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Distinct Situational Cue Processing in Individuals with Kleptomania: A Preliminary Study

Yui Asaoka, Moojun Won, Tomonari Morita, Emi Ishikawa, Yukiori Goto

Graduate School of Science, Kyoto University, Kyoto, Japan (Ms Asaoka); MRC Lab Clinic, Mitaka, Tokyo, Japan (Dr Won); Kyowa Hospital, Obu, Aichi, Japan (Mr Morita and Ms Ishikawa); Graduate School of Informatics, Kyoto University, Kyoto, Japan (Dr Goto).

Correspondence: Yukiori Goto, PhD, Department of Intelligence Science and Technology, Graduate School of Informatics, Kyoto University, Yoshida Honmachi, Sakyo-ku, Kyoto, Kyoto, 606-8501, Japan (goto.yukiori.5c@kyoto-u.ac.jp).

Abstract

Background: Impulse control disorder has been suggested to meet the criteria of addiction and is often considered a behavioral addiction; however, few studies have examined whether the disorder involves altered responses to situational cues that are associated with symptoms. In this study, we examined behavioral and neural responses to situational cues among individuals with an impulse control disorder: kleptomania.

Methods: Healthy adults and kleptomania patients whose symptoms were characterized by repetitive, uncontrolled shoplifting of sales goods in stores were recruited. Images with and without situational cues (e.g., a grocery store) were presented, and gazing patterns for the images were detected with the eye-tracker. Additionally, prefrontal cortical (PFC) responses were measured using functional near-infrared spectroscopy. PFC activities were further examined while participants were watching video clips in virtual reality with and without situational cues.

Results: Among kleptomania patients, the gazing pattern for an image with situational cues was distinct from gazing patterns for other images; such differences were not observed in healthy individuals. Consistent with gazing patterns, PFC local network responses by hemoglobin changes to images and videos with situational cues were substantially different from other images and videos in kleptomania patients, whereas PFC responses were consistent across all image and video presentations in healthy individuals.

Conclusions: These results suggest that kleptomania patients may perceive situational cues associated with their problematic behaviors differently from healthy individuals.

Keywords: Behavioral addiction, impulse control disorder, prefrontal cortex, eye tracking, fNIRS

Significance Statement

Impulse control disorders such as kleptomania have been suggested to meet the criteria of addiction and are often informally considered to be behavioral addictions. However, there is no consensus regarding the criteria for behavioral addictions. Herein, we show that patients with kleptomania exhibit altered processing of situational cues associated with its symptoms, thereby suggesting that some impulse control disorders may involve maladaptive learning regarding environments where the individuals can engage in the problematic behavior.

INTRODUCTION

Diagnostic manuals of psychiatric disorders such as the DSM-5 (American Psychiatric Association 2013) and International Classification of Diseases, 11th Revision (World Health Organization 2018) define substance use disorder (drug addiction) as "a chronic, relapsing disorder characterized by compulsive drug seeking and use despite adverse consequences" (National Institute on Drug Abuse 2020). Compulsive seeking of drugs in addiction could be explained by emotional problems, such as craving to pleasures by taking drugs and aversion to withdrawals by lack of drugs (Koob, 1996). However, a greater emphasis has been placed on the mechanisms of drug addiction such that drug addiction is envisioned by a maladaptive incentive learning process (Di Chiara and Bassareo, 2007; Berridge and Robinson, 2016; Everitt and Robbins, 2016).

In addition to drugs, people can be addicted to specific patterns of behavior, that is, behavioral addiction (Grant et al., 2010). The concept of behavioral addiction was initially proposed in the

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1960s with respect to compulsive, pathological gambling (Abrams et al., 1964), which is now formally categorized as an addictive disorder in diagnostic manuals. Furthermore, addiction to technology, such as the internet and gaming, has recently been recognized and included in the International Classification of Diseases, 11th Revision (World Health Organization, 2018). Although behavioral and drug addiction are suggested to share several core features (Griffiths, 2005), the concept of behavioral addiction is still debatable, and its definition has not yet been established to date, primarily due to insufficient investigations (Petry et al., 2018).

There is insufficient evidence to establish a clear definition of behavioral addiction; some psychiatric conditions currently categorized as "disruptive, impulse control and conduct disorders (referring as impulse control disorder hereafter)" in the diagnostic manuals have also been suggested to meet the criteria of addiction. Therefore, the term "behavioral addiction" is often used to describe a variety of symptoms (Grant et al., 2010). Kleptomania (KM) is one such psychiatric disorder categorized as an impulse control disorder and is suggested to meet the criteria for addiction. A problematic behavior, such as shoplifting, could be associated with not only KM but also other psychiatric disorders, such as borderline personality disorder (BPD). However, in BPD, such antisocial behavior could be driven primarily by negative emotions, such as self-destruction (injury) and depressive moods, whereas in KM, uncontrolled behavior could be driven primarily by positive emotions, such as cravings and elation. Thus, although problematic behavior could be similar between KM and BPD, the processes behind these disorders are clearly different (or even opposite). In particular, the experiences of craving and elation related to engaging in problematic behavior among patients with KM are consistent with those of addiction. We have previously shown that some affective and physiological features observed in KM patients overlap with those reported in individuals with drug addiction (Asaoka et al., 2020a, 2020b, 2020c, 2021). However, insufficient studies still make it difficult to comprehensively understand KM as a behavioral addiction, and further investigation is required.

In this preliminary and explorative study with a small sample size, we investigated how situational cues associated with their problematic behaviors were processed in KM patients to further evaluate KM as a behavioral addiction. In particular, behavioral and neural responses to image and video presentations with situational cues associated with KM symptoms were examined with eye-tracking analysis for gazing patterns and functional near-infrared spectroscopy (fNIRS) for PFC hemoglobin changes.

METHODS

Participants

This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Japanese Ministry of Health, Labor and Welfare. The experimental procedure was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine.

During this study, a total of 22 patients were diagnosed with KM and hospitalized in Kyowa Hospital (Obu, Aichi) in Japan. These patients were diagnosed with KM as an impulse control disorder (for Item 312.32 [F63.2] in DSM-5) due to repetitive, uncontrolled shoplifting of sales of goods and foods in stores; diagnosis was by a psychiatrist who has been working in psychiatric hospitals for over 20 years and who is an expert in addiction treatments. The patients were screened to identify for those who exhibited a clear and strong craving to engage in their problematic behaviors and who had no comorbid psychiatric disorders or minor conditions, if any. With this screening, 11 patients with KM agreed to participate in this study (4 males, 7 females; age = 36.7 ± 4.86 years old), of which 7 patients had no comorbidity and 4 had comorbidities with attention deficit/hyperactivity disorder (1 patient), gender dysphoria (1 patient), and eating disorders (2 patients). None of the participants were diagnosed with BPD. Healthy control individuals without smoking and psychiatric histories (CT; n = 27; 11 males, 16 females; age = 37.9 ± 2.02 [mean ± SEM] years old) were also recruited. Upon enrolling in the study, written informed consent was obtained from all participants in advance of the experiments.

A short form of the Japanese version of the Wechsler Adult Intelligence Scale-III, consisting of the information test in the Verbal Comprehension Index and the picture completion test in the Perceptual Organization Index, was administered to estimate the full-scale intelligence quotient (eFIQ) of participants (Kobayashi et al., 1993).

Image Presentation with Eye-Tracking and fNIRS

For image presentations, the following 6 static images (Figure 1a) were presented in pseudorandom order through the LCD monitor: a grocery store with (MKT+) and without (MKT) a person as situational cues, images of outside scenery with (OUT+) and without (OUT) a person, and sales products, particularly foods and stationaries. Each image was presented for 15 seconds along with a 5-second interval between images, during which a fixation point was presented in the center of the motor (Figure 1b); participants were asked to fix their gazes on the point. Each image was presented for 15 seconds, which was a sufficient length of time for measuring hemoglobin responses to stimuli using NIRS with a relatively low sampling frequency (0.5 Hz), but still short enough not to cause significant habituations in gazing patterns and hemoglobin responses. The interval between images was 5 seconds, which enabled hemoglobin responses to stabilize between images.

While images were presented, gazing patterns specifically, the number of fixations, the average duration of fixations, the average dispersion of fixations, the number of eye blinks, and changes expressed as coefficient of variation (CV) of pupil diameters over time during gazing were recorded using a wearable eye-tracker (Pupil Core, Pupil Labs GmbH, Berlin, Germany). The area of interest (AOI) was also set for later offline eye-tracking analysis around the person within the MKT+H and OUT+H images (Figure 1c).

In addition to eyetracking, prefrontal cortical (PFC) responses were measured with fNIRS. The NIRO-200 NIRS Image Processing and Measuring System (Hamamatsu Photonics K.K., Hamamatsu, Japan) was used for measurements. The system consisted of 2 emitters (E1, E2; delivering laser pulses at wavelengths of 775, 810, and 850 nm) and 8 detectors (CH1–CH8) with a distance of 3.0 cm between an emitter and a detector, thus enabling the measurement of oxygenated (oxy-Hb) and deoxygenated (deoxy-Hb) hemoglobin changes at 10 locations in the PFC area (R1–R10; Figure 3a), spanning the left and right rostral dorsal PFC (corresponding to Brodmann area 10/9/8), rostral dorsolateral superior PFC (corresponding to Brodmann area 10/9), caudal dorsomedial PFC (corresponding to Brodmann area 6/8), and caudal dorsolateral PFC (corresponding to Brodmann area 45/46/9) of MarsAtlas (Auzias et al., 2016). The sampling rate was 0.5 Hz, and the area under the curve as summations of oxy-Hb and deoxy-Hb changes

Figure 1. A design of image presentation. (a) Six images presented to participants, which are photos of the market with (MKT+) and without (MKT) a person, outside sceneries with (OUT+) and without (OUT) a person, and commodities, such as stationaries (STNY) and foods (FOD). (b) A schematic diagram of the image presentation procedure. (c) Images of MKT+ and OUT+ illustrating the area of interest (AOI) as yellow boxes.

over time were calculated at each recording site; subsequent data analysis was conducted with AUCs.

Video Presentation with fNIRS

PFC responses were also measured with fNIRS while participants were watching short video clips in virtual reality (VR). Store and outside sceneries were recorded using a 3D camera (Vuze Plus 3D 360 VR Camera, Humaneyes Technologies), and the recorded video clips, with the length of each clip being approximately 30 seconds, were presented to participants through a VR headset (Vive Pro, HTC). A longer duration than that of image presentation was selected for video presentation, as responses to watching videos were likely to be less habituated; however, the duration was still sufficiently short to avoid VR motion sickness. The video clips presented were the scenes of the store with (vMKT+) and without (vMKT) shoppers and the scenes of outside with (vOUT+) and without (vOUT) people walking around.

Data Analysis

Investigators who were not blinded to the experimental conditions conducted data collection and statistical analyses. Statistical analysis was conducted using JASP (JASP Team, 2022, JASP Version 0.16.3 [Computer Software]) and OrignPro (OriginLab Corporation). We utilized Bayesian over frequentist methods for statistical analysis, as the sample size in the current study was small, and thus, Bayesian methods were superior to frequentist methods as the former approach would not lose power and would retain precision in analysis (van de Schoot et al., 2014).

Although the eFIQ was lower in BA patients than in CT subjects (KM = 79.3 ± 4.88, CT = 100.8 ± 2.77; BF_{10} = 88.3, error% = 7.04e^{-7}), this factor was not considered in statistical analyses, as it is unlikely that the eFIQ exerted significant effects on the measurements evaluated in this study, such as gazing patterns and PFC responses to image and video presentations.

Data Availability

Datasets generated and analyzed as well as the materials (images and video clips) used in the current study are available from the corresponding author upon reasonable request.

RESULTS

Gazing Pattern on Image

To determine whether KM patients exhibited different behavioral responses to a situational cue associated with their symptoms compared with CT subjects, eye-tracking analysis was conducted to examine their gazing patterns on image presentations.

Bayesian independent sample *t* test for group comparisons revealed no difference between KM patients and CT participants in the number, duration, and dispersion of fixations, the number of eye blinks, and the CV of pupil size for each image (Table 1). However, there was weak, anecdotal evidence supporting the alternate hypothesis instead of the null hypothesis with respect to the duration of fixations made on the AOI of the MKT+ image (BF_{10} = 2.41, error% = 0.007) as well as those made on the OUT image (duration, BF_{10} = 4.51, error% = 0.001; dispersion, BF_{10} = 1.93, error% = 0.018). In particular, the duration of fixations made on the AOI of the MKT+ image tended to be shorter, whereas the duration and dispersion of fixations made on the OUT image tended to be longer and smaller, respectively, in KM patients than in CT participants (Table 1).

Although only subtle, if any, differences were observed between KM patients and CT participants with any of single measurements alone, it is possible that the combination of these measurements—that is, the pattern of gazing—could be different between groups. Thus, each data point of fixation duration, dispersion, and number, CV of pupil size, and the number of eye blinks were normalized, and principal component analysis

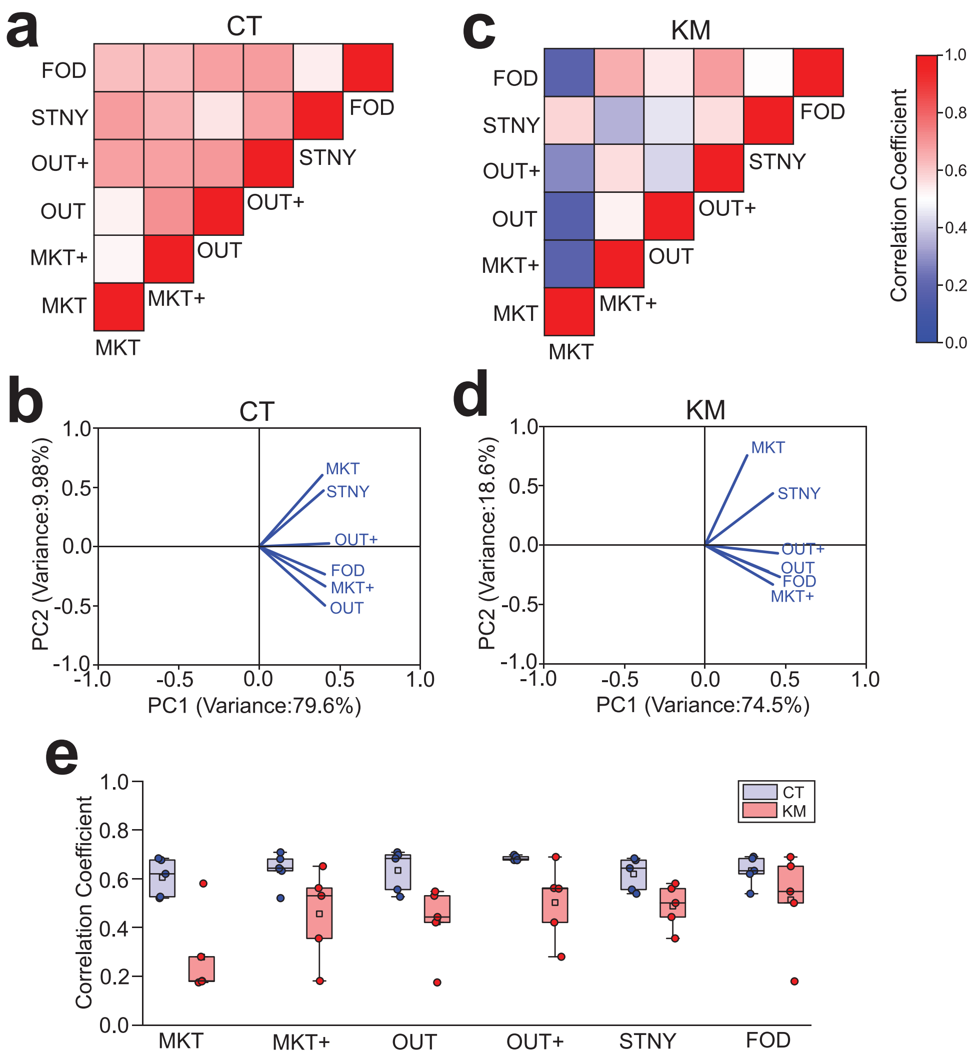

Figure 2. Correlations of gazing patterns to image presentations. A correlation matrix with color-coded correlation coefficients (a) and component loading plot (b) of gazing patterns between images in control (CT) participants. (c, d) A correlation matrix and component loading plot similar to (a) and (b) but showing those of kleptomania (KM) patients. (e) A box plot for correlation coefficients between one of the images and the rest of the others.

(PCA) was conducted to examine correlations of gazing patterns between images. This analysis unveiled that correlations of gazing patterns between MKT and the remaining images were substantially lower than those between other images among KM patients (Figure 2c–d), whereas this difference was not observed among CT participants (Figure 2a–b). Therefore, the correlations between MKT and other images in KM patients were weaker than the correlations observed among CT participants ($BF_{10}=8.27$, error% = 0.003; Figure 2e).

These results suggest that gazing patterns consisting of fixation duration, dispersion, and number, CV of pupil size, and the number of eye blinks made on a situational cue are different between KM patients and CT participants.

PFC Response to Image Presentation

To examine whether distinct gazing patterns on the image of a situational cue in KM patients were associated with neural processing, we further examined PFC responses to image presentations with fNIRS.

The Bayesian 1-sample *t* test supported the alternate hypothesis (increase or decrease from the baseline) over the null hypothesis at several recording sites in CT participants and KM patients (Figure 3b–c). These oxy-Hb and deoxy-Hb changes were relatively consistent across different images in both CT participants and KM patients. However, overall, more robust oxy-Hb and deoxy-Hb changes were observed in CT participants than in KM patients. Moreover, oxy- and deoxy-Hb changes were rather incongruent between KM patients and CT participants such that in CT participants, changes tended to be observed in the caudolateral and rostromedial regions (R3, R5, R7 in Figure 3a), whereas in KM patients, these tended to be in the rostrolateral and caudomedial regions (R2, R4, R6, R9 in Figure 3a) of the PFC. However, the Bayesian independent sample *t* test for group comparisons revealed no difference between CT participants and KM patients in recording sites, except oxy-Hb changes in R7, the right caudal dorsomedial PFC, where the difference was supported for all but MKT images (Figure 3d–e).

In addition, processing of images in the PFC local network consisting of oxy-Hb and deoxy-Hb changes at all 10 recording sites within the PFC was examined with PCA for correlations of PFC responses between images. This analysis unveiled that correlations of PFC local network responses were strong across all images in CT participants (Figure 4a–b), whereas in KM patients,

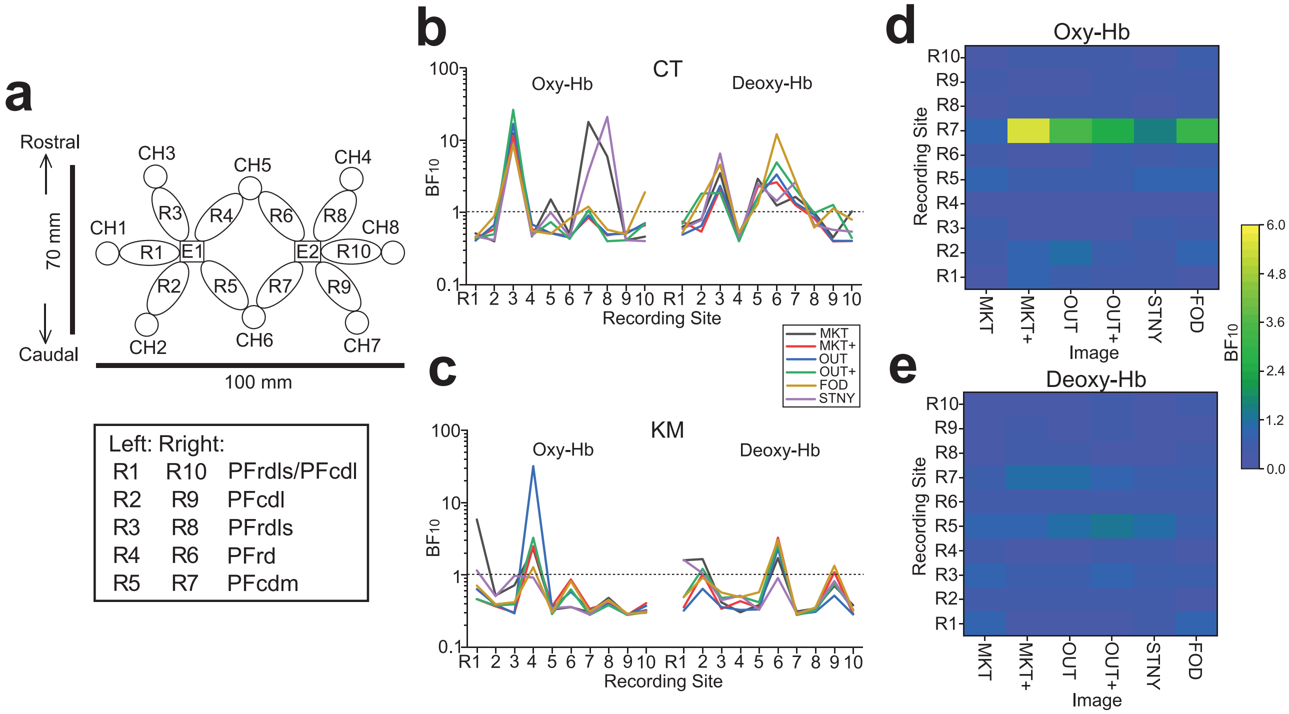

Figure 3. Prefrontal cortical (PFC) responses to image presentations. (a) A schematic diagram illustrating recording sites (R1-R10), with 2 emitter (E1, E2) and 8 detector (CH1-CH8) arrangements, in the PFC area. (b, c) Graphs showing Bayesian factors (BF_{10}) with Bayesian 1 sample t test for oxygenated (oxy-Hb) and deoxygenated (deoxy-Hb) hemoglobin changes at each recording site in control (CT) participants and kleptomania (KM) patients. Dashed lines indicate BF_{10} = 1.0, above or below which the alternate or null hypothesis is more supported, respectively. (d, e) Heatmaps showing color-coded Bayesian factors (BF_{10}) for comparisons of oxy-Hb and deoxy-Hb changes between KM patients and CT participants.

correlations were strong between images except those between MKT and the rest of the other images, where they were substantially lower (Figure 4c–d), and thus, correlations between MKT and other images in KM patients were lower than those of CT participants (BF_{10} = 31.2, error% = 1.33e^{-4}; Figure 4e).

These results suggest that, consistent with gazing patterns, processing of situational cue images may be distinct from processing of other images in the PFC local network of KM patients.

PFC Response to Video Presentation

We further examined whether a similar distinct pattern of PFC response associated with situational cue processing in KM patients was also observed with video presentations.

Consistent with image presentations, the number of recording sites within the PFC where oxy- and deoxy-Hb were increased or decreased from baseline in response to video presentations was overall lower in KM patients than in CT participants (Figure 5a–b). However, the Bayesian independent sample t test for group comparisons revealed no difference in oxy-Hb and deoxy-Hb changes at each video between CT participants and KM patients (Figure 5c–d).

In addition, correlations in PCA were strong across all videos in CT participants (correlation coefficient [COR] = 0.782–0.876; Figure 5e–f). In KM patients, correlations were overall weaker than those of CT participants (COR = 0.393–0.828; Figure 5g–h). Moreover, correlations between vMKT and any of the other videos (COR = 0.393–0.618) were even lower than those between the other videos (COR = 0.645–0.828; Figure 5g–h).

These results suggest that consistent with image presentations, KM patients, but not CT participants, exhibit a distinct pattern of the PFC local network response to watching the video of a situational cue.

DISCUSSION

In this preliminary and explorative study with a small sample size, we found that KM patients exhibit distinct behavioral and neural responses to images and videos with situational cues associated with their symptoms, that is, compulsive and impulsive stealing. In particular, when the image of a situational cue included a social signal, fixations on such a social signal might be shorter in KM patients than in CT participants. Moreover, the pattern of gazing (which included measurements of fixations, pupil size, and eye blinks) and the PFC network responses by hemoglobin changes to situational cues in KM patients were different from those for other images; such differences between image types were not observed in CT participants.

Our current study demonstrated that gazing patterns and neural responses to such a cue were at least distinct from responses to other cues in patients with KM. Although patients with KM who participated in this study exhibited craving related to their problematic behavior, it remains unclear whether the findings may be related to cue-induced craving, such as those observed in substance use disorder (Di Chiara and Bassareo, 2007; Berridge and Robinson, 2016; Everitt and Robbins, 2016) and behavioral addiction, such as gambling disorder (Limbrick-Oldfield et al., 2017), gaming disorder (Ko et al., 2009), problematic internet use (Niu et al., 2016), and pathological buying (Trotzke et al., 2014). Craving can be assessed with subjective, self-report measures (Goldstein et al., 2010) and objective, physiological signal measures, such as heart rate and skin conductance (Laberg and Ellertsen, 1987; Ooteman et al., 2006; Witteman et al., 2015), although such physiological responses in cue-induced craving are often controversial (Ooteman et al., 2006; Reid et al., 2006). Whether the current findings are associated with craving will be addressed in our future

Table 1. Descriptive Statistics and Bayesian *t* Test for Eye-Tracking Data

Image	Measure	Participant				BF_{10}	Error%
		KM		CT			
		Mean	SEM	Mean	SEM		
MKT+	Fix Dur	156.0	3.27	163.8	3.305	0.506	0.0004
	Fix Disp	0.760	0.041	0.785	0.022	0.912	0.001
	Fix N	24.82	7.447	26.96	4.933	0.639	0.0007
	CV Pupil	0.272	0.09	0.253	0.049	0.644	0.0007
	Blink N	1.455	0.578	2.444	0.451	0.64	0.0007
MKT+ AOI	Fix Dur	107.8	93.4	167.7	23.0	2.409	0.007
	Fix Disp	0.735	0.031	0.769	0.102	0.505	0.0009
	Fix N	3.636	1.889	10.85	2.684	0.930	0.004
OUT+	Fix Dur	181.5	10.725	154.7	4.965	0.662	0.0007
	Fix Disp	0.701	0.035	0.777	0.022	0.871	0.001
	Fix N	18.46	7.685	28.78	4.827	1.400	0.0009
	CV Pupil	0.282	0.088	0.188	0.032	0.493	0.0003
	Blink N	1.727	0.764	2.481	0.507	0.652	0.0008
OUT+ AOI	Fix Dur	152.7	31.98	164.6	14.65	0.509	0.0004
	Fix Disp	0.742	0.057	0.741	0.028	0.783	0.001
	Fix N	3.273	1.854	6.333	1.382	0.492	0.0003
MKT	Fix Dur	172.5	5.79	161.2	5.147	0.538	0.0005
	Fix Disp	0.769	0.024	0.764	0.028	0.811	0.001
	Fix N	26.55	8.391	29.33	5.32	0.575	0.0006
	CV Pupil	0.507	0.191	0.381	0.107	0.494	0.0003
	Blink N	1.636	0.527	2.407	0.484	0.642	0.0007
OUT	Fix Dur	230.7	22.41	164.8	4.153	4.514	0.001
	Fix Disp	0.611	0.046	0.736	0.025	1.927	0.018
	Fix N	23.27	7.295	29.70	4.846	0.645	0.0007
	CV Pupil	0.346	0.15	0.515	0.122	0.497	0.0003
	Blink N	3.000	0.953	2.593	0.451	0.553	0.0005
STNY	Fix Dur	155.1	6.327	158.6	3.118	0.494	0.004
	Fix Disp	0.752	0.052	0.814	0.017	0.945	0.008
	Fix N	22.36	6.815	28.85	4.509	0.582	0.0004
	CV Pupil	0.368	0.132	0.271	0.067	0.573	0.0003
	Blink N	1.091	0.343	1.704	0.452	0.695	0.0005
FOD	Fix Dur	156.7	7.683	153.8	4.276	1.067	0.0003
	Fix Disp	0.702	0.074	0.783	0.022	1.192	0.001
	Fix N	23.09	7.88	24.04	4.955	0.528	0.0006
	CV Pupil	0.291	0.114	0.345	0.089	0.492	0.0005
	Blink N	1.545	0.679	1.963	0.458	0.566	0.019

Abbreviations: Blink N, number of blinks; CT, control; CV pupil, coefficient of variation of pupil diameter changes; Fix Disp, dispersion of fixations; Fix Dur, duration (ms) of fixations; Fix N, number of fixations; KM, kleptomania; SEM, standard error of mean.

study. Another major limitation of the current study is the small sample size, which makes the findings rather preliminary. Thus, current findings need to be validated with a larger sample size.

Several primate studies have suggested an association between spontaneous eye blink rate and striatal dopamine D2 receptor availability, with higher availability increasing eye blink rate (Groman et al., 2014). This is highly controversial, however, as another study has also shown that the association of eye blink rate with D1 receptor availability is even stronger than that with D2 receptor availability (Jutkiewicz and Bergman, 2004). Most human studies are actually unable to replicate such DA-eye blink association (Dang et al., 2017; Sescousse et al., 2018; Trutti et al., 2019). Nonetheless, in some specific conditions, such as under the effects of psychostimulants, the association between eye blink rate and striatal D2 receptor availability has been demonstrated in healthy humans (Demiral et al., 2022). Moreover, an association

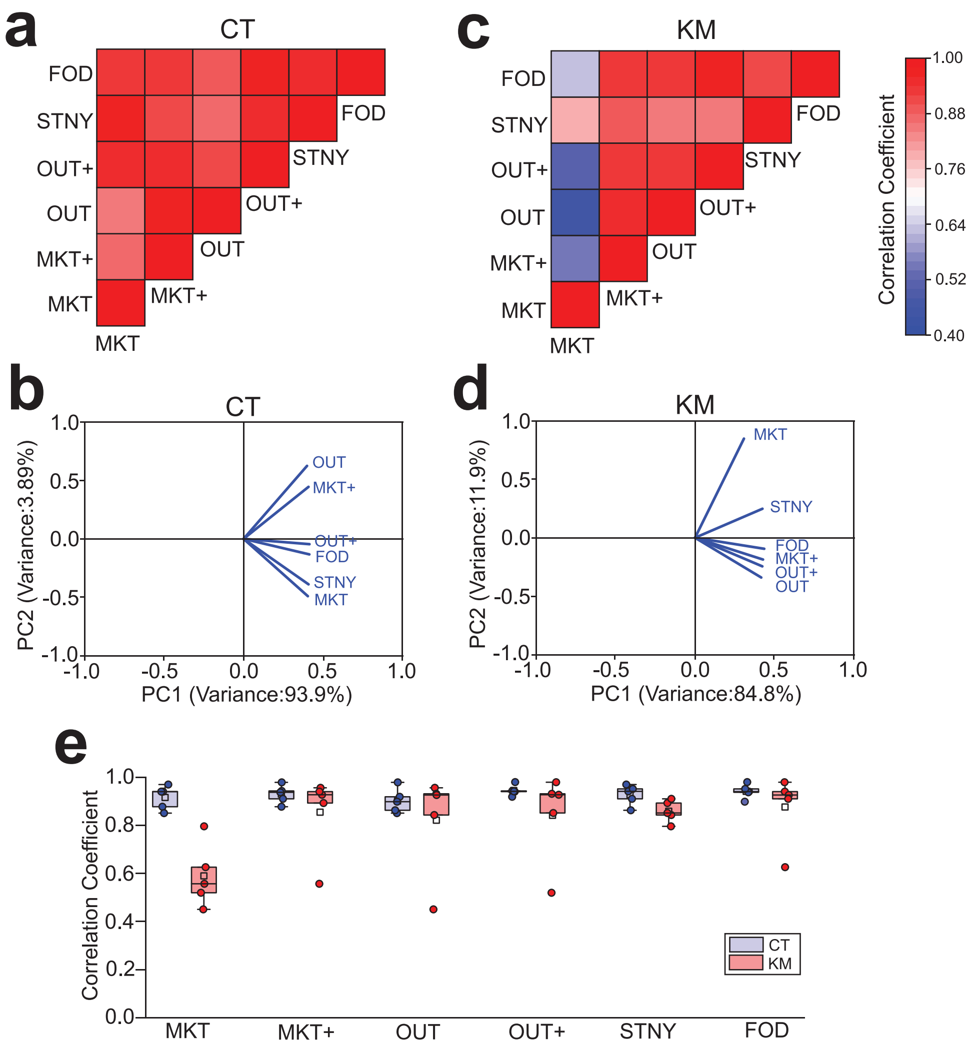

Figure 4. Correlations of prefrontal cortical (PFC) responses to image presentations. A correlation matrix with color-coded correlation coefficients (a) and component loading plot (b) of PFC responses between images in control (CT) participants. (c, d) A correlation matrix and component loading plot similar to (a) and (b) but showing those of kleptomania (KM) patients. (e) A box plot for correlation coefficients between one of the images and the rest of the others.

of eye blink rate has been reported with symptom severity in patients with gambling disorder and the amount of addictive substance consumption in healthy individuals (Mathar et al., 2018). In addition to eye blink rate, pupil diameter has also been suggested to reflect noradrenaline function (Preuschoff et al., 2011; Larsen and Waters, 2018); however, this association is not yet clear, as a recent study has demonstrated that dorsal raphe serotonin (5-HT) neuron activation also increases pupil size in rodents (Cazettes et al., 2021), suggesting that neither noradrenaline nor 5-HT alone but multiple facets of monoamine transmission may be involved in the regulation of pupil sizes. In the current study, the number of eye blinks and changes in pupil sizes were measured in an attempt to indirectly assess alterations in monoamine transmission. There was no difference among KM patients or among CT participants. 5-HT is also involved in the control of gazing to social cues in primates (Weinberg-Wolf et al., 2022). We observed moderate evidence of differences in fixations on the AOI (the person in the image) of the MKT+ image. Thus, KM patients tended to exhibit context-dependent gazing patterns to the social cues in the images that were different from those of CT participants, suggesting that if there is any, altered 5-HT transmission may be present in KM patients.

We also examined PFC oxy-Hb and deoxy-Hb changes as neural responses to image and video presentations. Although oxy-Hb and deoxy-Hb changes in responses to image and video presentations were observed in somewhat different regions within the PFC between KM patients and CT participants, the patterns of changes were quite consistent across different images within each group, except for the PFC responses to the MKT image and video in KM patients. MKT+ and MKT images were also distinct within KM patients, suggesting that whether a person is present in a situational cue appears to be an important factor for recognition of the cue in KM patients. The reason underlying incongruent PFC response patterns between KM patients and CT participants is unclear; however, since gazing patterns and PFC responses were also inconsistent with each other, the observed PFC responses may not represent gazing patterns but other aspects of cognitive processes associated with image recognition, such as attention given to the images or affective responses and controls over such affects. Functional neuroimaging studies have also demonstrated that increased responses in the anterior cingulate cortex, along with several other regions, including the medial and dorsolateral PFC, are associated with cue-induced craving of patients with behavioral addiction, such as gambling (Limbrick-Oldfield et al.,

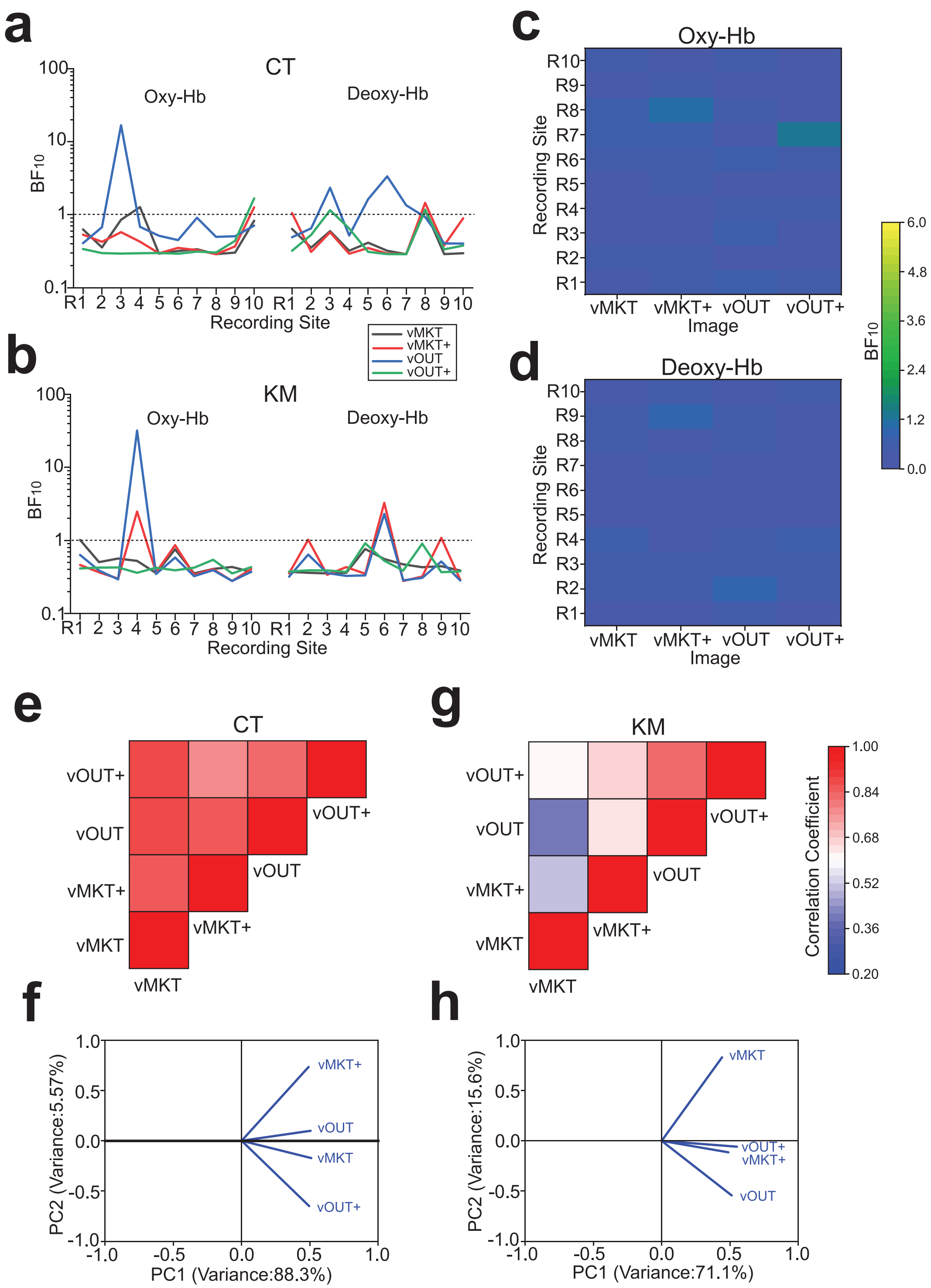

Figure 5. Prefrontal cortical (PFC) responses to watching videos. (a, b) Graphs showing Bayesian factors (BF_{10}) with Bayesian Wilcoxon singed-rank test for oxygenated (oxy-Hb) and deoxygenated (deoxy-Hb) hemoglobin changes at each recording site in control (CT) participants and kleptomania (KM) patients. Dashed lines indicate $BF_{10} = 1.0$, above or below which the alternate or null hypothesis is more supported, respectively. (c, d) Heatmaps showing color-coded Bayesian factors (BF_{10}) for comparisons of oxy-Hb and deoxy-Hb changes between KM patients and CT participants. (e, f) A correlation matrix with color-coded correlation coefficients (e) and component loading plot (f) of PFC responses between videos in CT participants. (g, h) A correlation matrix and component loading plot similar to (e) and (f) but showing those of KM patients.

2017) and gaming (Ko et al., 2009) disorders. Our current study found differences between KM patients and CT participants in the right caudal dorsomedial PFC to image presentations, except for the image of a situational cue in which the difference was not observed between groups; the finding in this study is rather inconsistent with those previous studies, and further investigation is warranted.

In conclusion, our study, despite the preliminary nature due to the small sample size, provides evidence that impulse control disorders such as KM may involve altered processing of situational cues. Whether this finding is also applicable to other impulse control disorders, such as paraphilia, remains unclear and needs further investigation.

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Author Contributions

Y.A., M.J.W., and Y.G. conceived of the research. Y.A., M.J.W., T.M., E.I., and Y.G. performed experiments. Y.A. and Y.G. analyzed the data. Y.A. and Y.G. wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

Interest Statement

The authors declare no financial and non-financial conflicts of interest.

References

Abrams JD, Jay BS, Mellerio J, Weale RA (1964) The compulsive gambler. *Lancet* **2**:133–134.

American Psychiatric Association (2013) *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: American Psychiatric Association.

Asaoka Y, Won M, Morita T, Ishikawa E, Goto Y (2020a) Higher risk taking and impaired probability judgment in behavioral addiction. *Int J Neuropsychopharmacol* **23**:662–672.

Asaoka Y, Won M, Morita T, Ishikawa E, Goto Y (2020b) Heightened negative affects associated with neurotic personality in behavioral addiction. *Front Psychiatry* **11**:561713.

Asaoka Y, Won M, Morita T, Ishikawa E, Lee YA, Goto Y (2020c) Monoamine and genome-wide DNA methylation investigation in behavioral addiction. *Sci Rep* **10**:11760.

Asaoka Y, Won M, Morita T, Ishikawa E, Goto Y (2021) Comparable level of aggression between patients with behavioural addiction and healthy subjects. *Transl Psychiatry* **11**:375.

Auzias G, Coulon O, Brovelli A (2016) MarsAtlas: a cortical parcellation atlas for functional mapping. *Hum Brain Mapp* **37**:1573–1592.

Berridge KC, Robinson TE (2016) Liking, wanting, and the incentive-sensitization theory of addiction. *Am Psychol* **71**:670–679.

Cazettes F, Reato D, Morais JP, Renart A, Mainen ZF (2021) Phasic activation of dorsal raphe serotonergic neurons increases pupil size. *Curr Biol* **31**:192–197.e4 e194.

Dang LC, Samanez-Larkin GR, Castrellon JJ, Perkins SF, Cowan RL, Newhouse PA, Zald DH (2017) Spontaneous eye blink rate (EBR) is uncorrelated with dopamine D2 receptor availability and unmodulated by dopamine agonism in healthy adults. *eNeuro* **4**:ENEURO.0211–ENEU17.2017.

Demiral SB, Manza P, Biesecker E, Wiers C, Shokri-Kojori E, McPherson K, Dennis E, Johnson A, Tomasi D, Wang GJ, Volkow ND (2022) Striatal D1 and D2 receptor availability are selectively associated with eye-blink rates after methylphenidate treatment. *Commun Biol* **5**:1015.

Di Chiara G, Bassareo V (2007) Reward system and addiction: what dopamine does and doesn't do. *Curr Opin Pharmacol* **7**:69–76.

Everitt BJ, Robbins TW (2016) Drug addiction: updating actions to habits to compulsions ten years on. *Annu Rev Psychol* **67**:23–50.

Goldstein RZ, Woicik PA, Moeller SJ, Telang F, Jayne M, Wong C, Wang GJ, Fowler JS, Volkow ND (2010) Liking and wanting of drug and non-drug rewards in active cocaine users: the STRAP-R questionnaire. *J Psychopharmacol* **24**:257–266.

Grant JE, Potenza MN, Weinstein A, Gorelick DA (2010) Introduction to behavioral addictions. *Am J Drug Alcohol Abuse* **36**:233–241.

Griffiths M (2005) A "components" model of addiction within a biopsychosocial framework. *J Subst Abuse* **10**:191–197.

Groman SM, James AS, Seu E, Tran S, Clark TA, Harpster SN, Crawford M, Burtner JL, Feiler K, Roth RH, Elsworth JD, London ED, Jentsch JD (2014) In the blink of an eye: relating positive-feedback sensitivity to striatal dopamine D2-like receptors through blink rate. *J Neurosci* **34**:14443–14454.

Jutkiewicz EM, Bergman J (2004) Effects of dopamine D1 ligands on eye blinking in monkeys: efficacy, antagonism, and D1/D2 interactions. *J Pharmacol Exp Ther* **311**:1008–1015.

Ko CH, Liu GC, Hsiao S, Yen JY, Yang MJ, Lin WC, Yen CF, Chen CS (2009) Brain activities associated with gaming urge of online gaming addiction. *J Psychiatr Res* **43**:739–747.

Kobayashi S, Fujita K, Maekawa H, Dairoku H (1993) *Simple administration method of Japanese version of WAIS-III*. Tokyo, Japan: Nihon Bunka Kagakusha Co., Ltd.

Koob GF (1996) Drug addiction: the yin and yang of hedonic homeostasis. *Neuron* **16**:893–896.

Laberg JC, Ellertsen B (1987) Psychophysiological indicators of craving in alcoholics: effects of cue exposure. *Br J Addict* **82**:1341–1348.

Larsen RS, Waters J (2018) Neuromodulatory correlates of pupil dilation. *Front Neural Circuits* **12**:21.

Limbrick-Oldfield EH, Mick I, Cocks RE, McGonigle J, Sharman SP, Goldstone AP, Stokes PR, Waldman A, Erritzoe D, Bowden-Jones H, Nutt D, Lingford-Hughes A, Clark L (2017) Neural substrates of cue reactivity and craving in gambling disorder. *Transl Psychiatry* **7**:e992.

Mathar D, Wiehler A, Chakroun K, Goltz D, Peters J (2018) A potential link between gambling addiction severity and central dopamine levels: evidence from spontaneous eye blink rates. *Sci Rep* **8**:13371.

National Institute on Drug Abuse (2020) Drug misuse and addiction. https://nida.nih.gov/publications/drugs-brains-behavior-science-addiction/drug-misuse-addiction. Accessed September 29, 2022.

Niu GF, Sun XJ, Subrahmanyam K, Kong FC, Tian Y, Zhou ZK (2016) Cue-induced craving for internet among internet addicts. *Addict Behav* **62**:1–5.

Ooteman W, Koeter MW, Vserheul R, Schippers GM, van den Brink W (2006) Measuring craving: an attempt to connect subjective craving with cue reactivity. *Alcohol Clin Exp Res* **30**:57–69.

Petry NM, Zajac K, Ginley MK (2018) Behavioral addictions as mental disorders: to be or not to be? *Annu Rev Clin Psychol* **14**:399–423.

Preuschoff K, t Hart BM, Einhauser W (2011) Pupil dilation signals surprise: evidence for noradrenaline's role in decision making. *Front Neurosci* **5**:115.

Reid MS, Flammino F, Starosta A, Palamar J, Franck J (2006) Physiological and subjective responding to alcohol cue exposure in alcoholics and control subjects: evidence for appetitive responding. *J Neural Transm* **113**:1519–1535.

Sescousse G, Ligneul R, van Holst RJ, Janssen LK, de Boer F, Janssen M, Berry AS, Jagust WJ, Cools R (2018) Spontaneous eye blink rate and dopamine synthesis capacity: preliminary evidence for an absence of positive correlation. *Eur J Neurosci* **47**:1081–1086.

Trotzke P, Starcke K, Pedersen A, Brand M (2014) Cue-induced craving in pathological buying: empirical evidence and clinical implications. *Psychosomat Med* **76**:694–700.

Trutti AC, Sjoerds Z, Hommel B (2019) Attentional blink and putative noninvasive dopamine markers: two experiments to consolidate possible associations. *Cogn Affect Behav Neurosci* **19**:1444–1457.

van de Schoot R, Kaplan D, Denissen J, Asendorpf JB, Neyer FJ, van Aken MAG (2014) A gentle introduction to bayesian analysis: applications to developmental research. *Child Dev* **85**:842–860.

Weinberg-Wolf HB, Fagan N, Dal Monte O, Chang SWC (2022) Increasing central serotonin with 5-hydroxytryptophan disrupts the inhibition of social gaze in nonhuman primates. *J Neurosci* **42**:670–681.

Witteman J, Post H, Tarvainen M, de Bruijn A, Perna Ede S, Ramaekers JG, Wiers RW (2015) Cue reactivity and its relation to craving and relapse in alcohol dependence: a combined laboratory and field study. *Psychopharmacology* **232**:3685–3696.

World Health Organization (2018) International classification of diseases for mortality and morbidity statistics (11th Revision). https://icd.who.int/browse11/l-m/en.