ABSTRACT

Introduction: There has been growing interest in a better understanding of the etiology of compulsive sexual behavior (CSB). It is assumed that facilitated appetitive conditioning might be an important mechanism for the development and maintenance of CSB, but no study thus far has investigated these processes.

Aim: To explore group differences in neural activity associated with appetitive conditioning and connectivity in subjects with CSB and a healthy control group.

Methods: Two groups (20 subjects with CSB and 20 controls) were exposed to an appetitive conditioning paradigm during a functional magnetic resonance imaging experiment, in which a neutral stimulus (CS+) predicted visual sexual stimuli and a second stimulus (CS-) did not.

Main Outcome Measures: Blood oxygen level-dependent responses and psychophysiologic interaction.

Results: As a main result, we found increased amygdala activity during appetitive conditioning for the CS+ vs the CS- and decreased coupling between the ventral striatum and prefrontal cortex in the CSB vs control group.

Conclusion: The findings show that neural correlates of appetitive conditioning and neural connectivity are altered in patients with CSB. The increased amygdala activation might reflect facilitated conditioning processes in patients with CSB. In addition, the observed decreased coupling could be interpreted as a marker for impaired emotion regulation success in this group.


Key Words: Amygdala; Conditioning; Emotion; Positive; Reward; Sexual Arousal

INTRODUCTION

The development in Internet and streaming services (eg, by smartphones) has provided new, fast, and anonymous ways to access sexually explicit material (SEM). Exposure to SEM is accompanied by specific subjective, autonomous, behavioral, and neural responses. Analyses in Britain in 2013 showed that approximately 10% of the Internet traffic were on adult sites that exceeded traffic across all social networks. An online questionnaire study investigating the motivation for Internet pornography identified four factors—relationship, mood management, habitual use, and fantasy. Although most of the predominantly male users have no problems with their SEM consumption, some men describe their behavior as a compulsive sexual behavior (CSB) characterized by excessive use, loss of control, and inability to decrease or stop the problematic behavior, resulting in considerable economically, physically, or emotionally negative consequences to self or others. Although these men often describe themselves as “sex or porn addicts,” there are competing theories regarding the nature and conceptualization of CSB. Investigators have interpreted this behavior as an impulse control disorder, mood regulation deficit, obsessive-compulsive disorder, or behavioral addiction disorder, whereas others have avoided etiologic associations by using the term non-paraphilic hypersexuality disorder. Other investigators have challenged the need for a distinct diagnosis in general. Therefore, neurobiological experiments investigating the neural correlates of CSB are important to gain more insight into the underlying mechanisms.

It has been proposed that facilitated appetitive conditioning might be a crucial mechanism for the development and maintenance of addictions and further psychiatric disorders. In appetitive conditioning paradigms, a neutral stimulus (CS+)...
is paired with an appetitive stimulus (UCS), while a second neutral stimulus (CS−) predicts the absence of the UCS. After a few trials, the CS+ elicits conditioned responses (CRs) such as increased skin conductance responses (SCRs), changes in preference ratings, and altered neural activity.16,18,19 Regarding the neural correlates of appetitive conditioning, a network has been identified that includes the ventral striatum, amygdala, orbitofrontal cortex (OFC), insula, anterior cingulate cortex (ACC), and occipital cortex.20–24 Hence, the ventral striatum is involved in appetitive conditioning because of its central role in anticipation, reward processing, and learning.25,26 However, in contrast to the ventral striatum, the role of the amygdala for appetitive conditioning is less clear. Although many animal and human studies have repeatedly confirmed the amygdala as the central region for fear conditioning,27 its involvement in appetitive conditioning has been investigated only rarely. Recently, animal and human studies have demonstrated that the amygdala is involved in the processing of appetitive stimuli, appetitive conditioning, and processing of CSB using various stimuli and designs.28–30 For instance, Gottfried et al29 found increased amygdala activation to the CS+ vs the CS− during human appetitive conditioning using pleasant odors as the UCS. Activations in the OFC, insula, ACC, and occipital cortex are often interpreted as conscious and/or in-depth evaluation processes of the stimuli.16

To date, only two functional magnetic resonance imaging (fMRI) studies have investigated the neural correlates of CSB and found increased activations in the amygdala and ventral striatum as well as altered neural connectivity in subjects with CSB during the presentation of related (sexual) cues.35,36 These structures are in line with other studies investigating the neural correlates of addiction disorders and impulse control deficits.37,38 For instance, meta-analytical findings have shown a significant correlation between amygdala activation and the intensity of craving.37 Another study that used diffusion tensor imaging found increased white matter microstructure integrity in prefrontal areas in subjects with CSB and a negative correlation between CSB and structural connectivity in the frontal lobe.39

In addition to the importance of appetitive conditioning processes, impairments in the inhibition of impulsive behavior are crucial for the development and maintenance of many psychiatric disorders and dysfunctional behaviors.40,41 These difficulties with inhibition can explain the loss of control of subjects with CSB when confronted with related cues. Regarding the neural correlates of impulsive behavior and its regulation, the ventral striatum and ventromedial prefrontal cortex (vmPFC) seem to be important antagonists: the ventral striatum is assumed to be relevant for initiating impulsive behavior, whereas its downregulation is driven by the vmPFC through reciprocal connections.42 For instance, previous results have linked impaired ventral striatal and prefrontal connectivity to trait impulsivity and to impulsive behavior.42,43

However, no study thus far has investigated the neural correlates of appetitive learning mechanisms or the loss of control in subjects with CSB compared with healthy controls. Based on the literature cited earlier, the first aim of the present study was to explore the hemodynamic responses of appetitive conditioning in these subjects compared with a matched control group. We hypothesized increased activation in the amygdala and ventral striatum in subjects with CSB compared with the control group. The second aim was to explore connectivity differences between the two groups. Identifying the neural substrate of altered appetitive conditioning and connectivity in these subjects would have implications not only for the understanding of the development and maintenance of this behavior but also for treatment strategies, which typically focus on behavioral modification through altered learning experiences (eg, cognitive behavioral therapy).34

**METHODS**

**Participants**

Twenty men with CSB and 20 matched controls were recruited by self-referral after an advertisement and referrals of a local outpatient clinic for cognitive behavioral therapy (Table 1). All participants had normal or corrected-to-normal vision and signed an informed consent. The study was conducted in accordance with the Declaration of Helsinki. All participants underwent structural clinical interviews to diagnose Axis I and/or Axis II diagnoses. Participants classified as

| Table 1. Demographic and Psychometric Measurements for CSB and Control Groups* |
|------------------------------|----------------|-----------------|----------------|
|                              | CSB group     | Control group   | Statistics     |
| Age                          | 34.2 (8.6)    | 34.9 (9.7)     | *t* = 0.23, *P* = .825 |
| BDI-II                       | 12.3 (9.1)    | 7.8 (9.9)      | *t* = 1.52, *P* = .136 |
| Time spent watching time     | 1,187 (806)   | 29 (26)        | *t* = 6.41, *P* < .001 |
| Axis I disorder              |               |                |                |
| MD episode                   | 4             | 1              |                |
| Recurrent MD disorder        | 4             |                |                |
| Social phobia                | 1             |                |                |
| Adjustment disorder          | 1             |                |                |
| Specific phobia              | 1             |                |                |
| Orgasmic-erection disorder   | 3             |                |                |
| Somatoform disorder          | 1             |                |                |
| Axis II disorder             |               |                |                |
| Narcissistic personality     | 1             |                |                |
| disorder                     |               |                |                |
| Psychiatric medication       |               |                |                |
| Amitriptyline                | 1             |                |                |

*Data are presented as mean (SD).
having CSB had to fulfill all criteria for hypersexuality adapted for CSB:1:

1. For at least 6 months, recurrent and intense sexual fantasies, urges, and sexual behavior must be associated with at least four of the following five criteria:
   a. Excessive time consumed by sexual fantasies and urges and by planning and engaging in sexual behavior
   b. Repetitively engaging in these sexual fantasies, urges, and behavior in response to dysphoric mood states
   c. Repetitively engaging in sexual fantasies, urges, and behavior in response to stressful life events
   d. Repetitive but unsuccessful efforts to control or significantly decrease these sexual fantasies, urges, and behavior
   e. Clinically significant personal distress or impairment in social, occupational, or other important areas of functioning associated with the frequency and intensity of these sexual fantasies, urges, and behavior

2. These sexual fantasies, urges, and behavior are not due to the direct physiologic effects of exogenous substances, medical conditions, or manic episodes

3. Age at least 18 years

Conditioning Procedure

The conditioning procedure was conducted while performing fMRI (see below for details). A differential conditioning procedure with 42 trials was used (21 per CS). Two colored squares (one blue, one yellow) served as the CS and were counterbalanced as CS+ and CS− across subjects. The CS+ was followed by 1 of 21 erotic pictures (100% reinforcement). All pictures depicted couples (always one man and one woman) showing explicit sexual scenes (eg, practicing vaginal intercourse in different positions) and were presented in color with 800 × 600 pixel resolution. The stimuli were projected onto a screen at the end of the scanner (visual field = 18°) using an LCD projector. Pictures were viewed through a mirror mounted on the head coil. The CS duration was 8 seconds. The erotic pictures (UCS) appeared immediately after the CS+ (100% reinforcement) for 2.5 seconds followed by the intertrial interval of 12 to 14.5 seconds.

All trials were presented in a pseudo-randomized order: The same CS was not presented more than twice in succession. The two CS were presented equally often in the first and second halves of the acquisition. The first two trials (one CS+ trial, one CS− trial) were excluded from the analyses because learning could not yet have occurred, resulting in 20 trials for each CS.15

Subjective Ratings

Before the experiment and immediately after the conditioning procedure, participants rated valence, arousal, and sexual arousal of the CS+, CS−, and UCS on a 9-point Likert scale and their UCS expectancy on a 10-point Likert scale. For the CS ratings, statistical analyses were performed by analysis of variance (ANOVA) in a 2 (CS type: CS+ vs CS−) × 2 (time: before vs after acquisition) × 2 (group: CSB vs control group) design followed by post hoc tests in SPSS 22 (IBM Corporation, Armonk, NY, USA) for each rating. Appropriate post hoc t-tests were conducted to analyze significant effects further. For the erotic pictures, two-sample t-tests were performed to analyze group differences.

Skin Conductance Measuring

The SCRs were sampled using Ag-AgCl electrodes filled with isotonic (NaCl 0.05 mol/L) electrolyte medium placed at the non-dominant left hand. An SCR was defined as a single phasic response after stimulus onset. Therefore, the largest difference between a minimum and subsequent maximum within the 1 to 4 seconds after CS onset was defined as the first interval response (FIR), that within the 4 to 8 seconds as the second interval response (SIR), and that within 9 to 12 seconds as the third interval response (TIR). The responses within the analysis windows were extracted using Ledalab 3.4.4.63 These responses are log (µS + 1) transformed to correct for violation of normal distribution of the data. Five subjects (three with CSB and two controls) did not show any SCRs (no increased responses to the UCS) and were excluded from the analysis. Mean SCRs were analyzed by ANOVA in a 2 (CS type: CS+ vs CS−) × 2 (group: CSB vs control group) design followed by post hoc tests using SPSS 22.

Magnetic Resonance Imaging

Hemodynamic Activity

Functional and anatomic images were acquired with a 1.5-Tesla whole-body tomograph (Siemens Symphony with a quantum gradient system; Siemens AG, Erlangen, Germany) with a standard head coil. Structural image acquisition consisted of 160 T1-weighted sagittal images (magnetization prepared rapid acquisition gradient echo; 1-mm slice thickness; repetition time = 1.9 seconds; echo time = 4.16 ms; field of view = 250 × 250 mm). During the conditioning procedure, 420 images were acquired using a T2*-weighted gradient echo-planar imaging sequence with 25 slices covering the entire brain (slice thickness = 5 mm; gap = 1 mm; descending slice order; repetition time = 2.5 seconds; echo time = 55 ms; flip angle = 90°; field of view = 192 × 192 mm; matrix size = 64 × 64). The first two volumes were discarded owing to an incomplete state of magnetization. Data were analyzed using Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK; 2008) implemented in MATLAB 7.5 (Mathworks Inc., Sherborn, MA, USA). Before all analyses, data were preprocessed, which included realignment, unwarping (b-spline interpolation), slice-time correction, co-registration of functional data to each participant’s anatomic image, and normalization to the standard space of the Montreal Neurological Institute brain. Spatial smoothing was executed with an isotropic three-dimensional
Gaussian filter with a full width at half maximum of 9 mm to allow for corrected statistical inference.

On the first level, the following contrasts were analyzed for each subject: CS+, CS−, UCS, and non-UCS (defined as the time window after CS− presentation corresponding to the time window of UCS presentation after the CS+). A stick function was selected for each regressor. Each regressor was independent of the others, did not include shared variance (cosine angle < 0.20), and was convolved with the hemodynamic response function. The six movement parameters of the rigid body transformation obtained by the realignment procedure were introduced as covariates in the model. The voxel-based time series was filtered with a high-pass filter (time constant = 128 seconds). The contrasts of interest (CS+ vs CS−; CS− vs CS+; UCS vs non-UCS; non-UCS vs UCS) were defined for each subject separately.

For the second-level analyses, one- and two-sample t-tests were conducted to investigate the main effect of task (CS+ vs CS−; UCS vs non-UCS) and differences between groups. Statistical corrections for region-of-interest (ROI) analyses were conducted with an intensity threshold of $P = .05$ (uncorrected), $k = 5$, and a significance threshold ($P = .05$; corrected for familywise error, $k = 5$), and whole-brain analyses were conducted with a threshold at $P = .001$ and $k > 10$ voxels. All analyses were computed with SPM8.

Although no group differences in UCS ratings and BDI scores were observed, we conducted further analyses including UCS ratings and BDI scores as covariates to account for potential confounding effects of UCS experiences and comorbidity. Results remained almost stable (no further group differences; reported group differences remained significant). Anatomic masks for ROI analyses of the amygdala (2,370 mm$^3$), insula (10,908 mm$^3$), occipital cortex (39,366 mm$^3$), and OFC (10,773 mm$^3$) were taken from the Harvard-Oxford Cortical and Subcortical Structural Atlases (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) (25% probability) provided by the Harvard Center for Morphometric Analysis and the ventral striatum mask (3,510 mm$^3$) from the Human Brain Project Repository database based on the BrainMap database. The Harvard-Oxford atlas is a probabilistic atlas based on T1-weighted images of 37 healthy subjects (N = 16 women). The vmPFC mask (11,124 mm$^3$) was created with MARINA and has been used in many previous studies.

Psychophysiologic Interaction Analysis

Psychophysiologic interaction (PPI) analysis, which explores the modulation of the connectivity between a seed region and other brain areas by an experimental task, the so-called psychological variable (CS+ vs CS−), was conducted. The seed regions, the ventral striatum and amygdala, were prespecified in two separate analyses based on the used ROIs (see above). In a first step, we extracted the first eigenvariate for each seed region as implemented in SPM8. Then, the interaction term was created by multiplying the eigenvariate with the psychological variable (CS+ vs CS−) for each subject and convolving it with the haemodynamic response function. First-level analyses were conducted for each subject including the interaction term as regressor of interest (PPI regressor) and the eigenvariate as well as the task regressor as nuisance regressors. At the second level, we analyzed group differences in connectivity (PPI regressor) between the CSB group and the control group using two-sample t-tests with the vmPFC as the ROI. Statistical corrections were identical to the previous fMRI analyses.

RESULTS

Subjective Ratings

ANOVA showed significant main effects of CS type for valence ($F_{1,38} = 5.68; P < .05$), arousal ($F_{1,38} = 7.56; P < .01$), sexual arousal ($F_{1,38} = 18.24; P < .001$), and UCS expectancy ratings ($F_{1,38} = 116.94; P < .001$). In addition, significant CS type × time interaction effects were found for valence ($F_{1,38} = 9.60; P < .01$), arousal ($F_{1,38} = 27.04; P < .001$), sexual arousal ($F_{1,38} = 39.23; P < .001$), and UCS expectancy ratings ($F_{1,38} = 112.4; P < .001$). Post hoc tests confirmed successful conditioning (significant differentiation between CS+ and CS−) in the two groups, showing that the CS+ was rated as significantly more positive, more arousing, and more sexually arousing than the CS− after ($P < .01$ for all comparisons), but not before the acquisition phase, indicating successful conditioning in the two groups (Figure 1). Further analyses showed that these differences were based on increased CS+ scores and decreased CS− scores over time (P < .05 for all comparisons). No group differences were found regarding valence ($P = .92$) and arousal ($P = .32$) ratings of the UCS (visual sexual stimuli).

Skin Conductance Responses

ANOVA showed a main effect of CS type in the FIR ($F_{1,33} = 4.58; P < .05$) and TIR ($F_{1,33} = 9.70; P < .01$) and a trend in the SIR ($F_{1,33} = 3.47; P = .072$) showing increased SCR to the CS+ and to the UCS, respectively, compared with the CS−. No main effects of group occurred in the FIR ($P = .610$), SIR ($P = .698$), or TIR ($P = .698$). In addition, no CS type × group interaction effects were found in FIR ($P = .271$) and TIR ($P = .260$) after correction for multiple comparisons (FIR, SIR, and TIR).

fMRI Analysis

Main Effect of Task (CS+ vs CS−)

When analyzing the main effect of conditioning (CS+ vs CS−), whole-brain results showed increased responses to the CS+ in the left ($x/y/z = -30/−94/−21$; maximum $z = 5.16$; corrected $P < .001$) and right ($x/y/z = 27/−88/−1$; $z = 4.17$; $P < .001$) occipital cortices. In addition, ROI analyses showed increased activation to the CS+ compared with the CS− in the ventral striatum and occipital cortex and trends in the insula and...
OFC (Table 2), indicating successful conditioning of hemodynamic responses across all participants.

Group Differences (CS+ vs CS−)

Regarding group differences, two-sample t-tests showed no differences in whole-brain analyses but did show increased hemodynamic responses in the CSB group compared with the control group (Pcorr = .012) for CS+ vs CS− (Table 2 and Figure 2A), whereas the control group did not show significantly enhanced activations compared with the CSB group (Pcorr > .05 for all comparisons).

UCS vs non-UCS

Regarding UCS vs non-UCS, group differences were explored using two-sample t-tests. No differences between groups occurred for this contrast, indicating that the differences in CRs were not based on differences in unconditioned responses.

Psychophysiologic Interaction

In addition to the appetitive conditioning results, we used PPI to explore the connectivity among the ventral striatum, amygdala, and vmPFC. PPI detects brain structures correlated with a seed ROI in a task-dependent manner. The ventral striatum and amygdala were used as seed regions because these areas are associated with emotion regulation and regulation of impulsivity. Whole-brain results showed decreased coupling between the ventral striatum as the seed region and the left prefrontal (x/y/z = −24/47/28; z = 4.33; Puncorr < .0001; x/y/z = −12/32/−8; z = 4.13; Puncorr < .0001), right lateral, and prefrontal (x/y/z = 57/−28/40; z = 4.33; Puncorr < .0001; Figure 1.

Table 2. Localization and Statistics of Peak Voxels for Main Effect of Stimulus and Group Differences for the contrast CS+ vs CS− (region-of-interest analysis)*

<table>
<thead>
<tr>
<th>Group analysis</th>
<th>Structure</th>
<th>Side</th>
<th>k</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Maximum z</th>
<th>Corrected P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main effect of stimulus</td>
<td>Ventral striatum</td>
<td>L</td>
<td>19</td>
<td>−15</td>
<td>−1</td>
<td>−2</td>
<td>2.80</td>
<td>.045</td>
</tr>
<tr>
<td></td>
<td>Occipital cortex</td>
<td>L</td>
<td>241</td>
<td>−24</td>
<td>−88</td>
<td>−8</td>
<td>4.28</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Occipital cortex</td>
<td>R</td>
<td>230</td>
<td>24</td>
<td>−88</td>
<td>−5</td>
<td>4.00</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>OFC</td>
<td>R</td>
<td>49</td>
<td>12</td>
<td>41</td>
<td>−2</td>
<td>2.70</td>
<td>.081</td>
</tr>
<tr>
<td></td>
<td>Insula</td>
<td>L</td>
<td>134</td>
<td>−36</td>
<td>17</td>
<td>17</td>
<td>3.05</td>
<td>.073</td>
</tr>
<tr>
<td>CSB vs control group</td>
<td>Amygdala</td>
<td>R</td>
<td>39</td>
<td>15</td>
<td>−10</td>
<td>−14</td>
<td>3.29</td>
<td>.012</td>
</tr>
</tbody>
</table>

CSB = compulsive sexual behavior; k = cluster size; L = left hemisphere; OFC = orbitofrontal cortex; R = right hemisphere.

*The threshold was P < .05 (corrected for familywise error; small volume correction according to SPM8). All coordinates are given in Montreal Neurological Institute space.

†No significant activations.

DISCUSSION

Previous theories have postulated that appetitive conditioning is an important mechanism for the development and maintenance of approaching behavior and related psychiatric disorders. Therefore, the aim of the present study was to investigate the neural correlates of appetitive conditioning in subjects with CSB compared with a control group and to determine potential differences in connectivity of the ventral striatum and amygdala with the vmPFC. Regarding the main effect of appetitive conditioning, we found increased SCRs, subjective ratings, and blood oxygen level-dependent responses in the ventral striatum, OFC, occipital cortex, and insula to the CS+ vs CS−, indicating overall successful appetitive conditioning across all subjects.

Regarding group differences, subjects with CSB displayed increased hemodynamic responses for CS+ vs CS− in the amygdala compared with controls. This finding is in line with a recent meta-analysis that showed that amygdala activation is often increased in patients with addiction disorders compared with controls and for other psychiatric disorders, which are discussed in context of CSB. Remarkably, the meta-analysis also provided evidence that the amygdala might play a significant role for craving in patients. In addition, the amygdala constitutes an important marker for stabilization of the learning signal. Thus, the observed increased amygdala reactivity could be interpreted as a correlate of a facilitated acquisition process, which renders formerly neutral...
Appetitive Conditioning

stimuli into salient cues (CS+) to more easily provoke approach behavior in subjects with CSB. In accord with this notion, increased amygdala reactivity has been reported to be a maintaining factor in many drug-related and non–drug-related psychiatric disorders. Therefore, one could hypothesize that increased amygdala activation during appetitive conditioning might be important for the development and maintenance of CSB.

Moreover, the present results allow speculation about different functions of the amygdala in fear and in appetitive conditioning. We assume that the different role of the amygdala in fear conditioning and appetitive conditioning might be due to its involvement in different CRs. For example, increased startle amplitude is one of the most valid CRs during fear conditioning and is mediated primarily by the amygdala. Hence, amygdala activations are a robust finding during fear conditioning and amygdala lesions lead to impairments of conditioned startle amplitude in fear conditioning. In contrast, startle amplitudes are decreased during appetitive conditioning, and other response levels such as genital responses (which are not primarily influenced by the amygdala) seem to be more appropriate markers for sexual conditioning. In addition, different amygdala nuclei are most likely involved in fear and appetitive conditioning and thus could serve different subsystems for appetitive and fear conditioning.

Moreover, we found decreased coupling between the ventral striatum and vmPFC in subjects with CSB compared with the control group. Altered coupling between the ventral striatum and prefrontal areas has been reported in the context of emotion downregulation, substance disorders, and control of impulsivity and has been observed in pathologic gambling. Several studies have suggested that dysfunctional coupling processes might be a correlate of impairment of inhibition and motor control. Therefore, the decreased coupling could reflect dysfunctional control mechanisms, which nicely fits with previous results showing altered connectivity in patients with impairments in inhibition control.

We observed significant differentiations between the CS+ and the CS− in subjective ratings and in SCRs in the two groups, indicating successful conditioning, but no group differences in these two response systems. This finding is in accord with other studies reporting subjective ratings as a reliable marker for conditioning effects (ie, significant differences between CS+ and CS−), but not for detecting group differences in conditioning. For instance, no group differences were found in subjective ratings and in SCRs during appetitive or aversive conditioning among various groups, whereas group differences were observed in other response systems such as startle or blood oxygen level-dependent responses. Notably, subjective ratings not only seem to be an insufficient marker of group differences but also seem to be relatively uninfluenced by a broad range of other experimental manipulations, such as extinction or overshadowing. We observed the same result pattern in SCRs, with significant differentiation between the CS+ and the CS− but no group-dependent effects. These findings support the idea that subjective ratings and SCRs might be regarded as stable indices for conditioning, whereas other measurements seem better for reflecting individual differences. One explanation could be that subjective ratings and SCRs recruit more amygdala-independent (eg, cortical or ACC) brain areas in contrast to response systems such as conditioned startle amplitude, which is innervated primarily by amygdala responses. For instance, it has been shown that conditioned SCRs, but not conditioned startle responses, are detectable in patients with amygdala lesions. Future studies should explore the underlying mechanisms potentially responsible for the dissociation of response systems in more detail and should include startle amplitude as an important measurement for assessing group differences.

In addition, it would be interesting to compare the neural correlates of subjects with CSB with a control group showing high SEM consumption levels but no further dysfunctional behavior. This approach would help to gain a better understanding of the general effects of increased SEM consumption levels in shaping neural processes of SEM.

Limitations

Some limitations have to be taken into account. We did not find differences in the ventral striatum between the two groups. One explanation for this could be that ceiling effects could have prevented potential group differences. Several studies have reported that sexual cues can provoke increased dopaminergic transmission more than other rewarding stimuli. Further, it should be noted that the vmPFC is not a well-defined region and might contain heterogeneous subdivisions involved in different emotional functions. For instance, the vmPFC activation cluster in other studies is more lateral and anterior to our result. Therefore, the present finding might reflect several processes because the vmPFC is involved in many different functions such as attention or reward processing.

Conclusion and Implications

In general, the observed increased amygdala activity and the concurrently decreased ventral striatal-PFC coupling allows speculations about the etiology and treatment of CSB. Subjects with CSB seemed more prone to establish associations between formally neutral cues and sexually relevant environmental stimuli. Thus, these subjects are more likely to encounter cues that elicit approaching behavior. Whether this leads to CSB or is a result of CSB must be answered by future research. In addition, impaired regulation processes, which are reflected in the decreased ventral striatal-prefrontal coupling, might further support the maintenance of the problematic behavior. With respect to clinical implications, we found significant differences in learning processes and decreased connectivity between the ventral striatum and vmPFC. Facilitated appetitive learning processes in combination with dysfunctional emotion regulation could hamper successful treatment. In line with this view, recent findings have postulated that altered ventral
striatal-PFC coupling could significantly increase the odds of relapse.71 This could indicate that treatments that focus on emotion regulation also might be effective for CSB. Evidence supporting this view has shown that cognitive behavioral therapy, which is based on these learning and emotion regulation mechanisms, is an effective treatment for many disorders.72 These findings contribute to a better understanding of the underlying mechanisms of CSB and suggest potential implications for its treatment.

Corresponding Author: Tim Klucken, PhD, Bender Institute of Neuroimaging, Justus Liebig University Giessen, Otto-Behaghel-Str. 10 H, 35390 Giessen, Germany. Tel: +49(0)641-992-6333; Fax: +49(0)641-992-6099; E-mail: tim.klucken@psychol.uni-giessen.de

Conflict of Interest: The authors report no conflicts of interest.

Funding: This study was funded by the German Research Foundation (STA 475/11-1)

STATEMENT OF AUTHORSHIP

Category 1
(a) Conception and Design
Tim Klucken; Sina Wehrum-Osinsky; Jan Schweckendiek; Rudolf Stark
(b) Acquisition of Data
Tim Klucken; Sina Wehrum-Osinsky; Jan Schweckendiek
(c) Analysis and Interpretation of Data
Tim Klucken; Sina Wehrum-Osinsky; Jan Schweckendiek; Onno Kruse; Rudolf Stark

Category 2
(a) Drafting the Article
Tim Klucken; Sina Wehrum-Osinsky; Jan Schweckendiek; Onno Kruse; Rudolf Stark
(b) Revising It for Intellectual Content
Tim Klucken; Sina Wehrum-Osinsky; Jan Schweckendiek; Onno Kruse; Rudolf Stark

Category 3
(a) Final Approval of the Completed Article
Tim Klucken; Sina Wehrum-Osinsky; Jan Schweckendiek; Onno Kruse; Rudolf Stark

REFERENCES

23. Klucken T, Wehrum S, Schweckendiek J, et al. 5-HTTLPR polymorphism is associated with altered hemodynamic
McLaughlin RJ, Floresco SB. The role of different subregions in appetitive associative conditioning. *Neuroscience* 2009;158:721-731.


McLaughlin RJ, Floresco SB. The role of different subregions of the basolateral amygdala in cue-induced reinstatement and extinction of food-seeking behavior. *Neuroscience* 2007;146:1484-1494.


Diekhof EK, Grober O. When desire collides with reason: functional interactions between anteroventral prefrontal cortex and nucleus accumbens underlie the human ability to resist impulsive desires. *J Neurosci* 2010;30:1488-1493.


71. Volkow ND, Baler RD. Brain imaging biomarkers to predict relapse in alcohol addiction. JAMA Psychiatry 2013;70:661-663.