# Huntington's disease and Scalar Expectancy Theory: A memory-based time perception deficit

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**Abstract**

Huntington's disease (HD) damages the basal ganglia dopaminergic circuits which are fundamental neural correlates of the timekeeping mechanism. In this work we investigated whether HD may impair temporal processing and if any component of the Scalar Expectancy Theory (SET) might be responsible of the timing defect. To achieve this result we explored time perception in early symptomatic HD patients and controls for seconds and milliseconds. Data showed an impaired time processing in HD patients that overestimated shorter time intervals and underestimated the longer ones for both seconds and milliseconds. This defect, called migration effect, may suggest a specific deficit in the memory component of SET.

**Keywords:** neuropsychology; Huntington's disease; time perception.

## Introduction

Huntington's disease (HD) is an autosomal-dominant, neurodegenerative disorder that typically produces a progressive atrophy of subcortical structures, especially of caudatus and putamen (Lawrence, Sahakian, & Robbins, 1998). With respect to basal ganglia and fronto-striatal circuits dysfunction, HD patients exhibit typical movement disorders, psychiatric symptoms and several neuropsychological deficits. An increasing amount of evidences suggest the basal ganglia and the fronto-striatal structures as a fundamental neural correlates of timekeeping functions (Meck & Benson, 2002).

Despite this literature, timing deficits in HD has been scarcely investigated. Furthermore, the very few studies focused prevalently on time production processes exclusively related to the motor performance (Beste et al., 2007; Paulsen et al., 2004). Moreover, empirical results are seldom interpreted in the light of time perception's theoretical models.

In this study, we take into account the Scalar Expectancy Theory - SET (Gibbon, 1991) - timekeeping model. It posits three different subsequent stages of time processing. The first one is the clock stage, in which an internal pacemaker, attention mediated, counts time pulses stored by an accumulator to reproduce a subjective time interval that correspond to the real time elapsed. The two other stages translate clock readings into behaviour: the memory stage stores the subjective time interval as transient (working memory) and permanent (reference memory) traces, to allow a suitable comparison during the decision stage that leads to the identification of an appropriate response. Changes in the internal clock speed would produce a systematic error in all the timing performance: Slowing down the internal clock pulses yields underestimation of time intervals, whereas accelerating them generates an overestimation of the elapsed time (Meck, 1996). Defects in the memory components may produce the migration effect (Malapani, Deweer, & Gibbon, 2002) which is the tendency to overestimate the shorter intervals and underestimate the longer ones.

In sum, this paper aims to assess whether HD patients are subject to an altered time perception and which stage of SET is eventually responsible of this alteration.

## Experiment

We investigated time perception in symptomatic HD patients employing the temporal bisection task, which requires subjects to compare temporal stimuli to durations held in memory. In particular, we used two temporal-bisection tasks, one in the second durations and the other in the millisecond durations. The temporal bisection procedure has three advantages: It has been specifically developed in the SET framework, it

does not place great demands on attentional processes and it is suitable to highlight time-perception deficits.

## Method

**Participants** Eleven symptomatic HD patients (6 women) were recruited at the Neurological Unit of the Hospital of Careggi (Florence, Italy). Eleven healthy subjects matched for age served as controls (7 women). UHDRS (Unified Huntington's Disease Rating Scale) motor scores were assessed by an experienced neurologist. HD patients were all in early clinical stages (range UHDRS 3-45). Disease severity measures such as mean CAG-length, age of onset and duration of the disease were collected and reported in Table 1. For each subject, an Italian short version of Verbal IQ (VIQ) test and MMSE were collected (see Table 1). The Ethics Committee approved the study and all subjects gave written consent.

Table 1: Mean and SDs of demographic, clinical and neuropsychological data of HD patients and controls. Data were compared with ANOVA. *<0.05

| | **HD Patients** | | **Controls** | |
|---|---|---|---|---|
| | Mean | (SD) | Mean | (SD) |
| ***Demographic data*** | | | | |
| Age (years) | 55.54 | (11.80) | 54.91 | (15.29) |
| ***Clinical data*** | | | | |
| Age of onset | 51.00 | (10.91) | | |
| Duration of disease (years) | 4.55 | (2.02) | | |
| CAG-length | 43.45 | (2.35) | | |
| UHDRS (motor score) | 33.82 | (16.70) | | |
| ***Neuropsychological assessment*** | | | | |
| MMSE | 26.09 | (1.93) | 28.27 | (1.85)* |
| Verbal QI | 104.30 | (7.29) | 106.01 | (9.51) |

**Stimuli and procedure** Two separate bisection tasks were employed for milliseconds (MS-task) and seconds (S-task). A 15 minutes interval divided the two tasks which were administered in counterbalanced order across the participants. The stimuli were tones at 700 Hz binaurally presented through a wireless Karma® headset by using Presentation 0.50 software. Each task consisted of three phases: training session, learning assessment and test phase. In the training session, participants had to listen to 10 subsequent presentations of the standard Short and Long durations, separated by random intervals from 1000 to 1500 ms.

In the learning assessment participants were requested to recognize standard Long and Short tones which were randomly presented 10 times. Feedback for incorrect responses was given and the learning assessment was repeated until the 100% correct responses were achieved. Afterward, in the test phase, participants were asked to say whether a randomly presented tone from a set of nine test stimuli was more similar to the standard Short or Long duration they had previously learned. After the participant's verbal response the experimenter pressed the appropriate response key (Short=S; Long =L) on the keyboard. The nine test stimuli presented were the standard Short and Long together with seven intermediate stimuli. Every bisection task consisted of 20 trials for each of the nine stimuli. No feedback was given about the accuracy of the responses during the test phase.

In the millisecond-task (MS), the standard Short tone was 400 ms (T1) and the standard Long tone was 800 ms (T9). The seven intermediate stimuli were: 450 ms (T2), 500 ms (T3), 550 ms (T4), 600 ms (T5), 650 ms (T6), 700 ms (T7) and 750 ms (T8).

In the second-task (S), the standard Short tone was 1000 ms (T1) and the standard Long tone was 2000 ms (T9). The seven intermediate stimuli were: 1125 ms (T2), 1250 ms (T3), 1375 ms (T4), 1500 ms (T5), 1625 ms (T6), 1750 ms (T7) and 1875 ms (T8).

**Data Analysis** A one- way ANOVA with Group at 2 levels (controls and HD) was used to compare HD and control participants for age, VIQ and MMSE (see Table 1).

Data from the Temporal Bisection tasks were separately computed for each participant as proportion of Long responses. These proportions were analysed with repeated measures ANOVA with Group (HD patients and controls) as between-subject variable, and Condition (MS- and S-bisection task) and Stimulus duration (T1, T2, T3, T4, T5, T6, T7, T8, and T9) as within-subject variables.

## Results

The main effect of Stimulus duration ($F(3,51) = 142.18$, $p<0.0001$) indicated a progressive growth of the proportions of Long responses as a function of the stimulus time-span (T1, T2, T3, T4, T5, T6, T7, T8, T9). In addition, the interaction Stimulus duration x Group was significant ($F(3, 51) = 4.13$, $p=0.014$), showing that HD patients significantly overestimated short durations (T1: $p<0.011$; T2: $p<0.03$) and underestimated the standard Long duration (T9: $p<0.015$). The main effect of Condition was not significant, suggesting the same defect in second and millisecond durations. In summary, HD patients were mainly impaired in judging the extreme values of the psychophysical curve as shown in Figure 1.

## Discussion

The aim of the present study was to explore the impaired timing mechanisms in HD subjects taking into account the SET model (Gibbon, 1991).

Our main finding was that in a temporal bisection task HD subjects, compared to controls, overestimated the Short stimuli durations and underestimated the Long ones. This temporal misrepresentation affected both millisecond and second durations in the same way, suggesting that identical mecha-

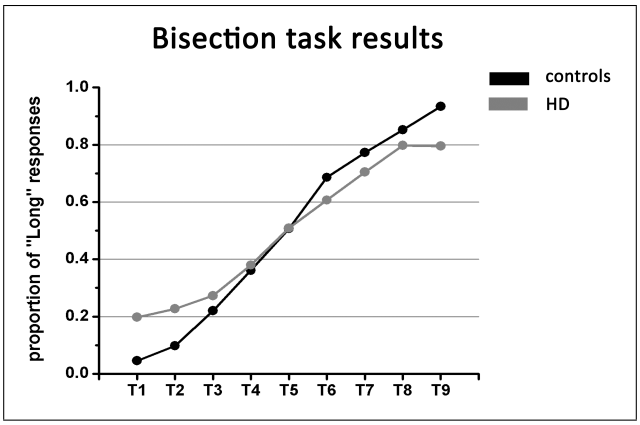


Figure 1: Psychophysical functions for the two bisection tasks: Proportion of long responses plotted against comparison stimulus duration for both Millisecond (MSe) and Second (Se) conditions in controls and HD subjects.

nisms are involved in the processing of durations over and under the second.

This result may not be attributed to an internal clock dysfunction, which would produce a unidirectional variation in the curve (i.e. a rightward shift for all the stimuli if the internal clock ran slowly). On the contrary, our findings bear a strong resemblance to a deficit already observed in Parkinson's disease (PD) patients and called migration effect (Malapani et al., 1998, 2002).

The study of Malapani et al. (1998) employed a peak-interval procedure in which PD subjects off-therapy were trained to learn two target durations in the seconds range. The patients tended to overestimate the shorter duration (8 s) and underestimate the longer one (21 s). This effect arises from the migration of the two peaks towards one another, so that the two targets might more likely be coupled. The migration effect may be attributed to memory retrieval difficulties (Malapani et al., 2002), suggesting an impairment in memory representations. In a similar way, our HD results imply a mutual attraction between the two time values (standard short and long) when they are laid down in memory or retrieved and compared to a current clock reading. The presence of deficits in the time representation system of HD patients may be related to the well documented difficulties in working memory (Lawrence et al., 1998) and episodic memory (Montoya et al., 2006). An open issue is whether the encoding, storage and/or retrieval systems, are responsible for distortions in the timed values to be estimated. Another concern is about what neural substrates are underlying the time memory deficit in HD. The temporal memory dysfunction might be associated to the structural changes that affected striatum, prefrontal cortex (or both) in the progression of the disease. HD occurs with a typical dorsal-to-ventral progression of the cell death in which the dorso-medial striatum is compromised earlier than ventral striatum. This damage progression severely affects a number of dopaminergic corticostriatal loops, primarily the circuits with a close relationship with the dorso-medial striatum, such as the dorsolateral prefrontal cortex (DLPC) (Montoya et al., 2006). This area is suggested to be a specialized system for the manipulation of information within working memory (Mottaghy et al., 2000) as well as in some facets of long term memory such as retrieval of novel material (Sandrini et al., 2003) and refreshing previously active representations (Raye et al., 2002). Damage in DLPC might affect both storage and retrieval processes of temporal memory in HD patients. In addition, the time representation processing might also be damaged by alterations in the dopaminergic cortico-striatal loops. In a similar way, it has been suggested that temporal memory storage is achieved by cortico-striatal circuits that operate through dopamine-modulated long-term potentiation processes (Matell & Meck, 2004). The dopaminergic deregulation might be responsible of temporal memory difficulties, since several studies reported a significant reduction of striatal D1 and D2 receptors in HD patients and a consequent impairment in functioning of both cortico-striatal and nigro-striatal loops (Pavese et al., 2003).

In conclusion, our finding of a migration effect in HD patients suggests a defective processing in the memory component of the SET model. Further investigations are needed to clarify whether the impairment involves storage and/or retrieval processes of temporal memory. Moreover, another open question is whether the mnestic deficit results from striatal pathology deafferentating prefrontal areas or from early cortical pathology *per se*.

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