

# IMPULSIVITY AND IRRITABILITY IN HUNTINGTON'S DISEASE: A COMMON FOUNDATION?

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## BACKGROUND

Impulsive behaviour and irritability were described in HD patients from the earliest clinical descriptions. Recent prevalence studies have described higher rates of both symptoms in HD patients compared to control subjects. Impulsivity is known to have multiple contributory mechanisms, but previous work in HD has been performed in small populations, and some aspects of impulsivity remain unexplored. Whilst irritability also has multiple contributory cognitive mechanisms (excessive response to provocation, and inhibition), none of which have been explored in a manifest HD population. Finally the contributions of impulsive behaviour to irritability and aggression in HD remain unknown.

## AIMS

- 1) Comprehensively explore the different aspects of impulsivity in HD, accounting for known confounding variables
- 2) Determine the cognitive mechanisms underlying irritable and aggressive behaviour in HD, including the contributions of impulsivity to irritable and aggressive behaviour.

## MATERIALS AND METHODS

### Participants and Analysis

We recruited 51 gene-positive HD participants (premanifest to disease stage 3) and 26 familial controls from the South Wales HD service as part of a wider study into the cognitive mechanisms underlying neuropsychiatric disorders in HD. All participants completed a medical and medication history, in addition to a cognitive assessment, demographic IQ score and motor assessment. Logistic regression models were constructed to compare HD cases and controls, and also irritable (Snaith Irritability Scale >13; or PBAs Irritability severity and frequency >1) versus non-irritable HD participants. Models were compared with and without potentially relevant confounders (calculated IQ, age, sex, medication, TMS and verbal fluency score) using likelihood ratio tests. The stop signal reaction time task model also included general reaction time to account for the motor disability of HD subjects.

### Irritability Questionnaires

**Problem Behaviours Assessment Short Form - Irritability subscore (PBAs Irritability)**<sup>1</sup>: a semi-structured interview assessing severity and frequency of neuropsychiatric symptoms.

**Snaith Irritability Scale (SIS)**<sup>2</sup>: a 18 item self-report instrument.

### Impulsivity Questionnaires

**Barrett Impulsivity Scale (BIS)**<sup>3</sup>: a 30 item scale with 3 sub-scales; attention, motor and non-planning.

**Negative Urgency, Lack of Pre-meditation, Lack of Persistence, Sensation Seeking, Positive Urgency (UPPSP)**<sup>4</sup>: a 56 item scale, reported as 5 sub-scales listed above.

### Cognitive Tasks: Impulsivity

**Stop Signal Reaction Time Task (SSRT)**<sup>5</sup> - motor inhibition). Participants were asked to react as quickly as possible to a visual stimulus, but withhold the response if the visual stimulus was followed by an auditory stimulus. The outcome measure was the stop signal reaction time - the time interval on which participants successfully inhibited 50% of responses.

**Kirby Delay Discounting Instrument (Delay Discounting)**<sup>6</sup>. Participants were offered a series of choices between smaller sums of money available immediately and larger sums available after a delay. The outcome measure was the kD, the calculated slope of the time discounting curve.

**Iowa Gambling Task (IGT)**<sup>7</sup> - Decision making under uncertainty). This established task asks participants to select cards from 4 different decks to win money and avoid losing money. Participants are asked to learn to avoid the worst performing decks. The outcome measure was selections from the worst performing deck in the last 25 trials of the task.

### Cognitive Tasks: Irritability

**Kloppel Task (Provocation)**<sup>8</sup>: This task has been used in a premanifest HD population, participants were asked to judge the difference in size of 2 squares and were inappropriately told they were wrong on 15% of trials. The outcome measure was post-task visual analogue scale scores for feelings of frustration, anger and irritability (max 300).

**Frustrative Non-Reward (FNR - Provocation)**: This novel task asked participants to complete a demographic questionnaire on the laptop, which generated an error message twice requiring data re-entry before allowing exit. The outcome measure was post-task visual analogue scale scores for feelings of frustration, anger and irritability (max 300).

## RESULTS

### Demographics and Irritability

HD patients had lower IQ, higher medication doses (olanzapine and fluoxetine equivalents), lower verbal fluency and higher TMS scores than controls. 20/51 HD participants scored as Irritable, whilst none of the control participants did.

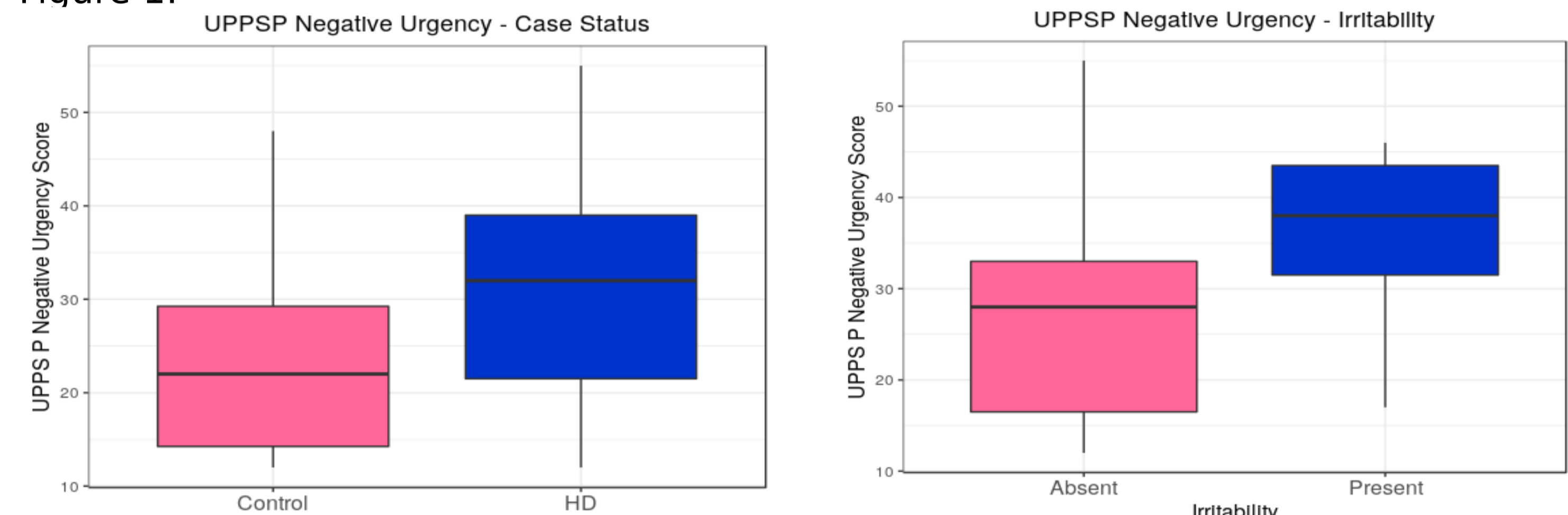
## RESULTS

### Impulsivity Questionnaires

**UPPSP**: HD patients had higher negative urgency scores (acting rashly under conditions of negative affect) than controls ( $p=1.50 \times 10^{-6}$ ), even with the inclusion of relevant confounders in the model. The irritable HD participants also had higher scores than non-irritable HD participants even with inclusion of relevant confounders ( $p=0.0077$ ). None of the other subscales showed a significant difference between groups.

**Barrett Impulsivity Scale**: Whilst the total score and all subscales showed higher scores in the HD group than controls, the initially significant difference did not survive inclusion of relevant confounders in the models. None of the subscales showed an association with irritability in HD.

Figure 1:



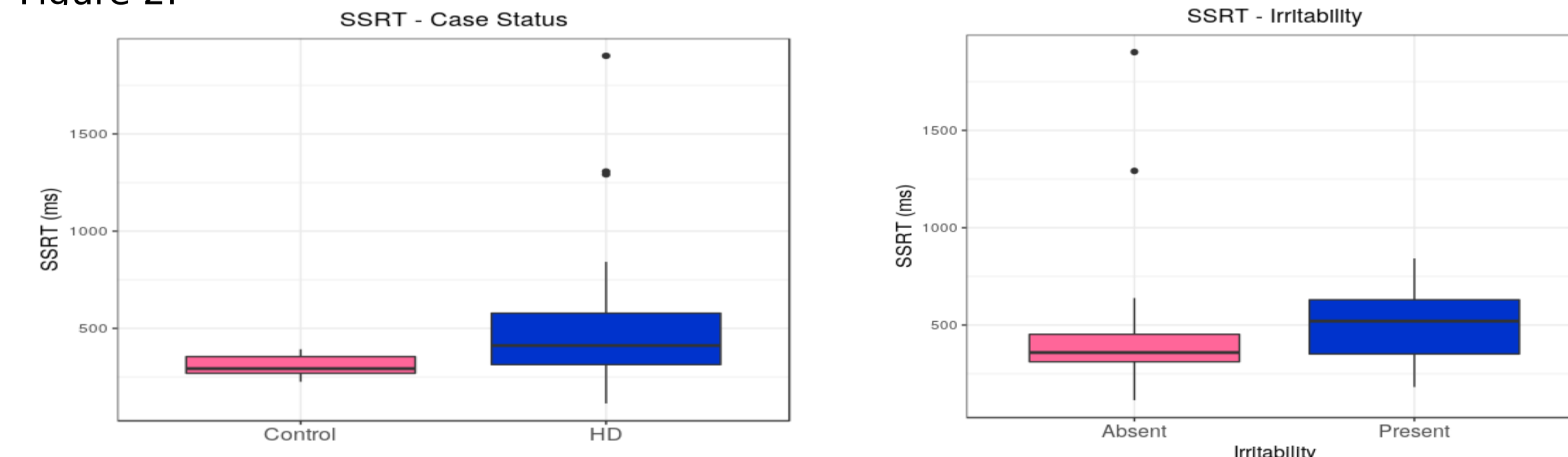
### Cognitive Tasks: Impulsivity

**Stop Signal Reaction Time Task**: HD patients had slower stop signal times than controls, even with the inclusion of relevant confounders (Olanzapine equivalent dose, reaction time) in the model ( $p=0.025$ ). No association between irritability status and SSRT was found in the HD group.

**Iowa Gambling Task**: HD cases made more selections from disadvantageous decks than controls ( $p=0.00024$ ) but this did not survive the inclusion of relevant confounders. No association between IGT performance and irritability status was seen in the HD group.

**Kirby Delay Discounting Instrument**: No differences between HD cases and controls was found. There was no association between task performance and irritability status in the HD group.

Figure 2:

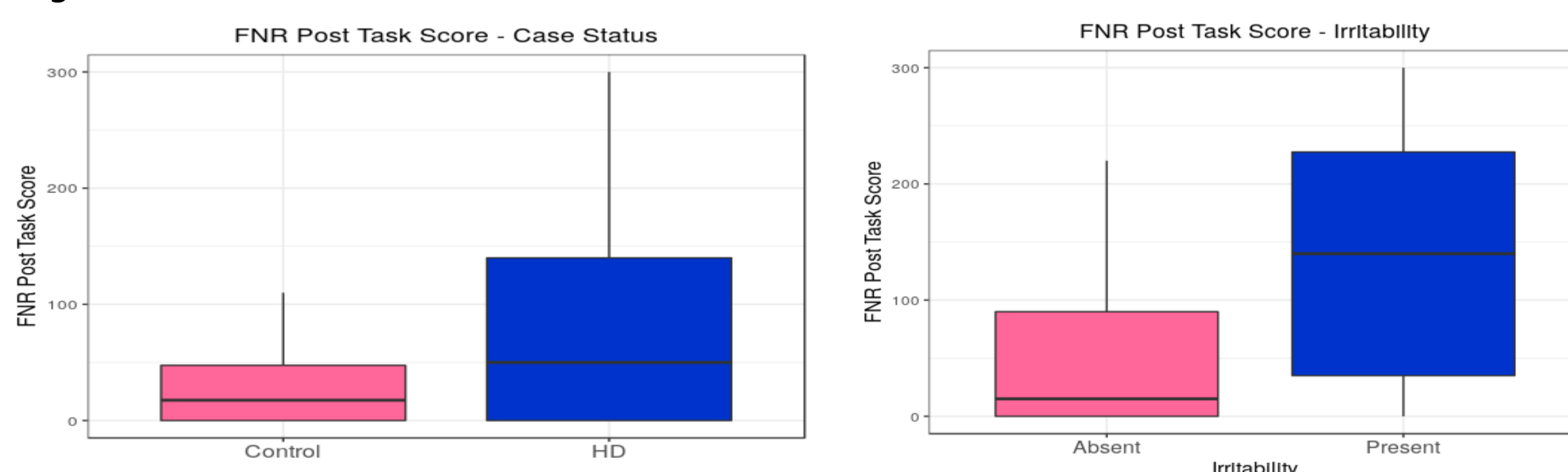


### Cognitive Tasks: Irritability

**Kloppel Task**: HD participants had higher post-task irritability score than controls, even when significant confounders were included in the model ( $p=0.00048$ ), but there was no association with irritability status in the HD group.

**Frustrative Non-Reward Task**: HD Participants had higher post-task irritability scores than controls, even after inclusion of significant confounders ( $p=3.81 \times 10^{-9}$ ). Post-task irritability score was associated with irritability status (no confounder improved the model;  $p=0.031$ ).

Figure 3:



## DISCUSSION

The main cognitive mechanism underlying irritability in HD is excessive response to provocation rather than failure of motor inhibition. HD patients do have impaired motor inhibition as evidenced by the SSRT, and worse negative urgency scores on the UPPSP, but we did not find differences on other measures of impulsive behaviour after accounting for relevant confounding variables.

### References:

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