Archival Report

Biological Psychiatry

Neural Response Patterns During Pavlovian-to-Instrumental Transfer Predict Alcohol Relapse and Young Adult Drinking

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ABSTRACT

BACKGROUND: Pavlovian-to-instrumental transfer (PIT) describes the influence of conditioned stimuli on instrumental behaviors and is discussed as a key process underlying substance abuse. Here, we tested whether neural responses during alcohol-related PIT predict future relapse in alcohol-dependent patients and future drinking behavior in adolescents.

METHODS: Recently detoxified alcohol-dependent patients (n = 52) and young adults without dependence (n = 136) underwent functional magnetic resonance imaging during an alcohol-related PIT paradigm, and their drinking behavior was assessed in a 12-month follow-up. To predict future drinking behavior from PIT activation patterns, we used a multivoxel classification scheme based on linear support vector machines.

RESULTS: When training and testing the classification scheme in patients, PIT activation patterns predicted future relapse with 71.2% accuracy. Feature selection revealed that classification was exclusively based on activation patterns in medial prefrontal cortex. To probe the generalizability of this functional magnetic resonance imaging–based prediction of future drinking behavior, we applied the support vector machine classifier that had been trained on patients to PIT functional magnetic resonance imaging data from adolescents. Strikingly, we found that those young social drinkers who were classified as abstainers showed a greater reduction in alcohol consumption at 12-month follow-up than those classified as relapsers ($\Delta = -24.4 \pm 6.0$ g vs. -5.7 ± 3.6 g; p = .019).

CONCLUSIONS: These results suggest that neural responses during PIT could constitute a generalized prognostic marker for future drinking behavior in established alcohol use disorder and in at-risk states.

Keywords: Alcohol dependence, Future drinking behavior, Multivoxel classification, Pavlovian-to-instrumental transfer, Relapse

https://doi.org/10.1016/j.biopsych.2019.06.028

Values of environmental cues can determine human behavior. As such, pavlovian-to-instrumental transfer (PIT) describes the observation that pavlovian conditioned stimuli can influence instrumental behavior (1). In addictive behaviors, drug-related cues are known to promote craving and drug intake and to facilitate drug dependence (2,3). Here, drug-related cues are thought to acquire incentive salience by pavlovian conditioning with the drug-induced reward and then shape instrumental behaviors characteristic of drug dependence. In line with this idea, current theories of alcohol dependence (AD) hypothesize PIT to be a core mechanism of relapse behavior following abstinence (4). Empirically, this hypothesis is supported by studies in rodents, in which reinstatement of alcohol drinking after abstinence was provoked by cues previously associated with alcohol availability (5,6).

Neurobiological studies in humans have shown that alcohol cues activate both subcortical areas such as the ventral striatum and cortical areas including the medial prefrontal cortex (mPFC) (7). Studies investigating PIT specifically point toward the ventral striatum, the amygdala, and the mPFC as essential structures involved in such adaptive behavior (8–11). Based on these findings, alcohol-related PIT has been suggested to reflect the dysfunctional regulation of prefrontal-striatal circuits in AD that interfere with goal-directed decision-making (12).

In the present study, we sought to investigate whether neural responses during PIT in humans can be used as a mechanistic biological marker to predict future drinking behavior. We used functional magnetic resonance imaging (fMRI) and multivoxel pattern analysis to predict future relapse in 52 detoxified alcohol-dependent patients (22 relapsers, 30 abstainers) from PIT-induced brain activation patterns. Multivoxel pattern analysis utilizes the full information contained in patterns of brain activity and has been shown to be more sensitive in detecting differences between clinical populations compared with conventional univariate analysis (13). We hypothesized that a

ISSN: 0006-3223

multivoxel pattern analysis–based classifier should successfully discriminate between future relapsers and future abstainers on the basis of PIT-induced activation patterns.

Importantly, in a next step we assessed whether PIT activation patterns could serve as an informative marker of future drinking behavior even in individuals not diagnosed with AD. To this end, we applied the classifier trained to predict relapse in patients to an independent sample of young social drinkers (n = 136). This sample included young men, a population known to be susceptible to problematic alcohol-related drinking behavior (14), who did not fulfill the criteria of AD. We reasoned that if PIT activation patterns constitute a useful and generic marker of future drinking behavior, a classifier trained on these patterns should make reasonable predictions for changes in drinking behavior even in an unrelated sample of healthy individuals. To quantify such changes, we focused on differences in average quantity recorded and frequency of drinking at baseline and 1-year follow-up.

METHODS AND MATERIALS

Participants

Data were collected at Charité–Universitätsmedizin Berlin and Universitätsklinikum Dresden/Technische Universität Dresden as part of the LeAD (Learning and Alcohol Dependence) study (NCT01679145, NCT01744834). Here, we investigated 2 independent cohorts of the LeAD study: 1) a sample of recently detoxified alcohol-dependent patients (Table 1) and 2) a sample of young male social drinkers without AD diagnosis for generalization (Table 2). Patients fulfilled diagnostic criteria for AD according to ICD-10 and DSM-IV-TR but displayed no relevant alcohol withdrawal symptoms at the time of the study (Clinical Institute Withdrawal Assessment for Alcohol scale score ≤3) (15). The young social drinkers included healthy men 18 years of age who reported regular alcohol intake (at least 2 drinking occasions within the last 3 months). After considering the exclusion criteria (see Supplement), the final sample consisted of 52 alcohol-dependent patients with 1-year follow-up relapse information and valid data (10 women; 21–64 years of age, mean ± SD 44.61 ± 10.40 years of age, mean duration of AD of 11 years) (see Table 1) who were abstinent from alcohol by a mean of 20.4 ± 11.0 days and young male social drinkers (n = 136; mean 18.38 ± 0.20 years of age, who reported their last alcoholic drink past a mean of 9.2 ± 16.3 days) (see Table 1). All participants gave written informed consent. Ethical approval for the study was obtained from both sites, and procedures complied with the Declaration of Helsinki.

Data Acquisition and Analyses

PIT Task. Participants performed an instrumental task (button presses to collect shells) while presented in the background with alcohol or water cues (for a detailed description, see the Supplement).

Functional MRI. fMRI was performed on a Siemens Trio 3T scanner (Siemens Healthineers, Erlangen, Germany) with an echo-planar imaging sequences (repetition time = 2410 ms; echo time = 25 ms; flip angle = 80°; field of view = 192 × 192 mm^2; voxel size = 3 × 3 × 2 mm^3) comprising 42 slices approximately −25° to the bicommissural plane (for preprocessing procedure and first-level analyses, see the Supplement). Statistical analysis at the single-subject level was based on general linear modeling. The model comprised onset regressors for the different cues (alcohol, water, and 5 monetary value levels) modeled as stick functions, each associated with parametric regressors for the trial-by-trial number of button presses (16,17). Trials without button presses for one of the cue conditions led to the exclusion of the subjects. To account for motor activity, an additional regressor containing all individual button presses was included. Regressors of no interest were the realignment parameters, with derivatives and one regressor for detecting bad slices with volume-to-volume motion larger than 1 mm (18). The effect of interest for the present investigation was the alcohol PIT effect, which was defined as the contrast between the parametric (number of button presses) modulators of alcohol and water cues (alcohol > water). Hence, this neural alcohol PIT effect captures the influence of alcohol-related stimulus values (or

Table 1. Sample Characteristics for the Cohort of Patients

	Relapsers (n = 30)	Abstainers (n = 22)	t, χ^2, U	p
Age, Years	44.72 ± 8.80	44.47 ± 12.05	0.09 (50)	.93
Female, %	20	18	0.04 (52)	.87
Education, Years	13.76 ± 2.69	14.81 ± 3.03	−1.28 (49)	.21
Social Status	1.74 ± 0.58	1.55 ± 0.67	1.02 (45)	.31
FTND (Sum)	3.73 ± 2.55	3.04 ± 2.77	0.91 (50)	.37
Years Since Initial AD Diagnosis (DSM-IV)	12.57 ± 10.58	8.89 ± 9.86	1.17 (46)	.25
Inpatient Detoxifications	5.22 ± 5.19	2.21 ± 2.567	2.28 (44)	.03
Severity of Disease (ADS Score)	16.34 ± 6.06	12.86 ± 6.55	1.94 (50)	.06
Amount Alcohol Intake/Occasion Last Year, g	232.80 ± 143.18	183.68 ± 112.88	1.27 (50)	.21
Frequency of Alcohol Intake Last Year	5 ± 0	5 ± 0	0.67 (50)	.51

Values are mean ± SD or %.

Social status was assessed from a self-rated score of social status affiliation to lower, middle, or upper class. Severity of nicotine dependence was computed as the sum score of the Fagerström Test for Nicotine Dependence (FTND) (34). To assess the severity of alcohol dependence, we used the Alcohol Dependence Scale (ADS) (35). Quantity and frequency of alcohol intake were assessed during the Munich-Composite International Diagnostic Interview with frequency of alcohol intake defined in categories of 0 (abstinent), 1 (less than a once a month), 2 (1–2 days a month), 3 (1–2 days a week), 4 (3–4 days a week), and 5 (almost daily alcohol intake) (36,37).

Table 2. Sample Characteristics for the Cohort of Young Social Drinkers

Characteristics	Mean ± SD (*n*) or %
Age, Years	18.38 ± 0.20 (136)
Female, %	0
Education, Years	11.62 ± 0.99 (135)
Social Status	2.19 ± 0.62 (133)
FTND (Sum)	0.21 ± 0.96 (136)
Severity of Disease (ADS score)	4.69 ± 4.15 (132)
Amount Alcohol Intake/Occasion Last Year, g	69.42 ± 41.98 (136)
Frequency of Alcohol Intake Last Year	2 ± 1 (136)

For details of the variables, see Table 1.

ADS, Alcohol Dependence Scale; FTND, Fagerström Test for Nicotine Dependence.

conditioned pavlovian stimulus values) on instrumental response rates. Such alcohol-related "transfer" responses have been suggested to engage subcortical areas such as the nucleus accumbens (NAc) (11) as well as cortical areas such as the anterior cingulate and the mPFC (19). The effect of interest for the present investigation was the alcohol PIT effect, which was defined as the contrast between the parametric (number of button presses) modulators of alcohol and water cues (alcohol > water). To compare the PIT effect with a more conventional "cue reactivity" contrast, we additionally computed the contrast between the nonparametric onset regressors of alcohol and water cues (alcohol > water).

Relapse Prediction Based on Neural PIT Responses

Our main goal was to test the hypothesis that neural PIT responses are predictive of future relapse in alcohol-dependent patients after detoxification. To this aim, we used linear support vector machine (SVM) (20) with a data-driven estimation of the cost parameter (21) to classify between future relapsers and future abstainers on the basis of whole-brain PIT contrast images. To guarantee independence between training and testing data within the classification scheme, an outer leave-one-out (LOO) cross-validation procedure was performed, such that in each fold, the SVM classifier was trained on all but one participant and then was tested on the left-out participant. Within this outer cross-validation loop, a nested inner LOO cross-validation loop was used to select the optimal number of voxels for classification (Figure 1). This feature (i.e., voxel) selection stage was based on a searchlight analysis (22) as follows. The general search space for the searchlight analysis was defined on the basis of a large coordinate-based meta-analysis summarizing brain areas in which alcohol-related stimuli elicit activation (7). The resulting search space (see Figure 2) consisted of 12 anatomical brain regions (superior frontal prefrontal gyrus; medial frontal gyrus; precuneus; parahippocampus; rostral, anterior, posterior, and subgenual cingulate gyri; caudate; globus pallidus; thalamus; NAc) that were reported by Schacht *et al.* (7) and that were derived from the JHU atlas (23). For each voxel within the search space, the activation pattern within a sphere around the voxel (radius 4 voxels) was extracted for all subjects within the training data set (N-1) of the current outer cross-validation fold. Next, one additional subject was left out and an SVM was trained on the remaining subjects (N-2) to predict relapse on the basis of the activation pattern given by the sphere surrounding the current voxel. This procedure was looped over all subjects in the training dataset and voxels within the search space and then averaged across subjects. As a result, we obtained—for each outer cross-validation loop—a single average searchlight accuracy map that could be used to rank the voxels within the search space. After obtaining a ranking of voxels, we then determined the optimal number of voxels and tested the performance of SVM classification (again using nested LOO cross-validation) while systematically increasing the number of voxels in steps of 100 voxels up to a maximum of 500 voxels. This procedure yielded an optimal number of voxels (350 ± 96 on average) as defined by the maximum achieved classification accuracy. In a final step, an SVM classifier was trained on the activation patterns of the entire training dataset (N-1), now using the computed optimal number of top-ranked voxels, and then used to predict relapse in the (outer) left-out subject (which, importantly, had not been involved at any point during the feature selection and training stage).

To compare the predictive capacity of alcohol PIT responses to monetary PIT responses and more conventional cue reactivity responses, we additionally performed classification on the basis of a simple cue reactivity contrast (alcohol > water) and the monetary PIT contrast, separately (see Supplement).

In addition to standard classification accuracy, we measured classification performance with balanced accuracy

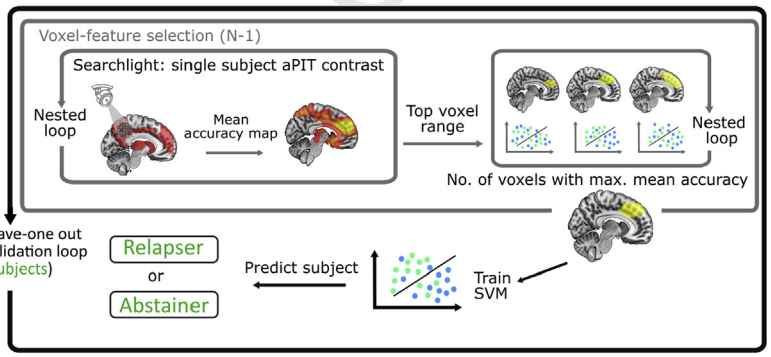

Figure 1. An illustration of the classification analysis. The protocol shows both the inner cross-validation loop for voxel-feature selection (gray frame) and the outer cross-validation loop (black), which consists of training a support vector machine (SVM) algorithm using the optimal number of voxels used to predict the initially left-out patient. aPIT, ●●●.

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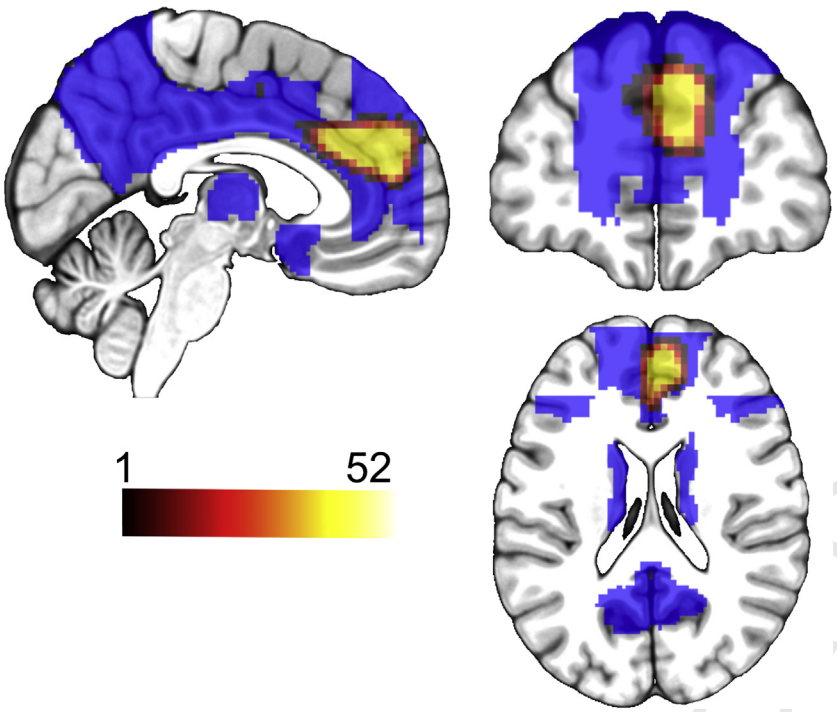

Figure 2. Searchlight-based feature selection. The blue area shows the overall search space based on a literature-informed region of interest for general cue reactivity responses (7). Voxels are colored according to how often they were selected for classification (up to a maximum of 52 corresponding to the number of cross-validation folds).

(24), which corrects for class imbalance and enables the computation of meaningful *p* values.

Predicting Future Drinking Behavior in Young Adults

To test whether PIT responses constitute mechanistically informative markers of future drinking behavior, we evaluated whether a classifier trained to predict relapse in alcohol-dependent patients makes useful predictions when applied to young social drinkers. We first trained the SVM classifier on the entire patient sample at once, whereby the number of voxels was set to the average number of optimal voxels from the original cross-validation procedure (350 voxels). The trained classifier was then applied to the 136 imaging datasets of the young social drinkers, assigning abstainer-classified and relapser-classified labels to each individual based on their PIT activation patterns. We then compared changes in drinking behavior (amount and frequency) over a 12-month period between young social drinkers classified as abstainers and classified as relapsers.

RESULTS

PIT Activation Patterns in the mPFC Predict Relapse

Our main research question concerned the prediction of future relapse in alcohol-dependent patients from neural PIT responses. Using a LOO cross-validation procedure in combination with nested feature selection, our classification scheme yielded 71.15% correct predictions (sensitivity = 83.33%; specificity = 54.55%; balanced accuracy = 68.9%; $p = .002$). Thus, as hypothesized, neural activation patterns underlying PIT successfully predicted future relapse.

To investigate which voxels contributed most to classification, we assessed how often each voxel was selected in the feature selection stage. Figure 2 shows the number of times each voxel had been selected (red-yellow-white color scale) overlaid on the literature-based search space (blue). We found that selected voxels constituted a confined cluster located in the mPFC (centered around Montreal Neurological Institute coordinates [4, 52, 20] within Brodmann areas 10 and 32). The prediction of relapse was therefore almost exclusively based on activation patterns in the mPFC during alcohol-related PIT, a region known to be involved in cognitive control. Other brain regions within our selected search space that have been previously implicated in the alcohol-related PIT effect, such as the NAc, have not been picked up by the feature selection stage and thus did not contribute to the relapse prediction.

To assess whether relapse prediction would work just as well on a more conventional cue reactivity contrast, we applied an identical classification scheme to cue reactivity contrast maps (alcohol > water). The accuracy was 53.9% (sensitivity = 56.7%; specificity = 50.0%; balanced accuracy = 53.3%), which was not above chance ($p = .32$). Thus, a simple cue reactivity contrast was not sufficient to predict relapse in alcohol-dependent patients, justifying the use of more elaborate PIT effects. To investigate whether successful relapse prediction is based on a general neurobiological mechanism underlying PIT, we repeated our analysis using monetary instead of alcohol-related fMRI PIT responses. Interestingly, while the overall accuracy for this model was considerably

lower, at 55.77%, and not significantly above chance performance (p = .26, sensitivity = 63.33%; specificity = 45.45%, balanced accuracy = 54.39%), we found that the voxels selected for classification showed a substantial overlap with the voxels selected for alcohol PIT analysis (see Supplement and Supplemental Figure S3).

Generalization to Changes in Drinking Behavior in Young Social Drinkers

We reasoned that if the PIT response patterns constituted a generic marker for the risk of future problematic drinking behaviors, they should predict longitudinal changes in drinking behavior in other samples as well. To test this hypothesis, we applied the SVM classifier trained on PIT activation patterns of alcohol-dependent patients to make predictions regarding future drinking behavior in an independent sample of young social drinkers. Overall, the amount of alcohol consumption per occasion in this cohort of young social drinkers decreased between a baseline measurement (also the time of fMRI) and a 12-month-follow up (mean ± SEM: baseline 69.4 ± 3.6 g, 12-month follow up 61.4 ± 4.2 g; $t_{109} = -2.9$, $p = .004$), although the frequency of consumption did not change (median ± absolute deviation: baseline 2 ± 1 (1–3 per month); 12-month follow-up 3 ± 1 (4–8 per month); Wilcoxon signed ranks [$Z_{111} = 1.441$, $p = .149$]). On the basis of this, we expected that young social drinkers labeled as abstainer-classified by the classification scheme would show stronger reductions in drinking behavior (amount of alcohol consumption per occasion) compared with those labeled as relapser-classified.

Indeed, young social drinkers classified as abstainers showed a reduction in the amount of alcohol consumed between baseline and 12-month follow-up (Δ = −24.4 ± 6.0 g; $t_{21} = 4.0$, $p < .001$), while no significant reduction was observed in those classified as relapsers (Δ = −5.7 ± 3.6 g; $t_{87} = 1.6$, $p = .12$) (Figure 3). This difference was itself significant ($t_{108} = 2.4$, $p = .019$). By contrast, no difference between these groups was observed with respect to changes in the frequency of alcohol consumption (Mann-Whitney $U = 0.275$ $p = .783$).

Taken together, our classification scheme trained to predict future relapse in alcohol-dependent patients made a meaningful prediction for changes in drinking behavior of young social drinkers, labeling as abstainer-classified those who showed improved future drinking behavior.

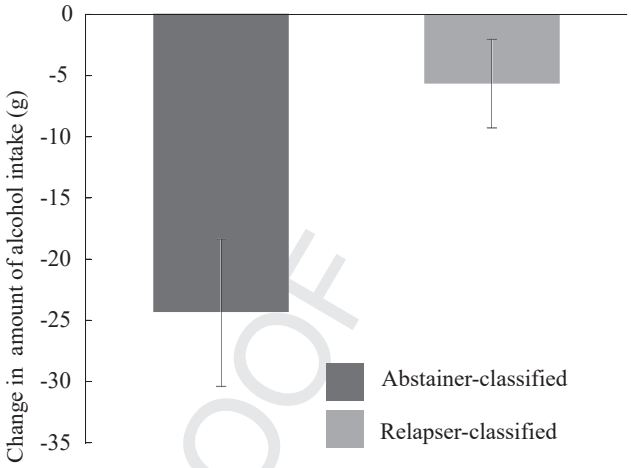

Figure 3. Changes in drinking behavior depending on whether young social drinkers were labeled as abstainer-classified or relapser-classified. Change in the amount (g) of alcohol intake per occasion within the follow-up period of 12 months.

DISCUSSION

We investigated the hypothesis that neural responses during PIT predict future relapse behavior in detoxified alcohol-dependent patients. Applying a machine learning classifier to PIT-induced brain activation patterns from fMRI, we showed that 83.3% of future relapsers and 54.5% of future abstainers could be correctly classified, corresponding to an overall accuracy of 71.12%. Moreover, we found that this classification scheme generalized to an independent sample of young social drinkers, in whom those labeled as abstainer-classified showed improved future drinking behavior compared with those labeled as relapser-classified. Together, these results provide evidence that the influence of alcohol-related cues on instrumental behavior is a promising candidate mechanism for the persistence and development of problematic drinking behaviors.

An inspection of the searchlight-based feature selection procedure revealed that the voxels most consistently selected for classification clustered in the mPFC. Interestingly, also in a complementary analysis for monetary PIT, the mPFC was identified as predictive for relapse, although overall classification accuracy was not significantly above chance. These findings are in line with previous studies reporting a relationship between relapse status and alcohol cue–related activity in the mPFC (3,7,25). Mechanistically, recent studies investigating decision making in the context of AD have implicated the mPFC in goal-directed behavioral control and found consistent reduced activation related to goal-directed behavior in the mPFC of alcohol use disorder patients (26,27). Moreover, the mPFC plays an important role in integrating cognitive-affective information and sends highly organized projections to subcortical sites including the NAc shell. Preclinical studies suggest an important role of these projections in alcohol-seeking behavior. For instance, ablation of mPFC neurons projecting to NAc block cue-induced reinstatement of alcohol seeking (28), and inactivation of the NAc shell decreases the extent to which alcohol-predictive cues control instrumental behavior (29). Beyond mediating alcohol reinstatement, mPFC-NAc projections also play a major role in PIT. In rats, the interaction between NAc shell and infralimbic PFC mediates PIT effects (30). Importantly, PIT effects (and their neural correlates in the NAc) are increased after chronic drug intake in animals (31) and humans (10), demonstrating the importance of this mechanism in drug addiction.

Because our classification scheme was based on alcohol-related PIT, it is tempting to conclude that dysfunction in areas such as the mPFC may result in the formation of cue-triggered craving, thus facilitating the loss of control upon alcohol intake. On the other hand, the spatial overlap with predictive voxels underlying monetary PIT classification, albeit in itself not statistically significant, furthermore also suggests

that the mPFC may reflect a more general process relevant for relapse. One might speculate that this might be mediated via a relaxing control over subcortical mechanism or dysfunction in other cognitive mechanisms associated with the mPFC, such as emotion and motivational regulation as well as reward circuitry (4,26,32). However, because within our study we could not provide evidence for behavioral differences indicative of a more general control dysfunction in relapsers, this interpretation warrants further investigation.

In contrast to the successful classification based on PIT, neural responses reflecting cue reactivity were not sufficient to make meaningful predictions about future relapse behavior. This result suggests that instead of neural responses to alcohol-related cues per se, it is specifically the neural response underlying the transfer to instrumental behavior that is related to relapse probability. Thus, apart from providing a promising neuroimaging-based biomarker for relapse prediction, our results also shed light on the mechanism underlying susceptibility to relapse.

Importantly, the claim that PIT-induced neural activation patterns represent a mechanistically valid marker was corroborated by our finding that the same classifier trained on the patient sample made meaningful predictions about changes in drinking behavior in an independent sample of young social drinkers. Specifically, the algorithm was able to distinguish between young adults who would and those who would not significantly reduce the quantity of future alcohol consumption. In contrast, changes in the frequency of alcohol consumption were not different between those labeled as abstainer-classified and those labeled as relapser-classified. Indeed, it may be unreasonable to expect that the number of opportunities for alcohol consumption changes much within a period of 1 year. In addition, the development of addiction is thought to involve stimuli paired with drug effects, becoming occasion setters (33). Such stimuli increase motivation for drug taking, so that occasion-dependent drug taking becomes probable. Thus, PIT-specific mPFC activation patterns may reflect cue-related loss of control rather than cue-independent alcohol-seeking behavior, as reflected by frequency of alcohol intake.

Overall, our work demonstrates that neural PIT responses can serve as a mechanistic marker for relapse susceptibility in alcohol-dependent patients and for changes in drinking behavior in healthy young individuals. Our findings highlight the mPFC as a key brain region explaining the differences in instrumental behaviors of relapsers and young adults at risk. Specifically, activation patterns in the mPFC may encode the effect of alcohol-related cues on goal-directed behaviors such as losing control over alcohol consumption. In short, our findings endorse neural responses during PIT both as a mechanism-based predictive marker for future drinking behavior in established AD, and in the development of problematic drinking in at-risk states.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by German Research Foundation (Deutsche Forschungsgemeinschaft, FOR 1617) Grant Nos. STE 1430/6-1, STE 1430/6-2, SCHM 3209/1-2, ZI 1119/3-1, ZI 1119/3-2, HE 2597/14-1, HE 2597/14-2, WI 709/10-1, WI 709/10-2, SM 80/7-1, SM 80/7-2, SFB 940, and Excellence Cluster Exc 257; Federal Ministry of Education and Research BMBF Grants Nos. 01ZX1311H, 01ZX1311D/1611D, and 01ZX1311E/1611E, and in part by Grant Nos. 01EE1406A and 01EE1406B; and the Charité Clinical Scientist Program, which funded by the Charité Universitätsmedizin Berlin and the Berlin Institute of Health (to KS).

The authors report no biomedical financial interests or potential conflicts of interest.

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Received Feb 3, 2019; revised Jun 19, 2019; accepted Jun 30, 2019.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2019.06.028.

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