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A Preliminary Study of the Neural Correlates of the Intensities of Self-Reported Gambling Urges and Emotions in Men with Pathological Gambling

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Abstract

Although self-reported gambling urge intensities have clinical utility in the treatment of pathological gambling (PG), prior studies have not investigated their neural correlates. Functional magnetic resonance imaging (fMRI) was conducted while 10 men with PG and 11 control comparison (CON) men viewed videotaped scenarios of gambling, happy or sad content. Participants rated the intensity of their emotions and motivations and reported the qualities of their responses. Relative to the CON group, the PG group reported similar responses to sad and happy scenarios, but stronger emotional responses and gambling urges when viewing the gambling scenarios. Correlations between self-reported responses and brain activations were typically strongest during the period of reported onset of emotional/motivational response and more robust in PG than in CON subjects for all conditions. During this epoch, corresponding with conscious awareness of an emotional/motivational response, subjective ratings of gambling urges in the PG group were negatively correlated with medial prefrontal cortex activation and positively correlated with middle temporal gyrus and temporal pole activations. Sadness ratings in the PG group correlated positively with activation of the medial orbitofrontal cortex, middle temporal gyrus, and retrosplenial cortex, while self-reported happiness during the happy videos demonstrated largely inverse correlations with activations in the temporal poles. Brain areas identified in the PG subjects have been implicated in explicit, self-referential processing and episodic memory. The findings demonstrate different patterns of correlations between subjective measures of emotions

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and motivations in PG and CON subjects when viewing material of corresponding content, suggesting in PG alterations in the neural correlates underlying experiential aspects of affective processing.

Keywords

Emotion; fMRI; Gambling urges; Motivation; Temporal pole

Introduction

Pathological gambling (PG), categorized as an impulse control disorder, may be considered a disorder of misdirected motivation in which gambling-related stimuli have prominent saliency (Potenza et al. 2003b; Zack and Poulos 2004). Consistently, individuals with PG choose to gamble excessively despite adverse consequences. Emotional factors may contribute to engagement in gambling among individuals with PG. For example, PG frequently co-occurs with depression (Desai et al. 2007; Petry et al. 2005), gambling to escape dysphoria is represented in the inclusionary criteria for PG (APA 2004), and shared genetic contributions exist for PG and major depression (Potenza et al. 2005). Thus, an improved understanding of the biological processes underlying emotional and motivational states in PG is clinically important.

Gambling urges may contribute importantly to maintenance and relapse in PG (Frost et al. 2001; Ledgerwood and Petry 2006; Oei and Gordon 2008). Self-reported gambling urges have been related to treatment outcome. For example, PG patients, particularly those with moderate to high gambling urges at treatment onset, demonstrate significant symptom improvement with the opioid antagonist naltrexone, and gambling urge intensity has been positively associated with treatment outcome amongst individuals receiving the opioid antagonists naltrexone or nalmefene (Grant et al. 2008; Kim et al. 2001). Given the clinical significance of self-reported gambling urges, an improved understanding of how the neural underpinnings of gambling urges relate to self-reported intensities is clinically relevant. Few neuroimaging studies in PG have directly examined gambling urges (reviewed in Potenza 2008). A recent study by Goudriaan and colleagues (2010) found a correlation between subjective reports of gambling urges in a PG group with activity in the ventrolateral prefrontal cortex, left insula and caudate. However, studies examining gambling urges and cue reactivity in PG have yielded mixed results, potentially due to the use of different paradigms, as well as the inclusion of diverse groups with PG (van Holst et al. 2010). Gambling urges represent a persistent and complex phenomena that may include conscious as well as unconscious factors. There has been little investigation into stages of processing of gambling stimuli as they relate to gambling urges and further, there is little understanding how these may compare to the experience of other emotions.

A prior functional magnetic resonance imaging (fMRI) study from our group identified neural correlates of gambling urges and sad and happy emotional states in men with PG as compared to control (CON) subjects without PG (Potenza et al. 2003b). In this study, different temporal epochs of motivational and emotional processing were associated with between-group differences in regional brain activations. Three specific periods of tape-viewing were studied with respect to brain activation patterns: (1) the initial period of tape-viewing prior to the onset of subjective response, as compared to the pre-tape baseline; (2) the period following onset of emotional/motivational response as compared to the immediately preceding period of tape-viewing; and (3) the final period of tape-viewing as compared to post-tape baseline. The initial period of viewing of the gambling scenarios (a period involving the presentations of general “triggers” that have been linked to the

initiation of gambling urges) identified the most robust between-group differences. Multiple cortical, basal ganglionic and thalamic brain regions showed relatively diminished activation in the PG group as compared to the CON group. This finding contrasted with those of cue provocation studies in obsessive compulsive disorder in which relatively increased activation of these regions has been reported (Breiter and Rauch 1996). Additionally, with respect to brain activations when viewing the gambling tapes, different patterns of brain activation differences were observed for the sad and happy tapes in which fewer between-group differences were observed in regional activation patterns. In the final period of viewing of the gambling scenarios (when the most robust gambling stimuli were presented), PG subjects showed relatively diminished activation of the ventromedial prefrontal cortex (vmPFC). This brain region had previously been implicated in risk/reward decision-making (Bechara 2003) and impulsive aggression (New et al. 2002; Siever et al. 1999) and has subsequently been implicated as showing relatively diminished activation in PG subjects during fMRI tasks involving cognitive control, simulated gambling, and decision-making (Potenza et al. 2003a; Reuter et al. 2005; Tanabe et al. 2007).

Here we extend our prior study by analyzing these data with respect to participants' subjective responses. Given data on neural circuits involved in the retrieval of emotional memories (Buchanan 2007), we hypothesized that activation of brain regions involved in emotional memory retrieval (e.g., the temporal gyrus, particularly the temporal pole and parahippocampal areas) would correlate with subjective reports of motivational and emotional responses to the gambling, sad and happy videotapes, and that PG subjects in particular would show strong correlations between subjective responses and regional brain activations during the viewing of the gambling and sad scenarios. We further hypothesized that these associations would be particularly robust during the epoch of motivational and emotional processing linked to the subjective onset of motivational and emotional response, given the relevance of this epoch to subjective emotional and motivational state awareness.

Materials and Methods

Participants

Participants consisted of 10 men who met criteria for PG and 11 healthy control (CON) subjects. All were right-handed native English speakers between the ages of 18 and 65 years. Detailed demographic and assessment information on participants are described elsewhere (Potenza et al. 2003b). With the exception of nicotine dependence, participants in the PG group had no other current comorbid conditions. However, several individuals met criteria for past disorders (≥3 months) including two for marijuana abuse, one for alcohol and cocaine abuse, one for alcohol abuse and major depression, one for alcohol abuse and cocaine dependence and one for alcohol dependence and cocaine dependence (Potenza et al. 2003b). All control participants reported having gambled, and all PG participants reported current/past-year gambling.

Measures

South Oaks Gambling Screen (SOGS): the SOGS is a 16-item questionnaire used to assess to identify probable individuals with PG with good reliability and validity (Lesieur and Blume 1987; Stinchfield 2002). A Kolmogorov–Smirnov Test established that the distribution of self-report scores for each video type were normally distributed within each experimental group, with the exception of the CON group's gambling urge responses to a gambling video to which participants provided responses of '0'. In order to gauge changes in gambling urge intensities before and after imaging, participants also completed a Gambling Urge Questionnaire (GUQ)—a modified version of the Alcohol Urge Questionnaire (AUQ)—prior to and following the imaging. This has been used in our prior studies (Potenza et al.

2003a, b). A similar version, the GUS, or Gambling Urge Scale (Raylu and Oei 2004), with nearly identical items based on the AUQ, has since been shown to have good predictive, concurrent and criterion-related validity. Although our version of the questionnaire was largely used as a precautionary measure, it is employed here in exploratory analyses with other subjective measures.

Experimental Task

The fMRI paradigm has been described previously (Potenza et al. 2003b; Wexler et al. 2001). Participants viewed two tapes each related to happy, sad and gambling scenarios in which young actors depicted each specific scene. The sad scenarios described a parental divorce and a loved one's death, the happy scenarios depicted a wedding and a surprise visit from a loved one, while the gambling scenarios described scenes of casino gambling. Specifically, each gambling scenario began with a perceived stressor and expressed frustration followed by free time and the receipt of unexpected money. The actor then described going to a casino and the excitement and feeling of gambling. The sad and happy scenarios acted both as experimental and active control conditions for the gambling scenarios. Following the viewing of each tape type, participants described the quality of their emotional response (e.g., sadness, happiness) and rated them on a scale of 0 (no response) to 10 (intense emotional response). Similarly, participants rated their motivational response (i.e. urge to gamble) on a scale of 0 (no response) to 10 (intense motivational response). Participants rested for 2.5 min between videotapes. Participants viewed happy, sad or gambling scenarios in a counterbalanced order, with each scenario being approximately 4 min long.

Forty-five seconds of gray-screen exposure prior to and following each scenario provided imaging baselines. While viewing the scenarios, participants pushed a button to indicate the onset of emotional or motivational responses. This procedure allows for a more clear delineation of the epochs related to individual emotional experience. A schematic representation of the experimental timeline is depicted in Fig. 1.

Image Acquisition

Images were obtained using a 1.5-T MRI system equipped with an echoplanar imaging system (GE Signa; GE Medical Systems, Milwaukee, Wis), a standard quadrature head coil, and a T2*-sensitive gradient-recalled, single-shot, echoplanar pulse sequence (Potenza et al. 2003b; Wexler et al. 2001; Wexler 1998). Conventional T1-weighted spin-echo sagittal anatomic images (echo time, 11 ms; repetition time, 667 ms; field of view, 24; slice thickness, 5 mm; 256 × 128 × 1, number of excitations) were obtained first for slice localization. Next, 12 T1-weighted oblique-axial slices (echo time, 14 ms; repetition time, 500 ms; field of view, 20 × 20 cm; 256 × 192 × 1, number of excitations) were obtained parallel to the plane transecting the anterior and posterior commissures, covering the entire brain, to serve as underlays for functional images acquired at the same locations. Functional images were obtained using a single-shot, echo-planar-gradient echo sequence (repetition time, 1,500 ms; echo time, 60 ms; flip angle, 60°; matrix, 64 × 64; field of view, 20 × 20 cm; slice thickness, 8 mm; skip, 1 mm; number of images per slice, 240) at the same locations.

Data Analysis

Data were motion corrected for 3 translational directions and 3 possible rotations (Friston et al. 1995). Runs with motion in excess of 1.5 mm of displacement and 2 of rotation were rejected; as a result 2 runs of the Happy condition and 3 runs of the gambling condition were excluded in the control group and in the PG group 1 run of the Happy condition and 3 runs of the sad condition were excluded. Corrected images were spatially filtered using a Gaussian filter with a full-width half-maximum of 6.5 mm.

Changes in the echoplanar imaging signal were evaluated in 3 pairs of successive epochs (Potenza et al. 2003b; Wexler et al. 2001). The first comparison (E0–B1) represents differences from baseline (B1) to the period of scenario-viewing prior to the onset of an emotional response (E0) up to the first 45 s of viewing. The second comparison (E1–E0) contrasts the period following a subjective emotional response (E1) to the immediately preceding period of tape viewing prior to subjective emotional response (E0). The third comparison (E2–B2) is between the final 45 s of scenario viewing independent of emotional response (E2) to the final gray-screen baseline period after scenario viewing (B2). In this way, the E0–B1 comparison can be considered as representing neural correlates associated with exposure to gambling stimuli prior to the onset of an emotional or motivational response; the E1–E0 comparison corresponds with the brain activity associated with the onset of a conscious emotional or motivational response; lastly, the E2–B2 contrast represents the final period of emotional/motivational processing, during which there may be a culmination of emotional/motivational response.

Data were analyzed using MATLAB and the Yale fMRI Bioimage Suite analysis package (Potenza et al. 2003b; Skudlarski et al. 1999; Wexler et al. 2001). Correlations between brain activity and emotional motivational responses were computed at each voxel for the 10 slices in Talairach space from $z = -12$ to $z = 50$ (Shaywitz et al. 1999; Skudlarski et al. 1999; Wexler et al. 2001). Signal arising at the lower part of the brain was evaluated in all cases to ensure that it was greater than 75% of the signal from cortical regions in more uniform areas. Only voxels belonging to a contiguous set of 25 voxels, each meeting the specified significance threshold, were included in the maps.

Data were analyzed using MATLAB and the Yale fMRI analysis package (Skudlarski et al. 1999). For each subject, separate percent signal change maps of 3 pairs of successive epochs were calculated separately for gambling, sad and happy tapes. Images for each subject were transformed into common stereotactic space by piece-wise linear warping (Friston et al. 1995; Talairach and Tournoux 1988). The percent signal change maps from individual subjects were the derived measure of task-related activity used to conduct voxel-based (whole brain) correlations. These correlations were designed to examine associations between brain activation (as assessed by blood oxygen level dependent (BOLD) signal change) and ratings of subjective gambling urge or emotional responses. As participants viewed two of each videotape type (i.e. two gambling, two sad, and two happy videos), correlations were computed from the mean of each participants' two subjective ratings with the mean percent signal change brain activation maps associated with each epoch.

The significance threshold for the voxel-based whole brain correlation analysis was set at $r = 0.7$ [uncorrected, extent threshold of 25 voxels, as has been done previously (Blumberg et al. 2003)]. The conjoint use of extent-based and voxel-based thresholds generates a more stringent significance threshold, as described elsewhere (Friston et al. 1995).

Results

Subjective Responses

As reported elsewhere (Potenza et al.2003b), there were no significant differences in the quality or magnitude of emotional responses to sad ($P = .81$) or happy ($P = .56$) scenarios between the PG and CON groups. Individuals with PG reported significantly greater intensities of emotional responses ($P = .03$) and gambling urges ($P < .001$) when viewing gambling scenarios than did those without PG (Potenza et al. 2003b). The quality of emotional responses appeared largely similar between experimental groups during the sad or happy scenarios. During the gambling scenarios, the PG group reported excitement,

aggravation and desires to gamble, while the CON group frequently reported emotions of annoyance, pity and frustration.

Relationship Between Emotional/Motivational Responses and SOGS and GUQ Scores

In the PG group, Pearson correlation coefficients were calculated between SOGS scores and the video types, revealing a positive relationship between scores on this measure and gambling emotion reported following the gambling tape viewing ($R = 0.64$; $P < 0.05$). In the PG group, SOGS scores were not correlated with subjective responses to the sad or happy scenarios or the gambling urge ratings during gambling tape viewing ($P > 0.05$). In the PG group, mean scores of gambling urges on the GUQ prior to scanning were significantly greater than in the control group ($P < 0.001$). In the PG group, Pearson correlation coefficients were calculated between the GUQ and the video types, revealing a positive relationship between scores on this measure (prior to scanning) and gambling motivations reported following the tape viewing ($R = 0.90$; $P < 0.001$). There was also a relationship between the GUQ and gambling emotion ratings ($R = 0.80$; $P < 0.01$). There were no significant correlations between the GUQ and subjective responses to the sad or happy scenarios or with scores on the SOGS ($P > 0.05$).

E0–B1 Comparison

Sad Emotion

PG Group: During the initial period of viewing as compared to pre-tape baseline and prior to the reported onset of emotional/motivational response, subjective intensities of sadness in the PG group during viewing of the sad scenarios were positively correlated with activation of the left ventral prefrontal cortex, corresponding with Brodmann's Area 4, and negatively correlated with activation of the right ventral medial prefrontal cortex and right cerebellum (Table 1). No correlations reached significance at $r > 0.7$ for PG subjects during this epoch for the happy and gambling scenarios, and none reached this threshold for the CON subjects for any of the tapes.

CON Group: No correlations reached significance at the $r > 0.7$ threshold for the CON subjects for any of the tapes.

E1–E0 Comparison

Gambling Urge

PG Group: Amongst PG subjects, subjective intensities of gambling urges correlated positively with activation in the temporal poles (bilateral), medial temporal gyrus and medial occipital gyrus and inversely with activation in left dorsal medial frontal cortex (Table 2; Fig. 2a).

CON Group: The CON group did not display any correlations at $r > 0.7$.

Gambling Emotion

PG Group: Intensities of gambling-related emotion, subjectively reported as excitement, aggravation and desire to gamble in the PG group, were positively correlated with bilateral temporal pole activation (Fig. 2b).

CON Group: CON subjects displayed no significant correlations at the 0.7 level.

Sad Emotion

PG Group: The largest number of brain regions showing significant correlations with subjective responses in the PG group was evidenced during the E1–E0 comparison. Subjective intensities of sadness in the PG group positively correlated with activation of the orbitofrontal cortex, medial temporal gyrus, precentral gyrus, precuneus, parahippocampal gyrus and the superior occipital gyrus (Fig. 2c).

CON Group: There were no significant correlations in CON subjects at the 0.7 level.

Happy Emotion

PG Group: In the PG group, subjective intensities of responses during viewing of the happy tape were negatively correlated with activation of the frontal, cingulate, parahippocampal, fusiform, and medial temporal gyri and the temporal pole (Fig. 2d).

CON Group: In the CON group, subjective intensities of responses during viewing of the happy tape positively correlated with bilateral cingulate activation.

E2–B2 Comparison

Happy Emotion

PG Group: During the final period of tape-viewing as compared to post-tape baseline, the PG group during the happy scenarios demonstrated negative correlations between subjective intensities of emotional responses and activation of the right superior and temporal gyrus and right medial frontal gyrus (Table 3). There were no correlations significant at $r > 0.7$ between the self-reported emotion and neural activations for the PG in the gambling and sad scenarios.

CON Group: There were no correlations significant at $r > 0.7$ between the self-reported emotion and neural activations for the CON group for any scenario.

Discussion

This study is the first to directly examine the relationship between subjective intensities of gambling urges and emotional states and regional brain activations in PG as compared to non-PG subjects. Consistent with our hypotheses, activations within brain regions involved with emotional memory processing correlated with subjective reports of motivational and emotional responses. Furthermore, these responses to the videotapes showed one pattern of correlations in PG subjects and a different pattern in CON subjects. Also consistent with our hypotheses, subjective intensities correlated with activations in brain regions previously implicated in the retrieval and processing of emotional memories, particularly amongst the PG subjects with respect to the sad and gambling conditions. In addition, the most robust correlations were observed during the E1–E0 epoch, corresponding with the subjective onset of motivational and emotional responses. The biological and clinical implications of the findings are discussed in relation to the three experimental time epochs.

E0–B1

Neural Correlates of Sadness—The PG group demonstrated significant positive correlations between self-reported sadness and activations in the left ventral prefrontal cortex and inverse correlations with activations in the right ventromedial prefrontal cortex (vmPFC) and the right cerebellum. The vmPFC is implicated in coding for the affective significance of stimuli even when this is processed implicitly (Damasio 1994; Elliott et al. 2000). The role of the cerebellum in affective and executive processing is increasingly being

noted as this area has significant projections through the thalamus to the cingulate and parahippocampal and prefrontal cortices (Bellebaum and Daum 2007; Lane et al. 1997; Malhi et al. 2007; Schmahmann 1996). Activation of these areas while viewing the sad scenarios prior to explicit report may signal differential sensitivity to negative cues. This observed pattern in PG but not CON subjects, seen prior to the conscious awareness of a negative emotion, suggests pathophysiological differences in affective processing that may reflect overlap between PG and other disorders (e.g., depression) involving affective dysregulation (Potenza et al. 2005).

E1–E0

Neural Correlates of Gambling Urges—The E1–E0 comparison contrasts the period of tape viewing immediately following subjective awareness of motivational or emotional response to the immediately preceding one, thereby representing the shift of attention from external to internal cues. Gambling urges in pathological gamblers recruited brain regions implicated in the retrieval and processing of emotion, including the temporal pole, medial prefrontal cortex and middle temporal gyrus; control participants did not show gambling-urge-related correlations at the same threshold (Gusnard et al. 2001; Kilts et al. 2001; Maguire and Mummery 1999).

Notably, gambling urge intensities were positively associated with temporal pole activations bilaterally (Fig. 2a), as well as with left middle temporal gyral activation. In addition to gambling urges, subjective reports of emotional responses in PG subjects were also associated with bilateral temporal pole activation (Fig. 2b). The similarities in neural correlation patterns between the motivational and emotional responses may reflect correlations between these measures as the most frequently reported emotional/motivational response in the PG group was ‘gambling’.

A role involving sensory-emotional linkage has been proposed for the temporal pole (Olson et al. 2007). The robust bilateral temporal pole association with gambling urges may relate to the affective saliency of addiction-related cues in the gambling film. Temporal pole activity is associated not only with episodic memory, but also more specifically with autobiographical memories (Maguire and Mummery 1999; Piefke et al. 2003). In particular, recent, positive, self-referential memories are linked with bilateral activation of the temporal poles, as well as the orbitofrontal cortex (OFC) and medial temporal lobe (Piefke et al. 2003). Therefore, although the videos viewed by participants were not autobiographical, temporal pole activation may reflect personally relevant information presented in the gambling videos or the retrieval of personally relevant emotional memories. Although the correlation of activation within this brain region with subjective reports of gambling urges is consistent with such a role, other possible explanations include the processing of acoustic stimuli as bilateral temporal pole activation has been observed during speech comprehension (Giraud et al. 2004).

The temporal pole has considerable and distinct reciprocal connections to the orbital and ventromedial prefrontal networks, as well as widespread projections to the amygdala (Kondo et al. 2005; Stefanacci et al. 1996). Connections to caudal OFC areas originate from the same temporal regions projecting to the amygdala, supporting the idea of this triadic network forming an anatomical substrate coding for emotionally significant events (Ghashghaei and Barbas 2002). Strong connections between the amygdala and temporal pole suggest an important role in long-term memory, whereby higher-order sensory signals are linked to an emotional context (Hoistad and Barbas 2008).

Gambling urges were also related to medial prefrontal cortex (MPFC) activity, specifically in an inverse fashion with left MPFC activity the PG group. The MPFC is implicated in

performance monitoring, particularly in error-detection and response conflict (Ridderinkhof et al. 2004). Moderate doses of alcohol decrease activity in this area and produce deficits in error-monitoring (Ridderinkhof et al. 2002). In contrast, individuals with obsessive–compulsive disorder (OCD) demonstrate hyperactivity in this frontal-subcortical circuitry (Baxter et al. 1992; Ursu et al. 2003; Yucel et al. 2007), potentially producing a faulty increase in error-signaling that generates the need for corrective actions (Pitman 1987). In the current study, the inverse correlation between MPFC activity and subjective gambling urges may be related to a diminished ability to flexibly monitor and control behavior. Explicit representations of self-relevance, mindfulness, as well as the attribution of mental states to others also recruit MPFC activity (Castelli et al. 2000; Creswell et al. 2007; Gusnard et al. 2001). This brain area has been ascribed a role in the default mode of brain operation, in particular with the processing of embodied representations of the self (Raichle et al. 2001). The inverse correlation seen here between MPFC activation and self-reported gambling urges in PG is consistent with a role for the MPFC in monitoring personal affect and attention, and the notion that an accurate representation of internal state is necessary for adaptive decision-making (Damasio 1994). Although the data are consistent with such an explanation, it is also possible that negative correlations might reflect inattention or indifference in participants in response to the stimuli.

Gambling urges in PG subjects also positively correlated with activation in the left middle temporal gyrus, corresponding to Brodmann's area 21. Kilts and colleagues (Kilts et al. 2001) reported inverse correlations between craving in cocaine-addicted individuals and left middle temporal gyral activation. Differences in the direction of the relationship (i.e. positive vs. negative) between our study and theirs may reflect differences in experimental paradigms or between the disorders, relating, for example, to cocaine influences on cortical structure and function (Beveridge et al. 2008). Nonetheless, the observation that function within this region relates to craving states in a " behavioral" and drug addiction suggests that middle temporal gyral function may represent a target for treatment development across addictions.

Similar to Crockford et al. (2005), we found that gambling urges in the PG group correlated with left medial occipital gyrus activation. Visual cortex involvement may therefore be related to the sustained attention given by the PG group to gambling-related stimuli. Similar selective activation of the occipital cortex during drug-related cues has been observed in cocaine-dependent individuals (Grant et al. 1996).

While the current study identified brain areas implicated in emotional memory, correlations of gambling urges with activations in mesolimbic structures (ventral striatum, OFC, including ventromedial prefrontal cortex (vmPFC)) were largely not observed. Prior analysis of the data from the same cohort found that relatively diminished activation of the ventral striatum and OFC was observed in PG as compared to control subjects during viewing of the gambling scenarios, similar to activations when cocaine dependent subjects (as compared to control subjects) viewed cocaine scenarios (Potenza 2008). Although this brain area is frequently implicated in addiction studies, the relationship between OFC activation and craving is relatively inconsistently observed. For example, only one-third of studies report OFC signal changes with drug craving (Dom et al. 2005; Wilson et al. 2004). The current study examined conscious appraisal of motivational and emotional responses at specific points in time; it is possible that other brain areas (e.g., temporal cortices) may more closely link to cognizant aspects of these processes, such as emotionally or motivationally salient events (Wang et al. 1999). Mesolimbic regions may also be involved, albeit less directly or robustly; examination of the correlations between subjective gambling urges in the PG group during viewing of the gambling tapes and the fMRI responses at $r > 0.6$ revealed signal increases in the vmPFC, corresponding with Brodmann's area 10. As such, and

consistent with prior studies (Potenza et al. 2003a; Reuter et al. 2005; Tanabe et al. 2007), vmPFC appears relevant to responses to gambling cues, albeit not as robustly related to subjective responses as are some other brain regions.

There was also no signal change in the amygdala and medial temporal lobe during urge states. Given the instrumental role of the amygdaloid complex and medial temporal lobe structures in conditioned reinforcement, one might expect urge-related activations in these areas. Autobiographical memories, rather than nonautobiographical ones, may produce greater medial temporal lobe activity (Fink et al. 1996) and controlling for arousal and attention-grabbing effects may also preclude amygdala activity (Kilts et al. 2001). Alterations in striatal dopamine release in individuals with PG, may further influence striatal projection areas (Steeves et al. 2009). Therefore, the absence of a relationship between subjective urges and striatal activity may be due to the contrast methodology used in the current study which may not detect similar neural events occurring during both the E0 and the E1 epochs. That is, the methodology used in the current experiment may highlight most those brain changes associated with conscious urges. Additionally, the development of compulsive aspects of addiction away from voluntary control has been neurobiologically described as a shift from limbic to associative and sensorimotor corticostriatal circuits (Chambers et al. 2003; Everitt and Robbins 2005). Therefore it is perhaps not surprising that the relationship observed with gambling urges in the PG group were those involved in emotional memory and representations of self-relevance.

Neural Correlates of Sadness

During the E1–E0 comparison in the PG group subjective reports of sadness were related to middle temporal gyrus activation, suggesting an overlap in neural circuitry involved in sadness and in gambling urges. Other correlations in this group included the vmPFC (or more specifically the medial OFC), more dorsal regions of MPFC and the precuneus—areas that have previously been implicated in both positive and negative affect-induction (Habel et al. 2005; Malhi et al. 2007; Posner et al. 2009). In addition, sadness ratings correlated with left parahippocampal gyrus activity, an area connected to retrosplenial areas and often implicated in affect induction and memory (Fink et al. 1996; Lane et al. 1997; Vandekerckhove et al. 2005). Altogether, the correlations in the PG group during the E1–E0 epoch overlap considerably with bilateral activations reported in autobiographical memory processing (Steinvorth et al. 2006).

Happiness

The findings from happy epochs are also consistent with activation profiles associated with autobiographical, episodic memory. CON, but not PG, participant happiness ratings were positively correlated with right cuneus and precuneus activity. Similar correlations in the right posterior cingulate and precuneus are evidenced in opiate dependent subjects during happiness as well as during craving states (Sell et al. 2000). The activation patterns manifested in the CON participants may therefore pertain to explicit retrieval of happy memories (Shallice et al. 1994). In the PG group, however, happiness ratings were inversely associated with signal changes in the superior and medial frontal gyrus and temporal gyrus on the left side and the temporal pole on the right side. These results further support the idea of overlapping, but differentially activated, neural circuitry involved in the processing of gambling and happy scenarios. An inverse correlation with parahippocampal activation was also evident on the right side (Fig. 2d). These areas constitute a network of frontal-temporal-extended limbic areas implicated in affect induction and episodic memory (Jatzko et al. 2006; Lane et al. 1997; Vandekerckhove et al. 2005). The similarity in activations to those produced by autobiographical memories may represent a correspondence of these scenarios to previously experienced contexts (Vandekerckhove et al. 2005).

E2–B2

Happiness—During this last epoch (E2–B2), the PG group demonstrated inverse correlations between subjective responses and activations in the right superior temporal and medial frontal gyri during the happy scenario. This is consistent with findings from the previous epoch comparison (E1–E0), recruiting areas implicated in episodic memory.

Strengths, Limitations and Future Directions—The findings of the current study have multiple limitations including a small sample comprised exclusively of men, which limits generalizability to women who may show different patterns of brain activations associated with subjective reports of motivational and emotional states (McClernon et al. 2008). Other individual differences besides gender have also been shown to influence neural activations. For example, genetic characteristics have been associated with brain responses to emotional stimuli (Hariri et al. 2002), and future studies involving larger samples should investigate the possible influences of commonly occurring allelic variants. Methodologically, the fMRI environment presents another drawback given extraneous noises and the dark, confined space. While we were able to elicit gambling urges in the PG participants in this environment, it is unclear how this precisely would translate to real-life settings. In addition, it is possible that the PG and CON groups may differ in their baseline activations in the ROIs. However, the design of the current study, consisting of comparisons between the successive epochs, does not address this possibility. Future studies using other imaging techniques [e.g., arterial spin labelling (Rao et al. 2010)] could be used to investigate this possibility directly.

Although the current study employed a significance threshold of 0.7 for the correlational analyses and a conjoint cluster level threshold of 25 contiguous voxels (more stringent than used in some prior studies (Blumberg et al. 2003), Type I errors are possible due to the relatively lenient stringency threshold and number of comparisons in the current, preliminary study. Given the preliminary nature of the current study, we have tried to maintain a balance between both Type 1 and Type II errors. The initial data therefore attempt to highlight not only the most robust effects, but also more subtle neural responses that may warrant further investigation. Future studies with larger samples are necessary to examine further the relationships between subjective responses and neural activations in PG subjects, including how other features (e.g., co-occurring disorders) might influence these processes.

Single-item Likert-type rating of subjective urges to gamble presents another drawback. Urges represent a complex construct, and a single self-reported item may provide relatively little specificity or information relating domains involving cognitive, behavioral or psychophysiological processes (Blumberg et al. 2003). While the ratings of subjective urges to gamble correlated closely with the reports of gambling emotions in the PG group, we did not systematically examine further the self-reported psychological experience of the individual, nor how such measures may relate to actual behavior. Similarly, it is possible that the explicit questions about emotion and gambling urges may have brought greater attention to these feelings and potentially have influenced subjective ratings. Some convergent validity, however, is suggested by the correlation between subjective urges to gamble following viewing of the videos and responses on the GUQ (administered prior to scanning). Urges following exposure to gambling videos may therefore not only relate to immediate subjective state, but also to some stable propensities over time. Nonetheless, the single, subjective measure used to examine gambling urges following video presentation is limited in providing information on the accurate introspective abilities of the participant and on how this conscious experience relates to actual gambling intentions and behaviors. Future

studies should examine directly the relationship between both subjective and neural responses to gambling and long-term outcomes.

It is also possible that specific affective states may play a role in contributing to the gambling urges in the PG group. This group consisted of men free of current comorbid conditions. However, past diagnoses of substance dependence or mood disorders may have influenced their susceptibility to gambling cues. This prospect can be addressed in future research with a larger and a more clinically diverse sample and including the use of substance dependent control populations. The use of structured measures of mood states, such as the Beck Depression Inventory, in future research could further examine the relationship between gambling urges and mood states. Indeed, future studies should incorporate clinical measures of depression or affective states, not only because of the high rates of comorbidity and shared genetic contributions to PG and major depression (Desai et al. 2007; Petry et al. 2005; Potenza et al. 2005), but also because of the close relationship observed between affective and gambling urge states in other PG studies (Romer Thomsen et al. 2009). Furthermore, emotion/motivation ratings could be collected immediately prior to and during viewing of the videotapes, in order to control for baseline differences and more clearly parcel out pre-existing versus experimentally-induced effects.

Another important factor to consider may be individual differences in access to gambling. Access to gambling out of the scanner may influence responses to cue exposure; although participants were informed as to the duration of the scanning procedure, gambling access was not directly assessed.

Conclusion

Prior experiments have not systematically examined the neural correlates of emotional and motivational states as related to self-reported responses in PG subjects. Given the relationship between self-reported gambling urges and clinical outcomes in treatment (Grant et al. 2008; Kim et al. 2001), these findings suggest neural targets for medication development in PG. Brain imaging techniques might help better define specific brain regions or circuits that are functioning differently in individuals with specific psychiatric disorders. This understanding could be used to investigate how therapies work, and whether different therapies (e.g., specific behavioral and pharmacological ones) might work in complementary or overlapping fashions (Brewer et al. 2008; Brody et al. 2004; Paulus et al. 2005). Additionally, individual differences in brain structure and function may exist such that individuals with similar subjective reports may display different patterns of brain activations. For example, PG and CON subjects may demonstrate similar subjective responses to sad scenarios but show differences in brain responses to sad stimuli. Such information could be relevant to developing improved treatment strategies for individuals with co-occurring PG and depression.

These results provide preliminary evidence that specific neural substrates of emotional and motivational responses are related to the magnitudes of subjective responses and provide further evidence of motivational and affective dysregulation in PG. Our results are consistent in implicating brain areas related to explicit as well as self-referential processing, similar to findings in drug addiction where the recall and imagery of autobiographical drug-related memories may in part account for the increased salience attribution and response disinhibition that characterize the disorder (Goldstein and Volkow 2002). Given the important role of urges in precipitating relapse in addictive disorders, future studies should further examine the interplay of these neural substrates and their role in the maintenance of gambling behaviors amongst individuals with PG.

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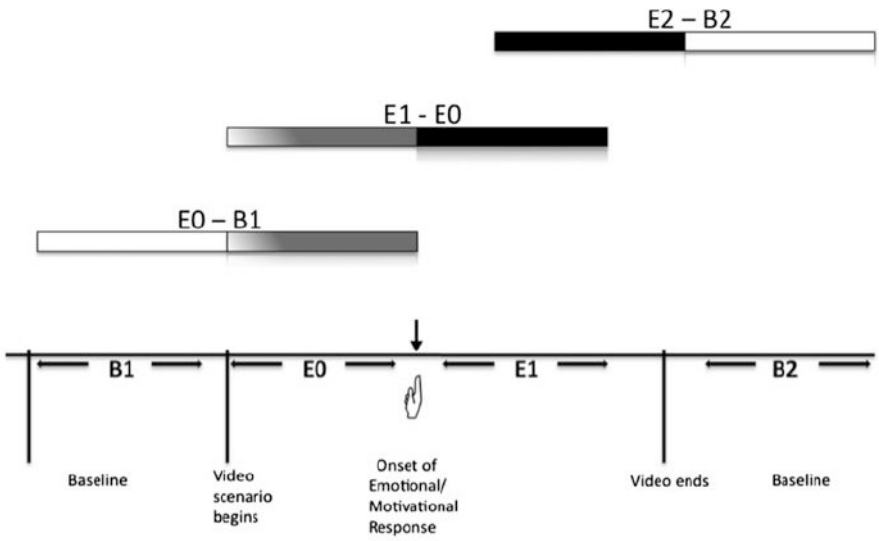

Fig. 1.

Schematic representation of time epoch comparisons for the study. B1 represents the first baseline; upon viewing of a the video, a *button press by the individual* indicates the onset of an emotional or motivational response ( ); E0 represents the epoch prior to the button press; E1 represents the epoch immediately following the button press; E2 represents the final period of the video viewing. *Horizontal bar lines* represent comparisons between different epochs

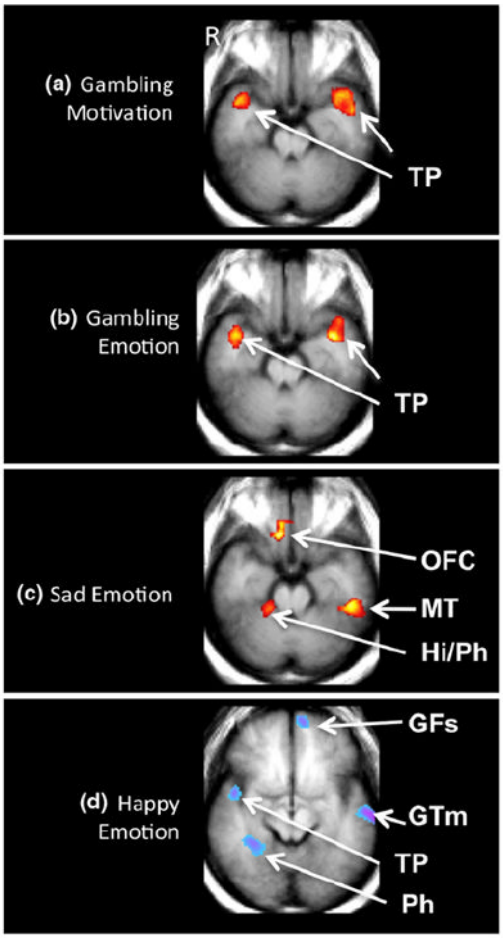

Fig. 2.

Functional magnetic resonance image correlational map of pathological gambling (PG) subjects ($n = 10$) after the reported onset of emotional or motivational response (E1–E0) during viewing of the Gambling (**a, b**), Sad (**c**), and Happy (**d**) scenarios. **a** Brain activation maps (z = −12) show positive correlations between the intensity of subjective reports of gambling motivations and bilateral temporal pole (TP) activity. **b** Brain activation maps (z = −12) show positive correlations between the intensity of subjective reports of gambling emotions and bilateral TP activity. **c** Brain activation map (z = −12) shows correlations between the intensity of subjective reports of sadness and brain activity in the orbitofrontal cortex (OFC), the right hippocampus (Hi) and parahippocampal gyrus (Ph) and the left medial temporal gyrus (MT) during viewing of the sad scenarios. **d** Brain activation map (z = −4) for the happy scenario show negative correlations between the intensity of subjective reports of happiness and brain activity in the left superior frontal gyrus (GFs), the left middle temporal gyrus (GTm), the right TP and the right Ph. Map displays correlations >0.7, with an extent threshold of 25 voxels. *Blue/purple* color indicates areas displaying inverse correlations and *red/yellow* color indicates areas displaying positive correlations. The *left side* of the brain is displayed on the *right side* of each image

Table 1

E0–B1 Subjective reports of motivational/emotional correlations with Talairach coordinates (x,y,z) of regional brain activity

Group	r-Value	Brain region	x	y	z	BA	Size (mmˆ3)	Size (voxel)	Radius
A. Positive correlations									
Sad emotion									
PG	0.76**	L Inferior frontal gyrus	−41	26	−1	45	3,987	134	7.87
HC		*No correlations at 0.7 level*							
B. Negative Correlations									
Sad Emotion									
PG	−0.75**	R Ventral medial prefrontal cortex	16	37	−5	–	3,005	101	9.45
	−0.75**	R Cerebellum	17	−49	−16	–	1,339	45	5.08
	−0.75**	L Cerebellum	−29	−55	−16	–	1,190	40	4.82
HC		*No correlations at 0.7 level*							

BA Brodmann's area

$r < 0.7$

** $P \leq 0.01$;

* $P \leq 0.05$

Table 2

E1–E0 subjective reports of motivational/emotional correlations with Talairach coordinates (x,y,z) of regional brain activity

Group	r-Value	Brain region	x	y	z	BA	Size (mmˆ3)	Size (voxel)	Radius
A. Positive correlations									
Gambling motivation									
PG	0.83**	L Middle temporal gyrus, medial occipital gyrus	−42	−69	14	37, 39	1,398	47	5.43
	0.75**	R Temporal pole	38	−1	−16	38, 21	1,696	57	5.79
	0.73*	L Temporal pole	−40	4	−16	21, 38	2,351	79	6.86
HC	0.80**	R Radiatio optica	30	−68	14	–	744	25	3.84
Gambling emotion									
PG	0.76**	L Temporal pole	−39	8	−18	21, 38	4,076	137	10.47
	0.75**	R Temporal pole	39	5	−16	21, 38	1,517	51	5.23
HC		*No correlations at 0.7 level*							
Sad emotion									
PG	0.87*	R Medial temporal gyrus	49	−63	5	37	3,302	111	8.02
	0.86*	Medial temporal gyrus	−48	−33	−16	20,21	2,142	72	6.53
	0.82*	R Precentral gyrus	56	−15	38	4, 6	2,320	78	7.60
	0.82*	L Superior, medial frontal gyrus	−12	45	41	8	3,154	106	9.71
	0.81*	Medial precuneus	−1	−68	23	31	1,190	40	4.96
	0.81*	R Inferior frontal gyrus	51	29	14	46	893	30	5.90
	0.78	Subthalamic nucleus	−48	12	−11	−5	893	30	4.15
	0.76	Radiatio optica	−26	−68	23	–	1,636	55	5.40
	0.72	Hippocampus, parahippocampal gyrus	8	−46	0	–	18,893	635	24.26
	0.70	Orbitofrontal cortex	0	25	8	–	20,976	705	20.69
	0.70	Precuneus	13	−42	50	–	2,529	85	8.31
HC		*No correlations at 0.7 level*							
Happy emotion									
PG		*No positive correlations at 0.7 level*							
HC	0.77*	R Precuneus/cuneus	0	−63	14	31	922	31	4.33

Group	r-Value	Brain region	x	y	z	BA	Size (mm^3)	Size (voxel)	Radius
B. Negative correlations									
Gambling motivation									
PG	−0.80	L Medial frontal gyrus	−5	32	41	8	1,488	50	5.12
HC		*No correlations at 0.7 level*							
Happy emotion									
PG	−0.88**	Cingulate gyrus	−5	24	41	32, 8	833	28	3.81
	−0.85**	Fusiform gyrus	−32	39	−16	37	744	25	3.68
	−0.84**	L Medial frontal gyrus	−9	58	−5	10	922	31	4.12
	−0.82**	R Temporal pole	44	0	−5	22	833	28	3.94
	−0.82**	L Middle temporal gyrus	−58	−14	−5	21	1,428	48	5.35
	−0.80*	R Parahippocampal gyrus	28	−44	−3	–	2,499	84	9.67
	−0.78*	L Superior frontal gyrus	−8	57	14	10	2,351	79	8.9
HC		*No negative correlations at 0.7 level*							

BA Brodmann's area

$r = 0.7$

** $P \leq 0.01$;

* $P \leq 0.05$

Table 3

E2–B2 subjective reports of motivational/emotional correlations with Talairach coordinates (x,y,z) of regional brain activity

Group	r-Value	Brain region	x	y	z	BA	Size (mm^3)	Size (voxel)	Radius
Negative correlations									
Happy emotion									
PG	−0.84**	R superior temporal gyrus	59	−26	14	42, 22	1,666	56	5.55
	−0.75**	R medial frontal gyrus	7	54	5	10	1,577	53	5.56
HC		*No correlations at 0.7 level*							

BA Brodmann's area

$r < 0.7$

** $P \leq 0.01$;

* $P \leq 0.05$