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Dissociation between decision-making under risk and decision-making under ambiguity in premanifest and manifest Huntington's disease

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ABSTRACT

We investigated decision-making under ambiguity (DM-UA) and decision making under risk (DM-UR) in individuals with premanifest and manifest Huntington's disease (HD). Twenty individuals with premanifest HD and 23 individuals with manifest HD, on one hand, and 39 healthy individuals divided into two control groups, on the other, undertook a modified version of the Iowa Gambling Task (IGT), an adaptation of a DM-UA task, and a modified version of the Game of Dice Task (GDT), an adaptation of a DM-UR task. Participants also filled in a questionnaire of impulsivity and responded to cognitive tests specifically designed to assess executive functions. Compared to controls, individuals with premanifest HD were unimpaired in performing executive tests as well as in decision-making tasks, except for the Stroop task. In contrast, individuals with manifest HD were impaired in both the IGT and executive tasks, but not in the GDT. No sign of impulsivity was observed in individuals with premanifest or manifest HD. Our results suggest that the progression of HD impairs DM-UA without affecting DM-UR, and indicate that decision-making abilities are preserved during the premanifest stage of HD.

1. Introduction

Huntington's disease (HD) is an inherited autosomal dominant neurodegenerative disorder caused by an unstable expansion of the trinucleotide repeat cytosine-adenine-guanine (CAG) in the *HTT* gene encoding huntingtin. Until recently, it was thought that the striatum was selectively targeted in the early stages of the disease (Vonsattel et al., 1985; Aylward et al., 2000; Douaud et al., 2009), but growing evidence suggests that individuals with early HD have both cortical and sub-cortical involvement, mainly affecting the frontal-subcortical brain circuits (Rosas et al., 2002; Thieben et al., 2002; Kassubek et al., 2004; Douaud et al., 2006; Henley et al., 2008). Since the neuronal loss in HD progresses along a dorsal-to-ventral axis (Hedreen and Folstein, 1995), the dorsomedial striatum (a component of the dorsolateral prefrontal cortex loop circuitry) is affected earlier than the ventral striatum (a component of the orbitofrontal cortex loop circuitry). HD is clinically characterized by progressive motor, cognitive and psychiatric symptoms. The deterioration of executive functions is commonly observed prior to the onset of motor or neurologic signs of HD, which classically defines the onset of disease (Ho et al., 2003; Kirkwood et al., 2000; Watkins et al., 2000). Moreover, it is commonly accepted that HD patients have difficulties in making decisions in their daily lives (Campbell et al., 2004; Stout et al., 2001; Eddy and Rickards, 2012).

The tasks commonly used to assess decision-making abilities in affected individuals versus healthy controls involve decision-making under ambiguity (DM-UA) and decision-making under risk (DM-UR). DM-UA tasks require learning the predictability of choices and estimation of the long-term gains and losses during the task to optimize final gains. Thus, the participants cannot establish an efficient strategy at the beginning of the task. DM-UA is classically assessed using the Iowa Gambling Task (IGT) (Bechara et al., 1994). In contrast, DM-UR tasks indicate the set rules for gains or losses, as well as the probabilities of winning, before starting the task, thus allowing participants to apply a long-term strategy aimed at increasing the outcome. DM-UR is assessed by various tasks, such as the Game of Dice task (GDT) (Brand et al., 2005), the Cambridge Gambling task (CGT) (Rogers et al., 1999), Cohen's task (Cohen et al., 2005), and the Ultimatum Game task (UGT) (Güth et al., 1982).

A significant association between performance in DM-UA tasks and executive performance on the Wisconsin Card Sorting Test (WCST) is

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observed only in the final stages of the task (Brand et al., 2007), whereas disadvantageous decision-making in DM-UR tasks is correlated with poorer performance in executive function from the beginning of the task. This suggests that executive functions such as cognitive flexibility, set-shifting, and monitoring are involved throughout the DM-UR task, whereas executive functions are involved only during the final stages of the DM-UA task when participants have figured out the rules and have to elaborate strategies. Indeed, in their final stages, DM-UA tasks, such as the IGT, turn into DM-UR tasks (Brand et al., 2007).

Usually, the orbitofrontal/ventromedial prefrontal cortex and interconnected subcortical areas such as the amygdala and the ventral striatum are considered as key mediating structures for DM-UA (e.g., Bechara et al., 1994; Bechara et al., 2000), as revealed by numerous neuroimaging studies (e.g., Hsu et al., 2005; Tanabe et al., 2007; Lawrence et al., 2009) as well as in studies on individuals suffering from prefrontal cortex damage (e.g. Bechara, 2004). Performance on DM-UR tasks appears to be closely linked to the activation of the dorsolateral prefrontal cortex, posterior parietal lobe, anterior cingulate and right lingual gyrus (Labudda et al., 2008; Schiebener and Brand, 2015), and to performance in tasks measuring executive functions (e.g., Brand et al., 2007). According to Bechara (2005) and Schiebener and Brand (2015), this neuroanatomical partition allows the operation of two decision-making systems: the impulsive system involving emotional reactions, conditioning, and somatic activity, and the reflective system involving the working memory, executive functions and reasoning.

Several studies addressing decision-making in individuals with manifest HD in the early and later stages of the disease have shown that alterations in decision-making, appearing in the later stages of the disease (Campbell et al., 2004; Holl et al., 2013), are often associated with other behavioral traits such as disinhibition and impulsivity/compulsivity. However, differential performances may appear according to the type of decision-making task used. In a DM-UA task, such as IGT, patients with manifest HD do not show impaired decision-making in the early stages of the disease, even though they may have some executive dysfunctions, such as altered reversal or shifts from one set of stimuli to another (Holl et al., 2013; Minati et al., 2011; Watkins et al., 2000). Symptomatic individuals make more disadvantageous choices in the second part of the task, whereas healthy individuals begin to show preferences for advantageous options (Campbell et al., 2004; Stout et al., 2001), suggesting a learning deficit rather than a propensity for risk-taking behavior in HD individuals. Several hypotheses have been proposed to explain these cognitive dysfunctions during implicit DM-UA tasks. Firstly, individuals with HD may have altered learning processes or poor memories of the consequences of risky situations because of the failure of the autonomous nervous system to mark negative outcomes (Campbell et al., 2004). Secondly, individuals with HD may develop an inability to correctly process the cue/outcome contingencies through trial-to-trial feedback processing (Holl et al., 2012). Lastly, individuals with HD may have a deficit of inhibitory processes, thus being less likely to suppress disadvantageous courses of action in response to punishment, due to a decreased sensitivity to large punishments (de Visser et al., 2011; Van den Bos et al., 2013, 2014).

In DM-UR tasks, individuals with early HD do not show performance difficulties. For instance, in one study using the CGT (Watkins et al., 2000), individuals with early HD recorded scores similar to those of controls. In another study using the UGT (Eddy and Rickards, 2012), individuals with HD tended to rate immoral behaviors less critically than controls and made more rejections of offers of money, thus showing deficits in explicitly risky decision-making. However, when completing a DM-UR task in which the rewards and risk options were explicitly known, symptomatic individuals with mild and early-stage HD made a series of independent choices between a low-risk/low-reward and a high-risk/high-reward option (Cohen and Ranganath, 2005; Cohen et al., 2005; van Wouwe et al., 2016). In the study by van Wouwe et al. (2016), individuals with HD made high-risk decisions as often as low-risk decisions, with a greater preference for high-risk decisions especially after being rewarded for a high-risk choice, whereas control individuals opted for a strategy of risk aversion, particularly after a high-risk decision was rewarded. For these authors, explicit decision-making in HD was more strongly driven by the outcome of decisions made in a preceding trial rather than by the nature of the risk itself.

In conclusion, individuals with early or mild stage HD experience difficulties in processing disadvantageous choices in both types of task, DM-UA and DM-UR, with a marked deficit in the second half of a DM-UA task when subjects have to apply explicit strategies based on various previously learnt contingencies. However, no study has yet been performed on individuals with premanifest HD to analyze the two types of decision-making, i.e. under ambiguity and under risk.

In our study, aimed at assessing decision-making abilities in individuals with HD according to the course of the disease, we evaluated the performances of individuals with premanifest and manifest HD using modified versions of the IGT for DM-UA, and the GDT for DM-UR. The GDT has been classically used for evaluating DM-UR in different pathologies, but has never been used in individuals affected with HD. Executive functions were also assessed to obtain neuropsychological scores for all the individuals tested. To the best of our knowledge, this is the first study investigating the two different types of decision-making abilities in individuals with HD.

The main questions addressed in this study were the following: (i) Can DM-UA and DM-UR impairments be identified in individuals with premanifest HD? On the basis of results previously obtained with individuals with early-stage HD, our hypothesis was that individuals

with premanifest HD would show no alteration in decision-making regardless of the task used; (ii) Is there any difference between DM-UA and DM-UR tasks in individuals with manifest HD? We hypothesized that the impairment would be more important in the DM-UA task, which requires the initial learning of contingencies between choices, rewards and penalties, than in the DM-UR task; (iii) Do these impairments appear at the beginning of the tasks or only when the contingencies are known and winning strategies have to be implemented? and (iv) Is decision-making performance associated with executive disorder regardless of the task?

2. Methods

2.1. Participants

Participants were recruited from the population of individuals with premanifest and manifest HD regularly examined at the Department of Neurology of the University Hospital of Angers. All individuals underwent neurological and psychiatric examination by experienced clinicians (neurological examination: CV, AP and CS; and psychiatric examination: BG).

This study was approved by the local research ethics committee and all participants gave their written informed consent in accordance with the Declaration of Helsinki.

2.1.1. Individuals with premanifest HD

Twenty individuals with premanifest HD, defined as persons carrying a pathogenic mutation in the *HTT* gene (CAG repeats > 35), without motor symptoms, participated in the study. Inclusion in the premanifest HD group required a UHDRS total motor score ≤5 (Tabrizi et al., 2009). The probability of premanifest individuals developing neurological symptoms within five years was determined using the tables published by Langbehn et al. (2004). The tables for CAG-repeat numbers between 36 and 56 indicate the probability of the onset of HD within certain time frames for ages from 0 to 95 years, conditional on the individual being currently pre-symptomatic. For each gene carrier, the probability of onset of the disease within five years was determined on the basis of the CAG-repeat length and current age (range 2–66%, mean = 23.31%, SD = 20%).