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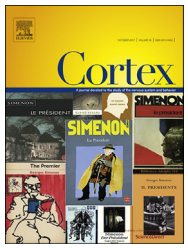

Behavioural Neurology

Cognitive decline in Huntington's disease expansion gene carriers

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ABSTRACT

Background: In Huntington's Disease (HD) cognitive decline can occur before unequivocal motor signs become apparent. As cognitive decline often starts early in the course of the disease and has a progressive nature over time, cognition can be regarded as a key target for symptomatic treatment. The specific progressive profile of cognitive decline over time is unknown.

Objective: The aim of this study is to quantify the progression of cognitive decline across all HD stages, from pre-motormanifest to advanced HD, and to investigate if CAG length mediates cognitive decline.

Methods: In the European REGISTRY study 2669 HD expansion gene carriers underwent annual cognitive assessment. General linear mixed models were used to model the cognitive decline for each cognitive task across all disease stages. Additionally, a model was developed to evaluate the cognitive decline based on CAG length and age rather than disease stage.

Results: There was significant cognitive decline on all administered tasks throughout pre-motormanifest (close to estimated disease onset) participants and the subsequent motormanifest participants from stage 1 to stage 4. Performance on the Stroop Word and Stroop Color tests additionally declined significantly across the two pre-motormanifest groups: far and close to estimated disease onset.

The evaluation of cognition performance in relation to CAG length and age revealed a more rapid cognitive decline in participants with longer CAG length than participants with shorter CAG length over time.

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Conclusion: Cognitive performance already shows decline in pre-motormanifest HD gene expansion carriers and gradually worsens to late stage HD. HD gene expansion carriers with certain CAG length have their own cognitive profile, i.e., longer CAG length is associated with more rapid decline.

1. Introduction

Huntington's disease (HD) is an autosomal dominant inherited, progressive neurodegenerative disorder caused by a CAG repeat expansion in the huntingtin gene on chromosome 4 (The Huntington's Disease Collaborative Research Group, 1993) and is characterized by motor and psychiatric symptoms, and cognitive decline. Typically, a formal clinical diagnosis of HD is based on the appearance of unequivocal motor signs (Roos, 2010). The importance of psychiatric symptoms and cognitive decline has become more recognized and new guidelines have been proposed, which include these signs for clinical diagnosis (Reilmann, Leavitt, & Ross, 2014). Still, these signs are insufficiently specified and to date it is arbitrary when these signs are disease specific and should be taken into consideration for a clinical diagnosis (Reilmann et al., 2014).

In the last decade, there has been a growing interest in the cognitive decline and many studies have focused on this aspect in HD. Nevertheless, there have been relatively few longitudinal studies to date to track the progression of cognitive functioning, and their results have been somewhat conflicting (Hart, Middelkoop, Jurgens, Witjes-Ane, & Roos, 2011; Ho et al., 2003; Lemiere, Decruyenaere, Evers-Kiebooms, Vandenbussche, & Dom, 2004; Paulsen, Smith, Long, investigators, & Coordinators of the Huntington Study, 2013; Stout et al., 2012; Witjes-Ane et al., 2003) which can be attributed to the diversity of study designs. The diversity in methodology is reflected in the selection of tasks administered, length of follow-up, sample size and characteristics of participant population. These different studies suggest that certain types of cognitive tasks are sensitive to particular stages of HD to track disease progression: simple psychomotor tasks have been shown to be particularly sensitive in the 5–10 years preceding motor symptoms onset (Dumas, van den Bogaard, Middelkoop, & Roos, 2013; Maroof, Gross, & Brandt, 2011; Snowden, Craufurd, Thompson, & Neary, 2002; Solomon et al., 2008) whereas performance on tasks of memory and executive function appear to decline particularly around the time of clinical disease onset (Maroof et al., 2011; Montoya, Price, Menear, & Lepage, 2006; Snowden et al., 2002; Solomon et al., 2007). It has also been demonstrated that simple psychomotor tasks are more sensitive to use in longitudinal studies than more complex tasks of executive function in pre-motormanifest and early HD (Bachoud-Levi et al., 2001; Ho et al., 2003; Snowden, Craufurd, Griffiths, Thompson, & Neary, 2001). Thus far studies of cognition in HD over time have been limited to the study of pre-motormanifest and/or early HD. To our knowledge no studies have longitudinally examined cognition across all separate disease stages with a large sample size, which is essential to fully understand the natural course of cognitive decline in HD. It is important to know if specific cognitive domains gradually worsen over time or if, and when, floor and ceiling effects occur. This knowledge is particularly useful for future clinical trials targeting cognition, in order to evaluate the effectiveness of potential interventions in stopping or slowing down cognitive decline in HD. In HD it is known that CAG negatively influences disease progression, i.e., earlier disease onset with longer CAG length (Penney, Vonsattel, MacDonald, Gusella, & Myers, 1997). As cognitive decline is associated with brain atrophy (Bohanna, Georgiou-Karistianis, Hannan, & Egan, 2008; Montoya et al., 2006), which in turn is also negatively influenced by CAG length (Penney et al., 1997), it is of interest to investigate if CAG length also mediates cognitive deterioration. If indeed CAG influences cognitive decline this could help to explain why HD gene carriers develop cognitive deficits at different ages. From a clinical point of view this could raise more awareness that certain individuals have a higher risk at developing early cognitive deficits. Additionally, this information can be used to inform the design of future trials, e.g., in defining the study population or to determine whether expensive MRI protocol is necessary or if cognitive tasks would be sufficient.

In 2004 the European Huntington's Disease Network (EHDN) launched the observational REGISTRY study (Orth et al., 2011), in which HD expansion gene carriers undergo annual assessment of motor function, cognition, behavior, and day-to-day functioning. After years of longitudinal data collection, the REGISTRY study provides the opportunity to explore cognitive change across all HD stages. The aim of this study is to evaluate the progression of cognitive decline in HD throughout the disease stages, from pre-motormanifest to advanced HD, and to evaluate if CAG length mediates cognitive decline. The second aim is to assess whether the individual cognitive tasks are efficacious for measuring cognitive decline across all disease stages or if the task sensitivity is disease stage specific.

2. Methods

Data was acquired from the European, multicenter, longitudinal, observational REGISTRY study which was conducted in 17 countries. All participating sites acquired ethical approval before conducting the study and all participants gave written informed consent. Study assessments were administered by trained professionals and all data was monitored. For a full description of the study, see Orth et al. (2011).