A DIFFERENT DEPRESSION: ANTIDEPRESSANT EFFICACY AND COGNITIVE MECHANISMS OF MOOD DISORDER IN HUNTINGTON'S DISEASE

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BACKGROUND

Depressed mood is very common in HD, with major effects on quality of life. Prior studies have shown higher rates of depression in gene carriers compared with non-carriers prior to genetic test results – implying a direct effect of HD neuropathology on mood disorder in patients. To date our knowledge of the best treatment and underlying mechanisms of depression in HD has relied on evidence from mood disorder in the general population. This study aims to address the gap in knowledge regarding mechanisms and treatment of depression in HD

AIMS

1) Use propensity scoring in the ENROLL HD observational cohort to determine the efficacy of different antidepressant classes on mood disorder in HD
2) Use a neuropsychological battery in a clinical cohort to determine the contributions of different cognitive mechanisms to mood disorder in HD

MATERIALS AND METHODS

Study 1: Antidepressant Efficacy in HD

Inclusion criteria: all gene positive patients started on an antidepressant for a depression indication.
Outcome measures: Primary outcome - Depression (PBAs[1] Depressed Mood severity and frequency >1; or Depression score from the Hospital Anxiety and Depression Score[2] {HADS} >7) at first follow-up (>2 weeks after medication initiation). Secondary outcome - depression at all subsequent follow-ups..
Intervention: Antidepressant class (based on published evidence recommendations for mood disorder in HD) – SSRIs, SNRIs, TCA, Tetracyclic antidepressants. (TeCA), Phenylpiperazines, Bupropion (Norepinephrine Dopamine Reuptake Inhibitor – NDRI), Unique (atypical agents including MAOIs).
Analysis: Propensity scoring creates a model to determine the probability (Propensity score - PS) of being given different treatments based on known variables. The PS is then included in an efficacy model to compare the effect of different treatments on outcome. We used the TWANG[3] and svyglm[4] packages in R, which use machine learning to compare PS models, and interrogates the efficacy of the process. Any variables not completely normalised by the PS are also included in the efficacy model in a doubly robust process. We included age, sex, psychiatric history, number of antidepressants, antidepressant dose, comorbidities, sedatives, composite disease stage, and risk factors for SSRI use in the propensity scoring process.

Study 2: Cognitive Mechanisms of Depression in HD

We recruited 51 HD gene positive patients and 26 controls (gene negative family members and local recruitment). Participants completed the HADS (for depression), Apathy Evaluation Score[5] (AES- apathy) and PBAs prior to the neuropsychological battery as well as the TMS and a medical history.
Our battery used the RDoC[6] criteria as a framework, all tasks were performed on a Lenovo laptop and were coded in e-prime.
Motivational anhedonia: *The Reward Reaction Time Task (RRTT)*. Participants in this variant of an established task[7] were asked to react as quickly as they could, with the knowledge that faster reaction times resulted in higher rewards. Rewards increased throughout the task. Reaction time in a non-rewarded practice level was included in the analysis to account for motor disability. The outcome measure was change in reaction time for reward corrected for time in task.
Learning from Reward and Punishment: the Probabilistic Selection Learning Task (PSLT)[8]: an established task of learning to avoid punishment and choose reward.
Consummatory anhedonia: we used the Reward subscale from the BISBAS as a measure of pleasure experienced from reward.
Response to negative outcome: Race Task. This novel assessment asks participants to rapidly press a button to assist a runner (race shown on screen). After the race (which was always unsuccessful) participants were asked how confident they were in their ability to make the slower runner win if the race were run again. This score (0-100) was the outcome measure.
Analysis: We used generalised linear mixed models of reaction time including fixed effects of TMS and time in task, then compared models using the Akaike Information Criterion) including the HADS and potential confounding variables(demographics, IQ, medication, psychiatric comorbidity) to analyse the RRTT. Logistic and linear regression models were used to compare HD cases with controls and to assess the effect of the independent variable on HADS depression score in the HD group were used for the remaining analyses. Likelihood ratio tests were used to compare regression models with and without potential confounding variables.

RESULTS

Study 1: Antidepressant Efficacy in HD

5486 (37.71%) participants received an antidepressant for low mood. SSRIs were most frequently prescribed (61.99% of all prescriptions). SSRIs and NDRI classes were most likely to be free from depression at first follow up (28.02% and 32.39% respectively), and at all follow ups (32.70% and 37.31% respectively). Using SSRIs as a comparator, on both the primary and secondary outcome measures, SSRIs outperformed SNRIs, whilst a trend level effect suggested superiority of NDRI over SSRIs on the secondary outcome measure.

Table 1:

ATE Analysis of Drug Class, SSRI as Reference Treatment

Outcome: Depression at First Follow-Up

	Estimate	P Value
(Intercept)	0.72	$<2x10^{-16}$
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

ATE Analysis of Drug Class, SSRI as Reference Treatment

Outcome: Depression at All Follow-Ups

	Estimate	P Value
(Intercept)	0.68	$< 2x10^{-16}$
NDRI	-0.080	0.011
Phenylpiperazine	0.063	0.022
SNRI	0.031	0.013
TCA	0.088	0.027
TeCA	0.081	$1.22x10^{-6}$
Unique	0.084	0.029

ATE Analysis of Drug Class with Doubly Robust Estimation, SSRI as Reference Treatment

Outcome: Depression at First Follow-Up

	Estimate	P Value
(Intercept)	0.61	$1.62x10^{-6}$
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

ATE Analysis of Drug Class with Doubly Robust Estimation, SSRI as Reference Treatment

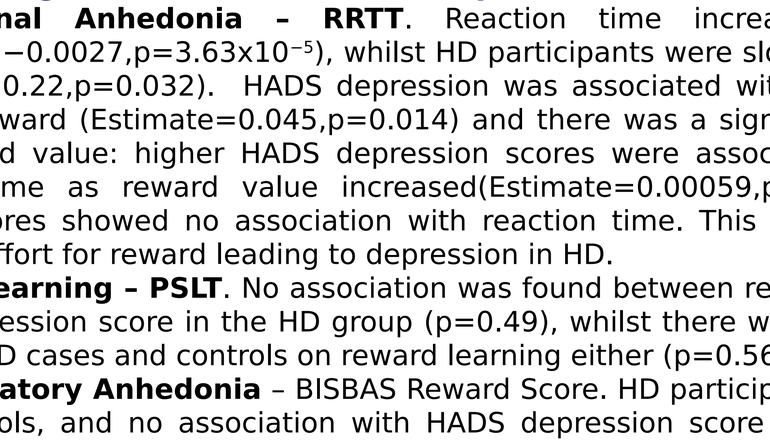
Outcome: Depression at All Follow-Ups

	Estimate	P Value
(Intercept)	0.62	$< 2x10^{-16}$
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

Study 2: Cognitive Mechanisms of Depression in HD

Motivational Anhedonia – RRTT. Reaction time increased for reward (Estimate=-0.0027,p=$3.63x10^{-5}$), whilst HD participants were slower than controls (Estimate=0.22,p=0.032). HADS depression was associated with slower reaction time for reward (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=$1.38x10^{-8}$). AES apathy scores showed no association with reaction time. This is consistent with impaired effort for reward leading to depression in HD.
Reward Learning – PSLT. No association was found between reward learning and HADS depression score in the HD group (p=0.49), whilst there were no differences between HD cases and controls on reward learning either (p=0.56).
Consummatory Anhedonia – BISBAS Reward Score. HD participants did not differ from controls, and no association with HADS depression score was found in HD participants.
Learning from Punishment – PSLT. HD participants were worse at learning from punishment than controls(p=0.00072), within the HD group no association was found between HADS depression score and punishment learning, but there was a significant negative association with AES score(p=0.030) not maintained with inclusion of confounders in the model.
Response to Negative Outcome – Race Task. HD cases had lower estimates of performance than controls(Estimate=-0.58,p<$2x10^{-16}$), but this was not associated with HADS depression score in the HD group.

Figure 1:



DISCUSSION

SSRIs and NDRIs are more effective at treating depression in HD than SNRIs which is the reverse of what is found in the general population.
Depression in HD is primarily mediated by motivational anhedonia, and not heightened response to negative outcome or consummatory anhedonia.
The most efficacious medications for depression in HD have the most major effects on motivational anhedonia.

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