Tit for Tat: Costly Punishment in Manifest Huntington's Disease

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Keywords

Huntington's disease · Altruistic punishment · Costly punishment · Revenge · Neuropsychological changes · Non-motor symptoms

Abstract

Objective: We aimed to investigate costly punishment in patients with Huntington's disease (HD). **Background:** HD is an autosomal dominant neurodegenerative disease with motor, cognitive, and psychiatric symptoms. As neuropsychiatric abnormalities often precede motor symptoms, we wanted to assess whether costly punishment is part of the neuropsychological profile of patients with HD. **Methods:** A total of 40 non-demented subjects were prospectively enrolled in this study with a between-subject design comparing manifest HD patients ($n = 18$) to healthy controls (HC; $n = 22$). All participants performed 8 rounds of a costly punishment task, in which money was shared unevenly in 5 rounds or in a fair manner in the remaining 3 rounds. Participants then had to decide whether they wanted to punish the trustee. Furthermore, all participants underwent neuropsychological background tasks. **Results:** HD patients performed worse in the neuropsychological background tests compared to HC (all p values < 0.05). Moreover, HD patients punished more often in fair (Wald $\chi^2 = 5.03$, $p = 0.025$) but not in unfair

rounds (Wald $\chi^2 = 1.63$, $p = 0.202$). **Conclusions:** Our results demonstrate increased costly punishment during fair conditions in HD patients. Whether this behaviour is due to a lack of recognition of social norms, an impairment in top-down inhibition, or an effect of antidopaminergic medication remains unclear.

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Introduction

Huntington's disease (HD) is a relentlessly progressive autosomal dominant neurodegenerative disorder with motor as well as cognitive, and behavioural decline. Neuropsychiatric abnormalities can often precede motor symptoms [1–3] and can be more debilitating for HD patients and their families. Several studies found impairment in decision-making [4], theory of mind [5], overcoming stimulus-response incompatibility and prepulse inhibition [6], obsessive-compulsive behaviours [7], impairment in social perception [8], and emotion processing [9, 10] in HD patients.

Costly punishment is defined as punishment at own costs with an intention to harm the proposer and yields no material gain [11]. The combination of costly punish-

Table 1. Demographic data

	HD	HC	<i>p</i> value
<i>n</i>	18	22	–
Gender (male:female)	7:11	10:12	0.12
Education, years $\pm$ SD	12.5 $\pm$ 4.0	13.9 $\pm$ 2.5	0.18
Age, years $\pm$ SD	50.6 $\pm$ 10.2	44.0 $\pm$ 15.3	0.17
CAG-repeats $\pm$ SD	44.4 $\pm$ 3.7	–	–
UHDRS-TMS $\pm$ SD	24.7 $\pm$ 14.3	–	–
Disease duration, years $\pm$ SD	3.5 $\pm$ 3.0	–	–

HC, healthy controls; HD, Huntington's disease; MoCA, Montreal Cognitive Assessment; UHDRS-TMS, Unified Huntington's Disease Rating Scale Total Motor Score.

ment and altruistic rewarding has been described before to be crucial in human cooperation, i.e., rewarding cooperative behaviour and punishing violations of social norms [12]. A recent study on costly punishment in patients with HD suggest that lacking of punishment when a norm violation occurred (e.g., punishment of unfair behaviour) is associated with impaired understanding of complex rules of social exchange and also associated executive dysfunctioning including working memory, inhibitory control. Furthermore, these patients performed also worse on “theory of mind” tasks [13]. In line with this, deficits in emotion recognition and emotion recognition of body language is also reduced in HD patients [10, 14] and correlated with the severity of motor symptoms [14]. Given these impairments of emotion recognition as well as difficulties understanding social norms, the high prevalence of irritability and aggression in HD [15], the known widespread brain atrophy [16], and the impairment in decision-making [4], we speculated that our manifest HD cohort would perform worse than healthy control (HC), i.e., punish more often than HC. Hence, we wanted to assess whether extensive punishment is part of the neuropsychological profile of patients with manifest HD using a costly punishment task where participants were asked in fair and unfair rounds to punish a virtual counterpart.

Methods

This study was approved by local Ethics Committee of the Medical University of Innsbruck, Austria, and all participants provided written informed consent according to the declaration of Helsinki.

Study Design

This study is a between-subject design comparing manifest HD patients to HC. A total of forty adult non-demented participants (i.e., a minimum of 26 points on the Montreal Cognitive Assessment [MoCA] Battery) were consecutively recruited via the specialized outpatient clinic of the Neurological Department of the Medical University of Innsbruck (see Table 1 for demographic data). All patients underwent a costly punishment task and neuropsychological tests including the Symbol Digit Modality Task (SDMT) and the Trail Making Test part A and B (TMT A and B). All patients were examined by the 2 clinicians (B.H. and M.P.), and neuropsychological test order was consistent as follows: MoCA, costly punishment task, SDMT, TMT A, and TMT B.

Study Participants

We included 18 genetically confirmed manifest HD patients with a mean disease duration of 3.5 ($\pm$ 2.9) years, and 22 HC without neurologic or psychiatric comorbidities or psychiatric co-medication. Only manifest HD patients with a diagnostic confidence score of 4 on the Unified Huntington's Disease Rating Scale were included (UHDRS). Detailed medical and psychiatric assessments as well as relevant demographic characteristics and family history were obtained from all participants. All participants were screened for cognitive deficits and excluded from the study if they scored <26/30 points on the MoCA test [17]. Participants with current depression, psychosis, alcohol or illicit drug abuse, aggressive behaviour, or other mental or neurological diseases other than HD were excluded. To reduce a possible impact on study results, participants were explicitly screened for apathy and depression and excluded if applicable.

Neuropsychological Background Tasks

Costly Punishment Task

We used a costly punishment game designed to assess altruistic punishment [12]. Details were published elsewhere [18].

Participants were told that they were playing live against 8 other human players but were in fact playing against the computer. Per round, participants played against one other player. Participants were told that each opponent had already been given EUR 10.00,- and that in every round the invested money was quadrupled. Thus, each of the 8 other players (opponents or trustees) received EUR 50.00,- in total. The trustee could either share equally (“fair” rounds; give back EUR 25.00,-) or could keep all the money (EUR 50.00,-; “unfair” rounds). All participants had the option to punish the trustee and were told that punishment would not only result in a decrease of the trustee's money but also reduce their own money. They would lose EUR 1.00,- for every EUR 2.00,- they punish their fellow players. Punishment options were no punishment, EUR 5.00,-, EUR 10.00,-, EUR 15.00,-, and EUR 20.00,-, to the expense of the participant's money of EUR 0.00,-, EUR 2.50,-, EUR 5.00,-, EUR 7.50,-, and EUR 10.00,-. In 3 of 8 rounds, participants were treated “fair” (receiving 50% = EUR 25.00,- back); in the other rounds (5 of 8), they were treated “unfair” (receiving EUR 0.00,- back). The investigator made sure that all participants understood the rules.

Symbol Digit Modality Task

Participants were presented with a paper-based page headed by a key that pairs the single digits 1–9 and 9 matched symbols [19]. The rows below only contain symbols and participants were told

to write the correct matching number in the spaces below the symbols. After guided completing the first 10 items, participants need to respond as many symbols as possible within 90 s. Correct answers and mistakes are calculated.

Trail Making Test A and B (TMT A and TMT B)

All participants were asked to complete the TMT part A and B [20]. Participants have to draw lines to conflate numbers in ascending order (part A). In part B, participants have to connect lines alternating between numbers and letters in ascending order (i.e., 1-A-2-B-3-C; part B). At the end, total time to completion was calculated (seconds).

Statistics

Statistical analyses were performed using SPSS 24.0. Parametric and non-parametric tests were used for statistical analysis depending on the distribution and the scale type of the variables.

Costly Punishment Task

Scores of all answers were calculated per patient and analysed using general linear models. Raw scores were 1 (no punishment) or, respectively, 2 for EUR 5.00,- punishment, 3 for EUR 10.00,-, 4 for EUR 15.00,-, and 5 for EUR 20.00,-. We used a generalized linear model (SPSS) with a multinomial cumulative logit link function to assess significance. Fair or unfair scores were modelled as dependent variables; group (HD or HC) was modelled as a fixed factor. We used Wald χ^2 (Wald χ^2) to assess statistical significance. Level of $p \leq 0.05$ was considered significant.

Symbol Digit Modality Task

Sum scores of correct and incorrect answers within 90 s were calculated per participant. A univariate general model ANOVA was used. Again group (HD and HC) was modelled as a fixed factor. Post hoc analysis of group differences was realized. All pairwise comparisons were Bonferroni corrected. A p value equal or below 0.05 was considered significant.

Trail Making Test Part A and Part B

Sum scores of time to completion for TMT A and TMT B were calculated per participant with a maximum of 240 s per task. A univariate general model ANOVA was used. Again group (HC, HD) was modelled as a fixed factor and gender and age were defined as covariates. Post hoc analysis of group differences was realized. All pairwise comparisons were Bonferroni corrected. A p value equal or below 0.05 was considered significant.

Results

This study assessed costly punishment in manifest HD patients. For demographic data see Table 1. There were no group differences between age, gender, or education. Most of the included HD patients had antidopaminergic medication: 5 had tiaprid, 7 quetiapine, 5 olanzapine, and 3 selective serotonin reuptake inhibitors (SSRI) including sertraline and citalopram, with 3 patients receiving a combination of quetiapine and sertraline.

Table 2. Neuropsychological tests, Bonferroni corrected

	HD (n = 18)	HC (n = 22)	p value
SDMT			
Correct $\pm$ SD	22.0 $\pm$ 12.2	47.6 $\pm$ 8.7	0.001***
Incorrect $\pm$ SD	0.8 $\pm$ 0.9	0.6 $\pm$ 1.8	0.682
TMT			
A, sec $\pm$ SD	115.7 $\pm$ 107.7	26.4 $\pm$ 7.4	$\leq$ 0.001***
B, sec $\pm$ SD	122.0 $\pm$ 114.2	52.0 $\pm$ 12.1	$\leq$ 0.001***

HC, healthy controls; HD, Huntington's disease; n, number; SD, standard deviation; SDMT, Symbol Digit Modality Task; sec, seconds; TMT A, Trail Making Test part A; TMT B, Trail Making Test part B; MoCA, Montreal Cognitive Assessment. All values are mean $\pm$ SD; all values are corrected for MoCA, education, and gender. *** $p \leq 0.001$.

Costly Punishment Task

We found a significant effect of group in fair rounds (Wald $\chi^2 = 5.35$, $p = 0.021$), but there was no group effect in unfair round (Wald $\chi^2 = 1.63$, $p = 0.202$). Post hoc analysis showed that HD patients punished significantly more often than HC in fair rounds (Wald $\chi^2 = 5.03$, $p = 0.025$).

Symbol Digit Modality Task

HD patients performed significantly slower than HC in the SDMT (less correct answers; $p < 0.001$), but there was no group difference regarding incorrect answers ($p = 0.682$) (Table 2).

Trail Making Test Part A and Part B

Furthermore, HD patients performed slower than HC in part A and B of the TMT (both p values ≤ 0.001) (Table 2).

Discussion

In this study, we found that HD patients performed worse than HC on the symbol digit modality task as well as on the trail making task, both tasks that require intact frontal lobe function [21]. Furthermore, we found that HD patients punished significantly more often than HC in fair but not in unfair rounds. Thus, HD patients decided to punish even when no norm violation occurred. This is particularly interesting and dovetails with one recent study which demonstrated a lack of altruistic punishment in HD patients when observing unfair behaviour from a third party perspective [22]. In this study, the altered behaviour was associated with poorer cognitive

flexibility, working memory, and inhibitory control [22]. Imaging studies have shown that costly punishment relies on a wide network including the ventral and dorsal striatal networks as well as the frontal lobe, especially the inferior frontal cortex [23]. While the caudate nucleus is involved in the amount of punishment, the frontal lobe, and particularly the right inferior frontal cortex plays a key role in the regulation of empathy [23]. In addition, imaging studies have shown that in HD patients, the prefrontal cortex is malfunctioning [23], which plays an important role in deciding whether punishment should be performed and is critically involved in top-down inhibitory control [24]. Furthermore, the majority of HD patients included in this study received antidopaminergic treatment. Dopamine plays an important role in social interaction and managing emotional control [25]. Therefore, it is possible that according to the inverted *U* shape hypothesis too little dopamine due to medication is maybe responsible for poorer task performance [26]. Another possible mechanism of the altered punishment behaviour may be explained by the “embodiment hypothesis,” which states that the perception of others’ behaviours is related to the activation of the motor system [27, 28]. Given the severe motor impairment in HD, altered punishment behaviour may be linked to basal ganglia degeneration. In line with this, it has been speculated that deficits in emotion recognition in HD may be linked to an impairment in the fronto-striatal network [29].

Limitations

Nevertheless, we also want to highlight the following limitations. The sample size of this study is small and future studies in a larger samples size are needed to replicate our results. Recruitment in HD is generally difficult as it is a rare disease affecting only 4–15 in 100,000 people of European descent [30] and a multicentre approach may be necessary. Secondly, the majority of our patients had chorea and therefore received antidopaminergic treatment. Neuroleptic drugs may, however, cause fatigue, cognitive slowing and may also interfere with task performance according to the *U* shape hypothesis [26], which states that both too little or too much dopamine can worsen cognitive performance. Finally, only one task assessing altruistic punishment was conducted and in order to avoid learning effects was only performed once.

Future Directions

In summary, we found a distinct punishment behaviour in HD which may be due to striatal dysfunction. Imaging studies further assessing fronto-striatal networks as

well as further more detailed behavioural studies with a larger sample size and manifest HD patients without antidopaminergic treatment may shed light on the mechanisms underlying altruistic punishment in HD.

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Statement of Ethics

The study was approved by local Ethics Committee of the Medical University of Innsbruck (approval reference number AN2014-0252 340/4.27, Austria), and all participants provided written informed consent according to the declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

(1) Research project: A. conception; (2) statistical analysis: A. design, B. execution, and C. review and critique; and (3) manuscript: A. writing of the first draft and B. review and critique.

B.H.: 1A, 2A, 2B, 2C, 3A.

M.P.: 2B, 2C, 3B.

C.S.: 2B, 2C, 3B.

S.M.H.: 2B, 2C, 3B.

J.M.P.: 2B, 2C, 3B.

P.E.: 2B, 2C, 3B.

K.S.: 1A, 2A, 2B, 2C, 3B.

A.D.T.: 1A, 2A, 2B, 2C, 3B.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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