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The Allure of High-Risk Rewards in Huntington's disease

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Abstract

Objectives: Huntington's disease (HD) is a neurodegenerative disorder that produces a bias toward risky, reward-driven decisions in situations where the outcomes of decisions are uncertain and must be discovered. However, it is unclear whether HD patients show similar biases in decision-making when learning demands are minimized and prospective risks and outcomes are known explicitly. We investigated how risk decision-making strategies and adjustments are altered in HD patients when reward contingencies are explicit. **Methods:** HD ($N = 18$) and healthy control (HC; $N = 17$) participants completed a risk-taking task in which they made a series of independent choices between a low-risk/low reward and high-risk/high reward risk options. **Results:** Computational modeling showed that compared to HC, who showed a clear preference for low-risk compared to high-risk decisions, the HD group valued high-risks more than low-risk decisions, especially when high-risks were rewarded. The strategy analysis indicated that when high-risk options were rewarded, HC adopted a conservative risk strategy on the next trial by preferring the low-risk option (i.e., they counted their blessings and then played the surer bet). In contrast, following a rewarded high-risk choice, HD patients showed a clear preference for repeating the high-risk choice. **Conclusions:** These results indicate a pattern of high-risk/high-reward decision bias in HD that persists when outcomes and risks are certain. The allure of high-risk/high-reward decisions in situations of risk certainty and uncertainty expands our insight into the dynamic decision-making deficits that create considerable clinical burden in HD. (*JINS*, 2016, *22*, 426–435)

Keywords: basal ganglia, neurodegenerative disease, cognition, executive test, decision-making, reward processing

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurological disorder causing pronounced neurodegeneration of neostriatal neurons and associated disruption to frontal-striatal circuitries. While known for producing involuntary choreiform movements, HD is accompanied by a range of neurobehavioral changes that often precede or coincide with the onset of motor symptoms (Albin, Young, & Penney, 1989; Duff et al., 2007; Mink, 1996; Mink & Thack, 1993). Clinically, among the most burdensome of these changes are decisions that are unduly impulsive, lacking forethought, or risky (Rosenblatt, 2007; Duff et al., 2010). Understanding the processes underlying these decisions is critical for developing novel interventions and revealing the scope of processes linked to frontal-striatal circuitry.

Risky decision-making in HD has been investigated primarily in situations where the rewarding or punishing consequences of decisions are uncertain and must be discovered through trial-and-error learning, for example, Stout and colleagues studied decision-making in HD using the Iowa Gambling Task (IGT) (Campbell, Stout, & Finn, 2004; Stout, Rodawalt, & Siemers, 2001). In this task, participants attempt to win money by making a series of selections from four available decks of cards. Whereas healthy controls show an emerging preference for the advantageous decks (i.e., cumulative monetary winnings exceed losses) across a series of decisions, HD patients are particularly drawn to the allure of the disadvantageous decks of cards that promise large immediate rewards despite greater long-term consequences.

Related work in HD using reversal learning paradigms has also revealed deficits in decision learning that involves

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adaptation to changing reward contingencies. In these paradigms, participants initially learn to dissociate decisions leading to reward and decisions that lead to punishment. The key measure is how committed participants are to the initially rewarding decisions when they cease to be rewarding and punishing alternatives now become rewarding (i.e., reward contingencies reverse for the competing decision options). Like the IGT, rewarding decisions and their subsequent devaluation must be discovered in a context of uncertainty. Human and animal (i.e., mice transgenic for HD) studies generally show that the initial learning of rewarding choices is preserved in HD, but compared to healthy controls, HD patients perseverate with these choices long after they cease to be rewarding (Abada, Nguyen, Ellenbroek, & Schreiber, 2013; Brandt et al., 2008; Brooks et al., 2012; El Massioui, Ouary, Cheruel, Hantraye, & Brouillet, 2001; Fink et al., 2012; Lawrence, Sahakian, Rogers, Hodge, & Robbins, 1999; van Raamsdonk et al., 2005). This inflexibility in adapting behavior to changing reward contingencies in situations of uncertain risk and outcomes appears to contribute to the risky decision-making in HD, particularly when confronted with novel circumstances.

Current Study

In the IGT and reversal learning paradigms, reward contingencies associated with specific decisions are discovered in a context of uncertainty about risks and potential outcomes. Deficits in these tasks can be attributed to problems with implicit learning of the associations between stimuli, decisions, and outcomes. In HD, deficits in learning processes critical to forming expectations and contingencies between stimuli, actions, and outcomes play a key role in patterns of decision-making in times of uncertainty. However, in many life situations, risks and potential outcomes of decisions are well known in advance. An extensive literature indicates that risk decisions in situations of uncertainty versus certainty about outcomes involve dissociable cognitive mechanisms and neurobiological systems (Euteneuer et al., 2009; Labudda et al., 2010; Schiebener, Zamarian, Delazer, & Brand, 2011). To our knowledge, the dynamics of risky decision-making in HD have not been investigated in situations where risk and reward contingencies associated with decision options are certain.

We used a risk-taking paradigm developed by Cohen and colleagues (Cohen and Ranganath, 2005; Cohen, Heller, & Ranganath, 2005) to investigate the effects of HD on reward-based decision-making when rewards and risk options are known explicitly. The task minimizes learning and working memory demands common to risk-taking under uncertainty by asking participants to make a series of choices between a more certain, but low reward option and a less certain, but high reward option. The magnitude and probability of reward associated with each option are made explicit to the participant at the beginning of the experiment, so they are fully aware of the risk associated with each option. Additionally, each decision is independent (in terms of outcome) of the next as participants are free to choose either option at each decision point. The paradigm measures general risk preference between high and low-risk decisions. Cohen and colleagues further showed that even though the task eliminates learning processes required to form stimulus-decision-outcome contingencies, it critically exposes sequential dependencies and adjustments in risk decision-making based on the outcomes of previous risk choices (e.g., how a participant adjusts risk preference when a prior high-risk choice is rewarded versus unrewarded).

We made specific predictions based on patterns of risk preferences and adjustments in healthy adults who performed the current explicit risk-taking task (Cohen and Ranganath, 2005; Cohen et al., 2005) and based on decision-making deficits in HD on measures of implicit decision-making and learning. First, because decisions in HD patients appear to be more sensitive to large rewards in situations where risk is discovered implicitly, we predicted that HD patients (in comparison to healthy controls) would show a higher preference for the high-risk option, which offers the prospect of obtaining a larger reward. Second, based on reversal learning studies that show HD patients tend to perseverate with previously rewarded choices, we predicted that HD patients would be more inclined to repeat a high-risk decision after high-risk decision was rewarded (i.e., a win-stay strategy). Establishing these decision patterns in a risk certain context that minimizes learning demands would offer evidence that HD has a direct impact on the way prospective rewards bias decision-making processes.

An additional advantage of the current risk-taking task is that risk preferences and sequential dependencies associated with those preferences have been modeled and linked to specific cortical-striatal circuitries that have been associated with reward and risk processing (Cohen & Ranganath, 2005; Cohen et al., 2005; Engelmann & Tamir, 2009; for a review, see Liu, Hairston, Schrier, & Fan, 2011). The model's estimated decision-outcome value parameters represent how reward influences an individual's preference for risky decision choices on the next event. For example, enhanced brain activity in orbitofrontal cortex (OFC), putamen, dorsal cingulate, and amygdala was linked to an increase in high-risk-taking on trials subsequent to a rewarded high-risk decision. Increased activity in bilateral inferior temporal cortex, on the other hand, predicted an increase in low-risk taking on the trial subsequent to a low-risk rewarded trial (Cohen & Ranganath, 2005). Thus, alterations in performance may provide clues regarding altered cortico-striatal circuitry associated with risky, impulsive decision-making in HD.

METHODS

Participants

Two groups participated in this study: patients diagnosed with mild and early-stage HD ($N = 18$), and HC ($N = 17$) matched for age. As shown in Table 1, the two groups were similar in age (HD = 48.72; HC = 45.88) and gender

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Table 1. Participant demographics (averages and standard deviation)

	HD	HC	*p*-Value
Sample size	18	17	
Age	48.7(12.6)	45.88(12.8)	0.51
Gender (M: F)	7:11	5:12	0.28
UHDRS	35.78(16.03)		
Disease duration	2.26(1.25)		

(HD = 7 male; HC = 5 male). HD patients had a mean Unified Huntington's Disease Rating Scale (UHDRS) score of 35.78, and disease duration of 2.26 years.

Participants with HD were recruited from a specialty Huntington's Disease Clinic where they had been diagnosed by movement disorder neurologists (M.B.H., D.O.C.). HD was genetically confirmed by CAG repeats greater than 40, and patients met the diagnostic criteria as based on UHDRS (Kieburtz et al., 1996). Patients were given a diagnosis of mild to moderate severity of HD, by a movement disorder neurologist, based on clinical symptoms and motor severity.

Healthy controls were recruited through community advertising. Exclusionary criteria for all participants included history of (other) neurological conditions, unstable mood disorders, bipolar affective disorder, schizophrenia, or other psychiatric or medical conditions known to compromise executive cognitive functioning. A Mini-Mental Status Exam (MMSE; Folstein, Folstein, & McHugh, 1975) score larger than 23 was used as an inclusion criterion. All patients were tested on their usual medication, that is, a combination of atypical antipsychotics, anti-depressants and anxiolytics.

Participation in the study was voluntary and participants received no reimbursement. Informed consent, compliant with the standards of ethical conduct in human research as governed by the University of Virginia and Vanderbilt University human investigation committees, was obtained from all participants.

Design and Procedure

Figure 1 shows an example trial of the risk-taking task. Patients participated subsequent to their clinic visit, but the testing procedures were identical for HD and HC groups. Participants completed an explicit risk-taking task in which they made a series of choices between two response options (Cohen and Ranganath, 2005; Cohen et al., 2005). The task was an in-house adaptation of Cohen's risk-taking task (time to respond was increased, inter-trial interval was shortened and the response options were modified) and run on an IBM-compatible computer using E-prime software (PST 2.0) in a quiet testing room. All stimuli were presented against a gray background on a 17-inch screen located approximately 1 meter from the participant and positioned such that the stimuli appeared at eye-level.

At the beginning of the task, subjects were instructed that they would be making a series of choices between two decision options, each of which offered a chance to win money. They were told that the goal of task was to win as much money as possible. Next, subjects were then given explicit information about the probabilities and reward magnitudes of each risk option. Specifically, subjects were told that choosing the low-risk option offered an 80% chance of winning $1.25, but a 20% chance of earning $0.00. In contrast, selecting the high-risk option carried a 40% chance of winning $2.50, but a 60% chance of earning $0.00.

Each risk option was assigned to a left or right hand button press (i.e., a left or right thumb press using handheld button grips), with the mapping between hand and risk option counterbalanced across subjects. Subjects were instructed to choose one of the risk options each time an asterisk symbol appeared in the center of the computer screen. In separate practice sessions, subjects next practiced choosing each option and observing the outcome (10 selections for each risk type). The experimenter ascertained that each subject understood the task and risk options before starting the experimental session.

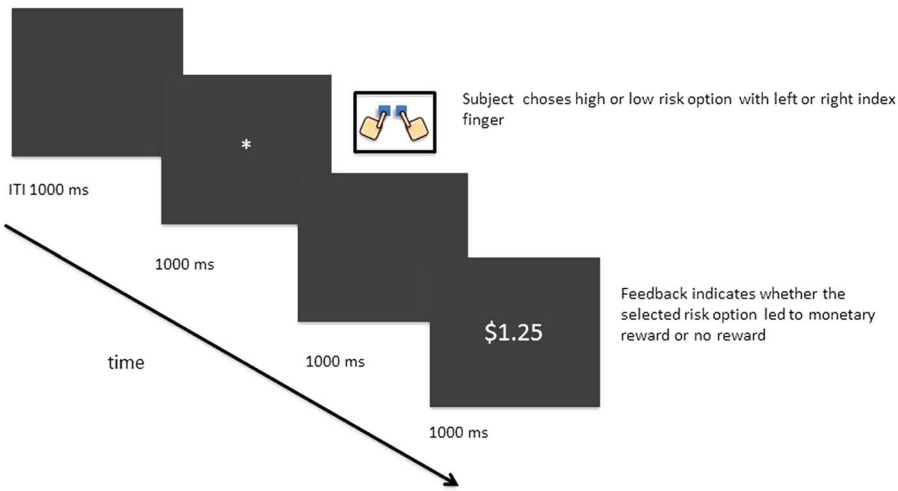

Fig. 1. Trial example from of the risk-taking task.

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Each trial began with a blank screen (1 s) followed by the appearance of the asterisk (1 s). Upon the presentation of the asterisk, subjects were given 2 s to decide between the high-risk and low-risk options by pressing the button assigned to that option. Feedback was then displayed on the computer screen (1 s) according to the probabilities associated with the selected option (i.e., subjects either won the expected reward or the decision was unrewarded). Outcomes were randomly determined on a trial-by-trial basis. Given that outcomes were probabilistic, the chances for reward on each trial were independent of the outcomes of prior trials. Overall, both decision options were equivalent in expected value ($0.8 \times \$1.25 = 0.4 \times \$2.5$), therefore, a particular choice strategy would not affect the overall outcome. Notably, the expected values of option decisions and overall outcomes were not mentioned to the subjects. Following feedback for a chosen option, the next trial began. For the experimental session, they performed five blocks of 26 trials. At the end of the experiment, the total earnings were displayed (but not actually paid) to the subject.

Data Analyses

Risk-taking strategies

We analyzed overall preference for the two risk strategies as well as conditional risk-taking strategies. The latter calculated the probability of choosing a high-risk option based on whether the previous trial decision was high or low-risk and rewarded or unrewarded. For example, for trials following a rewarded high-risk decision, we counted the number of high-risk and low-risk decisions and divided each count by the total number of rewarded high-risk decisions. This permitted analysis of how risk strategies adapted to previous risk decisions and outcomes and provides insight into the data from a trial-to-trial perspective. Both the risk-taking strategies as well as the modeling parameters were associated with the neural correlates as measured by Cohen and Ranganath (2005). The percentage of high-risk choices were analyzed using repeated-measures analysis of variance (RM-ANOVA), including a between-subjects factor group (HD, HC) and within-subjects factors PreviousRisk (High, Low) and PreviousOutcome (Rewarded, Unrewarded).

Decision-outcome value parameters

We applied a computational modeling approach similar to Cohen and Ranganath (2005, 2007), because it has a neurobiological basis (Montague, Hyman, & Cohen, 2004), and the value parameters estimated by this model have been shown to capture individual differences in cortico-striatal activity related to behavior on the task that might further confirm group differences in risk-taking preferences. Additionally, the model estimates a discount parameter, reflecting the influence of previous trials on current trial behavior; it captures value assigned to an individual's recent history of decisions. This parameter was used to exclude the possibility that group differences in risk-taking could be explained in terms of a memory deficit.

A subset of the subjects (16 HD, 16 HC) was included in the model parameter estimation analyses. The data from the two HD and one HC subjects excluded from the analysis did not converge to the model, that is, the model was not able to estimate parameters reliably because participants showed highly repetitive risk decisions (e.g., chose one option >85% of the time). First, decisions were categorized by their degree of risk (high *vs*. low) and reward (rewarded *vs*. unrewarded), which resulted in four decision-outcome categories: high-risk rewarded, high-risk no reward, low-risk rewarded, low-risk no reward. To investigate the effect of reward history on current choices, we calculated predictive values for each decision using a variation of a simple reinforcement learning algorithm (Barraclough, Conroy, & Lee, 2004; Cohen & Ranganath, 2005; Sutton & Barto, 1998). According to reinforcement learning models, a decision is based on the difference between the value functions (i.e., the expected reward) for each of the choices. The value function for trial t is noted as Vt(highrisk) for a high-risk choice, and Vt(lowrisk) for a low-risk choice. The probability of, for example, choosing a high-risk option on trial t is the log- transformation of the difference between the value functions (Christensen, 1997).

$$1.\quad p_t(\text{highrisk}) = \exp[V_t(\text{highrisk})] / (\exp[V_t(\text{lowrisk})] + \exp[V_t(\text{highrisk})]).$$

V_t is the value of each decision option on trial t and is updated on each trial according to the following formula:

$$2.\quad V_{t+1}(\text{highrisk}) = \alpha V_t(\text{highrisk}) + w_t(\text{highrisk}).$$
$$3.\quad V_{t+1}(\text{lowrisk}) = \alpha \text{Vt}(\text{lowrisk}) + w_t(\text{lowrisk}).$$

In this formula, α is the discount factor (i.e., the forgetting parameter, reflecting the influence of previous trials on current trial behavior) and w_t is a decision-outcome value that changes for each decision dependent on its outcome (four decision-outcome value parameters). Note that this model (as used by Cohen et al., 2005) is a variation of a simple reinforcement model[1]. However, since our task does not actually require learning of the contingencies (i.e., the outcome probabilities are known beforehand), this model does not include a learning rate but instead estimates a value parameter(w_t) for each decision-outcome combination. For example, when a subject decided to choose a high-risk decision and this was rewarded, the parameter w_{HR} (high-risk rewarded) would be updated on that trial, whereas the other value parameters remain unchanged. When a subject decided to choose the high-risk decision but it was not rewarded, w_{HN} (high-risk unrewarded) parameter would be updated.

[1] Vt+1 = Vt(choice) + learning rate × prediction error. The prediction error consists of the difference between expected and actual reward (reward-Vt(choice)). Thus the formula can be written as Vt+1 (choice)= (1-learning rate) × Vt(choice) + (learning ×reward), where the learning rate weighted by the reward value would be comparable to the estimated decision-outcome change values (w) for each of the risk and outcome combination.

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Similarly, low-risk rewarded and low-risk unrewarded choices would update, respectively, parameters w_{LR} (low-risk rewarded) and w_{LN} (low-risk unrewarded). A large w parameter indicates that participants highly value that particular decision and its outcome. Since the w value is a change parameter, it does not convey the participant's preference for a particular strategy or choice but merely the change in the subjective value of a decision option according to current reinforcements. For example, a high w_{HR} indicates that the participants highly value high-risk decisions that are rewarded and those decisions subsequently have a large influence on the value of a high-risk for the next trial. If the parameter is close to zero, this means that a high-risk reward has minimal influence on the future value of that decision. The sign of the parameter indicates whether the decision value for the next trial will increase or decrease on the next trial.

The five parameters (four decision-outcome value parameters and the discount parameter) were estimated in Matlab, using a maximum likelihood minimization procedure (Barraclough et al., 2004; Burnham & Anderson, 2002). Initial discount and decision-outcome values were set to zero. To evaluate the model fit, we calculated a pseudo R2 statistic using the following equation:

4. $\text{Pseudo R2} = (\text{R}-\text{L})/\text{R}$

L is the maximum log-likelihood for the estimated model given the data and R is log-likelihood of a model assuming random choice. A likelihood ratio test was used to evaluate whether the estimated model provides better a prediction of the data than a random choice model. The four value parameters were compared between groups by a RM-ANOVA with factors Group (HD, HC), Reward (Present, Absent), and Risk (High, Low). The discount parameter was compared between groups with an independent sample t test.

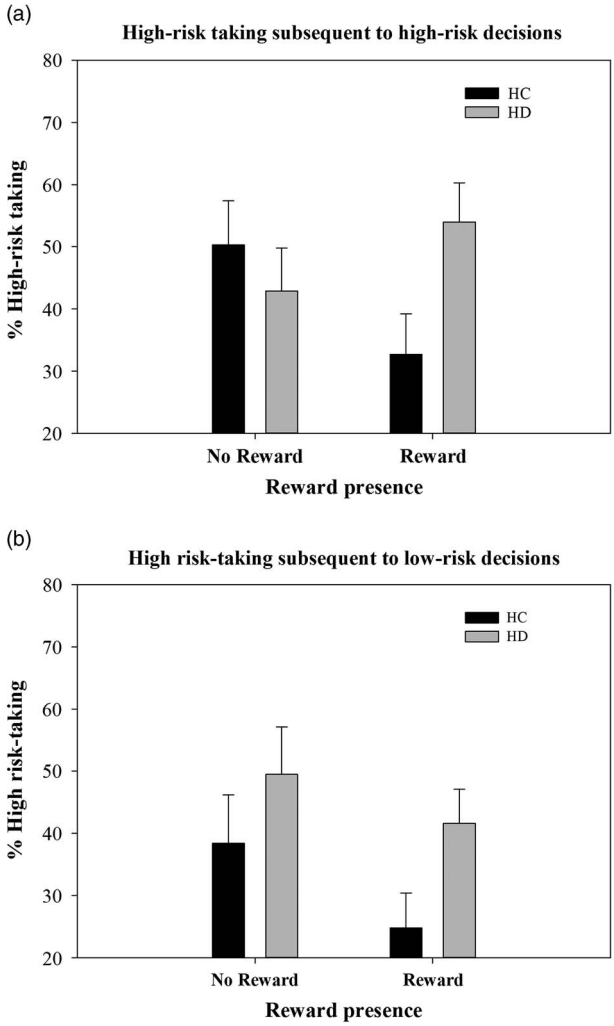

Fig. 2. Percentage of high-risks in HD and HC subsequent to previously rewarded and unrewarded high-risks (a) and low-risks (b).

RESULTS

Risk-Taking Strategies

Overall, HC participants adopted a more risk averse strategy, preferring the low-risk option (63.5%) over the high-risk option (36.5%). In contrast, HD patients were much more likely to take risks, preferring the high-risk option (47.0%) almost as much as the low-risk option (53.0%). Overall, irrespective of previous outcome or reward, the HD patients showed a higher preference for the high-risk option compared to HC participants, Group: $F(1,33) = 5.01$, $p < .05$, $\eta^2 = .13$.

Figure 2 shows group preferences for high-risk decisions subsequent to high-risk (a) and low-risk decisions (b) as a function of previous choice outcome. Preference for selecting a high-risk option did not vary as a function of the previous risk choice between high and low-risk options, (PreviousRisk: $F(1,33) = .82$; $p = .37$; $\eta^2 = .02$), a pattern that was consistent across the groups, (Group × PreviousRisk: $F(1,33) = .25$; $p = .62$; $\eta^2 = .01$). However, differences emerged between the groups in response to reward. Overall, when a decision was rewarded, irrespective of risk, participants generally become more risk averse; that is, following reward, participants were less likely to subsequently choose the high-risk option (38.3%) compared to their preference for the high-risk option (45.3%) following a unrewarded decision (PreviousOutcome: $F(1,33) = 6.50$; $p < .05$; $\eta^2 = .17$). However, when HC and HD groups were compared, the impact of reward on subsequent choices differed between the groups (PreviousOutcome × Group: $F(1,33) = 9.82$; $p < .01$; $\eta^2 = .23$). While HC were less likely to choose the high-risk option following a rewarded (28.8%) compared to an unrewarded (44.3%) decision (i.e., they were risk averse following rewarded decisions) (HC, $t(16) = 4.11$; $p < .01$; $r^2 = .51$), the HD group was just as likely to choose the high-risk option following a rewarded decision, selecting the high-risk option equally after rewarded (47.8%) and unrewarded (46.2%) decisions, (HD, $t(17) = .41$; $p = .69$; $r^2 = .01$).

The three-way interaction between Group, PreviousRisk, and PreviousOutcome showed a trend toward significance, suggesting a distinction between the HD and HC groups in their choice behavior after high-risks decisions, (Group × PreviousRisk × PreviousOutcome: $F(1,33) = 3.22$; $p = .08$; $\eta^2 = .09$). This prompted separate analysis of

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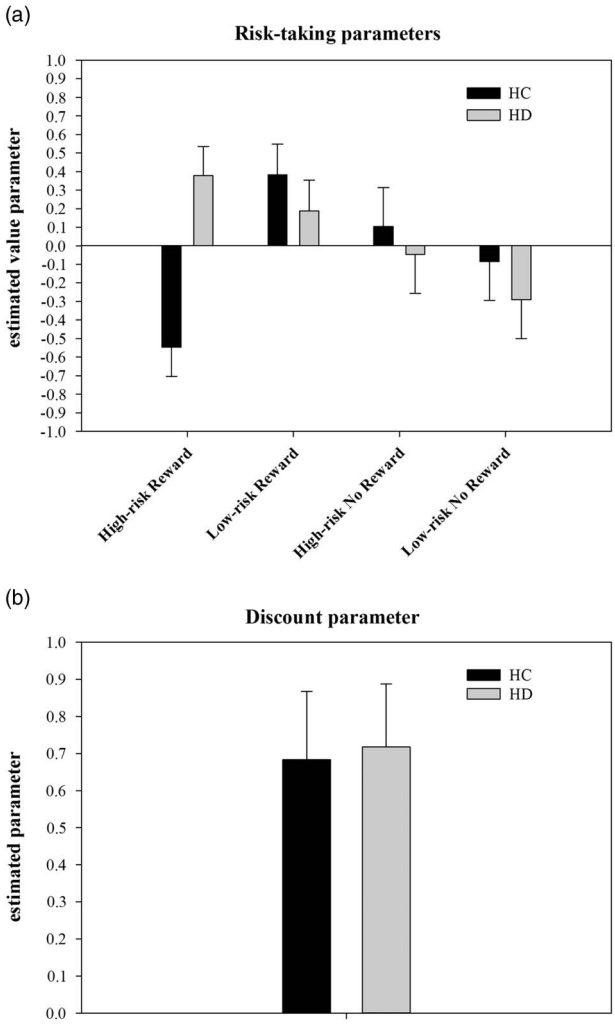

Fig. 3. Decision-outcome value taking parameters (a) and discount parameter (b) separately for HD and HC.

high- and -low-risks. As Figure 2 illustrates, subsequent to low-risk decisions, HD and HC participants showed a similar risk averse strategy (i.e., reduced preference for high-risk option) following low-risk decisions (Group: $F(1,33) = 2.63$; $p = .1$; $\eta^2 = .07$), and previous outcome did not change this pattern (PreviousOutcome × Group: $F(1,33) = .53$; $p = .47$; $\eta^2 = .02$). However, following high-risk decisions, HD showed an opposite pattern of preferences compared to the risk aversive HC group (PreviousOutcome × Group: $F(1,33) = 10.07$; $p < .005$; $\eta^2 = .23$). Whereas HC participants become risk averse after a high-risk decision was rewarded (i.e., win-shift strategy), HD patients became more risky (i.e., win-stay strategy) on a subsequent trial as evidenced by an increased preference for staying with the high-risk option, $t(33) = 2.36$, $p < .05$, $r^2 = .14$.

Decision-Outcome Value Parameters

Figure 3 shows the estimated decision-outcome value parameters (1) and the discount parameter (2) for both HD and HC groups.

The average individual pseudo-R^2 was .20, significantly better than a model predicting random choice for most subjects (97%, 31 of $n = 32$, likelihood ratio test, $p < .05$) and not different between HC ($R^2 = .18$) and HD ($R^2 = .21$), $F(1,31) = .66$, $p = .42$.

Overall, low-risk and high-risk options were valued equally (Risk: $F(1,30) = .97$; $p = .33$; $\eta^2 = .03$) and rewarded and unrewarded options were valued equally as well (Reward: $F(1,30) = 2.03$; $p = .17$; $\eta^2 = .06$). However, reward had a larger impact on the value of low-risks than on high-risks (Risk × Reward: $F(1,30) = 8.88$; $p < .01$; $\eta^2 = .23$). Overall, rewarded low-risk decisions were valued more positively (.28) than unrewarded decisions (−.19; $t(31) = 3.45$; $p < .01$; $r^2 = .28$), whereas reward did not make a difference with respect to the value of high-risk decisions (High-risk Reward = −.08; High-risk Unrewarded = .03; $t(31) = .56$; $p = .58$; $r^2 = .01$). Furthermore, the groups valued high and low-risk decisions differentially, (Group × Risk: $F(1,30) = 14.3$; $p < .01$; $\eta^2 = .32$). Whereas HCs valued low-risk decisions (.15) more positively than high-risk decisions (−.22) (Risk: HC, $F(1,15) = 7.33$; $p < .05$; $\eta^2 = .33$), HD patients showed the opposite pattern; they valued high-risk decisions (.17) more than low-risk decisions (−.05) (Risk: HD, $F(1,15) = 8.7$; $p < .05$; $\eta^2 = .37$).

Additionally, there was a clear group difference in valuation of rewarded and unrewarded choices (Group × Reward: $F(1,30) = 4.62$; $p < .05$; $\eta^2 = .13$), HCs valued rewarded and unrewarded decisions equally (Reward = −.08, Unrewarded = .01, $F(1,30) = .19$; $p = .67$; $\eta^2 = .01$), whereas HD patients valued rewarded decisions (.28) more than unrewarded (−.17) decisions ($F(1,30) = 10.1$; $p < .01$; $\eta^2 = .40$).

Also, the analysis confirmed groups differences in value parameters that reflected an interaction between risk and reward, (Group × Risk × Reward: $F(1,30) = 7.36$; $p < .05$; $\eta^2 = .2$). HD valued high-risk decisions that were rewarded (.38) significantly more than HC patients (−.55) ($F(1,30) = 17.28$; $p < .001$; $\eta^2 = .37$), whereas there were no significant differences between HD and HC groups on any of the other parameters (Fs < 1; *p*s > .4).

Analysis of the discount parameter, which captures value assigned to an individual's recent history of decisions, showed that the groups assigned similar value to recent choices, ($t(31) = .55$; $p = .59$; $r^2 = .01$). This suggests that any differences in risk-reward decision preferences cannot be attributed to more global differences in how the groups used outcomes of recent decisions to influence current decisions.

DISCUSSION

The present study provides novel insight into the decision-making strategies and preferences of HD patients, compared to HCs, in a relatively certain decision-making context (i.e., risks and outcomes are known explicitly). HCs showed a clear strategy toward risk aversion, particularly after a high-risk decision happened to be rewarded, which replicates previous studies with this task and a broader pattern observed across various risk-taking paradigms (Cohen & Ranganath, 2005;

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Cohen et al., 2005; Engelmann & Tamir, 2009; Tversky & Kahneman, 1981). In contrast, HD patients made high and low-risk decisions equally often, and increased their preference for high-risk decision-making after a high-risk choice had been rewarded (i.e., showed heightened risk propensity in the context of a previous high-risk decision and not in the context of a previous low-risk decision).

Previous investigations have emphasized the role of implicit learning processes as contributing to high-risk and reward persistence decisions in HD. In particular, HD patients appear less sensitive to losses in gambling situations where they attempt to discover optimal decision-making strategies under uncertainty (Campbell et al., 2004; Enzi et al., 2012; but see Busemeyer and Stout, 2002), and are slower at learning to shift away from previously positively reinforced decisions when these decisions unknowingly cease to be reinforcing (Abada et al., 2013; Brooks et al., 2012; El Massioui et al., 2001; Fink et al., 2012; Lawrence et al., 1999; van Raamsdonk et al., 2005).

The current findings expand on this work by demonstrating a preference for high-risk decisions among HD patients relative to HC even when uncertainty, learning, and working memory demands were minimized in the decision-making context (i.e., risks and rewards were made explicit). In comparison to HC participants, HD decision-making was more strongly driven by outcomes of decisions rather than the nature of risk on a preceding trial. Decision-making among HD patients was biased toward the high-risk, high reward option. Adjustments after low-risk decisions are similar to healthy controls, thereby excluding the alternative explanation that HD patients show a general absence of the normal risk aversion, instead high-risk preference depends on the context of the previous decision and outcome.

A previous analysis of Iowa Gambling Task performance in HD suggested that poor decision-making, in a context where risk and reward context were uncertain, may reflect reduced working memory abilities (Busemeyer and Stout, 2002); HD showed a heightened bias by more recent experiences, which leads to faster forgetting of more remote experiences). This is an unlikely account for the present findings because the current task minimizes the role of working memory and implicit learning, thus making each decision independent in terms of outcome. Second, the discount parameter modeled in the current data showed no difference between HD and HC, which indicates that the groups did not show a difference in general biases related to outcomes of recent decisions and experiences. Together, these findings demonstrate that there are different mechanism underlying risk-taking under uncertainty and risk-taking with explicit rules in HD.

Putative Neural Mechanisms

A recent meta-analysis of functional imaging studies by Liu et al. (2011) described several cortical (OFC, bilateral anterior insula, anterior and posterior cingulate corticies, inferior parietal lobule, and prefrontal cortex [PFC]) and basal ganglia (caudate, putamen, nucleus accumbens, thalamus) structures that are engaged across reward-based decision making tasks in healthy young adults. The neurodegenerative processes in HD directly impact several nodes of these cortico-basal ganglia circuitries (Hadzi et al., 2012; Paulsen, 2009; Vonsattel et al.,1985; Vonsattel & DiFiglia 1998). In the specific decision-task paradigm used in the current study, Cohen et al. (Cohen & Ranganath, 2005; Cohen et al., 2005) identified a subset of these cortico-basal ganglia regions whose activation corresponded to specific patterns of risk decision-making. First, they showed that higher preference for risky decisions was associated with increased functional connectivity between anterior cingulate cortex (ACC) and ventral striatum and between OFC and dorso-lateral PFC (Cohen et al., 2005). One implication is that HD produces a functional enhancement of connectivity in these circuitries that underlies their higher overall preference for the risky decision option compared to HCs. Alterations in ventral striatal activity, most notably in the left ventral striatum, have been linked to alterations in the anticipation of reward and punishment in individuals who are pre-symptomatic, gene-positive for HD (Enzi et al., 2012). Moreover, degenerative changes in ventral striatum and nucleus accumbens innervation of the ventral striatum are reported in early HD (Aylward et al., 2011; Rosas et al., 2003; Sánchez-Castañeda et al., 2013; van den Bogaard et al., 2011). Considered together, alterations to circuitry involving the ventral striatum may be critical to understanding the heightened preferences for high-risk reward decisions in early HD.

Additionally, Cohen and Ranganath (2005) reported that higher activation in the OFC, dorsal cingulate, putamen, and amygdala predicted increased likelihood that an individual would repeat a high-risk decision if they had just been rewarded for making a high-risk/high reward decision. Albeit an indirect speculation, these results suggest that HD patients may experience higher patterns of activation in these circuitries in a context of a recently rewarded high-risk decision. Thus, the changes in risk-taking and the influence of reward on risk-taking in HD in the current study may be explained by more pronounced signaling and activity in several key cortical-basal ganglia regions that are critical for mobilizing high-risk rewarding decisions. An important question for future research is determining how the progression of HD alters these circuitries in the context of decision-making and whether these circuitries are enhanced due to a more pronounced influence of reward processing or due to ineffective suppression of these circuitries that would promote the selection of safer, less risky decision options. The latter is particularly intriguing given evidence that HD alters synchronization between cortical regions (e.g., lateral PFC, ACC) that are critical for detecting conflict and mobilizing inhibitory control systems to suppress impulsive choices (Engelmann & Tamir, 2009; Kalkhoven, Sennef, Peeters, & van den Bos, 2014; Liu et al., 2011; Thiruvady et al., 2007).

The allure of high-risk rewards in HD might reflect progressive neuroanatomical alterations in reward-related cortico-basal ganglia circuitries, but might also reflect alterations in neuromodulators, like dopamine (DA). DA in

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healthy adults, and its alteration in Parkinson's disease, is tightly linked to variations in reward learning and reward-based risk decision-making (Cools et al., 2009; Frank, Seeberger, & O'Reilly, 2004; Rutledge et al., 2009; Schultz, 2002). The specific patterns of DA changes in HD are not fully understood yet and seem to vary non-linearly over the course of the disease (see Schwab et al., 2015 for a review). Of interest, Schroll, Beste, and Hamker (2015) investigated reward learning in HD using neuro-computational modeling and showed that simulated lesions of striatal neurons rather than DA modulation explained decrements in reward learning. The putative role of DA in reward processing in HD in patients at various stages of the disease (in unmedicated pre-manifest HD and in longitudinal studies of diagnosed HD patients) awaits future investigation.

LIMITATIONS AND CONCLUSIONS

There are certain limitations in the current study. One limitation is that patients were not withdrawn from medications aimed at treating their HD symptoms, including a handful of patients on DA antagonist medication, which could have altered reward processing. It would seem that DA antagonism would reduce rather than enhance the influence of reward, but how DA therapies alter reward circuitry in HD remains an empirical question.

Another limitation is the lack of detailed neuropsychological and clinical characteristics in our HD patient sample. We included non-demented patients in the early stage of the disease, and although neuropsychological functions are quite variable in early HD, we cannot entirely exclude the possibility that subtle neuropsychological changes moderated the patterns of risk decision-making. It is important to point out that the task used in the current study places very minimal demands on learning and working memory skills and, in fact, the discount parameter from the modeling ruled out any underlying memory differences across decision selections between HD and HC groups. However, it will be important to replicate the study in a sample of HD patients who are characterized with greater neuropsychological precision. HD patients also show higher susceptibility to depression, but notably depression is typically associated with reduced risk-taking and reward processing (Treadway & Zald, 2013; Whitton, Treadway, & Pizzagalli, 2015). However, how depression interacts with HD on reward system processing is also an open empirical question.

The computational model applied in the current study helped to exclude alternative explanations (i.e., the role of memory) and to link the risk-taking parameters to previous imaging studies. Although this model has been used before and is based on widely tolerated assumptions and parameter estimation strategies (Cohen & Ranganath, 2005, 2007; Montague, Hyman, & Cohen, 2004), we acknowledge that there may be a more optimal model to fit the decision-making data in the current paradigm. Future work with this paradigm would benefit from more formal testing of this model and plausible alternatives.

In conclusion, our findings point to specific alterations to reward valuation in the context of risky decision-making in patients with mild, early-stage HD. HD patients were more likely to repeat a high-risk decision immediately following a rewarded high-risk decision. The enhanced allure of reward in risky contexts in HD might have important implications for daily life decisions, such as financial choices. For example, in a recent review of pathological gambling in HD, Kalkhoven et al. (2014) concluded "HD patients may not have an increased tendency to start gambling, but they do have an increased chance of developing an addiction once they engage in gambling tendencies." In light of the current findings, we speculate that perhaps the initial exposure to a rewarded risky decision may be the trigger for repeating high-risk decisions that characterizes addictive, risky behaviors in HD.

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