Gambling Urges in Pathological Gambling

A Functional Magnetic Resonance Imaging Study

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Background: Gambling urges in pathological gambling (PG) often immediately precede engagement in self-destructive gambling behavior. An improved understanding of the neural correlates of gambling urges in PG would advance our understanding of the brain mechanisms underlying PG and would help direct research into effective treatments.

Methods: Echoplanar functional magnetic resonance imaging was used to assess brain function during viewing of videotaped scenarios with gambling, happy, or sad content. Participants rated the quality and magnitude of their emotional and motivational responses.

Results: Men with PG (n=10) reported mean±SD greater gambling urges after viewing gambling scenarios vs control subjects (n=11) (5.20±3.43 vs 0.32±0.60; \( \chi^2,119=21.71; P<.001 \)). The groups did not differ significantly in their subjective responses to the happy (\( P=.56 \)) or sad (\( P=.81 \)) videotapes. The most pronounced between-group differences in neural activities were observed during the initial period of viewing of the gambling scenarios: PG subjects displayed relatively decreased activity in frontal and orbitofrontal cortex, caudate/basal ganglia, and thalamus compared with controls. Distinct patterns of regional brain activity were observed in specific temporal epochs of videotape viewing. For example, differences localized to the ventral anterior cingulate during the final period of gambling videotape viewing, corresponding to the presentation of the most provocative gambling stimuli. Although group differences in brain activity were observed during viewing of the sad and happy scenarios, they were distinct from those corresponding to the gambling scenarios.

Conclusions: In men with PG, gambling cue presentation elicits gambling urges and leads to a temporally dynamic pattern of brain activity changes in frontal, paralimbic, and limbic brain structures. When viewing gambling cues, PG subjects demonstrate relatively decreased activity in brain regions implicated in impulse regulation compared with controls.

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Technical problems (eg, loss of data and excessive participant motion) led to the removal of 2 controls and 4 PG subjects. Participants were right-handed men, aged 18 to 65 years, native English speakers, and without a history of major neurologic injury or illness. All PG subjects met the criteria for PG and were free of other active Axis I disorders except nicotine dependence. Control subjects were free of Axis I disorders except nicotine dependence and had South Oaks Gambling Screen scores of 0. All control subjects reported having gambled. The Structured Clinical Interview for DSM-IV was used for PG subjects, and the nonpatient version was used for control subjects. We also administered the Structured Clinical Interview for Pathological Gambling (M.A.S., M.N.P., and B.J.R., unpublished data, 1998). The groups did not significantly differ in mean±SD age (PG subjects: 36.20±11.93 years; controls: 30.09±7.71 years; χ²(1,9)=1.99; P=.17) or smoking status according to mean±SD Fagerstrom Test for Nicotine Dependence scores (PG subjects: 2.10±2.81; controls: 0.46±1.51; χ²(1,9)=2.88; P=.19). Smoking status was assessed because nicotine dependence was the only non-PG active Axis I diagnosis not excluded and because many PG subjects smoked. Three PG subjects and 1 control were nicotine dependent (Fagerstrom Test for Nicotine Dependence score ≥3). All participants graduated from high school. The PG group consisted of 4 African Americans and 6 whites, and the control group consisted of 1 African American and 10 whites. Mean±SD South Oaks Gambling Scale scores were 12.60±4.27 for PG subjects and 0.00±0.00 for controls (χ²(1,9)=96.11; P<.001). The Zuckerman-Kuhlman Personality Questionnaire and the NEO Personality Inventory–Revised were administered. Men with PG met the criteria for past diagnoses (not active for ≥3 months) as follows: 2 for marijuana abuse, 1 for alcohol and cocaine abuse, 1 for alcohol abuse and major depression, 1 for alcohol abuse and cocaine dependence (CD), and 1 for alcohol dependence and CD. Participants denied psychoactive drug use, except for nicotine or caffeine, for 72 hours before functional magnetic resonance imaging (fMRI). None had structural MRI abnormalities.

**Videotaped Scenarios**

Scenarios were generated as described previously. Two young actors each created happy, sad, and gambling scenarios. The sad scenarios describe parental divorce and a relative’s death, and the happy scenarios describe an unexpected visit from a relative and a wedding. The gambling scenarios incorporate psychological cues and involve casino gambling forms that are common in 2 counterbalanced orders, with essentially half of each participant group receiving the videotapes in each order (order 1: G1, S1, H1, G2, H2, S2; order 2: S1, G1, H1, S2, H2, G2). Each scenario is 3.0 to 4.5 minutes long and is preceded and followed by 45 seconds of gray-screen illumination to provide before and after baselines for each imaging sequence. Data from 1 happy, 1 sad, and 1 gambling scenario each from 3 PG subjects were not analyzed because the scenarios involved actresses performing alternate scripts.

**Activation Tasks**

Because anticipatory states such as gambling urges share features of emotions (temporally dynamic, individually defined, and internal experiences), happy and sad induction states were used as active control conditions. For each scenario, participants were instructed to push a button at the onset of an emotional (eg, happiness, sadness, or anger) or motivational (eg, desire to eat, drink, or gamble) response; facilitating definitions of epochs based on individual emotional experience. After each scenario, participants described the quality and rated the peak and average intensities of their emotions and motivations (including gambling urges) using visual analog scales from 0 to 10 (0 indicates no; 1–3, mild; 4–7, moderate; and 8–10, intense emotional and motivational responses). Between-videotape rests of 2½ minutes were used, a duration found to be sufficient for induction of distinct emotional states from one scenario to the next. Before and after fMRI, participants completed a Gambling Urge Questionnaire (M.N.P. and S. S. O’Malley, PhD, unpublished data, 1998), modified from the Alcohol Urge Questionnaire, to assess changes in urges. If a participant scored higher after fMRI, a researcher debriefed him using successive questionnaire administrations to assess urges. Men with PG were provided referral information and were encouraged to seek treatment.

**Image Acquisition**

Images were obtained using a 1.5-T MR imaging 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. Conventional T1-weighted spin-echo sagittal anatomic images (echo time, 11 milliseconds; repetition time, 667 milliseconds; 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, 13 milliseconds; repetition time, 500 milliseconds; field of view, 40×40 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, echoplanar–gradient echo sequence (repetition time, 1500 milliseconds; echo time, 60 milliseconds; 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. Runs with motion in excess of 1.5 mm of displacement and 2° of rotation were rejected. 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 (Figure 1 and Table 1). The first comparison is between the initial period of scenario viewing before onset of subjective emotional response (E0) and the 45-second baseline period before scenario viewing (B1). The second comparison is between the initial period of scenario viewing after onset of subjective emotional response (E1), up to 45 seconds in duration and as determined by time of button press, and the immediately preceding period of scenario viewing before the self-reported onset of emotion (E0). The third comparison is between the final 45 seconds of scenario viewing independent of emotional response (E2) and the baseline period after scenario viewing (B2). To maintain sufficient comparability among participants in data sampling, comparisons were not made if any
Data were analyzed using MATLAB and the Yale fMRI analysis package. 8–10 Linear contrasts between conditions were used to calculate values for each voxel, and data randomizations were used to create distributions with which to assign statistical significance to observed between-group differences at each voxel location (relative signal change map generation) for the 6 slices from z = –4 to z = 40. 8–10 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 20 voxels, each meeting the specified significance threshold (corresponding to an area of 33.8 mm²), were included in the maps. Between-group relative signal change maps were examined at P < .005 and, if no activity difference was observed, at P < .01. Talairach (x, y) coordinates corresponding to activity change peaks at each z level were determined using the Yale fMRI analysis package. 18 Within-group activity maps were examined at a threshold of P < .05 to verify between-group differences. Super-ANOVA (Abacus Concepts Inc, Berkeley, Calif) was used to analyze data from personality inventories and subjective responses. 9

RESULTS

PERSONALITY MEASURES

Total scores on the Zuckerman-Kuhlman Personality Questionnaire were higher for PG subjects than for controls (Table 2). The most robust between-group differences involved impulsive sensation seeking, with greater impulsiveness and sensation seeking associated with PG. The only major personality cluster on the NEO Personality Inventory—Revised distinguishing PG subjects and controls at P < .05 was that of neuroticism. Of the neuroticism subcategories, the greatest between-group difference was in impulsiveness.

SUBJECTIVE RESPONSES

Subjective responses to sad and happy scenarios were generally moderate and similar in controls and PG subjects (Table 3). Although occasionally a participant did not report a response to a scenario, no participant reported sad emotions during the happy scenarios or happy emotions during the sad scenarios. Control subjects were interested in the gambling scenarios and reported comparatively robust (compared with the happy and sad scenarios) and varied emotional responses described as curiosity, disgust, or pity. Subjective response to the gambling scenarios was generally more robust in PG subjects than in controls. The greatest differences were observed in reports of gambling urges in response to the gambling scenarios. None of the PG subjects described gambling urges during the viewing of the sad or happy scenarios, but all 10 reported gambling urges when viewing the gambling scenarios. Three of 11 control subjects reported gambling urges when viewing a gambling scenario.

EPOCHS

Because cue-elicited states demonstrate temporally dynamic patterns, we generated comparisons of temporal epochs (Figure 1), some of which are tied closely to and others of which are largely or totally independent of subjective responses. 8 Specifically, we predicted that individual epochs of gambling videotape viewing would demonstrate unique neural correlates related to (1) early responses, before subjective awareness of internal state change; (2) middle responses, linked to onset of awareness of state change; and (3) late responses, around the time of presentation of the most provocative stimuli. 8 The E0-B1 comparison identifies activity changes in the initial period of videotape viewing, before subjective response, and is largely independent of subjective response. The E1-E0 comparison focuses on activity changes around the time of onset of reported emotional and motivational responses and is critically dependent on button press information. The E2-B2 comparison is independent of subjective response and focuses on activity changes during the final period of viewing.

E0-B1 Comparison

During initial viewing of the gambling scenarios, PG subjects demonstrated significantly less brain activity than controls (Figure 2A and Table 4). Relative decreases bilaterally in the cingulate gyrus (z = +40) in PG subjects were accounted for by decreased activity in PG subjects. There was decreased activity involving the precuneus and right inferior parietal lobule (z = +30 and 32, respectively) attributable to increased activity in controls and decreased activity in PG subjects. Between-group differences in activity in right (z = +30, 32, and 24) and left (z = +40) precentral and postcentral gyral regions were due mainly to increased activity in control subjects. Relatively decreased activity in PG subjects in the right superior frontal gyrus (z = +32) was accounted for by increased activity in controls and decreased activity in PG subjects. Relatively decreased activity in PG subjects was observed in the left superior frontal gyrus (z = +32), accounted for by a decrease in activity in PG subjects. Differences in lateral regions of the inferior frontal gyrus (lateral orbitofrontal cortex [OFC]) were attributable to increased activity in controls (z = +4). Significant differences were also demonstrated in right and left deep gray matter nuclei (z = +12 and 4, respectively; in the region of caudate, basal ganglia, and thalamus; mainly increased in control subjects, some decrease in PG subjects). During the E0-B1 portion of sad videotape viewing, no between-group differences were
noted at P < .005 (Figure 2B). During the corresponding epoch of the happy scenarios, PG and control subjects showed a likely artifactual difference due to increased signal activation over white matter in the internal capsule in controls (Figure 2C). Together, these data demonstrate relatively decreased activations in frontal cortical, OFC, basal ganglionic, and thalamic regions in PG subjects compared with controls during the initial period of videotape viewing of the gambling scenarios specifically. These activity differences were observed during presentation of multiple general cues associated with gambling and occurred before subjective awareness of changes in emotional or motivational state.

**E1-E0 Comparison**

Individuals with PG showed relatively increased brain activity during E1-E0 compared with controls (Figure 3 and Table 4). When viewing the gambling scenarios, relatively increased activity was seen involving the right cue.

### Table 1. Thematic Contents of Videotaped Scenarios

<table>
<thead>
<tr>
<th>Scenario and Epoch Comparisons*</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gambling</strong></td>
<td></td>
</tr>
<tr>
<td>E0-B1</td>
<td>Reports feeling criticized, acts stressed/annoyed regarding household chores, and criticizes others</td>
</tr>
<tr>
<td>E1-E0</td>
<td>Describes receiving funds (cash or check), shows funds to viewer, invites viewer to casino, and describes driving to and entering casino, purchasing chips, going to a table, gambling (cards or dice), the sensation of winning “big,” and purchases that could be made with winnings</td>
</tr>
<tr>
<td>E2-B2</td>
<td>Describes the “rush” or “thrill” of gambling and reiterates the invitation to go to the casino; 20-s clip of gambling (dice scenario only)</td>
</tr>
<tr>
<td><strong>Sad</strong></td>
<td></td>
</tr>
<tr>
<td>E0-B1</td>
<td>Begins to tell a story (death of uncle or parental divorce) in a sad manner</td>
</tr>
<tr>
<td>E1-E0</td>
<td>Describes a sad event (death of uncle or divorce of parents), relating memories of attending the funeral or growing up without a father, respectively</td>
</tr>
<tr>
<td>E2-B2</td>
<td>Concludes the sad story, tearfully describing crying at the funeral or the desire to know his “lost” father, respectively</td>
</tr>
<tr>
<td><strong>Happy</strong></td>
<td></td>
</tr>
<tr>
<td>E0-B1</td>
<td>Begins to tell a story (brother’s unexpected visit or attending brother’s wedding) in a happy manner, relating reminiscences of happy childhood play and experiences with the brother</td>
</tr>
<tr>
<td>E1-E0</td>
<td>Describes a happy event (brother’s unexpected visit or attending brother’s wedding), relating memories of performing in a play attended by the brother or meeting with family members for dinner and the wedding, respectively</td>
</tr>
<tr>
<td>E2-B2</td>
<td>Concludes the happy story, cheerfully describing receiving a gift and a hug from the brother or seeing the brother’s and family’s increasing happiness at the wedding, respectively</td>
</tr>
</tbody>
</table>

*Specific contents of E0-B1 and particularly E1-E0 vary depending on button-press information. See the “Data Analysis” subsection of the “Methods” section for temporal definitions of the epochs.

### Table 2. Personality Measures of Pathological Gambling Subjects and Control Subjects*

<table>
<thead>
<tr>
<th>Scale</th>
<th>Pathological Gambling Subjects (n = 10)</th>
<th>Control Subjects (n = 11)</th>
<th>χ²†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zuckerman-Kuhlman Personality Questionnaire (Form III)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>46.70 ± 11.23</td>
<td>33.73 ± 9.38</td>
<td>8.31</td>
<td>.01</td>
</tr>
<tr>
<td>Impulsive sensation seeking</td>
<td>12.90 ± 2.02</td>
<td>8.27 ± 4.20</td>
<td>10.00</td>
<td>.005</td>
</tr>
<tr>
<td>Impulsiveness</td>
<td>4.60 ± 1.43</td>
<td>2.54 ± 2.21</td>
<td>6.26</td>
<td>.02</td>
</tr>
<tr>
<td>Sensation seeking</td>
<td>8.30 ± 1.77</td>
<td>5.73 ± 2.65</td>
<td>6.70</td>
<td>.02</td>
</tr>
<tr>
<td>Neuroticism-anxiety</td>
<td>4.80 ± 2.57</td>
<td>3.36 ± 3.61</td>
<td>1.08</td>
<td>.31</td>
</tr>
<tr>
<td>Aggression-hostility</td>
<td>8.70 ± 4.85</td>
<td>5.00 ± 3.79</td>
<td>3.83</td>
<td>.06</td>
</tr>
<tr>
<td>Activity</td>
<td>10.70 ± 2.67</td>
<td>7.27 ± 3.80</td>
<td>5.61</td>
<td>.03</td>
</tr>
<tr>
<td>Sociability</td>
<td>8.20 ± 4.16</td>
<td>5.54 ± 4.78</td>
<td>0.031</td>
<td>.86</td>
</tr>
<tr>
<td>NEO Personality Inventory—Revised</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroticism</td>
<td>85.80 ± 20.85</td>
<td>63.36 ± 23.37</td>
<td>5.35</td>
<td>.03</td>
</tr>
<tr>
<td>Anxiety</td>
<td>13.90 ± 5.36</td>
<td>10.91 ± 5.58</td>
<td>1.56</td>
<td>.23</td>
</tr>
<tr>
<td>Angry hostility</td>
<td>13.40 ± 5.21</td>
<td>9.91 ± 4.01</td>
<td>2.99</td>
<td>.10</td>
</tr>
<tr>
<td>Depression</td>
<td>15.40 ± 6.36</td>
<td>9.45 ± 5.22</td>
<td>5.52</td>
<td>.03</td>
</tr>
<tr>
<td>Self-consciousness</td>
<td>14.90 ± 3.38</td>
<td>13.36 ± 4.78</td>
<td>0.71</td>
<td>.41</td>
</tr>
<tr>
<td>Impulsiveness</td>
<td>19.60 ± 3.69</td>
<td>12.73 ± 4.52</td>
<td>14.39</td>
<td>.001</td>
</tr>
<tr>
<td>Vulnerability</td>
<td>8.60 ± 6.22</td>
<td>7.00 ± 4.60</td>
<td>0.45</td>
<td>.51</td>
</tr>
<tr>
<td>Extraversion</td>
<td>121.30 ± 24.22</td>
<td>116.54 ± 24.17</td>
<td>0.20</td>
<td>.66</td>
</tr>
<tr>
<td>Openness</td>
<td>111.80 ± 18.81</td>
<td>120.27 ± 14.68</td>
<td>1.34</td>
<td>.26</td>
</tr>
<tr>
<td>Agreeableness</td>
<td>102.30 ± 27.36</td>
<td>121.54 ± 27.04</td>
<td>2.62</td>
<td>.12</td>
</tr>
<tr>
<td>Conscientiousness</td>
<td>110.30 ± 16.49</td>
<td>122.54 ± 25.23</td>
<td>1.69</td>
<td>.21</td>
</tr>
</tbody>
</table>

*Scores are given as mean ± SD.†df = 1, 19.
neus and right middle occipital gyrus (z=24; increased in PG subjects and decreased in controls) and bilateral (predominantly left) cuneus (z=24; increased in PG subjects and decreased in controls) (Figure 3A). During the corresponding epoch of sad videotape viewing, no significant between-group differences were observed (Figure 3B). The E1-E0 between-group comparison for viewing of the happy scenarios demonstrated relatively increased activity in the left superior frontal gyrus (z=40) attributable to increased activity in PG subjects (Figure 3C). Relative increases in right ventral striatum and posterior orbitofrontal gyrus (z=–4) and left inferior frontal gyrus (z=–4) were attributable to decreased activity in controls. Overall, when between-group differences were observed for the E1-E0 comparisons, PG subjects demonstrated relatively increased activity compared with controls in brain regions previously implicated in emotional and motivational responses.

**E2-B2 Comparison**

No significant differences were observed in brain activity responses to the gambling scenarios during the E2-B2 epoch between PG and control subjects at the *P*<.005 threshold (data not shown). At a threshold of *P*<.01, comparison signal change maps revealed that the only brain region distinguishing PG subjects from controls in the E2-B2 epoch of gambling videotape viewing was the ventral AC (vAC) (z=–4; decreased in PG subjects and increased in controls) (Figure 4A and Table 4). At the same threshold for the same epoch of viewing of the sad scenarios, differences were observed in the right inferior frontal gyrus (z=24; increased in controls and decreased in PG subjects) and in the right superior frontal gyrus (z=4; decreased in controls) (Figure 4B). The E2-B2 between-group comparison signal change maps for the happy scenarios identified no differences between PG subjects and controls (Figure 4C).

**COMMENT**

The findings that the neural correlates of cue-elicited anticipatory states in PG differ significantly from those of OCD are consistent with our initial hypothesis. The finding of decreased activity in the vAC in PG subjects differs from findings of studies of cocaine cravings and our initial hypothesis and suggests that PG shares a close relationship with nondrug disorders characterized by impaired impulse control. Given the clinical importance of anticipatory urges in PG (eg, often occurring immediately before engagement in gambling and leading to relapse), an understanding of the neural correlates of gambling urges has significant potential in the development of more effective prevention and treatment strategies for PG.
investigations2,20-26 provide strong evidence that men with PG are more impulsive and sensation seeking than control subjects.8 Similar to CD and control subjects viewing happy videotapes,8 Similar to CD and control subjects viewing cocaine scenarios, when viewing the gambling scenarios, control subjects were more likely to report annoyance, pity, or disgust and PG subjects were more likely to report excitement or the urge to gamble.8 The intensities of the emotional and motivational responses to the gambling videotapes were more robust for the PG group; however, there were no differences in the intensities of the subjective responses of the control subjects to the happy, sad, or gambling scenarios. These findings suggest that the 3 scenarios were of comparable interest to the control group and that the gambling scenarios had greater salience for the PG group. The greatest between-group difference in subjective reports was that of the intensity of gambling urges when viewing the gambling scenarios. These findings indicate that despite the space and sound limitations that accompany fMRI, the gambling scenarios were effective in eliciting gambling urges in PG subjects and that this state was rarely observed in control subjects.

NEURAL CORRELATES

E0-B1 Comparison

Robust differences in brain activity between PG subjects and controls viewing the gambling scenarios were observed before the reported onset of emotional or motivational response. Men with PG showed decreased activity in frontal cortical, basal ganglionic, and thalamic brain regions compared with controls. Increased activity in cortico-basal-ganglionic-thalamic circuitry has been described in general in OCD,6 and specifically during symptom provocation.20 These findings suggest that PG and OCD subjects are on opposite ends of control subjects in disorder-specific, cue-induced cortico-basal-ganglionic-thalamic activity. These differences could reflect clinical characteristics of the groups, for example, greater tendencies in OCD for excessive predecision contemplation and in PG for minimal predecision contemplation. The extent to which deficits in this neural pathway exist in nonurge states in PG subjects and the extent to which activity within this circuitry correlates with behavioral characteristics distinguishing PG and OCD subjects20 require direct examination.

The generation of internal, emotional states has been proposed as important in making appropriate deci-
sions. Decision-making processes regarding choice selection in gambling paradigms have been shown to involve anticipatory processes (as measured by skin conductance) that operate before subjective report of an understanding of the rational basis for choosing one option over another. Individuals with PG, CD, and OCD have been shown to perform disadvantageously on these gambling tasks, and individuals with substance dependence do not generate as robust skin conductance changes before gambling choice selection. It will be important to examine directly the neural correlates in individuals with PG compared with controls and other patient groups of decision-making processes relating to gambling and to determine the relationship between structured measures of impulsiveness and brain activities associated with decision making in these groups. However, the temporal similarity of physiologic abnormalities early in the experimental decision-making process and fMRI abnormalities before the reported onset of emotional or motivational response suggest a possible relationship between the two.

The presence of between-group differences at the earliest presentation of gambling cues, and before the onset of the conscious urge to gamble, shows the importance of physiologic response measures in identifying pathologic responses and the challenge posed to afflicted individuals who experience pathophysiologic responses before conscious awareness of a desire to engage in pathologic behaviors. A similar phenomenon was observed for CD subjects viewing cocaine scenarios. However, the nature of the activity differences during this initial period of videotape viewing was different in CD and PG subjects; for example, activation of ventral and dorsal AC was observed in the E0-B1 period in CD subjects. The extent to which brain activity differences in PG and CD subjects viewing disorder-related cues reflect the effects of acute or chronic drug exposure or differences in the inherent pathogenesis remains to be investigated directly. Such studies would not only advance the understanding of the neural correlates of addictive behavior but also provide insights into the neural mechanisms underlying the development and maintenance of gambling and other addictive disorders.

Figures 3 and 4 illustrate functional magnetic resonance images comparing brain activity differences in pathological gambling (PG) subjects and control subjects after the reported onset of emotional or motivational response. Brain activation comparison maps are shown for PG subjects–control subjects when viewing gambling (10 PG subjects and 10 controls) (A), sad (5 PG subjects and 8 controls) (B), and happy (8 PG subjects and 9 controls) (C) scenarios at the *P* < .005 threshold. Red/yellow indicates areas of relatively increased activity and blue/purple indicates areas of relatively decreased activity in PG subjects vs controls during viewing of the scenario after vs before the reported onset of emotional or motivational response (E1-E0). (See the “Data Analysis” subsection of the “Methods” section for temporal definition of the epoch E1-E10.) The left side of the brain is displayed on the right side of each image.
processes but also provide a rationale for targeted treatment strategies.

E1-E0 Comparison

The E1-E0 comparison is linked to the reported onset of an emotional or motivational response. In contrast to other epochs, PG subjects generally showed relatively increased brain activity compared with controls. As previously shown, changes during this epoch were in part in the opposite direction as those occurring in the E0-B1 epoch. Activity changes followed different temporal patterns in the PG and control groups; for example, superior frontal gyral activity increases occurred during viewing of the happy scenarios in the E1-E0 epoch for the PG group and in the E0-B1 epoch for controls. Distinct temporal patterns of brain activity changes were also observed in the CD and control groups. Together, these findings indicate that PG subjects and controls differ in the neural correlates of subjectively observed emotional states and that there exist neural correlates of affective dysregulation independent of disorder-specific urges in PG and CD groups. The extent to which these findings reflect between-group differences in subjective awareness, attention, and other aspects of neural processing requires further examination.

E2-B2 Comparison

The E2-B2 comparison focuses on brain activity during the culmination of the scenario and, for the gambling scenarios, includes the most provocative gambling stimuli. The finding that PG subjects and controls were distinguished solely by activity in the vAC during the E2-B2 epoch is important for several reasons. First, increased activity was observed in CD subjects in this brain region, indicating a difference between PG and CD subjects during this epoch of viewing disorder-specific stimuli. The cause of this difference is unclear; for example, the findings might be attributable to the effects of long- or short-term exposure to cocaine or differences in brain structure or function independent of drug exposure. Second, alterations in mood have been associated with changes in activity in the vAC, with decreased activity associated with positively valenced mood states. The extent to which the relatively decreased activity in the vAC of PG subjects during viewing of the gambling scenarios reflects a positively valenced mood state requires further examination. Third, the vAC has been implicated in decision-making processes that hold relevance in the consideration of appetitive urges. The somatic marker hypothesis posits that the generation of emotional states is critical to the selection of choices advantageous for future consequences, and data from accidentally injured (eg, Phineas Gage), stroke-lesioned, and substance-dependent patients implicate the ventromedial prefrontal cortex. These findings suggest that the lower activity in PG may be linked to disadvantageous decision making with regard to contemplated engagement in gambling. Fourth, decreased activity in the ventromedial prefrontal cortex (defined as including the vAC and medial OFC) has been associated with increased impulsiveness. Studies of imaginal aggression in healthy individuals found decreased activity in the ventromedial prefrontal cortex, and individuals with intermittent explosive disorder demonstrate abnormalities in cognitive (gambling task performance) and behavioral (odor identification) indirect measures of OFC function. Serotonergic challenge with fenfluramine hydrochloride or metchlorophenylpiperazine has been associated with relatively decreased activity in the vAC and medial OFC in individuals with impulsive aggression. Abnormalities in behavioral and neuroendocrine response to metchlorophenylpiperazine in PG and other subject groups characterized by impaired impulse control, together with clinical responses to selective serotonin reuptake inhibitors in PG subjects, further implicate frontal lobe serotonin pathways in the pathologic process of PG. Future studies are needed to determine the nature of ventromedial prefrontal cortex function in PG and the extent to which it changes during or predicts response to specific forms of treatment for PG.

In conclusion, this investigation is the first fMRI study of PG, to our knowledge. One limitation is the exclusive use of men; future studies should examine women with PG. A larger sample would allow for examination of effects of psychiatric comorbidity. An inevitable complication of cue elicitation studies is the possibility of between-group differences in familiarity with and salience of the phenomena being examined. Future studies directly comparing PG, CD, and OCD groups are warranted, and image acquisition parameters that maximize visualization of structures identified in the present study (eg, oblique coronal slices for determining OFC activity) should be considered. The finding of distinct patterns of neural responses to gambling-related stimuli that are unique from those to other internal (emotional) states has direct clinical implications and provides a basis for future experimentation in the prevention and treatment of PG. Examination of the neural correlates of treatment of PG with selective serotonin reuptake inhibitors seems particularly intriguing because of data suggesting the efficacy and tolerability of these drugs in the short-term treatment of PG and because of the effects of these drugs on cortico-basal-ganglionic-thalamic activity in OCD.

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