[8]; this sort of alexithymia may not only affect one's experience of oneself, but also may interfere with understanding the feelings of others.

Deficits in emotion recognition have been found in neurodevelopmental psychiatric disorders,

behavioral variant frontotemporal dementia (bvFTD)[9], Parkinson's disease (PD) and Alzheimer's disease (AD)[10], and each has been found to be associated with important clinical symptoms and with disruption of specific networks. For example, in AD, deficits in emotion recognition have been found to correlate with cognitive deficits and involve limbic rather than cortico-striatal circuitry[11]. In PD, impairments in emotion recognition, which correlate with progression of both motor and cognitive symptoms[12], are potentially associated with a distinct set of cortico-striatal connections between the amygdala, pulvinar and orbitofrontal cortex (OFC). In bvFTD, deficits in face emotion processing have been associated with alterations in the extended face processing system which includes the amygdala, orbitofrontal cortex, inferior frontal gyrus and insula[6]. Our Pre-HD cohort had a higher-than-expected age, this may reflect a CAG repeat length on the lower end of the pathological spectrum in our cohort and may represent a limitation. Nevertheless, understanding the neural basis of these deficits may provide greater understanding of other complex symptoms of HD. More importantly, the early identification of these deficits would warrant the use of early and cognitive and behavioral interventions, such as interactive biofeedback systems or other modern technologies, which could significantly improve patients' daily interactions, personal relationships and quality of life.

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Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' Roles:

Herminia Diana Rosas: Conceptualization, design, Methodology, Investigation, Resources, Writing -Original Draft, Supervision, Funding

Shahin Nasr: Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Data Curation, Writing -Review & Editing, Visualization, Methodology, Project administration, Supervision

Lydia Lewis: Data Curation, Investigation, Writing-Review & Editing

Natalie Connors: Investigation, interpretation of data, editing/critique;

Nathaniel Mercaldo: -Formal analysis, data curation, Writing-Review & Editing;

Relevant conflicts of interest/Financial Disclosures for the preceding 12 months: None
All authors have approved the final article.

Figure Legends:

Figure 1) Group-averaged activity map 'Face – Scene' contrast in controls and Pre-HDs. Red-to-yellow and blue-to-cyan indicates areas with significantly stronger response to faces and scenes, respectively. (A) Random-effects maps: face-selective areas including the OFA and FFA. (B) Fixed effects: localization of fSTS.

Figure 2) Group-averaged activity maps evoked by facial expressions, relative to blank presentation, in controls, and Pre-HDs. In both, facial expressions evoked a significant response in the visual cortex. In controls, but not Pre-HD's, there was significant evoked activity in fSTS.

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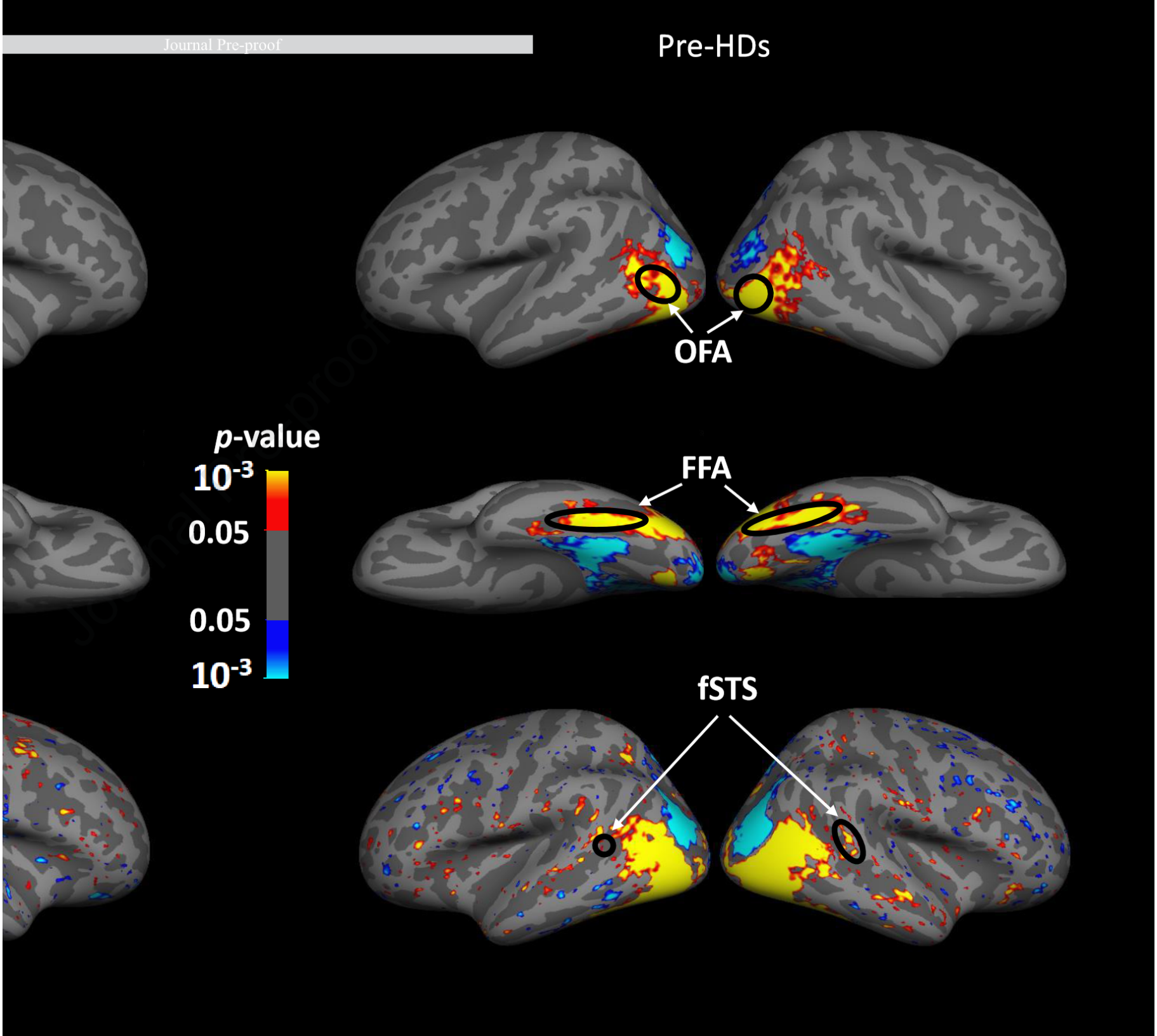

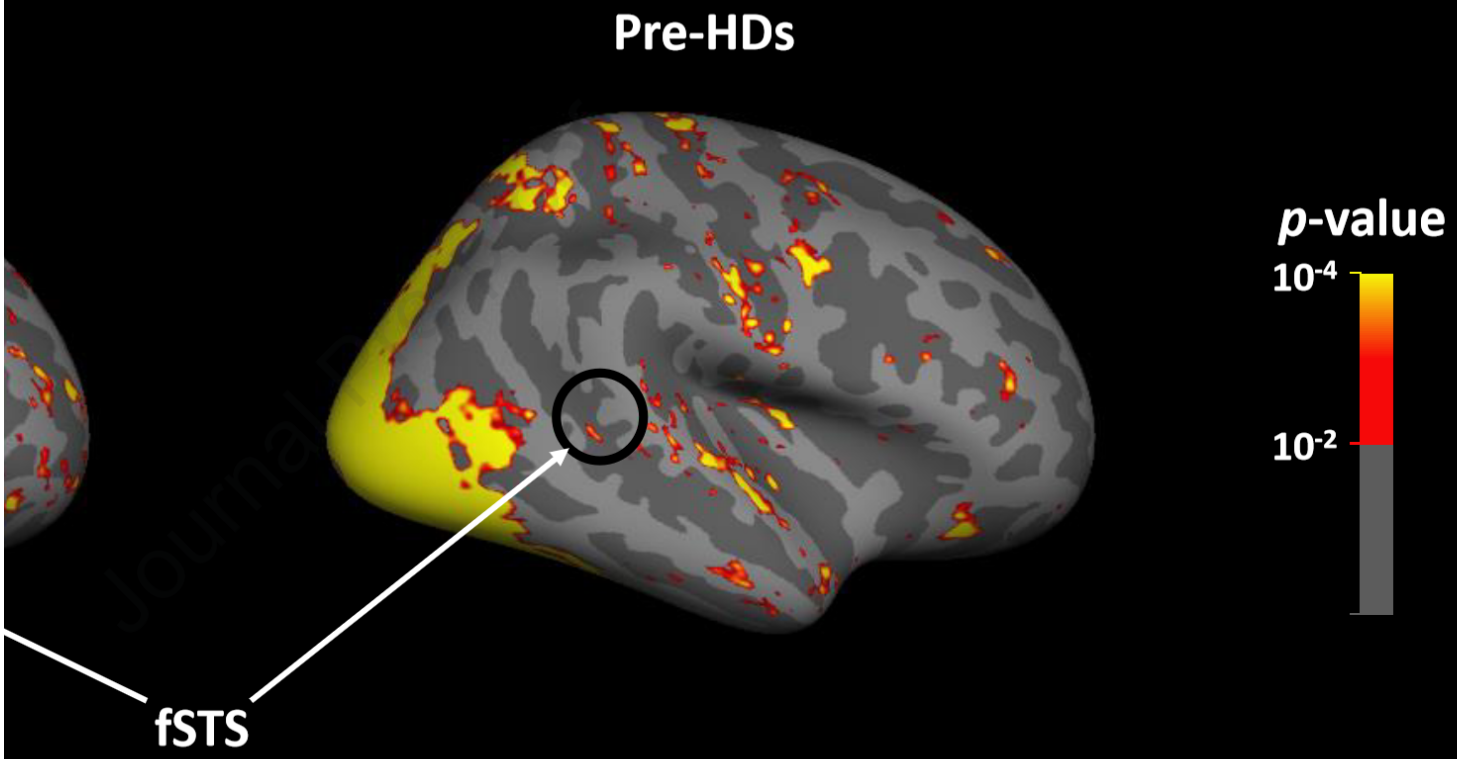

Highlights

Emotion recognition processing is altered during the HD prodrome.
These deficits could have profound impacts for interpersonal relationships.
Cognitive and behavioral strategies might be beneficial during the HD prodrome.