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Apathy and atrophy of subcortical brain structures in Huntington's disease: A two-year follow-up study

Verena Baake[a,b,*], Emma M. Coppen[a], Erik van Duijn[c,d], Eve M. Dumas[a,e], Simon J.A. van den Bogaard[a,e], Rachael I. Scahill[f], Hans Johnson[g], Blair Leavitt[h], Alexandra Durr[i], Sarah J. Tabrizi[f], David Craufurd[j,k], Raymund A.C. Roos[a], the Track-HD investigators

[a] Leiden University Medical Center, Department of Neurology, Leiden, The Netherlands
[b] Huntington Center Topaz Overduin, Katwijk, The Netherlands
[c] Leiden University Medical Center, Department of Psychiatry, Leiden, The Netherlands
[d] Mental Health Care of Center Delfland, Delft, The Netherlands
[e] Tongerschans General Hospital, Heerenveen, The Netherlands
[f] Huntington's Disease Centre, UCL Institute of Neurology, University College London, UK
[g] Department of Psychiatry, Carver College of Medicine, University of Iowa, Iowa City, IA, USA
[h] Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada
[i] ICM - Institut du Cerveau et de la Moelle Epinière, INSERM U1127, CNRS UMR7225, Sorbonne Universités – UPMC Université Paris VI UMR_S1127and APHP, Genetic Department, Pitié-Salpêtrière University Hospital, Paris, France
[j] Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester M13 9PL, UK
[k] Manchester Centre for Genomic Medicine, St. Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Oxford Road, Manchester M13 9WL, UK

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ABSTRACT

Background: Huntington's disease (HD) is characterized by motor and behavioral symptoms, and cognitive decline. HD gene carriers and their caregivers report the behavioral and cognitive symptoms as the most burdensome. Apathy is the most common behavioral symptom of HD and is related to clinical measures of disease progression, like functional capacity. However, it is unknown whether apathy is directly related to the neurodegenerative processes in HD.

Objective: The aim is to investigate whether an association between atrophy of subcortical structures and apathy is present in HD, at baseline and after 2 years follow-up.

Method: Volumes of 7 subcortical structures were measured using structural T1 MRI in 171 HD gene carriers of the TRACK-HD study and apathy was assessed with the Problem Behaviors Assessment-Short, at baseline and follow-up visit. At baseline, logistic regression was used to evaluate whether volumes of subcortical brain structures were associated with the presence of apathy. Linear regression was used to assess whether subcortical atrophy was associated with the degree of apathy at baseline and with an increase in severity of apathy over time.

Results: At baseline, smaller volume of the thalamus showed a higher probability of the presence of apathy in HD gene carriers, but none of the subcortical structures was associated with the degree of apathy. Over time, no association between atrophy of any subcortical structures and change in degree of apathy was found.

Conclusion: The presence of apathy is associated with atrophy of the thalamus in HD, suggesting that apathy has an underlying neural cause and might explain the high incidence of apathy in HD. However, no association was found between atrophy of these subcortical structures and increase in severity of apathy over a 2-year time period.

1. Introduction

Huntington's disease (HD) is an autosomal dominant inherited, progressive neurodegenerative disorder, characterized by motor and behavioral symptoms, and cognitive decline (Roos, 2010). Despite motor symptoms being the most specific to HD, the highest burden

* Corresponding author at: Leiden University Medical Center, Department of Neurology, P.O. Box 9600, 2300 RC Leiden, The Netherlands.
E-mail address: v.baake@lumc.nl (V. Baake).

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reported by HD gene carriers and caregivers are the cognitive and behavioral symptoms (Hamilton et al., 2003). Behavioral symptoms are diverse and the degree of severity fluctuates for the majority of symptoms throughout disease progression (Thompson et al., 2012; van Duijn et al., 2007). The most common behavioral symptoms are depressive mood, irritability, and apathy with a prevalence varying between 33% to 76% for each symptom dependent on definition, measurement tools used, and disease stage (van Duijn et al., 2007). Of these symptoms, apathy is the only behavioral symptom that worsens as the disease progresses (Thompson et al., 2012; Martinez-Horta et al., 2016a; Tabrizi et al., 2013). In general, apathy has clinically been defined as "a disorder of diminished motivation, as manifested by reduced goal oriented behavior, emotions, and cognitions" (Starkstein and Leentjens, 2008) and has a strong influence on psychosocial functioning, including relationships with partners and caregivers, e.g. apathetic individuals need to be prompted into starting daily tasks such as getting dressed (Leroi et al., 2012; Aubeeluck et al., 2012).

In HD, apathy can develop early in the course of the disease (Thompson et al., 2012; Kingma et al., 2008) and can even be mildly present in pre-motormanifest gene carriers (Martinez-Horta et al., 2016a; Tabrizi et al., 2009). Over the course of the disease, apathy worsens and eventually apathy is severely present in almost all late stage gene carriers (Thompson et al., 2012). In addition, apathy itself is negatively related to functional capacity, cognitive performance and motor impairment in HD (Thompson et al., 2002). To better understand this behavioral symptom it is of interest to investigate the presence, severity and course of apathy in relation to the structural neurodegenerative processes that occur in HD.

Previous research has shown that apathy is caused by an interruption of the prefrontal cortex – basal ganglia circuit (Levy, 2012), specifically the anterior cingulate circuit in the brain (Haegelen et al., 2009; Tekin and Cummings, 2002). This circuit functionally connects the anterior cingulate cortex, nucleus accumbens, olfactory tubercle, and the ventromedial parts of the caudate nucleus and ventral putamen (Tekin and Cummings, 2002). In subcortical neurodegenerative diseases, such as Parkinson's disease and progressive supranuclear palsy, there is evidence that atrophy of the basal ganglia results in apathy (Haegelen et al., 2009; Cummings, 1993). One study showed that the nucleus accumbens, an important subcortical structure of the reward circuit (Riba et al., 2008), is associated with apathy in Parkinson's disease (Martinez-Horta et al., 2016b). In HD, it is not clear whether the same or other structures are related to apathy. Since degeneration of the basal ganglia is a key feature of HD, it is likely that these structures are associated with the occurrence of apathy in HD.

Dependent on disease stage, grey matter atrophy can be found in almost all grey matter structures in HD (Tabrizi et al., 2013; Aylward et al., 2011; Hobbs et al., 2010). The caudate nucleus is known to already show atrophy in pre-motor manifest HD gene carriers, far from estimated disease onset (Aylward et al., 2011; Douaud et al., 2006; Paulsen et al., 2006; Thieben et al., 2002) and also shows the highest rate of degeneration as the disease progresses (Tekin and Cummings, 2002; Bohanna et al., 2008; Georgiou-Karistianis et al., 2013; Montoya et al., 2006), followed by the putamen (Tabrizi et al., 2009; Aylward et al., 1996; Paulsen et al., 2008; Vonsattel et al., 1985). Volume loss of the nucleus accumbens is already present in the late pre-motormanifest stage (van den Bogaard et al., 2011). It is expected that volume loss of subcortical structures of the anterior cingulate circuit will be related to the development of apathy in HD patients.

Given the progressive nature of apathy and its close relationship with measures of disease progression such as a decrease of cognitive function (van Duijn et al., 2010), and general functioning (Thompson et al., 2012), it is possible that apathy is related to a neurodegenerative progress of subcortical grey matter in HD. Therefore, the aim of this study is to investigate the relationship between volume loss of subcortical structures and apathy in HD and whether there are changes over time.

2. Methods

2.1. Participants

TRACK-HD was a multicenter, longitudinal, observational study conducted at 4 different sites in the following cities: Vancouver (Canada), Paris (France), London (United Kingdom), and Leiden (the Netherlands). Of the 222 TRACK-HD participants, a total of 171 HD gene carriers (91 pre-motormanifest HD gene carriers and 80 motormanifest HD gene carriers) completed the baseline and follow-up visit after 24 months and were included in this study. HD gene carriers had a confirmed genetic testing, i.e. CAG ≥ 39. HD gene carriers with no substantial motor signs at baseline, as indicated with a total motor score (TMS) of ≤5 on the Unified Huntington's Disease Rating Scale (UHDRS), were defined as pre-motormanifest gene carriers. This pre-motormanifest group was further divided into 'far from estimated disease onset' (PreHD-A: > 10.8 years) and 'close to estimated disease onset' (PreHD-B: < 10.8 years), as calculated by the Langbehn formula (Langbehn et al., 2004). The group consisting of motormanifest HD gene carriers, as defined by a TMS of > 5, was further divided into disease stage 1 and disease stage 2 based on the Total Functional Capacity (TFC) score (Shoulson and Fahn, 1979). All participating sites acquired ethical approval and all participants gave written informed consent prior study procedures. The study was conducted by trained professionals and all data was monitored, for a full description of the study, see Tabrizi et al. (Tabrizi et al., 2009).

2.2. Clinical measures

In addition to the collection of general sociodemographic and clinical characteristics, the short version of the Problem Behaviors Assessment (PBA-s) was administered. This is a semi-structured psychiatric interview designed for HD. The PBA-s consists of 11 items, each item measuring a different behavioral symptom such as apathy, depression and irritability. The PBA-s rates each behavioral symptom for both severity and frequency on a 5-point scale (Callaghan et al., 2015). Severity score ranges from absent (score 0) to severe (score 4) and frequency score ranges from absent (score 0) to every day/all day (score 4). In this study, both the product score of severity and frequency of the apathy item, and only the severity score of the apathy item were used.

In this study two concepts were evaluated: the degree of apathy and the presence of apathy (i.e. apathy is or is not present). To indicate the degree of apathy the product score of the apathy item is used. To indicate whether apathy is present a cut-off of ≥2 on only the severity apathy item was used.

2.3. MRI acquisition and processing

All participants underwent 3T MRI scanning at baseline and after 24 months follow-up on a Siemens or Philips whole body scanner depending on study site. 3D-T1-weighted image volumes were acquired with the following imaging parameters, as reported in the supplementary appendix in Tabrizi et al. (2009): TR = 2200 ms (Siemens)/7.7 ms (Philips), TE = 2.2 ms (Siemens)/3.5 ms (Philips), FA = 10° (Siemens)/8° (Philips), FOV = 28 cm (Siemens)/24 cm (Philips), matrix size 256 × 256 (Siemens)/224 × 224 (Philips), 208 (Siemens)/164 (Philips), sagittal slices to cover the entire brain with a slice thickness of 1.0 mm with no gap between slices.

Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) (Smith et al., 2004) was used for analyzing the structural T1-weighted images. Combined left and right volumes of the following seven subcortical brain regions were measured: nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, and thalamus, using FMRIB's Integrated Registration Segmentation Tool (FIRST) (Patenaude et al., 2011). All non-brain tissue was first removed from the T1-weighted image using a semi-automated