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Insensitivity to Loss is Associated with Apathy in Huntington's Disease.

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Loss and Apathy in HD

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Abstract

Background
Apathy is a deficit in goal-directed behavior that significantly affects quality of life and function. It is common in Huntington's disease (HD) and other disorders affecting cortico-striatal pathways. Deficits in processing of reward, altered effort and executive dysfunction are associated with apathy in other disorders, but the cognitive processes leading to apathy in HD remain largely unknown. A previously reported deficit in learning from losses in HD raises the possibility of a hitherto unrecognized mechanism leading to apathy. This study's objective was to delineate the cognitive processes associated with apathy in HD.

Methods
We tested 51 HD participants and 26 controls on a battery of novel and established measures to assess the contribution to apathy in HD of executive function, reward value, reward-effort calculations, instrumental learning and response to reward and loss.

Results
HD participants had deficits in instrumental learning with impaired response to loss, but no evidence to suggest altered reward-related behavior or effort. We also saw an executive dysfunction contribution to apathy in HD.

Discussion
We report the novel finding that apathy in HD is associated with blunted responses to losses and impaired instrumental learning. This association is consistent with the known early degeneration of the indirect pathway and amygdala involvement in apathy in HD, but is previously unreported in any disorder. In keeping with the comparative preservation of the ventral striatum and orbito-frontal cortex in HD, reward valuation and reward-effort calculations did not contribute to apathy.

Background

Apathy, a deficit in goal-directed behavior, is common in neurological diseases affecting frontal cortex, white matter and basal ganglia[1–5]. Apathy severely impairs function and quality of life for patients and carers[6–11].

A number of cognitive processes are hypothesized to contribute to goal-directed behavior: initiation; including option generation and selection (reward valuation and reward-effort calculations), planning (executive function), and outcome evaluation (learning from loss and reward)[12,13]. Deficits in reward valuation, reward-effort calculations, learning from reward and executive function leading to apathy have been demonstrated across disorders[14–16]. However, one important aspect of goal-directed behavior: avoiding aversive stimuli and stopping deleterious actions, has so far not been directly linked to clinical apathy.

Apathy occurs in up to 80% of patients with Huntington's disease (HD; an inherited neurodegenerative disorder focused on the striatum, affecting the indirect pathway earliest, before involving the direct pathway, cortex (progressing occipito-frontally), and white matter)[5,12,17–21]. Apathy is a core feature of HD: showing progression with disease course, occurring before motor onset and occurring at higher rates in HD gene carriers compared to non-gene carriers blinded to their genetic status[17,22,23].

Despite apathy's impact on HD patients and central status to the disease, knowledge of the cognitive processes underpinning apathy in HD is limited. Apathy in HD has been correlated with executive dysfunction[16,24], but none of the other potentially contributory processes have been probed.

Although apathy is common in diseases affecting cortico-striatal circuits, the distribution of neuro-pathology differs across diseases. This suggests that the mechanisms leading to apathy may also differ. Without knowing the relative contribution of different processes to apathetic behavior, targeted treatments cannot be developed. Since a selective deficit in learning from loss, but not reward[25] has been previously reported in HD, it may be that apathy in HD is associated with impaired sensitivity to loss. This is in keeping with the known preferential degeneration of the indirect pathway in HD[19,26–30].

We explored this concept using a battery of cognitive tasks measuring reward-value, reward-effort calculation, response to failure, and instrumental learning from loss and reward, to delineate the cognitive processes leading to apathy in HD.

Methods

All procedures were approved by the NHS research ethics committee for Wales (13/WA/0300) in accordance with the Declaration of Helsinki.

Recruitment and Inclusion Criteria

We recruited 51 genetically confirmed HD participants (pre-symptomatic to moderately affected) from the South Wales HD Service; and 26 control participants from university students, university staff, and family members not at risk of HD. All participants gave informed consent. We excluded pregnant women, children under the age of 18, and any participant with a history of neurological disorders other than HD, or previous brain injury. Participants were paid expenses (maximum £20), but were explicitly told this amount was not affected by task performance or study completion.

Initial Assessments

Prior to the cognitive tasks, participants completed the Apathy Evaluation Scale (AES)[31], Problem Behaviors Assessment for HD[32] (PBAs; the best-verified neuropsychiatric assessment in HD); a measure of reward, risk-taking and impulsivity (Behavioral Inhibition, Behavioral Activation Scale: BISBAS[33]); a review of their medical history; and a unified Huntington's disease rating scale (UHDRS) motor examination (total motor score (TMS)[34])if they had not been examined in the preceding 3 months.

Apathy Assessment

This study used the AES(range 18-72) and PBAs Apathy(range 0-16, product of the severity (0-4) and frequency (0-4)) scores as apathy measures.

BISBAS Reward Score

The BISBAS has four sub-scores – Reward, Fun-seeking, Drive and Inhibition. The BISBAS reward subscore was analyzed separately as a measure of subjective reward value.

Cognitive Tasks

All tasks were coded in E-Prime 2.0, breaks were encouraged ad libitum, and testing was performed in a distraction-free environment on a Lenovo ThinkPad laptop computer. Tasks were drawn from a larger battery of 14 cognitive tasks (including tasks measuring irritability and low mood), administered in random order. A schematic diagram of the novel assessments (Reward Reaction Time (RRTT) and Persistence tasks) is given in Figure 1, with further details in supplementary data.

Persistence (*Sensitivity to Failure, Learning from Failure*)

This novel task was designed to measure participants' sensitivity to failure. Participants were instructed to race against a computerized opponent. They were asked to keep tapping on the keyboard to make their car go, and to press Q if they wished to stop the race. The "opponent" was always faster: traveling more rapidly and passing through checkpoints more frequently (see Figure 1 for stimuli and information displayed to participants). To account for the memory and executive function deficits seen in HD, instructions were displayed on-screen at all times. The outcome variable was the total duration of the race (608s maximum).

Phonemic Verbal Fluency (PVF): (*Executive Function*)[35]. Impaired executive function is associated with disease progression and apathy in HD[16,24,36]. Participants were told they had a minute to think of as many words beginning with one letter as they could, there were three trials (letters F, A and S). The outcome variable was the total number of novel words generated across all trials (PVF score).

Balloon Analogue Risk Task (BART): (*Learning, Response to Stimulus*)[37]

This task was used to measure instrumental learning and response to loss and gain. Participants were instructed to inflate balloons to earn money (£0.05 per pump), and told that if the balloons became 'too big' they would pop and the points would be lost. Three types of balloon were shown (distinguished by color): each had a different risk of popping and maximum number of pumps. Consequently each type of balloon had an optimal number of pumps (the maximum number of pumps before expected gain exceeded expected loss: optimum pump value, (OPV)). The outcome variable was inaccuracy i.e. the number of pumps above or below the OPV. Although initially developed as a measure of risk-taking and impulsivity, a meta analysis has shown that impulsivity and related constructs make comparatively small contributions to performance[38]. Later work has shown BART performance is influenced by executive function and in particular, neural response to feedback[38–41].

Reward Reaction Time Task (RRTT): (*Change in Effort with increasing Reward Value)*

This task measured participants willingness to increase effort for higher rewards. Participants were instructed to react as quickly as possible to a visual stimulus (Fixation Cross 500ms-2500ms; Visual Stimulus: "PPPP" displayed in the center of the screen, timeout after 10000ms; Feedback 5000ms; 0ms inter-trial interval) by pressing spacebar, and that the points on offer increased as the task progressed. Thirty practice trials were included to assess mean reaction time in an unrewarded condition. Points scored in the 4 test blocks were based on mean reaction time to account for motor disability. 7000ms breaks were given between each level. Previous work has shown that in healthy participants, reaction times shorten for higher reward[42], whilst apathy in CADASIL and Parkinson's disease reduces effort expended for reward[15,43]. The outcome variable was reward sensitivity (reward-value related change in reaction time).

Analysis and Statistical Methods

Missing data (secondary to time constraints) was excluded on a pairwise basis. 46/51 HD participants completed the BART and Persistence tasks, whilst motor impairment (5) and software failure (4) limited RRTT completion to 37. The phonemic verbal fluency task was included later in the study, and completed by 24 HD participants. All controls completed the battery. Full scale intelligence quotient (IQ) was calculated using Crawford's demographic method, as reading-based IQ tests have proven unreliable in HD[44–46]. Dopaminergic and serotonergic medications were converted into olanzapine and fluoxetine equivalent doses[47,48]. Bonferroni corrected alpha was 0.013 for the linear regression models.
The demographic variables, executive function(PVF score), PBAs and BISBAS scores from Table 1 were all considered to be potential confounding variables and were included as such in the model analyses detailed below.

BISBAS Reward score, PVF score and Persistence duration: firstly, group effects (of cases compared with controls) were assessed by constructing regression models with task performance as the dependent variable and case status (HD versus control) as the independent variable. Secondly, regression models within the HD group were constructed to measure the association between cognitive task performance and apathy scores in HD. Simple regression models were constructed (of case status on task performance, and task performance on apathy score in HD participants) and then compared with models including confounding variables as fixed effects using likelihood ratio tests. Any significant confounding variables were included in the final multiple regression model. Formal testing (normality of residuals, Goldfeld-Quandt and Durbin Watson tests) of linear regression assumptions was satisfactory for all models, except for group comparisons of BISBAS reward and Persistence: Poisson and Gamma regressions, were used respectively.

BART Logistic Mixed Models
Our analyses focused on learning, and response to punishment and reward. The dependent variable was inaccuracy(number of pumps above or below OPV) for analyses 1&2, and absolute number of pumps for analysis 3. Analyses: 1) instrumental learning (change in inaccuracy over time and change in inaccuracy by balloon type: the independent variables were trial and balloon size), 2) immediate response to stimulus (change in inaccuracy in response to different stimulus value (magnitude of monetary loss or gain) and type of stimulus (loss or gain)), and 3) response to loss and gain over time: independent variables of stimulus value, stimulus type and trial. A weighting factor for OPV was included in logistic models.

RRTT Linear Mixed Models
Our analyses assessed change in effort for different reward value and decrement in effort with time in each block. RRTT linear mixed models included log reaction time (reaction time was positively skewed) as the dependent variable. TMS was included in all models as a separate fixed effect to account for motor disability. Analysis 1) the independent variable was an interaction term between maximum reward value (increasing from 10-40 points with block) and block order, to avoid the confounding effects of fatigue[49]. Analysis 2) the independent variable was trial number within block(1-30) to separate the effects of reward and effort.

Mixed Model Construction and Comparison
We compared interaction, fixed-effect and null models using AICtab in R as described by Bolker[50–53], and report the weight (the explanation of variation in the data, penalized for model complexity, maximum value=1.0). Model comparison within the whole group included independent variables of apathy score (AES&PBAs) and case status (HD compared with control), whilst model comparisons within the HD cohort included apathy score. Likelihood ratio tests were used to compare models with and without potential confounding demographic, medication, disease-related and

neuropsychiatric variables from Table 1. Unless otherwise stated, confounding variables did not improve the models. Further details of the analysis are outlined in supplementary data.

Results

Demographics and Questionnaires (Table 1)

HD participants had higher apathy scores than controls, in addition to lower IQ, and higher TMS, medication dose, impulsivity scores and neuropsychiatric scores.

Persistence Task (Figures 2A,B&C: *Sensitivity to Failures, Learning from Failures*)

The HD group had significantly prolonged duration of game play compared with controls (the model included olanzapine; case status - coefficient 0.40,p=0.0078), consistent with impaired response to failure. Regression models showed an association between longer Persistence duration and apathy score (PBAs: adjusted R^2 0.33, Persistence- coefficient 0.013,p=1.84x10^{-5}; AES: adjusted R^2 0.26, Persistence- coefficient 0.04, p=0.00021). Likelihood ratio tests showed that only age and IQ improved both models, whilst TMS score improved the PBAs model. Multiple regression models including Persistence duration, and confounders maintained the positive relationship between Persistence duration (impaired response to failure) and apathy score (PBAs: adjusted R^2=0.47, Persistence- coefficient 0.012, p=0.00012; AES: adjusted R^2=0.42, Persistence- coefficient 0.034,p=0.0014)(Supplementary data – Table S1A&S1B).

BISBAS Reward (Supplementary Figures S1A,B&C: *Subjective Reward Value*)

The model of case status adjusted for confounding variables (age), did not show group differences of BISBAS reward scores(coefficient -0.041,p=0.49). Regression models predicting apathy scores from BISBAS reward score in cases were also not significant (AES model: adjusted R^2=0.006, BISBAS reward- coefficient -0.24,p=0.26, PBAs model: adjusted R^2=-0.018, BISBAS reward- coefficient 0.25,p=0.75). Inclusion of significant confounders, did not change these relationships(Supplementary data – Table S1C&S1D).

Phonemic Verbal Fluency (Figures 2D,E&F: *Executive Function*)

Models of case status, IQ (as a significant confounder) and PVF score showed HD was associated with impaired executive function (adjusted R^2=0.31, coefficient −14.33,p=0.00061). Simple regression models showed inverse relationships between apathy scores and PVF score(PBAs adjusted R^2 =0.26, coefficient -0.22,p=0.0069; AES adjusted R^2 =0.24, coefficient -0.68,p=0.0083). Inclusion of significant confounders(TMS, PBAs depression score and Olanzapine dose for both scores, age for the PBAs), based on likelihood ratio tests resulted in loss of significance(Supplementary data – Table S1E&F).

BART (Figure 3A&B: Instrumental Learning)

The best model in the whole group (HD cases and controls; weight 1.0) showed a significant interaction between case, apathy and trial: apathy led to more inaccuracy over time in HD cases, consistent with an apathy related deficit in instrumental learning (PBAs model p=1.73x10^{-15}, AES model p<2x10^{-16}). Likelihood ratio tests of potential confounding variables from Table 1, showed that inclusion of IQ as a fixed effect improved the model (likelihood ratio tests: PBAs model p=0.0080, AES model p=0.0083; higher IQ score was associated with less inaccuracy- PBAs model p=0.0065, AES model p=0.0066) as did PBAs irritability score (likelihood ratio tests: PBAs model p=0.020, AES model p=0.041; increased irritability was associated with more inaccuracy- PBAs model p=0.018, AES model p=0.038). However, neither of these models altered the direction or significance of the case, apathy and trial interaction(Supplementary data - Table S2A). The best model in the HD group (weight=1.0) also included a significant interaction between trial and apathy

($p<2x10^{-16}$): confirming that apathy was associated with more inaccuracy over time. Models of balloon type and apathy in HD cases showed that apathy scores improved the model (weights for both PBAs and AES models=1.0). A significant interaction between balloon size and apathy showed that apathy impaired accuracy on smaller balloons ($p<2x10^{-16}$ for AES and PBAs models, supplementary data table S2E), which popped more frequently ($p<2x10^{-16}$), consistent with impaired learning from loss compared with reward associated with apathy in HD.

BART (Figure 3B: Response to Stimulus)
The best model (weight 0.54) in the whole group (including HD cases and controls) had an interaction between group and stimulus-value(size of loss/gain): the fixed effects showed higher inaccuracy in HD cases($p=0.014$) and less inaccuracy with larger stimulus value($p=1.9x10^{-12}$), with a trend level interaction between stimulus value and case, suggesting better accuracy in HD with increasing stimulus value ($p=0.097$). Models of stimulus value and stimulus type (gain or loss) in the HD group showed this was due to a dual dissociation: the best model (weight 1.0) showed an interaction between stimulus type, stimulus value and apathy: increasing apathy led to more inaccuracy following large loss (popped balloon) compared with large reward (banked balloon) ($p=7.33x10^{-8}$). Separate analysis of trials following reward and trials following loss in the HD group, showed apathy in HD led to more inaccuracy after large loss, (, $p=1.15x10^{-5}$), but less inaccuracy following large reward ($p=0.00030$).

Contrastingly, in controls, an interaction model of stimulus value and stimulus type showed inaccuracy improved more after large loss than large reward ($p=0.00018$). Separate analysis of trials following loss, and trials following reward in the control group showed that inaccuracy improved after both large loss($p=6.73x10^{-12}$), and large reward($p=1.85x10^{-5}$) (Supplementary data – Tables S2B&C)

BART (Supplementary Data Figure S2: Learning after Gain and Loss)
Models of pumps following losses and gains over time, showed a significant interaction between stimulus value, stimulus type, trial and apathy score: over time, apathetic HD participants made more pumps following large losses than large gains (PBAs interaction- coefficient 0.0033,$p=0.00087$; AES interaction- coefficient 0.0012,$p=3.64x10^{-10}$, Supplementary data Table 2D).

RRTT (Figure 3C: Reward Value and Effort)
All models of reaction time included TMS as a fixed effect (to account for motor disability). Models comparing the effect of the interaction between maximum reward value and block order on reaction time in the whole group (HD cases and controls) revealed that the best model (weight=0.61) included case as a separate fixed effect: higher maximum reward shortened reaction time overall ($p=0.011$), whilst cases had slower reaction times than controls ($p=0.013$). In the HD group, the relationship between maximum reward value and reaction time was present at trend level ($p=0.063$). Inclusion of apathy scores did not improve any of the models. Models assessing a decrement in maintained effort (slowing of reaction time over the course of each block), did not show a change in reaction time towards the end of each block in the whole group, or in HD participants, and were not improved by inclusion of case status or apathy score (Supplementary data– Tables S3A,S3B,S4A&S4B).

Discussion
Our findings show that apathy in HD is associated with blunted response to loss and deficits in instrumental learning; demonstrated on an established task of monetary loss and novel naturalistic task of sensitivity to failure. Furthermore, higher apathy in HD was associated with better accuracy

on the BART following large gains. In keeping with Cools et al[40], we found reward-related speeding of reaction time, but apathy in HD did not affect this behavior.

We considered alternative explanations for our finding of an association between apathy in HD and a selective deficit in response to losses. Executive dysfunction (associated with apathy in HD[16,24]) and perseverative behavior are common in HD, and could have led to inappropriate or excessive responses on the BART or Persistence task, but neither the PVF or PBAs perseveration scores altered the models. Memory impairment is also common in HD[36,54]. The Persistence task included instructions on-screen at all times, whilst a recall deficit would not explain the disparity between response after loss and response after reward found on the BART, as both would have been equally affected. Irritable and impulsive behavior (which may share underlying cognitive processes with apathy[55]) is also common in HD[18,56,57], and HD patients show altered risk-reward behavior,[58–60] but none of the BISBAS scores improved the models, whilst inclusion of the PBAs irritability score did not affect the significant interaction in the BART models.

Losses and gains are processed in separable networks[61–64], and a disparity between response to loss compared with response to reward, has been previously reported in HD and other neurological disorders. Palminteri found deficits in learning from loss, compared with learning from reward in patients with Huntington's disease and a cohort of patients with insular cortex damage[25]. Similarly, Perry et al[65] showed insensitivity to aversive stimuli but preserved response to rewarding stimuli (noxious and pleasant odors) in fronto-temporal dementia. Impaired sensitivity to monetary loss has also been seen in fronto-temporal dementia[66]. However, none of these groups looked for an association with apathy in the patient cohort. Apathy in Parkinson's disease has shown blunting of response to losses and reward, but no selective deficit in response to loss[67,68]. In HD, there are several neurobiological mechanisms by which differential learning from loss and reward might arise. The indirect pathway mediates learning from loss, whilst the direct pathway mediates learning from reward[25,28,69–72]. There is selective early degeneration of the indirect pathway at the level of the striatum compared with the direct pathway in HD[19,26,27] and apathy in HD has been correlated with altered resting state activity in a circuit centered on the dorsal striatum[73]. Apathy in HD has also been correlated with amygdala atrophy and hypoperfusion[74]. The amygdala is heavily involved in stimulus-response learning and there is evidence to suggest distinct neuronal groups are involved with learning from loss and reward[64,75,76].

This work suggests that effort for reward (HD cases had slower reaction times at all levels of reward on the RRTT, despite correction for TMS) was abnormal in HD cases compared with controls, but this deficit did not mediate apathy. Consistent with Cools et al[42], we found that increased reward led to faster reaction times. A reduction in effort for reward has been demonstrated in association with apathy in CADASIL and Parkinson's disease, and anhedonia in affective disorders [15,43,77,78]. The tasks used by these groups offered explicit choice between a series of options mediating effort and reward, whilst the choice in our task was less explicit, as the different values of reward available were not stated at the outset of the task. However, participants could still have withheld effort early in the task, only to increase effort later as reward on offer increased. Our findings are in keeping with the neurobiology of HD: reward networks (ventral striatum and orbito-frontal cortex) are relatively preserved until late in the disease course[20,79]. However our most severely affected patients could not complete the task, so any contribution to apathy in HD made by reward sensitivity or effort may have been missed. The RRTT had some limitations: practice effects are seen in reaction time tasks[35,80], but we included a practice block to avoid this. Given that maximum reward increased until the final level, reward-related speeding might have been confounded by fatigue: our analysis reports the interaction between reward value and block order to counter this problem. The possibility of fatigue confounding our results remains. Finally, we looked for a reduction of effort at the end of each trial block to isolate reward value from effort, but did not

find any effect of apathy or HD status. Future exploration of effort and reward in HD, should vary effort and reward on a trial-by-trial basis rather than by block.

In keeping with earlier studies[16,24], executive dysfunction and apathy are linked in HD. However, this relationship was only present at trend level in the multiple regression model. This may reflect the smaller sample size, a lack of robust control of confounders in previous studies, or that PVF may not be the executive function task most closely associated with apathy in HD. Previous work in HD showed associations between apathy and the symbol digit modality test, Stroop task and trail making test[16,24]. Furthermore, sequencing and planning processes are likely to have more significant involvement in goal directed behavior than those processes tested to date, which assess updating, attention and inhibition. A more robust task of planning (such as the Towers of London task - known to be impaired in HD[36,54]) should be included in future work.

In summary, we have shown that apathy in HD is associated with a deficit in response to losses, whilst altered response to reward, or altered reward-effort valuation is not necessary to develop apathetic behavior. This discovery facilitates the development of translational tasks of apathy for animal models, task-based functional imaging work to delineate the neurobiology, and paves the way for behavioral interventions to treat apathy in HD.

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Author Contributions
1. Research project: A. Conception, B. Organization, C. Execution
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique

DMcL – 1A, 1B, 1C, 2A, 2B, 3A
TL – 2A, 2B, 2C, 3B
DC – 1A, 2B, 3B
DEJL – 1A, 1B, 2C, 3B
AER – 1A, 1B, 2C, 3B

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1. Chow TW, Binns MA, Cummings JL, et al. Apathy Symptom Profile and Behavioral Associations in Frontotemporal Dementia vs Dementia of Alzheimer Type. Arch. Neurol. 2009;66(7):888–893.

2. Pluck GC, Brown RG. Apathy in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 2002;73(6):636–642.

3. Starkstein SE, Jorge R, Mizrahi R, Robinson RG. A prospective longitudinal study of apathy in Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 2006;77(1):8–11.

4. van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. J. Neuropsychiatry Clin. Neurosci. 2007;19(4):441–448.

5. van Duijn E, Craufurd D, Hubers AAM, et al. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). J. Neurol. Neurosurg. Psychiatry 2014;85(12):1411–1418.

6. Hamilton JM, Salmon DP, Corey-Bloom J, et al. Behavioural abnormalities contribute to functional decline in Huntington's disease. J. Neurol. Neurosurg. Psychiatry 2003;74(1):120–122.

7. Eddy CM, Rickards HE. Impact of cognitive and behavioural changes on quality of life in Huntington's disease. Basal Ganglia 2013;3(2):123–126.

8. D'Iorio A, Vitale C, Piscopo F, et al. Impact of anxiety, apathy and reduced functional autonomy on perceived quality of life in Parkinson's disease. Parkinsonism Relat. Disord. 2017;43:114–117.

9. Weintraub D, Moberg PJ, Duda JE, et al. Effect of Psychiatric and Other Nonmotor Symptoms on Disability in Parkinson's Disease. J. Am. Geriatr. Soc. 2004;52(5):784–788.

10. Merrilees J, Dowling GA, Hubbard E, et al. Characterization of Apathy in Persons with Frontotemporal Dementia and The Impact on Family Caregivers. Alzheimer Dis. Assoc. Disord. 2013;27(1):62–67.

11. Read J, Jones R, Owen G, et al. Quality of life in Huntington's disease: a comparative study investigating the impact for those with pre-manifest and early manifest disease, and their partners. J. Huntingt. Dis. 2013;2(2):159–175.

12. Le Heron C, Apps M a. J, Husain M. The anatomy of apathy: A neurocognitive framework for amotivated behaviour. Neuropsychologia 2017;

13. Ernst M, Paulus MP. Neurobiology of decision making: a selective review from a neurocognitive and clinical perspective. Biol. Psychiatry 2005;58(8):597–604.

14. Waltz JA, Frank MJ, Robinson BM, Gold JM. Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal-cortical dysfunction. Biol. Psychiatry 2007;62(7):756–764.

15. Le Heron C, Plant O, Manohar S, et al. Distinct effects of apathy and dopamine on effort-based decision-making in Parkinson's disease. Brain J. Neurol. 2018;141(5):1455–1469.

16. Baudic S, Maison P, Dolbeau G, et al. Cognitive impairment related to apathy in early Huntington's disease. Dement. Geriatr. Cogn. Disord. 2006;21(5–6):316–321.

17. Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. Lancet Neurol. 2013;12(7):637–649.

18. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington Disease. Neuropsychiatry. Neuropsychol. Behav. Neurol. 2001;14(4):219–226.

19. Deng YP, Albin RL, Penney JB, et al. Differential loss of striatal projection systems in Huntington's disease: a quantitative immunohistochemical study. J. Chem. Neuroanat. 2004;27(3):143–164.

20. Vonsattel JP, Myers RH, Stevens TJ, et al. Neuropathological classification of Huntington's disease. J. Neuropathol. Exp. Neurol. 1985;44(6):559–577.

21. Vonsattel JPG, Difiglia M. Huntington Disease. J. Neuropathol. Exp. Neurol. 1998;57(5):369–384.

22. Killoran A, Biglan KM, Jankovic J, et al. Characterization of the Huntington intermediate CAG repeat expansion phenotype in PHAROS. Neurology 2013;80(22):2022–2027.

23. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol. 2009;8(9):791–801.

24. Reedeker N, Bouwens JA, van Duijn E, et al. Incidence, course, and predictors of apathy in Huntington's disease: a two-year prospective study. J. Neuropsychiatry Clin. Neurosci. 2011;23(4):434–441.

25. Palminteri S, Justo D, Jauffret C, et al. Critical roles for anterior insula and dorsal striatum in punishment-based avoidance learning. Neuron 2012;76(5):998–1009.

26. Ferrante RJ, Kowall NW, Richardson EP. Proliferative and degenerative changes in striatal spiny neurons in Huntington's disease: a combined study using the section-Golgi method and calbindin D28k immunocytochemistry. J. Neurosci. Off. J. Soc. Neurosci. 1991;11(12):3877–3887.

27. Goto S, Hirano A, Rojas-Corona RR. An immunohistochemical investigation of the human neostriatum in Huntington's disease. Ann. Neurol. 1989;25(3):298–304.

28. Cox SML, Frank MJ, Larcher K, et al. Striatal D1 and D2 signaling differentially predict learning from positive and negative outcomes. NeuroImage 2015;109:95–101.

29. Frank MJ, Seeberger LC, O'reilly RC. By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science 2004;306(5703):1940–1943.

30. Doll BB, Frank MJ. Chapter 19 - The basal ganglia in reward and decision making: computational models and empirical studies [Internet]. In: Dreher J-C, Tremblay L, editors. Handbook of Reward and Decision Making. New York: Academic Press; 2009 p. 399–425. [cited 2019 Feb 13] Available from: http://www.sciencedirect.com/science/article/pii/B9780123746207000194

31. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res. 1991;38(2):143–162.

32. Callaghan J, Stopford C, Arran N, et al. Reliability and Factor Structure of the Short Problem Behaviors Assessment for Huntington's Disease (PBA-s) in the TRACK-HD and REGISTRY studies. J. Neuropsychiatry Clin. Neurosci. 2015;27(1):59–64.

33. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. J. Pers. Soc. Psychol. 1994;67(2):319–333.

34. Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group. Mov. Disord. Off. J. Mov. Disord. Soc. 1996;11(2):136–142.

35. Benton AL. Development of a multilingual aphasia battery: Progress and problems. J. Neurol. Sci. 1969;9(1):39–48.

36. Stout JC, Paulsen JS, Queller S, et al. Neurocognitive Signs in Prodromal Huntington Disease. Neuropsychology 2011;25(1):1–14.

37. Lejuez CW, Read JP, Kahler CW, et al. Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). J. Exp. Psychol. Appl. 2002;8(2):75–84.

38. Lauriola M, Panno A, Levin IP, Lejuez CW. Individual Differences in Risky Decision Making: A Meta-analysis of Sensation Seeking and Impulsivity with the Balloon Analogue Risk Task. J. Behav. Decis. Mak. 2014;27(1):20–36.

39. Blair MA, Moyett A, Bato AA, et al. The Role of Executive Function in Adolescent Adaptive Risk-Taking on the Balloon Analogue Risk Task. Dev. Neuropsychol. 2018;43(7):566–580.

40. Campbell JA, Samartgis JR, Crowe SF. Impaired decision making on the Balloon Analogue Risk Task as a result of long-term alcohol use. J. Clin. Exp. Neuropsychol. 2013;35(10):1071–1081.

41. Kóbor A, Takács Á, Janacsek K, et al. Different strategies underlying uncertain decision making: higher executive performance is associated with enhanced feedback-related negativity. Psychophysiology 2015;52(3):367–377.

42. Cools R, Blackwell A, Clark L, et al. Tryptophan Depletion Disrupts the Motivational Guidance of Goal-Directed Behavior as a Function of Trait Impulsivity. Neuropsychopharmacology 2005;30(7):1362–1373.

43. Le Heron C, Manohar S, Plant O, et al. Dysfunctional effort-based decision-making underlies apathy in genetic cerebral small vessel disease. Brain 2018;141(11):3193–3210.

44. Crawford JR, Millar J, Milne AB. Estimating premorbid IQ from demographic variables: a comparison of a regression equation vs. clinical judgement. Br. J. Clin. Psychol. 2001;40(Pt 1):97–105.

45. O'Rourke JJF, Adams WH, Duff K, et al. Estimating premorbid functioning in huntington's disease: the relationship between disease progression and the wide range achievement test reading subtest. Arch. Clin. Neuropsychol. Off. J. Natl. Acad. Neuropsychol. 2011;26(1):59–66.

46. Crawford JR, Parker DM, Besson JA. Estimation of premorbid intelligence in organic conditions. Br. J. Psychiatry J. Ment. Sci. 1988;153:178–181.

47. Leucht S, Samara M, Heres S, et al. Dose equivalents for second-generation antipsychotics: the minimum effective dose method. Schizophr. Bull. 2014;40(2):314–326.

48. Hayasaka Y, Purgato M, Magni LR, et al. Dose equivalents of antidepressants: Evidence-based recommendations from randomized controlled trials. J. Affect. Disord. 2015;180:179–184.

49. Woods DL, Wyma JM, Yund EW, et al. Factors influencing the latency of simple reaction time [Internet]. Front. Hum. Neurosci. 2015;9[cited 2019 Feb 7] Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4374455/

50. Bolker BM, Brooks ME, Clark CJ, et al. Generalized linear mixed models: a practical guide for ecology and evolution. Trends Ecol. Evol. 2009;24(3):127–135.

51. Bolker B, Team RDC. bbmle: Tools for General Maximum Likelihood Estimation [Internet]. 2017.Available from: https://CRAN.R-project.org/package=bbmle

52. Magnusson A, Skaug H, Nielsen A, et al. glmmTMB: Generalized Linear Mixed Models using Template Model Builder [Internet]. 2017.Available from: https://CRAN.R-project.org/package=glmmTMB

53. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2015.Available from: https://www.R-project.org/

54. Lawrence AD, Sahakian BJ, Hodges JR, et al. Executive and mnemonic functions in early Huntington's disease. Brain J. Neurol. 1996;119 (Pt 5):1633–1645.

55. Lansdall CJ, Coyle-Gilchrist ITS, Jones PS, et al. Apathy and impulsivity in frontotemporal lobar degeneration syndromes. Brain J. Neurol. 2017;140(6):1792–1807.

56. Johnson PL, Potts GF, Sanchez-Ramos J, Cimino CR. Self-reported impulsivity in Huntington's disease patients and relationship to executive dysfunction and reward responsiveness. J. Clin. Exp. Neuropsychol. 2017;39(7):694–706.

57. Thompson JC, Harris J, Sollom AC, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. J. Neuropsychiatry Clin. Neurosci. 2012;24(1):53–60.

58. van Wouwe NC, Kanoff KE, Claassen DO, et al. The Allure of High-Risk Rewards in Huntington's disease. J. Int. Neuropsychol. Soc. JINS 2016;22(4):426–435.

59. Galvez V, Fernandez-Ruiz J, Bayliss L, et al. Early Huntington's Disease: Impulse Control Deficits but Correct Judgment Regarding Risky Situations. J. Huntingt. Dis. 2017;6(1):73–78.

60. Stout JC, Rodawalt WC, Siemers ER. Risky decision making in Huntington's disease. J. Int. Neuropsychol. Soc. JINS 2001;7(1):92–101.

61. O'Doherty J, Kringelbach ML, Rolls ET, et al. Abstract reward and punishment representations in the human orbitofrontal cortex. Nat. Neurosci. 2001;4(1):95–102.

62. O'Doherty J, Rolls ET, Francis S, et al. Representation of pleasant and aversive taste in the human brain. J. Neurophysiol. 2001;85(3):1315–1321.

63. Delgado MR, Nystrom LE, Fissell C, et al. Tracking the hemodynamic responses to reward and punishment in the striatum. J. Neurophysiol. 2000;84(6):3072–3077.

64. Zhang X, Li B. Population coding of valence in the basolateral amygdala. Nat. Commun. 2018;9(1):5195.

65. Perry DC, Datta S, Sturm VE, et al. Reward deficits in behavioural variant frontotemporal dementia include insensitivity to negative stimuli. Brain J. Neurol. 2017;

66. Massimo L, Powers JP, Evans LK, et al. Apathy in Frontotemporal Degeneration: Neuroanatomical Evidence of Impaired Goal-directed Behavior. Front. Hum. Neurosci. 2015;9:611.

67. Fitts W, Massimo L, Lim N, et al. Computerized assessment of goal-directed behavior in Parkinson's disease. J. Clin. Exp. Neuropsychol. 2016;38(9):1015–1025.

68. Martinez-Horta S, Sampedro F, Pagonabarraga J, et al. Non-demented Parkinson's disease patients with apathy show decreased grey matter volume in key executive and reward-related nodes. Brain Imaging Behav. 2016;

69. Schroll H, Beste C, Hamker FH. Combined lesions of direct and indirect basal ganglia pathways but not changes in dopamine levels explain learning deficits in patients with Huntington's disease. Eur. J. Neurosci. 2015;41(9):1227–1244.

70. Kravitz AV, Tye LD, Kreitzer AC. Distinct roles for direct and indirect pathway striatal neurons in reinforcement. Nat. Neurosci. 2012;15(6):816–818.

71. Menegas W, Akiti K, Amo R, et al. Dopamine neurons projecting to the posterior striatum reinforce avoidance of threatening stimuli. Nat. Neurosci. 2018;21(10):1421.

72. Pessiglione M, Seymour B, Flandin G, et al. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature 2006;442(7106):1042–1045.

73. McColgan P, Razi A, Gregory S, et al. Structural and functional brain network correlates of depressive symptoms in premanifest Huntington's disease. Hum. Brain Mapp. 2017;

74. Martínez-Horta S, Perez-Perez J, Sampedro F, et al. Structural and metabolic brain correlates of apathy in Huntington's disease. Mov. Disord. Off. J. Mov. Disord. Soc. 2018;

75. McHugh SB, Barkus C, Huber A, et al. Aversive Prediction Error Signals in the Amygdala. J. Neurosci. 2014;34(27):9024–9033.

76. Belova MA, Paton JJ, Morrison SE, Salzman CD. Expectation Modulates Neural Responses to Pleasant and Aversive Stimuli in Primate Amygdala. Neuron 2007;55(6):970–984.

77. Treadway MT, Bossaller NA, Shelton RC, Zald DH. Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. J. Abnorm. Psychol. 2012;121(3):553–558.

78. Treadway MT, Buckholtz JW, Schwartzman AN, et al. Worth the 'EEfRT'? The Effort Expenditure for Rewards Task as an Objective Measure of Motivation and Anhedonia. PLOS ONE 2009;4(8):e6598.

79. Kassubek J, Juengling FD, Kioschies T, et al. Topography of cerebral atrophy in early Huntington's disease: a voxel based morphometric MRI study. J. Neurol. Neurosurg. Psychiatry 2004;75(2):213–220.

80. Del Rossi G, Malaguti A, Del Rossi S. Practice Effects Associated With Repeated Assessment of a Clinical Test of Reaction Time. J. Athl. Train. 2014;49(3):356–359.

Table and Figure Legends

Figure 1

A Persistence Task. Diagram of racing screen and checkpoint screens, with race ending screens shown below.
B Reward Reaction Time Task. The fixation cross, visual stimulus and feedback screens for the practice level (below) and rewarded task (above) are shown).

Figure 2
Persistence (A,B&C) & Phonemic Verbal Fluency (D,E&F): HD participants had longer Persistence duration and lower PVF scores than controls. Apathy was associated with increased Persistence duration and lower PVF score.

Figure 3
BART Behavior (A,B,C&D) Apathy in HD was significantly associated with impaired instrumental learning, worse accuracy following large losses, and better accuracy after large reward.
RRTT (E,F) Higher rewards led to faster reaction times in the whole group analysis

Table 1
Significance: * <0.05 ** <0.01 *** <0.001
Means and range (in brackets) are shown.
Abbreviations: HD - Huntington's disease, IQ - full scale intelligence quotient, PBA - Problem Behaviors
Assessment (Short Form), BISBAS - Behavioural Inhibition Scale Behavioural Activation Scale.
AES - Apathy Evaluation Scale

Supplementary Data

Description of Tasks

Persistence
Participants were instructed "You must race against a second player. Tapping quickly on the 's' key makes your car go faster. There are 2 races; in the second race, your car's speed will increase. If you wish to end the race at any point, press 'Q'." The opponent was always faster – the opponent's 'distance travelled' incremented by 2 units every 250ms in race 1, and 3 units every 250ms in race 2, whilst the maximum the player could travel was 1 unit every 250ms in both races. Checkpoints were shown for the opponent and the player every time they travelled another 50 units. If participants asked "does this race end", they were told that it did, any other questions were met with "all I can tell you is keep pressing S to go or Q to quit", participants who withdrew completely from any activity for more than 60 seconds were asked if they wished to stop the task. Instructions were displayed at all times during the task on-screen (Figure 1A). The outcome variable was the total duration of the race (608s maximum).

Balloon Analogue Risk Task
Participants were instructed "You must inflate balloons to earn money. The larger the balloon gets, the more money you win. If the balloon pops the money is lost and the next trial starts. Pressing 'bank' saves the money and ends each trial". Each pump gained the participants £0.05. Participants were told they would not receive the total at the end of the game, but to compete to win as much as possible. There were 90 trials, and 3 types of balloon distinguished by colour and maximum possible value of pumps. The number of pumps before the balloon popped randomly varied on each trial between the following values for each balloon: yellow balloons 2-16 pumps, pink balloons 2-32 pumps and blue balloons 2-128 pumps. Each pump increased the points total for the trial, but also increased the risk of losing all points for the trial. Successful performance on this task required participants to learn the optimum value of each balloon (the highest number of pumps where expected gain exceeded expected loss). The outcome variable used was inaccuracy: number of pumps above or below optimum pump value.

Reward Reaction Time Task
Participants received instructions stating; 1) the aim of the task was to win as many points as possible, 2) the faster they reacted, the more points they would win, and 3) the maximum points on offer would increase during the task. They were told that if they did not react quickly enough, they would not win points. Participants were given a practice run of 30 trials (feedback screen shown in Figure 1B), followed by the live task, where trials were rewarded with points (feedback screen shown above). If participants did not react within the timeout window, they scored 0 points. There were 5 blocks including the practice level (points available (0 – practice level, 0-10, 0-20, 0-40, 0-40 respectively), each block consisted of 30 trials minimum. Participants could not progress to the next block until they had scored the equivalent of maximum points for 30 trials for the current block. Maximum points were scored for responses quicker than mean baseline reaction time (calculated from the practice run), zero points were awarded for responses slower than 6 x mean reaction time and 50% of maximum points were scored for response between these parameters. Breaks (7000ms) were given between each block.

BART - Calculation of Optimum Pump Value and Inaccuracy
Optimum pump value was calculated for each of the 3 balloons as the maximum number of pumps before expected gain (probability of gain x magnitude of gain) exceeded expected loss (probability of loss x magnitude of loss). In practice this was equal to 50% of the maximum pump value for each balloon. Proportional inaccuracy was calculated as number of pumps greater or less than the optimum pump value, divided by optimum pump value. BART logistic models included proportional inaccuracy as the dependent variable (weighted for total number of potential 'successes' or 'failures' i.e. optimum pump value).

Model Construction

** denotes interaction*
+ denotes fixed effect

Whole cohort (HD cases and controls)

Full Interaction Model
dependent variable = independent variable * case status * apathy + random effect (individual subject)

Apathy Interaction Model
dependent variable = independent variable * apathy + random effect (individual subject)

Case Interaction Model
dependent variable = independent variable * case status + random effect (individual subject)

Full Fixed Effect Model
dependent variable = independent variable + case status + apathy + random effect (individual subject)

Apathy Fixed Effect Model
dependent variable = independent variable + apathy + random effect (individual subject)

Case Fixed Effect Model
dependent variable = independent variable + case status + random effect (individual subject)

Simple Model
dependent variable = independent variable + random effect (individual subject)

Null Model
dependent variable = random effect (individual subject)

HD Cohort (HD cases only)

Apathy Interaction Model
dependent variable = independent variable * apathy + random effect (individual subject)

Apathy Fixed Effect Model
dependent variable = independent variable + apathy + random effect (individual subject)

Simple Model
dependent variable = independent variable + random effect (individual subject)

Null Model
dependent variable = random effect (individual subject)

Table S1A - Persistence Group Comparison

	Persistence	
	Estimate	P Value
(Intercept)	5.57	$<2x10^{-16}$
Case HD	0.40	0.0078
Olanzapine Equivalent (mg)	0.018	0.20
Log Likelihood	−483.91	
Akaike Inf. Crit.	973.82	

Abbreviations: HD - Huntington's disease

Table S1B - Persistence Regression

	PBA Apathy		AES	
	Estimate	P Value	Estimate	P Value
(Intercept)	−0.29	0.81	21.59	0.00002
Persistence	0.013	$1.84x10^{-5}$	0.040	0.00021
R^2	0.34		0.27	
Adjusted R^2	0.33		0.26	
F Statistic (df = 1; 44)	23.068^{***}		16.37^{***}	
(Intercept)	−1.050	0.85	5.14	0.61
Persistence	0.012	0.00012	0.034	0.0014
Age	0.065	0.22	0.22	0.24
TMS	0.035	0.23	0.20	0.069
IQ	−0.037	0.42	–	–
R^2	0.47		0.42	
Adjusted R^2	0.41		0.38	
F Statistic	8.49^{***} (df = 4; 39)		10.31^{***} (df = 3; 42)	

Note: *p<0.1; **p<0.05; ***p<0.01

Abbreviations: IQ - full scale intelligence quotient, AES - Apathy Evaluation Scale
PBA - Problem Behaviors Assessment (Short Form), TMS - total motor score

Table S1C - BISBAS Reward Group Comparison

	BISBAS Reward	
	Estimate	P Value
(Intercept)	2.99	$<2\text{x}10^{-16}$
Case HD	−0.041	0.49
Age	−0.0029	0.13
Log Likelihood	−200.06	
Akaike Inf. Crit.	406.12	

Abbreviations: HD - Huntington's disease

Table S1D - BISBAS Reward Regression

	PBA Apathy		AES	
	Estimate	P Value	Estimate	P Value
(Intercept)	8.90	0.018	41.99	0.0017
BISBAS Reward	−0.25	0.26	−0.24	0.75
R^2	0.026		0.002	
Adjusted R^2	0.006		−0.018	
F Statistic (df = 1; 49)	1.32		0.10	
(Intercept)	7.72	0.20	30.037	0.047
BISBAS Reward	−0.25	0.37	−0.57	0.39
TMS	0.088	79	0.30	0.0066
PBA Perseveration	0.14	0.55	0.58	0.41
Olanzapine Equivalent (mg)	1.11	0.0068	0.54	0.13
Age	−0.095	0.19	–	–
PVF Score	–	–	0.092	0.61
R^2	0.62		0.36	
Adjusted R^2	0.51		0.29	
F Statistic	5.64*** (df = 5; 17)		5.085*** (df = 5; 45)	

Note: *p<0.1; **p<0.05; ***p<0.01

Abbreviations: PVF - Phonemic Verbal Fluency, PBA - Problem Behaviors Assessment (Short Form), BISBAS - Behavioural Inhibition Scale Behavioural Activation Scale, TMS - total motor score.

Figure S1A - BISBAS Reward Group Comparison

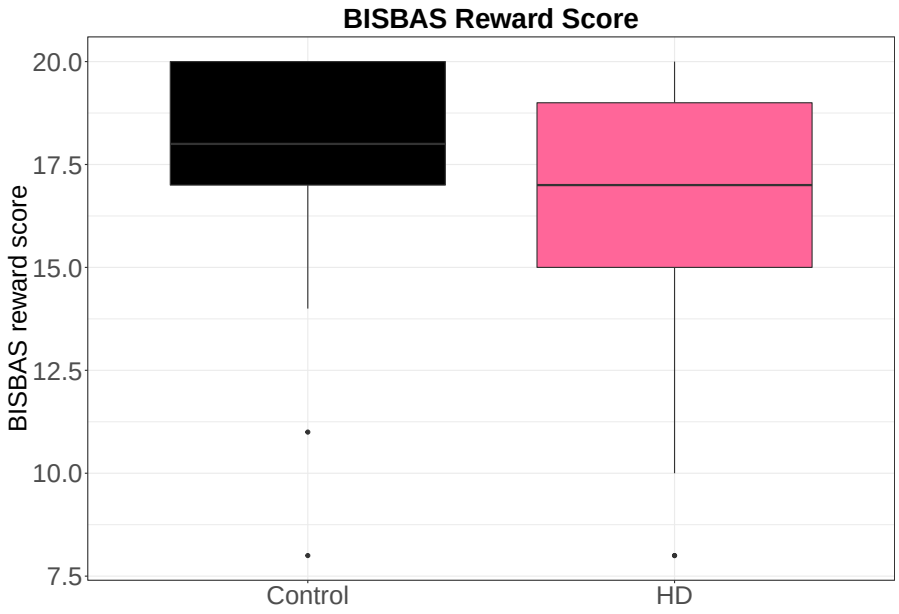

Figure S1B - BISBAS Reward - PBA Apathy

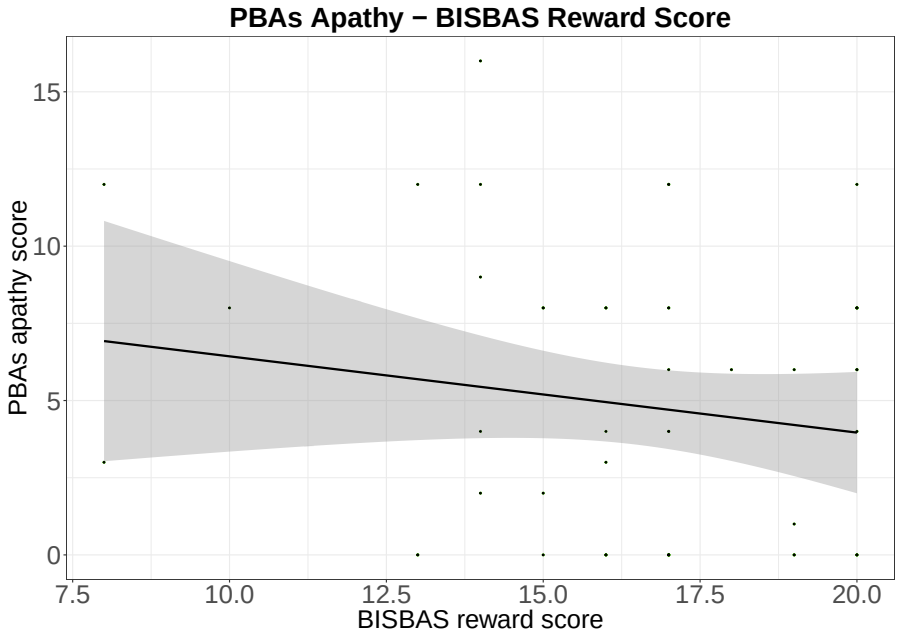

Figure S1C - BISBAS Reward - AES Score

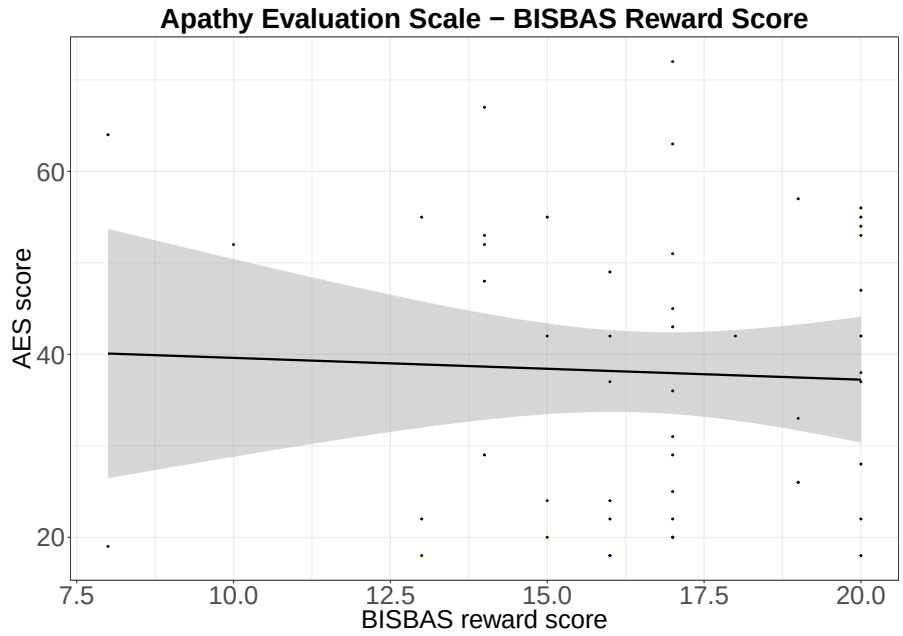

Table S1E - Verbal Fluency Group Comparison

	Verbal Fluency	
	Estimate	P Value
(Intercept)	2.74	0.89
Case HD	−14.33	0.00061
IQ	0.39	0.036
R^2	0.34	
Adjusted R^2	0.31	
F Statistic	11.31*** (df = 2; 44)	

Abbreviations: HD - Huntington's disease
IQ - full scale intelligence quotient

Table S1F - Phonemic Verbal Fluency Regression

	PBA Apathy		AES	
	Estimate	P Value	Estimate	P Value
(Intercept)	11.26	$6.46x10^{-6}$	56.036	$1.5x10^{-7}$
Verbal Fluency	−0.22	0.0069	−0.68	0.0083
R^2	0.29		0.28	
Adjusted R^2	0.26		0.24	
F Statistic (df = 1; 22)	8.89**		8.40**	
(Intercept)	3.34	0.39	33.83	0.00088
Verbal Fluency	−0.12	0.071	−0.32	0.097
TMS	0.075	0.057	0.302	0.0019
PBA Depression	−0.15	0.53	−0.47	0.50
Olanzapine Equivalent	1.051	0.014	3.90	0.0026
Age	0.044	0.51	–	–
R^2	0.69		0.72	
Adjusted R^2	0.60		0.66	
F Statistic	7.92*** (df = 5; 18)		12.39*** (df = 4; 19)	

p<0.05; **p<0.01; ***p<0.005
Abbreviations: PVF - Phonemic Verbal Fluency,
PBA - Problem Behaviors Assessment (Short Form), TMS - total motor score.

Table S2A - Effect of Apathy on Instrumental Learning

	Inaccuracy	
	Estimate	P Value
(Intercept)	0.88	$5.29\text{x}10^{-14}$
Case HD	0.55	0.00095
PBA Apathy	0.094	0.30
Trial	−0.016	$<2\text{x}10^{-16}$
Case HD*PBA Apathy*Trial	0.0028	$1.73\text{x}10^{-15}$
Log Likelihood	−25,065.78	
Akaike Inf. Crit.	50,149.55	
Bayesian Inf. Crit.	50,210.44	
(Intercept)	−0.97	0.35
Case HD	2.55	0.015
AES	0.10	0.064
Trial	$0.018<2\text{x}10^{-16}$	
Case HD*AES*Trial	0.0028	$1.75\text{x}10^{-15}$
Observations	6,408	
Log Likelihood	−25,037.33	
Akaike Inf. Crit.	50,092.66	
Bayesian Inf. Crit.	50,153.55	

* denotes interaction
Abbreviations: HD - Huntington's disease,
PBA - Problem Behaviors Assessment (Short Form)

Table S2B(i)- Response to Stimulus in Whole Group

	Inaccuracy	
	Estimate	P Value
(Intercept)	0.32	0.0021
Stimulus Value	−0.42	$1.9\text{x}10^{-12}$
Case HD	0.32	0.014
Case HD*Stimulus Value	−0.12	0.097
Observations	6,408	
Log Likelihood	−28,054.3	
Akaike Inf. Crit.	56,118.6	
Bayesian Inf. Crit.	56,152.4	

* denotes interaction
Abbreviations: HD - Huntington's disease

Table S2B(ii)- Response to Stimulus in Cases

	Inaccuracy	
	Estimate	P Value
(Intercept)	0.59	$5.85\text{x}10^{-7}$
Stimulus Value	−0.11	0.16
Prior Loss	0.45	$<2\text{x}10^{-16}$
PBA Apathy	−0.0021	0.91
Stimulus Value*Prior Loss*PBA Apathy	0.13	$7.33\text{x}10^{-8}$
Observations	4,094	
Log Likelihood	−17,851.44	
Akaike Inf. Crit.	35,720.89	
Bayesian Inf. Crit.	35,777.74	
(Intercept)	0.52	0.014
Stimulus Value	0.13	0.37
Prior Loss	0.67	$1.43\text{x}10^{-15}$
AES	0.0016	0.77
Stimulus Value*Prior Loss*AES	0.043	$7.13\text{x}10^{-10}$
Observations	4,094	
Log Likelihood	−17,847.83	
Akaike Inf. Crit.	35,713.67	
Bayesian Inf. Crit.	35,770.52	

* denotes interaction
Abbreviations: PBA - Problem Behaviors Assessment (Short Form)
AES - Apathy Evaluation Scale

Table S2B(iii)- Response to Losses in Cases

	Inaccuracy Following Losses	
	Estimate	P Value
(Intercept)	1.0084	$7.07\text{x}10^{-16}$
Stimulus Value	−1.89	$<2\text{x}10^{-16}$
PBA Apathy	−0.038	0.057
Stimulus Value*PBA Apathy	0.096	$1.15\text{x}10^{-5}$
Observations	1,104	
Log Likelihood	−4,420.29	
Akaike Inf. Crit.	8,850.59	
Bayesian Inf. Crit.	8,875.62	
(Intercept)	1.13	$4.47\text{x}10^{-7}$
Stimulus Value	−2.62	$<2\text{x}10^{-16}$
AES	−0.0081	0.15
Stimulus Value*AES	0.031	$3.13\text{x}10^{-7}$
Observations	1,104	
Log Likelihood	−4,417.002	
Akaike Inf. Crit.	8,844.003	
Bayesian Inf. Crit.	8,869.037	

* denotes interaction
Abbreviations: PBA - Problem Behaviors Assessment (Short Form),
AES - Apathy Evaluation Scale

Table S2B(iv)- Response to Rewards in Cases

	Inaccuracy Following Reward	
	Estimate	P Value
(Intercept)	0.57	$4.54\text{x}10^{-6}$
Stimulus Value	−0.038	0.62
PBA Apathy	0.00057	0.98
Stimulus Value*PBA Apathy	−0.045	0.00030
Observations	2,990	
Log Likelihood	−13,264.92	
Akaike Inf. Crit.	26,539.84	
Bayesian Inf. Crit.	26,569.85	
(Intercept)	0.48	0.030
Stimulus Value	0.25	0.078
AES	0.0024	0.67
Stimulus Value*AES	−0.013	0.00016
Observations	2,990	
Log Likelihood	−13,264.40	
Akaike Inf. Crit.	26,538.81	
Bayesian Inf. Crit.	26,568.82	

* denotes interaction
Abbreviations: PBA - Problem Behaviors Assessment (Short Form)
AES - Apathy Evaluation Scale

Table S2C(i)- Response to Stimulus in Controls

	Inaccuracy	
	Estimate	P Value
(Intercept)	0.28	0.0027
Stimulus Value	−0.31	0.000015
Prior Loss	0.17	0.000056
Stimulus Value*Prior Loss	−0.52	0.00018
Observations	2,314	
Log Likelihood	−10,128.89	
Akaike Inf. Crit.	20,267.77	
Bayesian Inf. Crit.	20,296.51	

* denotes interaction

Table S2C(ii) - Response to Rewards in Controls

	Inaccuracy Following Reward	
	Estimate	P Value
(Intercept)	0.28	0.0018
Stimulus Value	−0.30	$1.85\text{x}10^{-5}$
Observations	1,690	
Log Likelihood	−7,326.67	
Akaike Inf. Crit.	14,659.34	
Bayesian Inf. Crit.	14,675.64	

* denotes interaction

Table S2C(iii) - Response to Losses in Controls

	Inaccuracy Following Losses	
	Estimate	P Value
(Intercept)	0.45	0.00019
Stimulus Value	−0.85	$6.73\text{x}10^{-12}$
Observations	624	
Log Likelihood	−2,708.98	
Akaike Inf. Crit.	5,423.97	
Bayesian Inf. Crit.	5,437.28	

* denotes interaction

Table S2D - Response to Loss and Reward Over Time

	Pumps	
	Estimate	P Value
(Intercept)	−2.22	$<2x10^{-16}$
Stimulus Value	−0.084	0.46
PBA Apathy	0.025	0.19
Trial	0.019	$<2x10^{-16}$
Prior Loss	−0.22	0.0052
Stimulus Value*PBA Apathy*Trial*Prior Loss	0.0033	0.00087
Observations	4,094	
Log Likelihood	−17,481.47	
Akaike Inf. Crit.	34,996.95	
Bayesian Inf. Crit.	35,104.34	
(Intercept)	−2.27	$<2x10^{-16}$
Stimulus Value	−0.40	0.054
AES	0.0045	0.42
Trial	0.020	$<2x10^{-16}$
Prior Loss	−0.53	$1.47x10^{-6}$
Stimulus Value*AES*Trial*Prior Loss	0.0012	$3.64x10^{-10}$
Observations	4,094	
Log Likelihood	−17,480.41	
Akaike Inf. Crit.	34,994.83	
Bayesian Inf. Crit.	35,102.22	

* denotes interaction
Abbreviations: PBA - Problem Behaviors Assessment (Short Form)
AES - Apathy Evaluation Scale

Figure S2 - Influence of Apathy on Learning following Gain and Loss

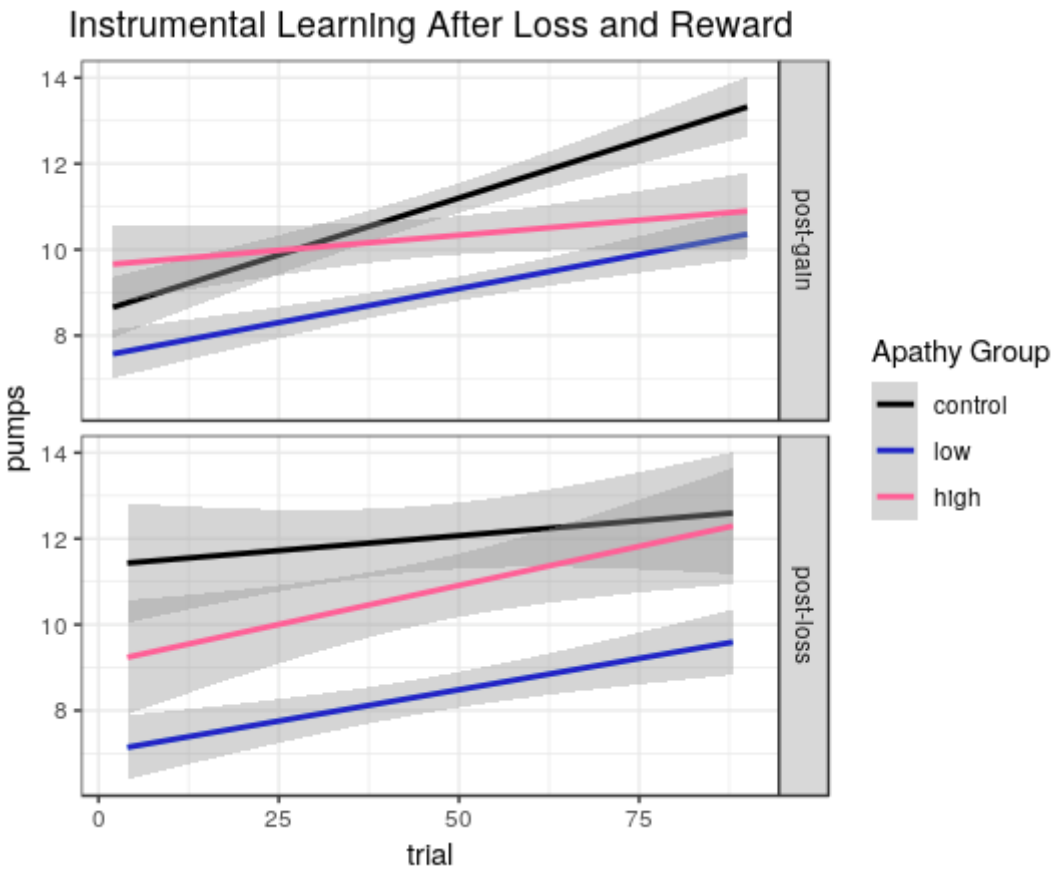

Table S2E - Influence of Apathy on Accuracy by Size of Balloon

	Inaccuracy	
	Estimate	P Value
(Intercept)	−0.87	$4.59\text{x}10^{-11}$
Maximum Balloon Value	0.022	$<2\text{x}10^{-16}$
PBA Apathy	0.023	0.27
Maximum Balloon Value*PBA Apathy	−0.00058	$<2\text{x}10^{-16}$
Observations	4,094	
Log Likelihood	−12,377.13	
Akaike Inf. Crit.	24,764.27	
Bayesian Inf. Crit.	24,795.85	
(Intercept)	−1.046	$1.20\text{x}10^{-5}$
Maximum Balloon Value	0.024	$<2\text{x}10^{-16}$
AES	0.0076	0.20
Maximum Balloon Value*AES	−0.00013	$<2\text{x}10^{-16}$
Observations	4,094	
Log Likelihood	−12,403.15	
Akaike Inf. Crit.	24,816.30	
Bayesian Inf. Crit.	24,847.88	

* denotes interaction
Abbreviations: PBA - Problem Behaviors Assessment (Short Form)
AES - Apathy Evaluation Scale

Table S3A(i)- Effect of Reward Value on Reaction Time in Whole Group

	Log Reaction Time	
	Estimate	P Value
(Intercept)	5.71	$<2x10^{-16}$
Block Order	0.040	0.10
Maximum Reward	0.0057	0.0026
Case HD	0.22	0.013
TMS	0.0084	0.000028
Block Order*Maximum Reward	−0.0015	0.011
Observations	7,246	
Log Likelihood	−3,805.65	
Akaike Inf. Crit.	7,627.29	
Bayesian Inf. Crit.	7,682.40	

* denotes interaction
Abbreviations: HD - Huntington's disease, TMS - total motor score

Table S3A(ii)- Effect of Reward Value on Reaction Time in Cases

	Log Reaction Time	
	Estimate	P Value
(Intercept)	5.95	$<2x10^{-16}$
Block Order	0.037	0.30
Maximum Reward	0.0058	0.033
TMS	0.0082	0.00011
Block Order*Maximum Reward	−0.0016	0.063
Observations	4,235	
Log Likelihood	−2,634.31	
Akaike Inf. Crit.	5,282.61	
Bayesian Inf. Crit.	5,327.07	

* denotes interaction
Abbreviations: TMS - total motor score

Table S3B - Non-Log Transformed Reaction Time

	Reaction Time	
	Estimate	P Value
(Intercept)	260.33	0.00034
Block Order	41.38	0.16
Maximum Reward	5.57	0.012
Case HD	96.91	0.11
TMS	6.07	$8.7x10^{-5}$
Block Order*Maximum Reward	−1.63	0.019
Observations	7,246	
Log Likelihood	−54,981.14	
Akaike Inf. Crit.	109,978.30	
Bayesian Inf. Crit.	110,033.40	

* denotes interaction
Abbreviations: HD - Huntington's disease, TMS - total motor score

Table S4A - Effect of Maintained Effort on Reaction Time

	Log Reaction Time	
	Estimate	P Value
(Intercept)	5.86	$<2x10^{-16}$
Trial	−0.00072	0.18
Case HD	0.22	0.013
TMS	0.0084	$2.77x10^{-5}$
Observations	7,246	
Log Likelihood	−3,800.30	
Akaike Inf. Crit.	7,612.59 Bayesian Inf. Crit.	7,653.92

* denotes interaction
Abbreviations: HD - Huntington's disease, TMS - total motor score

Table S4B - Effect of Maintained Effort on Reaction Time in Cases

	Log Reaction Time	
	Estimate	P Value
(Intercept)	6.089	$<2x10^{-16}$
Trial	−0.0015	0.048
TMS	0.0082	0.00011
Observations	4,235	
Log Likelihood	−2,625.037	
Akaike Inf. Crit.	5,260.074	
Bayesian Inf. Crit.	5,291.83	

* denotes interaction
Abbreviations:TMS - total motor score

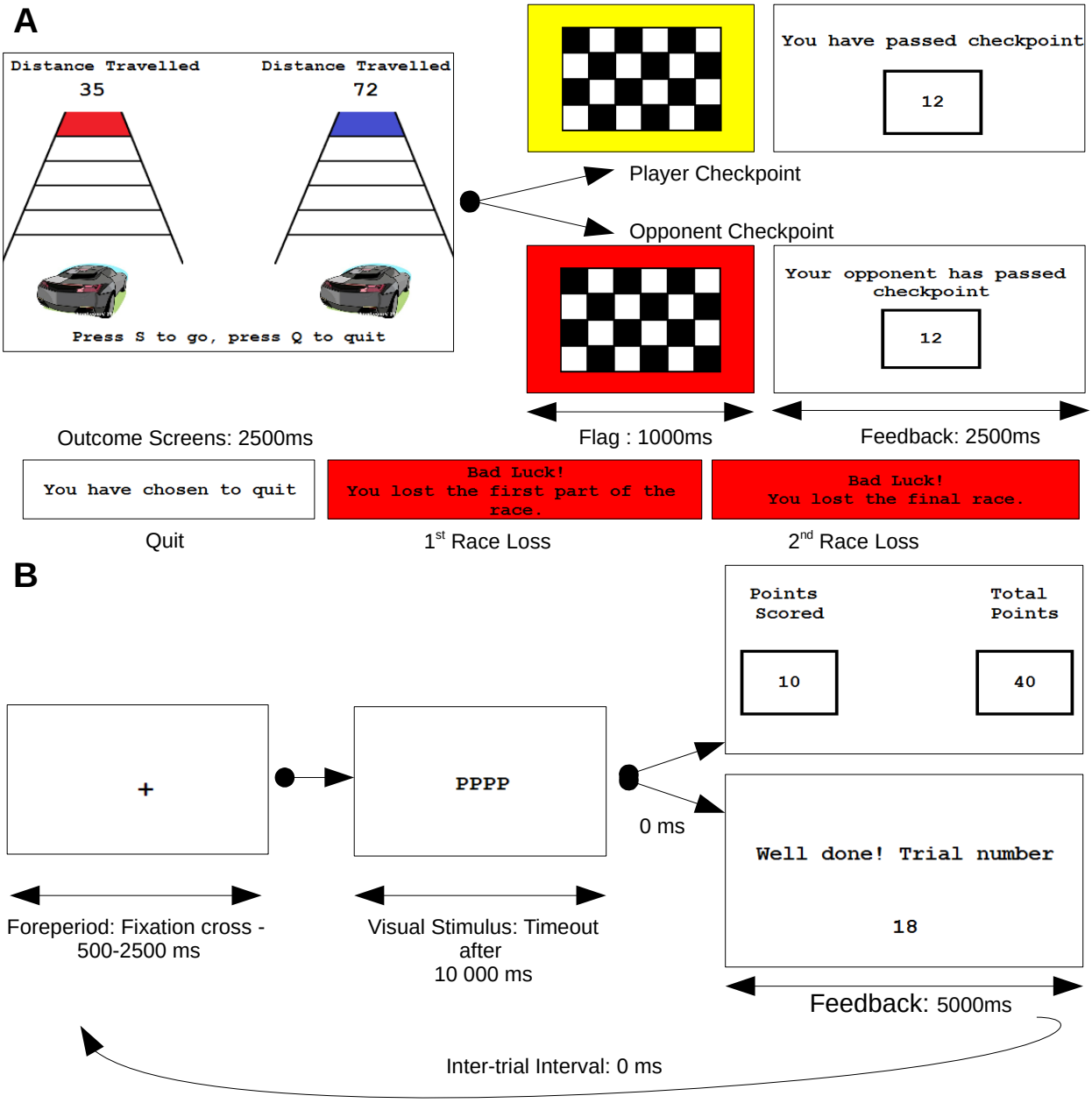

Figure 1
A Persistence Task. Diagram of racing screen and checkpoint screens, with race ending screens shown below.
B Reward Reaction Time Task. The fixation cross, visual stimulus and feedback screens for the practice level (below) and rewarded task (above) are shown).

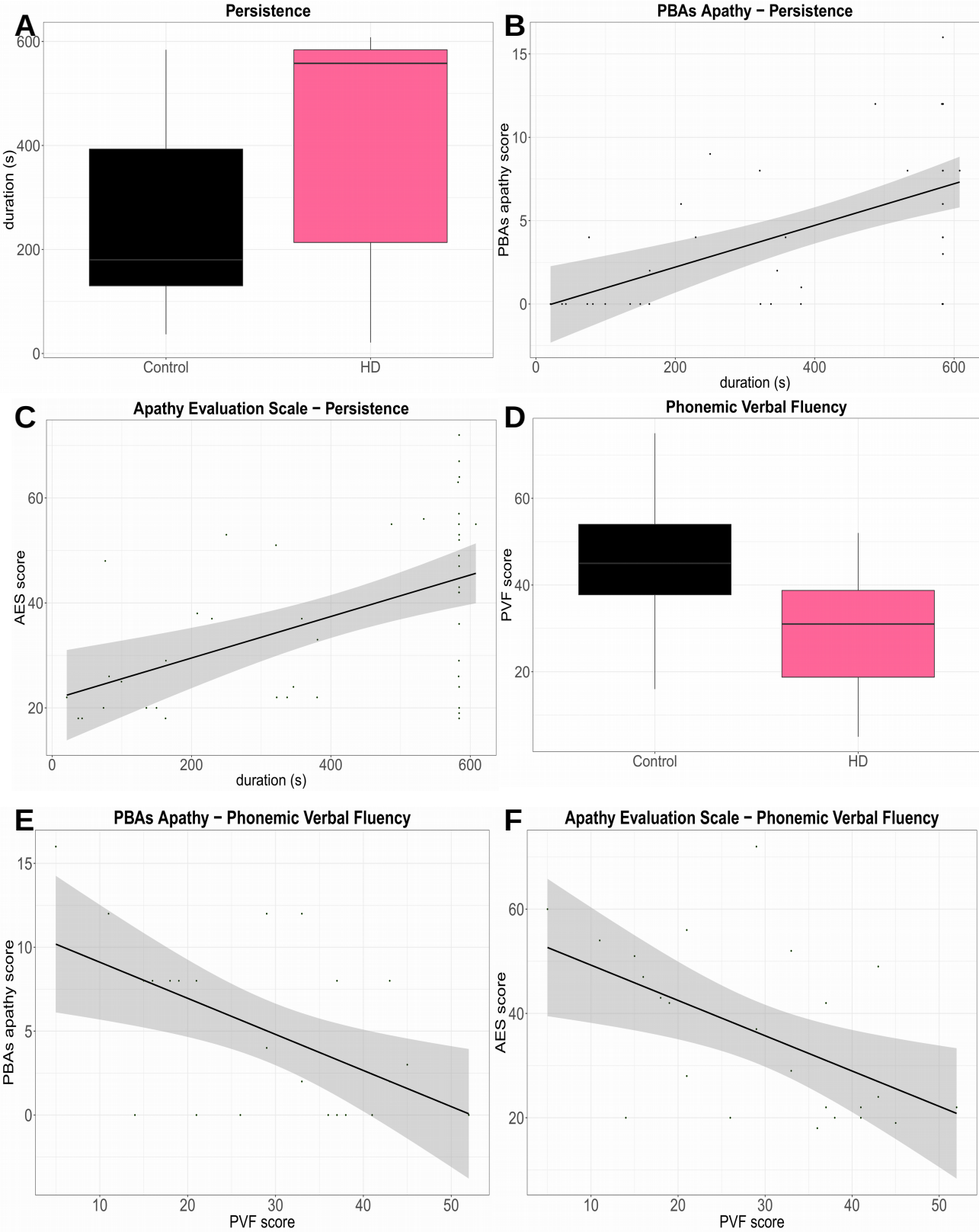

Figure 2
Persistence (A,B&C) & Phonemic Verbal Fluency (D,E&F): HD participants had longer Persistence duration and lower PVF scores than controls. Apathy was associated with increased Persistence duration and lower PVF score.

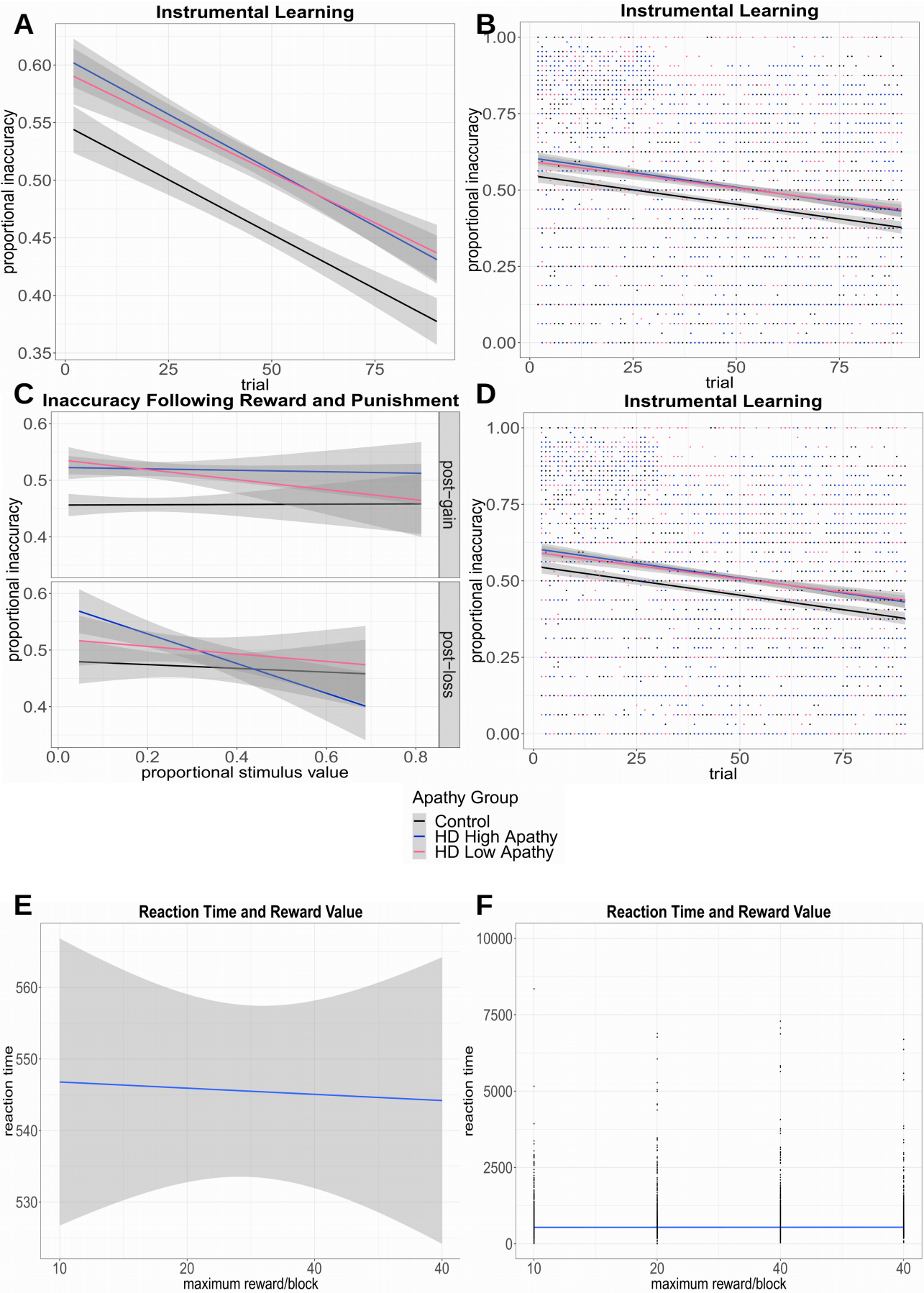

Figure 3
BART Behavior (A,B,C&D) Apathy in HD was significantly associated with impaired instrumental learning, worse accuracy following large losses, and better accuracy after large reward.
RRTT (E,F) Higher rewards led to faster reaction times in the whole group analysis.

Table 1 - Demographics and Neuropsychiatric Scores

	Case Status		
	HD	Controls	
Age	53.27 (33-82)	46.85 (20-75)	
IQ	103.55 (88.75-125.27)	109.73 (89.79-128.51)	*
Gender	26/51 female	17/26 female	
Antipsychotic dose (Olanzapine Equivalent - mg)	1.92 (0-41.25)	0	***
Antidepressant dose (Fluoxetine Equivalent - mg)	22.27 (0-146.5)	2.4 (0-22.2)	***
CAG Repeat Length	42.5 (38-50)	-	
Total Motor Score	35.49 (0-89)	1.48 (0-6)	***
Disease Burden	366.04 (90-575)	0	
AES	38.48 (18-72)	18.85 (18-86)	***
PBA Apathy	5.02 (0-16)	0.5 (0-4)	***
PBA Perseveration	1.9 (0-12)	0	***
PBA Disorientation	2.12 (0-8)	0.12 (0-2)	***
PBA Irritability	3.12 (0-12)	0.38 (0-2)	***
PBA Aggression	2.08 (0-12)	0.31 (0-4)	***
PBA Depression	3.14 (0-12)	1.81 (0-9)	
PBA Suicidal Ideation	0.37 (0-6)	0.04 (0-1)	
PBA Anxiety	2.69 (0-12)	1.69 (0-6)	
PBA Obsessions and Compulsions	0.8 (0-12)	0.12 (0-3)	
PBA Delusions	0.43 (0-9)	0	
PBA Hallucinations	0.16 (0-8)	0	
BISBAS Inhibition	19.31 (3-28)	22.38 (10-28)	*
BISBAS Reward	16.51 (8-20)	17.54(8-20)	*
BISBAS Drive	9.12 (4-16)	8 (4-16)	
BISBAS Fun Seeking	10.33 (4-16)	9.38 (6-13)	

Significance: * <0.05 ** <0.01 *** <0.001
Means and range (in brackets) are shown.
Abbreviations: HD - Huntington's disease, IQ - full scale intelligence quotient, PBA - Problem Behaviors Assessment (Short Form), BISBAS - Behavioural Inhibition Scale Behavioural Activation Scale.
AES - Apathy Evaluation Scale