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Supplemental Information

Dissociable Motivational Deficits

in Pre-manifest Huntington's Disease

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Computational modelling of choice

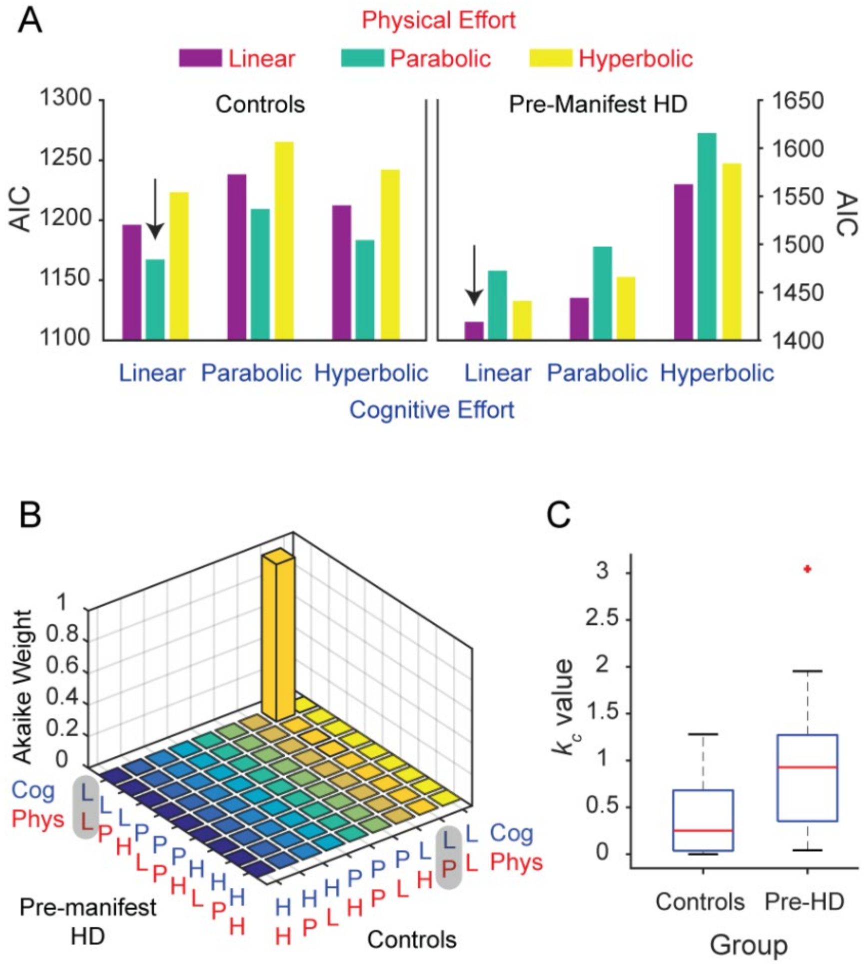

Figure S1. **Computational modelling revealed a dissociation between cognitive and physical effort discounting across pre-manifest HD and controls, in keeping with the analyses reported in the main text** (related to *Figures 3* and *S2*). Effort discounting is typically modelled as a monotonically decreasing 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

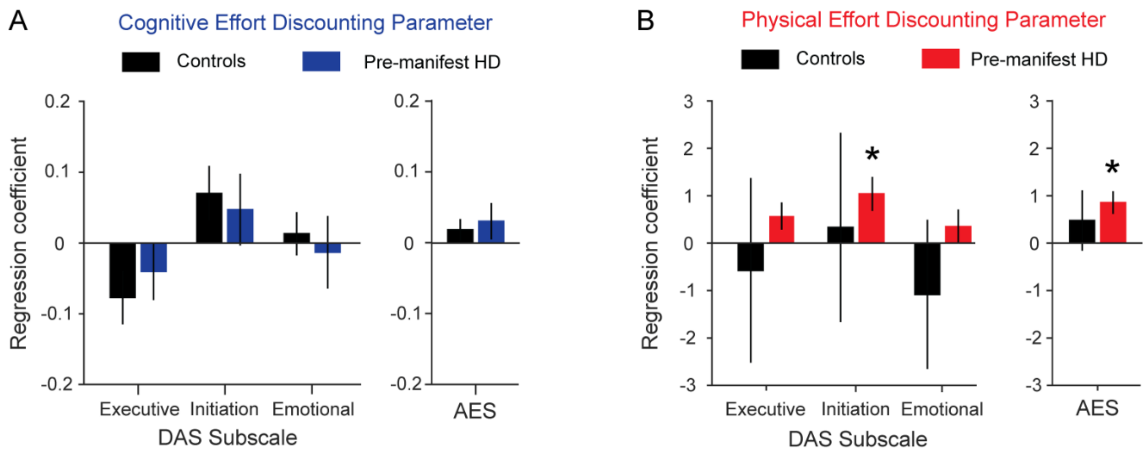

Figure S2. **As a secondary goal, we also examined whether the effort discounting parameters within the (A) cognitive and (B) physical domains related to responses on clinical rating scales of apathy** (related to *Figures 3* and *S1*)**.** In each of the two groups, we performed robust regressions with 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]