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Different depression: motivational anhedonia governs antidepressant efficacy in Huntington’s disease

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Depression is more common in neurodegenerative diseases such as Huntington’s disease than the general population. Antidepressant efficacy is well-established for depression within the general population: a recent meta-analysis showed serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants and mirtazapine outperformed other antidepressants. Despite the severe morbidity, antidepressant choice in Huntington’s disease is based on Class IV evidence. We used complementary approaches to determine treatment choice for depression in Huntington’s disease: propensity score analyses of antidepressant treatment outcome using the ENROLL-HD data set, and a dissection of the cognitive mechanisms underlying depression in Huntington’s disease using a cognitive battery based on the Research Domain Criteria for Depression. Study 1 included ENROLL-HD 5486 gene-positive adult patients started on an antidepressant medication for depression. Our outcome measures were depression (Hospital Anxiety and Depression Scale or Problem Behaviours Assessment ‘Depressed Mood’ item) at first follow-up (primary outcome) and all follow-ups (secondary outcome). The intervention was antidepressant class. We used Svyglm&Twang in R to perform propensity scoring, using known variables (disease progression, medical comorbidity, psychiatric morbidity, sedatives, number of antidepressants, demographics and antidepressant contraindications) to determine the probability of receiving different antidepressants (propensity score) and then included the propensity score in a model of treatment efficacy. Study 2 recruited 51 gene-positive adult patients and 26 controls from the South Wales Huntington’s Disease Management Service. Participants completed a motor assessment, in addition to measures of depression and apathy, followed by tasks measuring consummatory anhedonia, motivational anhedonia, learning from reward and punishment and reaction to negative outcome. We used generalised linear models to determine the association between task performance and depression scores. Study 1 showed selective serotonin reuptake inhibitors outperformed serotonin norepinephrine reuptake inhibitors on the primary outcome ($P = 0.048$), whilst both selective serotonin reuptake inhibitors ($P = 0.00069$) and bupropion ($P = 0.0045$) were superior to serotonin norepinephrine reuptake inhibitors on the secondary outcome. Study 2 demonstrated an association between depression score and effort for reward that was not explained by apathy. No other mechanisms were associated with depression score. We found that selective serotonin reuptake inhibitors and bupropion outperform serotonin norepinephrine reuptake inhibitors at alleviating depression in Huntington’s disease. Moreover, motivational anhedonia appears the most significant mechanism underlying depression in Huntington’s disease. Bupropion is improves motivational anhedonia and has a synergistic effect with selective serotonin reuptake inhibitors. This work provides the first large-scale, objective evidence to determine treatment choice for depression in Huntington’s disease, and provides a model for determining antidepressant efficacy in other neurodegenerative diseases.

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Abbreviations: AES = Apathy Evaluation Scale; ATE = average treatment effect; ATT = average treatment effect among the treated; BISBAS = Behavioural Inhibition Scale Behavioural Activation Scale; CADASIL = Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; GLM = general linear model; GLMM = generalised linear mixed models; HADS = Hospital Anxiety and Depression Scale; MAOIs = monoamine oxidase inhibitors; MDD = major depressive disorder; NDRI = noradrenaline–dopamine reuptake inhibitor; PBAs = Problem Behaviours Assessment (short form); PSLT = Probabilistic Selection Learning Task; RCT = randomised controlled trial; RDoC = Research Domain Criteria; RRTT = Reward Reaction Time Task; SNRIs = serotonin–norepinephrine reuptake inhibitors; TCA = tricyclic antidepressants; TeCAs = tetracyclic antidepressants; UHDRS-TFC = Unified Huntington’s disease Rating Scale Total Functional Capacity; UHDRS-TMS = Unified Huntington’s disease Rating Scale Total Motor Score

Graphical Abstract
Introduction

Mood disorder is common in neurodegenerative diseases, with a higher prevalence of depression found in many disorders compared with the general population. Huntington’s disease (a trinucleotide repeat disorder that leads to progressive neurodegeneration of cortico-striatal networks), causes cognitive impairment and neuropsychiatric disorders that predate the onset of motor symptoms such as chorea.

Depression is very common in Huntington’s disease: systematic reviews and large observational studies suggest a lifetime prevalence of 33–69%, compared with 15% in the general population. Neuropsychiatric symptoms have more impact on quality of life and functional decline in Huntington’s disease than motor symptoms, for both patients and carers. Furthermore, depression in Huntington’s disease can be a direct result of the neurodegeneration, or a reaction to the diagnosis. Higher rates of depression are seen prior to genetic testing in gene carriers compared with gene negative individuals at risk for Huntington’s disease, whilst depression-like behaviour has been found in animal models of Huntington’s disease that can be rescued with inactivation of the Huntington mutation. Such findings suggest that depression is an integral part of the pathology of Huntington’s disease.

Despite the severe morbidity, objective evidence of effective treatment for depression in Huntington’s disease is very limited. Randomized controlled trials of atropine for executive function and bupropion for apathy both excluded patients with significant depression at entry but still showed a reduction in depression scores in the intervention groups. One open-label study of venlafaxine as a treatment for depression showed a reduction in depression scores and reports on other antidepressants were limited to case studies.

The cognitive–behavioural mechanisms underlying depression in Huntington’s disease are also under-explored. Work using experimental behavioural tasks in MDD has shown that both anhedonia (reduced response to rewarding stimuli) and hypersensitivity to negative stimuli contribute to the development of depression. These findings informed the Research Domain Criteria (RDoC) for Depression: anhedonia may be mediated by deficits in the experience of pleasure (consummatory anhedonia), impaired effort for reward (motivational anhedonia) or impaired learning from rewarded stimuli (anticipatory anhedonia). Immediate hypersensitivity to negative stimuli, negative future thinking, low self-esteem and excessive rumination (dwelling on negative outcomes and experiences) also contribute to the depressive phenotype. Because the cognitive–behavioural components of depression have been associated with different neurotransmitter systems, such a differentiation can also lead to more precise treatment for depressive syndromes.

A recent network meta-analysis demonstrated that the most effective medications for treating MDD were predominantly tricyclic antidepressants (TCAs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and mirtazapine [tetracyclic antidepressants (TeCAs)] classes, with selective serotonin reuptake inhibitors (SSRIs) and bupropion (a noradrenaline–dopamine reuptake inhibitor: NDRI) generally proving less effective. It is also increasingly recognized that certain antidepressants are more effective at reversing selected cognitive processes underlying MDD compared with others: SSRIs are ineffective at treating (and may even worsen) consummatory anhedonia, whilst drugs that increase noradrenergic tone are associated with increased arousal but may reduce effort for reward.

Current treatment options for depression in Huntington’s disease rely on evidence gleaned from MDD; however, the mechanisms of depression in Huntington’s disease may differ: it is known that Huntington’s disease patients are comparatively insensitive to negative stimuli, and the cognitive impairment may limit rumination in Huntington’s disease. Furthermore depression in other neurodegenerative diseases may not respond to antidepressants in the same way as MDD. Hence the most effective drug classes for depression in Huntington’s disease may also be different to those in MDD.

In the absence of randomized controlled trial (RCT) evidence, propensity score analysis of observational data can provide evidence of the effectiveness of treatments. In observational studies, treatments are selected based on variables such as clinician preference and disease severity. Participants in a propensity score analysis are ascribed a probability of receiving a particular treatment based on known variables (the propensity score), treatments are then compared either by direct matching on propensity score or including the propensity score as an inverse weight in a model. Although this method cannot account for unknown confounders, there is evidence to suggest unknown confounding variables are associated with known confounding variables. Furthermore in contrast to RCTs, a more representative sample of the wider patient population is included, improving generalizability. In this study, we combined a propensity score analysis of the effect of antidepressants on depression scores in a large observational study data set of Huntington’s disease participants (ENROLL-HD) with an experimental study dissecting the mechanisms underlying depression in Huntington’s disease. The aim was to use two complementary approaches to improve our understanding of the neuropsychological mechanisms of depression in Huntington’s disease and inform optimised pharmacological treatment.

Materials and methods

All study procedures were performed in accordance with the declaration of Helsinki. Formal ethical approval for this work was gained from the NHS Research Ethics Council for Wales (13/WAL/0300) and the NHS Research Ethics Council for Scotland (13/SS/0169).
**Study 1: effect of antidepressant class on depression in Huntington’s disease using propensity score analysis**

**Inclusion criteria**
Participants were selected for this analysis from the ENROLL-HD longitudinal observation study. This is a prospective worldwide cohort study (including participants previously part of the Europe-wide REGISTRY study), recruiting participants with genetic confirmation of Huntington’s disease, those at risk, gene negative controls and not-at-risk family controls. All participants complete annual assessments of function (Unified Huntington’s disease Rating Scale Total Functional Capacity—UHDRS-TFC), motor examination (Unified Huntington’s disease Rating Scale Total Motor Score—UHDRS-TMS), cognition (Stroop task, symbol digit modality task and verbal fluency), psychiatric symptoms (Problem Behaviours Assessment short form—PBAs), Hospital Anxiety and Depression Score—HADS, and the UHDRS—Behavioural Scale and demographic changes such as comorbidities, medication and drug use.

We included any participant with genetically confirmed Huntington’s disease, started on an antidepressant for low mood (low mood indications: Supplementary Table 1).

**Intervention: antidepressant class comparison**
Antidepressants are typically categorised into selective serotonin reuptake inhibitors (SSRIs), SNRIs, monoamine oxidase inhibitors (MAOIs), TCAs or atypical agents. As sleep disturbance and apathy are significant problems in Huntington's disease, recent clinical guidelines for treatment of Huntington’s disease, recommend mirtazapine, trazodone or related antidepressants for the treatment of depression and comorbid insomnia; and a trial of an activating antidepressant such as bupropion is recommended if apathy is present. Our analysis plan therefore included separate classes for (i) tetracyclic antidepressants (TeCA: mirtazapine, mianserin and maprotiline), (ii) phenylpiperazines (trazodone, nefazodone), and (iii) bupropion as a NORDI, in addition to SSRIs, SNRIs, MAOIs and TCAs. Any antidepressant with a unique mechanism of action, accounting for <1% of all prescriptions was included in the ‘Unique’ class for the analysis.

**Outcome measures**
Psychiatric symptoms in ENROLL-HD were measured using the HADS (a self-report measure with good validity for depression in HD) and the PBAs [a semi-structured interview comprising 12 psychiatric symptom domains commonly seen in Huntington’s disease; each symptom is rated for severity (0–4) and frequency (0–4)], whilst REGISTRY used the UHDRS behaviour score (an earlier iteration of the PBAs semi-structured interview with 12 psychiatric symptom domains seen in Huntington’s disease; each symptom is rated for severity and frequency from 0–4). The ‘Depressed Mood’ item was common to both the PBAs and UHDRS behaviour score. Participants were classified as having depressed mood if they either: (i) scored >7 on the HADS depression score; (ii) had scores of >1 on both the severity and frequency subscores of the PBAs ‘Depressed Mood’ item; or (iii) had severity and frequency subscores greater than 1 for the UHDRS behaviour score ‘Depressed Mood’ item.

We used depressed mood at first follow-up (the next ENROLL or REGISTRY visit following antidepressant start date, provided this occurred at least 10 days after antidepressant prescription and within 1 year) as the primary outcome, and depressed mood at all subsequent follow-ups (including any follow-up visit occurring at least 10 days after antidepressant start date) as the secondary outcome.

**Statistical analysis: propensity scores**
In observational studies, treatments are selected based on inherent participant characteristics such as severity of illness or presence of relevant comorbidities. Propensity scoring measures each participants probability of being assigned a particular treatment based on known variables. This process is known to account for unobserved as well as observed variables, as well as giving a precise effect of each independent variable on treatment allocation.

We used the svyglm and twang packages in R, which employ machine learning to improve model fit to data over 5000 iterations. These packages compare models with different combinations and coefficients for all variables, to determine the best model to describe treatment allocation: that is they create a mathematical model to determine which variables influence treatment selection (choice of antidepressant class). As all participants received an intervention (class of antidepressant), models tested the ‘average treatment effect’ (ATE: which treatment was best for any given member of the study population), rather than the ‘average treatment effect among the treated’ (ATT: used to compare treatment to no intervention in the treated population). Following the propensity scoring model selection, post hoc Kolmogorov–Smirnov tests were used to check the effectiveness of the process (Supplementary Tables 27 and 28).

The propensity score variable was then included as an independent variable in a generalized boosted model measuring the effect of antidepressant class on the primary and secondary outcomes. Any variables not completely equalized across treatment groups in the best propensity score model were included in the generalized boosted model as fixed variables in a ‘doubly robust’ process as described by Ridgeway, McCaffrey et al.

We selected the variables age, gender, psychiatric morbidity (previous suicide attempt, psychiatric hospitalisation or current high psychiatric comorbidity [any PBAs item score > 4]), total number of antidepressants, number of comorbidities, concurrent benzodiazepine or antipsychotic use, total number of antidepressant prescriptions (either dose escalation or change of drug), dose of antidepressant, composite disease progression score (a highly sensitive measure of disease progression in Huntington’s disease combining,
cognitive, motor and functional scores) and risk factors for SSRI use (cardiac or gastrointestinal disease) in the propensity scoring model. We used ANOVAs to test the effect of antidepressant class on model fit.

**Study 2: cognitive mechanisms of depression in Huntington’s disease**

**Participant recruitment and consent**

We recruited 51 Huntington’s disease participants from the South Wales Huntington’s disease service as part of a wider study of neuropsychiatric symptoms in Huntington’s disease (disease stage: pre-symptomatic to Stage IV), and 26 controls were recruited both from family members not at risk of Huntington’s disease, and university staff and students through local advertising. We excluded participants under the age of 18, Huntington’s disease participants without a confirmatory gene test, pregnant women, and any participant with brain injury or brain disorder other than Huntington’s disease. All subjects gave informed consent.

**General procedures**

All subjects completed a medical history, medication history, and formal Huntington’s disease motor examination (total motor score (TMS) from the Unified HD Rating Scale) prior to the questionnaires and neuropsychological tasks. Participants received expenses (maximum £20) for any costs incurred by participation but were specifically informed that the expenses were not related to task performance.

**Questionnaire assessments of psychopathology**

Prior to the neuropsychological task battery all participants completed the Hospital Anxiety and Depression Scale, a robust, well-validated self-report measure of depression in Huntington’s disease; the Apathy Evaluation Scale to assess apathy; Problem Behaviours Assessment—short form (PBAs): the best validated assessment of psychopathology in Huntington’s disease (used in the ENROLL-HD study); and an assessment of reward value and impulsivity—the Behavioural Inhibition Scale Behavioural Activation Scale (BISBAS), from which we used the reward subscale (BISBAS Reward) as a measure of subjective reward value.

**Neuropsychological assessment procedure**

All tasks were programmed in E-Prime 2.0 and performed on a Lenovo Thinkpad laptop. Testing was performed in a quiet environment, free from external distractions. Participants were seated at a comfortable distance from the computer, so they could easily read text and respond appropriately. Breaks were encouraged ad libitum. Tasks were drawn from a larger battery of 14 assessments (including measures of instrumental learning, planning, inhibition, temporal discounting) designed to probe cognitive processes underlying other common psychiatric symptoms in Huntington’s disease (apathy, impulsivity and aggressive behaviour), and were administered in random order.

**Neuropsychological tasks**

This battery encompassed the RDoC domains contributing to depression: reward [positive valence systems: measures of reward value (reward responsiveness), effort for reward (motivational anhedonia), and learning from positive outcome)]; and loss (negative valence systems: measures of response to negative outcome, and learning from negative outcome).

**Reward reaction time task (RRTT)—motivational anhedonia**

This task measured willingness to exert effort for reward (known to be impaired in MDD) and was based on a protocol by Cools et al. Participants were instructed that the task involved reacting as quickly as possible to a visual stimulus to win a reward (points), and that as they completed each block, the maximum reward on offer would increase. They were further informed that reacting too slowly would result in no reward. Short breaks were given between blocks. The 4 test blocks (each of 30 trials) were preceded by a practice block. Scoring was based on proportional improvement in mean reaction time during the practice block to account for motor disability. The outcome measure was reward sensitivity: change in reaction time with maximum value of reward (corrected for block order).

**BISBAS reward**—reward responsiveness

This well-verified self-report questionnaire measures reward value as one of its four subscales.

**Probabilistic Selection Learning Task**

Impaired reward learning and heightened recall of negative outcome are both found in MDD. Participants were shown three different pairs of visual stimuli (Mandarin characters) and asked to select which in each pair is likely to be correct. Participants were told that one stimulus in each pair was correct more often than the other—they must learn which one and select it every time it was displayed. In pair AB, A was correct on 80% of trials; for pair CD, C was correct on 70% of trials and in pair EF, E was correct on 60% of trials. The task included a training phase (which terminated when participants selected the correct symbol in each pair at greater than 60% probability or after 374 trials) and a testing phase of 100 trials when either A or B was paired with one stimulus from C, D, E, and F and participants did not receive feedback. The testing phase showed whether participants learned better from reward (‘choose A’) or from punishment (‘avoid B’). Outcomes were the total score in the testing phase (as a measure of instrumental learning), reward learning score (total of A pairs correct in the testing phase), punishment learning score (total of B pairs correct in the testing phase) and an interaction model to compare punishment and reward learning.
Race task—response to negative outcome

This novel task was designed to measure pessimistic future prediction and excessive response to negative feedback, processes known to be abnormal in MDD. In this task, participants were first asked to perform a timed tapping assessment. They were then shown a race between two figures. Immediately following the race participants were asked if they felt they could improve the slower runner’s performance sufficiently to make them win. This involved tapping repeatedly on the keyboard, taking into account their baseline tapping speed. Participants gave a probability of performance improvement from 0 (certain of being unable to make the slower runner win) to 100 (certain of making the slower runner win). Following the rating, participants attempted to speed the slower runner, using rapid keyboard tapping. The slower runner still lost. Participants were then asked again about ability to improve performance if given a second attempt. The outcome variables were predicted performance following negative feedback (0–100) (absolute score and change from baseline rating).

Statistical analysis—cognitive mechanism

Missing data was excluded on a pair wise basis. Owing to the time constraints associated with the completion of the wider task battery (of cognitive tasks designed to probe processes leading to impulsive, apathetic and aggressive behaviour), 43 of 51 Huntington’s disease participants completed the race task, whilst motor impairment (5) and software failure (4) further limited RRTT completion to 46. The Probabilistic Selection Learning Task (PSLT) was introduced later in the experiment and was completed by 35 Huntington’s disease participants. All controls completed the full battery. Premorbid IQ tests based on reading ability have been shown to be unreliable in manifest Huntington’s disease, and hence we used Crawford’s demographic method to calculate premorbid IQ. Serotonergic and dopaminergic medication used by participants was converted to equivalent doses of Fluoxetine and Olanzapine, as described in meta-analytic work on effect sizes.

All statistical analyses were completed in R. Group comparisons of Huntington’s disease participants and controls used models including case (Huntington’s disease versus control) as a variable. Within the Huntington’s disease group, regression models were constructed to assess the predictive value of neuropsychological task performance on current measures of depression in Huntington’s disease. The assumptions underlying linear regression were formally assessed using the Akaike information criterion and models assessed using the Akaike information criterion and models.

Mixed model analysis—RRTT data

We created Gamma generalized linear mixed models (GLMMs) with a dependent variable of reaction time and independent variable of maximum reward value. The random effect term was the individual participant. We included TMS to account for motor disability (fixed effect) and block order (as an interaction with maximum reward) to account for the effects of fatigue. We compared models using Bolk’s method: the goodness of fit was assessed using the Akaike information criterion and models were compared for explanatory power using the bbmle package and the weight (explanatory power corrected for complexity, maximum value 1.0) is reported. To study the effect of case on change in reaction time for different reward, we used data for all participants (cases and controls) and compared models without case status, including case status as a fixed effect, and with case status as an interaction with maximum reward value. We then assessed the effect of HADS depression score on change in reaction time within the Huntington’s disease group (controls were excluded) using the same model comparison process. Potential confounding variables were assessed using the model comparison approach described for the regression models.

Data availability

Anonymized data are available on reasonable request.

Results

Study 1: effect of antidepressant class on depression in Huntington’s disease using propensity score analysis

Prescribing Patterns for Depression in Huntington’s disease

In the ENROLL-HD data set, 5486 (37.71%) participants (Table 2 and Supplementary Table 2) received at least one prescription for an antidepressant for low mood in the course of the study. There were a total of 9968 antidepressant prescriptions. Table 2 shows that the majority of antidepressant prescriptions (61.99%) were for selective serotonin reuptake inhibitors (SSRIs), followed by SNRIs; 15.29% and TeCA; 11.38%. Citalopram, sertraline and venlafaxine were the most frequently prescribed individual medications. The treated cohort had a high frequency of both psychiatric comorbidity (comorbid psychiatric symptoms, previous mental health history or suicide attempt) and concurrent prescription of benzodiazepine or antipsychotic drugs (Table 1). Moclobemide was the only MAOI
prescribed for low mood and comprised a small minority of total prescriptions (0.20%); hence it was included in the unique class for the purposes of the analysis.

### Efficacy of different antidepressant classes for depression in Huntington's disease

At first follow-up, treatment with SSRIs or an (Fig. 1A and B, Tables 3–6, Supplementary Tables 3–6) NDRI resulted in the highest frequency of remission from depression (28.02% and 32.39% respectively). SNRIs and TeCAs had intermediate efficacy with remission in 21.23% and 22.26% of individuals, whilst remission of depression was lowest in the groups receiving phenylpiperazines (14.75%), TCAs; 17.59% or agents with a unique mechanism of action (unique; 15.09%). Across all subsequent follow-ups, remission from depression improved in all antidepressant classes, but SSRIs (remission in 32.70%) and NDRIs (remission in 37.31%) remained the most effective treatments.

### Table 1 Demographics and neuropsychiatric scores

| Enroll-HD cohort 5486 participants |
|-----------------------------------|
| **Age** 50.43 (18–92) |
| **Gender** 55.25% female |
| **Total motor score** 33.72 (0–122, 70.70% manifest) |
| **Disease burden** 395.08 (16.5–1020) |
| **Disease progression score** 8.83 (-7.34–23.2) |
| **Psychiatric comorbidity** 97.5% |
| **Total comorbidities** 4 (0–58) |
| **Number of antidepressants** 1 (0–12) |
| **SSRI risk factor** 17.41% |
| **Sedative use** 71.83% |
| **Antidepressant dose (fluoxetine equivalent—mg)** 33.23 (0–150) |

| Cognitive task cohort 77 participants |
|--------------------------------------|
| **Case status** Huntington's disease Controls Significance |
| **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, 78.43% manifest) 1.48 (0–6) *** |
| **Disease burden** 366.04 (90–575) 0 *** |
| **Cognitive impairment (phonemic verbal fluency score)** 30.41 45.46 *** |
| **HADS depression** 5.82 (0–17) 1.88 (0–9) *** |
| **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 depressed mood** 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 *** |

Significance: * < 0.05 ** < 0.01 *** < 0.001. Means and range (in brackets) are shown. SSRI, selective serotonin reuptake inhibitor; IQ, full scale intelligence quotient; PBA, Problem Behaviours Assessment (Short Form); BISBAS, Behavioural Inhibition Scale Behavioural Activation Scale; AES, Apathy Evaluation Scale; ‘manifest’, Huntington’s disease participant diagnosed with motor onset.

### Table 2 Frequency of use by drug class

| Drug class | Frequency | Percentage |
|------------|-----------|------------|
| SSRI       | 6179      | 61.99      |
| SNRI       | 1524      | 15.29      |
| TeCA       | 1134      | 11.38      |
| NDRI       | 441       | 4.42       |
| TCA        | 435       | 4.36       |
| Phenylpiperazine | 175 | 1.76 |
| Unique     | 60        | 0.60       |
| MAOI       | 20        | 0.20       |

Frequency includes total number of prescriptions—including dose escalations. SSRI, selective serotonin reuptake inhibitor; TeCA, tetracyclic antidepressant; SNRI, serotonin–noradrenaline reuptake inhibitor; NDRI, noradrenaline–dopamine reuptake inhibitor.
with SSRIs. The doubly robust estimation model showed that treatment with SNRIs, or Unique agents was associated with inferior remission rate at first follow-up compared with SSRI treatment. A propensity score analysis of depression at all follow-ups (secondary outcome measure), and SSRI treatment as comparator showed superiority in remission from depression with an NDRI compared with an SSRI, whilst all other drug classes proved inferior to SSRIs. The doubly robust estimation model showed that treatment with SNRIs, or Unique agents was associated with inferior remission rate at first follow-up compared with SSRI treatment. A propensity score analysis of depression at all follow-ups (secondary outcome measure), and SSRI treatment as comparator showed superiority in remission from depression with an NDRI compared with an SSRI, whilst all other drug classes proved inferior to SSRIs. The doubly robust estimation model showed that treatment with SNRIs, or Unique agents was associated with inferior remission rate at first follow-up compared with SSRI treatment. A propensity score analysis of depression at all follow-ups (secondary outcome measure), and SSRI treatment as comparator showed superiority in remission from depression with an NDRI compared with an SSRI, whilst all other drug classes proved inferior to SSRIs. The doubly robust estimation model showed that treatment with SNRIs, or Unique agents was associated with inferior remission rate at first follow-up compared with SSRI treatment. A propensity score analysis of depression at all follow-ups (secondary outcome measure), and SSRI treatment as comparator showed superiority in remission from depression with an NDRI compared with an SSRI, whilst all other drug classes proved inferior to SSRIs. The doubly robust estimation model showed that treatment with SNRIs, or Unique agents was associated with inferior remission rate at first follow-up compared with SSRI treatment. A propensity score analysis of depression at all follow-ups (secondary outcome measure), and SSRI treatment as comparator showed superiority in remission from depression with an NDRI compared with an SSRI, whilst all other drug classes proved inferior to SSRIs. The doubly robust estimation model showed that treatment with SNRIs, or Unique agents was associated with inferior remission rate at first follow-up compared with SSRI treatment. A propensity score analysis of depression at all follow-ups (secondary outcome measure), and SSRI treatment as comparator showed superiority in remission from depression with an NDRI compared with an SSRI, whilst all other drug classes proved inferior to SSRIs. The doubly robust estimation model showed that treatment with SNRIs, or Unique agents was associated with inferior remission rate at first follow-up compared with SSRI treatment. A propensity score analysis of depression at all follow-ups (secondary outcome measure), and SSRI treatment as comparator showed superiority in remission from depression with an NDRI compared with an SSRI, whilst all other drug classes proved inferior to SSRIs.

Figure 1 Treatment response to antidepressants. Percentage of population with depression at follow-up following treatment with different classes of antidepressant; ANOVAs comparing models with, and without antidepressant (drug class) variable are reported (N = 5486 for both). (A) At first follow-up, F = 5.062 df = 6,2440 P = 3.32 × 10–5; (B) at all follow-ups, F = 4.63, df = 6,12555, P = 0.00011. Outcome: dark, depressed; light, non-depressed.

Table 3 ATE analysis of drug class; outcome: depression at first follow-up

|                     | Estimate | P-value |
|---------------------|----------|---------|
| SSRI as reference treatment |          |         |
| (Intercept)         | 0.72     | <2 × 10⁻¹⁶ |
| NDRI                | −0.085   | 0.21    |
| Phenylpiperazine    | 0.13     | 0.0066  |
| SNRI                | 0.051    | 0.056   |
| TCA                 | 0.077    | 0.40    |
| TeCA                | 0.017    | 0.67    |
| Unique              | 0.14     | 0.056   |
| SSRI as reference treatment, doubly robust estimation |          |         |
| (Intercept)         | 0.61     | 1.62 × 10⁻⁶ |
| NDRI                | −0.060   | 0.42    |
| Phenylpiperazine    | 0.10     | 0.059   |
| SNRI                | 0.058    | 0.048   |
| TCA                 | 0.15     | 0.14    |
| TeCA                | 0.0076   | 0.86    |
| Unique              | 0.22     | 0.00028 |
| Age                 | 0.0016   | 0.33    |
| Sex (Male)          | −0.0082  | 0.85    |
| Disease progression score | −0.0058 | 0.27    |
| SSRI risk factors   | −0.0059  | 0.33    |
| Comorbidities       | 0.0042   | 0.93    |
| Number of antidepressants | 0.020 | 0.00067 |
| Sedative            | 0.044    | 0.45    |
| Fluoxetine equivalent dose (mg) | −2.85 × 10⁻⁶ | 0.84 |

ATE, actual treatment effect; SSRI, selective serotonin reuptake inhibitor; NDRI, norepinephrine–dopamine reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; TeCA, tetracyclic antidepressants.

Table 4 ATE analysis of drug class, outcome: depression at all follow-ups

|                     | Estimate | P-value |
|---------------------|----------|---------|
| SSRI as reference treatment |          |         |
| (Intercept)         | 0.68     | <2 × 10⁻¹⁶ |
| NDRI                | −0.080   | 0.011   |
| Phenylpiperazine    | 0.063    | 0.022   |
| SNRI                | 0.031    | 0.013   |
| TCA                 | 0.088    | 0.027   |
| TeCA                | 0.081    | 1.22 × 10⁻⁶ |
| Unique              | 0.084    | 0.029   |
| SSRI as reference treatment, doubly robust estimation |          |         |
| (Intercept)         | 0.62     | <2 × 10⁻¹⁶ |
| NDRI                | −0.061   | 0.092   |
| Phenylpiperazine    | −0.0040  | 0.90    |
| SNRI                | 0.045    | 0.00069 |
| TCA                 | 0.060    | 0.21    |
| TeCA                | 0.026    | 0.16    |
| Unique              | 0.057    | 0.17    |
| Age                 | −0.0045  | 0.64    |
| Sex (Male)          | 0.00099  | 0.96    |
| Disease progression score | −0.0060 | 0.021   |
| SSRI Risk Factors   | −0.0057  | 0.049   |
| Comorbidities       | 0.026    | 0.27    |
| Number of antidepressants | 0.023 | <2 × 10⁻¹⁶ |
| Sedative            | 0.095    | 0.0017  |
| Fluoxetine equivalent dose (mg) | 1.28 × 10⁻⁵ | 0.029 |

ATE, actual treatment effect; SSRI, selective serotonin reuptake inhibitor; NDRI, norepinephrine–dopamine reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; TARC, tetracyclic and related antidepressants.
Table 5 ATE analysis of drug class; outcome: depression at first follow-up

| SNRI as reference treatment                              | Estimate | P-value     |
|----------------------------------------------------------|----------|-------------|
| (Intercept)                                              | 0.77     | <2 x 10^{-16}|
| NDRI                                                     | -0.14    | 0.053       |
| Phenylpiperazine                                         | 0.082    | 0.12        |
| SSRI                                                     | -0.051   | 0.056       |
| TCA                                                      | 0.025    | 0.78        |
| TeCA                                                     | -0.034   | 0.44        |
| Unique                                                   | 0.088    | 0.24        |

SNRI as reference treatment, doubly robust estimation

| (Intercept)                                              | 0.67     | 4.11 x 10^{-7}|
|----------------------------------------------------------|----------|-------------|
| NDRI                                                     | -0.12    | 0.13        |
| Phenylpiperazine                                         | 0.047    | 0.42        |
| SSRI                                                     | -0.58    | 0.048       |
| TCA                                                      | 0.089    | 0.37        |
| TeCA                                                     | -0.050   | 0.29        |
| Unique                                                   | 0.16     | 0.012       |
| Age                                                      | 0.0016   | 0.33        |
| Sex (Male)                                               | -0.0082  | 0.85        |
| Disease progression score                                | -0.0058  | 0.27        |
| SSRI risk factors                                        | -0.059   | 0.33        |
| Comorbidities                                            | 0.0042   | 0.93        |
| Number of antidepressants                                | 0.020    | 0.00067     |
| Sedative                                                 | 20.044   | 0.45        |
| Fluoxetine equivalent dose (mg)                          | -2.86 x 10^{-6} | 0.84 |

ATE, actual treatment effect; SSRI, selective serotonin reuptake inhibitor; NDRI, norepinephrine–dopamine reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; TECa, tetracyclic and related antidepressants.

Table 6 ATE analysis of drug class; outcome: depression at all follow-ups

| SNRI as reference treatment                              | Estimate | P-value     |
|----------------------------------------------------------|----------|-------------|
| (Intercept)                                              | 0.71     | <2 x 10^{-16}|
| NDRI                                                     | -0.11    | 0.00082     |
| Phenylpiperazine                                         | 0.032    | 0.27        |
| SSRI                                                     | -0.031   | 0.013       |
| TCA                                                      | 0.058    | 0.16        |
| TeCA                                                     | 0.050    | 0.0091      |
| Unique                                                   | 0.054    | 0.18        |

SNRI as reference treatment, doubly robust estimation

| (Intercept)                                              | 0.66     | <2 x 10^{-16}|
|----------------------------------------------------------|----------|-------------|
| NDRI                                                     | -0.111   | 0.0045      |
| Phenylpiperazine                                         | -0.049   | 0.14        |
| SSRI                                                     | -0.045   | 0.00069     |
| TCA                                                      | 0.015    | 0.75        |
| TeCA                                                     | -0.019   | 0.38        |
| Unique                                                   | 0.012    | 0.77        |
| Age                                                      | -0.00045 | 0.64        |
| Sex (Male)                                               | 0.00099  | 0.96        |
| Disease progression score                                | -0.0060  | 0.021       |
| SSRI risk factors                                        | -0.0057  | 0.049       |
| Comorbidities                                            | 0.026    | 0.27        |
| Number of antidepressants                                | 0.023    | <2 x 10^{-6}|
| Sedative                                                 | 0.095    | 0.0017      |
| Fluoxetine equivalent dose (mg)                          | 1.28 x 10^{-5} | 0.029 |

ATE, actual treatment effect; SSRI, selective serotonin reuptake inhibitor; NDRI, norepinephrine–dopamine reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; TECa, tetracyclic and related antidepressants.

Robust model showed the superiority of an NDRI to SSRIs in depression remission across all follow-ups persisted at trend level only, whilst SNRIs remained inferior to SSRIs.

A propensity score analysis for the primary outcome measure (depression at first follow-up) with SNRIs as the comparator treatment group (Table 5 and 6) suggested superiority of SSRI or NDRI treatment over SNRI at remission from depression at first follow-up but only at trend level. Doubly robust estimation confirmed that SSRIs but not NDRIs outperformed SNRIs at first follow-up. Across all follow-ups, remission from depression was higher with SSRIs or an NDRI, compared to SNRIs, whilst TeCAs were inferior to SNRIs. The model with doubly robust estimation, supported the superiority of SSRIs and the NDRI classes over SNRIs, with a larger effect size for NDRIs. ANOVAs confirmed the importance of antidepressant class on both the primary (F = 5.092, P = 3.32 x 10^{-5}) and secondary outcome (F = 4.63, P = 0.00011).

Depression and apathy scores are strongly positively correlated in the ENROLL-HD data set (P < 2 x 10^{-16}). ANOVAs showed that inclusion of all apathy scores following antidepressant prescription improved both depression outcome models (primary: F = 3.49, P = 0.0020; secondary: F = 3.23, P = 0.0036). However, this did not influence the results: SSRIs remained superior to Unique agents and SNRIs, on both the primary and secondary depression outcomes. ANOVAs of the effect of antidepressant class on PBAs apathy score only proved significant at first follow-up (F = 3.33, P = 0.0029), and showed superiority of SSRIs to unique agents but no other antidepressants (Supplementary Tables 3–6). This analysis is consistent with improved remission from depressed mood in Huntington’s disease with an NDRI or SSRIs compared with other antidepressants, with a limited effect of antidepressants on apathy.

**Study 2: cognitive mechanisms of depression in Huntington’s disease**

**Demographics and Psychopathology Questionnaires**

The Huntington’s disease participants had lower (Table 1) premorbid IQ scores, were taking higher doses of antipsychotic (anti-dopaminergic) medication and antidepressant medication, and had worse scores on formal motor examination. The burden of psychopathology was also higher in the Huntington’s disease group, who had higher scores than controls on the HADS depression score, AES, PBAs apathy, perseveration, disorientation, irritability and aggression subscales.

**Reward reaction time task: motivational anhedonia**

As we have previously reported, mean reaction time (Fig. 2A, B and C, and Supplementary Tables 7–10) was faster for higher reward value trials in the whole group.
(estimate = −0.0027, \( P = 3.63 \times 10^{-5} \)), whilst Huntington’s disease cases had slower reaction times than controls (best model included case status: weight = 0.62, estimate = 0.22, \( P = 0.032 \)), even when corrected for TMS, which was also strongly associated with slower reaction times (\( P = 4.98 \times 10^{-5} \)) (Fig. 1B). To assess the effect of low mood on reward related reaction time in Huntington’s disease, we compared models including the HADS depression score in the Huntington’s disease group. The best model (weight = 1.0), included the HADS depression score as an interaction with reward value. Higher HADS depression score was associated with slower reaction time overall (estimate = 0.045, \( P = 0.014 \)) and there was a significant interaction with reward value: higher HADS depression scores were associated with slower reaction time as reward value increased (estimate = 0.00059, \( P = 1.38 \times 10^{-8} \)) (Fig. 1C). In this model TMS was also associated with reaction time impairment (estimate = 0.0099, \( P = 0.00015 \)). Likelihood ratio tests of potential confounding variables (demographic variables and psychopathology scores from Table 1) did not improve on any of the models. Even accounting for motor disability, Huntington’s disease cases have blunted effort for reward compared with controls, and depression in Huntington’s disease leads to reduced effort at higher reward value.

**BISBAS Reward Score: reward responsiveness**

The model comparing (Supplementary Fig. 1A and B, Supplementary Tables 11 and 12) the effect of case status on BISBAS reward score did not show a significant effect of having Huntington’s disease (\( P = 0.28 \)) and was not improved by any potential confounder. BISBAS reward score was not associated with HADS depression score in the Huntington’s disease group before or after inclusion of significant confounders (\( P = 0.57 \) and 0.54, respectively).

**PSLT: instrumental learning from reward and punishment**

Huntington’s disease participants (Supplementary Fig. 1C and D, Supplementary Tables 13–20) took longer to reach criterion (estimate = 0.45, \( P = 0.00079 \)) and had lower total learning score (estimate = -12.54, \( P = 0.0092 \); sum of punishment and reward learning scores) compared with controls. Huntington’s disease participants did not differ from controls on reward learning (\( P = 0.56 \)) but had lower scores on punishment learning (estimate = -0.29, \( P = 0.00072 \)), an effect that was not maintained when confounders (TMS, olanzapine equivalent dose) were added to the model. Reward learning scores were not associated with HADS depression score in the Huntington’s disease group (\( P = 0.49 \)). The interaction between reward learning and punishment learning, also did not predict HADS depression score. In contrast, higher AES score in the Huntington’s disease group was associated with lower punishment learning score (estimate = -0.0079, \( P = 0.036 \)), although this did not survive inclusion of confounders (TMS, olanzapine equivalent dose) in the model. The interaction between punishment learning and reward learning score (higher reward learning compared to punishment learning) was also associated with higher AES score (estimate = 0.00036, \( P = 0.030 \)), although significance was not maintained after inclusion of confounders (TMS, olanzapine equivalent dose). We found no evidence to support an association between either reward learning or punishment learning and depression in Huntington’s disease, but in keeping with our previous findings,\(^6\) our results suggest an association between impaired punishment learning and apathy.

**Race task: response to negative outcome**

**Post-task predicted performance (absolute and change from baseline).** The Huntington’s disease group had lower estimates (Supplementary Fig. 2, Supplementary Tables 21–26) compared with controls for performance following negative feedback (estimate = \( -0.27, \ P = 5.13 \times 10^{-11} \)), an effect that was strengthened by the addition of potential confounders (estimate = \( -0.58, \ P < 2 \times 10^{-16} \)). However, in the Huntington’s disease group, post-task estimate was not associated with HADS depression score, before or after inclusion of significant confounders (\( P = 0.89 \) and 0.77, respectively). When the baseline prediction of performance was accounted for (post-task minus pre-task prediction), no differences were seen between Huntington’s disease cases and controls before or after inclusion of confounders (\( P = 0.22 \) and 0.40 respectively). Within the Huntington’s disease group, the change in predicted performance from baseline was not associated with HADS depression score before or after inclusion of confounders (\( P = 0.16 \) and \( P = 0.40 \), respectively). No association was found between AES score and either measure. These findings suggest that Huntington’s disease cases estimate their performance more negatively than controls overall, but this is not selectively affected by negative feedback, and is not associated with depression in Huntington’s disease.

**Discussion**

To our knowledge, this is the first study to demonstrate objective evidence of treatment effectiveness for depression in Huntington’s disease to inform clinical decision-making and is supported by the cognitive mechanism data from Study 2. Study 1 demonstrates that unlike MDD, the most effective treatments for depression in Huntington’s disease are drawn from SSRI and NDRI classes, whilst Study 2 shows that depression in Huntington’s disease is associated with motivational anhedonia but not with alterations in learning from reward, reward responsiveness or hypersensitivity to negative outcomes. Finally, we found a dissociation between apathy and depression in Huntington’s disease; depression, but not apathy, was associated with motivational anhedonia: a core dopaminergic process.\(^{138–120}\)

Here we have shown that SSRI and NDRI antidepressants were superior to other antidepressant classes in treating depression in Huntington’s disease: our analysis demonstrated they were the only antidepressant classes to show superiority
to SNRIs. Furthermore our data suggest possible superiority of Bupropion over SSRIs, with a larger effect size for depression remission compared to SSRIs in the propensity score analysis using SNRIs as the comparator, and trend level superiority at treatment efficacy in our secondary outcome when directly compared with SSRIs. This starkly contrasts with MDD, where a large meta-analysis demonstrated superior efficacy of TeCAs, TCAs and SNRIs over the majority of SSRI and NDRIs. Determining why some antidepressants are more effective at treating MDD is difficult owing to the diversity of neurobiological mechanisms linked with the condition.\textsuperscript{121,122} Whilst evidence is limited, no differences in efficacy between antidepressant classes have been seen in reducing inflammatory induced depression,\textsuperscript{123–127} or efficacy at normalizing the hypothalamic–pituitary axis in MDD (reviewed in Nandam \textit{et al.} \textsuperscript{128}). Deficits in hippocampal neurogenesis have been found in both MDD and Huntington’s disease.\textsuperscript{129,130} Intriguingly, both in humans\textsuperscript{131–133} and in animals,\textsuperscript{134} SSRIs have shown superiority over other antidepressant classes at improving hippocampal neurogenesis, whilst SSRIs have also improved hippocampal neurogenesis in animal models of Huntington’s disease.\textsuperscript{133,136} SSRIs and NDRIs rescued depression-like phenotypes in animal models,\textsuperscript{137,138} and showed effects on cognition and motor phenotypes of Huntington’s disease animal models\textsuperscript{139,140} (though not in human subjects\textsuperscript{128}). Finally, damage to the serotonergic dorsal raphe nuclei has been associated with depression in Huntington’s disease\textsuperscript{141}: hence increasing serotonergic tone may be particularly useful in ameliorating depression in Huntington’s disease.

SSRIs and SNRIs also differ in their effects on cognitive processes underlying MDD. The RDoC emphasise the contributions of the Loss and Reward domains to MDD.\textsuperscript{38,92} Whilst limited evidence suggests equivalent effect of antidepressant classes on behavioural changes in the loss domain,\textsuperscript{142,143} reward related behaviours are differentially affected by antidepressant class. Noradrenergic neurons originating in the locus coeruleus encode effort required for an action,\textsuperscript{144} and increasing noradrenergic tone does not affect, or even reduces effort for reward.\textsuperscript{57,58,145,146} The role of noradrenaline and effort for reward is complex: locus coeruleus activity is closely linked with effort required for an action,\textsuperscript{144} and acute reduction in noradrenergic tone reduces effort for reward.\textsuperscript{147} Correspondingly SNRIs are comparatively less effective at increasing effort for reward, than other

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Effort for reward—group comparisons and association with depression score. (A). Whole group (Huntington’s disease cases and controls) effect of reward value on reaction time. (B). Whole group: effect of case status on change in reaction time with reward value (AIC weight 0.62, N = 74). Pink: Huntington’s disease; blue: control. (C). Huntington’s disease cases: effect of HADS depression score on change in reaction time with reward value (AIC weight 1.0, N = 46). Pink: HADS high > 7; blue: HADS low < 8.}
\end{figure}
antidepressants. In contrast, although SSRIs are associated with emotional blunting (consummatory anhedonia), and acutely bupropion and SSRIs have little effect on dopaminergic tone or effort for reward, more recent data suggests that chronic use improves motivational anhedonia. Animal studies show that bupropion and serotonergic stimulation increase effort for reward, and reverse depressive-like behaviours in animal models of Huntington’s disease; whilst increasing dopamine and serotonergic tone concurrently has a synergistic effect on effort for reward. Studies in human controls suggest that effort learning and effort for reward are increased with SSRIs and bupropion, whilst both SSRIs and bupropion have shown specific improvements in measures of anergia and motivational anhedonia in MDD.

The behavioural study findings support the propensity score analysis in pointing to a key role of the mesolimbic system. We found a major contribution of motivational anhedonia to depression in Huntington’s disease but no deficits in reward responsiveness, reward learning or heightened response to loss. Decision-making regarding effort costs and reward value is mediated by a distributed network including the anterior cingulate cortex, amygdala, ventral striatum, and orbito-frontal cortex. These areas are all affected by the neurodegeneration caused by Huntington’s disease. The anterior cingulate cortex has a major role in tracking effort costs, whilst increasing tone in the dopaminergic mesolimbic circuitry increases effort for reward. Damage to the anterior cingulate cortex is particularly associated with depression in Huntington’s disease, with evidence of selective interneuron loss in the anterior cingulate cortex mediating a ‘mood’ phenotype, and imaging parameters (reduced fractional anisotropy measured by diffusion tensor imaging) suggesting reduced integrity of the white matter underlying the anterior cingulate cortex, insula and cerebellum being linked with depression scores.

Prior work in MDD has demonstrated an association with hyper-responsiveness to negative stimuli: feedback-related negativity on EEG in response to task based punishment, BOLD signal in the amygdala during negative feedback. However, we did not replicate this association with depression in Huntington’s disease. Deficits in response to negative stimuli are well documented in Huntington’s disease: impairments in learning from losses, and effort to avoid losses have been demonstrated in both pre-symptomatic and symptomatic patients, with an association shown between apathy in Huntington’s disease and deficits in this process. This association was replicated in the PSLT data: we found a limited effect of antidepressants on apathy outcomes. Previous reports in Parkinson’s disease, CADASIL and schizophrenia, have found deficits in effort for reward in association with apathy, but did not report the effect of depression despite higher scores in their patient cohorts. An association between a deficit in effort for reward and apathy has also been reported in Huntington’s disease.

This work does have some limitations. Propensity scoring analyses are not yet established as being equivalent (or superior) to randomised controlled trials, which remain the gold standard in assessing treatment efficacy by eliminating unknown sample bias. This work on depression in Huntington’s disease presents separate, but complementary analyses which point to a central role for motivational anhedonia in the pathophysiology, and suggest superior efficacy of antidepressants primarily acting on motivational anhedonia. Our findings should not influence antidepressant choice at present, but argue for inclusion of NDRI and SSRI arms in future randomised controlled trials. The race task has not been previously used but similar tasks have been used in MDD populations—with a clear demonstration of increased response to negative feedback seen in individuals with MDD. Our control group did include familial (gene negative) Huntington’s disease controls but also had control subjects drawn from the general population, which may have reduced our ability to control for psychosocial stresses (of being at risk for Huntington’s disease or caring for a family member with Huntington’s disease); future studies could recruit control subjects exclusively from family members to avoid this possibility. We used a sample of Huntington’s disease participants that included individuals with motor symptoms and those without. It is possible that mechanisms of depression in Huntington’s disease may change with disease stage, but our models did include motor score as a confounding variable to account for this problem. Finally, we used the BISBAS Reward scale as a measure of reward responsiveness (consummatory anhedonia), which is not the most commonly used instrument for this purpose, although it has previously been used to show dysfunction within a network critical to experiential pleasure.
In summary, propensity score analysis of the Enroll-HD data set revealed that, in contrast to MDD, SSRI and NDRI antidepressant classes are superior to other major antidepressant classes at treating depressed mood in Huntington’s disease. This is supported by our prospective behavioural study which demonstrated that motivational anhedonia is a core process of depression in Huntington’s disease. Conversely, increased response to negative feedback does not contribute to depression in Huntington’s disease. Finally apathy and depression in Huntington’s disease are dissociable on a task of effort and reward. The importance for future research and clinical practice is that the effectiveness of medications for depression in neurodegenerative disease is not necessarily the same as in MDD. This knowledge is important both for the refinement of treatment approaches and for improved mechanistic research in animal models, and highlights the need for a randomised controlled trial to confirm our findings.

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Competing interests

D.J.M., D.C., D.E.J.L. and T.L. reported no biomedical financial interests or potential conflicts of interest relating to this work. Professor Rosser reports a consultancy fee from the European Huntington’s Disease Network.

Supplementary material

Supplementary material is available at Brain Communications online.

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