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Almost winning: Induced MEG theta power in insula and orbitofrontal cortex increases during gambling near-misses and is associated with BOLD signal and gambling severity

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ABSTRACT

In slot machine gambling, the "near-miss effect" (when a losing display physically resembles an actual win display) has been implicated in pathological gambling (PG). Functional magnetic resonance imaging (fMRI) with PG and non-PG participants shows that near-misses recruit reward-related circuitry, but little is known about the temporal dynamics and oscillatory changes underlying near-misses. The present multi-modal imaging study investigated the near-miss effect by combining the spatial resolution of blood oxygen-level dependent (BOLD)-fMRI with the spatial and temporal resolution of magnetoencephalography (MEG) during a slot machine task in PG and non-PG groups. Given previous findings on outcome (win and near-miss) processing, functional overlap was hypothesized between induced changes in temporal oscillations and BOLD response to wins and near-misses in PG. We first validated our task in a sample of varying gambling severity using BOLD-fMRI and then compared PG and non-PG participants using MEG to investigate changes in induced oscillatory power associated with win and near-miss, relative to loss, outcomes. Across both modalities, near-misses recruited similar brain regions to wins, including right inferior frontal gyrus and insula. Using MEG, increased theta-band (4–7 Hz) oscillations to near-misses were observed in the insula and right orbitofrontal cortex (OFC). Furthermore, this theta-band activity was positively associated with gambling severity. These findings demonstrate that the near-miss effect in insula and OFC is associated with induced theta oscillations. The significance of these findings for theories of PG and the development of potential biomarkers and therapeutic targets is discussed.

Introduction

Internationally, the prevalence of pathological gambling (PG) is growing. In the United Kingdom, for instance, approximately 1% of the population meets the DSM-IV criteria for PG (Wardle et al., 2012). Consistent with modern perspectives of PG as a behavioral addiction, treatment-seeking gamblers show symptoms such as withdrawal, craving, and relapse similar to those seen in substance abuse (Clark and Limbrick-Oldfield, 2013; Frascella et al., 2010; Leeman and Potenza, 2012; Petry, 2007). It has been argued that electronic gaming machines (EGMs), like slot machines, may lead to problematic gambling behavior due in part to the way outcomes are scheduled and displayed (Parke and Griffiths, 2006). Structural features of EGMs such as the "near-miss", which occurs when a losing display physically resembles an actual win display (i.e., the presentation of two out of three matching symbols on a payline), play a role in maintaining gambling behavior (Parke and Griffiths, 2006). Non-PG participants show greater gambling persistence, initiate trials faster, and rate their chances of winning as higher following near-misses relative to wins or (full) losses (Billieux et al., 2012; Clark et al., 2009; Dillen and Dixon, 2008; Dixon and Schreiber, 2004; Dixon et al., 2013; Kassinove and Schare, 2001; MacLin et al., 2007; Parke and Griffiths, 2006). Identifying the neurocognitive mechanisms underlying the near-miss effect, and its association with gambling severity, is therefore a key focus of research with considerable diagnostic and therapeutic potential.

Functional magnetic resonance imaging (fMRI) studies highlight a crucial role for ventral striatum, rostral anterior cingulate cortex

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(rACC), insula, and midbrain (substantia nigra/ventral tegmental) regions in distinguishing between win and loss outcomes, and in differentiating between PG and non-PG participants (Balodis et al., 2012; Breiter et al., 2001; Chase and Clark, 2010; Clark et al., 2009; Habib and Dixon, 2010; Joutsa et al., 2012; Reuter et al., 2005; Shao et al., 2012). Near-misses evoke overlapping activation with wins in an extended network encompassing ventral striatum and anterior insula bilaterally in non-PG participants (Breiter et al., 2001; Clark et al., 2009; Joutsa et al., 2012; Reuter et al., 2005; Shao et al., 2012) and in the same network including medial prefrontal cortex (PFC) in PG (Chase and Clark, 2010; Habib and Dixon, 2010). These fMRI findings indicate a potential mechanism by which near-misses maintain excessive slot machine gambling by activating reward-related circuitry (Chase and Clark, 2010; Clark et al., 2009). Moreover, non-PG participants' susceptibility to gambling-related cognitive distortions (GRCS; Raylu and Oei, 2004) is positively correlated with anterior insula responses to near-misses (Clark et al., 2009). Similar activation to win and near-miss outcomes has been found in PG; however, here, blood oxygen-level dependent (BOLD) responses to near-misses in the midbrain, rather than in the insula correlated with gambling severity (Chase and Clark, 2010).

Using BOLD-fMRI, the near-miss effect is now relatively well characterized. However, conflicting neuroimaging findings in PG indicating both diminished and increased activation in reward-related circuitry during anticipation or receipt of rewards (Balodis et al., 2012; Blum et al., 2011; Crockford et al., 2005; de Ruiter et al., 2009; Goudriaan et al., 2010; Leyton and Vezina, 2012; van Holst et al., 2010, 2012) suggest that there is a need to adopt complementary measures of neural activity to fully identify the neurobehavioral mechanisms underlying PG. The advent of magnetoencephalography (MEG), for instance, has made it possible to study the neural mechanisms of gambling with excellent temporal resolution and good spatial resolution (Donner and Siegel, 2011; Hansen et al., 2010; Jensen and Mazaheri, 2010; Singh, 2012; Thomsen et al., 2013), which is important because oscillations in different frequency ranges may reflect different aspects of cortical processing, such as active inhibition versus enhancement of regional activity (Donner and Siegel, 2011; Jensen and Mazaheri, 2010; Singh, 2012). MEG can therefore go beyond the simple and ill-defined measures of "neural activity" revealed by BOLD-fMRI (Singh, 2012). Measuring a more direct neuronal signal with MEG is therefore beneficial for confirming the spatial, and, for the first time, elucidating the temporal dynamics of neural responses to gambling outcomes in PG, and examining their association with gambling severity.

No previous imaging study in PG has used MEG to examine induced changes in temporal oscillations during slot machine gambling (cf. Hudgens-Haney et al., 2013). However, temporal fluctuations in outcome processing identified from event-related potential (ERP) research show that win outcomes result in larger induced oscillations in theta-band power (4–7 Hz) than loss outcomes (Cohen et al., 2007; Kamarajan et al., 2009; Marco-Pallares et al., 2008), with sources localized in mediofrontal regions (Christie and Tata, 2009; Donamayor et al., 2011). Reward-related theta-band oscillations may indicate the functional coupling of mediofrontal regions during outcome processing (Christie and Tata, 2009). Indeed, increased theta power to wins over losses during early (200–250) and late (250–500) outcome periods also corresponds to specific ERP components, feedback related negativity (FRN) and P300, respectively, which have been localized in posterior and medial PFC and ACC, with later activation in the insula (Christie and Tata, 2009; Gehring and Willoughby, 2002; Kamarajan et al., 2009). In the context of simulated slot machine tasks, near-misses and losses both evoke FRN and may indicate a role for mediofrontal regions like OFC in the evaluation that one has almost won (Donkers et al., 2005; Luo et al., 2011; Qi et al., 2011). However, most of the existing ERP evidence comes from studies conducted with non-PG participants; the neuroanatomical generators of these theta-band induced changes in the near-miss effect have yet to be identified in PG.

In line with continuum approaches to PG (Toce-Gerstein et al., 2003), we first measured BOLD-fMRI in a mixed sample of PG and non-PG participants focusing on the overlap between activation related to wins and near-misses (by contrasting wins vs. 'full' losses, and near-misses vs. losses), and examined the associations with gambling severity and a trait measure of cognitive distortions (GRCS). Consistent with previous neuroimaging findings (Chase and Clark, 2010; Clark et al., 2009; Habib and Dixon, 2010), we hypothesized that similar activation patterns would be seen in the near-miss > loss contrasts and win > loss contrasts, and that BOLD responses in the insula to near-misses would be predicted by a trait measure of gambling distortions. Next, we compared separate probable PG and non-PG groups using MEG to investigate changes in induced oscillatory power associated with win and near-miss, relative to loss, outcomes. Due to the difficulty in recording from subcortical sites with MEG, our current spatial focus was on OFC/ACC and insula regions previously implicated in fMRI studies of PG. The main aim of the MEG study was to identify functional overlap (convergent results) between changes in oscillatory power (and changes in BOLD) in response to wins and near-misses. In addition, we determined how power changes in frontal and insula regions of interest were related to gambling severity and gambling-related cognitions. We were particularly interested in whether near-miss outcomes would induce greater theta power in PG than in non-PG in frontal and insula regions of interest (Christie and Tata, 2009; Gehring and Willoughby, 2002; Kamarajan et al., 2009). A specific group effect for near-misses, but not wins or losses, would be consistent with a quadratic, rather than linear, interaction between group and outcome.

Materials and methods

Participants

Participants were right handed (Oldfield, 1971) males recruited from newspaper/online advertisements and campus announcements. The advertisements stated that the study was examining brain activation during simulated gambling and, for the recruitment of gamblers only, asked, "Do you gamble and have you experienced any of the following: Trouble controlling your gambling? Gambled more than intended? Tried to stop gambling but couldn't? Frequent thoughts about gambling?" Interested potential participants then completed an MRI safety questionnaire and the *South Oaks Gambling Screen* (SOGS; Lesieur and Blume, 1987).

Table 1
Characteristics of PG and non-PG participants.

	fMRI	MEG	Test statistics
n	18	PG: 16 non-PG: 18	
Age	24.82 (7.09)	PG: 27.13 (7.2) non-PG: 23.94 (5.1)	ns
Education		PG: 15 (2.98) non-PG: 15.28 (2.27)	ns
SOGS	4.3 (3.6)	PG: 7.38 (4.62) non-PG: 0.56 (0.78)	$t = 2.217$, $df = 32$, $p = 0.041$* $t = 6.179$, $df = 32$, $p < 0.0001$**
GRCS***	71.71 (23.48)	PG: 70.06 (4.89) non-PG: 45.89 (4.99)	$t = 3.248$, $df = 29$, $p < 0.05$**
MINI		PG: 56% non-PG: 63%	c^2 (1,34) = 0.17, $p = 0.68$

PG, pathological gambling; SOGS, *South Oaks Gambling Screen*; GRCS, *Gambling-Related Cognitions Scale*; MINI, *Mini International Neuropsychiatric Interview* (percentage of sample reporting possible past or current psychiatric symptoms).

* When the fMRI sample and PG participants from the MEG study are compared.

** When PG and non-PG participants from the MEG study are compared.

*** $n = 17$ for GRCS data from the fMRI study and $n = 12$ for GRCS data from PG participants in the MEG study.

The fMRI study consisted of one group of eighteen PG and non-PG males, aged between 18 and 47 ($M = 24.82$, $SD = 7.09$), of varying gambling severity (SOGS: $M = 4.3$, $SD = 3.6$, range 0–15; see Tables 1, S1, S2). This mixed sample of probable PG and non-PG participants was recruited from the staff and student community of Bangor University and via newspaper advertisements. The MEG study included two groups; one of sixteen PG males, aged between 19 and 46 ($M = 27.13$, $SD = 7.2$), with a mean SOGS score of 7.38 ($SD = 4.62$, range 3–18), and one of eighteen non-PG healthy male controls, aged between 18 and 39 ($M = 23.94$, $SD = 5.1$), with a mean SOGS score of 0.56 ($SD = 0.78$, range 0–2; see Tables 1, S1, S2, and Fig. S1). Groups in the MEG study did not differ in age ($p = 0.144$) or years in education (PG: $M = 15$, $SD = 2.9$; non-PG: $M = 15.2$, $SD = 2.2$; $p = 0.388$). The non-PG control group for the MEG study consisted of staff and students recruited from Cardiff University who scored 0–2 on the SOGS, while individuals recruited via local newspaper/online advertisements scoring 3 or above on the SOGS (indicating potential problem gambling; Lesieur and Blume, 1987) comprised the probable PG group (Fig. S1).

In both studies, all subjects attended a single scanning session and completed the GRCS (Raylu and Oei, 2004) either before or after the scanned slot machine task. All subjects in the MEG study also completed the *Mini International Neuropsychiatric Interview* (MINI: Sheehan et al., 1998) to measure possible past or present psychiatric symptoms after completing the task. While subjects in both MEG groups reported the presence of possible past or current psychiatric symptoms on the MINI, the frequency did not differ between healthy volunteers (56% of group reporting any current or previous symptoms) and regular gamblers (63% of group reporting any current or previous symptoms), $c^2(1,34) = 0.17$, $p = 0.68$, (specific comorbidities are shown in Table S1). None of the fMRI subjects reported any history of psychiatric symptoms or diagnoses. All participants gave written informed consent and were fully debriefed and paid £20 in shopping vouchers (MEG study) or cash (fMRI study) upon completion. The Bangor University School of Psychology Ethics Committee approved the fMRI study, while the Cardiff University School of Psychology Research Ethics Committee approved the MEG study.

Task design

Participants completed 120 trials of a slot machine task (Habib and Dixon, 2010). The display consisted of a three-reel slot machine with accumulated total winnings and task instructions (Fig. 1 and Supplementary material). Participants familiarized themselves with the response box and then commenced the task with £10 credit to increase baseline motivation. There was no cost to spin, £1 in winnings was added to the total following a win, and the concurrent total amount won was displayed after each trial. A 'loss' in this task was therefore a 'non-win' (omission of a reward); we decided not to incur a monetary punishment because the number of losses was so high (75–83% of trials, see below). Our focus was on the overlapping motivational effects of wins and near-misses in PG (the 'near-miss effect') rather than on the effects of financial losses, which are associated with a different aspect of gambling behavior (e.g., 'chasing losses'; Campbell-Meiklejohn et al., 2008). To maintain motivation, participants were informed that they would have the opportunity to win extra vouchers/money worth approximately 1/10th of their winnings depending on their total score in the slot machine task (in fact, all participants finished the task with the same amount of winnings and were paid an extra £4). The particular outcome stimuli displayed were randomly determined on each trial and were chosen from the set of twenty symbols. Win (three matching symbols), near-miss (two out of three matching symbols) and loss (no matching symbols) outcomes were displayed in a pseudo-random order across subjects in both studies. Each of the reels displayed one of up to twenty images of items commonly used in modern slot machines, such as cherries, gold bars, pineapples, and bells.

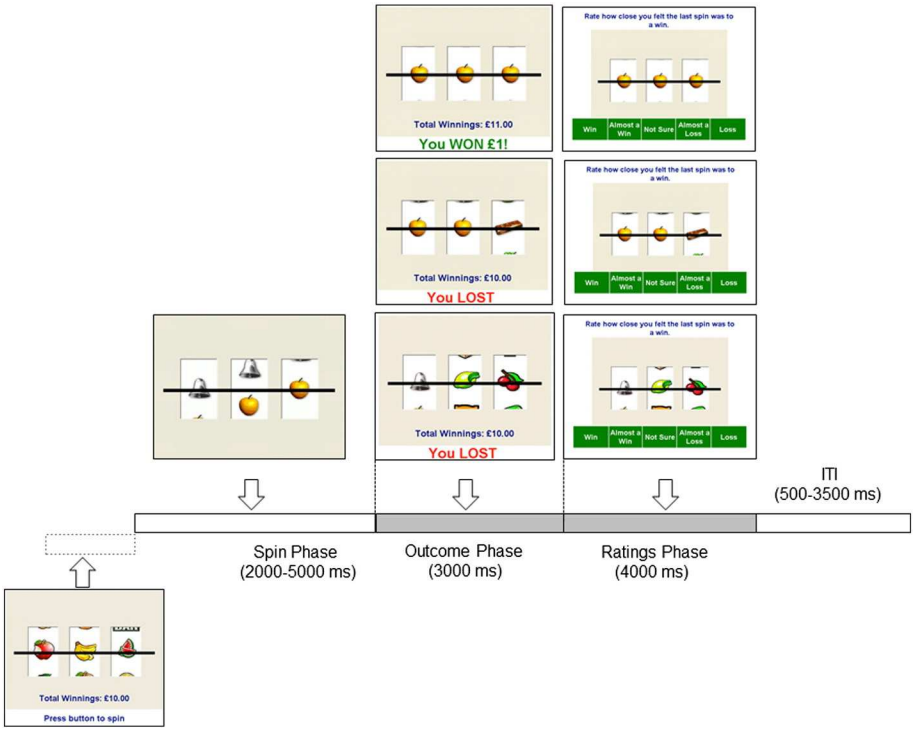

Fig. 1. Overview of slot machine task. Each trial of the slot machine task consisted of a spin phase, an outcome phase, a ratings phase, and an inter-trial interval (ITI). During the *spin* phase (duration 5000 ms minus time to initiate a spin), the three reels spun and stopped simultaneously. The *outcome* phase (duration 3000 ms) commenced when the reels stopped spinning. Win outcomes consisted of three identical symbols on the payline; near-miss outcomes consisted of two matching symbols on the payline, with the third symbol just above or below; and loss outcomes consisted of three different stimuli on the payline. The *ratings* phase (duration 4000 ms) occurred after a quarter of all trials, with subjects rating how close the previous outcome was to a win. The ITI ranged between 500 and 3500 ms, and then the next trial began with the presentation of "press button to spin".

Trials consisted of a *spin* phase, an *outcome* phase, a *ratings* phase, and an inter-trial interval (ITI). During the spin phase, which lasted between 2000 and 5000 ms (determined by the time taken to initiate a spin on the previous trial) the three reels spun and stopped simultaneously. The outcome phase (3000 ms duration) commenced when the reels stopped spinning. Outcomes were presented in a pseudo-random trial order for 120 trials and in the MEG study were comprised of 30 wins, 40 near-misses, and 50 full losses (i.e., omission of reward). In the fMRI study, outcomes were comprised of 20 wins, 40 near-misses and 60 full losses. The increased number of wins (30) in the MEG study was designed to maximize our power to detect significant induced power changes; 20 win trials were deemed sufficiently powerful for the determination of BOLD responses. The frequency of near-misses (33%) was the same in both tasks. Wins consisted of three identical symbols on the payoff line; near-misses consisted of two matching symbols on the payoff line, with the third symbol just above or below the payline. On half of the near-miss trials, the non-matching symbol was displayed on either right or left (Ghezzi et al., 2006). Losses consisted of three different stimuli on the payline (see Fig. 1). After the outcome phase, subjects rated, "how close were you to a win?" using, in the MEG study, a 5-point scale (1 = *Loss*, 2 = *Almost a Loss*, 3 = *Not Sure*, 4 = *Almost a Win*, 5 = *Win*) and, in the fMRI study, a 4-point scale (as above, but with *Not Sure* removed). Ratings, which had to be made within a time limit of 4000 ms, were made following 30 predetermined trials (10 with each outcome). At the end of trials with a ratings phase, there was a 500–3500 ms ITI. Trial durations were 12,500 ms with a rating phase and 8500 ms without. Total task duration was 19 min.

Imaging procedure and analysis

Whole-brain fMRI data were acquired on a 3T Philips Achieva MR Scanner equipped with an 8-channel SENSE head coil. Stimuli were presented using E-Prime and an LCD projector, and participants viewed the display through a mirror mounted above the head coil. An echo-planar imaging sequence was used to detect the BOLD signal during the task, with each brain volume consisting of 30 axial slices covering the whole brain. Imaging parameters were TR = 3000 ms; TE = 35 ms; flip angle = 90; matrix = 96 × 96; FOV = 192 × 192; slice thickness = 3 mm, resulting in a voxel size of $2 \times 2 \times 3 mm^3$. In addition, a three-dimensional high-resolution T1-weighted MPRAGE anatomical image (isotopic voxel of 1 mm^3) was obtained for functional to anatomical image registration. SPM8 (Welcome Department of Imaging Neuroscience, Institute of Neurology, London, UK) was used to preprocess and analyze fMRI data. Results were thresholded at $p < 0.005$ with an extent threshold of 500 voxels, which resulted in a corrected cluster threshold of $p < 0.05$ (Poline et al., 1997). Major contrasts-of-interest were win > full loss and near-miss > full loss outcomes (Table S3).

MEG data were recorded using a 275 channel whole-head system (CTF Systems Inc., a subsidiary of VSM MedTech Ltd.) in a magnetically-shielded room at a sample rate of 600 Hz (with an anti-alias low-pass filter cut-off of 150 Hz) using an axial gradiometer configuration, with the primary sensors analyzed as synthetic third-order gradiometers. Additional vertical and horizontal electro-oculograms were acquired to quantify eye movements (see Supplementary material). Head position was recorded using three fiduciary markers placed on the nasion, 1 cm anteriorly from both the left and right tragi. Each subject's data were then co-registered offline with anatomical landmarks from the MR scan (verified using high-resolution digital photographs taken during fiducial placement). MEG data were first epoched from −5 to 1.25 s around stimulus onset, trials were visually inspected, and data with gross artifacts excluded from further analysis (a total of 1–2 excluded trials per participant). For localization of the MEG oscillatory response, a multiple, local-sphere forward-model was derived by fitting over-lapping spheres (Huang et al., 1999) to the brain surface extracted by the Brain Extraction Tool (Smith, 2002) of the participant's T1-weighted MR image. Source analysis was performed using Synthetic Aperture Magnetometry (SAM), a non-linear 'beamforming' technique based on fixed-aperture radar technology. Covariance matrices were generated for delta (0–4 Hz), theta (4–7 Hz), alpha (8–15 Hz), beta (15–25 Hz) and gamma (30–70 Hz) frequency ranges. Using the beamformer algorithm (Robinson and Vrba, 1999), sets of beamformer weights were computed for the entire brain at 4 mm isotropic voxel resolution without regularization of the covariance matrix. For SAM image reconstruction, virtual sensors were constructed for each beamformer voxel and Student-*t* images of source power changes computed for win versus full loss outcomes in both the early (0–500 ms) and late (500–1000 ms) time windows following outcomes. Statistically thresholded group beamformer images were computed using randomization testing (Singh et al., 2003) and thresholded using omnibus voxelwise correction to $p < 0.05$.

Results

Ratings

Participants rated near-miss outcomes as closer to a win than a loss (fMRI: $M = 2.59, SD = 0.13$; MEG: [PG] $M = 3.48, SD = 0.54$; [non-PG] $M = 3.37$, $SD = 0.63$; Fig. S2). In the MEG study, there was a main effect of outcome ($F(2, 27) = 4.03$, $p < 0.001$; with wins > near-misses > losses), but no effect of group, or group × outcome interaction ($p > 0.5$; Table S4). The fMRI participants' ratings revealed a similar significant main effect of outcome only ($F(2, 46) = 54.217$, $p < 0.001$; with wins > near-misses > losses). These data reconfirm behavioral findings showing that near-misses are rated as closer to a win than a loss (Clark et al., 2009; Dillen and Dixon, 2008; Dixon and Schreiber, 2004; Kassinove and Schare, 2001; MacLin et al., 2007).

BOLD-fMRI

We first examined the outcome contrasts of win > all losses, win > full losses, and near-miss > full losses to spatially localize the "near-miss effect" (and overlap with wins) in our slot machine task. Significant win > full loss activation was observed in extended prefrontal regions including right inferior frontal gyrus (IFG) to right insula, left insula, ventral striatum, OFC, and right supplementary motor area (SMA; Fig. 2 and Table S3). Additional activations were observed in cingulate and parietal regions (Table S3). For the near-miss > full loss contrast, we observed an extended prefrontal activation from right insula to IFG and middle frontal gyrus (MFG), activations in left insula, bilateral inferior parietal lobe, and right thalamus (see Table S3). This pattern of activation was very similar to the win > full loss contrast.

As a follow-up analysis to address the issue of orthogonality, we further examined the win > all loss contrast and obtained similar patterns of activation in bilateral insula, extended prefrontal areas, and bilateral parietal regions. This reduces the possibility that similar activation patterns between the near-miss > loss and win > loss contrasts is merely the result of a common 'loss' baseline.

To explore the functional significance of the insula activations, we extracted the percentage signal change from the peak voxel within the insula clusters during near-miss trials (relative to the implicit baseline, which was a blank screen displayed during the ITI). Consistent with prior findings (Clark et al., 2009), we found a significant positive correlation between percentage BOLD signal change in right (but not left) insula to near-misses and gambling-related cognitions (GRCS; $r = 0.49$, $p < 0.05$; Fig. 3; with left insula, $r = 0.06$, $p > 0.05$). Activation during win (right insula, $r = 0.27$; left insula, $r = -0.23$) or full loss trials (right insula, $r = 0.39$; left insula, $r = 0.00$) did not correlate with GRCS scores (all $p > 0.05$).

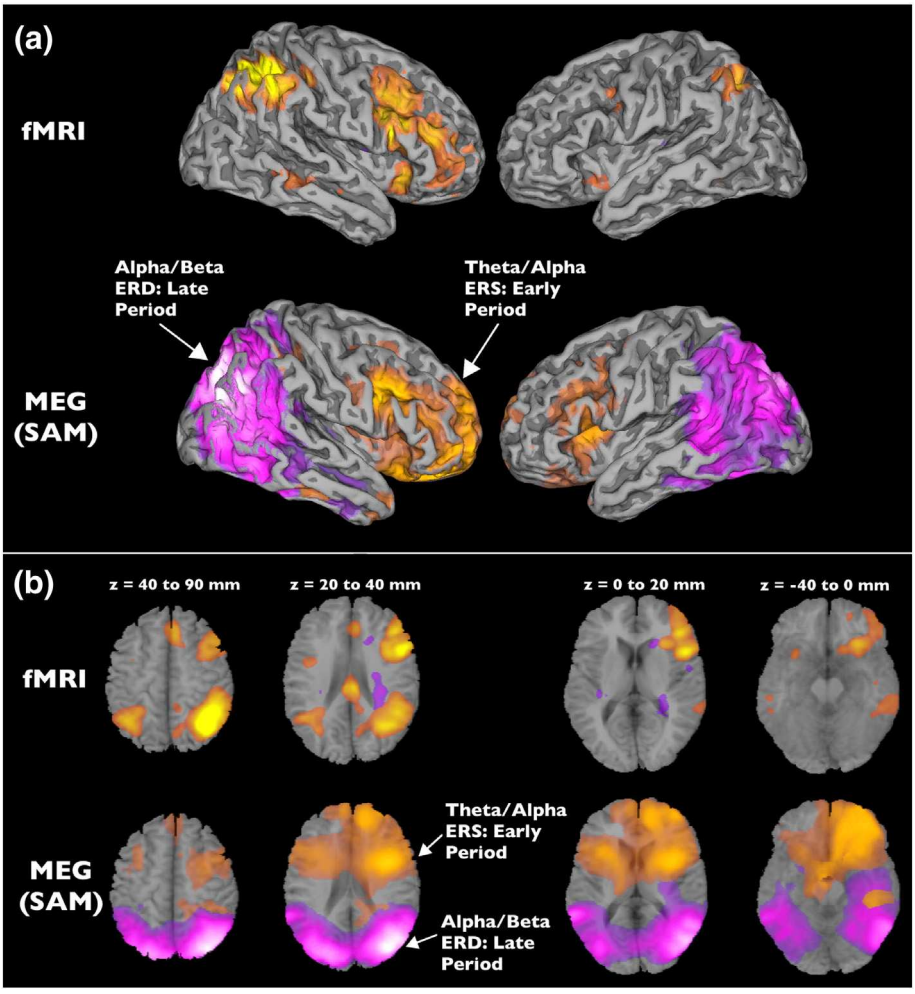

Fig. 2. Spatial and temporal correspondence of BOLD-fMRI and MEG signal changes to win > loss outcomes. (a) The upper panel shows group-averaged BOLD-fMRI activation to wins minus full loss outcomes overlaid on a partially inflated 3D reconstruction of a template brain. The red–orange–yellow color map indicates increasing BOLD amplitude changes. The lower panel shows MEG/SAM functional images overlaid on a template brain at various distances showing the absolute peak signal change (activation) for theta (4–7 Hz), alpha, and beta frequencies. (b) As above, both panels show BOLD-fMRI and MEG/SAM functional images but in axial orientations at various points along the *z*-dimension. Overall, the MEG/SAM images show signal power changes signifying either Event-Related Desynchronization (ERD) or Event-Related Synchronization (ERS). Theta/alpha frequency power increases (ERS) 0–500 ms post-outcomes are distributed over frontal/insula regions and display a high degree of spatial correspondence with BOLD activity. Alpha/beta oscillatory power decreases (ERD) 500–1000 ms post-outcomes are localized to posterior regions of the cortex, in particular occipito-parietal areas, and are indicated by a purple–pink–white color map, with the scaling indicating power decreases. Note how the low-frequency ERD in the late period also shows a similar spatial distribution to the BOLD activity in parietal regions. These BOLD-fMRI and MEG/SAM contrast maps are based on separate groups of participants performing the same slot-machine task. For the MEG/SAM overlay only statistically significant voxels, thresholded at $p < 0.05$ (corrected using randomization testing), are shown. For the fMRI overlay, voxels with a T-score of less than 3.34 are suppressed, which is equivalent to an uncorrected $p < 0.001$. The major BOLD clusters shown on these figures and reported in the text also met a corrected cluster-level criterion of $p < 0.05$.

MEG: Theta power changes to wins and near-misses

Whole-brain source analysis contrasting wins and full losses identified five clusters/sources in our frontal and insula ROIs that showed significantly greater power changes in response to wins than losses; these consisted of increases in alpha- and theta-bands within 500 ms of outcomes (Fig. S3). Examining amplitude envelope time-series from virtual electrodes in these regions revealed that, as expected, the strongest changes in all regions were in theta band power and there was a clear linear association between change in oscillatory amplitude and outcome, with win > near-miss > loss (see Fig. 4). These five sources were approximately (due to limited spatial source localization of MEG) localized to the anterior medial PFC (BA10), right anterior OFC (BA 47), right lateral frontal cortex (BA8), left anterior insula (BA13) and right inferior frontal/insula cortex (Fig. 2). As expected, because ROIs were identified on the basis that power was greater for wins compared to full losses, the findings indicated significant main effects of outcome in all regions (all $p \leq 0.001$), with highly significant linear trends (win > near-miss > loss). There were no main effects of group on theta power in the five ROIs but there was a significant (quadratic) interaction between group and outcome in the R OFC, ($F(1, 30) = 5.5$, $p = 0.025$). Planned comparisons indicated greater R OFC theta-band responses in PG than in non-PG participants

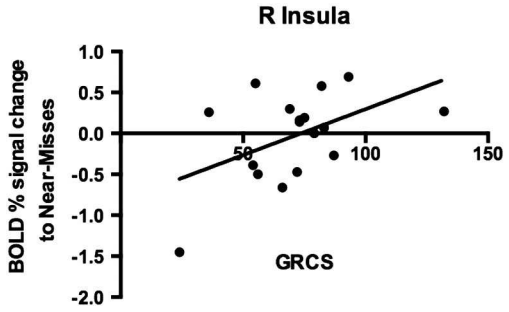

Fig. 3. BOLD insula activation to near-misses correlated with a trait measure of gambling propensity. In the fMRI study, scores from the mixed probable PG and non-PG sample on the *Gambling Related Cognitions Scale* (GRCS) predicted BOLD % signal change to near-miss outcomes (contrast of near-misses > baseline) in the right insula.

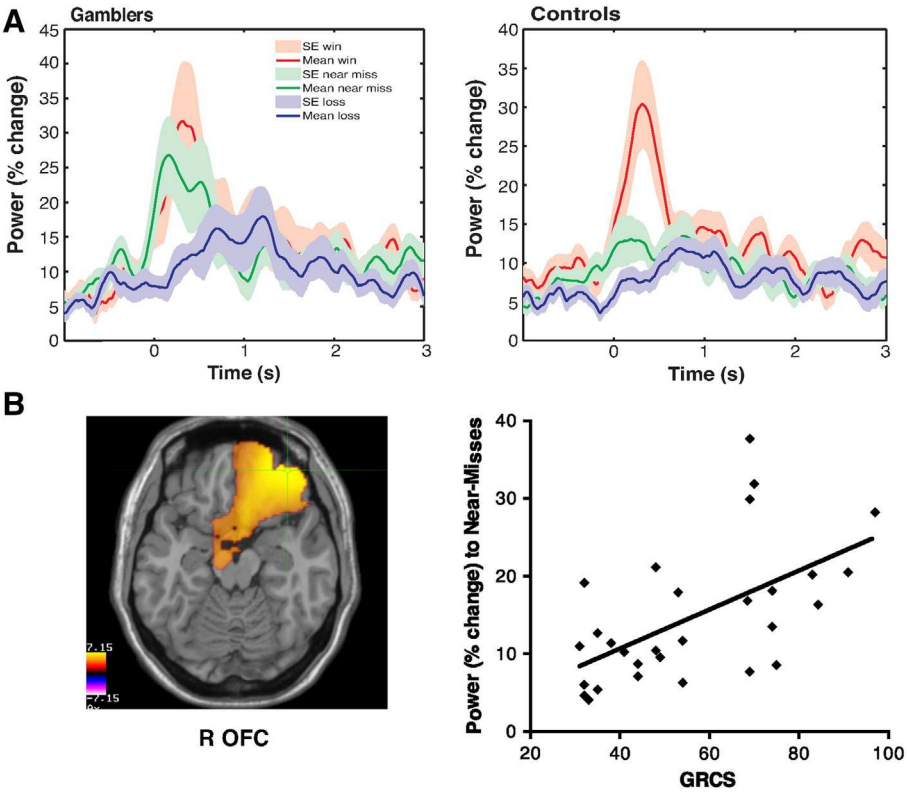

Fig. 4. Theta power changes in R OFC. (A) Percentage changes in theta band power in R OFC between 0 and 3 s after win, near-miss, and loss outcome displays in PG ('Gamblers') and non-PG controls. A linear association was found between change in oscillatory amplitude and outcome: win > near-miss > loss.Non-PG controls (right panel) showed increased theta power during the processing of win relative to other outcomes, whilst PG participants (left panel) showed comparable theta power increases to wins and near-misses within 1 s of the outcome. (B) Axial image of activation cluster from the win minus full loss contrast. Scores on the GRCS predicted near-miss related theta power changes in R OFC in the whole sample ($r = 0.57$, $p = 0.001$) and at trend levels in non-PG control participants ($r = 0.51$, $p = 0.036$) and PG ($r = 0.53$, $p = 0.077$).

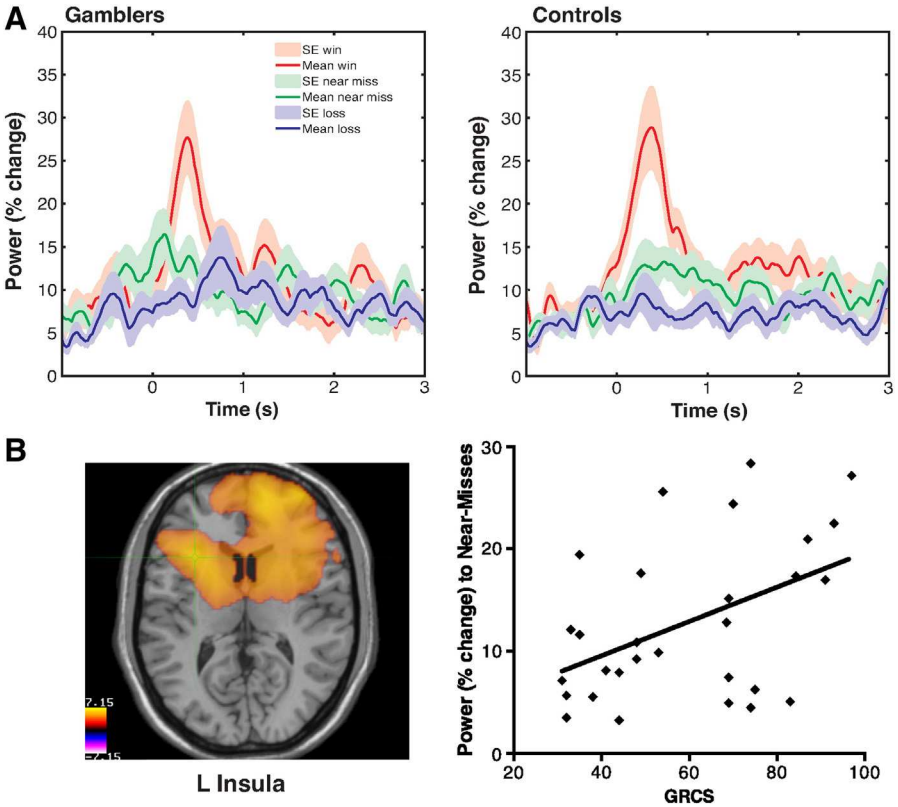

Fig. 5. Theta power changes in L insula. (A) Percentage changes in theta band power in L anterior insula between 0 and 3 s after win, near-miss, and loss outcome displays in PG ('Gamblers') and non-PG controls. (B) Axial image of activation cluster from the win minus full loss contrast. GRCS scores predicted near-miss related theta power changes in L anterior insula in the whole sample ($r = 0.46$, $p = 0.012$).

evoked by near-miss outcomes only ($F(1,30) = 6.22$, $p = 0.018$; see Fig. 4).

Consistent with this between-group difference, theta responses to near-misses in the right OFC were positively correlated with gambling severity (SOGS) in the combined group ($n = 32$, $Rs = 0.43$, $p = 0.015$), and with gambling related cognitions (GRCS; Fig. 4), both in the combined sample for whom measures were available ($n = 29$, $r = 0.57$, $p = 0.001$) and at significant or trend levels within non-PG ($n = 17$, $r = 0.51$, $p = 0.036$) and PG participants ($n = 12$, $r = 0.53$, $p = 0.077$), respectively. Moreover, SOGS and GRCS scores were correlated within the combined PG and non-PG sample ($n = 31$, $r = 0.62$, $p < 0.01$; note — Spearman's ranked correlations (Rs) were conducted on SOGS scores due to their non-normal distribution).

Theta increases in response to near-misses in the left anterior insula were also positively correlated with the GRCS scores in the whole sample ($n = 29$, $r = 0.46$, $p = 0.012$; see Fig. 5; note this was not significant for the right IFG/insula theta responses to near-misses ($r = 0.11$, $p > 0.05$)). There was also a positive association between theta responses to losses in the right IFG/anterior insula and gambling severity (SOGS) ($Rs = 0.39$, $p = 0.036$) (not observed in the left insula ($Rs = 0.036$, $p > 0.05$)). These insula findings, while showing some hemispheric differences, are generally consistent with both current (Fig. 3) and previous BOLD-fMRI findings in non-PG individuals (Clark et al., 2009).

Finally, eye movements and changes in lower frequency bands (slow-wave evoked potentials (0.75–1.75 Hz) and delta (2–3 Hz) oscillations) did not account for the theta oscillation results (Tables S6 and S7).

Spatial correspondence of BOLD-fMRI and MEG signal changes

Fig. 2 shows the spatial distribution of group-averaged BOLD-fMRI and MEG signal power changes for the initial win > full loss contrast. A high degree of spatial correspondence between increases in BOLD and the induced MEG signal power changes is evident. Interestingly, BOLD signal increases spatially co-localize with both MEG oscillatory power increases in the theta/alpha band during early processing and also alpha/beta oscillatory power decreases during late outcome processing.

Discussion

This multimodal imaging study identified for the first time the spatial and temporal neural dynamics, via convergent fMRI and MEG, of the near-miss effect and its association with gambling severity/cognitions during simulated slot machine play. Several novel findings were obtained. First, increases in BOLD signal and theta power to near-misses in the insula, and (for theta) the right OFC, were associated with trait measures of gambling severity. To our knowledge, this is the first MEG demonstration that oscillatory power changes are linked to PG, and the spatial localization of such responses to the insula shows striking overlap with current and previous gambling-associated BOLD responses (Balodis et al., 2012; Breiter et al., 2001; Chase and Clark, 2010; Clark et al., 2009; Habib and Dixon, 2010; Joutsa et al., 2012; Reuter et al., 2005). Second, the temporal localization of the near-miss effect (overlapping with win-responses) to increased theta power is consistent with EEG findings showing increased theta oscillations to monetary wins vs. losses (Donkers et al., 2005; Gehring and Willoughby, 2002; Kamarajan et al., 2009; Luo et al., 2011; Qi et al., 2011). Third, these data also contribute to our general understanding of the correspondence between task-related changes in the BOLD-fMRI signal and induced neural oscillations measured with MEG. We will address each of these points in turn.

The overlap in BOLD/theta responses to wins and near-misses, and the correlation between anterior insula activation during near-misses and a trait measure of gambling propensity (GRCS), replicate previous findings (Chase and Clark, 2010; Clark et al., 2009; Habib and Dixon, 2010). Together with our data, there is now convincing evidence of a role for reward-related brain responses to near-miss outcomes, particularly in the insula, in maintaining PG. Our novel MEG data further suggest that the temporal basis of this insula near-miss effect was an increase in induced theta oscillations, which were also associated with gambling-related cognitive distortions. Increased theta power is believed to reflect active task-related cognitive/affective processing of winning/losing outcomes while theta desynchronization indicates suppressed outcome processing (Christie and Tata, 2009; Donamayor et al., 2011). The role of the insula in mediating the near-miss effect is consistent with its involvement in mediating subjective craving in response to drug (Garavan et al., 2000; Naqvi and Bechara, 2008), food (Pelchat et al., 2004; Tang et al., 2012), and other addiction-related cues (Clark and Limbrick-Oldfield, 2013; Hommer et al., 2011). Insula activation is typically attributed to the interoception (neural representation of bodily states) and conscious feelings generated during a range of physiologically arousing experiences, including reward, punishment and risk processing (Delgado et al., 2000; Naqvi and Bechara, 2008; Paulus et al., 2003). Moreover, recent work with non-gamblers has observed increased physiological arousal (electrodermal activity) in response to wins and near-misses relative to full losses (i.e., with near-misses again resembling wins), lending support to the interoceptive role of the insula in response to near-misses (Clark et al., 2011; Dixon et al., 2013). The present multi-modal imaging findings therefore confirm a key role for insula activation in PG, which was underpinned by oscillatory theta power changes during near-miss outcomes.

Increased theta responses to near-misses in the right OFC were also positively associated with gambling severity and cognitions. While previous fMRI findings suggest increased activation in the vmPFC/OFC to near-misses generally, findings in PG have been unclear, suggesting reduced vmPFC responses to rewards or mixed outcomes (Chase and Clark, 2010; Clark et al., 2009; Habib and Dixon, 2010; Joutsa et al., 2012; Reuter et al., 2005), but increased OFC activation during risky gambles and reward expectancy (Diekhof et al., 2012; Dymond et al., 2013; Power et al., 2012; van Holst et al., 2012). The current finding of increased "win-like" theta power in the right OFC to near-misses in PG is, however, generally consistent with neuroimaging studies showing enhanced cue-reactivity in this region in drug addiction (Dom et al., 2005). Given that activity in the vmPFC/OFC encodes subjective reward value, predicts subsequent decisions and actions, and is associated with increased levels of approach motivation to anticipated rewards (Berridge and Kringelbach, 2008; Dom et al., 2005; Levy and Glimcher, 2012; Nusslock et al., 2012; Paulus et al., 2003), exaggerated OFC responses to near-misses in PG may reflect a greater reward value or anticipated reward value being attributed to these outcomes (van Holst et al., 2012), thus motivating further gambling. Indeed, our data suggest that a similar increase in right OFC theta power to wins and near-misses was evident in PG ($t(13) = .64$, $p = .54$; see Fig. 4), whereas in non-PG participants the increase in response to wins was approximately twice as large as that to near-misses ($t(18) = 2.88$, $p = .01$).

The current multi-modal imaging approach provides more comprehensive and sensitive information about the neural mechanisms underlying PG than conventional single modality approaches. MEG allows the assessment of task-related changes in multiple time-windows and multiple frequency bands from the same dataset (Carl et al., 2012; Hillebrand and Barnes, 2002), facilitating investigation of whether different functional components, represented as multiple oscillatory modulations, are sensitive to behavioral trait markers indicative of PG. In contrast, the BOLD-fMRI signal presumably represents the physiological load associated with multiple neurophysiological markers and is potentially less sensitive to component-specific effects (Singh, 2012).

Indeed, we found that different components of the induced MEG signal power changes corresponded spatially with BOLD signal increases during outcome processing (see Fig. 2): specifically, increases in the theta/alpha band were observed 0–500 ms following outcomes,while decreases in the alpha/beta band were observed 500-1000 ms following outcomes. The characteristic time-period of a single theta oscillation cycle is approximately 200 ms, which fundamentally limits our ability to temporally localize modulations in the amplitude of theta. It is not therefore possible to adjudicate whether the theta power envelope is maximum at a time consistent with specific ERP components such as the P300 or the FRN: the peak theta response could be related to either of these components.

However, not all gambling-related activations showed overlap between modalities; responses in the right OFC were only observed for theta power measured with MEG. The increased sensitivity of MEG vs. fMRI to detect these OFC responses may be due to the known reduced signal-to-noise ratio in this region in fMRI (due to susceptibility artifacts). Alternatively, it is possible that transient shifts in oscillatory dynamics may not lead to significant change in metabolic demand and hence result in no discernable BOLD response in fMRI.

Induced oscillatory changes in theta band power in insula and OFC during near-misses may have potential as a biomarker of vulnerability to behavioral addiction involving impaired reward processing and diminished subjective control, and could suggest therapeutic targets in the treatment of PG (Agrawal et al., 2012; Potenza, 2013; Potenza et al., 2013). Adapting the near-miss effect to test therapeutic interventions to reduce gambling behavior is one possibility; one would predict diminished theta power to near-miss outcomes, as well as related changes in behavioral latencies and self-report ratings, in a group that received an intervention compared to those that did not. Interventions might include brain stimulation of prefrontal cortex, which is interconnected with midbrain sites known to be involved in gambling behavior (e.g., Chib et al., 2013; Davis et al., in press; Rosenberg et al., 2013), as well as behavioral interventions like altering the frequency of near-misses, training gamblers in understanding the nature of probability, and varying the structural characteristics of the task. To our knowledge, only one study has sought to directly alter the near-miss effect. Dixon et al. (2009) altered non-PG participants' "closeness to win" ratings of near-miss outcomes through a relational learning intervention that cross-matched the words "win", "loss" and "almost" with actual win, loss and near-miss outcome displays. The impacts of behavioral interventions like this, as well as the effectiveness of brain stimulation methods for reducing problematic gambling behavior are relatively understudied topics. Our findings highlight the need for further translational research on potential biomarkers and other measures of therapeutic change (Potenza et al., 2013). Both behavioral and brain stimulation intervention methods used in conjunction with the present multi-modal imaging approach, may thus hold promise as a means of ameliorating the near-miss effect in PG.

The physical similarity of near-miss displays with win displays may result in the former acquiring some of the conditioned reinforcing properties of the latter via stimulus generalization (Ghirlanda and Enquist, 2003; Skinner, 1953). Our task may have contributed to enhanced perceptual generalization between win and loss outcomes occurring on near-miss trials (cf. Clark et al., 2009). In our three-reel task, only two out of three matching symbols were visible on the payline, symbols passed through the payline too quickly to notice whether or not a matching symbol stopped short of or passed through the payline prior to the reels stopping, and the non-matching symbol was displayed on either the right or left of the payline (Fig. 1). In this way, our task partially resembles modern multi-line slot machines where reels stop spinning consecutively from left to right, and where lines of matching and nonmatching symbols are displayed above, below, and in proximity to a diagonal, not horizontal, payline (Dixon et al., 2010). Near-misses presented in this manner obscure the fact that one is actually losing, which may have facilitated generalized reinforcement via spatial/temporal proximity and perceptual similarity of near-miss with win displays. This account, while parsimonious, is speculative, and further neuroimaging research is needed to investigate the neural basis of the near-miss effect and its interaction with perceptual features of gambling tasks, such as different types of near-miss displays, as well as further delineating the effects of outcome density (e.g., here, win density varied across studies) in facilitating generalization processes in PG and non-PG.

Conclusions

The near-miss effect in PG is associated with an increase in induced theta oscillations and BOLD responses in the anterior insula and, for theta, R OFC. Our multimodal imaging findings support previous BOLD-fMRI evidence that near-misses recruit reward-related brain circuitry and suggest that increases in theta power are associated with the enhanced sensitivity of PG participants to these 'almost-winning' outcomes. Diagnostic and treatment implications of these findings might include attenuating theta oscillations and BOLD responses evoked by near-misses.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.01.019.

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