Elevated Functional Connectivity in a Striatal-Amygdala Circuit in Pathological Gamblers

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Abstract

Both substance-based addiction and behavioural impulse control disorders (ICDs) have been associated with dysfunctions of the ventral striatum. Recent studies using functional connectivity techniques have revealed increased coupling of the ventral striatum with other limbic regions such as amygdala and orbitofrontal cortex in patients with substance abuse disorders and attention-deficit hyperactivity disorder. In the present study, we re-analyzed previously published functional magnetic resonance imaging data acquired in pathological gamblers and controls during value-based decision-making to investigate whether PG is associated with similar functional connectivity effects. In line with previous studies in other ICDs, we observed reliable increases in functional coupling between striatum and bilateral amygdala in gamblers vs. controls. Implications of these findings for neural models of self-control and addiction are discussed.

Introduction

Impulse control disorders (ICDs) including substance abuse are associated with impairments in value-based decision-making [1,2], and non-substance based addictions such as pathological gambling (PG) share many features with substance-based addictions [3]. One of the most extensively-studied behavioural-economic correlates of ICDs is increased temporal discounting [2,4,5], i.e. an increased propensity to prefer smaller-but-sooner (SS) over larger-but-later (LL) rewards [6]. Pathological gamblers show increased temporal reward discounting compared to control participants [7–11] and also have the tendency for increased risk-taking [11–13].

The neural mechanisms underlying these problematic alterations in decision-making in gamblers are debated, but one candidate mechanism is striatal dysfunction [14], which is also implicated in substance abuse [1]. A number of functional magnetic resonance imaging studies in pathological and problem gamblers have revealed modulations in striatal and medial prefrontal response during the processing of reward information [11,15–21]. Taken together, however, these findings are inconsistent with a simple model in which PG is associated with generally elevated or diminished reward-related responses. Rather, factors such as the analyzed task phase (e.g. reward anticipation vs. outcome), analysis procedure (e.g. model-based vs. categorical analysis), gambling-relatedness of task and stimuli and reward type (e.g. primary vs. secondary reinforcers) jointly appear to influence whether PGs show elevated or attenuated striatal signals [11,22–25].

In addition to examining such task-related neural activations [15–17], or parametric neural responses [11,26], a complementary approach is to examine functional connectivity (i.e. time series correlations) between regions in relation to ICDs. Functional connectivity between the striatum, amygdala and orbitofrontal cortex is increased in drug addiction and attention-deficit hyperactivity disorder [27–29]. Ventral striatum and medial orbitofrontal cortex/ventromedial prefrontal cortex (mOFC/vmPFC) are part of the limbic loop of the thalamo-cortico-basal-ganglia circuit [30], a loop that also has dense interconnections with hippocampus and amygdala [31]. But whether PG is associated with similar functional connectivity effects is unclear.

Interactions between striatum and amygdala are of particular interest in the context of reward processing. Animal work has consistently pointed towards an important role of functional interactions between striatum and amygdala in regulating reward-guided behaviour [32–34]. In the light of previous findings in other ICDs [27–29] it is therefore important to assess increased functional connectivity in this circuit in PGs, in order to determine whether this may constitute a mechanism underlying ICDs in general.

One previous study on functional connectivity in PGs focused on response inhibition tasks rather than reward-based decision-making [35]. To address the role of functional connectivity in pathological gamblers during decision-making, we re-analyzed previously published data in controls and pathological gamblers performing two different value-based decision-making tasks during fMRI [11]: delay discounting (i.e. choosing between smaller-sooner and larger-later rewards) and probability discounting (i.e. choosing between smaller-certain and larger-riskier rewards). To directly assess the limbic basal-ganglia-thalamocortical circuit...
[14,30], we focused on group differences in functional connectivity with the left and right ventral striatal seed voxels.

Methods

General Overview

This study constitutes a re-analysis of a previously published functional magnetic resonance imaging (fMRI) data set [11] using functional connectivity analyses. All participants provided informed written consent, and the study procedure was approved by the local institutional review board (Ethics Committee of the Hamburg Board of Physicians). For a detailed description of the sample characteristics, task procedures, and fMRI data acquisition parameters please refer to Miedl et al. (2012). In short, participants (n = 16 pathological gamblers and n = 16 age- and education-matched control subjects) performed a value-based decision-making task during fMRI. Two randomly intermixed conditions were included: delay discounting and probability discounting [26]. In delay discounting trials, subjects made choices between 20′ available now and larger but delayed rewards. In probability discounting trials, subjects made repeated choices between 20′ with 100% probability and larger amounts with lower probabilities. The immediate/certain option of 20′ was not displayed. Trial timing was as follows: 1) 500 m fixation, 2) 2500 ms presentation of the delayed/risky option, 3) 3000–7000 ms jitter (drawn from uniform distribution), 4) max. 2500 ms choice screen (accept/reject delayed/risky option), 5) 3000–7000 ms jitter (drawn from uniform distribution).

We fit hyperbolic models of delay and probability discounting [6,26] to each participant’s choice data using maximum-likelihood techniques [11]. Based on these single-subject model fits, we then calculated estimates of the subjective value of the larger-later (delay discounting) or the larger-riskier (probability discounting) reward on each trial. These estimates were then included as parametric regressors in a model-based fMRI analysis [36].

Trials for the fMRI task were generated in a subject-specific manner based on a behavioural pre-test. As PGs are characterized by excessively steep reward discounting, larger amounts of LL rewards are required for PGs compared to controls to obtain similar subjective reward values. The procedure of computing subject-specific offers ensured that subjective reward values were similar in the PG and control groups.

FMRI Preprocessing

Preprocessing was carried out using SPM08 (Wellcome Department of Cognitive Neurology, University College London). Scans were slice-time corrected to the onset of the middle slice, and realigned to the mean functional scan using a 6-parameter affine transformation. Functional images were then co-registered with the high-resolution anatomical T1-weighted image. The anatomical scan was then segmented into grey matter, white matter, and CSF. Functional images were normalized to MNI space using the normalization parameters obtained from the segmentation procedure, and finally smoothed using an 8 mm full-width-half-maximum Gaussian kernel.

Functional Connectivity Analyses

We used psycho-physiological interaction analyses (PPI) [37] as implemented in SPM08 to examine group differences in functional connectivity. For the connectivity analysis, delay and probability trials were modelled as 8s mini-blocks. From this first level model, seed time courses were extracted using the Volume of Interest (VOI) function of SPM08. Seeds were placed in the left and right ventral striatum at peaks from the main effect of subjective value (SV) across conditions and groups (i.e. striatal peaks showing a positive correlation with SV[larger later] and SV[risky option] across controls and gamblers).

For each seed region, a first level PPI model was set up including the following user-specified regressors: 1) the time course of the seed region, 2) a regressor coding for the experimental condition (−1: delay discounting, −1: probability discounting), 3) the interaction term, i.e. the multiplication of regressors 1 and 2, and 4) the six parameters from the realignment procedure modelling movement-related effects. Single-subject contrast images for each of these three regressors were created. Because we were primarily interested in overall group differences in striatal connectivity, rather than group x condition interaction effects in connectivity, we took the contrast image for the striatal timecourse regressor to a second-level random-effects analysis (two sample t-test model). In keeping with our previous analysis [11] we included gambling severity [38], smoking behaviour [39] and depression scores [40] as group-specific covariates in this second-level model. Separate analyses were carried out for the seed in the left striatum, and for the seed in the right striatum.

In an additional control analysis, we extracted the seed time course in a condition-specific manner, i.e. separately for delay and probability trials. This allowed us to assess potential group x task interaction and conjunction effects. A first level PPI model was set up for each subject for this analysis using the following regressors: 1) the time course of the seed region during delay discounting trials, 2) a regressor coding for delay discounting trials (1 for delay discounting trials, 0 otherwise), 3) the time course of the seed region during probability discounting trials, 4) a regressor coding for probability discounting trials (1 for probability trials, 0 otherwise), and 5) the six parameters from the realignment procedure modelling movement-related effects. The contrast images for each striatal time course correlation (one contrast image for the seed timecourse during delay discounting, probability discounting) were taken to a second-level random-effects analysis in a 2 (controls/gamblers) x 2(delay/probability) full factorial model. We tested striato-amygdala coupling additionally in a conservative conjuction analysis [41], i.e. coupling gamblers>controls in delay discounting AND coupling gamblers>controls in probability discounting.

Correction for Multiple Comparisons

Correction for multiple comparisons was performed using small-volume-correction (p<0.05). For the ventral striatum we used 8 mm spheres centered at 14±10 −10 [42]. For the amygdala we used unilateral anatomical masks from the FSL software package (50% probability threshold).

Results

Main Effect of Subjective Value Across Groups and Conditions

In order to identify an unbiased ventral striatal activation peak as a seed region for the functional connectivity analyses, we first carried out a parametric analysis of subjective value of the delayed or risky option. We set up a second-level factorial model with the factors group (gamblers/controls) and task (delay discounting/probability discounting). The model included gambling severity [38], smoking behaviour [39] and depression [40] as group-specific covariates, as in our previous report [11]. Within this model, we now searched for regions showing a positive correlation with the value of the delayed/risky option across both groups and tasks (i.e. an overall main effect of subjective value; contrast vector [1 1 1 1]). The strongest activation in this contrast was localized in
Group Differences in Striatal Functional Connectivity

We carried out two analyses. First, we analyzed striatal connectivity across the entire session. Regions showing greater functional connectivity with left striatum in gamblers vs. controls are listed in Table 1. Regions from the same analysis for right ventral striatum are listed in Table 2. For the left striatal analysis, regions including bilateral amygdala showed strong increases in striatal coupling for gamblers vs. controls (Figure 2b, left amygdala: −20, −4, −12, z-value = 4.17, p_fdr < .001, right amygdala: 22, −2, −12, z-value = 3.79, p_fdr = .005). Similar increases were seen in vmPFC (−12, 40, 12, z-value = 3.62). As can be seen from Table 2, these same regions showed increased coupling with the right ventral striatum in gamblers vs. controls. No regions showed greater functional connectivity with left or right striatum in controls vs. gamblers at p<0.001 uncorrected. We did not observe associations between the degree of striatal-amygdala connectivity and inter-individual differences in delay/probability discounting or gambling severity within the gamblers group.

We next examined a model in which the seed time course was extracted in a condition-specific manner (see methods), which allowed us to examine group x task interaction effects. We obtained separate contrast images reflecting the degree of striatal functional connectivity for delay trials and probability trials, again separately for left and right striatal seeds. These images were taken to a second-level random effects analysis using a group (controls vs. gamblers) x task (delay vs. probability discounting) factorial model. Covariates were identical to the previous model. Tables 3 and 4 show results from the main effect of group (striatal connectivity gamblers>controls) again for left and right striatal seeds, respectively. As in the previous analysis, we observed an increase in striatal-amygdala functional connectivity in gamblers vs. controls (p_fdr < .05 for both left and right amygdala). This effect was also significant in the left amygdala (p_fdr < .05) when a conservative conjunction analysis [41] across both delay and probability trials was examined (Figure 2). No regions showed a significant group x task interaction at p<0.001 uncorrected.

Finally, we examined whether the observed effects in the gamblers were attributable to an increase in positive connectivity or a decrease in negative connectivity. We therefore carried out a triple conjunction analysis in the previous factorial model, searching for regions showing 1) a positive correlation with the striatum in the control group, 2) a positive correlation with the striatum in gamblers and 3) a greater effect of striatal coupling with the right ventral striatum in gamblers vs. controls. This analysis yielded again activity in the amygdala (−18, −2, −12, z-value = 3.97 [right striatal seed], −20, −2, −12, z-value = 3.40 [left striatal seed]), showing that positive striatal-amygdala connectivity in the gamblers was elevated.

Discussion

Addiction has been consistently linked to ventral striatal dysfunction [1]. Pathological gambling shares many features with substance-based addiction, and reward-related responses in striatal and frontal regions consistently show modulations in gamblers compared to control subjects [11,14–21]. One approach that may provide additional insight into the neurobiological mechanisms underlying such impulse control disorders (ICDs) are analyses of functional connectivity [43]. In resting state functional connectivity studies, correlations between the time series of different brain regions are examined in the absence of a cognitive task. Striatal resting state connectivity has previously been associated with ICDs, e.g. in children with ADHD [27], heroin addicts [28,29] and smokers [44].

Alternatively, as in the present study, group differences in functional connectivity can also be examined performance of a cognitive task [35]. This previous study examined differences in functional connectivity between controls and problem gamblers during a response inhibition paradigm [35]. In contrast, we examined differences in striatal functional connectivity during performance of two different value-based decision-making tasks (delay and probability discounting), in a re-analysis of previously published data [11]. One advantage of analyzing task-related vs. resting state connectivity is that value-based decision-making is known to reliably induce variance in a striatal-limbic system.
Striatal functional connectivity: gamblers > controls in DD and PD

[26,45]. Across both delay and probability discounting trials, a main effect of group was observed, such that coupling between striatum and, among other regions, bilateral amygdala was significantly enhanced in gamblers compared to control subjects. This effect was similar for both left and right striatal seeds, and similar for delay and probability discounting conditions (i.e., no group x task interaction was observed).

Our results converge with previous findings of enhanced limbic connectivity in resting state analyses in other ICDs [27–29]. In healthy controls, striatal-amygdala functional connectivity is increased during highly rewarding situations, e.g. when listening to pleasurable music [46], but also more generally during the processing of salient stimuli [47]. Fronto-limbic connectivity was also increased in pathological computer game players in a cue reactivity study [48]. Interestingly, interactions between striatum

Table 1. Anatomical Site, Cluster Size, maximum Z value, and MNI coordinates of the local maxima for the connectivity analysis (seed in left ventral striatum [MNI coordinates −10 9 −9], connectivity gamblers > controls).

| Region                        | cluster-size | Z    | MNI-coordinates         |
|-------------------------------|--------------|------|-------------------------|
| R Superior/Middle Temporal Gyrus | 129          | 4.38 | 58−24−4                 |
|                               |              | 3.86 | 64−32−4                 |
|                               |              | 3.26 | 52−12−10                |
| L Amygdala/Lentiform nucleus   | 194          | 4.19 | −8−0−10                 |
|                               |              | 4.17 | −20−4−12                |
| R Amygdala                    | 73           | 4.06 | 22−0−12                 |
| L Superior Temporal Gyrus      | 40           | 3.78 | −40−52−22               |
| L Insula                      | 46           | 3.78 | −46−6−2                 |
| L Anterior Cingulate/vmPFC     | 39           | 3.62 | −12−40−12               |
| L Precentral Gyrus            | 20           | 3.53 | −52−12−10               |
| L Middle Temporal Gyrus       | 21           | 3.48 | −64−28−0                |
| L Parahippocampal Gyrus       | 67           | 3.44 | −16−30−6                |
|                               |              | 3.32 | −24−26−8                |
|                               |              | 3.28 | −30−24−16               |
| R Precuneus                   | 14           | 3.32 | 4−54−32                 |
| L Inferior Frontal Gyrus      | 10           | 3.25 | −28−10−12               |
| R Posterior Cingulate Gyrus   | 10           | 3.25 | 2−42−30                 |

Clusters were thresholded at p<0.001 uncorrected and a minimum size of 10 voxels. doi:10.1371/journal.pone.0074353.t001

Table 2. Anatomical Site, Cluster Size, maximum Z value, and MNI coordinates of the local maxima for the connectivity analysis (seed in right ventral striatum [MNI coordinates 10 10 −2], connectivity gamblers > controls).

| Region                        | cluster-size | Z    | MNI-coordinates         |
|-------------------------------|--------------|------|-------------------------|
| L Amygdala                    | 261          | 4.64 | −18−4−12                |
| L Inferior Frontal Gyrus      | 73           | 3.73 | −30−12−12               |
| R Parahippocampal Gyrus       | 62           | 4.43 | 28−32−12                |
| R Amygdala                    | 78           | 4.25 | 20−4−12                 |
| L Parahippocampal Gyrus       | 196          | 4.12 | −14−40−6                |
|                               |              | 4.05 | −22−26−8                |
|                               |              | 3.29 | −30−34−6                |
| R Superior Temporal Gyrus     | 43           | 4.04 | 56−26−2                 |
| L Middle Temporal Gyrus       | 27           | 3.84 | −64−30−0                |
| R Superior Temporal Gyrus     | 38           | 3.71 | 40−48−20                |
| R Posterior Cingulate Gyrus   | 17           | 3.54 | 4−36−28                 |
| L Insula                      | 33           | 3.5  | −30 10 8                |
| L Parahippocampal Gyrus       | 11           | 3.38 | −24−32−20               |
| L Cuneus                      | 10           | 3.36 | −28−88−22               |

Clusters were thresholded at p<0.001 uncorrected and a minimum size of 10 voxels. doi:10.1371/journal.pone.0074353.t002
and amygdala have been shown to underlie a range of reward-related behaviours in animal models. For example, input from the basolateral amygdala to the ventral striatum regulates reward-related striatal activity [32]. Coherence between striatum and amygdala is increased during the processing of reward-predictive cues [33] and inhibition of the amygdala-striatal projection reduces reward-seeking behaviour [34]. Taken together, these findings are compatible with the idea that impulsive behaviour (e.g. in ICDs) may be in part driven by increases in functional coupling in networks that regulate reward-guided behaviour in animal models.

Self-control refers to the ability to overcome the urge to select tempting but ultimately inferior decision options, e.g. smaller-sooner rewards during delay discounting, or larger rewards that have a very low probability in probability discounting tasks. Pathological gamblers show impairments in tasks that require self-control [7–10,12]. This was also observed in the present dataset [11] although the effect of increased risk-taking was only a statistical trend. A prominent neural model suggests that self-control may occur through top-down control of limbic regions via the (lateral) prefrontal cortex [49–51]. Increased coherence among these limbic regions may reduce the ability of the PFC to exert top-down modulatory control, and may thus constitute a potential bottom-up mechanism driving impulsive behaviour.

How may group differences in functional connectivity arise? One possibility is that they arise from group differences in anatomical connectivity. For example, in healthy subjects, the degree of amygdala-striatal anatomical connectivity, estimated using diffusion tensor imaging (DTI) based probabilistic tractography, predicts functional connectivity between these regions [52]. Greater anatomical connectivity between striatum and amygdala is also associated with increased novelty seeking [53], a typical personality correlate of pathological gambling [54–56]. Future studies may further explore links between these domains by acquiring both structural and functional connectivity data in patients suffering from ICDs.

Our analyses did not reveal correlations with behavioural markers or gambling severity, but gamblers tended to be overall more impulsive in both experimental conditions (i.e., the impact of delay was enhanced, whereas the impact of probability tended to be attenuated). How modulations in task-related (or parametric) neural responses relate to the presently observed modulations in functional connectivity in gamblers remains unclear. We previously observed both increases and decreases in striatal value coding in gamblers, depending on the task [11], whereas the present data show elevated striatal-amygdala coupling across both tasks. Striatal-amygdala coupling therefore does not simply enhance or attenuate striatal value coding, but how these effects relate to each other (if at all) remains to be clarified. One possibility is that parametric striatal value coding may not be directly related to impulsive behaviour, but may rather reflect the degree of gambling-relatedness of a task. In contrast, elevated striatal-amygdala coupling may impair the ability of the prefrontal cortex to exert top-down modulatory control, and may thus constitute a potential bottom-up mechanism driving impulsive behaviour.

### Table 3. Anatomical Site, Cluster Size, maximum Z value, and MNI coordinates of the local maxima for the connectivity analysis (seed in right ventral striatum [MNI coordinates 10 10 −2], connectivity gamblers>controls, main effect across delay and probability discounting trials).

| Region                      | cluster-size | Z    | MNI coordinates |
|-----------------------------|--------------|------|-----------------|
| L Amygdala                  | 85           | 4.03 | −18 −4 −12      |
| R Superior Temporal Gyrus   | 38           | 3.92 | 60 −24 −4       |
| R Superior Temporal Gyrus   | 37           | 3.86 | 40 −48 20       |
| R Posterior Cingulate       | 56           | 3.72 | 4 −38 26        |
| R Ventral Striatum          | 46           | 3.64 | 16 12 6         |
| R Anterior Cingulate/vmPFC  | 38           | 3.63 | −14 44 6        |
| L Insula                    | 59           | 3.62 | −34 6 8         |
| L Ventral Striatum          | 26           | 3.5  | −18 12 6        |
| L Middle Temporal Gyrus     | 15           | 3.46 | −68 30 0        |

Clusters were thresholded at p<0.001 uncorrected and a minimum size of 10 voxels.

### Table 4. Anatomical Site, Cluster Size, maximum Z value, and MNI coordinates of the local maxima for the connectivity analysis (seed in left ventral striatum [MNI coordinates −10 9 −9], connectivity gamblers>controls, main effect across delay and probability discounting trials).

| Region                      | cluster-size | Z    | MNI-coordinates |
|-----------------------------|--------------|------|-----------------|
| L Anterior Cingulate/vmPFC  | 122          | 4.17 | −12 40 10       |
| L Ventral Striatum          | 52           | 3.97 | −14 10 −6       |
| L Insula                    | 176          | 3.92 | −36 2 8         |
| R Inferior Parietal Lobule  | 24           | 3.58 | 44 48 22        |
| R Inferior Frontal Gyrus    | 41           | 3.53 | 48 34 −2        |
| L Inferior Frontal Gyrus    | 66           | 3.52 | −48 14 −6       |
| L Middle Temporal Gyrus     | 14           | 3.34 | −68 30 2        |
| R Superior Temporal Gyrus   | 11           | 3.33 | 56 −36 4        |

Clusters were thresholded at p<0.001 uncorrected and a minimum size of 10 voxels.
may benefit from the use autonomic measures to control for e.g. arousal. Nonetheless, it is possible that tasks such as these may generally be more rewarding for gamblers, an interesting possibility that would be in line with recent data showing a relative over-valuation of monetary vs. primary rewards in pathological gambling and substance use disorders. Nonetheless, it is possible that tasks such as these may generally be more rewarding for gamblers, an interesting possibility that would be in line with recent data showing a generally be more rewarding for gamblers, an interesting possibility that would be in line with recent data showing a relative over-valuation of monetary vs. primary rewards in pathological gambling and substance use disorders.

A shortcoming of our cross-sectional approach is that our data cannot reveal whether the observed increases in connectivity are the cause or the consequence of PG. However, on-going longitudinal studies such as IMAGEN [27] will hopefully shed light on whether increases in connectivity are a cause or a consequence of ICDs. Finally, unlike previous studies in other ICDs, we did not examine the resting state [27–29] but connectivity during a value-based choice task (although this is not strictly speaking a limitation). Future studies are therefore required to establish whether the present findings extend to the resting state.

Taken together, our data reveal a reliable enhancement of striatal-amygdala functional interactions in pathological gamblers during value-based decision-making. Interactions between these regions have been implicated in other ICDs, as well as in animal models of reward-guided behaviour. Our results in pathological gamblers therefore add to increasing evidence that elevated connectivity in limbic circuits may contribute to both substance-associated [28,29] and behavioural ICDs [27].

Author Contributions
Conceived and designed the experiments: JP SFM CB. Performed the experiments: SFM. Analyzed the data: JP SFM. Contributed reagents/materials/analysis tools: JP. Wrote the paper: JP SFM CB.

References
1. Kalivas PW, Volkow ND (2005) The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry 162: 1405–1413.
2. Bickel WK, Miller ML, Yr R, Kossal RP, Lindquist DM, et al. (2007) Behavioral and neuroeconomics of drug addiction: competing neural systems and temporal discounting processes. Drug Alcohol Depend 90 Suppl 1: 885–91.
3. Leeman RF, Potenza MN (2012) Similarities and differences between pathological gambling and substance use disorders: a focus on impulsivity and compulsivity. Psychopharmacology (Berl) 219: 469–490.
4. Peters J, Buechel C (2011) The neural mechanisms of inter-temporal decision-making: understanding variability. Trends Cogn Sci 15: 227–239.
5. Reynolds B (2006) A review of delay-discounting research with humans. Behav Processes 73: 107–130.
6. Green L, Myerson J (2004) A discounting framework for choice with delayed and probabilistic rewards. Psychol Bull 130: 769–792.
7. Dixon MR, Marley J, Jacobs EA (2003) Delay discounting by pathological gamblers and drug users. J Appl Behav Anal 36: 449–458.
8. Petry NM (2001) Pathological gamblers, with and without substance use disorders, discount delayed rewards at high rates. J Abnorm Psychol 110: 348–427.
9. Petry NM, Casarella T (1999) Excessive discounting of delayed rewards in substance abusers with gambling problems. Drug Alcohol Depend 56: 25–32.
10. Alessi SM, Petry NM (2003) Pathological gambling is associated with impulsivity in a delayed discounting procedure. Behav Processes 64: 355–354.
11. Miedl SF, Peters J, Buechel C (2012) Altered neural reward representations in pathological gamblers revealed by delay and probability discounting. Arch Gen Psychiatry 69: 177–186.
12. Liguori R, Sescousse G, Barbalat G, Domenach P, Dreher JC (2012) Shifted risk preferences in pathological gamblers. Psychol Med 1–10.
13. Holt DD, Green L, Myerson J (2005) Is discounting impulsive? Evidence from temporal and probability discounting in gambling and non-gambling college students. Behav Processes 64: 355–367.
14. Bickel WK, Yi R, Kowal BP, Lindquist DM, et al. (2007) Behavioral and neuroeconomics of drug addiction: competing neural systems and temporal discounting processes. Drug Alcohol Depend 90 Suppl 1: 885–91.
15. Reuter J, Raedler T, Rose M, Hand I, Glascher J, et al. (2005) Pathological gambling and substance use disorders. Arch Gen Psychiatry 71: 749–757.
16. van Holst RJ, Veltman DJ, Buechel C, van den Brink W, Goudriaan AE (2012) Distorted expectancy coding in problem gambling: is the addictive in the anticipation? Biol Psychiatry 71: 741–748.
17. Balodis IM, Kober H, Worhunsky PD, Stevens MC, Pearlson GD, et al. (2012) Diminished frontostriatal activity during processing of monetary rewards and losses in pathological gambling. Biol Psychiatry 71: 749–757.
18. de Ruiter MB, Veltman DJ, van den Brink W, Goudriaan AE (2012) Right on cue? Striatal reactivity in problem gamblers. Biol Psychiatry 72: e23–24.
19. Peters J, Buechel C (2009) Overlapping and Distinct Neural Systems Code for Subjective Value during Intertemporal and Risky Decision Making. J Neurosci 29: 15727–15734.
20. Tomasi D, Volkow ND (2012) Abnormal functional connectivity in children with attention-deficit/hyperactivity disorder. J Child Neuropsychiatry 71: 443–456.
21. Liu J, Liang J, Qin W, Tian, J, Yuan K, et al. (2009) Dysfunctional connectivity patterns in chronic heroin users: an fMRI study. Neurosci Lett 460: 72–77.
22. Ma N, Liu, Li N, Wang CX, Zhang H, et al. (2009) Addiction related alteration in resting-state brain connectivity. Neuroimage 49: 738–744.
23. Haber SN, Knutson B (2010) The reward circuit: linking primate anatomy and human imaging. Neupyschopharmacology 35: 4–26.
24. Carmichael ST, Price JL (1995) Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. J Comp Neurol 363: 615–641.
25. Ambroggi F, Ishikawa A, Fields HL, Nica SC (2008) Basolateral amygdala neurons facilitate reward-seeking behavior by exciting nucleus accumbens neurons. Neuron 59: 648–651.
26. Popeau AT, Popa D, Pape D (2009) Coherent gamma oscillations couple the amygdala and striatum during learning. Nat Neurosci 12: 801–807.
27. Stuber GD, Sparta DR, Stamataki AM, van Leeuwen WA, Hardjoprajitno JE, et al. (2011) Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking. Nature 475: 377–380.
28. van Holst RJ, van der Meer JC, McLearen DG, van den Brink W, Veltman DJ, et al. (2013) Interactions between affective and cognitive processing systems in problematic gamblers: a functional connectivity study. PLoS One 7: e49923.
29. O’Doherty JP, Hampton A, Kim H (2007) Model-based (MRI) and its application to reward learning and decision making. Ann N Y Acad Sci 1104: 35–53.
30. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, et al. (1997) Psychophysiological and modulatory interactions in neuroimaging. Neuroimage 6: 218–229.
31. Petry J (1996) Psychotherapie der Glücksspielsucht. Weinheim: Beltz/Psychologie Verlag Union.
32. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO (1991) The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. British Journal of Addictions 86: 1119–1127.
33. Beck AT, Steer RA (1987) Beck Depression Inventory - Manual. San Antonio, TX: Psychological Corporation.
34. Nichols T, Brett M, Andersson J, Wager T, Poline J (2005) Valid conjunction inference with the minimum statistic. Neuroimage 22: 653–660.
35. O’Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, et al. (2004) Disinhibitory roles of ventral and dorsal striatum in instrumental conditioning. Science 304: 452–454.
36. Humford TF, Kouloufig LT, Frecker RC, Fagerstrom KO (1991) The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. British Journal of Addictions 86: 1119–1127.
37. Buck AT, Steer RA (1987) Beck Depression Inventory - Manual. San Antonio, TX: Psychological Corporation.
49. Figner B, Knoch D, Johnson EJ, Krosch AR, Lisanby SH, et al. (2010) Lateral prefrontal cortex and self-control in intertemporal choice. Nat Neurosci 13: 538–539.

50. Hare TA, Camerer CF, Rangel A (2009) Self-control in decision-making involves modulation of the vmPFC valuation system. Science 324: 646–648.

51. Knoch D, Gianotti LR, Pascual-Leone A, Treyer V, Regard M, et al. (2006) Disruption of right prefrontal cortex by low-frequency repetitive transcranial magnetic stimulation induces risk-taking behavior. J Neurosci 26: 6469–6472.

52. Cohen MX, Elger CE, Weber B (2008) Amygdala tractography predicts functional connectivity and learning during feedback-guided decision-making. Neuroimage 39: 1396–1407.

53. Cohen MX, Schoene-Bake JC, Elger CE, Weber B (2009) Connectivity-based segregation of the human striatum predicts personality characteristics. Nat Neurosci 12: 32–34.

54. Forbush KT, Shaw M, Graeber MA, Hovick L, Meyer VJ, et al. (2008) Neuropsychological characteristics and personality traits in pathological gambling. CNS Spectr 13: 306–315.

55. Shin YC, Lim SW, Choi SW, Kim SW, Grant JE (2009) Comparison of temperament and character between early- and late-onset Korean male pathological gamblers. J Gambl Stud 25: 447–453.

56. Jimenez-Marcia S, Alvarez-Moya EM, Stinchfield R, Fernandez-Aranda F, Granero R, et al. (2010) Age of onset in pathological gambling: clinical, therapeutic and personality correlates. J Gambl Stud 26: 233–248.

57. Schumann G, Loth E, Ranaschewski T, Barbot A, Barker G, et al. (2010) The IMAGEN study: reinforcement-related behaviour in normal brain function and psychopathology. Mol Psychiatry 15: 1128–1139.