Neuropsychologia 51 (2013) 748–759

Contents lists available at SciVerse ScienceDirect

Neuropsychologia

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

Is non-recognition of choreic movements in Huntington disease always pathological?

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ARTICLE INFO

Article history:
Received 4 May 2012
Received in revised form
5 December 2012
Accepted 10 December 2012
Available online 21 December 2012

Keywords:
Anosognosia
Huntington disease
Insight
Concurrent awareness
Chorea

ABSTRACT

Clinical experience and prior studies suggest that Huntington disease (HD) patients have low insight into their motor disturbances and poor real-time awareness (concurrent awareness) of chorea. This has been attributed to sensory deficits but, until now, concurrent awareness of choreic movements has not been compared to the degree of insight that presymptomatic carriers of the HD gene and healthy control subjects have into non-pathological involuntary movements. To further investigate loss of insight into motor dysfunction in HD patients, we administered a video-recorded interview and 4 experimental tasks to 68 subjects from the TRACK-HD cohort, including 28 high-functioning patients in early stages of HD, 28 premanifest mutation carriers and 12 controls. All underwent full neurological and neuropsychological evaluations and 3 T MRI examinations. Subjects were asked to assess the presence, body location, frequency, practical consequences and probable causes of motor impairments, as well as the presence and body location of involuntary movements during 4 experimental tasks. The accuracy of their judgments, assessed by comparison with objective criteria, was used as a measure of their insight into motor disturbances and of their concurrent awareness of involuntary movements.

Insight was poor in early HD patients: motor symptoms were nearly always underestimated. In contrast, concurrent awareness of involuntary movements, although also poor, was essentially indistinguishable across the 3 groups of subjects: non-pathological involuntary movements were as difficult to perceive by controls and premanifest carriers as was chorea for early HD patients. GLM analysis suggested that both concurrent awareness and perception of practical consequences of movement disorder had a positive effect on intellectual insight, and that mental flexibility is involved in concurrent awareness.

Our results suggest that low insight into motor dysfunction in early HD, although marginally modulated by cognitive factors, is mainly non-pathological, and parallels a general tendency, shared by healthy subjects, to neglect self-generated involuntary movements in real time. This tendency, combined with the paucity of functional consequences of incipient chorea, could explain the difficulty of its discovery by the patients.

1. Introduction

Huntington disease (HD), an autosomal dominant neurodegenerative disease, is one of several neurological and psychiatric conditions, including hemiplegia with unilateral neglect, Alzheimer disease, fronto-temporal dementia, bipolar disorder and some psychoses, in which patients underestimate or fail to acknowledge their disturbances (Banks & Weintraub, 2008; Ho, Robbins, & Barker, 2006; Prigatano, 2009; Rankin, Baldwin, Pace-Savitsky, Kramer, & Miller, 2005). Anosognosia, lack of knowledge of or insight into impairment (Davies, Davies, & Coltheart, 2005), is usually considered as a main feature of HD. Insight into the disease, however, should be distinguished, both conceptually and

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http://dx.doi.org/10.1016/j.neuropsychologia.2012.12.005

empirically, from insight into particular symptoms. The diffuse disruption of motor, associative and limbic cortico-striatal circuits contributes to the clinical signs of HD (Delmaire et al., in press). These signs are diverse: the disease is characterized by psychiatric disturbances, cognitive decline, and progressive motor dysfunction with abnormal movements such as chorea and dystonia (Bates, Harper, & Jones, 2002). Chorea is the term used to describe abnormal movements with "unpredictable timing, which are asymmetric, asynchronous, and randomly changing from one body part to another" (Valls-Solé, 2007). Impaired awareness has been reported for every one of the symptoms in HD: motor, psychiatric, and cognitive (Duff et al., 2010; Hoth et al., 2007; Sitek et al., 2011; Snowden, Craufurd, Griffiths, & Neary, 1998; Vitale et al., 2001), but our study focused on awareness of motor symptoms.

Insight is a cognitive phenomenon (Evers, Kilander, & Lindau, 2007; Sturman & Sproule, 2003). It involves patients' judgments about their own condition and symptoms. But insofar as ascribing insight implies the evaluation of the accuracy of those judgments, insight is essentially a normative concept, where the degree of insight corresponds to the degree of concordance between the subjects' own judgments and the actual facts about their condition or symptoms.

The study of insight requires the consideration of two conceptual and empirical distinctions that were advanced by previous studies but are often conflated. The first concerns the timing of the awareness of symptoms: patients' knowledge of their symptoms (usually assessed in an interview) has to be distinguished from their ability to detect symptoms in real time. The phenomenon where a general acceptance of or knowledge about the symptoms can coexist in the same individual with their denial in real time has been called "online anosognosia" (Shenker, Wylie, Fuchs, Manning, & Heilman, 2004) or "concurrent unawareness of impairment" (Davies et al., 2005). A similar distinction, although this time considered from the other end of the insight-anosognosia continuum, was reported under the labels "online awareness" vs. "metacognitive knowledge" (Toglia & Kirk, 2000). Marcel, Tegner, and Nimmo-Smith (2004) reported a double dissociation, between concurrent unawareness of the impairment and its denial of impairment in an interview, in hemiplegic patients. Similarly, in HD, some patients are able to concede that they suffer from a particular symptom when evidence of it is presented by the physician, yet they cannot recognize the symptom in real time (Shenker et al., 2008). Taking this into account, we use the expression "insight into motor symptoms" or "intellectual insight" (Crosson et al., 1989) to refer to the subject's awareness of having a propensity for motor disturbances. Subjects thus have good insight if they know that they have them, can describe them correctly and have a good idea of their frequency. Conversely, we use the expression "anosognosia" to refer to low (or lack of) intellectual insight, i.e.: the subject's underestimation of symptoms. And we use the expression "concurrent awareness" to refer to the subject's ability to detect and acknowledge the symptom in real time.

In this study, our objective was to investigate concurrent awareness and intellectual insight into motor symptoms in early HD and to assess the plausibility of several competing hypotheses about the causes of anosognosia for motor dysfunction. Special attention was addressed to involuntary movements and the fact that not all involuntary movements are pathological. As previous studies have shown, subtle involuntary movements are not exclusive to HD or other movement disorders but are also present in healthy subjects (de Boo, Tibben, Hermans, Maat, & Roos, 1998). But to our knowledge there are no previous studies measuring the degree of insight that presymptomatic HD carriers and healthy controls have into such movements.

We designed a video-questionnaire about motor disturbances and involuntary movements that can be administered to both patients and controls. We analyzed, scored and compared insight into motor problems, concurrent awareness of involuntary movements and subjective reports of practical consequences in three groups of subjects: healthy control subjects, premanifest genetic carriers of HD, and early HD patients with chorea but no dementia. This was completed by an investigation of the implicated factors, such as clinical and MRI findings.

2. Methods

2.1. Participants

We included 68 individuals: 28 early HD patients, 28 premanifest carriers and 12 control subjects. Premanifest gene carriers had more than 40 CAG repeats in the Huntingtin (Htt) gene, a burden score, age $\times$ [CAG $-$ 35.5] (Penney, Vonsattel, MacDonald, Gusella, & Myers, 1997) greater than 250, and a total score of 5 or less on the motor assessment of the Unified Huntington Disease Rating Scale (UHDRS), thus indicating the absence of significant motor disturbances (Huntington Study Group, 1996). Early HD patients had a total motor score greater than 5 on the UHDRS 99 and a Total Functional Capacity (TFC) score of 7 or more, thus indicating preserved autonomy (Tabrizi et al., 2009). Controls were mutation-negative siblings, spouses or partners of individuals with premanifest or early HD. All participants were part of the TRACK-HD Paris cohort, a multicentric study to identify sensitive and reliable biomarkers in premanifest carriers of mutated Htt and in individuals with early HD (Tabrizi et al., 2009, 2010). They were seen at the Center for Clinical Investigations of the Pitié-Salpêtrière University Hospital, Paris, France. All tests were performed during either one visit or two visits less than 30 days apart. The protocol was approved by the local ethics committee (University Hospital Pitié-Salpêtrière, Paris, France). All participants gave their written informed consent to be included in the study.

2.2. Clinical and functional assessments

Motor involvement was assessed with the UHDRS, including measures of ocular pursuit, saccade initiation, saccade velocity, dysarthria, tongue protrusion, thumb/index opposition, pronation and supination, rigidity, bradykinesia, dystonia, chorea (including body location), retropulsion pull tests, gait and tandem walking; the total score ranges from 0 (best) to 124 (worst). We also used the chorea subscore (max 28 = worst). *Functional capacity* was assessed with the TFC, which evaluates performance of daily activities such as shopping, cleaning, dressing, etc.; the total score ranges from 0 (worst) to 13 (best).

2.3. Cognitive and neuropsychiatric assessments

The *cognitive battery* included assessments of visual working memory (Spot the Change) (Luck & Vogel, 1997), mental flexibility and set keeping (the difference in seconds between parts A and B of the Trail Making Test [TMT]) (Lezak, Howieson, & Loring, 2004). A vocabulary task (Mill Hill part B) (Raven, Court, & Raven, 1986) was used to estimate verbal IQ. Insofar as verbal IQ is believed to remain relatively unaffected in early HD, the Mill Hill test was also used as an estimation of pre-morbid intelligence. *Depression* was assessed with the Beck Depression Index (BDI II) (Beck, Steer, & Brown, 1996). *Apathy* was assessed with the apathy sub-score of the Problem Behaviors Assessment (PBA), short version (Craufurd, Thompson, & Snowden, 2001).

2.4. Cerebral MRI

3 T MRI data were acquired using T1 and T2 protocols, as previously described (Tabrizi et al., 2009). Rigorous quality control was performed on all image datasets (IXICO, London, UK). Semi-automated measurements of whole-brain volumes were calculated with MIDAS; fully automated segmentation, whole brain, caudate, and putamen tissue volume were calculated on collected images with Brain Research: Analysis of Images, Networks, and Systems (BRAINS, Iowa City, IA).

2.5. Insight assessment

We developed a 15-min video-recorded interview based on a structured questionnaire (Appendix A) relating to involuntary movements and motor dysfunction and their perception by the subject. Subjects were informed that the interview concerned their opinion about their movements and motor performance. The video-recorded interview was pre-tested on three early HD patients in the presence of an experienced clinician, to confirm that it did not cause distress.