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Dissociable Motivational Deficits in Pre-manifest Huntington's Disease

Highlights

- We examine cognitive and physical effort discounting in pre-manifest HD
- Individuals with pre-manifest HD are less cognitively motivated than controls
- There are no differences in physical motivation between the two groups
- This dissociation is not confounded by neuropsychological or psychiatric factors

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In Brief

Motivational impairments are common in striatal disorders, such as Huntington's disease (HD). Atkins et al. show that individuals in the pre-manifest stage of HD are less cognitively motivated than controls but equally physically motivated. These results provide empirical support for theories that posit the existence of dissociable subtypes of apathy.

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Report

Dissociable Motivational Deficits in Pre-manifest Huntington's Disease

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SUMMARY

Motivation is characterized by a willingness to overcome both cognitive and physical effort costs. Impairments in motivation are common in striatal disorders, such as Huntington's disease (HD), but whether these impairments are isolated to particular domains of behavior is controversial. We ask whether HD differentially affects the willingness of individuals to overcome cognitive versus physical effort. We tested 20 individuals with pre-manifest HD and compared their behavior to 20 controls. Across separate trials, participants made choices about how much cognitive or physical effort they were willing to invest for reward. Our key results were that individuals with pre-manifest HD were less willing than controls to invest cognitive effort but were no different in their overall preference for physical effort. These results cannot be explained by group differences in neuropsychological or psychiatric profiles. This dissociation of cognitive- and physical-effort-based decisions provides important evidence for separable, domain-specific mechanisms of motivation.

INTRODUCTION

A fundamental component of daily life is the willingness to engage in cognitively and physically demanding behavior. Motivation is the process that allows us to overcome effort in pursuit of reward. A growing body of work has implicated the striatum and its connections to the prefrontal cortex as the core of a decision-making network critical to motivated behavior.[1–6] The importance of this network to motivation is exemplified by the frequency of apathy in disorders such as Huntington's disease (HD), which are characterized by dysfunction to the striatum and its cortical connections. Apathy is a disorder of motivation that can be particularly debilitating and have a significant effect on quality of life, but relatively little is known about its underlying mechanisms.

HD is a progressive neurodegenerative disease whose pathognomonic feature is early striatal cell loss. HD is caused by the expansion of a trinucleotide cytosine-adenine-guanine (CAG) repeat in the *huntingtin* gene.[7–9] Because it is a highly penetrant, monogenic disease, we can identify asymptomatic gene carriers years before it becomes clinically manifest.[9] The prevalence of apathy closely tracks disease progression—rising from 11% in its earliest (pre-manifest) stage to up to 76% in clinically manifest disease.[10–12] The rise in apathy with disease progression mirrors the progressive involvement of corticostriatal pathways, particularly those that have been implicated in facilitating motivation.[13,14]

Importantly, motivation is not a unitary phenomenon and has been fractionated into subtypes that drive different domains of behavior (e.g., cognitive versus physical effort). A topical controversy has been whether impairments of motivation in one domain are necessarily accompanied by impairments in another (i.e., are "domain general") or whether such impairments are dissociable across multiple domains (i.e., are "domain specific"). To date, however, no clinical study—in HD or any other patient group—has directly addressed the domain specificity of effort-based decisions. The majority of patient studies have focused on motivation in the physical domain alone,[15–19] with fewer examining motivation in the cognitive domain[20,21] and none comparing motivation across both domains within the same individuals. Furthermore, interpreting differences in motivation between patient groups relative to healthy controls can in general be challenging, given that clinical populations are likely to have comorbid motor, cognitive, or psychiatric symptoms that may confound any such differences.[22]

Here, we asked whether individuals in the pre-manifest stage of HD exhibit dissociable patterns of cognitive and physical motivational deficits compared to healthy controls. Pre-manifest HD offers a unique opportunity to study the distinct consequences of HD on cognitive and physical motivation while minimizing the

Table 1. Summary of participant demographics means (SD)

	Healthy Controls	Pre-manifest HD	Group Difference
N	20	20	n.s.
Age (years)	50.8 (12.8)	46.2 (12.8)	p = 0.27
Gender (M:F)	8:12	6:14	p = 0.51
Handedness (R:L)	20:0	19:1	p = 1.0
Apathy Evaluation Scale[a]	27.6 (6.4)	27.4 (5.7)	p = 0.94
Dimensional Apathy Scale – total[b]	22.6 (6.7)	19.7 (8.3)	p = 0.29
- Executive	5.7 (3.4)	4.35 (4.1)	p = 0.17
- Initiation	8.4 (3.3)	7.20 (3.6)	p = 0.22
- Emotional	8.5 (3.0)	8.15 (3.6)	p = 0.99
Hospital Anxiety and Depression Scale[c]			
- Anxiety	5.00 (3.5)	4.75 (3.2)	p = 0.84
- Depression	2.95 (2.8)	2.15 (2.4)	p = 0.28
Montreal Cognitive Assessment[d]	27.3 (1.9)	27.2 (2.4)	p = 0.83
Hopkins Verbal Learning Test – R			
- Total recall	27.0 (3.2)	26.6 (4.3)	p = 0.76
- Delayed recall	9.00 (2.2)	8.33 (2.2)	p = 0.13
- Discrimination index	10.5 (2.0)	10.8 (1.7)	p = 0.58
Symbol Digit Modalities Test	56.6 (12.4)	53.6 (13.2)	p = 0.48
CAG repeats	N/A	41.3 (1.9) [38–45]	N/A
Total functional capacity	N/A	12.9 (0.3) [12–13]	N/A
Disease burden score	N/A	254 (82.7) [147–435]	N/A
Total motor score (UHDRS)[e]	N/A	1.35 (0.44) [0–4]	N/A

n.s., not significant
[a]Range from 18 to 72. Proposed cutoff scores for apathy in HD are >40[34] or >41.[35]
[b]Proposed cutoff score for apathy >28.5.[36]
[c]Proposed cutoff score of >8 for each of the depression and anxiety subscales.[37]
[d]Cutoff <26.
[e]Total motor score (on the Unified Huntington's Disease Rating Scale) has a maximum of 124.

more profound behavioral and motor effects that accompany advanced disease.[23–25] Importantly, our pre-manifest HD and control groups did not differ across several critical features, including mood, attention, processing speed, and episodic memory, indicating that any differences in motivation between groups could not be due to co-existent clinical features.

To sensitively measure the effect of HD on cognitive and physical motivation, we adopted a neuroeconomic approach to quantify the amount of effort individuals are willing to trade off for a given reward.[26–29] Typically, individuals are averse to investing effort, and effort devalues (or "discounts") the amount of reward that is available. Effort discounting has proven to be a useful approach to quantifying individual differences in motivation—one that is capable of detecting even subclinical levels of motivational impairment in patient populations.[21,30]

To disentangle cognitive and physical motivation, we designed two tasks that parametrically varied effort requirements in one domain while holding those in the alternate domain constant. Notably, these two tasks were closely matched in their temporal and demand characteristics. After training participants on both tasks, they were asked to decide how much effort they would be willing to invest in each domain for a given reward. By requiring participants to make separate decisions for the cognitive and physical effort tasks, we could derive separate measurements of motivation for each domain of motivation.

RESULTS

We recruited 20 individuals in the pre-manifest stage of HD. These individuals were genetically confirmed to have ≥38 CAG repeat expansions in the *huntingtin* gene and had a diagnostic confidence level of <4 on the Unified Huntington's Disease Rating Scale (UHDRS). We compared their performance to 20 healthy controls, matched for age and gender (Table 1; STAR Methods). Importantly, the groups did not differ across several performance-based cognitive measures, including a standard cognitive screening tool (the Montreal Cognitive Assessment [MoCA]) as well as neuropsychological tests of episodic memory (Hopkins

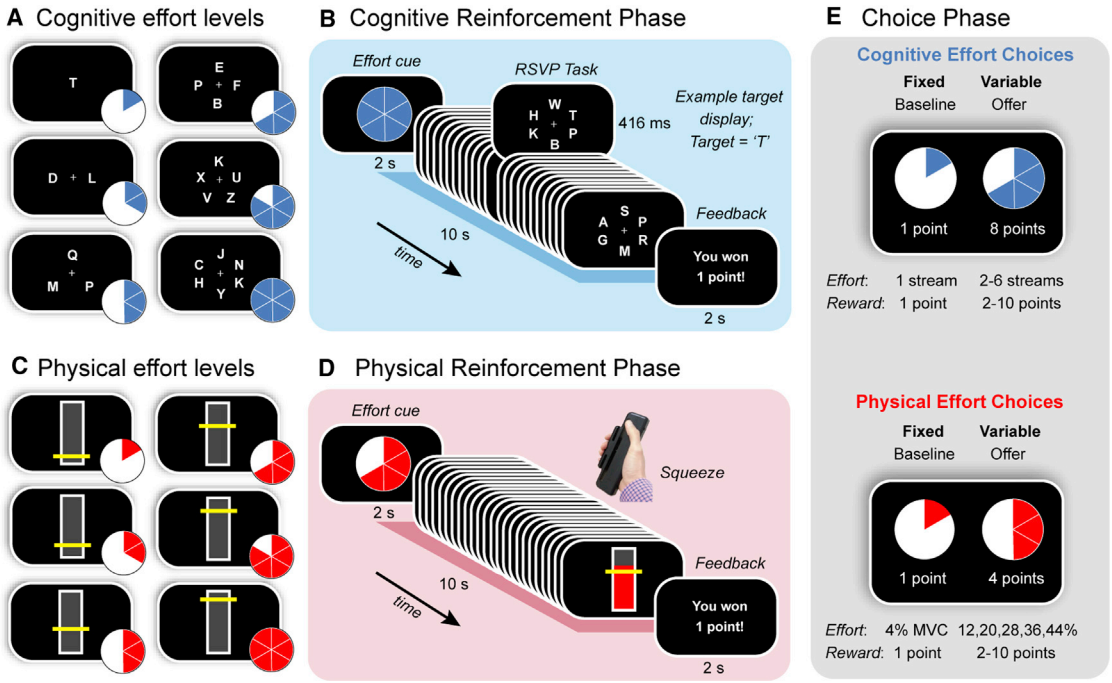

Figure 1. Task Design

Participants were first trained on (A and B) a cognitively effortful task and (C and D) a physically effortful task before (E) indicating their preference for investing effort for reward.

(A) The cognitive effort task required participants to monitor one to six RSVP streams for a target letter ("T").

(B) Each trial began with a blue pie chart indicating the number of streams they had to monitor on that trial. After completing each effort level, participants received feedback on their performance. Each trial lasted 10 s.

(C) The physical effort task required participants to sustain variable amounts of force on a hand-held dynamometer, with the target levels of force defined as a function of each individual's maximum voluntary contraction (MVC) (4%, 12%, 20%, 28%, 36%, and 44%).

(D) Each trial began with a red pie chart indicating the amount of force they had to apply on that trial. Trial durations were identical to those for the cognitive effort task (10 s). At the conclusion of each trial, participants received feedback on their performance.

(E) The choice phase required participants to decide how much effort they were willing to invest for reward. The choice was always between a fixed baseline option (the lowest level of effort for the lowest reward; one point) and a variable high-effort/high-reward offer (higher levels of effort; rewards of two to ten points). Separate choices were made for cognitive and physical effort.

Verbal Learning Test-Revised [HVLT-R]) and attention/psychomotor speed (Symbol Digit Modalities Test [SDMT]). Groups were also matched on scores of clinical anxiety and depression (Hospital Anxiety and Depression Scale)[31] and apathy (Apathy Evaluation Scale;[32] Dimensional Apathy Scale[33]).

Participants were tested in a single session, during which they completed an effort-based decision-making task, followed by a cognitive test battery. The overall structure of the decision-making task was similar to a previous study examining cognitive- and physical-effort-based decisions in healthy adults (see STAR Methods).[5] This task was divided into three phases (Figure 1). The first two ("reinforcement") phases involved training participants on both a cognitively effortful task (Figures 1A and 1B)[21] and a physically effortful task (Figures 1C and 1D),[5] in counterbalanced order. Within each task, we parametrically varied effort demands over six levels in the target domain (e.g., cognitive) while keeping those in the other (e.g., physical) constant. In the cognitive effort task, participants had to attend to between one and six streams of rapidly changing letters for a target letter, "T." In the physical effort task, participants had to exert one of six levels of force on a hand-held dynamometer, quantified as proportions of each participant's individually calibrated maximum voluntary contraction (MVC).

Finally, to examine participants' willingness to exert cognitive and physical effort, the reinforcement phases were followed by a critical "choice" phase. In this phase, participants revealed their preference between a fixed, low-effort/low-reward baseline option and a variable, high-effort/high-reward offer. The fixed baseline option was always the option to exert the lowest amount of effort for the lowest reward (one point). In contrast, the variable offer was the option to exert a higher amount of effort (levels 2–6) for a greater reward (2–10 points). Each choice was always between two options in the same domain, which allowed us to separate individuals' willingness to exert cognitive and physical effort (Figure 1E).

First, we present data from the reinforcement phases, which allowed us to confirm that (1) our cognitive and physical effort manipulations were effective in manipulating task load (i.e., higher levels of effort were objectively more challenging than low levels) and (2) that participants had the capacity to complete all levels of effort, regardless of increasing load (to exclude the possibility that subsequent choices could be influenced by task success).

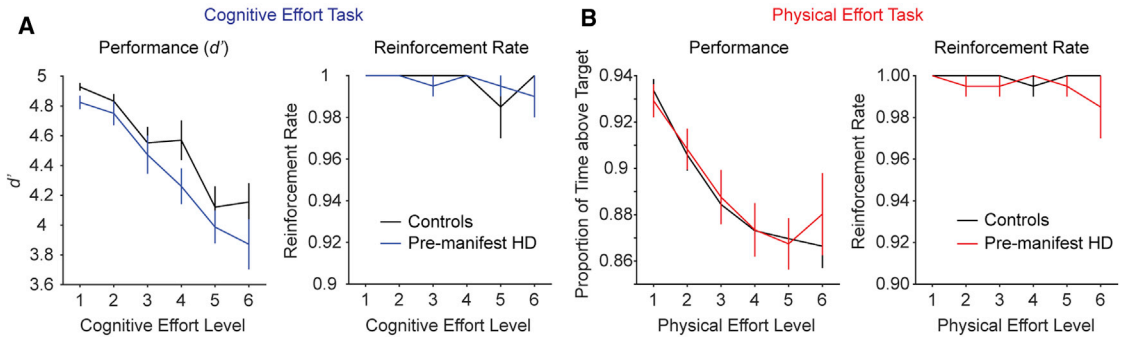

Figure 2. Performance in the Cognitive and Physical Effort Tasks (Mean ± 1 SEM)

(A) In the cognitive effort task, target detection sensitivity (left panel) and reinforcement rates (right panel) were identical across groups. Controls are shown in black and pre-manifest HD in blue.

(B) In the physical effort task, pre-manifest HD and controls did not differ in the proportion of time they were able to maintain their grip over the target effort level (left panel), which was reflected in identical reinforcement rates between groups (right panel). Controls are shown in black and pre-manifest HD in red.

Task Performance Did Not Differ between Groups

We quantified performance in the cognitive effort task in terms of target detection sensitivity, *d'* (*Z*(hits) – *Z*(false alarms)), and in the physical effort task as the proportion of time that the generated force was maintained above the target effort level. Using two-way repeated-measures ANOVAs on each of these variables as a function of group (pre-manifest HD, controls) and effort level (1–6), we found that, for each task, performance decreased with increasing effort (Figures 2A and 2B, left panels). Importantly, however, there were no group differences in performance in either the cognitive or physical effort tasks (cognitive: effort $F(3.5, 134) = 36.4$, $p < 0.001$; group, $F(1, 38) = 2.17$, $p = 0.15$; interaction, $F(3.5, 134) = 0.75$, $p = 0.54$); physical: effort, $F(2.1, 79.3) = 33.4$, $p < 0.001$; group, $F(1, 38) = 0.04$, $p = 0.85$; interaction, $F(2.1, 79.3) = 0.56$, $p = 0.58$). These data confirm that our cognitive and physical manipulations were successful in increasing task demands for the respective tasks.

To ensure that subsequent effort-based decisions were based on the aversiveness of each effort level and not the probability of being able to successfully accomplish them, we next verified that the ability of participants to perform each effort level to the required threshold (their reinforcement rates) was at ceiling (Figures 2A and 2B, right panels). The two-way group × effort ANOVA on reinforcement rates revealed no significant main effects or interactions in either the cognitive or physical tasks (cognitive: group, $F(1, 38) = 0.04$, $p = 0.84$; effort, $F(5, 190) = 1.19$, $p = 0.32$; group × effort, $F(5, 190) = 0.82$, $p = 0.54$; physical: group, $F(1, 38) = 1.39$, $p = 0.25$; effort, $F(5, 190) = 0.48$, $p = 0.79$; group × effort, $F(5, 190) = 0.88$, $p = 0.49$). Together, these data confirm that (1) our tasks effectively increased cognitive and physical loads, (2) both groups were capable of performing each effort level to the required threshold, and (3) there were no significant differences between groups in their ability to perform the tasks or to be rewarded at each level of effort.

Cognitive, but Not Physical, Motivation Was Lower in Individuals with Pre-manifest HD versus Controls

The critical question in this study was whether the pre-manifest HD group differed from controls in their willingness to exert cognitive or physical effort for reward (Figure 3). We examined participants' choices using a mixed-model ANOVA, with the between-subjects factor of group and within-subjects factors of domain (cognitive and physical), effort (2–6), and reward (2–6).

The key result was that the pre-manifest HD group accepted significantly fewer effortful offers compared to controls but only for the cognitive effort task and not the physical effort task. This was captured in the two significant higher order interactions involving group: group × domain ($F(1, 38) = 4.83$; $p = 0.03$) and group × domain × effort ($F(2.1, 80.2) = 3.60$; $p = 0.03$). Decomposing these interactions with Bonferroni-corrected pairwise comparisons indicated that controls were more motivated than individuals with pre-manifest HD. However, this was only the case for the cognitive task and at higher levels of cognitive effort (level 2, $p = 0.27$; levels 3–6, $p \leq 0.014$). Importantly, there were no differences between the groups for any level of the physical effort task (all $p \geq 0.15$). The other interactions involving group were not significant (group × effort, $F(2.36, 89.78) = 1.86$, $p = 0.15$; group × reward, $F(1.58, 60.1) = 2.50$, $p = 0.10$; group × domain × reward, $F(2.94, 112) = 0.96$, $p = 0.41$; group × effort × reward, $F(4.54, 172) = 0.63$, $p = 0.66$; group × domain × effort × reward, $F(8.33, 327) = 0.84$, $p = 0.57$).

The remaining significant main effects and interactions (i.e., not involving group) simply reflected the well-established phenomenon of effort discounting across the entire cohort. The main effects of effort and reward were significant, and this was qualified by a significant effort × reward interaction (effort [$F(2.36, 89.7) = 68.1$; $p < 0.001$]; reward [$F(1.58, 60.1) = 68.0$; $p < 0.001$]; effort × reward [$F(4.54, 172.4) = 12.5$; $p < 0.001$]). This interaction was driven by effort discounting being steepest at the lowest levels of reward and minimal at the highest levels of reward (reflecting the tendency to accept all offers when rewards were high). In addition, the main effect of domain was significant and interacted significantly with effort and reward (domain [$F(1, 38) = 6.41$, $p = 0.016$]; domain × effort [$F(2.11, 80.2) = 5.55$, $p = 0.005$]; domain × reward [$F(2.94, 111.9) = 4.39$, $p = 0.006$]; domain × effort × reward [$F(8.33, 317) = 1.90$, $p = 0.057$]). Decomposing these interactions indicated that, overall across both groups, effort discounting was more pronounced for the physical relative to the cognitive domain, with lower acceptance rates for the physical relative to the

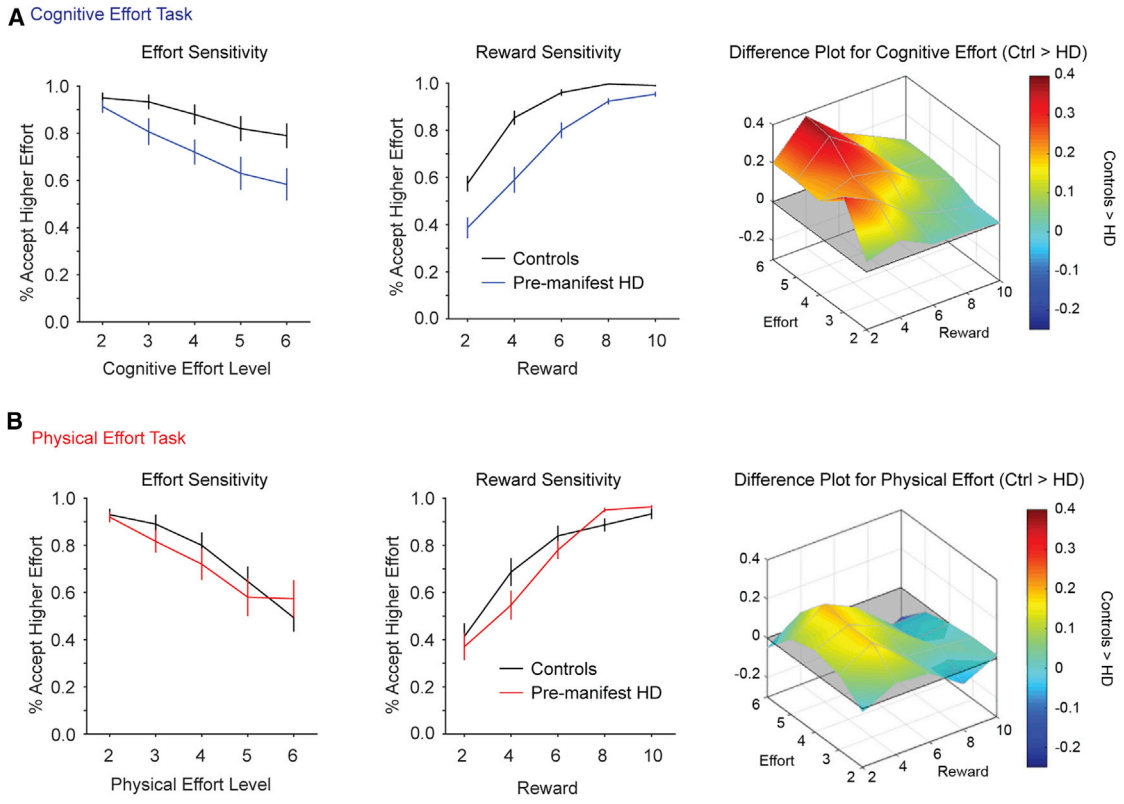

Figure 3. Choices in the Cognitive and Physical Effort Tasks (Mean ± 1 SEM)

Acceptance rates for the higher-effort/higher-reward offer are plotted as a function of effort (left column) and reward (center column). Difference plots illustrate choice differences between controls and pre-manifest HD across the two-dimensional effort-reward space (right column). Red indicates greater motivation in controls than pre-manifest HD.

(A) For cognitive-effort-based choices, pre-manifest HD was less willing to accept the higher-effort/higher-reward offers.

(B) For the physical-effort-based choices, decisions were similar between groups.

See also Figures S1 and S2.

cognitive effort task at the higher levels of effort (levels 2–4, $p \geq 0.22$; levels 5–6, $p \leq 0.02$).

In sum, our key result was that the pre-manifest HD group was significantly less cognitively motivated than controls and that choices for the physical effort task did not differ between the two groups.

Performance Differences Did Not Account for the Lower Cognitive Motivation in Pre-manifest HD

To ensure that the lower cognitive motivation in pre-manifest HD relative to controls was not simply due to a lower capacity of the HD group to perform the cognitive effort task, we performed two control analyses. First, we performed a mixed-effects ANOVA on the acceptance rates for the cognitive effort task (group × effort × reward) while controlling for performance by including each participant's mean *d'* as a covariate. This analysis again showed that the pre-manifest HD group were willing to invest less cognitive effort than controls, particularly for the higher levels of cognitive effort (group × effort interaction, $F(1.9, 71.3) = 4.44$, $p = 0.016$, with group differences at levels 3–6 [$p \leq 0.022$], but not level 2 [$p = 0.246$]). Importantly, performance did not have a significant effect on acceptance rates (performance, $F(1, 37) = 0.011$, $p = 0.92$; performance × effort, $F(1.93, 71.3) = 1.26$, $p = 0.29$; performance × reward, $F(1.54, 56.9) = 1.13$, $p = 0.35$; performance × effort × reward, $F(5.2, 193.2) = 1.66$, $p = 0.14$).

Second, we quantified the null effect of performance on acceptance rates by performing the Bayesian equivalent of the preceding analysis. We included subject as a random intercept in all models. Thus, the null model for all comparisons was a model including the grand mean but also subject as an additive factor. We compared the null model together with the full model space of all simple effects and their interactions. These model comparisons showed that the data were best fit by a model that did not include performance as a factor (namely, group + effort + reward + group × effort + group × reward + effort × reward). The posterior probability of this model was 0.648. The best-fitting model that incorporated performance as a factor was the third best-fitting model overall, with a probability of 0.145. Comparing these two models revealed a Bayes factor of 4.457 in favor of the former—thus providing substantial evidence[38] in favor of the best-fitting model *without* performance as a factor relative to the best model *with* performance as a factor.

This result was reaffirmed when we compared the family of models that contained performance to equivalent models

stripped of its effect. We computed the model-averaged results for each simple effect (group, effort, reward, and performance) and interaction. Most importantly, the family of models that included performance as a predictor had a posterior inclusion probability of 0.178. This corresponded to an exclusion Bayes factor of 4.627 for performance, again providing substantial evidence for excluding it as a predictor. Together, these analyses indicate that the lower cognitive motivation in pre-manifest HD relative to controls is unlikely to have been driven by any group differences in the ability to perform the cognitive effort task.

Computational Models of Choice Confirmed the Dissociation between Cognitive and Physical Effort

Finally, to allow for comparisons between our data and those from previous studies on effort discounting, we applied computational models of effort discounting to choice data from both groups.[21,28,39,40] This analysis allowed us to capture individual differences in the preference for cognitive and physical effort, with model comparisons revealing a pattern of results that complemented the dissociation between cognitive and physical motivation noted above. Details of these analyses are presented in the Supplemental Information (Figures S1 and S2).

DISCUSSION

This study examined motivation across multiple domains in pre-manifest HD. Our key findings were that cognitive and physical motivation were differentially affected in individuals with pre-manifest HD relative to healthy controls. The pre-manifest HD group had clear motivational deficits in the cognitive domain, as demonstrated by their lower willingness to exert cognitive effort for reward. In contrast, decisions in the physical domain were unaffected by disease. Importantly, these differences were not confounded by age, gender, neuropsychological or neuropsychiatric issues, or the capacity to successfully perform each task. These data provide empirical support for frameworks proposing that cognitive- and physical-effort-based decisions are dissociable and inform current debates on the role of domain-general versus domain-specific corticostriatal pathways in motivated behavior.[13,41,42]

Apathy is commonly described as a syndrome in which motivation is diminished across multiple domains.[33,43–46] A recent approach to investigating motivation has been through effort-discounting paradigms, which quantify the amount of effort individuals are willing to exert in return for reward.[15,18,21,47] Such paradigms provide a platform to test a critical assumption of prevailing multidimensional theories of apathy—that motivational deficits should be dissociable across separate domains of effort. Here, we provide strong evidence in favor of such theories by demonstrating a selective involvement of cognitive over physical motivation in pre-manifest HD. Beyond its theoretical implications, this result stresses the clinical importance of recognizing the heterogeneity of apathy, particularly with a view to developing potential treatments that are targeted to the affected domain/s.

A key advantage of focusing on HD in the pre-manifest stage was that it allowed us to examine motivation in individuals who were otherwise very closely matched to their healthy counterparts. Several previous studies that have examined cost-benefit decision making in clinical populations have found differences in patterns of effort discounting but in the setting of baseline differences in their neuropsychological or neuropsychiatric profiles. It can therefore become difficult to determine the relationship between group differences in effort discounting and issues with mood or clinical apathy. Here, the HD and control groups did not differ in their ratings of depression or clinical apathy, neuropsychological measures of episodic memory or processing speed, or their ability to successfully perform the cognitive or physical tasks. Thus, our data indicate that motivational impairments can occur independently of comorbid neuropsychiatric issues, neuropsychological disturbance,[23,24] or an inability to perform the tasks themselves. Rather, the group differences in motivation most likely reflected a primary motivational deficit.

Our finding that cognitive motivation is more significantly impacted in the early stages of HD could potentially be explained by the characteristic progression of HD pathology. Striatal atrophy in HD typically proceeds along a dorsomedial-to-ventrolateral gradient.[48–51] In pre-manifest disease, the most consistent finding is dorsal striatal atrophy, which is detectable up to 20 years before diagnosis.[7–9,52,53] In addition, other subcortical regions, such as the amygdala, are variably affected in early HD.[8,54,55] As the disease advances, there is increasing cortical involvement, particularly of frontal cortical areas.[56,57] This progressive corticostriatal dysfunction is believed to underpin the cognitive and behavioral phenotype of HD,[58–63] as well as the rising prevalence of apathy as the disease advances.[14,25]

Importantly, however, recent studies have suggested that components of these corticostriatal pathways may be differentially sensitive to specific motivational domains. For example, areas that are typically affected earlier in HD (e.g., the dorsal striatum and amygdala) have been more selectively implicated in cognitive motivation. The dorsal striatum has been proposed as an important node specifically in the development of cognitive apathy.[13] This is supported by data showing that deactivating or lesioning the rodent dorsal striatum impairs the allocation of cognitive,[64] but not physical,[65–68] effort. Furthermore, the dorsal striatum has been implicated in decisions to exert cognitive over physical effort,[1] which is consistent with its broader role in behavioral flexibility and cognitive control.[69–71] In addition, other subcortical areas affected in pre-manifest HD—such as the amygdala—play a unique role in cognitive versus physical motivation.[5,72]

In contrast, those networks typically affected later in the course of HD (e.g., the ventral striatum and its prefrontal connections)[73] have been implicated in physical or domain-general motivation. For example, deactivating the rodent nucleus accumbens disrupts physical-effort-based decisions,[65–68] although the impact on cognitive-effort-based decisions is less clear.[64] Similarly, human imaging studies have implicated the ventral striatum and its prefrontal connections in the valuation of both physical[1,74] and cognitive effort costs.[1,2,75,76] Taken together, the spatiotemporal progression of HD could therefore lead to differential effects on motivation in the cognitive and physical domains, with pathways affected earlier in the course of HD preferentially involved in cognitive relative to physical motivation.

One question that remains is the extent to which our findings may generalize to other forms of cognitive motivation. Prominent

theoretical frameworks argue that dopamine and the basal ganglia play a central role in the allocation of effort in any cognitive domain that is capacity limited.[40,77] Data in support of such theories have been derived from multiple paradigms, which have manipulated effort in terms of perceptual demand, attention, working memory, and arithmetic and across multiple species, including rodents and humans.[1,2,21,78–81] These data predict that, relative to controls, the aversion of the pre-manifest HD group to attentional load should generalize to other types of cognitive effort, but it remains for future studies to empirically confirm this prediction.

The issue of whether cognitive- and physical-effort-based decisions are dissociable is central to current neurobiological theories of motivation. Here, we showed that the willingness of individuals to invest cognitive and physical effort is differentially affected in HD, prior to the clinical onset of motor disease. These data exemplify the utility of neuroeconomic paradigms in providing sensitive measurements of motivated behavior and provide broad support for frameworks that posit separable, domain-specific mechanisms of motivation.

Limitations of Study

The absence of neuroimaging data in our study limits the extent to which we can ascribe our behavioral dissociation to dysfunction within a specific network. Furthermore, our study only tested a cohort of individuals with pre-manifest HD at a single time point. An important focus of future work should be to combine longitudinal neuroimaging studies in HD with behavioral tasks that are sensitive to different motivational subtypes. Such studies will provide valuable information on how changes in corticostriatal pathways over time drive the development and progression of apathy across different domains of behavior.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.xcrm.2020.100152.

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AUTHOR CONTRIBUTIONS

All authors were involved in study design. K.J.A. collected the data. K.J.A. and T.T.-J.C. analyzed the data and wrote the manuscript. All authors reviewed the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited Data		
Analyzed reinforcement and choice data for cognitive and physical effort tasks, in the control and pre-manifest HD groups	This paper	N/A
Software and Algorithms		
MATLAB	Mathworks, USA	https://www.mathworks.com
Psychtoolbox	psychtoolbox.org	http://psychtoolbox.org
Presentation	Neurobehavioral Systems	https://www.neurobs.com
JASP	University of Amsterdam	https://jasp-stats.org

RESOURCE AVAILABILITY

Lead contact

Further information and requests should be directed to and will be fulfilled by the Lead Contact, Trevor Chong (trevor.chong@monash.edu).

Materials availability

This study did not generate unique reagents or other materials.

Data and Code availability

The datasets supporting the current study are available from the corresponding author on request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

We recruited 20 individuals in the pre-manifest stage of HD. These individuals were genetically confirmed to have $\geq$ 38 CAG repeat expansions in the *huntingtin* gene, and had a diagnostic confidence level of $<$ 4 on the Unified Huntington's Disease Rating Scale (UHDRS). We compared their performance to 20 healthy controls, matched for age and gender (Table 1). Exclusion criteria included a history of neurological disease (other than HD, in the case of the pre-manifest group), major traumatic brain injury, cerebrovascular accident, or substance abuse. Participants were recruited from our internal research database, the Calvary Bethlehem Hospital in Melbourne, and the wider community. This study received approval from the Monash University Human Research Committee and all participants provided informed consent in accordance with the Declaration of Helsinki.

We assessed cognition using several performance-based measures, including: a standard cognitive screening tool (the Montreal Cognitive Assessment, MoCA), as well as neuropsychological tests of episodic memory (Hopkins Verbal Learning Test – Revised, HVLT-R), and attention/psychomotor speed (Symbol Digit Modalities Test, SDMT). We used the self-reported Hospital Anxiety and Depression Scale[31] to measure depressive symptoms. Apathy was assessed using the Apathy Evaluation Scale (AES), which provides a total apathy score[32], and the Dimensional Apathy Scale (DAS), which separates apathy into 'Executive', 'Initiation' and 'Emotional' subtypes[33]. Importantly, the pre-manifest HD and control groups did not differ in any of these measures (Table 1).

METHOD DETAILS

Participants were tested in a single session, during which they completed an effort-based decision-making task, followed by the battery of cognitive tests. The overall structure of the decision-making task was similar to a previous study examining cognitive and physical effort-based decisions in healthy adults[5]. The task was divided into three phases (Figure 1). The first two ('Reinforcement') phases involved training participants on both a cognitively effortful task (Figures 1A and 1B)[21] and a physically effortful task (Figures 1C and 1D)[5], in counterbalanced order. Within each task, we parametrically varied demands in the target domain (e.g., cognitive), while keeping those in the other (e.g., physical) constant. The Reinforcement phases were followed by a final 'Choice' phase, during which participants were asked to choose between a fixed low-effort/low-reward option, and a variable high-effort/high-reward offer (Figure 1E). These decisions allowed us to quantify the willingness of individuals to exert distinct types of effort.

Reinforcement phases

Cognitive Effort Task. For the cognitive effort task, we utilized a rapid serial visual presentation (RSVP) paradigm, previously described by McGuigan et al.[21] Participants were required to monitor a series of rapidly changing letters (Arial, 26-point font, Figures 1A and 1B) and press a button whenever they detected the target letter, 'T'. We parametrically manipulated cognitive demand by increasing the number of letter streams from one to six. In the least effortful condition (Level 1), a single stream was presented at the central fixation point. In the more effortful conditions (Levels 2-6), between two to six streams were positioned equiangularly and equidistantly from fixation. The target letter could appear randomly in any stream, and the timing of the target stimuli was pseudorandom such that they could not appear in consecutive stimulus frames (to avoid an attentional blink). Each effort level comprised 24 stimulus frames, each of which lasted 416 ms, for a total trial duration of 10 s.

Each trial of the Reinforcement phase commenced with a *blue* pie chart, which acted as a cue to indicate the level of cognitive effort required on that trial. Participants then completed the required level of effort, after which they received feedback with regards to their success. They were rewarded with one point if they were able to complete each trial above a threshold level of performance (more than one hit; fewer than three false alarms); otherwise they received no points. Participants were instructed that their task was to maximize the number of points won. Participants completed two blocks of 30 trials (i.e., 10 trials per effort level, randomly allocated), with an opportunity to rest after each block. These experimental blocks were preceded by a practice block of 12 trials (two per effort level). Responses were registered on a Cedrus button box, and the task was implemented on Presentation software (Neurobehavioral Systems).

Physical Effort Task. In the physical effort task, participants were required to exert one of six levels of force on a hand-held dynamometer (SS25LA, BIOPAC systems, USA) using their dominant hand (Figures 1C and 1D) – an approach similar to the physical effort task described in Chong et al.[5] At the beginning of the experiment, we determined individuals' maximum voluntary contraction (MVC), which was defined as the maximum of three consecutive squeezes. To standardize effort requirements across participants, we defined the target effort levels for each individual as a function of their own MVC (4, 12, 20, 28, 36, 44%). Target levels were visually depicted as a horizontal yellow line on a vertical bar, and participants received real-time visual feedback of their applied force.

Each trial in the physical effort task commenced with a *red* pie chart, which cued the level of physical effort required on that trial. Participants then had to initiate their contraction, and maintain it above the required effort level for at least 50% of the total trial duration (i.e., $\geq$ 5 of 10 s) to be positively reinforced. Importantly, the physical effort task was identical to the cognitive effort task in terms of the trial durations (10 s per effort level); number of trials per effort level; and overall block structure. The physical effort task was implemented on Psychtoolbox (http://psychtoolbox.org) running in MATLAB (Mathworks, USA).

Choice phase

Participants revealed their preference between a fixed, low-effort/low-reward baseline option, and a variable, high-effort/high-reward offer. We sampled the entire effort-reward space evenly and randomly across both domains over a total of 150 trials. Participants made their selection with a button press, and trials were self-paced. To reduce the impact of fatigue on subsequent decision-making, participants were not required to execute their choices, but simply indicate their preferred option. They were explicitly told that their decisions were hypothetical, in that points did not alter remuneration, but that they should select the option that was most preferable to them. This protocol is consistent with previous studies.[3,5,21,39]

QUANTIFICATION AND STATISTICAL ANALYSIS

Statistical analyses were performed in MATLAB (Mathworks Inc, USA) and JASP v 0.12.2 (University of Amsterdam). Statistical details of the analyses are presented in the main text and Supplemental Information. For the frequentist analyses, violations to sphericity were addressed with Greenhouse-Geisser correction, and pairwise comparisons were corrected for multiple comparisons with the Bonferroni method. For the Bayesian analyses, we specified a multivariate Cauchy prior on the effects, with a distribution centered around zero and a width parameter of 0.707. Bayes Factors were used to quantify evidence in favor of each hypothesis, and interpreted according to Jeffreys.[38]

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Supplemental Information

Dissociable Motivational Deficits in Pre-manifest Huntington's Disease

Kelly J. Atkins, Sophie C. Andrews, Julie C. Stout, and Trevor T.-J. Chong

Computational modelling of choice

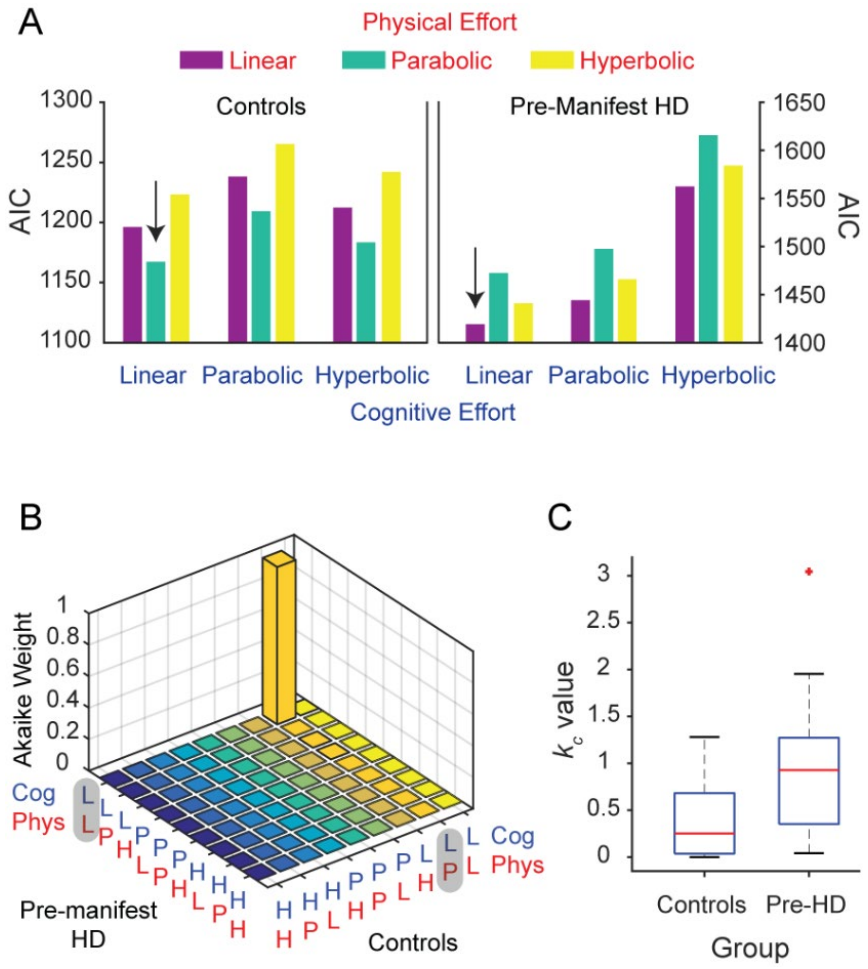

Figure S1. **Computational modelling revealed a dissociation between cognitive and physical effort discounting across pre-manifest HD and controls, in keeping with the analyses reported in the main text** (related to *Figures 3* and *S2*). Effort discounting is typically modelled as a monotonically decreasing function, with its gradient indicated by a subject-specific effort discounting parameter (k), which can be used to capture an individuals' motivation (a steeper slope, or higher k value, implies greater apathy).

(A) To examine how HD affects effort discounting in the cognitive and physical domains, we fit participants' choices with linear, parabolic and hyperbolic functions typically used to capture effort discounting:

Linear (L): $SV(t) = R(t) - k \cdot E(t)$

Parabolic (P): $SV(t) = R(t) - k \cdot E(t)^2$

Hyperbolic (H): $SV(t) = R\,(t) \cdot \frac{1}{1+k \cdot E(t)}$

where S$V(t)$ represents the subjective value of the offer on trial t; R is the reward in points (2, 4, 6, 8, 10); E is the effort involved (1 to 6 streams for cognitive effort; the % MVC in the physical domain); and k is the subject-specific effort discounting parameter. For each participant, we fit these three functions to choices in the cognitive and physical effort tasks. The subjective value of each offer for each subject was referenced to the subjective value of the baseline offer, and decisions were modelled with a *softmax* function and maximum likelihood estimation.

We compared model fits for each group with the Akaike Information Criterion (AIC). Model comparisons are shown separately for controls (left) and pre-manifest HD (right). In controls, the winning model showed that cognitive effort discounting was best described by a linear function, and physical discounting by a parabolic function. This model won by 16 AIC units, and is consistent with previous findings of cognitive [21] and physical [5, 18, 39] effort discounting in healthy individuals. In pre-manifest HD, cognitive effort discounting was best described by the same linear function as the control group. However, choices in the physical domain were best fit, not by the parabolic function seen in controls, but instead by a linear discounting function. This winning model in pre-manifest HD won by 22 AIC units. Together with the analyses presented in the main text on overall acceptance rates, our results indicate that the motivational differences between pre-manifest HD and controls in our study followed distinct, domain-specific patterns.

(B) To quantify the likelihood that this combination of models best accounted for choice behaviour across the entire group of pre-manifest HD and control participants, we computed the Akaike weights (i.e., the relative likelihood of a model) for each of the $9^2 = 81$ models across the entire model space.[e.g.,21] This analysis revealed that the relative likelihood that this combination of effort discounting functions (highlighted in grey) best explained motivation across the group was in excess of 0.99.

(C) To confirm the veracity of the model outcomes, we compared the subject-specific cognitive effort discounting parameters (i.e., k_c) between pre-manifest HD and controls. These values were significantly greater in the pre-manifest group (medians: 0.93 vs 0.25; Mann-Whitney $U = 97$, $p = .006$), which was consistent with the acceptance rate data in the main text. This also echoes the findings of a recent study using the same cognitive effort task, which revealed a similar pattern of results in PD compared to controls.[21] The central red line of the boxplot indicates the median of the k_c values for each group, and the boundaries of box the interquartile range. The whiskers extend to the most extreme respondents not considered outliers; and outliers are plotted separately ('+'). There was no difference in the inverse temperature parameter between groups (medians: pre-manifest HD 1.36 vs controls 2.53; $U = 139$, $p = .10$). No statistical comparisons were undertaken for the physical effort discounting parameters (k_p) given they were derived from different functions.

Relationship between effort discounting and subjective apathy ratings

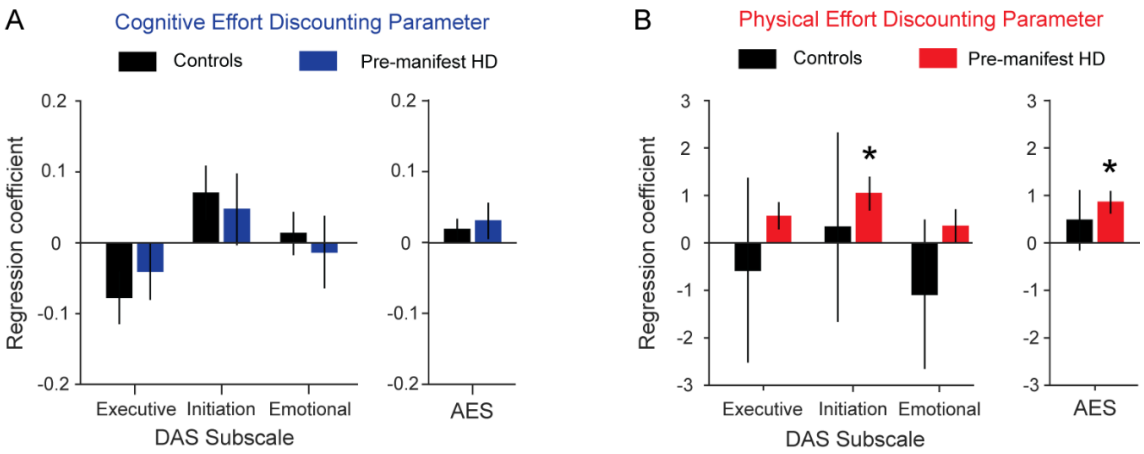

Figure S2. **As a secondary goal, we also examined whether the effort discounting parameters within the (A) cognitive and (B) physical domains related to responses on clinical rating scales of apathy** (related to *Figures 3* and *S1*)**.** In each of the two groups, we performed robust regressions with Huber's method of correction with k_c or k_p, as observed variables, against each subscale of the DAS (*left panels*) and AES (*right panels*) as explanatory variables. Regression coefficients are plotted ± 1 SEM. Significant regression coefficients (i.e., $\beta > 0$, $p < .05$) are indicated with an asterisk.

(A) There were no significant relationships between the cognitive effort discounting parameter, and responses on the DAS or AES. The regressions between k_c values and either apathy scale did not reveal any significant relationships in either group. Control data are plotted in black, and pre-manifest HD data in blue.

(B) In contrast, effort discounting parameters in the physical domain were positively related to scores on the DAS and AES, but only in the pre-manifest HD group, and not controls. In pre-manifest HD, the regression between k_p and the DAS revealed a significant positive relationship between k_p and the Initiation subscale ($\beta = 1.04$, $p = .01$), and a trend towards a positive relationship with the Executive ($\beta = 0.57$, $p = .06$), but not the Emotional ($\beta = 0.35$, $p = .35$), subscale. A significant positive relationship was also found between k_p values and total scores on the AES ($\beta = 0.86$, $p = .002$). The direction of these relationships was as expected – the higher the k value (i.e., the steeper the effort discounting function), the higher the apathy rating. In contrast, there were no significant relationships between controls and responses on the clinical rating scales. Control data are plotted in black, and pre-manifest HD data in red.

In summary, although the results in the main text showed that HD resulted in a greater aversion to cognitive compared to physical effort-based decisions, effort discounting parameters in the pre-manifest HD group were only related to apathy ratings in the physical, and not cognitive, domain. This suggests that the objectively measured dysfunction in cognitive effort-based decisions may provide a unique measure of motivation to which current rating scales, such as the AES and DAS, are less sensitive (although its relationship with other tools is unknown). Moreover, the relationship between k_p values and apathy ratings was only evident in the pre-manifest HD group and not controls, potentially because impairments may only become behaviourally apparent once a disease has passed a critical threshold.[e.g.,29]