Damage to Insula Abolishes Cognitive Distortions during Simulated Gambling

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Abstract

Gambling is a naturalistic example of risky decision-making. During gambling, players typically display an array of cognitive biases that create a distorted expectancy of winning. This study investigated brain regions underpinning gambling-related cognitive distortions, contrasting patients with focal brain lesions to the ventromedial prefrontal cortex (vmPFC), insula or amygdala ('target patients') against healthy comparison participants and lesion comparison patients (i.e., with lesions that spare the target regions). A slot machine task was used to deliver 'near-miss' outcomes (i.e. non-wins that fall spatially close to a jackpot), and a roulette game was used to examine the gambler's fallacy (color decisions following outcome runs). Comparison groups displayed a heightened motivation to play following near-misses (compared to full-misses), and manifested a classic gambler's fallacy effect. Both effects were also observed in patients with vmPFC and amygdala damage, but were absent in patients with insula damage. Our findings indicate that the distorted cognitive processing of near-miss outcomes and event sequences may be ordinarily supported by the recruitment of the insula. Interventions to reduce insula reactivity could show promise in the treatment of disordered gambling.

Significance Statement

Gambling games are associated with a distorted psychological processing of random sequences (the gambler's fallacy) and unrewarded outcomes that fall close to a jackpot (near-misses). Problem gamblers appear more susceptible to these effects. Here, we show that these two gambling distortions are disrupted in patients with brain injury affecting the insula, compared to patients with damage to the ventromedial prefrontal cortex or amygdala. In a roulette task (red/black predictions), comparison groups chose either color less after longer runs of that color outcome. On a slot machine task, comparison groups rated higher motivation following near-misses relative to full-misses. Our results generate a clinical hypothesis that in disordered gambling, these cognitions may be underpinned by excessive recruitment of insula circuitry.

Introduction

Gambling is a widespread activity with a lifetime prevalence of 78% in the US (1) and a past-year prevalence of 73% in the UK (2). The widespread recognition that 'the house always wins', reflecting the negative expected value of gambling, makes gambling an enduring puzzle for psychological and economic models of choice behavior. Cognitive approaches to gambling explain this non-normative behavior with reference to a number of cognitive distortions and irrational beliefs that occur during gambling play, which cause the gambler to over-estimate his likelihood of winning (3, 4). The *illusion of control* refers to how superficial features of a game, such as a choice or instrumental response, promote erroneous perceptions of skill over outcomes that are determined only by chance (5). *Near-miss* outcomes (non-wins that fall close to the jackpot) increase motivations to play, plausibly by fuelling beliefs about skill acquisition (6). The *gambler's fallacy* is a bias in the processing of randomness, whereby recent consecutive outcomes are considered less likely to repeat, and conversely, outcomes that have not occurred in the recent history are perceived as 'due' (7).

These distortions are reliably observed in field studies, e.g. casino environments (8), and are not confined to gambling; illusory control and the gambler's fallacy are observed in stock traders (9), and near-misses influence decision-making in occupational settings (10). In the laboratory, these distortions can be elicited with gambling games, allowing the comparison of these biases between different clinical groups. The overall level of distorted thinking is elevated in people with gambling problems (11, 12) and these cognitions can be targetted effectively in psychological therapy for disordered gambling (13).

The neurobiological basis of these gambling-related distortions has received little attention to date. Functional imaging studies of pathological gambling have focussed largely on abnormalities in appetitive processing, reinforcement learning and executive functions (14-17). These studies identify dysregulation across an extended brain network (sometimes termed the 'brain reward system') that includes the ventromedial prefrontal cortex (vmPFC), striatum, amygdala and insula. However, in these experiments the direction of signal abnormality (i.e. hyperactivity vs hypoactivity) is not consistent, and the precise neural signatures are highly task dependent (18). A previous fMRI study of a simplified slot machine found that near-misses recruited overlapping neural circuitry to the jackpot wins in the ventral striatum and insula, and that insula responses increased with higher levels of trait-related susceptibility to gambling distortions (6, 19). Other neuroimaging work has indicated sensitivity of insula and medial prefrontal cortex to sequences of consecutive outcomes, and subsequent updating of choice strategy (20-22).

The aim of the present study was to investigate brain regions underlying gambling distortions, by studying patients with focal brain injury. Unlike functional neuroimaging, this neuropsychological approach allows causal inferences to be made concerning the necessary role of candidate brain regions in psychological processes (23). We identified cases with focal brain damage affecting either the vmPFC, the insula or the amygdala; injury to these regions impairs real-life decision-making and emotional behavior (24-26). Furthermore, neuropsychological testing in pathological gamblers has identified a profile of impaired risky choice that is highly reminiscent of vmPFC damage in particular (27, 28). Given the exaggeration of gambling-related cognitive distortions in problem gamblers, an intuitive prediction might be that the lesion groups would show an *enhanced* sensitivity to near-miss outcomes, illusory control, and gambler's fallacy. However, the alternative prediction is also plausible: given that these non-normative gambling biases also occur in healthy participants, in whom they are underpinned by the recruitment of reward-related neural circuitry (6, 19, 20), the lesion groups might be immunized against these gambling distortions.

Results

Patients with lesions affecting the vmPFC (n=17; see Fig S1), insula (n=8; see Fig. 1) and amygdala (n=6; see Fig. S2) completed two gambling tasks. A slot machine task (see Fig. 2A) measured the sensitivity to near-miss outcomes, and included a manipulation of personal choice that provides a measure of the illusion of control. A roulette task (see Fig. 2B) measured the susceptibility to the gambler's fallacy. With the inclusion of multiple lesion subgroups of fairly small sizes, the first stage of analysis collapsed the three groups into a pooled 'target group' (n=31), for comparison against healthy participants (n=16) and a lesion comparison group (n=13; see Fig S3) that comprised a mixture of patients with posterior, lateral temporal and superior frontal cortex damage. This approach maximises power to detect an effect in regions that are anatomically interconnected, and likely to operate as a functional circuit (26). At a second stage of analysis, the target group was separated into the constituent subgroups to directly compare the effects of vmPFC, insula and amygdala damage, given evidence for differential functional specialisations of these regions (29-31). In both analyses, the groups did not differ significantly in terms of age, years of education or sex distribution (see Table S1). When asked about their gambling involvement in real life, most participants reported "none" or "occasional" involvement; with only two cases (one vmPFC, one lesion comparison patient) reporting "regular" gambling. Two lesion patients reported that their gambling had increased following their brain injury; both were males in the vmPFC lesion group, and one of these was the only participant identified as a probable pathological gambler on a screening instrument, the South Oaks Gambling Screen (32) (threshold ≥5; this participant scored 6). There

were no group differences on the Gambling Related Cognitions Scale (33), a trait-related measure of their beliefs about gambling and susceptibility to gambling biases.

Slot Machine Task

A simulated two-reel slot machine was used to deliver wins, as well as 'near miss' and 'full miss' non-winning outcomes. On half the trials, the participant was asked to select a 'play icon' from six alternatives on the left reel; on the remaining trials, the play icon was selected automatically by the computer. Following this icon selection, the right hand reel spun and slowed to a standstill. If the right reel aligned with the selected icon on the left reel, the participant received a hypothetical win ("Win $1!"). All other outcomes were designated non-wins ("No win"). On-screen Likert scales were presented following icon selection ("Please rate your chances of winning") and following the outcome message ("How pleased are you with that result?"; "How much do you want to continue the game?").

On the ratings of "chances of winning", all groups manifested a higher expectancy of winning when selecting the play icon themselves, compared to when the play icon was selected automatically (main effect: $F(1,47) = 7.03$, $p = .011$). This influence of personal choice is consistent with an illusion of control. The effect did not vary significantly across groups (main effect of Group: $F(2,47) = 0.49$, $p = .613$; Group x Choice interaction $F(2,47) = 1.00$, $p = .377$) (see Table S2).

Comparing the subjective ratings following winning outcomes against all non-win outcomes, the wins were rated as more pleasant ($F(1,45) = 90.3$, $p < .001$) and there was a significant Group x Outcome interaction ($F(2,45) = 4.32$, $p = .019$). Win responsivity was blunted in the lesion comparison group ($\Delta = 45.5$. $SD = 56.8$) compared to the target group ($\Delta = 108.3$, $SD = 53.9$, $p = .005$) and the healthy participants ($\Delta = 87.5$, $SD = 54.2$, $p = .071$), who did not differ ($p = .247$) (see Fig. S4). Pleasantness ratings did not vary as a function of personal choice ($F(1,45) = 1.66$, $p = .204$). Wins also increased the motivation to continue ($F(1,43) = 11.4$, $p = .002$), and this effect did not vary across groups ($F(2,43) = 0.64$, $p = .532$) or as a function of personal choice ($F(1,43) = 0.68$, $p = .413$).

The next set of tests compared the near-misses against the full-misses; both non-win outcomes that are objectively equivalent. On the motivation rating, a statistically reliable Outcome x Control interaction was seen ($F(1,43) = 6.03$, $p = .018$) (see Fig. 3A). Consistent with past observations with this task, the interaction was driven by the participant-chosen trials, on which near-misses tended to increase the motivation to continue playing ($M = 45.2$, $SD = 29.2$) compared to full-misses ($M = 43.6$, $SD = 29.9$), although this effect was marginally significant ($t_{45} = 1.69$, $p = .10$). On trials without personal control, near-misses and full-misses did not differ ($t_{45} = 0.76$, $p = .453$). In addition, there was a significant Outcome x Group interaction ($F(2,43) = 3.69$, $p = .033$) such

that the motivational effect of near-misses was attenuated in the target group (Δ = -0.70, SD = 3.51) compared to healthy participants (Δ = 1.91, SD = 3.01; p = .019) and the lesion comparison group (Δ = 1.92, SD = 2.81; p = .068). There were no significant effects in the equivalent model for pleasantness ratings.

Subdividing the target group into the vmPFC, insula and amygdala subgroups, the overall task sensitivities were similar to the first model: the perceived chances of winning was higher on personal choice trials, and winning outcomes were rated as more pleasant and increased the motivation to continue the game. An additional effect was a further manifestation of the illusion of control: an Outcome x Choice interaction was observed on the pleasantness ratings following wins compared to non-wins ($F(1,20) = 12.1$, $p = .002$), such that participant-chosen wins were rated as more pleasant (M = 69.9, SD = 31.5) than computer-chosen wins (M = 61.1, SD = 33.5) ($t_{22} = 2.87$, $p = .009$). This effect did not vary across groups ($F(2,20) = 0.402$, $p = .674$). Critically, the motivational ratings to near-misses compared to full-misses revealed a further dissociation between the three lesion sites (Outcome x Group interaction: $F(2,21) = 3.47$, $p = .050$). The insula group showed a smaller (and in fact inverted) motivational response to near-misses (minus full-misses: Δ = -3.2, SD = 3.6) compared to the amygdala group (Δ = +1.4, SD = 2.1) (p = .018) (see Fig. 3B). The insula group also differed at trend from the vmPFC group (Δ = -0.3, SD = 3.4) (p = .074).

Roulette Task

Participants played 90 successive trials on a binary-choice roulette task. The roulette wheel displayed an equal number of red and blue segments, and on each trial, the participant first guessed 'red' or 'blue', and then gave a confidence rating on 21-point visual analogue scale. After these two responses, the wheel spun briefly and the outcome was displayed for that trial. Consecutive outcomes of the same color are referred to as "runs" (i.e. blue, red, red, red is an outcome run of length 3), and consecutive correct or incorrect predictions are referred to as "streaks".

To quantify the gambler's fallacy, we calculated the probability of choosing either color as a function of the run length of that color (7). In a model comparing the target group, lesion comparison group, and healthy participants, there was a strong main effect of run length ($F(4,200) = 8.83$, $p < .001$), with decreasing choice of either color after longer runs of that color. This gambler's fallacy effect did not vary across groups (main effect of Group: $F(2,50) = 1.14$, $p = .327$; Group x Run Length interaction $F(8,200) = 0.56$, $p = .728$) (see Fig. 4A).

Comparing the subgroups of target patients (15 vmPFC, 6 insula, 6 amygdala), the analysis of color choice again showed the main effect of Run Length ($F(4,96) = 3.55$, $p = .010$), as well as a significant Group x Run Length interaction ($F(8,96) = 2.14$, $p = .039$). Calculating a change score

based on the difference between shorter run lengths (1 and 2) and longer run lengths (3, 4 and 5), the insula group showed positive recency on average (Δ = -0.09, SD = 0.18), differing significantly from the vmPFC group (Δ = 0.14, SD = 0.16) ($p = .005$) and the amygdala group (Δ = 0.16, SD = 0.14) ($p = .012$) who did not differ in expression of the typical gambler's fallacy ($p = .831$) (see Fig. 4B).

We also examined confidence ratings on the roulette game, as a function of winning and losing streaks. Comparing the target group against the lesion comparison group and healthy participants, subjective confidence did not vary significantly as a function of either winning streak length ($F(4,184) = 0.25$, $p = .833$) or losing streak length ($F(4,184) = 1.61$, $p = .192$). As such, there was no discernible 'hot hand' effect in our data (7) (although see also Table S3). The effects of streak length did not interact significantly with group status (all $F < 1.39$, $p > .259$), and there were no additional effects within the target group. Several additional metrics were derived to characterize choice behavior on the roulette task. There were no differences between groups in the overall choice of red vs blue, or the 'stickiness' of choice according to either the previous choice or the previous outcome (see Table S4). We computed variables reflecting win-stay and lose-shift biases; there was a significant difference between the target group, lesion comparison group and healthy participants in the lose-shift score ($F(2,50) = 3.25$, $p = .047$) but not the win-stay score ($F(2,50) = 0.39$, $p = .679$). Target patients were more likely to switch color choice following an unsuccessful prediction than healthy controls ($p = .023$), but this tendency did not vary significantly between the vmPFC, insula and amygdala subgroups ($F(2,24) = 0.362$, $p = .700$).

Discussion

The key effect described here is that a group of patients with stable brain injury affecting the insula region show a marked attenuation of two cognitive distortions that were elicited in healthy participants and patients with lesions to other structures, and which can be widely observed during naturalistic gambling across various games. On the slot machine task, near-miss outcomes (where the reel stopped one position from a win) typically increase the self-reported motivation to continue with the game (6, 34); this effect was selectively absent in the insula group. On the roulette task, binary choice displayed a classic negative recency, where the choice of either color decreased as a function of the preceding run of that color (7); the insula group did not manifest this avoidance of recent outcomes. These data provide the first evidence for the causal involvement of the insula region in some of the cognitions characteristic of gambling behavior.

The roulette task used here was simple guessing game, tapping strategic decision-making that may be modulated – erroneously – by the recent outcome history. Here, insula patients distributed their choices between the two color options, and showed no apparent differences in

basic 'stickiness' or self-reported confidence, but they deviated from the other groups in that they did not show a gambler's fallacy bias. An intriguing feature is that the averaged data for the insula group displayed modest *positive* recency in their roulette color choice (Fig. 4B). On the slot machine task, near-misses were similarly observed to be *de*-motivating (Fig. 3B). This apparent inversion implies some systematic tendency in the insula patients, but based on an alternative model of the task contingencies (and supported by different regions of the decision-making network). In a probabilistic environment, it is beneficial to select recently-reinforced options, and a recent fMRI study indicated that dorsal striatal responses track reinforcement learning parameters in such a task (35). Other work highlights involvement of dorsolateral prefrontal cortex in detecting pattern violations (36) and switching responding after longer runs (37). One relevant procedural difference in the 'matched pennies' task used by Xue et al (37) is that a history bar was presented, showing participants the recent outcomes. After long runs of the same outcome, the history bar may serve as a direct cue to switch, thus lessening any reliance on participants' internal model of the task. Further behavioral work could usefully compare strategic choice in the presence or absence of such cues for the reinforcement history.

In light of evidence that gambling cognitions are increased in disordered gambling (11, 13), these data generate a testable hypothesis that over-recruitment of insula circuitry may underlie gambling-related cognitive distortions. In fact, functional neuroimaging provides some support for this idea. In healthy participants, insula responsivity to near-miss outcomes correlated positively with their trait susceptibility to gambling distortions on a self-report scale (6, 38). Using a monetary incentive delay task in treatment-seeking pathological gamblers, over-activity of anterior insula during loss anticipation was correlated with gambling severity scores (39). These effects may be mediated by the established role of the insula in the representation of bodily states, i.e. interoception (40). Certainly, gambling is an intensely exciting, visceral activity, and near-misses were previously shown to induce physiological changes in skin conductance and heart rate (34, 41). One could hypothesize that the central processing of these peripheral signals is abolished by insula damage. Via a similar mechanism, insula activity has been linked to drug craving, such that smokers who suffered infarcts to the insula region quit smoking and described an abolition of the urge to smoke (42). Animal models have corroborated these effects of insula damage on drug self-administration, with lesions centred on posterior, granula insula (43, 44). Therapeutic strategies to reduce insula responsivity, such as mindfulness- or meditation-based techniques (45, 46) or GABA-ergic medications (47), may usefully augment cognitive therapy for psychological distortions in the treatment of problem gambling.

In addition to its interoceptive functions, the insula is increasingly thought to play a critical role in decision-making under uncerainty. fMRI studies indicate heightened insula signal following outcomes from risky decisions, and these responses vary across subjects as a function of risk-taking propensities (22, 48, 49). Anterior insula appears to represent risk predictions during choice, and risk prediction errors in response to decision outcomes (50). Such predictions about the uncertainty of the environment are relevant to both the near-miss effect (51) and gambler's fallacy (35), and arguably less relevant to the illusion of control effect that did not vary across lesion groups here. Past work in cases with insula lesions has shown increases in risk-taking and impaired discrimination between risky gains and risky losses (31, 52). Using an investment task in which most participants are loss averse, patients with brain injury to either vmPFC, insula or amygdala achieved higher profits (26), and these effects were strongest in the insula subgroup (n=4), who also failed to modify their investment behavior as a function of prior outcome (i.e. losses vs wins) – an effect that resembles the abolition of the gambler's fallacy (Table S5 also displays an analogous effect in icon selection on the slot machine task). While the target group in the present study showed a greater lose-shift tendency on the roulette task, this effect did not vary across groups (and was numerically weakest in the insula subgroup), and thus seems unlikely to contribute to their positive recency across successive red or black outcomes.

At the current time, it is not known whether the insula involvement in decision-making and risky choice is dissociable from its interoceptive functions. While an integrative model has been proposed that anterior insula represents predictions of both internal states and decision uncertainty (53), other work highlights functional segregation within the insula, in which decision-making localises to the anterior, agranular insula adjacent to the orbitofrontal region, and visceral representations may be located more posteriorly (54, 55). Neuropsychological studies in stroke cases lack the specificity to resolve anterior – posterior insula effects, but we note that the insula lesion overlap in the present study was located posteriorly.

In the patients with injury to the vmPFC and amygdala, the effects of near-misses and the gambler's fallacy were comparable to those of participants in the healthy and lesion comparison groups. Data from neuropsychological testing and functional neuroimaging in pathological gamblers provide much evidence for disruption of the vmPFC and orbitofrontal cortex (16, 27, 28, 56), as well as preliminary evidence for amygdala involvement in loss aversion (57) and gain expectancies (17). Nevertheless, our data do not support the involvement of these regions in either the near-miss effect or gambler's fallacy. Concerning the lack of effect in the vmPFC lesion group, it may be pertinent that neither of our gambling tasks loaded heavily on risk-*taking* or representations of expected value (31, 58). Rather, the slot machine task primarily measured emotional reactivity. Past

studies have also found no effects of vmPFC lesions on the responses to obtained financial gains (59), mood induction (60) or emotional images, providing attentional engagement is adequate (61). We did observe some diminution of win responsivity in the lesion comparison group on pleasantness ratings. Given that this effect was not predicted, and the heterogeneous nature of the damage in the lesion comparison group, this effect is treated with caution.

Some further observations require additional testing to fully resolve. In our insula group, damage extended into the dorsal part of the basal ganglia in some patients. Single case analysis (see Table S6) indicated that these patients were most disrupted on the two distortions, but also showed that some attenuation was clearly present in the insula cases with no striatal involvement. Larger studies are needed to resolve the functional dissociations between insula and (dorsal) striatum (62). It could be reasoned that striatally-mediated effects should also interfere with win processing and the personal choice manipulation (63, 64), which was not the case. Lastly, the disruption of both the near-miss effect and the gambler's fallacy in the insula cases implies some linkage of these two gambling distortions, raising a broader question of how the various gambling-related cognitive distortions should be organised at a psychological or neural level. In conclusion, we provide neuropsychological evidence for the causal involvement of the insula in two gambling-related cognitive distortions, generating a testable hypothesis of insula over-activity in disordered gambling.

Materials and Methods

Participants. Neurological patients were recruited from the Patient Registry in the Department of Neurology at the University of Iowa. All patients had focal, stable lesions that were predominantly adult-onset, and all sustained at least one year prior to testing. All of the lesion cases have undergone extensive screening and neuropsychological evaluation that rule out dementia and diffuse cognitive deficits, and these measures have been presented in prior studies (24, 30, 31, 52). Exclusion criteria were a history of mental retardation, learning disability, or psychiatric illness including substance abuse. Patients were selected for eligibility on the basis of neuroanatomical status obtained from MRI or CT scanning (see below). For the vmPFC group (see Fig. S1), the criterion for inclusion was damage in the unilateral or bilateral portions of the mesial orbital/ ventromedial sector of the prefrontal cortex and/or the frontal pole. None of the vmPFC group had damage involving the amygdala or the insular cortex. Lesion aetiology in the vmPFC group was haemorrhage due to ruptured aneurysm of the anterior communicating artery or benign tumour resections, and the group including a mixture of bilateral (n=12), right unilateral (n=3) and left unilateral (n=2) lesions.

In the insula lesion group (see Fig. 1), the lesion involved damage to any part of the insular cortex (anterior and/or posterior) and/or the adjacent secondary somatosensory cortex (SII). In the insula group, lesion aetiology was a middle cerebral artery stroke in all cases, and all lesions were unilateral (left n=4, right n=4). In individual cases, some lesions extended medially into the edge of the basal ganglia (internal capsule and possible putamen) (see Table S6 for single case analysis), laterally into superior temporal lobe, posteriorly into the inferior parietal cortex, and anteriorly into the inferior frontal gyrus. None of the cases had damage that reached the medial temporal lobe or the medial prefrontal cortex.

In the amygdala lesion group (see Figure S2), the lesion involved selective bilateral damage to the amygdala in one case (due to Urbach-Wiethe disease), or unilateral left-sided damage in the other 5 cases. In the unilateral cases, lesion aetiology was surgical resection to treat pharmacoresistent epilepsy, and the damage included the amygdala but extended to adjacent regions of the hippocampus, parahippocampal gyrus, and entorhinal cortex. None of the cases had damage that reached the insula or the medial prefrontal cortex.

The lesion comparison group (see Fig. S3) involved brain damage sparing the target brain regions described above, i.e. the lesion did not include any insula, amygdala or mesial orbital/ ventromedial prefrontal cortex. These cases had unilateral damage that was mostly due to strokes and a few benign tumour resections.

A further 16 healthy participants were recruited through community advertising. The study was approved by the human subjects committee at the University of Iowa. Before enrolment in the study, written informed consent was acquired in accordance with the Declaration of Helsinki. Participants were testing in quiet laboratory conditions. In addition to the two gambling tasks (see below), participants completed the South Oaks Gambling Screen (32), a self-report symptom checklist for pathological gambling, and the Gambling-Related Cognitions Scale (33), a 24-item questionnaire assessing trait susceptibility to gambling cognitions.

Neuroanatomical Analysis. Lesion location was generally confirmed using Magnetic Resonance Imaging (MRI), with a 1.5T General Electric scanner with a spin gradient sequence, in 1.5mm contiguous T_1 weighted coronal slices. MRI scanning was not available in every case (see corresponding figure legends); for those cases, a computerized axial tomography (CT) scan was acquired instead using either a Picker 1200 or Toshiba Express SX scanner, with tilt angle optimised per subject to avoid clip-related artefact (zoom 2.4, field of view 51cm, fovea 212.5mm, slice thickness 2-4mm). For all mappable lesions, the lesions of individual patients were transferred manually onto a normal reference brain using the MAP-3 technique (65).

Slot Machine Task. Participants completed 60 trials (following 4 practice trials) on a simplified two-reel slot machine task, described in detail in Clark et al. (6). The screen background colour (white or black) designated two choice conditions: either participant-chosen trials, in which the participant selected the 'play icon' on the left reel by scrolling the reel up or down, and computer-chosen trials, in which the play icon was selected automatically. Following icon selection, the right reel spun and decelerated (mean spin time: 4.2 s) to deliver a win ($1), near-miss, or full-miss outcome (outcome duration 6 s). Current earnings were displayed in the inter-trial interval (duration 5 s); instructions specified that the participant was playing for 'pretend money'. The outcomes and choice condition (participant-chosen, computer-chosen) occurred in a fixed pseudo-random sequence such that wins occurred on 1/6, and near-misses on 1/3 trials. On each trial, three Likert ratings were taken: following icon selection, "How do you rate your chances of winning?" (0 to +100), and following the outcome, "How pleased are you with the result?" (-100 to +100) and "How much do you want to continue to play?" (0 to +100).

Roulette Task. This binary choice task was modified from (7). The roulette wheel displayed an equal number of red and blue segments, and on each trial, the participant first guessed red or blue, and then gave a confidence rating on 21-point scale. Following the colour choice and confidence rating, the wheel spun for 800-1200ms, and the outcome was presented (e.g. "Blue: you win"). Participants completed 3 practice trials, followed by a total of 90 trials, using a pre-specified colour sequence in order to deliver runs of 1-5 consecutive outcomes of the same colour. This fixed sequence had an equal probability of either colour, and a probability of alternation of 0.48.

Statistical Analysis. Some patients could not be tested on all measures (see Table S1), and there are further exclusions on the 2 tasks for participants who did not vary their ratings at all (on the slot machine task), or did not vary their choice behaviour sufficiently on the roulette game (>95% to either red or black). Although such uniform responding is a reasonable approach that does not violate the rules of either task, these cases would be inherently insensitive to the distortions of interest here. ANOVA models used the Greenhouse-Geisser correction, with two-tailed $p<.05$. Post-hoc comparisons were tested using Least Significant Differences, as is appropriate for 3-group designs (66).

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Figure Legends

Figure 1. Lesion overlap in the insula lesion group. On the coronal slices, the radiological convention (right=left) is applied. Warmer colors represent greater lesion overlap across patients. Seven of the 8 patients had lesions that were mappable from MRI scans; one further patient had a CT scan that was not of sufficient quality for lesion mapping, but clinically inspected for verification of lesion location in the insula. In the right sided patients, there is maximal lesion overlap in the insula and SII area in all 4 patients (red). In the left sided patients, the overlap in the 3 mappable cases (yellow) is in the insula, but is relatively small because damage in one patient was focussed on the anterior insula.

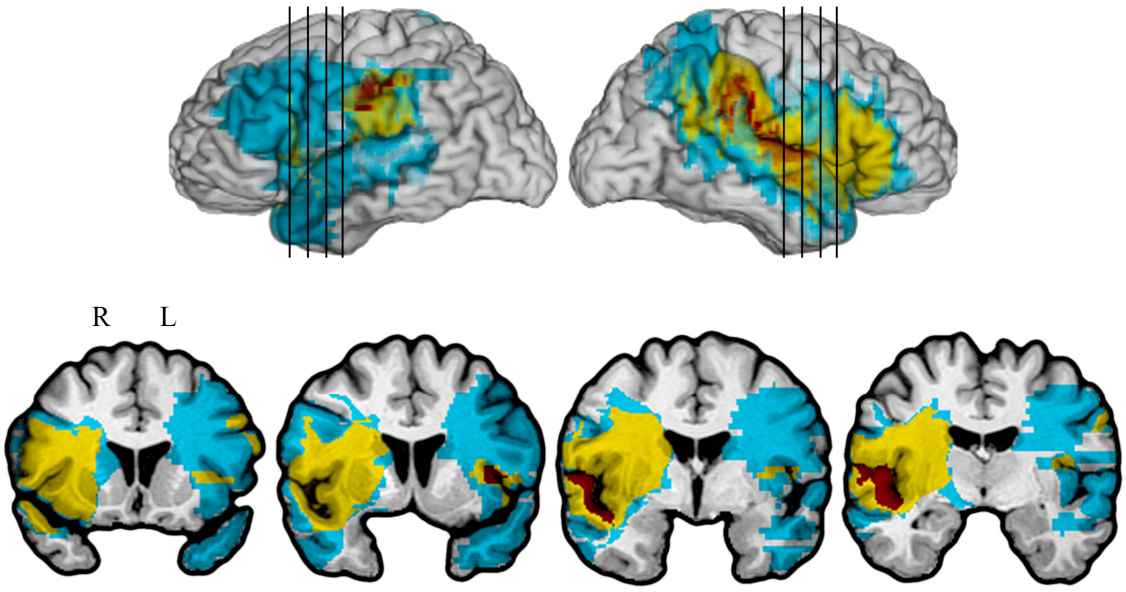


Figure 2: Graphical illustration of the two gambling simulations: A) The slot machine task was used to measures the effects of near miss outcomes (shown) on post-outcome ratings. B) The roulette task involved red / blue color choices, to measure the gambler's fallacy.

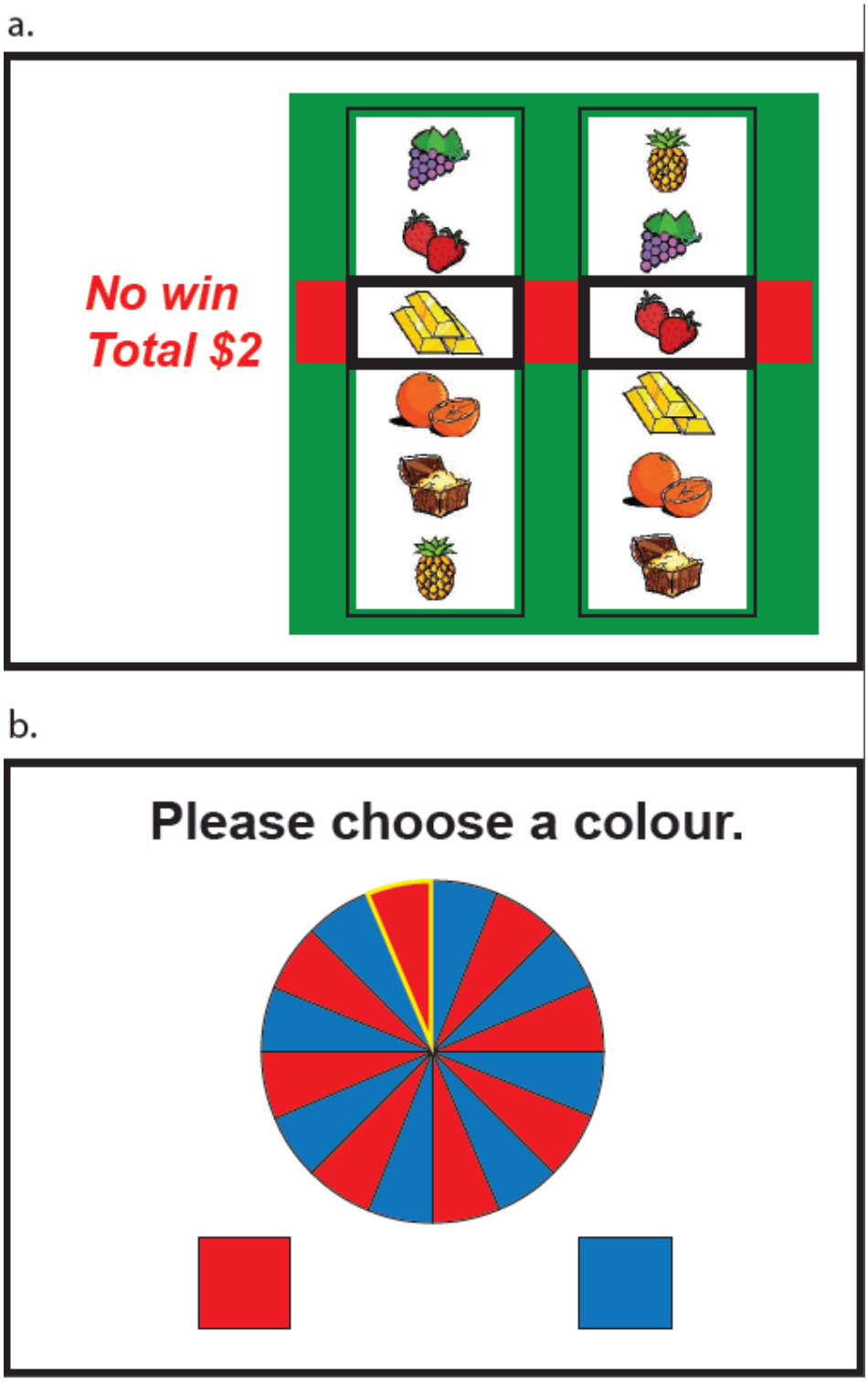


Figure 3: Motivational ratings of near-miss outcomes on the slot machine task, displayed separately for participant-chosen and computer-chosen trials. A) Target group, lesion comparison group and healthy participants, B) Change scores (Δ) for the motivational ratings after near-misses (minus full-misses) for the target subgroups. Error bars indicate standard error of the mean.

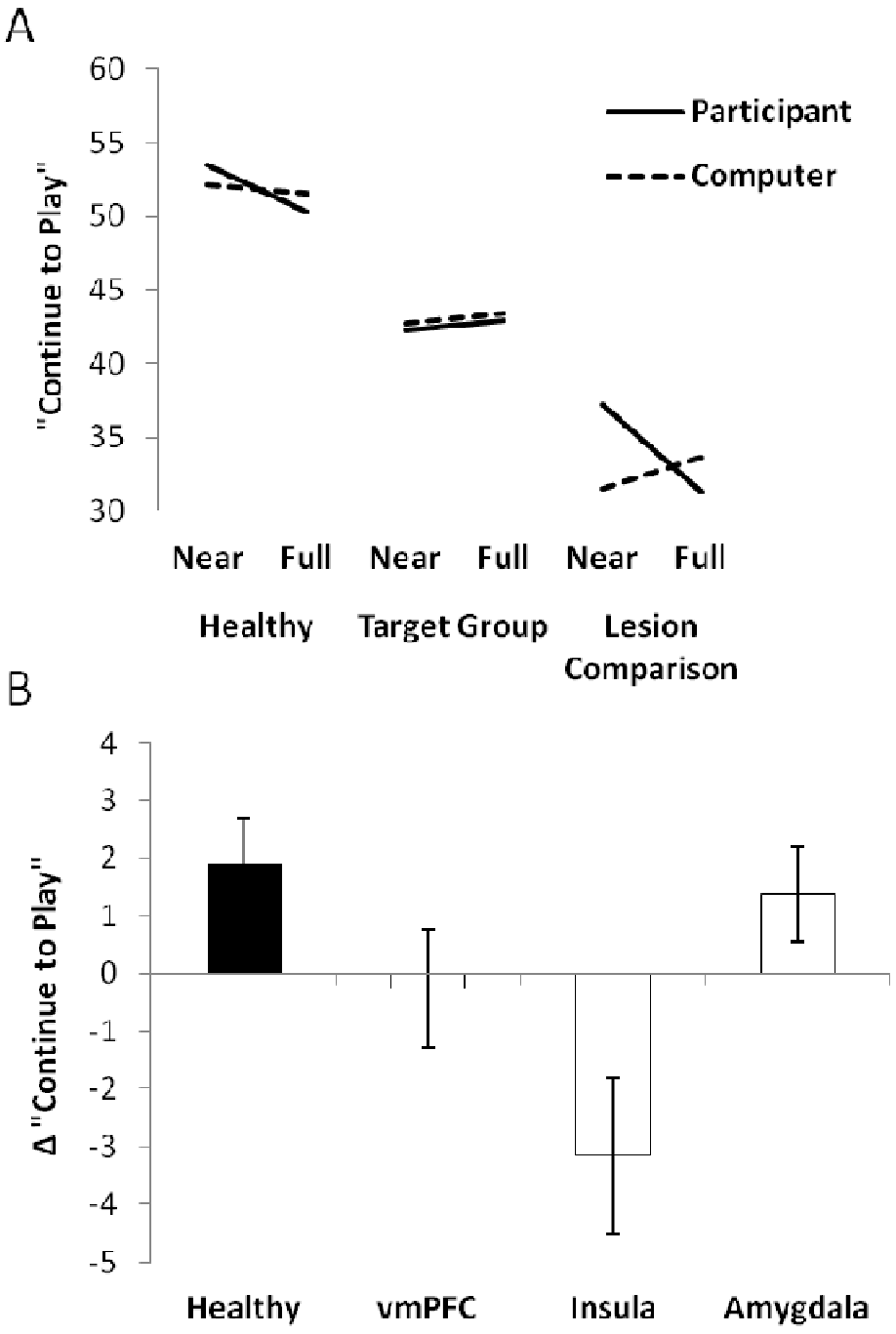
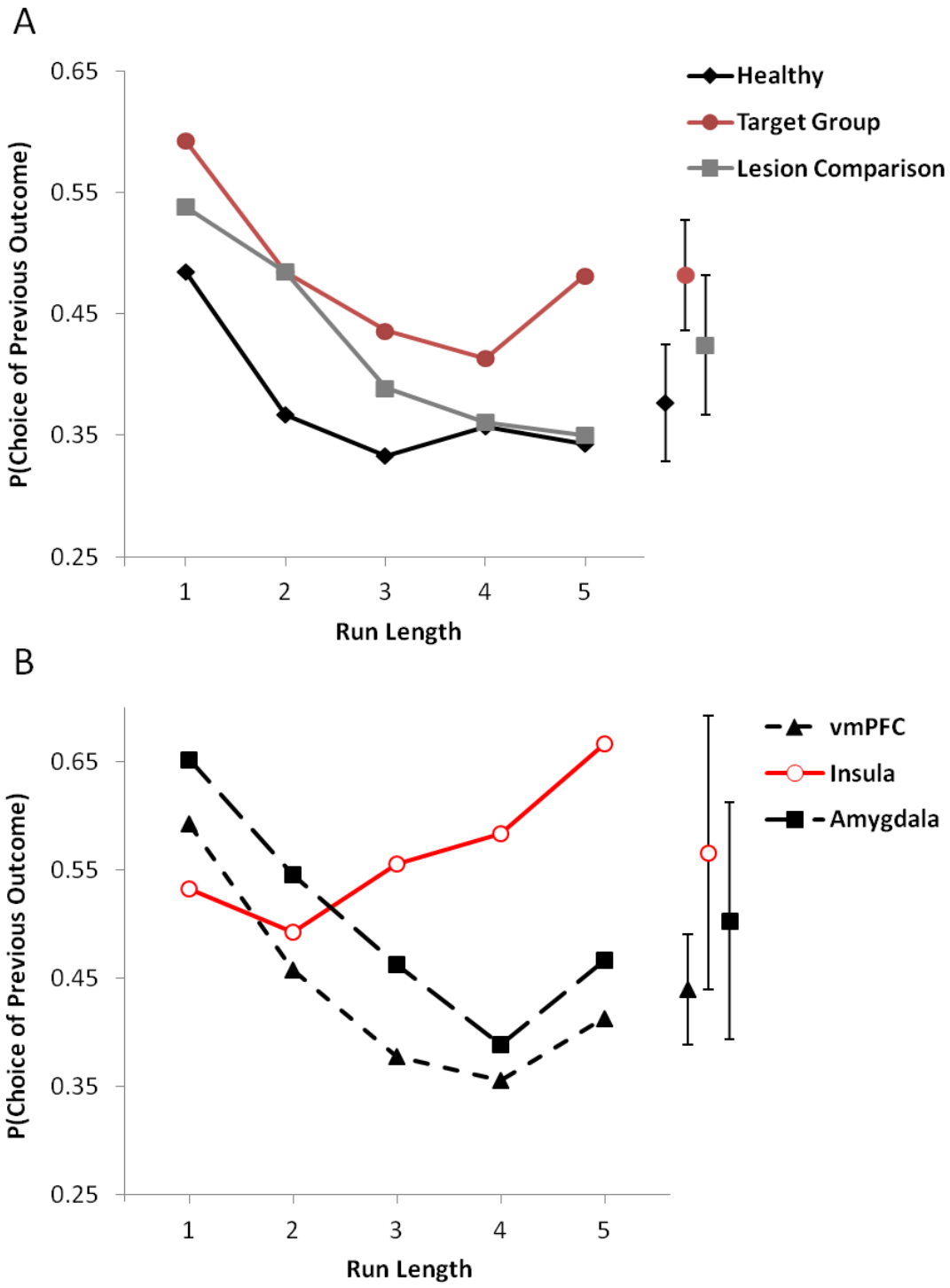


Figure 4: Choice behavior on the roulette task: A) Target group, lesion comparison group and healthy participants, and B) Subdividing the target group to display the insula, vmPFC and amygdala lesion patients. The ordinate presents the proportion of trials on which the participant's color choice matched the outcome of the previous spin.



Supporting Information

Figure S1. Lesion overlap in the vmPFC lesion group, in views of the lateral and medial surfaces (top row), and in coronal sections (bottom row) with slices taken at each of the lines shown on the brain surfaces in the top row. On the coronal slices, the radiological convention (right=left) is applied. All 17 vmPFC lesion patients had mappable scans. Warmer colors represent greater lesion overlap across patients, with maximal overlap (red, across all 17 cases) in the mesial orbital / ventromedial sector of prefrontal cortex and frontal pole. In one case (blue), the lesion is broader, extending posteriorly into the anterior cingulate and basal forebrain, and superiorly into the superior frontal gyrus. None of the lesions include the insula or the medial temporal lobe.

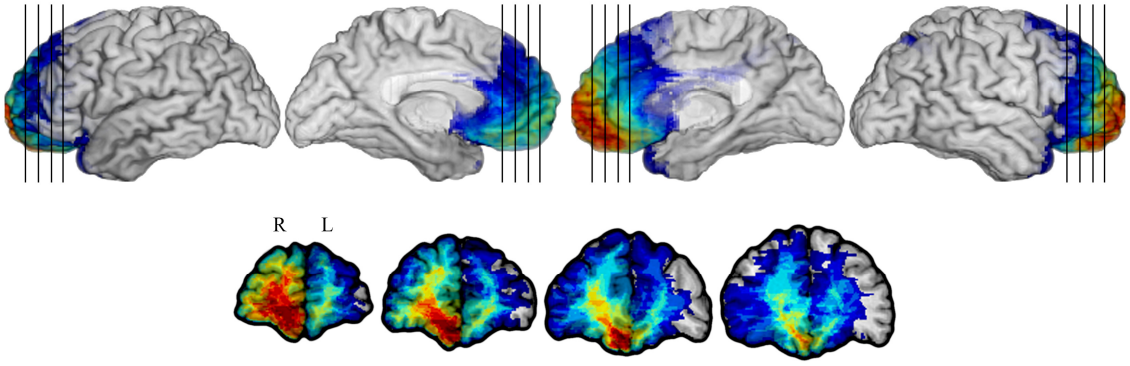


Figure S2: Lesion overlap in the amygdala lesion group, in views of the left and right lateral surfaces (top row), and in coronal sections (bottom row) with slices taken at each of the lines shown on the brain surfaces in the top row. On the coronal slices, the radiological convention (right=left) is applied. All 6 amygdala patients had MRI scans that were mappable. One case had a selective bilateral lesion (n=1) in the amygdala due to Urbath-Wiethe disease; the other cases had unilateral left-sided lesions (n=5). There is maximal lesion overlap (reflected by red color followed by a yellowish and green color) across the group in the left amygdala, which extending to adjacent sectors of temporal lobe in the unilateral cases (the blue color). None of the cases had lesions involving the insula or the vmPFC.

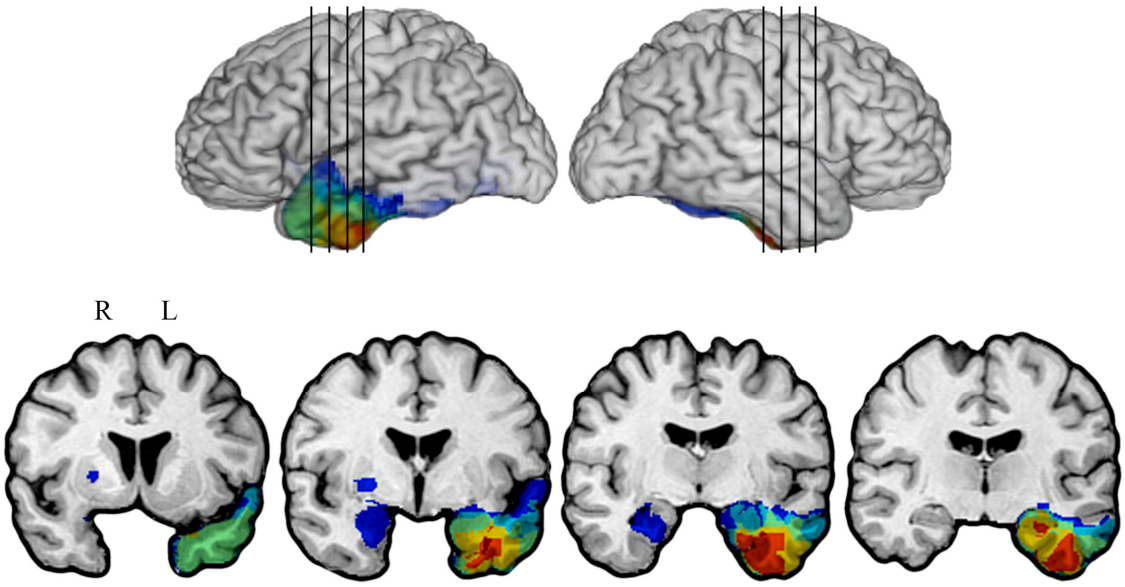


Figure S3: Lesion overlap in the lesion comparison group, in views of the lateral and medial surfaces (top row), and in coronal sections (bottom row) with slices taken at each of the lines shown on the brain surfaces in the top row. On the coronal slices, the radiological convention (right=left) is applied. Only 6 out of the 13 lesion control patients had mappable scans; the remaining 7 patients had CT scans that were clinically verified for lesions excluding the target areas, but did not undergo the high resolution MRI scan to allow lesion mapping. The lesions in the mappable group were variable with some areas of overlap as reflected in yellowish color (overlap of 3 lesions) and cyan color (overlap of 2 lesions). The lesions were primarily in the occipital region of the brain, with some extending into the inferior occipitotemporal region. Most importantly, none of the lesions had damage in any of the target areas: the vmPFC, insular cortex, or amygdala.

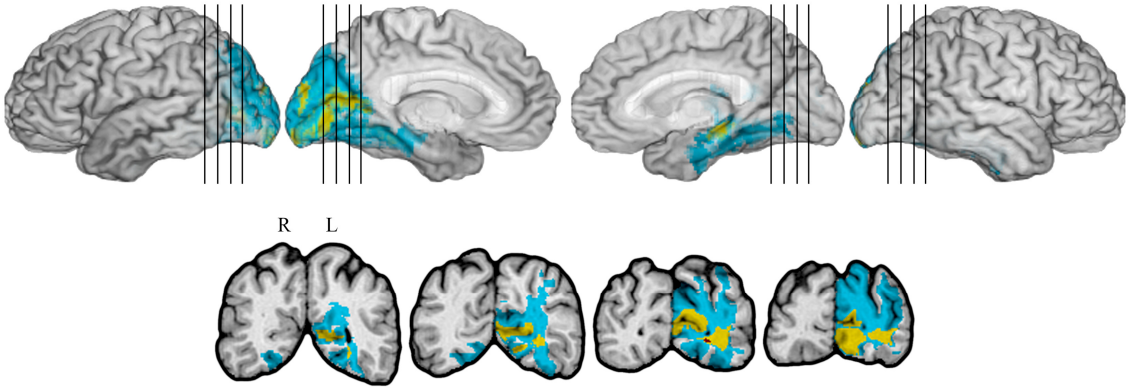


Figure S4: Hedonic ratings ("How pleased are you with the result?") in the target group, lesion comparison group and healthy participants, following wins compared to non-winning outcomes outcomes on the slot machine task, displayed separately for participant-chosen and computer-chosen trials.

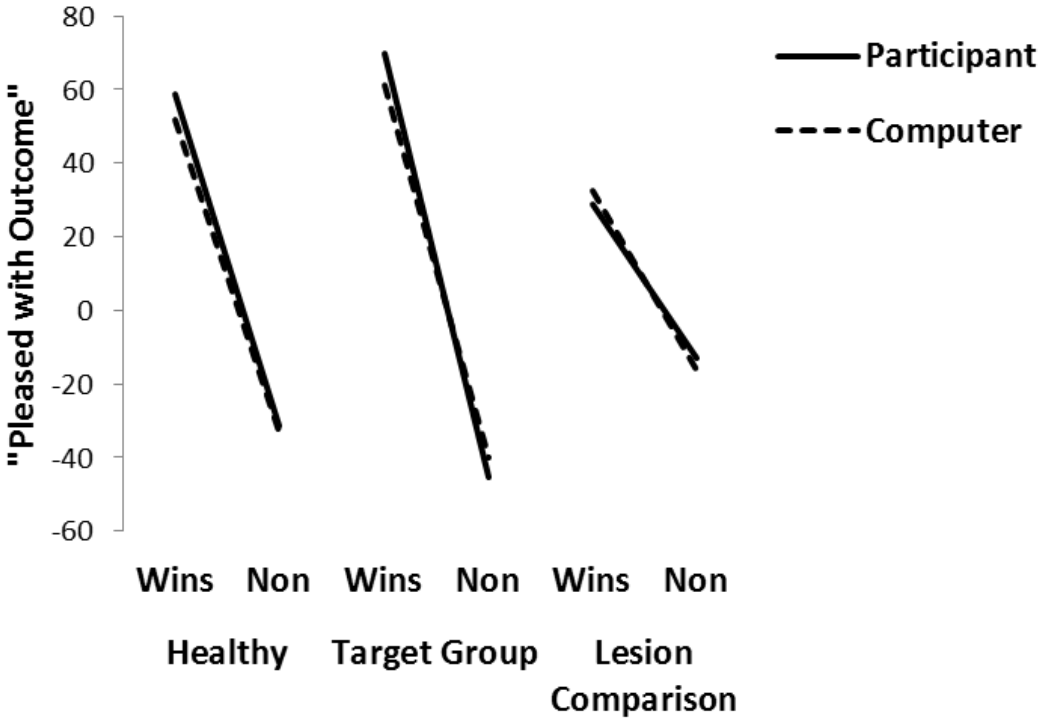


Table S1. Demographic and neurological characteristics of the groups (Mean (S.D.))

	Healthy	**Target**	**Lesion Comp.**	
N	16	31	13	
Age	60.1 (9.8)	51.9 (15.3)	51.9 (19.5)	F=1.71, p=0.19
Gender (F:M)	6:10	12:19	5:8	χ^2=.007, p=0.99
Education	14.7 (2.3)	14.1 (3.2)	14.4 (2.7)	F=0.23, p=0.80
Lesion Side (B:L:R)	--	13:11:7	2:7:4	χ^2=2.9, p=0.24
Real-life gambling	6:10:0	19:8:1	4:3:1	χ^2=6.8, p=0.15
SOGS[†]	0.8 (1.4)	0.4 (1.2)	0.4 (0.7)	F=0.44, p=0.65
GRCS[†]	44.8 (16.1)	41.9 (24.4)	34.6 (15.6)	F=0.70, p=0.50
	vmPFC	**Insula**	**Amygdala**	
N	17	8	6	
Age	52.1 (16.8)	53.3 (16.8)	49.7 (9.9)	F=0.09, p=0.91
Gender (F:M)	6:11	3:5	3:3	χ^2=0.41, p=0.81
Education	14.2 (2.5)	13.8 (4.7)	14.2 (3.1)	F=0.06, p=0.94
Lesion Side (B:L:R)	13:2:3	0:4:4	1:5:0	χ^2=18.8, p=.001
Real-life gambling	8:5:1	6:2:0	5:1:0	χ^2=2.1, p=.72
SOGS	0.8 (1.6)	0.0 (0.0)	0.2 (0.4)	F=1.38, p=0.27
GRCS	48.4 (31.1)	36.6 (14.2)	33.0 (9.6)	F=1.07, p=0.36

[†] South Oaks Gambling Screen (SOGS), Gambling Related Cognitive Scale (GRCS) scores and real-life gambling involvement (0=none, 1=occ, 2=reg) were unavailable for 9 lesion participants, giving reduced degrees of freedom (2,49) in the ANOVA. B:L:R = bilateral, left-sided, right-sided.

Table S2: Subjective ratings on the slot machine task (mean (SD))

		Healthy Subjects	Target Group	Lesion Comparison
"How do you rate your chances of winning?" (0=very low, 100=very high)				
	Participant	35.7 (21.3)	40.7 (22.9)	30.8 (18.5)
	Computer	32.5 (20.1)	34.6 (21.0)	29.1 (19.1)
"How pleased are you with the result?" (-100=very unhappy, 0=neutral, +100=very happy)				
Wins	Participant	58.9 (31.6)	69.9 (31.5)	28.9 (37.7)
	Computer	51.6 (32.0)	61.1 (33.5)	32.7 (49.8)
Near-misses	Participant	-32.1 (33.8)	-44.4 (30.2)	-14.2 (15.2)
	Computer	-32.1 (34.3)	-42.3 (34.1)	-14.7 (19.6)
Full-misses	Participant	-30.8 (34.1)	-46.0 (31.6)	-12.2 (16.6)
	Computer	-33.8 (36.4)	-38.9 (33.0)	-17.8 (17.2)
"How much do you want to continue to play?" (0=not at all, +100=a lot)				
Wins	Participant	64.4 (28.2)	57.8 (29.0)	38.4 (40.5)
	Computer	62.4 (26.9)	55.6 (30.2)	38.0 (40.9)
Near-misses	Participant	53.5 (28.8)	42.3 (27.1)	37.3 (37.0)
	Computer	52.2 (30.7)	42.7 (28.7)	31.5 (38.8)
Full-misses	Participant	50.3 (29.8)	43.0 (27.7)	31.3 (37.6)
	Computer	51.6 (29.9)	43.5 (27.8)	33.6 (37.4)

		vmPFC	Insula	Amygdala
"How do you rate your chances of winning?" (0=very low, 100=very high)				
	Participant	33.8 (23.4)	53.6 (16.2)	40.6 (23.6)
	Computer	29.9 (22.9)	40.1 (14.3)	38.3 (24.2)
"How pleased are you with the result?" (-100=very unhappy, 0=neutral, +100=very happy)				
Wins	Participant	60.8 (31.7)	74.9 (32.1)	79.3 (32.0)
	Computer	52.6 (30.7)	71.9 (38.2)	62.3 (34.2)
Near-misses	Participant	-49.0 (28.3)	-41.2 (31.3)	-40.5 (36.3)
	Computer	-51.1 (34.9)	-29.8 (29.6)	-42.2 (38.9)
Full-misses	Participant	-47.9 (31.5)	-43.7 (32.0)	-45.6 (36.9)
	Computer	-42.3 (34.4)	-33.6 (32.0)	-39.1 (37.1)

"How much do you want to continue to play?" (0=not at all, +100=a lot)				
Wins	Participant	53.2 (29.1)	68.0 (36.4)	54.3 (19.6)
	Computer	51.8 (27.6)	63.0 (40.6)	54.0 (24.1)
Near-misses	Participant	39.6 (24.5)	49.0 (35.4)	39.5 (24.8)
	Computer	39.5 (27.5)	50.3 (35.4)	39.8 (25.5)
Full-misses	Participant	39.1 (27.0)	53.4 (31.9)	37.8 (25.1)
	Computer	40.5 (26.4)	52.2 (35.0)	38.7 (23.3)

Table S3: Effects of feedback streaks on confidence ratings on the roulette game (mean (SD))

	Healthy Subjects	**Target Group**	**Lesion Comparison**
Short Win Streak	0.03 (0.21)	-0.03 (0.17)	-0.01 (0.12)
Long Win Streak	0.03 (0.68)	0.06 (0.35)	-0.19 (0.50)
Short Loss Streak	-0.03 (0.24)	0.01 (0.15)	0.00 (0.17)
Long Loss Streak	0.22 (0.35)	0.10 (0.61)	0.11 (0.31)

	vmPFC	**Insula**	**Amygdala**
Short Win Streak	-0.04 (0.21)	-0.03 (0.17)	0.00 (0.06)
Long Win Streak	0.03 (0.31)	0.22 (0.35)	-0.06 (0.42)
Short Loss Streak	0.00 (0.12)	0.00 (0.19)	0.06 (0.19)
Long Loss Streak	0.26 (0.63)	-0.34 (0.48)	0.19 (0.55)

Confidence ratings were taken on a scale from 1-21 'How confident are you in your decision?' with poles labelled 'No confidence' to 'High confidence'. Raw ratings were then *z* standardized for each participant based on their distribution (mean and standard deviation) of ratings.

In the primary ANOVA model with streak length as a 5-level repeated-measures factor, there were no statistically-reliable main effects of winning or losing streaks, Group status, or Group by Streak Length interactions (see main text). However, aggregating the streaks into shorter (1 and 2 length) vs. longer (3, 4 and 5 length) streaks, there was a main effect of Loss Streak length ($F(1,46) = 3.62$, $p = .063$), such that participants were more confident following several consecutive losses. This is presumably a further manifestation of the Gambler's Fallacy, i.e. their over-confidence is linked to their prediction that the other outcome is 'due'. In the aggregated models, there were no effects of Group status or Group by Streak Length interactions.

Table S4: Roulette task: further choice and strategy metrics (mean (SD))

	Healthy Subjects	**Target Group**	**Lesion**	
			Comparison	
P (red)	0.58 (0.14)	0.49 (0.11)	0.53 (0.14)	F=2.6, p=.086
P (same as previous outcome)	0.42 (0.14)	0.53 (0.18)	0.49 (0.12)	F=2.2, p=.120
P (same as previous choice)	0.63 (0.13)	0.56 (0.13)	0.64 (0.13)	F=1.9, p=.164
P (win-stay)	0.55 (0.19)	0.60 (0.21)	0.62 (0.18)	F=0.4, p=.679
P (lose-shift)	0.31 (0.18)	0.47 (0.24)	0.35 (0.16)	F=3.3, p=.047

	vmPFC	**Insula**	**Amygdala**	
P (red)	0.51 (0.09)	0.47 (0.18)	0.47 (0.06)	F=0.5, p=.620
P (same as previous outcome)	0.51 (0.16)	0.54 (0.24)	0.58 (0.20)	F=0.3, p=.745
P (same as previous choice)	0.54 (0.13)	0.65 (0.15)	0.54 (0.12)	F=1.5, p=.243
P (win-stay)	0.55 (0.17)	0.70 (0.32)	0.62 (0.19)	F=1.1, p=.352
P (lose-shift)	0.47 (0.24)	0.40 (0.26)	0.53 (0.27)	F=0.4, p=.700

The two metrics, *P(same as previous outcome)* and *P(same as previous choice)*, were calculated from trials 2-90 in the sequence. *P(same as previous outcome)* describes the tendency (i.e. proportion of trials) of red choices if the last roulette spin landed on red, or blue choices where the last spin landed on blue. The gambler's fallacy is a specific instance of this category, as a function of the number of consecutive identical outcomes. In contrast, *P(same as previous choice)* describes the tendency to repeat one's prior choice: the proportion of trials where one chooses red having chosen red on the previous trial (or chooses blue having chosen blue on the previous trial). It is evident that the mean values for this 'choice stickiness' are above 0.5 and somewhat higher than the values for 'outcome stickiness'. Choice stickiness further informs the metrics for win-stay and lose-shift. *P (win-stay)* is the proportion of trials after a correct prediction where one chooses the same colour as the previous choice. *P (lose shift)* is the proportion of trials after an incorrect prediction where one chooses the opposite colour to the previous choice.

Table S5: Icon selections on the slot machine task (mean (SD)). On participant-chosen trials, how likely were participants to choose the same icon as the previous trial, as a function of the outcome on the previous trial?

	Healthy Subjects	**Target Group**	**Lesion Comparison**
% reselection after a…			
Win	18.1 (12.8)	20.3 (15.5)	27.8 (20.9)
Near Miss	25.6 (12.2)	23.7 (11.7)	22.9 (13.6)
Full Miss	27.9 (10.9)	22.9 (13.6)	34.2 (12.9)

	vmPFC	**Insula**	**Amygdala**
% reselection after a…			
Win	16.9 (12.5)	27.0 (18.6)	20.0 (17.9)
Near Miss	22.7 (14.4)	25.7 (7.9)	23.3 (10.3)
Full Miss	31.5 (17.6)	22.2 (14.2)	28.9 (19.2)

In the first model (healthy subjects vs target group vs lesion comparison), there was a main effect of Outcome ($F(2,98) = 5.10$, $p = .018$), such that participants tended to avoid reselecting the same icon following wins, and following near-misses, compared to full-misses ($p = .009$ and $p = .002$, respectively). This is likely to reflect a further manifestation of the gambler's fallacy (see L Clark et al. 2013 *Journal of Behavioral Decision Making*). There was no main effect of Group or Group x Outcome interaction. In the second model (vmPFC vs insula vs amygdala), there were no significant effects in the ANOVA model, although the effect in healthy subjects was also visually apparent in the vmPFC and amygdala groups, but not within the insula cases.

Table S6: Insula Group – single case analysis by striatal involvement. (mean (SD))

	Striatal Involvement?	Near Miss	Gambler's Fallacy
Healthy Subjects	N/A	1.91 (3.01)	0.08 (0.21)
Lesion Comparison Group	N/A	1.92 (2.81)	0.14 (0.21)
Insula Cases			
1	N	[b]	[a]
2	Y	-3.9	-0.07
3	Y	-4.9	-0.36
4	N	-1.0	0.06
5	Y	-9.8	-0.18
6	Y	-1.4	[b]
7	N	-2.5	0.14
8	N	1.4	-0.12

[a] Selected >95% from one colour, allowing no further analysis of choice strategies on the roulette task. [b] Task not completed.

On the near-miss summary variable, the mean score for insula cases with striatal involvement was -5.0 (SD = 3.5), and the mean for cases without striatal damage was -0.7 (SD = 2.0). On the gambler's fallacy summary variable, the mean score for insula cases with striatal involvement was -0.20 (SD = 0.15), and without was 0.02 (SD = 0.13).Thus, while both effects are stronger in the cases where damage encroaching into the striatum, it is equally clear that the normative effects in the two comparison groups are nevertheless attenuated in the insula cases with no striatal involvement.