

Choice-option evaluation is preserved in early Huntington and Parkinson's disease

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The ability to choose effectively when faced with potential risks and rewards is fundamental for adaptive survival. The striatum has a well-established role supporting learning from the outcomes of decisions, but it remains unclear whether this structure is also necessary for computing expected value (i.e., advantageousness of potential decisions) when all information is explicitly given. We addressed this question presenting simple monetary gambles, where all decisional parameters were given and outcome feedback was absent, to patients with early Huntington's and Parkinson's disease, taken as complementary models of striatal dysfunction. Behavioural responses and associated times were found to be unaltered. This negative finding suggests that striatal activity may not be essential for decision-making in situations where all information is provided and

learning from outcomes is unnecessary. *NeuroReport* 22:753–757 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

NeuroReport 2011, 22:753–757

Keywords: decision-making, Huntington's disease, Parkinson's disease, prospect theory, risk, striatum

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Received 20 June 2011 accepted 11 July 2011

Introduction

Everyday life is pervaded by situations, such as managing one's finances or crossing a road to catch a bus, which require deciding among options associated with outcome probabilities, risks and potential rewards. Although several theoretical accounts of decisional behaviour are available, the neuroanatomical substrates of our ability to evaluate and choose among risky options remain incompletely understood [1,2]. Broadly it is hypothesized that the integration of available information subserving the calculation of expected value (EV) takes place mainly in the dorsolateral and ventrolateral prefrontal cortex, whereas the abstract value of possible actions is represented in the dorsomedial and ventromedial prefrontal cortex and outcome feedback as well as strategic aspects are processed primarily in the orbitofrontal cortex [3,4]. These regions are intensely interconnected with the basal ganglia through multiple reentrant loops [5].

The exact functional involvement of the basal ganglia in decision-making, in particular of the striatum, remains partly unclear. The mesolimbic dopaminergic system, including the ventral tegmental area and ventral striatum, has a well-established role in generating and embodying reward and reward prediction error signals, that is, supporting decisions in situations where learning from feedback is essential [6]. One fundamental question which remains unsettled is whether the striatum is also actively involved in the more elementary process of

evaluating the available choice-options in a situation where all information is available, that is, in calculating associated values and risks.

In a recent functional MRI study, Tõn *et al.* [7] presented healthy controls with simple monetary gambles in a task where no outcome feedback was provided and reward delivery signals were therefore absent. They reported that activity in the dorsal and ventral striatum was strongly correlated with EV and predicted individual risk propensity. Although suggestive, these findings do not necessarily imply a functional role of the striatum in driving choice among risky options, and in fact it has been shown that when value computation and reward prediction are separated the striatum responds specifically to reward expectation, and that striatal engagement varies with the predictability of outcomes independently of EV [8,9].

Here, we have explored the involvement of the striatum in risky decision-making through behavioural study of patients with early Huntington's disease and Parkinson's disease. Although both disorders eventually lead to significant neocortical degeneration, in early stages the burden of pathology is mostly confined to midbrain and basal ganglia structures [10,11]. Early Huntington's disease and Parkinson's disease may therefore be taken as empiric 'system lesion' models of striatal dysfunction with relative sparing of the prefrontal cortex. We have come to the

conclusion that it is necessary to remove this sentence because it may be misleading. We have employed a decisional paradigm similar to that of Tom *et al.* [7], involving evaluation of hypothetical gambles without outcome feedback.

Methods

Participants

Ten patients with Huntington's disease (age 39 ± 9 years, 7 women, education 13 ± 3 years), 11 patients with idiopathic Parkinson's disease (age 54 ± 11 years, 3 women, education 13.0 ± 2 years) and 16 controls (age 45 ± 14 years, 7 women, education 14 ± 3 years) free from neurological and psychiatric disorders were enrolled. There were no significant age or education differences between patients and controls.

The experiment was approved by the review boards of Fondazione IRCCS Istituto Neurologico 'Carlo Besta' (no. BEHAV-DM) and Brighton & Sussex Medical School (no. 10/056/MIN). Written informed consent was obtained from all participants, who did not receive any money or material compensation and were not playing with real currency.

All participants were native Italian speakers, right-handed [12] and naive to the task. The diagnosis of Huntington's disease was genetically confirmed and the number of CAG repeats was 45 ± 2 (mean $\pm$ standard deviation). Six patients with Huntington's disease had already developed motor symptoms, with Unified Huntington's Disease Rating Scale score 17 ± 9 and Total Functional Capacity score ≥ 11 , whereas the remaining four were still asymptomatic, with predicted onset in 9 ± 3 years [13]. The diagnosis of Parkinson's disease was established according to the UK Parkinson's disease brain bank criteria [14] and full neurologic examination was conducted to exclude atypical parkinsonism. The patients with Parkinson's disease had a Hoehn & Yahr score $< III$, Unified Parkinson's Disease Rating Scale score 18 ± 7 and disease duration 3 ± 1 years. All were taking dopamine replacement therapy, Levodopa Equivalent Daily Dose 140 ± 120 mg, and tested while on their usual medication.

Neuropsychiatric and neuropsychological testing

All participants had depression and anxiety scores in the normal range [15] (depression 34 ± 6 for controls, 38 ± 7 for Huntington's disease and 39 ± 11 for Parkinson's disease patients; anxiety 32 ± 6 for controls, 38 ± 6 for Huntington's disease and 42 ± 8 for Parkinson's disease patients), but on average patients had higher anxiety levels than controls ($P = 0.005$ for Parkinson's disease, $P = 0.03$ for Huntington's disease patients). Psychiatric symptoms were assessed through the Brief Psychiatric Rating Scale and excluded for all participants.

On the Montreal Cognitive Assessment battery [16], probing multiple aspects of general intellectual function,

all participants had scores in the normal range (27 ± 2 for controls, 26 ± 2 for Huntington's disease and 28 ± 1 for Parkinson's disease patients) without differences between patients and controls. All participants had normal scores in the backward digit-span test (5.8 ± 1.6 for controls, 4.7 ± 1.4 for Huntington's disease and 5.0 ± 0.8 for Parkinson's disease patients), Stroop test (17 ± 7 s for controls, 22 ± 15 s for Huntington's disease and 16 ± 8 s for Parkinson's disease patients) and Trail-Making Test part B-A (69 ± 40 for controls, 80 ± 37 for Huntington's disease and 65 ± 48 for Parkinson's disease patients), without any group difference.

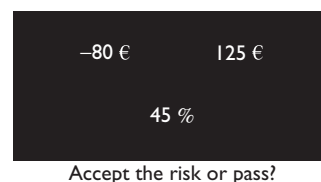
Decision-making task

We presented individual mixed-gambles (Fig. 1) explicitly reporting potential loss (k_{lose}) and win (k_{win}), and probability of winning (p). These appeared simultaneously in white Arial 36 font over a black background on a 19 inch screen located 1 m away from the head.

The displayed parameters determined the EV of each gamble according to $EV = p \times k_{\text{win}} - (1-p) \times k_{\text{lose}}$. Participants were asked to carefully consider the convenience of each gamble, and decide to accept or reject (i.e., choose between a safe $EV = 0$ option and a risky $EV \neq 0$ option) using their 'gut feeling', without mathematical computation and as rapidly as possible, within a maximum of 6 s. This time limit was indicated to reduce variability but not actually enforced. No feedback was provided on the outcome of individual gambles. Participants were informed that the computer would record their responses as a 'virtual bank-account' starting from a balance of 0 € and updated with the amount won or lost each time, and that outcomes were not pre-determined. They were asked to choose as if playing with real money, aiming to earn as much as possible, and were told that the final balance would be revealed.

For each session, the gambles were randomly drawn from a pool of 10 000 items. Across sessions, the range for k_{win} and k_{lose} was between 0 and 300 €, whereas p was between 0.1 and 0.9. According to Mann-Whitney test, there was no difference between the distributions of k_{win} (92 ± 72 €, median 90 €) and k_{lose} (92 ± 72 €, median 88 €). According

Fig. 1



Gamble presentation format, depicting potential loss (k_{lose}), gain (k_{win}) and winning probability (p).

to one-sample *t*-test, the distribution of *EV* ($-1 \pm 44\text{€}$, median -3€ , range -202€ to 202€) was centred around 0€ . The linear correlation coefficients with respect to *EV* were similar across the three parameters displayed, that is, $r = 0.36$ for k_{win} , $r = 0.41$ for k_{lose} and $r = 0.32$ for p . These features ensured that the statistical properties of the gambles would not bias the behavioural findings.

Responses were entered by button-press using the index and middle fingers of both hands, according to a four-level scale, that is, 'confident reject', 'unsure reject', 'unsure accept' and 'confident accept'. Participants were asked to make use of all levels, even though there was no difference in the consequences of confident and unsure responses. As in [7], four response levels were employed to prompt reflecting deeply on the subjective palatability of each gamble instead of using a fixed rule.

Each session included 240 gambles, of which the first 40 were considered practice trials and discarded from analysis. The task was self-paced and a new gamble was presented immediately upon response to the previous one. Overall, task duration was 15.4 ± 6.6 min.

Data analysis

The reaction times were *z*-normalized within each participant, and responses for which these fell outside three standard deviations from the average were discarded.

For each participant, the proportion of positive-*EV* gambles accepted and negative-*EV* gambles rejected, referred to as '*EV*-discrimination accuracy', and the overall proportion of gambles accepted, referred to as 'acceptance', were calculated. The proportion of confident responses was also determined. Further, the total amount earned was computed as the sum of *EV* across all accepted gambles. Individual 'decision-weighting' curves, representing acceptance probability as a function of *EV*, were also obtained.

Four logistic regressions were performed, modelling acceptance/rejection separately as a function of k_{win} , k_{lose} , p and *EV*. To obtain a further measure of risk aversion in addition to acceptance, we calculated the ratio of regression coefficients $\lambda = -\beta_{\text{lose}}/\beta_{\text{win}}$ as in [7], representing how much losses are weighted with respect to gains.

The average reaction times were also calculated, and linear regressions were performed to model the effect of k_{win} , k_{lose} , p and *EV* on normalized reaction times.

Patients with Parkinson's disease and Huntington's disease were separately compared with controls through nonparametric Mann–Whitney tests.

Results

The scatter plots for reaction times, *EV*-discrimination accuracy, acceptance, proportion of confident responses,

amount earned and logistic regression coefficients are shown in Fig. 2.

Overall, participants performed the task beyond chance level, preferentially choosing positive-*EV* gambles (*EV*-discrimination accuracy 0.74 ± 0.08 , median 0.72 ; $P < 0.001$) and earning a positive amount of money ($1930 \pm 850\text{€}$, median 1890€ ; $P < 0.001$). Participants accepted significantly less than half of the gambles (0.40 ± 0.10 , median 0.39 ; $P < 0.001$), and weighted potential losses significantly more than equivalent gains ($\lambda = 1.4 \pm 1.1$, median 1.2 ; $P < 0.001$).

There were no differences between patients and controls on any behavioural measure, including the logistic regression coefficients modelling accept/reject response (referred to as β_{win} , β_{lose} , β_p and β_{EV} in Fig. 2) and the linear regression coefficients modelling the effect of the economic parameters on the reaction times.

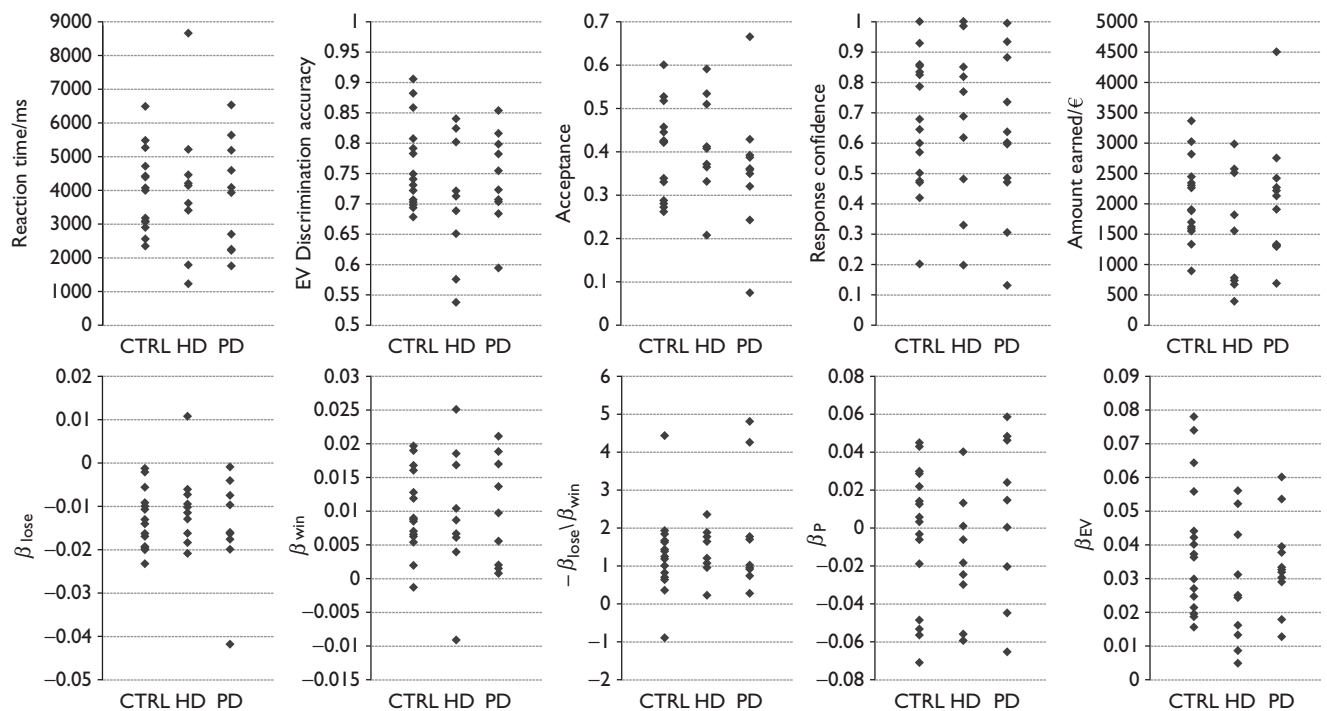
Similarly, the 'decision-weighting' curves substantially overlapped among the three groups (Fig. 3).

Discussion

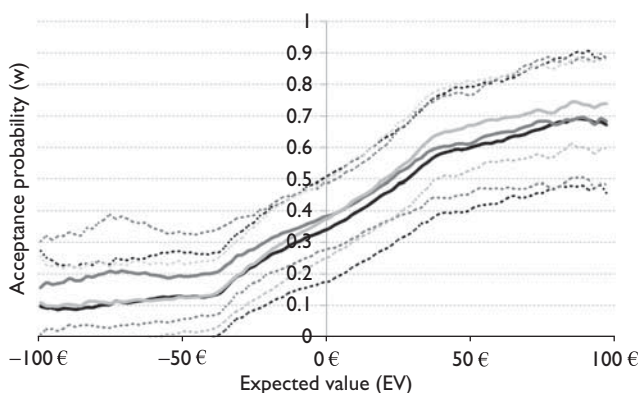
Despite the lack of real monetary involvement, participants exhibited significant risk aversion, that is, preferentially rejected $EV \cong 0$ gambles and overweighed potential losses with respect to gains, in line with the predictions of prospect theory and with the behavioural results obtained by Tom *et al.* [1,2,7]. We did not observe any significant difference in choice patterns and reaction times between patients with Huntington's disease and Parkinson's disease and controls. As visible in Figs 2 and 3, the associated behavioural parameters and decision-weighting curves substantially overlapped between groups.

It is widely agreed that patients with Parkinson's disease perform poorly on tests of decision-making under ambiguity, such as the Iowa gambling task, where information is incomplete and the ability to process reward prediction error signals is critical [17,18]. By contrast, recent work found that decision-making under risk, where all information about available options is given and feedback is not essential for performance, is intact [18]. Along the same lines, there is evidence that while executive and strategic reasoning can be impaired in Huntington's disease, decision-making under risk is spared [19].

Our observations agree with and extend these results, indicating that the incipient striatal pathology accompanying the early phases of Parkinson's disease and Huntington's disease does not affect the representation of the economic parameters characterizing monetary gambles. Abstract representation of *EV* is hypothesized to take place primarily in the ventromedial prefrontal cortex [20], and our results suggest that while the *EV* of available options modulates striatum activity, such activity is likely not to be fundamental to support

Fig. 2

Scatter plots for the behavioural parameters across the three groups (CTRL, healthy controls; HD: Huntington's disease patients; PD, Parkinson's disease patients).

Fig. 3

Acceptance probability versus expected value for patients with Huntington's disease (dark grey), patients with Parkinson's disease (black) and controls (light grey). Dotted lines represent one standard deviation.

decision-making under situations of risk without ambiguity, that is, when one simply needs to choose among available options without relying on feedback from rewards and punishments. The role of the striatum seems related to the representation of reward and reward prediction error signals, which are necessary for adaptive behaviour in some decisional tasks but not necessarily

relevant to others [8,9]. The roles of the dorsal and ventral striatum are also likely sensitive to the nature of decisions, emotional involvement and urgency [21].

To retain anatomical specificity and minimize potential effects of neocortical pathology, only early-stage and presymptomatic patients were tested, and it is possible that the burden of striatal degeneration may have been insufficient to generate significant behavioural differences on this task. Although we cannot exclude this possibility outright, it seems unlikely considering that in Huntington's disease substantial striatal pathology begins to accumulate more than a decade before the predicted onset of motor symptoms, leading to progressive atrophy [10,22]. Indeed, a range of cognitive and emotional disturbances can be observed well before motor symptoms ensue [23] and it has been hypothesized that the striatum may even develop abnormally [24]. Similarly, in Parkinson's disease the pathological process begins decades before the onset of motor symptoms and by the time a clinical diagnosis is made, a significant proportion of substantia nigra neurons and striatal dopaminergic synapses have already been lost [25].

Conclusion

Our results on the evaluation of monetary gambles in patients with Huntington's disease and Parkinson's disease indicate that, while the striatum plays a central role in tasks where feedback processing is essential for

performance, its engagement may not be actively subserving the decisional process in situations where all information about available options is provided explicitly and all that is required is to represent and compare their values.

Acknowledgements

L.M. was wholly funded by the Fondazione IRCCS Istituto Neurologico Carlo Besta (FINCB) during the core period of this study. This research forms part of a BSMS doctoral dissertation (10/056/MIN) and is based on preparatory work conducted while L.M. was still employed by BSMS. All behavioural data were acquired by S.P. and E.F. at the FINCB.

Conflicts of Interest

There are no conflicts of interest.

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