Neuropsychologia 70 (2015) 80–89

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

The role of the amygdala during emotional processing in Huntington's disease: From pre-manifest to late stage disease

Sarah L. Mason [a,*], Jiaxiang Zhang [c], Faye Begeti [a], Natalie Valle Guzman [a], Alpar S. Lazar [a], James B. Rowe [b,c], Roger A. Barker [b,c,1], Adam Hampshire [d,1]

[a] John Van Geest Centre for Brain Repair, University of Cambridge, UK
[b] Department of Clinical Neuroscience, University of Cambridge, UK
[c] MRC Cognition and Brian Sciences Unit, University of Cambridge, UK
[d] Division of Brain Sciences, Imperial College London, UK

ARTICLE INFO

Article history:
Received 20 July 2014
Received in revised form
15 January 2015
Accepted 13 February 2015
Available online 17 February 2015

Keywords:
fMRI
Theory of mind
Amygdala
Effective connectivity
Reading the mind in the eyes

ABSTRACT

Background: Deficits in emotional processing can be detected in the pre-manifest stage of Huntington's disease and negative emotion recognition has been identified as a predictor of clinical diagnosis. The underlying neuropathological correlates of such deficits are typically established using correlative structural MRI studies. This approach does not take into consideration the impact of disruption to the complex interactions between multiple brain circuits on emotional processing. Therefore, exploration of the neural substrates of emotional processing in pre-manifest HD using fMRI connectivity analysis may be a useful way of evaluating the way brain regions interrelate in the period prior to diagnosis.

Methods: We investigated the impact of predicted time to disease onset on brain activation when participants were exposed to pictures of faces with angry and neutral expressions, in 20 pre-manifest HD gene carriers and 23 healthy controls. On the basis of the results of this initial study went on to look at amygdala dependent cognitive performance in 79 Huntington's disease patients from a cross-section of disease stages (pre-manifest to late disease) and 26 healthy controls, using a validated theory of mind task: "the Reading the Mind in the Eyes Test" which has been previously been shown to be amygdala dependent.

Results: Psychophysiological interaction analysis identified reduced connectivity between the left amygdala and right fusiform facial area in pre-manifest HD gene carriers compared to controls when viewing angry compared to neutral faces. Change in PPI connectivity scores correlated with predicted time to disease onset ($r=0.45$, $p<0.05$). Furthermore, performance on the "Reading the Mind in the Eyes Test" correlated negatively with proximity to disease onset and became progressively worse with each stage of disease.

Conclusion: Abnormalities in the neural networks underlying social cognition and emotional processing can be detected prior to clinical diagnosis in Huntington's disease. Connectivity between the amygdala and other brain regions is impacted by the disease process in pre-manifest HD and may therefore be a useful way of identifying participants who are approaching a clinical diagnosis. Furthermore, the "Reading the Mind in the Eyes Test" is a surrogate measure of amygdala function that is clinically useful across the entire cross-section of disease stages in HD.

1. Introduction

Huntington's disease (HD) is an incurable, progressive, neurodegenerative disorder characterised clinically by a triad of motor, cognitive and psychiatric problems (Bates et al., 2002) which is caused by an expanded cytosine–adenine–guanine (CAG) repeat in exon 1 of the huntingtin gene. Neuropathological changes can be detected decades before clinical signs emerge (Aylward et al., 2004; Paulsen, 2010) beginning in the striatum and progressing to widespread brain atrophy (Vonsattel et al., 2008). Although HD is diagnosed based on the presence of unequivocal motor abnormalities, cognitive abnormalities can be detected in most gene carriers prior to this point.

* Correspondence to: John Van Geest Centre for Brain Repair, Forvie Site, Robinson Way, Cambridge CB2 0PY, UK. Fax: +44 1223 331174.
E-mail address: slm64@cam.ac.uk (S.L. Mason).
[1] Both senior authors contributed equally to the work contained in this manuscript.

http://dx.doi.org/10.1016/j.neuropsychologia.2015.02.017

The cognitive profile of manifest HD includes deficits in executive function, emotional processing and memory (Ho et al., 2003; Henley et al., 2012; Tabrizi et al., 2013; Holl et al., 2013; Nicoll et al., 2014; Georgiou-Karistianis et al., 2013, 2014; Johnson et al., 2007; Stout et al., 2011; Begeti et al., 2013). In the prodromal phase the impairment is more subtle but abnormalities in psychomotor processing speed, verbal fluency and the recognition of negative emotions are common (Tabrizi et al., 2013, 2012; Begeti et al., 2013). The direct functional implications of these cognitive changes are still unclear (Kirkwood et al., 2002; Duff et al., 2010; Van Liew et al., 2013) but, reduced occupational performance and difficulty managing finances can be seen in pre-manifest HD gene carriers (pre-HD) who are approaching diagnosis (Beglinger et al., 2010). Furthermore, changes in personality and difficulties with social interaction are key features of early HD. One explanation for these occupational and social problems is an emerging impairment in emotional oversight e.g. accurately identifying, interpreting and responding to the emotions and intentions of others all of which are necessary for maintaining interpersonal interactions and socially appropriate behaviour.

Multiple studies have shown that HD patients are impaired on emotion recognition tasks (Johnson et al., 2007; Sprengelmeyer et al., 2006, 1996; Milders et al., 2003; Henley et al., 2008; Gray et al., 1997; Hennenlotter et al., 2004; Montagne et al., 2006; Wang et al., 2003; Hayes et al., 2007; Mitchell et al., 2005). A recent systematic review of the literature demonstrated that anger recognition is the most consistently reported impairment, closely followed by disgust and fear recognition (Henley et al., 2012) in manifest disease. While in PMGC's, selective impairments in disgust recognition have been found (Sprengelmeyer et al., 2006; Gray et al., 1997; Hennenlotter et al., 2004) and a relationship between anger recognition and proximity to estimated time of disease onset has been reported (Johnson et al., 2007). However, some studies argue that there is a more generalised impairment encompassing all negative emotions (Johnson et al., 2007), with change in negative emotion recognition over a three year period having positive predictive value for identifying PMGC's who reached a clinical diagnosis during that time (Tabrizi et al., 2013). As such, emotion recognition may be a useful marker of very early disease related changes in HD.

The underlying neural substrates of emotion recognition deficits in HD have typically been established using correlative structural MRI studies (Tabrizi et al., 2013; Johnson et al., 2007; Henley et al., 2008; Kipps et al., 2007). Such studies have identified correlations between tissue degeneration in the striatum associated with impaired recognition of surprise, disgust, anger and fear (Henley et al., 2008); between the cerebellum (Scharmuller et al., 2013) and anger recognition and between the anterior insula and disgust recognition in both manifest (Henley et al., 2008; Hennenlotter et al., 2004; Kipps et al., 2007) and pre-manifest patients (Hennenlotter et al., 2004). It has been argued however, that disease-related behavioural changes in HD are more likely to relate to disruption of the complex interactions between multiple brain circuits rather than as a result of distinct regional tissue degeneration (Paulsen, 2009) which cannot be measured on structural MRI.

Functional MRI has been used to interrogate emotional processing in PMGC's in a small number of studies which look at changes in Bold Oxygen Level Dependent (BOLD) response in brain regions during emotional processing. This approach can therefore detect disease related changes earlier than the classic approach. Dogan et al. (2013) asked PMGC's to complete an emotion recognition task whilst undergoing fMRI and reported that negative stimuli evoked decreased activation in the amygdala, hippocampus, striatum, insula, cingulate and prefrontal cortices, as well as in sensorimotor, temporal and visual areas. Other studies measure implicit emotion perception to reduce the confounding effects of performance on BOLD response, by asking participants to perform a distracter task such as a gender decision task. Hennenlotter and colleagues (Hennenlotter et al., 2004) looked at neural activation to grey scale pictures of faces displaying either disgusted, surprised or neutral expressions in PMGC's. BOLD response was reported to be lower than controls in the left dorsal (intermediate) anterior insula/opercular region and left putamen during disgust (relative to neutral) processing. However, Novak and colleagues found activation differences in a widely distributed network of brain regions involved including prefrontal, partietal and cingulate cortices during disgust, anger and happiness processing which was not restricted to any particular emotional expression or emotion valence (Novak et al., 2012).

ToM refers to an individual's ability to understand the presence of beliefs, feelings, intentions and interests in other people that can differ from their own and from reality (Baird and Astington, 2004). The ability to attribute mental states to others is likely to have a central role on human social interaction as it allows us to predict the behaviour of others. Furthermore, affective ToM and emotion recognition have been shown to activate overlapping brain regions, namely the inferior frontal gyrus, the superior temporal sulcus, the temporal pole and the amygdala (Mier et al., 2010) Despite this, ToM is an area of research that has received relatively little attention in HD. Changes in empathy have been found in patients with manifest HD demonstrated by their impaired interpretation of humorous cartoons and story vignettes (Snowden et al., 2003). Further abnormalities have been shown in similar populations of HD patients on ToM tasks such as the "Reading the Mind in the Eyes Task" (RMET) and the faux pas task (Eddy et al., 2012, 2014; Allain et al., 2011) with deficits in ToM found to relate to executive functioning (Allain et al., 2011; Brune et al., 2011) however, to our knowledge however, ToM has not been studied in PMGC's. In this study the RMET was used as a surrogate clinical measure of amygdala function on the basis of previous studies (Adolphs et al., 2002), rather than to interrogate ToM in HD.

In the current study we used an implicit emotional processing task to look for differences in neural activation between PMGC's and healthy controls when viewing grey scale pictures of angry and neutral faces. Unlike previous studies, the pictures of faces were contrasted with pictures of buildings and participants were asked to respond indicating whether they saw a face or a house on the screen. Houses were used as a contrast in this task to increase the power to functionally detect differences in BOLD response during the processing of angry but not neutral faces and not to mask the effect of brain regions which have been previously shown to be activated, non-discriminately by all facial emotions (Fitzgerald et al., 2006).

Connectivity analysis of the results indicated that abnormalities in the way that activity in the amygdala covaries with other brain regions during emotional processing may be an early disease related marker in PMGC's. To identify whether this could be measured clinically, a validated theory of mind test (ToM) which has previously been shown to impaired in patients with lesions to the amygdala (Stone et al., 2003): the Reading the Mind in the Eyes Test (RMET) (Baron-Cohen et al., 2001), was used in a population of PMGC's (11 of whom also underwent the fMRI study) and extended to a population of manifest patient from all different stages of the disease.

The combination of the two experiments provides a comprehensive assessment of amygdala related emotional processing in HD from the earliest pre-manifest stage of the disease through to advanced HD. On the basis of the existing literature we initially predicted that PMGC's would have decreased activation in and connectivity in a wide network of brain regions compared to