Investigating the cognitive mechanisms underlying apathy in Huntington's Disease using an fMRI gambling task

Master's Thesis
Brain and Cognition
Universitat Pompeu Fabra

1st July 2021

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Abstract

Huntington's Disease (HD) is a genetic neurodegenerative disease that leads to a range of progressive motor, cognitive and psychiatric deficits. Apathy is the most prevalent psychiatric symptom in HD patients, having a strong impact on their quality of file. According to neuroimaging studies, apathetic behavior may be the result of disruptions in reward-processing areas. Even though these regions are not supposed to be damaged in early-stage HD patients, recent studies suggest a more widespread neurodegeneration. In the present study, we implemented a gambling task to investigate the cognitive mechanisms and neural correlates of apathy in HD during the processing of rewards. We found that monetary losses have a greater impact in apathetic HD patients, which may be explained by disruptions in the supplementary motor area, thalamus and precentral gyrus that lead to deficits in the integration and execution of motivated behavior. We found specific alterations in part of the ventral striatum, suggesting a more widespread neurodegeneration. Furthermore, we found abnormal activity in the insula in HD manifest patients, possibly reflecting an enhanced aversion to negative events. As such, our results help to better understand the cognitive mechanisms that cause apathy, thus having important clinical implications for developing new therapeutic strategies and improving the quality of life of apathetic HD patients.

1 Introduction

1.1 Basal Ganglia and Huntington's Disease

Huntington's Disease (HD) is a rare, inherited neurodegenerative disease that results from an expansion of the trinucleotide cytosine-adenineguanine (CAG) in the huntingtin gene (MacDonald et al., 1993). This mutation eventually causes progressive death of neuronal cells giving rise to a characteristic triad of symptoms including motor (e.g. chorea, dystonia), cognitive (e.g. executive function, working memory) and psychiatric (e.g. apathy, depression) deficits. Formal clinical diagnosis of HD is made on the basis of motor dysfunction (Kalkhoven, Sennef, Peeters, & Van Den Bos, 2014; Ross et al., 2014), which allows differentiating the theoretical state of the patient before (*premanifest*) and after (*manifest*) the appearance of motor impairments.

The disease eventually causes progressive death of neuronal cells in the basal ganglia, a group of interconnected structures that are essential in controlling the initiation of goal directed behaviors (Albin, Young, & Penney, 1989). Its main components comprise the globus pallidus, substantia nigra, subthalamic nucleus, dorsal striatum (caudate nucleus and putamen) and ventral striatum (nucleus accumbens, ventral portions of the caudate and the putamen, olfactory tubercle, and the anterior perforated substance) (Haber & Knutson, 2010). The dorsal striatum is particularly affected by the disease, leading to devastating implications due to its fundamental role in numerous cognitive processes. In particular, the striatum is responsible for transmiting information from the cortex to the globus pallidus and substantia nigra, regions that then signal the information back to cortical areas via the thalamus (Kalkhoven et al., 2014; Utter & Basso, 2008). One of the most relevant models of basal ganglia explains that the striatum transmits information through a direct or indirect route, depending upon whether action should be elicited or inhibited. Specifically, the direct striatal pathway inhibits activity between the cortex and the thalamus, thus facilitating motor, cognitive and sensory functions. On the other hand, the indirect pathway stimulates thalamocortical activity, thus promoting mo-

tor, cognitive and sensory activity. Adaptive behavior of a healthy brain is the result of a delicate and sophisticated balance between these pathways (Kalkhoven et al., 2014). In HD patients, however, striatal neurons of the indirect pathway are severely affected, disrupting the interaction between cortico-basal regions and leading to a loss of inhibitory control over motor and cognitive functions (Albin et al., 1989).

Thus, information in the brain flows from cortical areas to the basal ganglia throughout the striatum (disrupted in HD), forming parallel cortico-striatal circuits that connect basal ganglia subregions with distinct functional areas (Draganski et al., 2008). For instance, the putamen, which is located in the dorsal region of the striatum, is connected to primary and secondary motor areas and serves a fundamental function in the execution and initiation of motor movements (Alexander & Crutcher, 1990; Leh, Ptito, Chakravarty, & Strafella, 2007). The caudate nucleus, which is similarly considered part of the dorsal striatum, is more connected to executive functioning areas, such as the dorsolateral prefrontal cortex and the anterior cingulate cortex (ACC) representing the associative loop. The limbic circuit (reward and emotional processing), is formed by projections from the orbitofrontal cortex, ventromedial cortex, ACC, hippocampus and amygdala into the ventral striatum.

Neuroimaging studies in HD have shown that some parts of the striatum deteriorate more rapidly than others (Kassubek et al., 2004; Vonsattel & DiFiglia, 1998). This has huge implications in the progresion of the disease, as different subregions of the striatum play a role in different functions of behavior. For instance, the putamen and caudate nucleus undergo neuroanatomical alterations years before the emergence of motor symptoms, being present in both premanifest and manifest patients (Aylward et al., 2011; Weir, Sturrock, & Leavitt, 2011). On the other hand, neuronal degeneration in the ventral striatum is thought to arise in later stages of the disease. Even though this dorsal-to-ventral gradient of neurodegeneration has been found in the literature, recent evidence suggests that the atrophy may be less uniform and more widespread than previously believed (Galvin, Roe, Xiong, & Morris, 2006; Thieben et al., 2002; van den Bogaard et al., 2011), suggesting that alterations in the ventral striatum may already be observable in the early stages of HD.

1.2 Apathy in Huntington patients

As a result of neural degeneration, HD patients experience a series of progressive symptoms, including motor, cognitive, and psychiatric deficits such as apathy (Ramos & Garrett, 2017). Defined as a decrease of goal-directed behavior due to

a lack of mood, interest, and motivation, apathy is the earliest and most prevalent psychiatric symptom in HD (Barker & Mason, 2018; Marin, 1991). Present in 46-76 % of premanifest and manifest HD individuals, it has a direct impact on the quality of life of both patients and their caregivers (Chase, 2011; Paoli et al., 2017). Apathy also hinders the efficacy of clinical interventions, leading to a worse prognosis for the patient. Additionally, apathy is the only psychiatric symptom that tracks the declines in cognitive and functional abilities up to ten years before motor onset, thus representing a biomarker of HD pathology (Baake et al., 2018; Martinez-Fernandez et al., 2016; Tabrizi et al., 2013; van Duijn et al., 2014). Therefore, it is vital to understand the causes of this symptom to develop effective treatments and improve patient quality of life. The potential of this research extends beyond HD, since many other neurodegenerative disorders affecting the basal ganglia (such as Parkinson's disease, Alzheimer's disease, and frontotemporal dementia) are also associated with apathy (Le Heron, Holroyd, Salamone, & Husain, 2019).

Despite the importance and prevalence of apathy in HD, the exact mechanisms underlying its development remain unknown. Several pathologies associated with apathy affect executive-frontal and basal ganglia regions, suggesting that the damage to these circuits and cognitive processes are responsible for apathy (Le Heron et al., 2019). Indeed, studies examining the neuroimaging correlates of apathy have identified consistent associations with the disruption of specific frontal regions such as the orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC) and ACC, as well as subcortical structures such as the ventral striatum (Kos, van Tol, Marsman, Knegtering, & Aleman, 2016; Le Heron, Apps, & Husain, 2018). This is supported by studies showing that apathy emerges after damage to these areas (Levy & Dubois, 2006). Furthermore, direct associations have been found across modalities between apathy severity and reduced grey-matter (De Paepe et al., 2021; Martínez-Horta et al., 2018) and white-matter volume (Delmaire et al., 2013; De Paepe et al., 2019). In the study of De Paepe et al. (2021) for instance, they found that grey-matter volume atrophy in the middle cingulate cortex (MCC) predicted the severity and progression of apathy in HD patients.

Even though apathy is a disorder of loss of goal-directed behavior and motivation, few research has investigated its functional correlates during the processing of rewards. A corpus of the literature agrees that apathetic behavior in disease may be related to a decreased sensitivity during reward-processing (Le Heron et al., 2019), however, the results appear to go in opposing directions. On the one hand, apathy in HD appears to be related to a reduced sensitivity to process positive events and

rewards. For instance, apathetic HD patients are impaired in the recognition of socially rewarding stimuli as compared to non-apathetic patients of the same group (Osborne-Crowley et al., 2019). These results go in line with research carried out in similar neurological diseases. During a gambling task, Parkinson's patients exhibited diminished amplitude differences in feedback negativity potentials, suggesting a compromised processing of rewards (Martínez-Horta et al., 2014). Another study on Parkinson's showed that the sensitivity to rewards was modulated by the dopaminergic state of the patients (Muhammed et al., 2016). Additionally, amotivation has been shown to be correlated with reduced activation in the OFC and ventral striatum in response to reward information (Simon et al., 2010; Strauss, Waltz, & Gold, 2014). On the other hand, recent evidence suggests that apathetic behaviour in disease may be related to a reduced sensitivity to punishments and negative emotions, rather than to rewards. For instance, McLauchlan, Lancaster, Craufurd, Linden, and Rosser (2019) employed several reward-related tasks in HD patients to determine the cognitive processes leading to apathy, where they discovered a correlation between the degree of apathy and a reduced sensitivity to loss. This is also consistent with the fact that HD pathology has been predominantly attributed to the processing of negative emotions (Campbell, Stout, & Finn, 2004).

1.3 Neuroanatomy of motivated behavior

Given that apathy is characterised by the loss of motivation, it is relevant to understand the neuroanatomical correlates of this process. Motivated behavior is defined as the exertion of substantial effort to obtain a particular reward, which can be summarized by three main processes (Le Heron et al., 2019). Firstly, we evaluate the stimulus based on its rewarding or punishing potential, as well as its costs, such as the time and effort it will take to perform the action. For this, a group of regions including the vmPFC, OFC, ventral striatum, rostral-caudate, ventral putamen and amygdala allow us to evaluate the affective value of stimuli, predicting expected rewards and punishments, control our emotions and learning from previous reward-outcomes to make better decisions in the task (Haber & Behrens, 2014; Manes et al., 2002; O'Doherty et al., 2004; van Duijn et al., 2014). Secondly, this information must be integrated into motor regions to produce behavioral responses. The ventral striatum and the ACC are involved in this process under the influence of the neurotransmitter dopamine (DA), which is released to these regions from the ventral tegmental area (VTA) (Grace, Floresco, Goto, & Lodge, 2007; Sesack & Grace, 2010; Wise, 2004). In particular, it is believed that increases or decreases

in DA levels indicate whether a given stimulus is better or worse than anticipated, which guide our behavior in the future. Last, a motor system produces behavior towards the motivationally salient stimulus, achieved by the posterior MCC (pMCC), supplementary motor area (SMA) and dorsal striatum (Le Heron et al., 2019).

1.4 Objectives and hypotheses

In light of the overlap between the brain regions damaged in HD, and those associated with apathy and motivated behaviour, the main goal of this study is to dissociate the cognitive mechanisms and neural correlates that are altered in reward processing and that underlie apathy in HD. In particular, we hypothesize that apathy is related to an insensitivity to process rewards and/or punishments, which is what leads to the lack of motivation exhibited by apathetic individuals. To study this, we recorded functional magnetic resonance imaging data during a gambling task in order to identify disrupted reward-related regions in HD and identify those regions that may describe apathetic symptoms. Although the classical pattern of neurodegeneration in HD poses a relatively preserved mesocorticolimbic pathway in the early and middle stages of the disease, different findings suggest that this pathway may also be altered at such stages (Galvin et al., 2006; Thieben et al., 2002; van den Bogaard et al., 2011). As such, we expect that individual differences in apathy may be explained by different alterations of this brain circuit. These regions may include, dorsal and ventral striatum, ACC, OFC, insula, SMA, and amygdala.

2 Materials and Methods

2.1 Participants

Participants' demographics are detailed in Table 2.1. We recruited fourty-six HD gene-carriers (67% female, age: Mean ± STD = 44.14 ± 9.34) at different stages of the disease and thirty-four healthy control participants (50% female, age: Mean ± STD = 44.00 ± 10.66) who were matched for sex, age and years of education. Huntington's disease individuals were defined as carriers of the genetic mutation with 36 repeats. 23 of the gene-carriers were manifest Huntington's disease patients, defined as those gene-carriers with a Diagnostic Confidence Score (DCS) of four on the Unified Huntington's Disease Rating Scale (UHDRS) (Group, 1996), which corresponds to a confidence of 99% that the motor abnormalities are due to Huntington's disease. 23 of the gene-carriers were premanifest Huntington's disease individuals, defined as carriers of the genetic mutation with a DCS of less than four. Despite the fact that HD is clinically diagnosed based on motor onset, pathological changes are often present long before motor symptoms (Martinez-Fernandez et al., 2016; Thompson et al., 2012). As such, when examining the association between apathy with functional activity and behavior, we studied the disease as a continuum. No participants reported previous history of traumatic brain injury or neurological disorder other than HD. The study was approved by the ethics committee of Bellvitge Hospital in accordance with the Helsinki Declaration of 1975 and all participants provided written informed consent.

2.1.1 Clinical evaluation

All HD individuals underwent the UHDRS evaluation (Group, 1996), a scale that allows assessing and identifying abnormalities in cognitive (UHDRS-cogscore) and motor (UHDRS-TMS) functions. In order to further characterise the HD sample, the standardized CAG-Age Product (CAP) score, computed as $CAP = 100 \times age \times$

	Controls	Premanifest	Manifest
N	34	23	23
Sex (f/m)	17/17	19/4	12/9 (N=21)
Age (years)	44.00 +/- 10.66	37.00 +/- 8.74	51.28 +/- 9.95
Education (years)	12.74 +/- 2.71	13.70 +/- 3.97	11.64 +/- 3.91
UHDRS-TMS	-	1.86 +/- 3.67 (N=22)	21.52 +/- 12.67 (N=21)
UHDRS-cogscore	-	296.09 +/- 59.44 (N=22)	177.53 +/- 60.06 (N=17)
CAG	-	43.95 +/- 2.66	43.95 +/- 3.25
CAP	-	48.58 +/- 16.86	63.96 +/- 16.72
TFC	-	12.76 +/- 0.73 (N=17)	11.18 +/- 1.92 (N=22)

Table 2.1: **Demographic and clinical information of the participants.** The data is represented as Mean ± Standard deviation. N = Number of participants, f = females, m = males, UHDRS-cogscore = Unified Huntington's Disease Rating Scale total cognitive score (Group, 1996); UHDRS-TMS = Unified Huntington's Disease Rating Scale total motor score; CAG = Hungtintin gene length; CAP = standardized age-CAG product; TFC = Total functional capacity (Ross et al., 2014).

$(CAG–35.5)/627$, was employed, as a measurement of HD state (Ross et al., 2014). In addition, total functional capacity (TFC) served as a measure of independence in daily activities, ranging from thirteen (full capacity) to zero (total incapacity) (Group, 1996). Furthermore, global apathy in HD patients was measured using the Lille Apathy Rating Scale, short-form (LARS-s), a self-rating questionnaire that measures global apathy with scores ranging from 15 to +15, with higher scores representing a higher degree of apathy. All evaluations were carried out by neuropsychologists and psychiatrists specialized in movement disorders.

2.2 Experimental design

Our experiment used a modified version of the monetary gambling task originally designed by Gehring and Willoughby (2002). Participants were visually presented with two numbers (5 and 25), colored in black, on a screen with a white background. Two combinations could be presented: [5 25] and [25 5]. Using the left or right index fingers, the participants had to select one of the two numbers, with a maximum time of 2500 ms to make the choice. The number they chose was shown in underline to confirm that they bet that amount. Thereafter, a red or green background appeared on the number they chose, showing the outcome of the bet (Figure 2.1). If the background of the number they selected turned green, it indicated a corresponding gain of the same amount in Euro Cents, whereas if it turned red, it lead to a loss of that amount. The task described above happened in 2/3 of the trials (standard trials), however, in the remaining 1/3, participants experienced unexpected rewards or losses (boost trials). In this condition, regardless of the chosen magnitude (5 or

25), participants won or loss an amount of 125 Euro Cents, again indicated by a green or red background surrounding the numbers.

Each participant was given a 10€ initial sum, and were instructed to win as much as they could. At the end of the experiment, participants received the same monetary compensation as their final score in the experiment. The experiment was designed as an event-related paradigm with a total of 120 trials (40 Gain, 40 Loss and 40 Boost), which were preceded by a fixation cross at the center of the screen for 500 *ms*. Each possible combination of feedback was counterbalanced and presented in random order for the standard trials ([5 25], [25 5], [5 25], [25 5]) and for the boost trials ([125 25], [25 125], [5 125], [125 5]). During the gambling, if the participant did not press a button before 2.5 seconds a text saying *rapido!* [fast!] was displayed in the screen and no gain or loss feedback was provided for that trial. These trials were not modelled in the analysis.

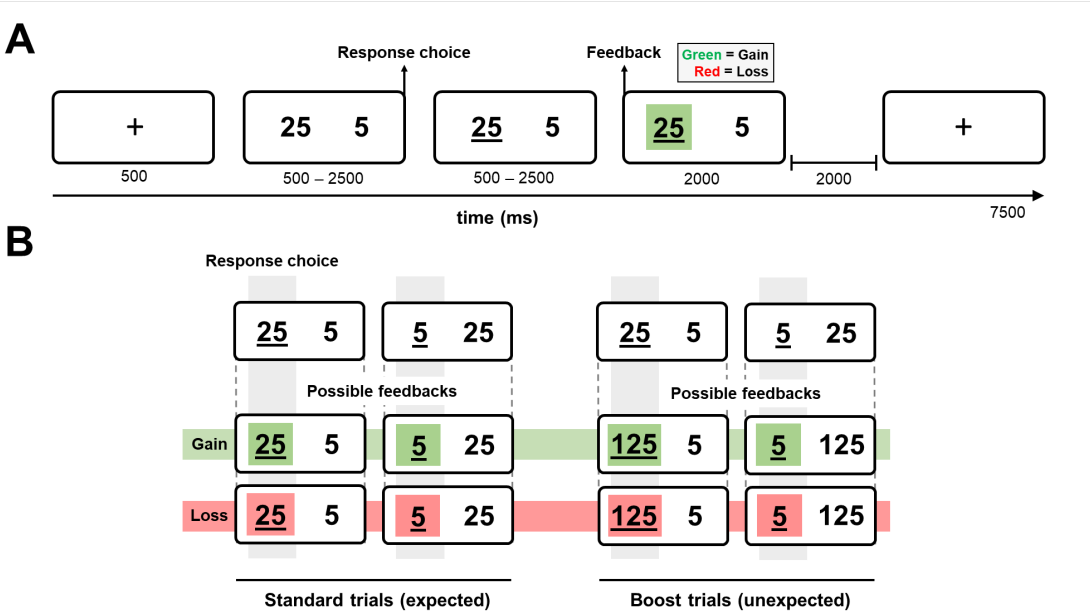

Figure 2.1: **Design of the gambling task. A)** Sequence of stimulus presentation and response events. Numbers surrounded in green represent a gain and those surrounded in red a loss. **B)** Possible feedbacks and outcomes in standard trials (left) and boost trials (right). Adapted from Camara et al. (2010).

2.3 Behavioral analysis

First of all, we examined the behavioral performance of the participants in the gambling task. In particular, we assessed their sensitivity to the obtained reward/pun-

ishment by measuring their tendency to take or avoid risks. Choosing to bet at 25 implies a higher risk than betting at 5, as the monetary amount that can be lost is higher (25 Euros) as apposed to the latter choice (5 Euros). Similarly, the amount of money that can be gained is also higher. Thus, we defined risk-taking behavior as the times each participant bet to 25 divided by the total number of bets.

However, this analysis does not provide a complete and accurate picture of risky behavior, as participants may change their betting strategies according to what they obtained on their previous bet. As an example, risky gamblers may continue to bet on 25 after an unfavourable previous outcome, while more conservative participants may bet to 5 after a loss trial. To analyse this further, we calculated the probability of making a risky choice based on the outcome of their previous bet. We defined this as:

$$\frac{N^{o} \textit{ of bets to 25 when previous outcome was } X}{N^{o} \textit{ of trials in which the previous outcome was } X} \tag{2.1}$$

With X either being Gain 5, Gain 25, Gain 125, Loss 5, Loss 25 or Loss 125 trials.

2.4 MRI acquisition

All MRI data was acquired on a 3T Siemens Magnetom Trio (Siemens Medical Solutions, Erlangen, Germany) at the Hospital Cínic in Barcelona while using a a 32-channel head coil. Anatomical images were acquired using a high-resolution T1-weighted MPRAGE (magnetisation-prepared rapid-acquisition gradient echo) sequence with the following parameters: 208 sagittal slices, TR = 1970 ms, TE = 2.34 ms, flip angle = 9°, inversion time = 1050 ms, FOV = 256 x 256 mm^2, voxel size = 1 x 1 x 1 mm^3. Functional images were obtained with a T2*-weighted gradient-echo imaging sequence (30 axial slices, TR = 2000 ms, TE = 30 ms, flip angle = 80^{o}, matrix size = 64 x 64 mm^2, voxel size = 4 x 4 x 4 mm^3, 336 whole-brain volumes).

2.5 fMRI preprocessing

All data preprocessing was performed using SPM12 software (http://www.fil.ion.ucl .ac.uk/spm) and custom MATLAB scripts. First, we performed slice-timing correction to correct for the time difference between brain slice acquisitions. Then, the data was co-registered via an affine rigid-body transformation (i.e. translation and rotations) with the first brain volume as reference to correct for head motion. Since HD causes uncontrolled movements, motion needs special care in this

particular clinical population. For this reason, we further preprocessed the data using ARTREPAIR (https://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html), a software that is used for patients with large motion artefacts. Following the recommended pipeline (Mazaika, Whitfield-Gabrieli, Reiss, & Glover, 2007), we first smoothed the affine motion corrected images with a 4mm FWHM Gaussian kernel before repairing for motion outliers. These outliers were identified as the scans with more than 1.8% variation from the mean global signal and were repaired via interpolation to the two adjacent unaffected scans. To preserve the nature of the BOLD signal, we did not repair more than two consecutive volumes that were identified as outliers. In this way, only two subjects had more than 7% of the volumes to repair (11.33% and 12.05%), and only one subject was excluded from the study due to excessive motion (>20%). Spatial transformations were computed to coregister anatomical and functional volumes and to wrap these into the standard Montreal Neurological Institute (MNI) space. One of the subjects could not be succesfully normalized into MNI space due to excessive distortions in the OFC, resulting in being excluded from the study as well. Finally, brain images were smoothed with a 7mm FWHM Gaussian kernel resulting in a total smoothing of 8mm. Following the recommendations of the ARTREPAIR software (Mazaika et al., 2007), some subjects underlied a slightly different preprocessing as we identified substantial low frequency drifts from the global signal. These subjects (6 out of 77) were high-pass filtered using a 37-tap filter before the spatial smoothing of 4mm and were not repaired through interpolation, the rest of the steps were identical.

2.6 fMRI analysis

Subject-level analyses were based on a least-square estimation using a general linear model approach (GLM). Experimental conditions were modelled using a box-car regressor waveform and convolved using a canonical hemodynamic response function (HRF) (Friston et al., 1998). Regressors of interest included the experimental conditions of Gain5, Gain25, Gain125, Loss5, Loss25 and Loss125. To account for movement-related noise, the six rigid-body motion parameters were included as nuisance regressors in the design matrix. In addition, we also included the onsets in which participants were presented with the fixation cross as regressor of non-interest. The data was then high-pass filtered to a maximum of 1/128 Hz and an autoregressive model (AR(1)) was considered in the computations to account for the temporal noise auto-correlation in the model estimates. After estimating the model, we calculated the main effect for each of the following contrasts of interest: Gain(5+25+125)

vs. Loss(5+25+125), Gain(5+25+125) vs. baseline and Loss(5+25+125) vs. baseline.

2.6.1 Main contrasts of interest

First, we performed a one-sample t-test with the entire sample (i.e. both Control and Huntington groups combined together), in order to reveal the reward network engaged during the fMRI gambling task. For this, we used the contrast Gain vs. Loss. Effects were considered significant at a whole-brain level if they exceeded a voxel-wise threshold of $p < 0.001$ (k > 20 voxels extent) and cluster-level family wise error (FWE) correction for multiple comparisons of $p < 0.05$.

Then, we performed a one-way ANOVA to assess the differences in activation between Controls and HD patients during the processing of Gain vs. Loss. Since we expect the premanifest and manifest HD subgroups to differ distinctly with respect to Controls, we entered each factor separately, and then used the contrast of Controls vs. (Premanifest + Manifest) to assess for the global alterations due to the disease. In this case, we used a more exploratory approach and considered effects significant if they exceeded a voxel-wise threshold of $p < 0.001$ (k > 20 voxels extent). Those areas that were found significant were further analyzed to evaluate the effect between HD patient subgroups (Controls vs. Premanifest vs. Manifest). This was achieved by creating region-of-interest (ROI) masks of these activations. These ROI masks were later applied separately to each subject to extract the estimated beta coefficients (i.e. activation effect sizes). To ensure that we were extracting sufficient information, we created the ROI masks using an uncorrected p<0.05 value. Furthermore, two-sample t-tests served to directly distinguish the differences between Controls and Premanifest/Manifest patients during the processing of gains and losses separately. Here, we used a threshold of $p < 0.001$ (k > 20 voxels extent).

2.7 Relationship between reward processing and apathy

In order to study the relationship between apathy and reward processing at a behavioral-level we performed multiple linear regression analyses between the LARS-s global apathy score and measures of risk-taking behavior. Both premanifest and manifest patients were combined together in the regression model in order to have a wider range of values and to investigate the disease as a whole. Controlling variables

such as CAP, Age and Sex were also included to rule out any potential variance explained by these factors. Correlations were considered significant if they exceeded a threshold of $p < 0.05$.

Similarly, we performed multiple regression analyses between apathy and fMRI activity to explore the functional correlates of apathetic behavior during the processing of rewards/punishments. We applied the analyses at a whole-brain level for the contrast of Gain vs. baseline and of Loss vs. baseline. We also controlled for CAP, Age and Sex, and included both HD subgroups together. Correlations were considered significant if they exceeded a voxel-wise threshold of $p < 0.001$ ($k > 20$ voxels extent). Furthermore, we created ROIs from the brain regions that were found significant to further evaluate the potential differences between premanifest and manifest HD patients.

3 Results

3.1 Risk-taking behavior

First, we evaluated the proportion in which participants made a risky bet (bet to 25). An independent t-test showed that this proportion did not differ between healthy participants (Mean $\pm$ STD $= 0.55 \pm 0.14$) and HD patients (Mean $\pm$ STD $= 0.52 \pm 0.11$), implying a similar risk-taking behaviour in both groups ($t(76)$=1.22, p=0.233). When analyzing their behavior based on the outcome of their previous bet, we found a clear difference in behavior between gains and losses (Figure 3.1). When participants on on the preceding trial, both Control and Huntington groups performed similarly at chance level, showing no particular risk-taking or risk-avoiding behaviour. However, in the case of losses, we found significant differences between groups ($F(2,75)$=3.97, p=0.028) when participants made a risky choice and lost on the previous trial (Loss 25). In particular, we found both premanifest ($t(55)$=2.52, p=0.015) and manifest ($t(57)$=2.21, p=0.031) HD patients to take significantly less risks than Controls. No significant differences were found between premanifest and manifest HD subgroups ($t(44)$=-0.11, p=0.913).

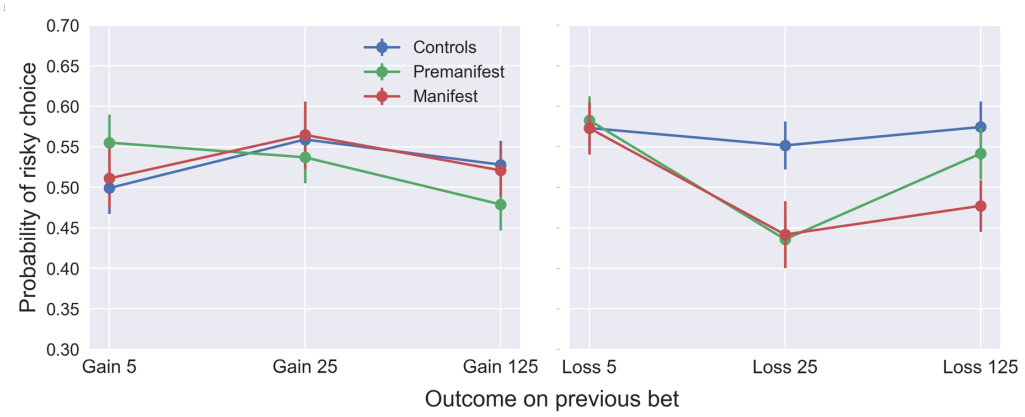

Figure 3.1: **Probability of making a risky choice based on the outcome of the preceding trial (Equation 2.1)**. The dots indicate the average of each group: Controls (blue), Premanifest HD (green) and Manifest HD (red). Error bars indicate the standard error of the mean (SEM).

In light of these results, we wondered whether apathy modulated the effect shown in HD patients. Based on previous findings suggesting that apathy is associated with a reduced impact to loss, we expected patients with higher levels of apathy to make riskier choices after confronting an unfavourable risky choice in the previous trial (i.e. Loss 25). To test this, we performed a multiple linear regression between LARS-s apathy score and the proportion of betting to 25 (as opposed to 5) when the previous outcome was Loss 25. We found that our model was statistically significant (R^2= 0.248, $F(4,38) = 3.13$, p=0.037), with the level of apathy as measured by LARS being a significant predictor (b = -0.013, t =-2.15, p =0.038). None of the control variables (CAP, age, sex) were found to be significant predictors (CAP, b = -0.001, t =-0.85, p =0.402; age, b = 0.001, t =0.64, p =0.526; sex, b = 0.099, t =1.78, p =0.083). Opposite to our expectations, these results show that the likelihood of making a risky choice after a desfavorable bet decreases with apathy, possibly reflecting an enhanced impact to loss in apathetic HD patients (Figure 3.2).

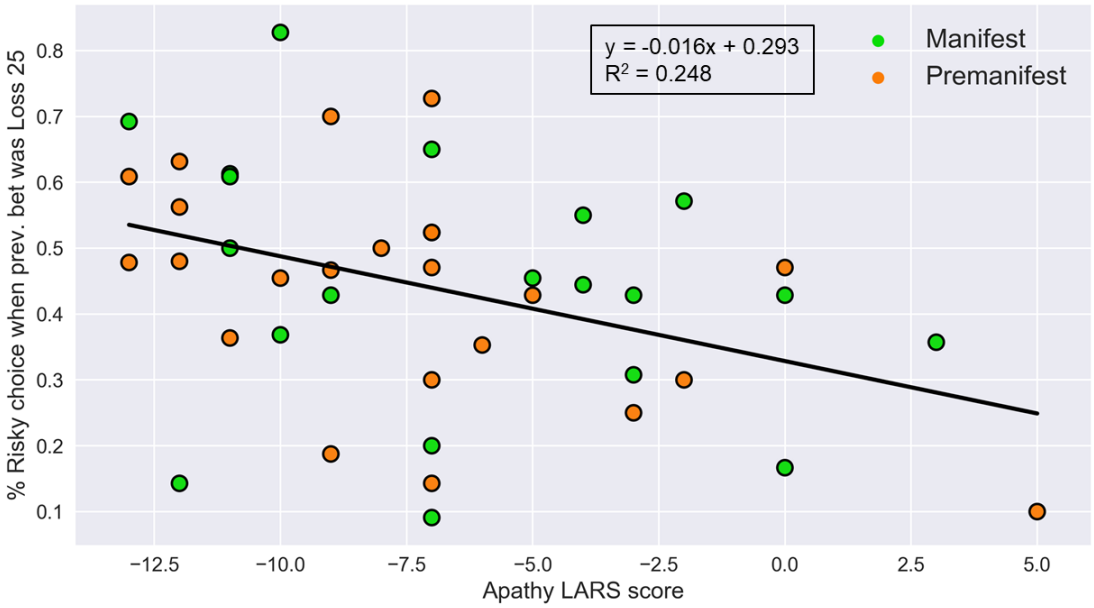

Figure 3.2: **Negative correlation between LARS global apathy and the probability of making a risky when the previous trial was Loss 25.** Manifest patients are colored in green and premanifest patients in orange.

3.2 Brain activity in the fMRI gambling task

We first carried out a one-sample t-test with both Control and Huntington groups combined together, in order to identify the reward network engaged during the fMRI

gambling task. Whole brain analysis showed significant activations in the pMCC, the ACC extending to the OFC, thalamus, VTA, as well as in the rostral caudate nucleus and rostral-ventral putamen (ventral striatum) (Figure 3.3). Parietal, occipital and precentral areas were also found to be active during the processing of gains more than losses.

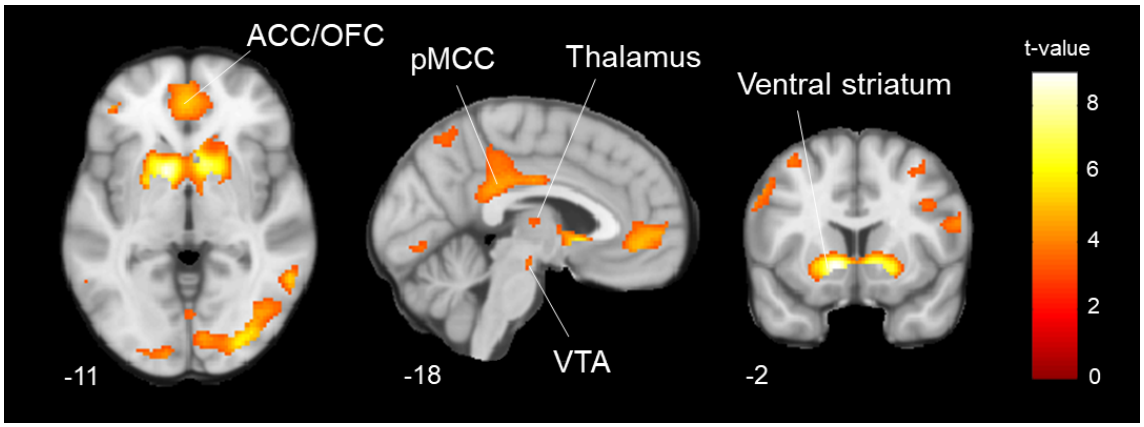

Figure 3.3: **Common activations in both Control and HD patient groups at the Gain > Loss contrast.** Relevant slices showing activations in reward-related areas such as the VTA, ACC/OFC, pMCC and ventral striatum.

	MNI coordinates					
Anatomical area	**x**	**y**	**z**	**T stat**	**pFWE**	**k_E**
Putamen L	-12	10	-4	8.92	<0.001	246
Caudate R	10	12	-2	7.43	<0.001	160
Middle Occipital Gyrus R	34	-84	0	6.10	<0.001	205
Middle Temporal Gyrus R	58	-52	-4	5.95	0.001	67
precentral Gyrus R	-44	-2	38	5.75	0.001	66
Posterior Cingulate Gyrus L	0	-34	28	5.56	0.003	101
Superior Parietal Lobule R	32	-64	46	5.39	0.005	208
ACC/OFC L	0	46	-4	5.36	0.005	70

Table 3.1: **Whole sample brain activity analysis in the contrast Gain vs. Losses** (p<0.001-corrected at cluster level , p< 0.05, cluster extent 20 voxels). R = Right, L = Left, pFWE = Family-wise error rate corrected p-value, k_E = N^{o} of voxels in cluster.

3.2.1 Functional differences Controls vs. Huntington

We found a reduced level of activity in the reward network for the Huntington group compared with the controls. Specifically, HD individuals presented significant lower levels of activity during Gain vs. Loss in the ventral striatum, medial frontal gyrus, anterior insula and ACC (Figure 3.4 left).

Post-hoc analyses at an ROI-level were further performed on these areas to analyze the effect between HD patient subgroups (Controls vs. Premanifest vs. Manifest) (Figure 3.4, right). As expected from the group activation maps, we found significant differences between groups in the four of the regions (one-way ANOVAs: Ventral striatum, $F(2,75)=6.57$, $p=0.002$; Anterior insula, $F(2,75)=8.18$, $p<0.001$; ACC/OFC, $F(2,75)=11.08$, $p<0.001$, Medial Frontal Gyrus, $F(2,75)=10.01$. $p<0.001$). Independent t-tests showed significant differences in effect size (i.e. beta coefficients) between manifest patients and controls in the ROIs of ventral striatum ($t(55)=3.22$, $p=0.002$), anterior insula ($t(55)=3.39$. $p=0.001$), ACC ($t(55)=4.20$, $p<0.001$) and Medial Frontal Gyrus ($t(55)=3.86$, $p<0.001$). All of them were related to a reduced activity in the processing of Gain vs. Loss as compared to the activity in Controls. Premanifest patients only showed significantly less activity than controls in the ventral striatum (($t(57)=2.96$, $p<0.001$) and ACC ($t(57)=2.81$, $p=0.007$). Differences between manifest and premanifest patients were further found in the insula, ACC and Medial frontal gyrus, with manifest patients showing reduced activity as compared to premanifest. When analyzing the beta coefficients separately for the Gain vs. baseline and Loss vs. baseline contrasts, we found no significant differences at these regions.

Furthermore, we analyzed at a whole-brain level the differences between Controls and HD subgroups during the processing of gains and losses separately (Figure 3.5). During the processing of gains, premanifest patients showed significantly less activity ($p < 0.001$, k > 20 voxels extent) as compared to controls in the left amygdala and the thalamus, while manifest patients showed reduced activity in the right amygdala and insula. During the processing of losses, premanifest patients showed reduced activity in the right amygdala, whereas manifest patients showed less activity in the caudate nucleus bilaterally and thalamus. A two-sample t-test between premanifest and manifest subgroups did not show any significant differences in either gain or loss conditions.

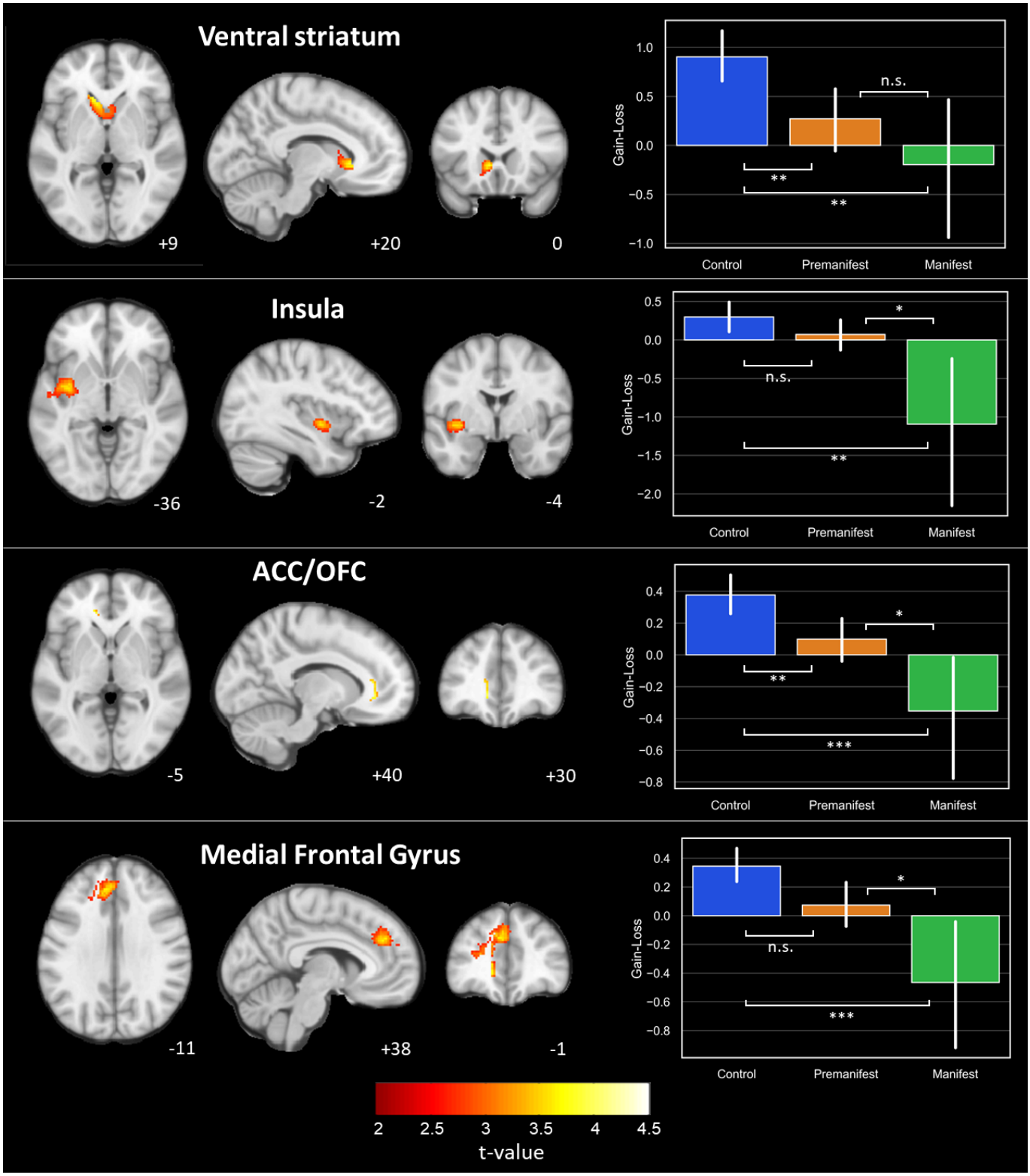

Figure 3.4: **Differences in brain activity during Gains > Losses between Controls and HD patients.** These differences (left) were used as ROI masks to extract the estimated beta coefficients for each subject (right). The barplots represent the average activity found for each group: Controls (blue), premanifest (orange), manifest (green). Error bars indicate the standard error of the mean.

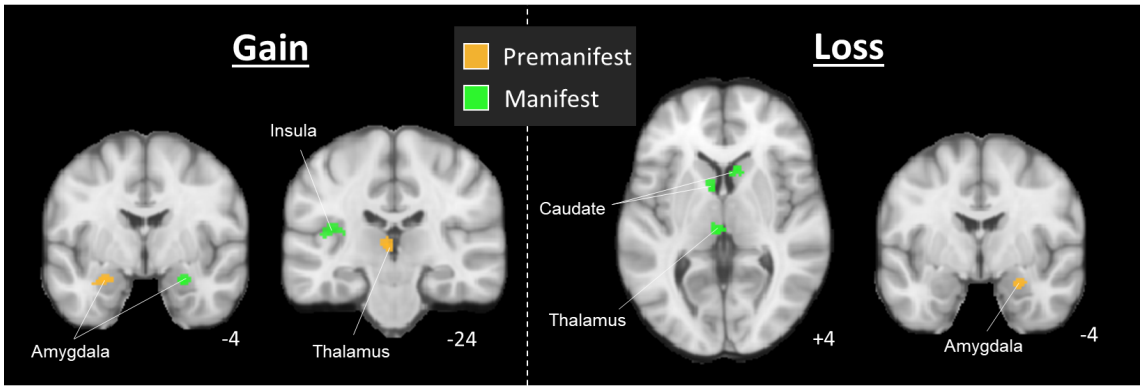

Figure 3.5: **Differences in brain activity during gains (left) and losses (right) between Controls and HD premanifest patients (orange) and HD manifest patients (green).** Voxels represent significant differences exceeding a voxel-wise threshold of $p < 0.001$ (k $>$ 20 voxels extent).

3.2.2 Relationship between altered reward processing and apathy

In light of the functional differences during the processing of rewards between healthy controls and HD patients, and the large variability found in the underlying activity, we investigated whether the altered functional correlates in the reward circuit underlie apathetic behavior in HD. Thus, utilizing a whole brain approach, we examined the relationship between reward processing (Gain vs. baseline and Loss vs. baseline) and apathy severity. In particular, we found that an increase in apathy levels was significantly associated with an activity reduction during monetary gains in the thalamus, SMA, precentral gyrus extending to the inferior frontal gyrus (IFG), Middle frontal gyrus, as well as other parietal and occipital areas. In addition, increased activations in a small portion of the superior temporal gyrus was related to increased levels of apathy. We found very similar associations during the processing of losses, with higher levels of apathy related to decreasing levels of brain activity in the thalamus, SMA, precentral/IFG, MCC and parietal areas.

We then analysed whether there were any differences between patient subgroups in the activity of these regions, calculating the mean beta coefficients for each group (Controls, premanifest, manifest). We only found a significant difference in the thalamus during the processing of losses ($F(2,75)=3.66$, $p=0.031$), where manifest patients showed reduced activity compared to controls ($t(55)=2.36$, $p=0.022$) and premanifest patients ($t(44)=2.01$, $p=0.052$).

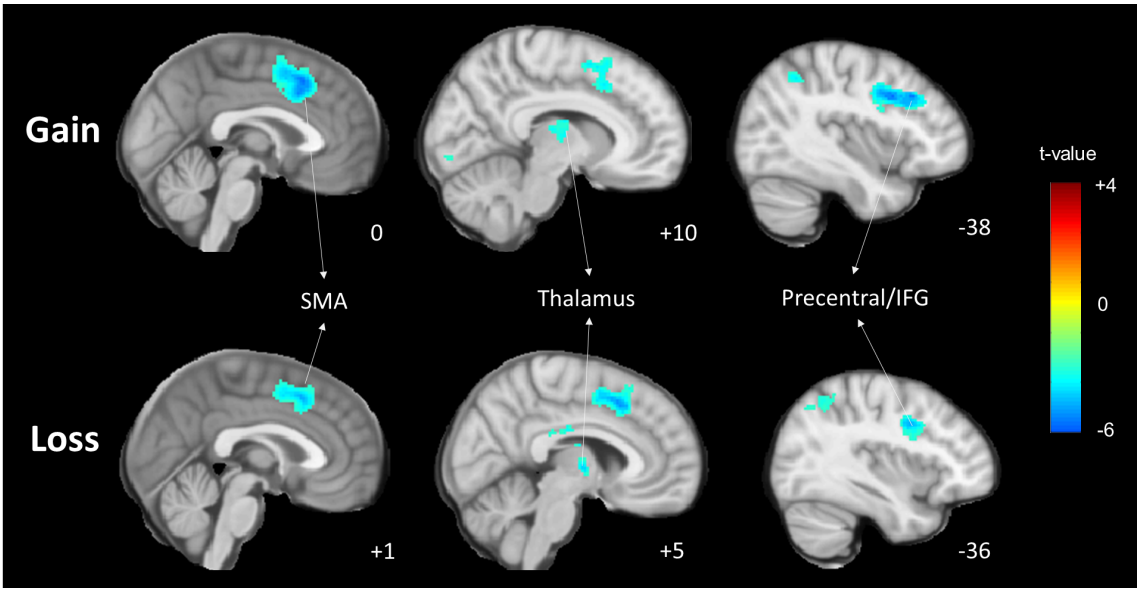

Figure 3.6: **Correlations between apathy and brain activity at the SMA, thalamus and precentral/IFG during the processing of gains (top) and losses (bottom).**

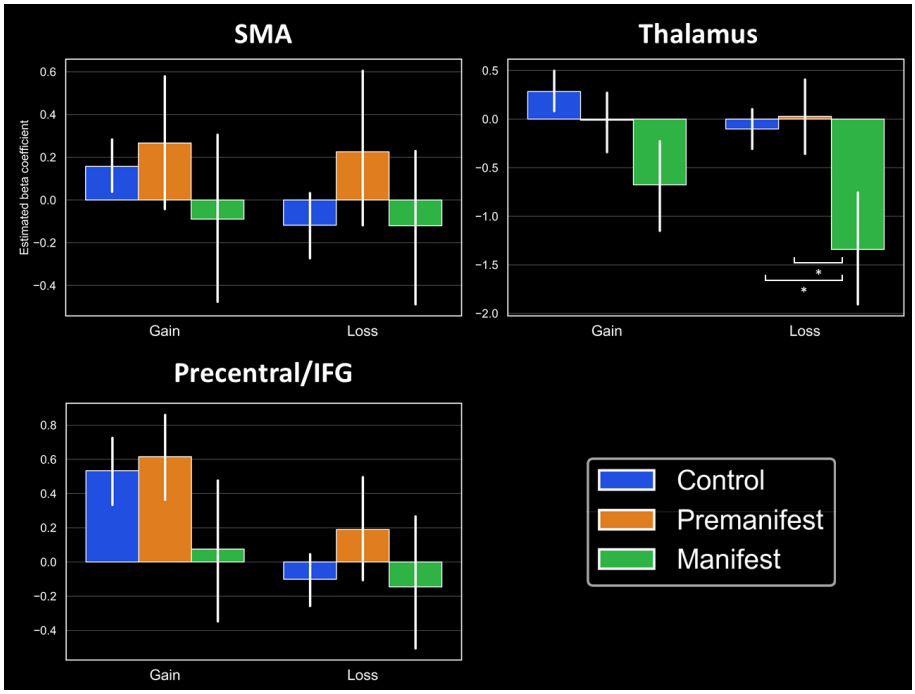

Figure 3.7: **Group differences at the regions found significantly associated with apathy (SMA, thalamus and precentral/IFG) during the processing of gains and losses**. The barplots reflect the mean beta coefficients measured for each group: Controls (blue), premanifest (orange), manifest (green). Error bars indicate the standard error of the mean.

4 Discussion

The present study aimed at investigating the cognitive mechanisms underlying apathy in HD using a gambling task. First, we evaluated the performance of the participants at a behavioral level, where we focused on studying their tendency to make risky choices (i.e. betting to 25 as opposed to 5). Overall, we found no significant differences between groups in their gambling strategy. However, when categorising their bets based on the outcome of the previous gamble, we found that HD patients made less risky choices after trials in which they took a risk and lost, as compared to controls. These results challenge previous findings suggesting that HD patients are less sensitive to punishments (Campbell et al., 2004) and have difficulties to identify negative emotions (Ille et al., 2011; Johnson et al., 2007). Furthermore, other studies have suggested that insensitivity to losses and impulsive decisions only arise at intermediate stages of the disease (Holl, Wilkinson, Tabrizi, Painold, & Jahanshahi, 2013; Watkins et al., 2000). However, in this study we found that both premanifest and manifest HD patients (early and intermediate stages of HD, respectively) show an increased impact to loss.

Based on this effect, we explored whether apathy was modulating the tendency of HD patients to make riskier or more secure choices after failing a risky move. Previous research has shown that insensitivity to loss increases with apathy levels in HD (McLauchlan et al., 2019), and thus, we hypothesized that higher apathy levels would be related to riskier choices. We found a significant negative correlation between apathy and risk-taking behavior. Overall, our data consistently shows that HD patients are more sensitive to punitive events, and that the higher the apathy as measured by LARS self-report, the lower it is the likelihood of making a risky choice. An explanation for these findings could be that, in our case, the global Apathy LARS scale measured mostly cognitive deficits in executive-functioning related to apathy. Difficulties to elaborate behavior towards a goal (in this case, to gain as much money as possible) could explain why these patients produced a more conservative, or "blind", strategy in the task. In fact, the global LARS apathy report measures a combination of three dimensions of apathetic behavior (De Paepe et al., 2019; Levy

& Dubois, 2006), one of them being related to executive-functioning impairments.

Next, we investigated the functional differences during the processing of rewards between Controls and Huntington patients. We first demonstrated that both populations engaged the reward circuit, including areas such as ACC, pMCC, VTA and ventral striatum. Differences in activation in the processing of gains more than losses were further found at several regions. We found that controls elicited increased activations in the ventral striatum and ACC for monetary gains more than losses, whereas premanifest and manifest patients showed similar brain activity when winning or losing a reward. This indicates that in HD patients both rewards and punishments are processed indistinctly in this regions, suggesting a deficit to evaluate the affective value of the stimuli (Haber & Behrens, 2014; O'Doherty et al., 2004). The findings at the ventral striatum are particularly interesting, as neurodegeneration at this region has been previously associated with later stages of HD. Confirming more recent research (Rosas et al., 2005; Thieben et al., 2002; van den Bogaard et al., 2011), our findings suggest a more widespread neurodegeneration of the mesocorticolimbic pathway at early and intermediate stages of HD. Furthermore, we found significant differences at the anterior insula. Manifest patients activated more this region during the processing of losses more than gain trials as compared to controls and premanifest patients. In the context of reward, the anterior insula has been consistently associated with the evaluation of risks to predict possible outcomes (Preuschoff & Bossaerts, 2007; Preuschoff, Quartz, & Bossaerts, 2008). As such, more brain activity in this region during loss trials could imply an enhanced aversion to punishments, only manifested at intermediate stages of the disease. In line with our results in risk-taking behavior, this suggests that HD patients, and in particular manifest patients, evaluate more the risks of obtaining a reward in order to avoid the possible negative events.

We then looked at the differences in brain activity between controls and each HD subgroup (i.e. premanifest and manifest) separately for gains and losses. As compared to controls, we found reduced activity during the processing of gains at the left amygdala and thalamus in premanifest patients, and at the right amygdala and posterior insula in manifest patients. During the processing of losses, we found reduced activity (as compared to controls) at the right amygdala in premanifest patients and caudate nucleus as well as thalamus in manifest patients. Interestingly, we found significant differences in both gain and loss trials at the amygdala and thalamus. Previous research suggests that the amygdala is involved in processing both unpleasant and pleasant events (Hamann, Ely, Grafton, & Kilts, 1999; Phan, Wager, Taylor,

& Liberzon, 2004), thus, our findings imply an impaired processing of rewarding and punishing events at both early and intermediate stages of HD. On the other hand, the thalamus is responsible to integrate and mediate the reward-information to further processing areas (Haber & Knutson, 2010). Therefore, alterations in this region could be due to deficits to integrate rewards and punishments. Overall, these findings imply deficits to process rewards and punishments indistinctly. When looking directly at the differences between premanifest and manifest patient subgroups, we did not find any significant differences, suggesting similar neuroanatomical alterations in both populations related to reward-processing.

When exploring the functional correlates of apathetic behavior at a whole-brain level, we found significant relations during the processing of monetary gains and losses in several regions, including the thalamus, SMA, precentral gyrus/IFG, Middle frontal gyrus, MCC and other parietal and occipital areas. The SMA, thalamus and precentral/IFG showed similar correlations in the processing of gains and losses, presumably because these regions process rewards and punishments indistinctively. As previously mentioned, the thalamus communicates reward information to other brain regions (Haber & Knutson, 2010), being thus unaffected by the valence of the stimulus. In particular, we found a negative relationship between the brain activity in this area and apathy severity, which could reflect impairments in the integration of reward-information in apathetic patients. ROI-analyses showed that these thalamic impairments were more prominent in manifest patients during loss trials, possibly due to a more advanced stage of the disease. Similarly, we found a negative correlation in the SMA and precentral gyrus, regions that are involved in the execution and planning of motor-movements (Le Heron et al., 2019). Thus, apathy in HD could be related to difficulties in the production of motivated behavior, with higher degrees of apathy implying higher difficulties to execute a motor response towards the rewarding stimuli. Again, this appears to go in line with our behavioral results. Apathy in HD may suppress the desire of obtaining rewards through alterations in the SMA, precentral gyrus and thalamus, in turn leading to more conservative responses when faced with a previously unsuccessful risky decision.

Our study included several limitations as well. First, we only included HD patients that were in the early and intermediate stages of the disease. Further studies should investigate the progression of reward-related impairments and apathy at later stages. Also, apathy has previously been related to effortful actions (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001; Mega, Cummings, Salloway, & Malloy, 1997). It would be interesting to investigate the functional correlates of apathy in more nat-

ural reward tasks that require effortful decision-making. An example of this might be the Iowa gambling task (Bechara, Damasio, Tranel, & Damasio, 1997), an experimental paradigm that requires modulating behaviour and making decisions based on rewards. In contrast, our study did not require effortful decision-making, as there were only two choices to make and there was no underlying advantage or disadvantage in each option. However, our study also shows that even in such simple decision-making strategies, apathy significantly influences the behavior of HD patients.

In conclusion, the present study sheds light into the cognitive mechanisms underlying apathetic behavior in HD. We found that monetary losses have a greater impact in apathetic HD patients, which may be explained by disruptions in the SMA, precentral gyrus/IFG and thalamus that lead to deficits in the integration and execution of motivated behavior. Furthermore, we found abnormal activity in the insula in manifest patients, possibly reflecting an enhanced aversion to negative events. We also found differences between HD patients and healthy controls in the ventral striatum, a region that is involved in the affective valuation of rewards. Moreover, neuroanatomical alterations in premanifest and manifest patients were found in the amygdala and thalamus for both gain and loss processing, implying a similar processing of rewards and punishments in these areas. Further research should investigate the functional correlates of reward processing and apathetic behavior in HD or similar prefrontal and basal ganglia disorders. Considering the importance of apathy in so many disorders, we consider fundamental to understand the cognitive mechanisms that result in this motivational impairment. A better understanding of the impact of rewards and punishments in this population, and their functional correlates, could help develop new therapeutic strategies to improve their day-to-day lives.

Statement of contribution

Initials

Dr. Estela Cámara Mancha: **EC**

David Cucurell Vega: **DC**

Iñigo de Vicente: **IV**

- Conceptualization ideas: formulation or evolution of overarching research goals and aims $\Longrightarrow$ **EC**
- Methodology development or design of methodology; creation of models $\Longrightarrow$ **IV, EC, DC**
- Software programming, software development: designing computer programs, implementation of the computer code and supporting algorithms, testing of existing code components $\Longrightarrow$ **IV, DC**
- Investigation: conducting a research and investigation process, specifically performing the experiments, or data/evidence collection $\Longrightarrow$ **EC, DC**
- Formal analysis: application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data. $\Longrightarrow$ **IV**
- Visualization: preparation, creation and/or presentation of the published work, specifically visualization/data presentation $\Longrightarrow$ **IV**
- Writing; original draft preparation, creation and/or presentation of the published work, specifically writing the initial draft $\Longrightarrow$ **IV**

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