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What are the odds? A Functional Imaging Study on Loss Anticipation, Positive Punishment and Negative Reinforcement in Problem Gamblers and Healthy Controls

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If the doors of perception were cleansed everything would appear to man as it is, infinite.

William Blake, The Marriage of Heaven and Hell, 1790

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Glossary

ACC - anterior cingulate cortex

BA - Brodmann area

BOLD - blood-oxygenation-level-dependent

C - matched controls

CBF - cerebral blood flow

DLPFC - dorsolateral prefrontal cortex

EPI - echo planar images

HG - habitual gamblers

MCC - medial cingulate cortex

NAcc - nucleus accumbens

OFC - orbitofrontal cortex

PCC - posterior cingulate cortex

PG - problem gamblers

SMA - supplementary motor cortex

SOGS - Southern Oaks Gambling Scale

VLPFC - ventrolateral prefrontal cortex

YC - young control

1.0 Introduction

1.1 Overview

In everyday life, we need to anticipate and correctly predict future outcomes based on the information we are given. These expectations need to be updated regularly and processed accordingly. In this study, we investigate the neural correlates of anticipation and probability perception during operant conditioning. In addition, we compare problem gamblers (PG) and habitual gamblers (HG), with matched controls (C) and young controls (YC). Gambling participants (HG and PG) appear to be a group in which the anticipatory process may be impaired, explaining their extensive willingness to accept future risk (Potenza, 2008, 2013; Miedl *et al.*, 2010; Gelskov *et al.*, 2016). Interestingly, most investigations of HG and PG have focused on reward anticipation, while this study focuses on loss anticipation. For this purpose, we used the probability of a positive punishment (an electric shock) as a manageable and easily controllable loss stimulus in the laboratory (Berns *et al.*, 2008).

1.2 Operant Conditioning

In the late 19th century E. Thorndike (1898) was the first to describe operant conditioning techniques, a subject that was later extensively studied by B.F. Skinner and other behavioural psychologists. The paradigm of associative learning, also called trial-and-error-learning, is divided in five different outcome possibilities: positive and negative punishment, positive and negative reinforcement, as well as extinction. Generally, punishment has been described to decrease behaviour by adding a punishment stimulus (positive punishment), for example by the use of an electrical shock electrode, or removing an appetitive stimulus (negative punishment). Reinforcement, however generally increases behaviour and is based on the adding of a positive stimulus comparable to a reward (positive reinforcement), while the subtraction of a negative stimulus (e.g. electrical shock) will result in a negative reinforcement outcome.

Furthermore, extinction may occur when previously reinforced or punished behaviour is no longer rewarded by the above reinforcement techniques (Kandel, Schwartz, Jessel, 1991; Jean-Richard-Dit-Bressel, Killcross and McNally, 2018).

1.3 Loss and Reward Anticipation

The distinction between loss and reward anticipation at the spatiotemporal level is still a matter of research, since both appear to activate similar neural networks (Watson *et al.*, 1999; Berns *et al.*, 2008; Knutson and Greer, 2008; Balodis *et al.*, 2012). Furthermore, the operant modality of an outcome (positive and negative reinforcement, positive and negative punishment, and extinction) may drive the anticipation process. However, most studies use positive reinforcement as a reward stimulus; less frequently, positive or negative punishment is used as a loss stimulus. All of the above modalities share associations with the orbitofrontal cortex (OFC), the ventromedial and dorsomedial prefrontal cortex, the nucleus accumbens (NAcc), the anterior, medial and posterior cingulate cortex (ACC, MCC and PCC), the insular cortex, the amygdala, and the ventral tegmental area as well as with the raphe nuclei (Knutson and Greer, 2008; Liu *et al.*, 2011; Nakamura, 2013; Macoveanu, 2014; Dugré *et al.*, 2018). Yet, for paradigms involving an outcome of positive or negative punishment, i.e., loss anticipation, previous reports stress the importance of the medial cingulate cortex (Shackman *et al.*, 2011; Dugré *et al.*, 2018).

1.4 Prospect Theory

According to prospect theory, subjects tend to overweight small probabilities and underweight high probabilities of an outcome in behavioural experiments (Kahneman and Tversky, 1979). Among others, Drazen Prelec mathematically formalized the weighting function of prospect theory in 1998. The Prelec function describes the relationship of decision weight *w(p)* to loss probability *p* by an inverted S-shaped function. Albeit widely accepted, the biological manifestation of prospect theory, which has often been studied using functional imaging techniques, is still a matter of research because the theory does not account for all situations, leaving the previously suggested linear model of expected utility still in the running (Trepel, Fox and Poldrack, 2005; Preuschoff, Bossaerts and Quartz, 2006; Schultz *et al.*, 2008; Hsu *et al.*, 2009; Rudorf, Preuschoff and Weber, 2012; Bossaerts and Murawski, 2015). For example, Preuschoff *et al.* (2006) showed a linearly increasing BOLD response to probability in the ventral striatum and putamen. This would implicate a processing relating to the expected utility hypothesis. However, Hsu *et al.* (2009) described a nonlinear activation pattern according to the probability of a rewarding outcome in the striatum, supporting the behaviourally described prospect theory. Moreover, a quadratic relationship between brain response and probability comprehension was described (Preuschoff, Bossaerts and Quartz, 2006; Tobler *et al.*, 2007; Rudorf, Preuschoff and Weber, 2012). Based on the processing of probabilities, these findings add a further dimension to the anticipation of an outcome. Most recent studies, however similar in models and in the general perception of probability processing, solely investigate reward anticipation, while loss anticipation is overlooked.

1.5 Problem Gambling

Gambling disorder is currently the only behavioural addiction listed in the DSM-V (2013) and therefore appears as the prototypical model for behavioural addictions. It is widely recognised as a problematic public health issue, with substantial personal and social costs, poor physical and psychiatric health, elevated suicide rates and other comorbidities (Cowlishaw *et al.*, 2012). Currently, estimates of worldwide adult prevalence range from 0.2 to 5.3 %, varying across screening instruments and methods

used, as well as accessibility and availability of gambling opportunities (Hodgins, Stea and Grant, 2011). While the DSM-V includes individuals to have a gambling disorder when they meet 3 or more diagnostic criteria, the term PG may be used as a broader term at a lower threshold, also including the previously used terms of pathological gambling and disordered gambling (Nautiyal *et al.*, 2017).

Even though the pathophysiology of PG is not fully understood, research describes a distinct phenotype of affected individuals. They include risky decision-making, increased impulsive behaviour, increased sensation seeking, increased compulsivity, the occurrence of cognitive distortions, as well as an altered reward sensitivity (Rogers *et al.*, 1999; Preuschoff, Bossaerts and Quartz, 2006; Balodis *et al.*, 2012; Gelskov *et al.*, 2016).

With these concepts in mind, problem gambling appears as a perfect model in which individuals frequently show risky and uncertain behaviour in the estimation of future outcomes. Concurrently, there is strong evidence for functional differences at the molecular and macroscopic levels in brain regions that are relevant to both loss and reward anticipation (for review see Potenza, 2008; Miedl *et al.*, 2010; Choi *et al.*, 2011; Brevers *et al.*, 2016; Ring *et al.*, 2018). We included HG in our study in an attempt to compare their neural response during anticipation with that of the non-gambling participants (C and YC) and PG. To our knowledge, comparatively few studies have addressed gambling pathology and the concept of anticipation in a single study involving a large sample of participants.

1.6 Scientific Questions

Here, we present our findings regarding loss anticipation via positive punishment using event-related fMRI. The findings are based on the subjects' participation in a card game that uses an aversive electric shock stimulus and on a behavioural approach inspired by our previous publications (Ring and Kaernbach, 2015; Ring *et al.*, 2018). Do we process aversive contingencies of decisions in a nonlinear manner, according to the Prelec function? How does the brain compute the probability of an outcome? Which brain regions process certainty or uncertainty for negative outcomes? How do individuals with problematic gambling habits differ in these entities, and can we see a grading among non-gambling subjects, HG, and PG?

2.0 Methods

2.1 Participants

In total, our sample consisted of 88 subjects who fully participated in the study, and 83 subjects (mean age (M)= 36.18, standard deviation (SD)= 14.3, Median= 30 years) eligible for further analysis. For one participant, the MRI data was lost due failure in data handling, another was not eligible for further participation due to excessive alcohol consumption and one aborted the experiment because of health problems. For the remaining two subjects, data had to be discarded due to extensive head movements in the scanner. All participants were German native speakers and had no history of psychiatric or neurological disorder. Study proceedings were in accordance with the latest revision of the declaration of Helsinki (*WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects*, 2013) and approved by the Ethics Committee of the University Hospital Kiel (AZ.: A 106/14).

We recruited 40 gamblers through advertisement in the local newspaper and flyers in the casino. A clinical psychologist conducted a semi-structured interview for impulse control disorders, used and written by the Department of Neurology at the University Hospital Kiel (Probst *et al.*, 2014). Additionally, participants filled out a self-reporting Southern Oaks Gambling Screen (SOGS) (Lesieur and Blume, 1987). Based on the two measures we were able to divide the gamblers into a group of 22 PG (mean age (M)= 39.45, standard deviation (SD)= 15.47, Median= 38 years, two self-reported left-handed) and 18 HG (mean age (M)= 38.33, standard deviation (SD)= 13.76, Median= 37 years). Additionally we recruited 23 healthy, two left-handed, matched C (mean age (M)= 41.43, standard deviation (SD)= 15.07, Median= 42 years) and a sample of 20 Y (mean age (M)= 25.14, standard deviation (SD)= 3.03, Median= 24 years), both with no previous history for problematic or pathological gambling habits.

2.2 Experimental Design and Procedure

All subjects underwent the same general study procedures. Y additionally received an electroencephalography to the fMRI discussed elsewhere. The study procedure consisted of one or two appointments, depending on whether the first screening procedure and demographic data collection were done at home. Participants who took part in the experiment completed questionnaires and received a description of the study procedure before the appointment.

Before the start of the experiment, participants gave written and informed consent. They answered questions about demographics, neurological and psychiatric disorders, mood, alcohol, drug consumption. Subsequently, subjects were screened with a semi-structured interview for impulse control disorders and SOGS. Exclusion criteria for the study were problematic alcohol or drug consumption (alcohol: more than 1 unit (0.33 l beer, 0.2 l wine or 0.02 l hard liquor) per day; other drugs: more than once a week) and a history of psychiatric or neurological disorder.

The present experiment was part of a larger study and also comprised a behavioural and EEG-measurement. EEG data with a similar paradigm structure is reported elsewhere. To avoid confounding, the order of EEG- or fMRI-measurements was counterbalanced. In between EEG and fMRI measurements, subjects answered questions regarding time preferences of money gain and played financial risk lotteries for behavioural measure.

Preceding the start of the Experiment, we determined the strength of electric shocks that served as punishment in the paradigm. Attached to the phalanx of the second and third toe of the right foot, electric shocks were given via Ag-AgCl electrodes with a diameter of 10 mm. The stimulator (Rehastim, HasoMed GmbH, current = 0-126 mA, pulse width = 500 microseconds, frequency = 100 Hertz (Hz)) was placed outside the scanner and connected to the electrodes by BNC cables approved for usage in the scanner. Subjects were told to give feedback about their perception of the strength of the shock. Starting at the lowest shock strength, we slowly increased the strength until the subject indicated a painful stimulus. To create an unpleasant, but not painful shock perception, we used the previous level as the standard adjustment for the following experiment.

2.3 Paradigm Structure

The paradigm is a modified version from Preuschoff, Bossaerts & Quartz (2006). It has been successfully used to show differences in skin conductance response depending on punishment probability in a prior study (Ring and Kaernbach, 2015; Ring *et al.*, 2018).

Our paradigm was programmed using Matlab 7.1 (Math Works Inc., Natwick, U.S.A.) and the software package Psychtoolbox-3 (www.psychtoolbox.org). The card game was based on a set of 10 covered cards containing all numbers from 1 to 10. The participant, as well as the computer drew a card and depending on the bet type, the higher or the lower drawn card won. This was all explained to the participant prior to the experiment.

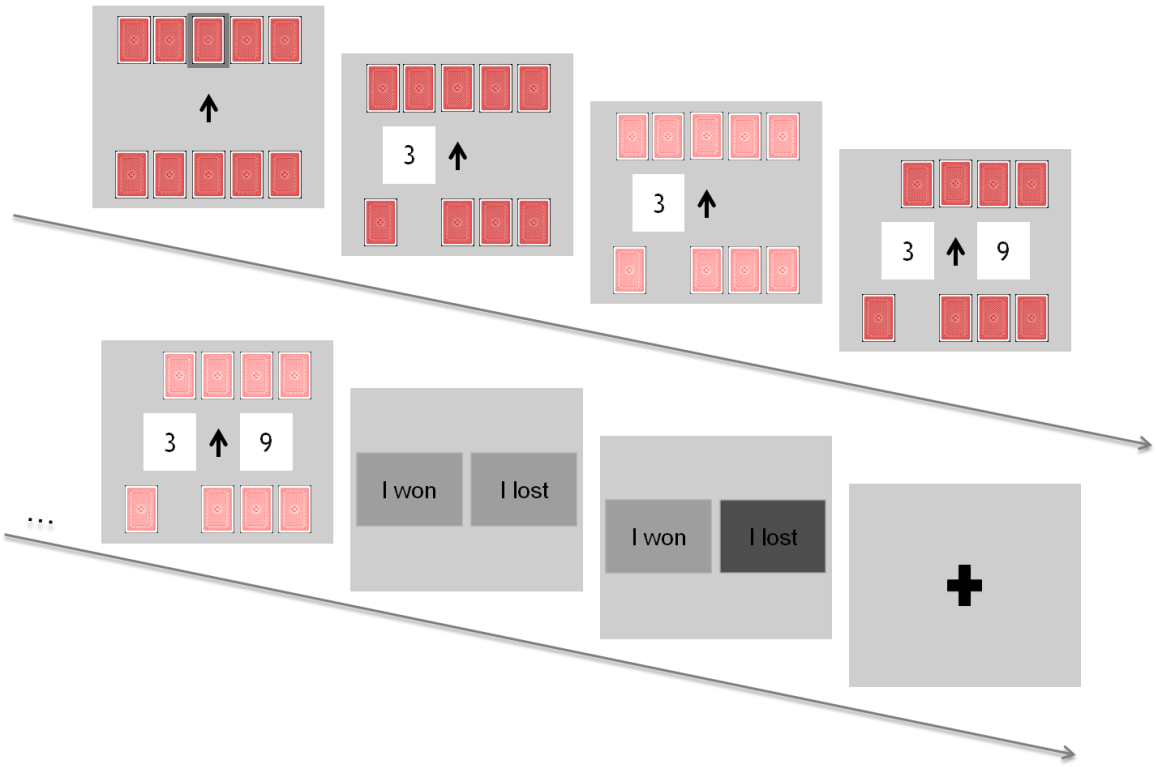

Figure 1: Paradigm Structure. After participants actively choose a card, a second card is chosen by the game, both in pseudo-randomized manner. Based on the indicating arrow, the lower or higher card wins the trial (in this case the participant loses, since the card he chose is lower, and the arrow indicates that the higher card wins). We were particularly interested in the anticipation phase, when participants are able to calculate the odds of winning or losing a trial.

Each trial began by presenting the covered set of 10 cards in 2 rows and an arrow (↑ or ↓, with equal frequency) indicating whether the higher or the lower drawn card was going to win the trial. Arrow key presses enabled the participants to choose a card from the covered set of 10 cards for the bet. If the participant took longer than three seconds, the first selected card was chosen. The card was turned around and moved to the centre of the screen (mean= 1250ms, range= 1000 – 1500), which revealed the probability to win or lose the bet. For instance, a bet type indicating "high card wins" (↑), while the participant drew a 10, the win was sure. If instead the drawn card showed a 7 the probability to loose was 3/9 (nine cards left, three are higher than 7). Consequently, there were 10 different probabilities of losing: p=0, p=0.12, p=0.22, p=0.34, p=0.44, p=0.56, p=0.66, p=0.78, p=0.90 and p=1. Subsequently, the computer chose a card from the remaining set of cards (after a jittered interval, mean = 7s, range= 5 to 9.5s) and placed next to the first card chosen by the participant. It was turned around (duration ~1000ms) and shown for approximately 6 seconds (range= 3 to 9s). If a trial was lost by the participant, he received an electric shock in 50 per cent of the cases at the instant the second card was revealed. To avoid habituation, participants were explicitly informed, that for the remaining 50 per cent of the cases, the electric shock was absent. For the instance of a won trial no punishment followed in a 100 per cent of cases. A control question was shown after each trial, asking the subject whether the trial was won or lost. An electric shock was applied, if the participant failed to answer the question correctly within 3 seconds. Then, a fixation cross was shown for a mean of 4.17 seconds (jittered interval, range= 2 to 3s, except in four trials for 15s), followed by the next trial.

Participants were informed that each trial consisted of a new random order of 10 cards, indicating no possibility to know which card would be drawn next. They each played three sessions consisting of 30 trials, each lasting 12.68 minutes during which fMRI acquisition took place. To ensure enough trials per probability level, we predetermined and pseudo-randomized the values of the drawn cards. This resulted in three trials per cases for each probability per session, as well as 15 losses and 7 or 8 shocks per session.

2.4 Financial Risk Elicitation Task

Amongst other behavioural measurements, participants played a paper-based lottery task knowing that their reimbursement for participation would be partially based on the outcome of the game. The task was proposed by Vieider et al. (2015) and elicits, as indicated by the name, a risk assessment during binary monetary lotteries and various sure monetary outcomes. It enabled us to separately measure risk attitudes in the gain domain, loss domain, calculate probability weights in both domains, as well as the degree of loss aversion. For the purpose of this study, we used these probability weights for further modelling with the BOLD-contrast. Paradigm structure and further results can be found in our previous publication (Ring *et al.*, 2018).

2.5 Functional Magnetic Resonance Imaging (fMRI)

Our experiment rests upon the principals of functional imaging of the brain via fMRI, a method based on the idea that regional cerebral blood flow (CBF) may reflect neuronal activity. Ogawa et al. (1990) were the first to directly describe the effect by using a contrast they coined as blood oxygenation level dependency (BOLD). The contrast is based on the physical differences of haemoglobin in its magnetic properties. While deoxyhaemoglobin is an endogenous paramagnetic agent, haemoglobin is diamagnetic. Changes in concentration in the cerebral vascular system then lead to differences in MRI signal intensity and provide an indirect measure for brain activity (Kim and Bandettini, 2006). Although the theoretical formulation was clear, it was not until 2001 that Logothetis and colleagues described a direct relationship of the local field potential generated by neuronal activity and the BOLD contrast and thereby verified its use as an indirect measure for a neural signal.

2.5.1 Regression Analysis and the General Linear Model (GLM)

In the present study, fMRI data analysis is based on the principle of model testing. Regression analysis offers an approach that rests on the timing and duration of an evoked neural response, usually through a controlled event. It assumes that the observed data (y) is composed of two sources, a linear combination of regressors (x_i), together with its variable parameter weighting (β_i), as well as the residual noise or error in the measurements (ε). The involvement of all factors, held constant throughout the experiment, is depicted in the total parameter weight β_0 (Huettel, Song and McCarthy, 2014). The regressors (x_i) correspond to retrieving of memory, visual processing, head movement during the scan, age and gender. As for the present study, among others the participant's keypress was implemented in the design. The basic formula for regression analysis

$$\mathbf{y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n + \varepsilon}$$

depicts how the single factors contribute to the observed data (y). By the use of this model, it is possible to minimize the error term and ideally isolate the contribution of the hypothesized evoked response. Eventually, the statistical significance of a regressor is determined by the amount of variability it explains (when multiplied with its parameter weight) and compared to the amount of variability that is explained by the error term (Huettel, Song and McCarthy, 2014).

The statistical approach to separate the regressors in data sets with many dependent variables is implemented in the GLM. Among others, Friston et al. (1995) proposed the implementation of the GLM for MRI usage. The statistical test postulates that a linear combination of different model factors, together with uncorrelated noise, contribute to the experimental data. Therefore, with MRI data, the unidimensional formula given above is replaced by two-dimensional formula given in figure 2. The **data matrix (Y)** is comprised of time points (*n*) and voxels (*V*). The **design matrix (G)** consists of time points (*n*) and regressors (*M*) and specifies how model factors change over time. The **parameter matrix (β)** contains voxels (*V*) and parameter weights (*M*), resulting in a specification of β-weight for each voxel. At last, the **error matrix (ε)** depicts the error in measurement for the two-dimensional space with time points (*n*) for each voxel (*V*). While the experimental data is obtained during the experiment, the parameter weights and residual error are calculated during the analysis. However, for the design matrix regressors must be chosen by the experimenter, based on the previously formulated hypothesis.

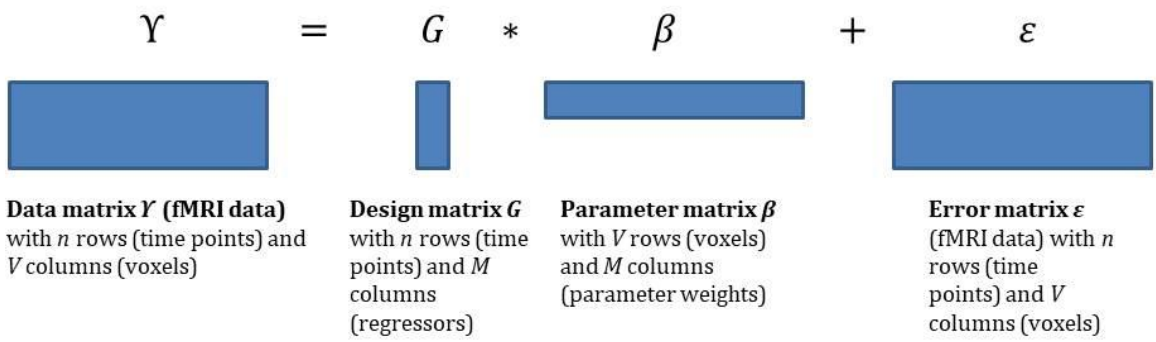

Figure 2: The basic elements of the GLM based on a figure from Huettel *et al.* (2014). The data matrix Y comprises the original fMRI data and is dependent on the design matrix (G), the parameter matrix (β) and the error matrix (ε). While the simple regression model is based on a unidimensional approach, the GLM uses a two-dimensional space to meet the statistical requirements of the fMRI.

2.5.2 Image Acquisition

Images were obtained in the Neurocenter at Kiel University hospital using a 3 Tesla whole-body MRI scanner (Achieva; Philips, Best, the Netherlands). A 32-channel head coil was used to acquire 310 T2*-weighted whole brain echo planar images (EPI) per fMRI session. Repetition time (TR) was 2500 ms, echo time (TE) = 35 ms, flip angle (FA) = 90° and field of view (FOV) = 216 x 216 mm. Each EPI had 38 slices with a 64 x 64 matrix and a slice thickness of 3mm (plus an inter-slice gap of 0.3 mm). Additionally, T1- and T2-weighted structural images were acquired for each subject.

For the fMRI measurement, participants received ear plugs to protect them against the scanner noise. The presentation of stimuli was achieved via a MR-compatible VisualSystem from NordicNeuroLab with integrated vision correction.

2.6 fMRI Analysis

For the fMRI analysis, we used Statistical Parametric Mapping 12 (SPM12, Wellcome Department of Cognitive Neurology, London, United Kingdom) implemented into Matlab 14a (Mathworks Inc., Natick, U.S.A.).

2.6.1 Preprocessing

Due to unsatisfactory coregistration of EPI images to the bias-corrected T1 image, we used a different approach to prepare our data for statistical analysis. First, EPI images were resliced and realigned to correct for head motion. Second, we normalized the EPI images to an EPI template provided by SPM. The normalized fMRI images were then spatially smoothed in the x, y, and z axes (Gaussian kernel of 8 mm, full-width at half-maximum)

2.6.2 1st Level Analysis

At the 1st level, we modeled the BOLD-signal with a general linear model including 26 regressors, according to the events of the paradigm. The onset of all cards for selection was parametrically modulated by the number of key presses to choose a card (regressor nr. 1 and 2). Second, the analysis contained all separate probability levels for losing the trial, p(L), revealed at card one as 10 separate conditions (nr. 3 – 12). Next, the onset of the second card was divided into 3 conditions: Loss without shock, loss with shock and win, each parametrically modulated by the *a priori* probability of the respective outcome (nr. 13 – 18). Additionally, we included the answering of the control question as a condition and modulated it with the according keypress (nr. 19 and 20). At last, movement parameters from realignment were entered as separate regressors (nr. 21 – 26) (Friston *et al.*, 1996).

2.6.3 2nd Level Statistical Group Analysis

For the 2nd level statistical group analysis, contrasts of interest were set up for:

1) first card shown (weight of 1 for all regressors, independent of the probability level)

2-11) separate contrasts for each probability level to lose p(L)= 0, 0.12, 0.22, 0.34, 0.44, 0.56, 0.66, 0.78, 0.9, 1.0 (e.g. for the average BOLD-response in trials with the loss probabilitiy of 50%, a contrast weight of 1 would be placed at the regressor for p(L)=0.5)

12) low loss probability p(L) = 0.12, 0.22, 0.34 (weight of 1 for each of those regressors)
13) medium loss probability p(L)= 0.44, 0.56, 0.66 (ditto)
14) high loss probability p(L)= 0.78, 0.9, 1.0 (ditto)
15) high versus low loss probability (1 on p(L) = 0.78, 0.9, 1.0, -1 on p(L) = 0.12, 0.22, 0.34)
16) high versus medium loss probability (accordingly)
17) medium versus low loss probability (accordingly)
18) linear function, based on the ideas of the expected utility theory (Von Neumann and Morgenstern, 1944; Knutson and Peterson, 2005; Abler *et al.*, 2006; Tobler *et al.*, 2007) (weights see table 1)
19) quadratic function as a correlate for certainty (Preuschoff et al. 2006) (weights see table 1)
20) Prelec function (1998), based on our behavioural data from the lottery game of PG, HG and Controls (Figure 3, Ring et al. 2018) (weights see table 1)

Table 1: Contrast weights vectors for the linear function, certainty function, and the Prelec function according to each probability level to lose p(L) for each 1st level regressor.

Probability level p(L)	**0**	**0.12**	**0.22**	**0.34**	**0.44**	**0.56**	**0.66**	**0.78**	**0.9**	**1.0**
Linear function weights (contrast 18)	9	7	5	3	1	-1	-3	-5	-7	-9
Certainty function weights (quadratic, contrast 19)	6	2	-1	-3	-4	-4	-3	-1	2	6
Prelec function weights (contrast 20)	8.9	5.1	3.3	1.8	0.5	-0.7	-1.9	-3.2	4.7	-9.1

We were interested in generalized effects of probability processing during anticipation of a negative outcome. The probability weighting functions by Prelec (1998)

$$w(p) = exp(-\beta(-ln\ p)^{\alpha})$$

were fitted from choice data of PG, HG, and C using non-linear estimation techniques. The procedure and results are described in Ring et al. 2018. As we did not find evidence for systematic differences in the loss domain, we used the same probability weighting function in all groups. The resulting decision weights were used as the weights vector for the corresponding BOLD-contrast of the objective probability level p(L), as shown in contrast 20. This was compared to the results with linear probability weighting of contrast 18. To increase validity and the size of the sample we extended our statistical model with group Y that did not contribute behavioural data for non-linear estimation. Previous metanalysis have not shown any differences in risk assessment regarding the age (Mata *et al.*, 2011). Yet, to omit confounding of the age disparity of Y compared G, HG and C, an ANOVA confirmed no significant group differences in the contrasts of interest.

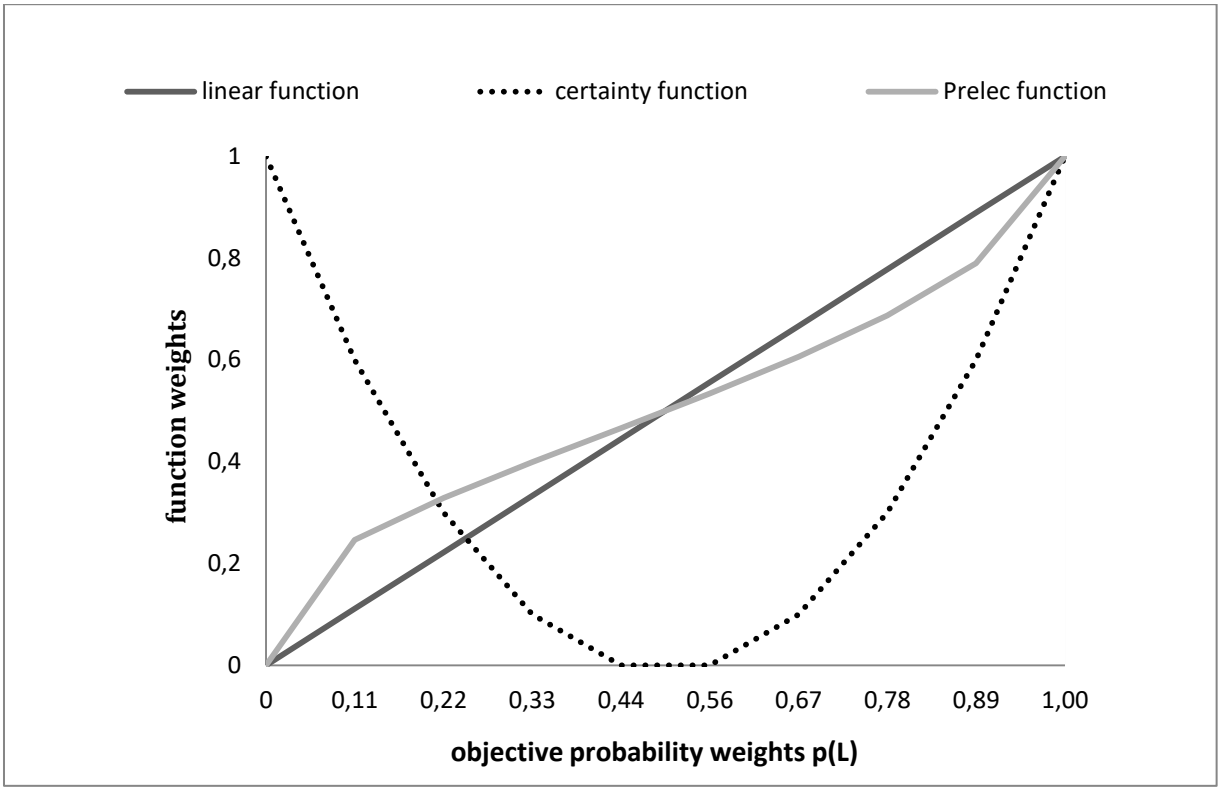

Figure 3: The black line shows the linear function model used in contrast 18 of a monotonical increase in function weight, according to the objective probabilitiy. Similar to Preuschoff et al. (2006), certainty of the outcome (1/risk) was implemented as u-shape function (contrast 19). The grey line depicts the modelled probability weighting function by Prelec (1998) (contrast 20), as found in our behavioural data (Ring et al., 2018).

Furthermore, we were interested in the perceptive correlates of uncertainty, based on previous assumptions stated by Preuschoff et al. (2006) who depicted this uncertainty as a form of risk. They hypothesized a quadratic relationship of reward probability and risk (i.e. uncertainty) with minimum values at p(L) = 0 and p(L) = 1, and a maximum value at p(L) = 0,5. Due to the nature of our paradigm we expected a similar activation for our participants. We extended this relationship to the inverse quadratic relationship (U-shape function, minima at p(L) = 0, p(L) = 1 and minima at p(L) = 0.5) to model the converse sensation of certainty. Hence, objective probability weights at p(L) = 1 and p(L) = 0 should produce a subjective expectation and certainty of the trial outcome (certain loss or no loss, contrast 19 and figure 3). Similar to the modelling of the Prelec function, we fitted the quadratic function to the fMRI data during the anticipation of the trial outcome.

3.0 Results

3.1 Task Performance

The participants won in 50.09% +/- 1.7% of all trials and reported the outcome (won or lost) correctly in 97.92% +/- 3.23% of the cases. In 22.35% +/- 0.72% of all trials, the participants received a shock. For the correctly reported outcome, group comparison did not show any significant differences, indicating good overall compliance with the paradigm for both the gambling and control groups (chi2-test, $p<0.05$).

3.2 Southern Oaks Gambling Scale

The SOGS was recorded for the HG, PG and C. It proved to be a valid measure for detecting gambling participants and confirmed the outcome of the semi-structural interview for impulse control disorders. On the SOGS scoring system (0 = no problem with gambling, 1-4 = some problems with gambling, > 5 = probable PG), the participants in the PG group scored a median of 8.5 (mean 8.73 +/- 3.9), those in the HG group scored a median of 3.5 (mean 3.12 +/- 2.52), and the controls scored a median of 0 (mean 0.22 +/- 0.6) (Lesieur and Blume, 1987). The Kruskal-Wallis test and post hoc pairwise comparison using Dunn's test revealed significant differences between the groups ($p<0.05$, Bonferroni corrected).

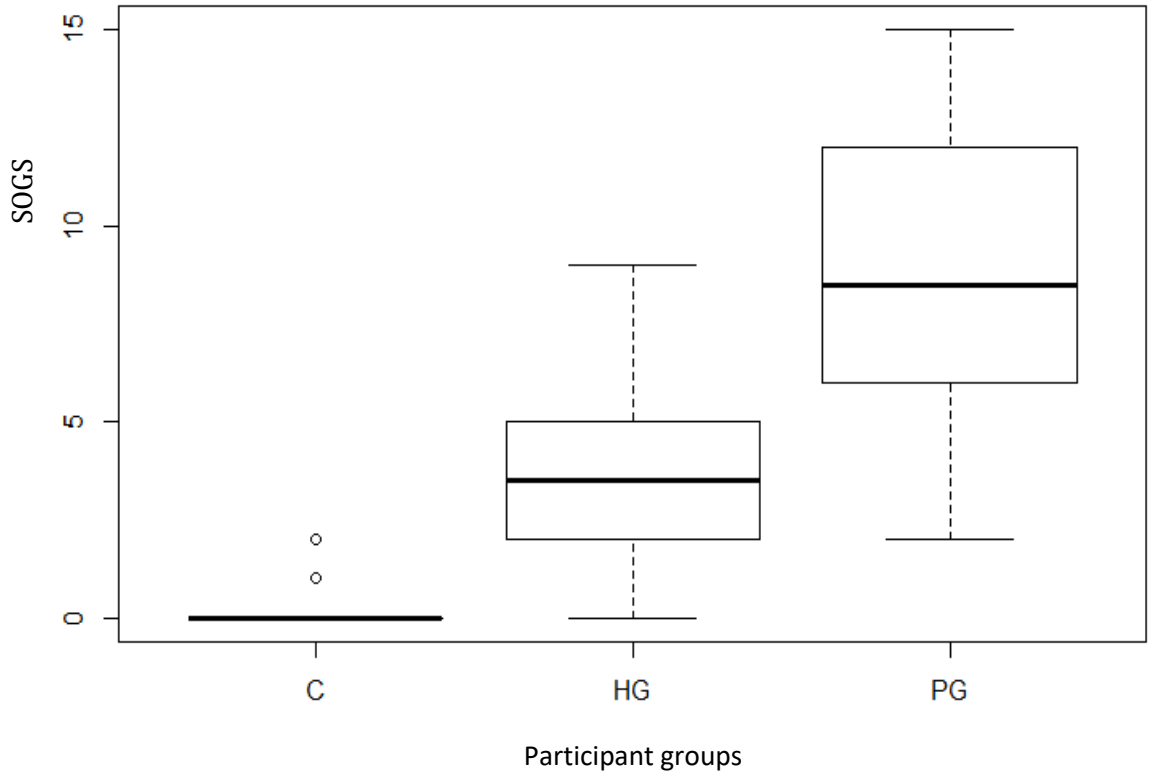

Figure 4: Self-reported SOGS as a valid measure for problem gambling (Lesieur and Blume, 1987). The figure depicts the sum-score on the y-axis and the participant groups on the x-axis.

3.3 fMRI Results

3.3.1 Identification of Loss Anticipation Effects (contrast 1)

We used event-related fMRI to investigate the neural response during the anticipation of a negative stimulus. After revelation of the first card, the participants were able to assess the probability of winning or losing the trial and, in case of a loss trial, subsequently received an electric shock. This general effect of anticipation resulted in strong event-related activation in a number of brain regions. The cerebellum, bilateral insula, anterior and posterior cingulum, bilateral middle frontal gyrus, bilateral ventral striatum, thalamus, amygdala, SMA and fusiform gyrus showed significant BOLD responses (Figure 5, Table 2; $p<0.05$, FWE-corrected).

We were also interested in the decrease in brain activity during loss anticipation. A decrease in BOLD signal intensity was observed in regions such as the anterior and medial cingulum as well as in the OFC, the left medial temporal lobe and the precuneus. Furthermore, activity in the SMA and the postcentral gyrus was decreased.

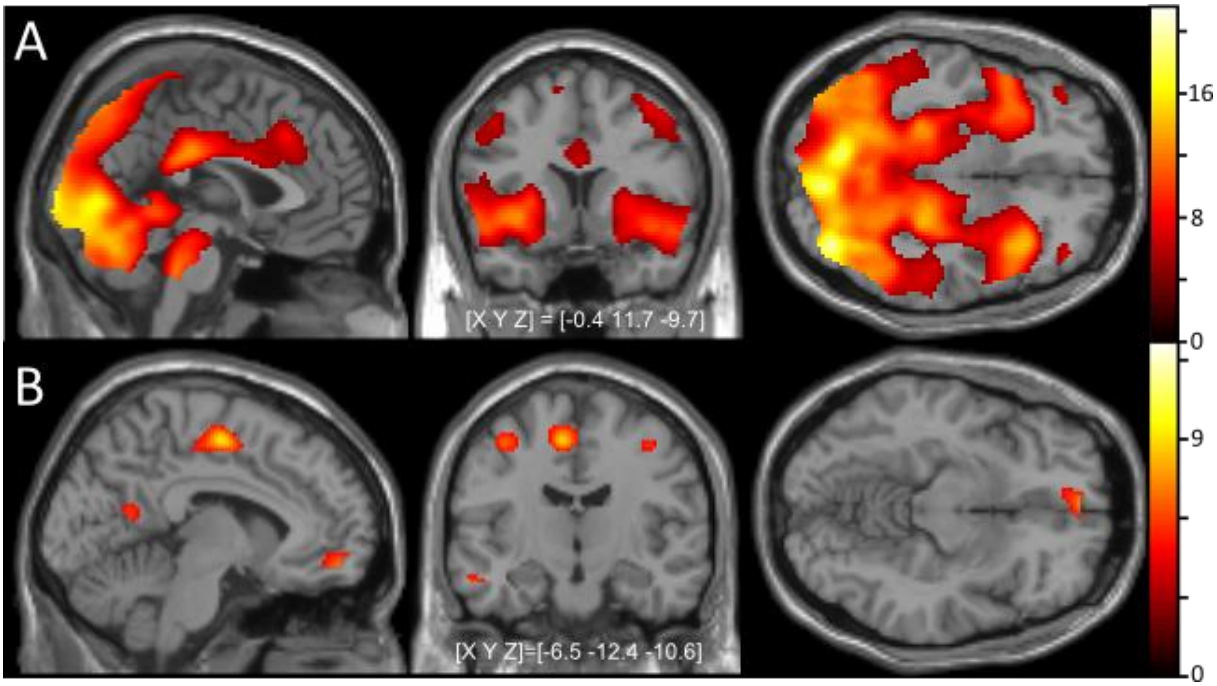

Figure 5: A: Areas with increased and **B:** decreased BOLD response after revealing the first card, in anticipation of the trial outcome (contrast 1, $p<0.05$, FWE-corrected). The colour indicates regional t-values according to the reference scale.

Table 2: Anticipation after revealing the first card (contrast 1, p<0.05, FWE-corrected)

AAL label **Increase in BOLD-response**	**side**	**X**	**Y**	**Z**	**t-value**
cerebellum	R	44	-70	-18	21.6
anterior insula	R	38	22	-10	14.43
anterior insula	L	-36	16	-6	13.96
PCC	/	0	-26	30	13.02
	L	-3	-26	31	11.46
	L	-6	-26	35	6.33
medial frontal gyrus	R	46	28	34	10.96
	R	46	44	16	10.75
	R	48	36	24	10.27
putamen	L	-24	16	-1	9.62
thalamus	R	14	-25	4	8.49
amygdala	L	-26	0	-16	8.08
ACC	R	2	26	38	8.01
	R	6	32	32	7.45
putamen	R	28	-4	10	7.98
PCC	R	8	-26	34	7.97
thalamus	L	-14	-8	2	7.29
amygdala	R	26	0	-18	6.91
SMA	L	-6	4	70	5.53
	L	-10	14	62	5.19
fusiform gyrus	L	-30	-4	-38	5.23

AAL label **Decrease in BOLD-response**	**side**	**X**	**Y**	**Z**	**t-value**
postcentral gyrus	L	-36	-24	54	12.69
SMA	L	-8	-8	56	9.61
SMA	R	10	-2	56	7.12
precuneus	R	22	-44	12	7.88
precuneus	L	-10	-58	14	6.3
temporal inferior gyrus	L	-50	-6	-28	7.35
OFC	L	-4	54	-12	7.28
precentral gyrus	R	40	-10	52	6.24
ACC	R	2	34	-4	5.22

3.3.2 Linear function, Prelec function and Certainty (contrasts 12, 13, and 14)

Our main interest was in determining which regions are involved in probability processing during anticipation of a negative stimulus. Due to our experimental design, we were able to finely map 10 events based on the probability of the outcome. Accordingly, we followed the activation patterns after revelation of the first card corresponding to loss probabilities of 0% (p(L)=1), 12%, 22%, 34%, 44%, 56%, 66%, 78%, 90%, and 100% (p(L)=10). Based on the behavioural data obtained from the PG, HG and C in the lottery game, we modelled a nonlinear function according to Prelec (1998) for all groups, depicting activation in brain regions that followed the Prelec function. We found that there was a positive correlation with increasing probability of losing in the SMA, the ACC ($p<0.05$, FWE-corrected), the inferior frontal gyrus, the supramarginal gyrus and the dorsolateral prefrontal cortex (DLPFC) ($p<0.001$, uncorr.). In addition, a strong negative correlation with the nonlinear model according to Prelec was found for the occipital cortex, the bilateral caudate, the superior and middle frontal gyrus, the OFC, the putamen and DLPFC and the frontopolar prefrontal cortex (Tab. 3). However, we found that for anticipation of an aversive stimulus, both the linear and the Prelec function could explain the brain activation (FWE-corrected, $p<0.05$, Table 3). A paired t-test could not separate the BOLD contrasts adequately, leaving our question regarding linear and nonlinear processing partially unanswered. Based on the assumption that uncertainty (or risk, according to Preuschoff et al. 2006) or certainty of a reward may be depicted by a quadratic function, we modeled a U-shaped function for further investigation. No significant results were found in the domain of uncertainty, while the negative correlation (certainty = (1/uncertainty)) was correlated with strong activation in the bilateral insula, the OFC, the ACC, the PCC, the frontopolar prefrontal cortex, and the angular gyrus ($p<0.05$, FWE-corr., Table 3). Figure 6 shows the 2nd-level results in the relevant brain regions; they follow the Prelec function (green and red) or certainty (cyan) when peak activation is mapped as a function of the probability of losing.

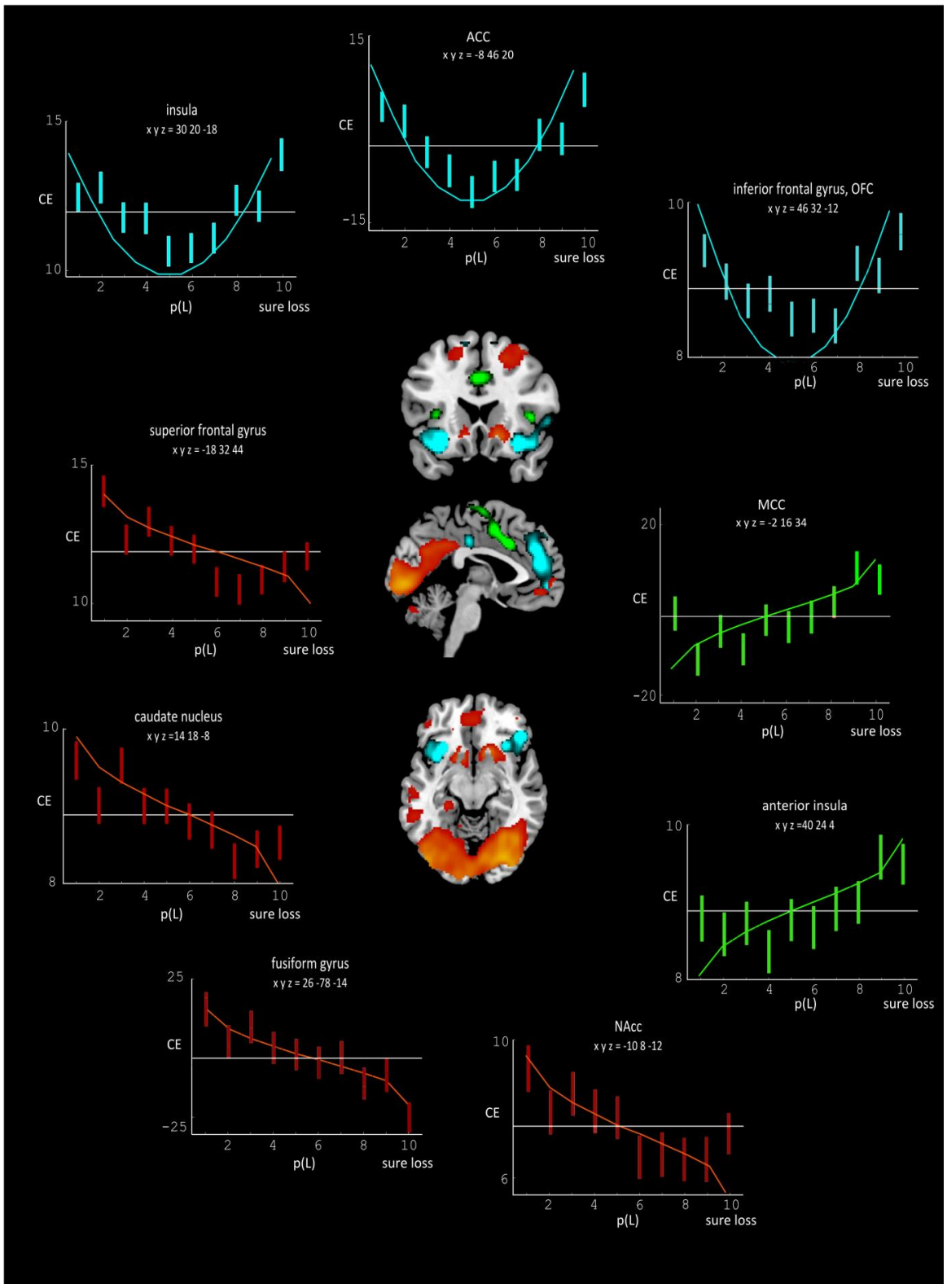
insula
x y z = 30 20 -18
ACC
x y z = -8 46 20
inferior frontal gyrus, OFC
x y z = 46 32 -12
superior frontal gyrus
x y z = -18 32 44
MCC
x y z = -2 16 34
caudate nucleus
x y z =14 18 -8
anterior insula
x y z =40 24 4
fusiform gyrus
x y z = 26 -78 -14
NAcc
x y z = -10 8 -12
CE
p(L)
sure loss

Figure 6: Differential model according to the Prelec funtion (positive correlation orange and negative correlation green) and quadratic function (cyan) via t-test during probability processing for a negative stimulus (all FWE-corrected, $p<0.05$, except insula*, x y z = 40 24 4). Probability levels itemized according to its corresponding regions, thru flexible factorial model. The orange and green plots show activation according to the behavioural data of C, HG and PG based on Prelec function. An increase to the chance to lose is shown in red including the caudate nucleus, superior frontal gyrus, fusiform gyrus and NAcc. Cyan plots present brain regions that follow the hypothesis of certainty in a u-shape model and show corresponding activation in the Insula and ACC. The respective coloured curves refer to the regressors utilized for modelling.

Table 3: Anticipation contrast after revealing the first card modelled with Prelec function and the U-shape function (FWE-corrected, $p<0.05$, except marked regions (*) uncorrected, $p<0.001$)

AAL label	**side**	**X**	**Y**	**Z**	**t-value**
Activation following Prelec function					
calcarine sulcus	L	4	-84	-2	11.12
occipital inferior lobe	R	36	-86	-4	10.41
fusiform area	R	26	-78	-14	10.1
caudate nucleus	R	14	18	-8	8.01
hippocampus	R	20	12	-14	7.27
ventral striatum	L	-18	10	-14	7.39
NAcc	L	-10	8	-12	6.64
OFC	L	-14	18	-10	6.23
middle frontal gyrus	R	30	10	60	6.78
superior frontal gyrus	R	26	30	52	6.19
	R	20	18	48	6.1
superior frontal gyrus	L	-18	32	44	6.72
middle frontal gyrus	L	-34	10	54	5.82
superior frontal gyrus	L	-20	14	54	5.61

AAL label	side	X	Y	Z	t-value
primary motor cortex	R	10	-34	70	5.97
OFC	R	36	44	-14	5.95
white matter	R	28	-22	0	5.87
putamen		32	-10	-4	5.24
OFC	R	42	50	-8	5.86
frontopolar prefrontal cortex	L	-4	60	-2	5.83
DLPFC	L	-42	52	-4	5.78
Activation following the decrease in Prelec function					
SMA	R	10	-4	64	5.39
	L	-12	-10	68	5.28
ACC	L	-2	16	34	4.87
	L	-8	2	44	4.85
inferior frontal gyrus, pars triangularis	R	40	24	4	4.62*
	L	-36	10	10	4.52*
supramarginal gyrus	L	-60	-30	18	4.19*
DLPFC	L	-38	40	36	3.43*
inferior frontal gyrus, pars opercularis	L	-52	0	2	3.41*
	R	54	4	-2	3.21*
	L	-16	-50	64	3.19*

AAL label	**side**	**X**	**Y**	**Z**	**t-value**
Activation following the U-shape function					
insula,	R	30	20	-18	8.05
inferior frontal gyrus,	R	46	32	-12	7.66
pars triangularis	R	54	22	2	5.6
insula,	L	-28	20	-14	8.01
inferior frontal gyrus,					
pars triangularis					
ventromedial prefrontal cortex,	L	-8	46	20	7.57
ACC	L	-8	42	28	7.48
	L	-2	56	-4	6
angular gyrus, superior temporal gyrus	L	-54	-68	30	6.33
	L	-54	-66	28	6.22
	L	-56	-52	40	4.81
angular gyrus, superior temporal gyrus	R	64	-48	20	6.24
	R	58	-50	32	5.14
MCC	L	-2	-22	36	5.64
medial temporal gyrus	R	66	-40	-6	5.25
Superior frontal gyrus, BA 8	L	-12	22	58	5.05
BA 10	R	16	60	28	5.04
BA 8	R	12	22	60	4.94
SMA	R	12	4	66	4.75

3.3.3 Group Comparison According to Prelec Function.

Next, we were interested in the differential activation of specific brain regions in YC, C, HG and PG. As mentioned in our previous publication (Ring *et al*., 2018), behaviour during the lottery game did not show any significant differences in the loss domain. However, at the functional level, the t-test suggests that there is an increased nonlinear response to the weighting of probabilities of gambling participants (HG and PG) compared to non-gambling participants (YC and C) in the bilateral temporal pole, the right anterior insula and the MCC (cluster-level, uncorr., $p<0.05$; peak-level, uncorr., $p<0.001$, Figure 7A). Figure 7B illustrates the focal changes in probability processing in the right temporal pole extending into the anterior insula. Changes in temporal lobe activity in gamblers during decision-making have been reported by other groups, who reported focal abnormalities in clinical EEG recordings (Regard *et al.*, 2003) as well as in event-related fMRI (Miedl *et al.*, 2010). In addition, the insula and the cingulate cortex were highlighted in the search for the neural substrate of risk assessment in pathological gambling (Potenza, 2008, 2013; Moccia *et al.*, 2017).

Table 4: Group differences for gambling and nongambling participants for probability processing according to the Prelec function and to the U-shape function of certainty.

AAL label	**side**	**X**	**Y**	**Z**	**statistic**	**cluster size (in voxels)**
Y+C < HG+PG anticipation processing according to Prelec function						
superior temporal gyrus	L	-44	6	-18	4.50	71
anterior insula	R	44	14	-20	4.15	208 (cluster-level, p<0.05, uncorr.)
	R	38	20	-14	3.87	
medial cingulate cortex	L	-10	-6	36	3.32	3
Y+C < HG+PG certainty processing according to U-shape function						
amygdala	L	-18	4	-16	3.76	19
PCC	R	18	-48	10	3.52	10
	L	-18	-52	12	3.27	1
ACC	R	2	34	-4	3.37	7

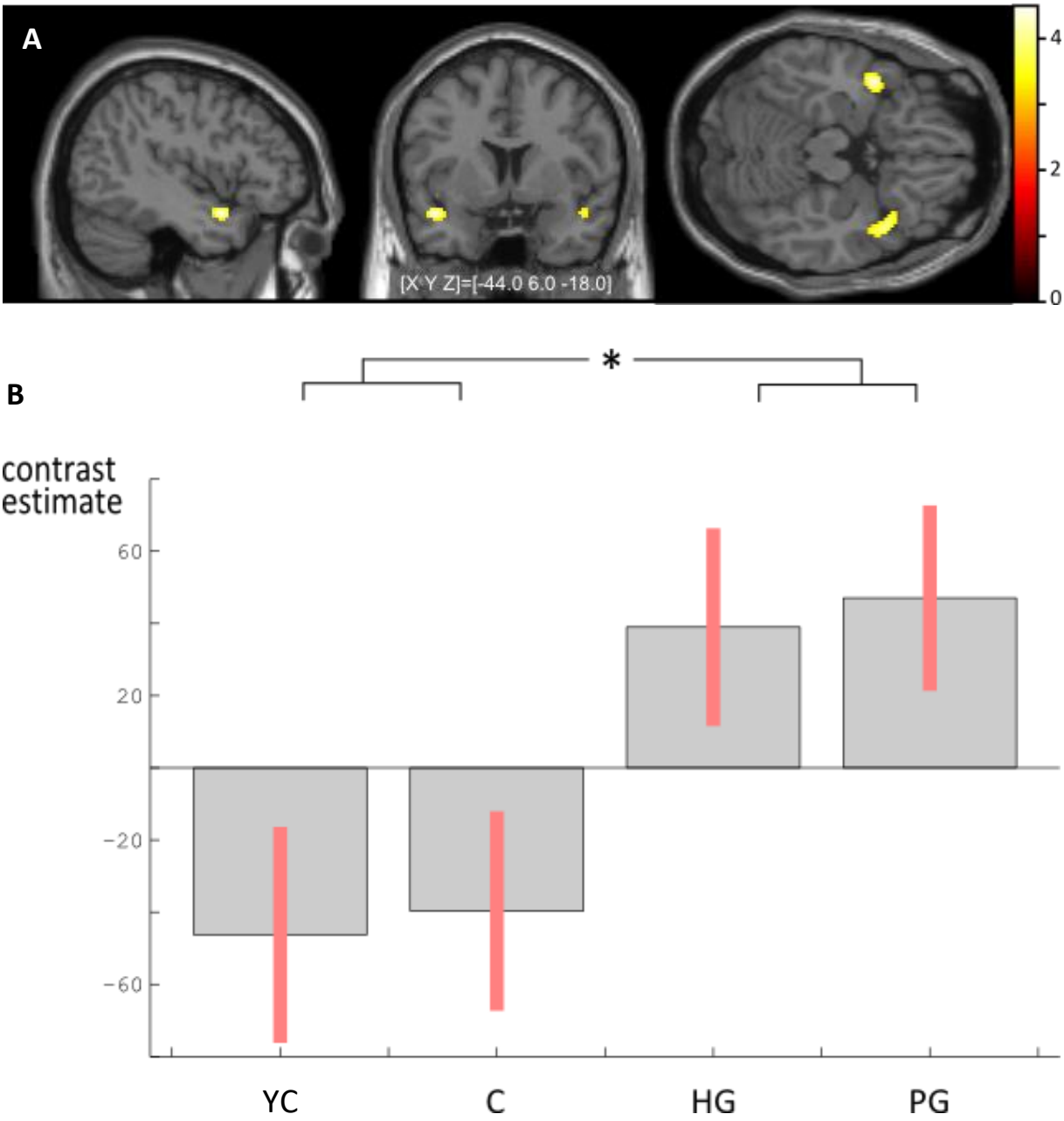

Figure 7: Group differences between PG, HG and C displayed in the right temporal pole for the Prelec function, extrapolated from behavioural data according to the Prelec function ($p<0.001$, uncorr.). **A:** The colour indicates regional t-values according to the reference scale **B:** Plotted group differences for YC, C, HG and PG on the x-axis and contrast estimate on the y-axis.

4.0 Discussion

With the present paradigm, we were able to map brain activation at 10 different probability levels while participants were in anticipation of a negative outcome. We found that systematic increases and decreases in activity may depend on the probability of losing. This supports our hypothesis of a finely tuned perception of single probabilities and partially confirms previous findings regarding that matter (Preuschoff, Bossaerts and Quartz, 2006; Berns *et al.*, 2008; Hsu *et al.*, 2009). Furthermore, we compared gambling participants to non-gambling participants (Y and C) and we found an increased brain response in regions that are active during arousal and anticipation, such as the MCC, the anterior insula and the superior temporal gyrus. Finally, we investigated how overall loss anticipation is processed; contrary to other suggestions, the general perception of loss anticipation did not differ in gambling and non-gambling participants.

4.1 Loss Anticipation (contrast 1)

4.1.1 Division of Reward and Loss Anticipation

First, we measured the general effect of anticipation for a negative stimulus (i.e., main effect of anticipation) after the revelation of the first card during a trial, disregarding single probability units. Without any significant differences at the group level, we included all 83 participants in calculating the overall BOLD response statistics. Our experiment revealed strong activation in the ACC, the anterior insula, the putamen, the thalamus and the SMA. Furthermore, we found activation in the MCC, the PCC, the DLPFC and the anterior prefrontal cortex, as well as in hippocampal and parahippocampal areas extending to the fusiform gyrus. The former regions, in particular, have been shown to be active during both reward and loss anticipation (i.e. anticipatory affect), while the latter regions seem to define the valence or quality of the outcome, i.e., loss anticipation (Knutson and Greer, 2008; Liu *et al.*, 2011; Dugré *et al.*, 2018). Regions that are active during loss and reward anticipation have routinely been reported to contribute to affective functions in the brain. For example, tasks that elicit positive emotions appear to activate these regions (Knutson *et al.*, 2001; Chandrasekhar *et al.*, 2008; Suardi *et al.*, 2016); however, negative stimuli such as viewing fearful and angry

faces, social conflict, listening to sad music or receiving a painful stimulus also seem to do so (Koelsch, 2010; Palermo *et al.*, 2015). This connection has frequently been suggested to stem from a shared connection between positive and negative emotions in the salience network and the corticolimbic circuit that integrates the uncertainty-induced arousal experienced in an unknown situation (Menon and Uddin, 2010; Liu *et al.*, 2011).

The ACC, anterior insula, putamen, thalamus and SMA are most often reported to be solely active during loss anticipation, a finding that suggests the existence of a separate network that may define the specific valence of the outcome. In particular, the BOLD response in large parts of the cingulate cortex, insula, amygdala and prefrontal areas suggests a complex network of loss anticipation. A meta-analysis by Dugré et al. (2018) showed that the MCC was predominantly active during loss anticipation, and this was confirmed in the present study. The MCC has been suggested to serve as a goal-directed hub for information about incoming punishment that is then used to guide further action induced by negative stimuli (Shackman *et al.*, 2011). Shackman *et al.* (2011) also showed a notable shift of activity from the medial OFC during reward anticipation to the ventrolateral prefrontal cortex (VLPFC) in loss anticipation. In the present study, however, we found increased activation in the DLPFC rather than in the VLPFC. This may be due to the difference in paradigm structure; in our study, the previous necessity to choose a card may have increased the activation of the DLPFC, which has been linked to decision making and cognitive flexibility (Greene *et al.*, 2001; Donahue and Lee, 2015).

4.1.2 Group Differences in Loss Anticipation

When comparing loss anticipation (contrast 1), we could not show any significant differences between gambling (PG and HG) and non-gambling (C and Y) participants. Several reasons could account for this outcome. Specifically when taking into consideration the previously suggested concept of duality in reward and loss anticipation. Here we can assume that differences related to gambling and non-gambling may only be present during reward anticipation. During loss anticipation, however, the brain response appears to be similar to that of healthy individuals. Problem gamblers have often been reported to have functional changes in the ventral striatum and the medial OFC, while areas that are vital for loss anticipation do not underlie significant changes. This hypothesis is corroborated by findings at the behavioural and neural levels. For example, individuals with gambling disorders were found to show a decreased physiological brain response in the ventral striatum and the ventromedial prefrontal cortex during winning (Reuter *et al.*, 2005). Furthermore, Balodis *et al.* (2012) found decreased activation in the ventral striatum during reward anticipation but not during loss anticipation. To our knowledge, only one study reported slight decreases in brain activation in pathological gamblers during loss anticipation, specifically in the caudate nucleus and the temporal pole (Choi *et al.*, 2012). However, these group differences did not survive FWE-correction at a cluster size of 8 and 7 voxels. Based on the previous literature and given the statistical power of the present experiment, we therefore propose that at least during loss anticipation, gamblers may not differ from healthy controls in their brain response.

4.2 Probability Weighting According to Behavioural Models (contrasts 12-14)

A central question in the present study was the processing of probability levels during loss anticipation. Does brain activation follow the predictions of prospect theory as the probability of positive punishment or negative reinforcement increases? Is there a neural correlate of the sensation of certainty? To investigate this matter, we modelled the behaviourally measured probability weighting function according to Prelec (1998) using our BOLD data during loss anticipation (Ring *et al.*, 2018). A few studies have attempted to determine whether the function is linear, following the expected utility model or nonlinear, thus following the Prelec function (Preuschoff, Bossaerts and Quartz, 2006; Berns *et al.*, 2008; Hsu *et al.*, 2009; Rudorf, Preuschoff and Weber, 2012). However, none of these studies arrived at a definite conclusion. In the present study, we found that increasing and decreasing probability levels influence the cognitive representation and perception of individual probability levels (Figure 6). In addition, we could show a pronounced activation of certainty for an outcome (without valence, U-shaped), as has already been suggested by another group (Berns *et al.*, 2008).

The prospect theory stresses the overweighting of small probabilities and the underweighting of high probabilities, while the prelec function is the fitted formalization of this theory. We used the behavioural data as regressors and found an increase in brain activity in response to increased probability of losing, mainly in the MCC, SMA, anterior insula and DLPFC. These findings are consistent with the suggestion that the MCC acts as a hub for incoming negative stimuli, integrating information as a basis for further action in anticipation of a shock (Shackman *et al.*, 2011). The increased activation in the SMA may represent the suppressed or unsuppressed planning of motor functions for possible punishment avoidance. Furthermore, with increasing probability of positive punishment, we could show activation of the anterior insula; this may be attributed to its role during arousal (Wu *et al.*, 2014; Dugré *et al.*, 2018). Involvement of the insula in both reward and loss anticipation, as well as its nonlinear response to probability, was shown previously (Berns *et al.*, 2008; Knutson and Greer, 2008; Liu *et al.*, 2011; Dugré *et al.*, 2018).

Interestingly, we found a strong negative correlation of activity in some brain areas with increased probability of losing. Striatal components and their dopaminergic projections, namely the NAcc, caudate nucleus, putamen, OFC, and DLPFC, showed a strong inverse correlation with the behavioural model (Figure 6, red). This is consistent with the recent literature regarding probability perception, specifically for anticipation of positive reinforcement. Hence, we assume that with a decrease in punishment probability, activation follows the increasing probability of not suffering the loss-associated outcome. The behavioural advantage of avoidance of negative outcomes can be called negative reinforcement. We therefore infer that negative reinforcement triggers brain responses that are similar to those, triggered by positive reinforcement.

A similar response can be seen in the reward paradigm proposed by Hsu *et al.* (2009). Those authors used a paradigm containing 6 rather than 10 probability levels. In their investigation, they found nonlinear activation in the striatum, cingulate gyrus, motor cortex and cerebellum. In comparison, we used a card game similar to that used by Preuschoff *et al.* (2006). The latter paradigm involved the presentation of the aim (to have a higher or lower card) and the subsequent presentation of two cards, while the temporal segment between the presentation of the two cards constituted the time of anticipation. Preuschoff *et al.* found distinct activation of the ventral striatum and the putamen; however, the activation increased linearly with the increase in the probability of winning. The linearity may therefore reflect the physiological equivalent of a linear perception of probability and contradict the idea of a physiological correlate following prospect theory.

To our knowledge, only one study has investigated the prospect theory at the neural level using an evoked response (positive punishment), similar to the one used in the present study. That study used a loss anticipation delay-conditioning paradigm with 5 probability levels and revealed a nonlinear response in relevant regions such as the anterior insula, the superior temporal gyrus, the cingulate gyrus and the inferior parietal gyrus (Berns *et al.*, 2008). As in the present study, the authors found a U-shaped activation, which may resemble a form of certainty, as well as the assumed S-shaped model according to the prospect theory. Furthermore, they showed a significant positive correlation of the increased probability of a negative stimulus with activity in the superior frontal gyrus, which has been shown to contribute to anticipatory signaling (Hsu *et al.*, 2009; Seidel *et al.*, 2015). Similar to the present experiment, a nonlinear negative correlation with probability was found in the ACC, which has been suggested to be involved in the integration of probability weighting (Berns *et al.*, 2008). Meta-analyses of loss and reward anticipation emphasize the presence of a shared anticipation network and support the importance of these areas (Dugré *et al.*, 2018).

Similar to Berns *et al.* (2008), we observed a U-shaped dependence of activation on probability level (Figure 6). This may reflect a sensation of certainty regarding the outcome of the trial. In both studies, the activation involved the insula and the superior temporal gyrus. In addition, we found activation in the ventromedial prefrontal cortex, the ACC and the MCC. These regions have been suggested to contribute greatly to anticipatory cognition and decision-making (Liu *et al.*, 2011; Shackman *et al.*, 2011; Dugré *et al.*, 2018). Based on these results, we propose that the five regions mentioned above regions may integrate the probability of an outcome, giving the individual feedback for use in future situations during decision-making.

The insula has been suggested to play an integrative role in the anticipation process, and some groups have found that it is involved in the perception of certainty (Preuschoff, Quartz and Bossaerts, 2008; Seidel *et al.*, 2015). Interestingly, Preuschoff *et al.* (2008) found activation of the anterior insula during risk prediction (i.e., uncertainty) and risk prediction error (i.e., certainty), but they separated the neural response both spatially and temporally. They argue for a distinction in anticipatory signaling in the anterior insula. On the one hand, it may mediate a learning process for future probability predictions, and on the other hand, it may contribute to an anticipatory process before a potential risk is realized. Unfortunately, our data does not allow such a temporal division; however, taken together, the distinct activation observed in the anterior insula during loss anticipation (see previous paragraph) and the association of activation with the probability level supports these findings.

4.3 Group Differences

Finally, we were interested in whether non-gamblers and gamblers show differences in brain activation during probability weighting. In our previous publication based on the behavioural data of the present study, we did not find group differences in the loss domain during a time preference paradigm (Ring *et al.*, 2018). Nevertheless, we hypothesized that changes occur in the brain response, since there are assumptions that propose a pathological neurophysiology in multiple cognitive domains, such as anticipation, response inhibition, conflict monitoring, decision making, and cognitive flexibility (Choi *et al.*, 2011; for review see Moccia *et al.*, 2017). In fact, we found evidence that the temporal pole and the anterior insula present increased activation in gambling participants during the processing of probabilities according to our behavioural model based on the Prelec function (1998). This was true when we compared non-gambling (Y and C) and gambling (PG and HG) participants and was still present in the comparison of C and PG ($p<0.001$, uncorr.). The temporal pole, as an extension of the superior temporal gyrus and the anterior insula, was linked to gambling in previous studies. Choi *et al.* (2011) described decreased activation in the temporal pole and anterior insula when individuals with a gambling disorder were compared with controls. They argue that the decrease in activity in the anterior insula may be due to the function of that region as a mediator in the emotional processing of adverse events. This does not fit with our results, however the present approach was profoundly different, and the differences may explain the divergence in the results. While the contrast employed in our study may detect the difference in the evolution of perceived probability levels, Choi *et al.* compared loss anticipation in general, similar to our approach in contrast 1 (i.e., general loss anticipation).

A different group used the Iowa Gambling Task to test PG poker players during monetary decision making. During card selection, gamblers showed mildly increased bottom-up connections from the ventral striatum to several cortical regions, including the superior and middle temporal gyrus (Brevers *et al.*, 2016). The authors interpreted their findings as indicating the presence of a physiological correlate of increased salience during sensory processing. These findings show that there are changes during the processing of loss probabilities in gambling participants. However, the differences appear stronger for reward anticipation, specifically in the striatum and related networks of reward (Moccia *et al.*, 2017).

4.4 Limitations

For the present study, limitations arise predominantly from the experiment structure. Due to the design of the paradigm, there was no possibility to compare the two entities of reward and loss anticipation. Future research could therefore include a reward stimulus in the design, creating an opportunity for direct comparison. Furthermore, the 50% chance of receiving a punishment stimulus blurred the measured emotions of risk and uncertainty. Risk is predominantly modelled in a U-shape curve in paradigms that apply a 100% risk of receiving a punishment, while uncertainty is often modelled in a strictly randomized manner. By informing the participants of the 50% chance to receive a punishment stimulus beforehand, the present study may have merged both risk and uncertainty. Furthermore, the implemented probability weighting was based on an unrelated task and performed outside the scanner. For future research a probability weighting based on the choices during the paradigm could increase the explanatory power of the experiment.

4.5 Conclusion

Answering the questions from the introduction, our results paint a picture of discrete regional probability processing with increasing loss anticipation in the SMA, the MCC and the anterior insula. Conversely, there was increased activation with increased probability of evading a loss in the fusiform gyrus, the NAcc, the caudate nucleus and the superior frontal gyrus. Additionally, we found that other brain regions, including the insula, the OFC and the ACC, show a U-shaped pattern of activity, which we interpreted as a function of certainty.

Furthermore, we compared the gambling (PG and HG) and non-gambling (C and Y) participants, and we found evidence for an increased activity in the superior temporal lobe, the insula and the MCC of gamblers during probability prediction according to the Prelec function. This indicates that anticipation of adverse events may be mediated in different ways in gamblers and non-gamblers.

Moreover, we found a distinct pattern of activation during loss anticipation and found activation in regions commonly described with affect and arousal: the anterior insula, the ACC, the putamen, the thalamus and the SMA. Consistent with the recent literature, the neural pattern observed in those brain areas during loss anticipation is closely shared with the pattern associated with reward anticipation (Dugré *et al.*, 2018). However, the valence of loss is determined by the involvement of the MCC, the PCC, the DLPFC, the anterior prefrontal cortex, the hippocampus, the parahippocampus and the fusiform area. Interestingly, no differences in the general anticipation of negative stimuli could be found in gambling and non-gambling participants, suggesting an exclusive deficit in gambling individuals in the reward domain.

5.0 Summary

Objective: With this study, we aim to arrive at a better understanding of the neural mechanisms underlying the anticipation of losses due to unpleasant electric shock stimuli. According to prospect theory – currently the most important descriptive model of decision making under uncertainty in economics – subjects overweight small probabilities and underweight high probabilities. Here, we analyzed to what extent prospect theory is manifested in biological data. Does the human brain process aversive contingencies of decisions in a nonlinear manner according to the probability weighting function underlying prospect theory? Which brain regions process certainty or uncertainty regarding an outcome regardless of its valence? How do individuals with problematic gambling habits differ in these entities?

Methods: The present study included a total of 83 participants (22 problem gamblers, 18 habitual gamblers, 23 age-matched subjects and 20 young control subjects). Each participant was evaluated by psychologists through a semi-structured interview and the self-reported Southern Oaks Gambling Scale. The study participants engaged in a card game in which unambiguous situations with various risk levels for aversive events (unpleasant but not painful electric shocks) were created. Apart from neural responses during anticipation of an aversive event, our paradigm allowed us to measure how neural activity during expectation is modulated by the probability of the outcome. Furthermore, we used the participants' attitudes towards risk to account for the subjective evaluation of probabilities, as suggested by prospect theory.

Results: We confirmed existing knowledge about the active network during anticipation of aversive events in a large sample. Specifically, in response to our experimental stimuli, the BOLD (blood oxygen level dependent) signal increased in the anterior and medial cingulate cortex, the anterior insula, the amygdala, the thalamus and the medial frontal regions. Based on economic studies and on our previous behavioural results, we modelled the expected outcomes according to uncertainty and prospect theory. With increasing chances of avoiding punishment, we found that the BOLD signal increased in the orbitofrontal cortex, the striatum, the hippocampus, the precuneus, and the posterior cingulate cortex. Conversely, with increasing certainty of a positive or negative outcome (U-shaped from most certain loss to no loss), we found activation patterns in the medial superior frontal cortex, the anterior cingulate cortex, the anterior insula, the

frontopolar prefrontal cortex and the angular gyrus. Furthermore, we found evidence for group differences in cerebral activation in the bilateral superior temporal pole, the anterior insula and the medial cingulate cortex during the perception of distinct probability levels according to the nonlinear probability weighting function. Interestingly, these regions are relevant both in loss anticipation paradigms and in functional imaging studies describing pathological gambling.

Conclusion: Our results support the concept that the neural response to anticipation is determined by its valence. Although it has frequently been reported that gamblers and non-gambling individuals show differences in reward anticipation, during loss anticipation gambling participants do not differ in their neural activation patterns. We also tested whether specific regions of the brain follow a nonlinear brain response according to prospect theory and the certainty of an outcome. When their BOLD responses during probability perception were compared, non-gambling and gambling individuals did show differences in the perception of probabilities. This provides new evidence that simultaneously occurring cognitive processes are represented in different sets of brain regions. Specifically, neurobiological correlates of loss anticipation were found in areas known to be involved in dopaminergic reinforcement learning and in the corticolimbic circuit, while regions known to subserve decision making, conflict monitoring and punishment showed correlation with the certainty of the outcome.

6.0 References

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