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Neural correlates of cue-induced changes in decision-making distinguish subjects with gambling disorder from healthy controls

Alexander Genauck[1,2] | Caroline Matthis[4,2] | Milan Andrejevic[7] | Lukas Ballon[1] | Francesca Chiarello[5] | Katharina Duecker[6] | Andreas Heinz[1] | Norbert Kathmann[3] | Nina Romanczuk-Seiferth[1]

[1]Department of Psychiatry and Psychotherapy, Charité–Universitätsmedizin Berlin, Berlin, Germany

[2]Bernstein Center for Computational Neuroscience Berlin, Berlin, Germany

[3]Department of Psychology, Humboldt-Universität zu Berlin, Berlin, Germany

[4]Institute of Software Engineering and Theoretical Computer Science, Neural Information Processing, Technische Universität Berlin, Berlin, Germany

[5]Psychiatry Unit, Department of Health Sciences, University of Florence, Florence, Italy

[6]Department of Psychology, Carl-von-Ossietzky Universität Oldenburg, Oldenburg, Germany

[7]Melbourne School of Psychological Sciences, The University of Melbourne, Melbourne, Victoria, Australia

Correspondence
Alexander Genauck, Department of Psychiatry and Psychotherapy, Charité–Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.
Email: alexander.genauck@charite.de

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Abstract

In addiction, there are few human studies on the neural basis of cue-induced changes in value-based decision making (Pavlovian-to-instrumental transfer, PIT). It is especially unclear whether neural alterations related to PIT are due to the physiological effects of substance abuse or rather related to learning processes and/or other etiological factors related to addiction. We have thus investigated whether neural activation patterns during a PIT task help to distinguish subjects with gambling disorder (GD), a nonsubstance-based addiction, from healthy controls (HCs). Thirty GD and 30 HC subjects completed an affective decision-making task in a functional magnetic resonance imaging (fMRI) scanner. Gambling-associated and other emotional cues were shown in the background during the task. Data collection and feature modeling focused on a network of nucleus accumbens (NAcc), amygdala, and orbitofrontal cortex (OFC) (derived from PIT and substance use disorder [SUD] studies). We built and tested a linear classifier based on these multivariate neural PIT signatures. GD subjects showed stronger PIT than HC subjects. Classification based on neural PIT signatures yielded a significant area under the receiver operating curve (AUC-ROC) (0.70, $p = 0.013$). GD subjects showed stronger PIT-related functional connectivity between NAcc and amygdala elicited by gambling cues, as well as between amygdala and OFC elicited by negative and positive cues. HC and GD subjects were thus distinguishable by PIT-related neural signatures including amygdala–NAcc–OFC functional connectivity. Neural PIT alterations in addictive disorders might not depend on the physiological effect of a substance of abuse but on related learning processes or even innate neural traits.

KEYWORDS

decision making, fMRI, gambling disorder, Pavlovian-to-instrumental transfer

1 | INTRODUCTION

In addictive disorders, a cue can be any formerly neutral stimulus that has been repeatedly paired with the effects of the addictive behavior.[1] The effect of increased responsivity toward addiction-related cues is termed cue reactivity and is pivotal in explaining a range of behaviors related to addictive disorders, such as arousal, attentional bias, craving, and relapse.[1–3]

In line with this, subjects suffering from gambling disorder (GD) display increased neural activity elicited by addiction-related cues and a reduced neural response toward stimuli signaling natural rewards,[4,5] just like patients suffering from substance use disorders (SUDs).[2,3]

Besides cue reactivity, and again just like in SUDs, GD subjects display impaired value-based decision making. For example, GD subjects show increased risk taking, higher discounting of delayed rewards (delay discounting), and reduced loss aversion.[6–10]

Impaired value-based decision making in addiction may partly be explained, or even further exacerbated, by cues that modulate decision-making processes. The modulating influence of conditioned cues on instrumental behavior (e.g., cue-related increase of vigor with which a behavior is displayed or increase of likelihood of choosing a certain option) has been termed Pavlovian-to-instrumental transfer (PIT).[11,12] Interestingly, PIT effects can persist even when the outcome of the instrumental behavior has been devalued,[13,14] and a stronger PIT has been associated with heightened impulsivity[15] and with reduced model-based behavior.[16] Therefore, PIT has gained considerable attention in addiction research. Increased PIT has been associated with SUDs in animal studies[17,18] and in human studies.[19,20] It is especially important to know whether these effects are related to substance abuse or also present in behavioral addictions, such as GD.

Indeed, there is evidence that delay discounting is increased under the influence of high-craving gambling cues versus low-craving gambling cues.[21,22] Further, Genauck et al.[23] used a mixed-gambles task coupled with emotional and gambling-related cues (affective mixed-gambles task) to estimate subject-specific behavioral PIT parameters with regards to loss aversion. The authors found that gambling-cue-related shifts in general gamble acceptance especially contributed to distinguishing GD subjects from healthy control (HC) subjects. Cue-induced changes in loss-aversion, however, did not contribute. In the present study, subjects performed a very similar affective mixed-gambles task in a functional magnetic resonance imaging (fMRI) scanner. Genauck et al.[23] successfully used the behavioral data of the present study as an independent sample to validate their HC–GD classifier. However, it remains to be elucidated which neural correlates of PIT distinguish GD from HC.

If there are neural PIT signatures associated with GD, then this would be additional evidence for functional brain changes related to addictive disorders independent of a substance of abuse.[5,24,25] Our study is the first to investigate functional brain changes in GD compared with HC related to cue-induced changes in value-based decision making. We expected that neural PIT signatures derived from SUD studies should underlie behavioral PIT increase also in GD and thus lend themselves to distinguish GD from HC subjects.

At the neural level, PIT depends on the functions of amygdala and the ventral striatum (VS/nucleus accumbens [NAcc]).[12,26] Garbusow et al.[19] distinguished alcohol-dependent relapsers from abstainers using a NAcc PIT signal, reaching an accuracy of 71% in leave-one-out cross-validation. Note that cue reactivity, which PIT arguably is based upon, is also associated with altered activity of amygdala and NAcc in addictive disorders.[3]

In addition to possible activity differences in limbic regions being associated with PIT, NAcc–amygdala connectivity plays a role in decision-making changes due to emotional cues.[27] Other authors have argued that Pavlovian influence on instrumental behavior require the modulation of ongoing processes in the striatum by the amygdala.[28] Bidirectional NAcc–amygdala connectivity could thus be enhanced in GD subjects during presentation of addiction-relevant cues. Holmes et al.[29] further suggest a contribution of the orbital frontal cortex in integrating information about Pavlovian and instrumental processes, together with the striatum and amygdala. The affective neuroscience of decision through reward-based evaluation of alternatives (ANDREA) model makes similar predictions when explaining transient changes in gamble acceptance in decision-making tasks[30] (**Figure S3**). In particular, the ANDREA model suggests that the evaluation of a gamble involving possible gains and losses leads to a subjective value signal in the orbitofrontal cortex (OFC). Amygdala inputs to OFC can modulate those subjective value representations when positively valued or salient stimuli (e.g., gambling cues) are shown in the background. Because there is some evidence that GD subjects show cue-induced changes in instrumental behavior and decision making in response to gambling cues, putatively related to stronger behavioral PIT effects,[21–23] this could mean that gambling cues increase the subjective gamble value represented in OFC via amygdala projections. We thus expected that stronger gambling-cue PIT-related functional connectivity from amygdala to OFC should help distinguish GD from HC.

In summary, we hypothesized that a neural PIT signature made up of several PIT-related fMRI contrasts could distinguish GD from HC subjects. We therefore compiled per subject a feature vector comprised of cue reactivity and PIT-related contrasts in amygdala and NAcc and of functional connectivity parameters in a network of NAcc, amygdala, and OFC. Hence, the feature vector represented each subject's neural PIT signature, in the form of multiple fMRI aggregates.[31,32] We used all subjects' neural PIT signatures to estimate a classifier that would distinguish GD from HC subjects. We expected that PIT-related predictors would be found among the most important ones followed by the cue-reactivity predictors. Using cross-validation, we assessed the generalizability of this classifier to new samples. Classifying GD and HC subjects using multivariate patterns aims to bring us closer to a clinically relevant characterization of the neural disturbances related to GD, especially when there are many relevant variables involved.[31,33–35] To our knowledge, our study is the first one to use fMRI-based classification for investigating GD and its neural basis of increased PIT.

2 | METHODS AND MATERIALS

2.1 | Sample

The GD group consisted of subjects who were active gamblers (mainly slot machine), whereas the HC group consisted of subjects that had none or little experience in gambling. We recruited GD subjects via eBay classifieds and notices in Berlin casinos and gambling halls. GD subjects were diagnosed using the German short questionnaire for gambling behavior (KFG) (cutoff ≥16).[36] The KFG classifies subjects according to DSM-IV criteria for pathological gambling. However, in the following, we use the DSM-5 term "gambling disorder" interchangeably, because the criteria largely overlap. For further information on administered questionnaires, see Supplement S1.1. There were 13 subject dropouts due to technical errors, positive drug screenings, incidental cerebral anatomical findings, or MRI contraindications. We dropped five more subjects to improve the matching of the groups on covariates of no interest (age, smoking severity, education, and see Table 1). The final sample consisted of 30 GD and 30 HC subjects (Table 1). GD and HC were matched on relevant variables (net personal income, age, and alcohol use), except for years in school (primary and secondary). We thus tested for stability of our classifier by adjusting for years in school.

2.2 | Procedure and data acquisition

Before scanning, all subjects underwent urine drug testing to exclude any influence of cannabis, amphetamines, cocaine, methamphetamines, opiates, or benzodiazepines. They then were instructed on the task and completed the affective mixed gamble task in a 3-Tesla SIEMENS Trio MRI (two runs of about 23 min). Echo-planar imaging (EPI) scans were acquired, as well as structural MRI. For further details on MRI sequences, see Supplement S1.5.

2.3 | Affective mixed-gambles task

We built on established mixed-gambles tasks[10,37] and cued mixed-gambles tasks.[23,27] As affective cues, four sets of images were assembled: (1) 67 gambling images, showing a variety of gambling scenes, and paraphernalia (*gambling cues*); (2) 31 images showing negative consequences of gambling (*negative cues*); (3) 31 images showing positive effects of abstinence from gambling (*positive cues*); and (4) 24 neutral International Affective Picture System (IAPS) images (*neutral cues*). For a detailed description of the images and their categories, see Supplement S1.2. Subjects were each given 20€ for wagering during the task (Figure 1). Gambles were created by randomly drawing with replacement from a matrix with possible gambles consisting of

TABLE 1 Sample characteristics, means, and *p* values calculated by two-sided permutation test

Variable	HC (30)	SE	GD (30)	SE	Pooled SE	*p* perm test
Years in school	10.87	0.19	10.13	0.24	0.21	0.031
Vocational school	2.73	0.29	2.07	0.25	0.27	0.108
Net personal income	1028.61	92.27	1105.89	138.93	115.6	0.667
Personal debt	8500	3396.88	24 000	9590.36	6493.62	0.097
Fagerström	1.97	0.43	3.03	0.51	0.47	0.138
Age	35.37	1.66	37.37	2.01	1.84	0.459
AUDIT	4.8	0.59	4.87	1.05	0.82	1
BDI-II	5.1	1.03	11.57	1.72	1.38	0.002
SOGS	1.73	0.47	8.8	0.67	0.57	<0.001
KFG	2.37	0.74	35	1.64	1.19	<0.001
BIS-15	31.8	0.99	36.33	1.08	1.03	0.004
GBQ persistence	1.96	0.2	3.28	0.19	0.2	<0.001
GBQ illusions	2.41	0.24	3.73	0.22	0.23	<0.001
Ratio female	0.20	—	0.20	—	—	1.000
Ratio unemployed	0.17	—	0.20	—	—	1.000
Ratio smokers	0.60	—	0.77	—	—	0.262
Ratio right-handed	0.97	—	0.84	—	—	0.204

Note: chi-square test used; years in school, years in primary and secondary school; vocational school is vocational school and university; *Fagerström*, smoking severity.

Abbreviations: AUDIT, alcohol use disorders identification test; BDI II, Beck's Depression Inventory; BIS-15, short version of the Barratt Impulsiveness Scale for impulsivity; GBQ persistence and GBQ illusions, from the Gamblers' Beliefs Questionnaire; KFG, *Kurzfragebogen zum Glückspielverhalten*, Short Questionnaire Pathological Gambling, German diagnostic tool and severity measure based on the DSM-IV; SE, bootstrapped standard errors; SOGS, South Oaks Gambling Screen (for sources of questionnaires, see Supplement S1.1).

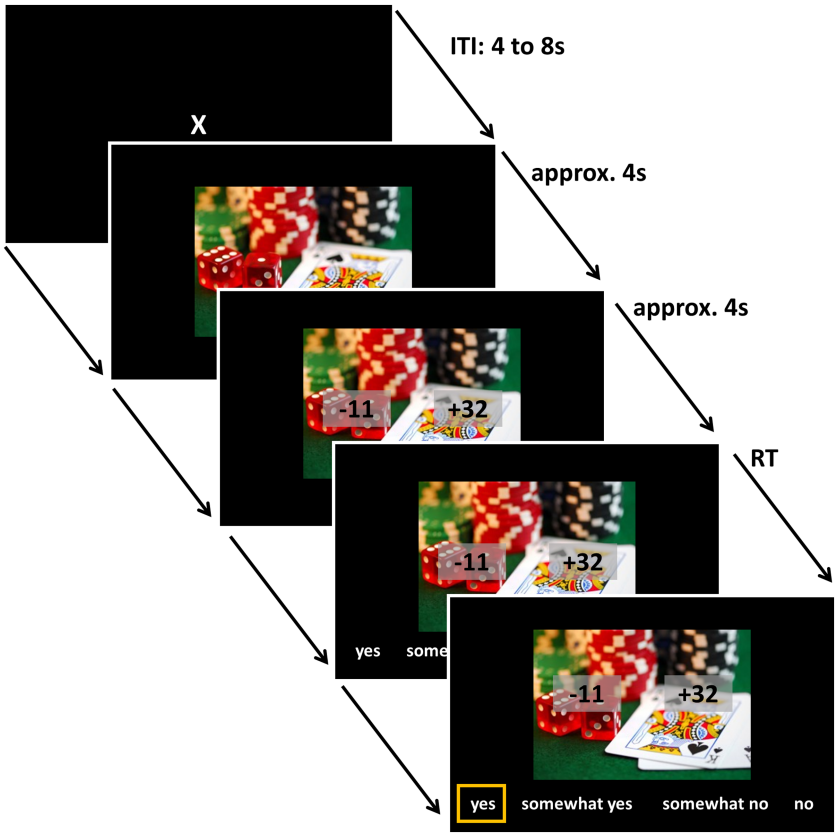

FIGURE 1 The affective mixed-gambles task. One trial is depicted. Subjects first saw a fixation cross with variable intertrial-interval (ITI, 4 to 8 s). Then, a cue with randomly chosen affective content (67 gambling related, 45 drawn with replacement from 31 with positive consequences of abstinence, 45 drawn with replacement from 31 with negative consequences of gambling, 45 drawn with replacement from 24 neutral images, i.e., 202 trials) was presented for about 4 s. Subjects were instructed to remember the cue for a paid recognition task after all trials. Then, a gamble involving a possible gain and a possible loss was superimposed on the cue (e.g., −11 and +32). Subjects were instructed to shift their attention at this point to the proposed gamble and evaluate it (decision phase). Position of gain and loss was counterbalanced (left/right). Gain was indicated by a "+" sign and loss by a "−" sign. After again 4 s (jittered) the response options appeared and subjects were asked to indicate their willingness to accept the gamble between four levels of acceptance (yes, somewhat yes, somewhat no, no[37]; here translated from the German version, which used "ja, eher ja, eher nein, nein") (motor phase). Direction of options (from left to right or vice versa) and side of gain amount was random. Directly after decision, the ITI started. If subjects failed to respond within 2.5 s, ITI started and trial was counted as missing. RT: reaction time

12 levels of gains (14, 16, …, 36) and 12 levels of losses (−7, −8, …, −18).[10,37,38] In every subject, we stratified gambles according to mean and variance of gain, loss, gamble variance, and Euclidean distance from gamble matrix diagonal (*ed*, i.e., gamble difficulty). We informed subjects that after completing the experiment, five of their gamble decisions with ratings of "somewhat yes" or "yes" would be randomly chosen and played for real money.

2.4 | Cue ratings

After the task, subjects rated all cues using the Self-Assessment Manikin (SAM) assessment technique (valence, arousal, and dominance)[39] and additional visual analog scales. Additional questions were: (1) "How strongly does this image trigger craving for gambling?"; (2) "How appropriately does this image represent one or more gambles?"; (3) "How appropriately does this image represent possible negative effects of gambling?"; and (4) "How appropriately does this image represent possible positive effects of gambling abstinence?" All cue ratings were *z*-standardized within subject. Cue ratings were analyzed one-by-one using linear mixed-effects regression, using lmer from the lme4 package in R,[40] where cue category (and, in the respective models, clinical group) denoted the fixed effects and subjects and cues denoted the sources of random effects. Model comparisons were used to test for the effect of cue category and group and their interaction using χ^2-square difference tests. We report relevant contrast-βs only if the overall effect of the relevant factor (group, category, and groupXcategory) was significant. For significance testing of those contrast-βs, we use Wald *z* tests as implemented in lme4.

2.5 | Behavioral data

Choice data were modeled within each subject's behavioral data by submitting dichotomized choices (somewhat no and no: 0;

somewhat yes and yes: 1) into logistic regression. We dichotomized choices to increase the precision when estimating behavioral parameters, in line with previous studies.[10,23,37] Predictors were centralized values of gain, centralized absolute values of loss, Euclidean distance (*ed*) from gamble matrix as indicator of gamble simplicity (see Figure S1),[37] and cue category (**c**). 12 steps of gain (14, 16, 18, …, 36) and 12 steps of loss (−7, −8, −9, …, −18) formed a 12-by-12 gamble matrix, which was aggregated to 4-by-4 (e.g., gain steps 14, 16, and 18 were all denoted as 16 and loss steps −18, −17, and −16 were denoted as −17) as done in previous fMRI versions of this task.[10,37] We defined the gamble value (*Q*) on single-trial level as

$$Q = \beta_0 + x_{\text{gain}} * \beta_{\text{gain}} + x_{\text{loss}} * \beta_{\text{loss}} + ed \cdot \beta_{ed} + c^T * \beta_c. \quad (1)$$

We call this model the **laec** model. Here, $c^T$is a transposed column vector, denoting the dummy code of the cue's category on any given trial and β_c is a column vector holding the regression weights describing the shift in gamble value with respect to the cue category. Hence, $c^T * \beta_c$ is a scalar product describing the additive effect of cue category. We fit the logistic regression based on Equation 1 with …

$$P(\text{gamble acceptance}) = \frac{1}{1+\exp(-Q)}, \quad (2)$$

within a generalized linear mixed-effects model, using glmer from the lme4 package in R.[40] Here, gain, loss, *ed*, and cue category denoted the fixed effects and subjects and cues denoted the sources of random effects. To test if the groups differed in the parameters of the **laec** model, we expanded the model by an additional fixed effect of group modulating the effect of gain, loss, *ed*, and cue category (**laecg**). Statistical testing of the model comparison was performed using χ2-difference tests and by comparing the Akaike (and Bayesian) information criterion of the baseline model (laec) with that of the full model (laecg). For statistical tests of single parameters in the **laecg** model, we used Wald *z* tests as implemented in lme4. For more analyses of the behavioral data, please see Sections S1.4 and S2.1. Because the current behavioral experiment was used almost in an identical fashion in a different sample of 30 HC and 30 GD subjects[23] and because in that study a classifier was trained on the basis of the behavioral data to distinguish GD from HC subjects at a performance of area under the receiver operating curve (AUC-ROC) = 0.689, p = 0.002, the analysis of behavioral data was of minor importance for the current study in favor of the analysis of neural data. We thus applied the classifier of Genauck et al.[23] to the current data set to see if similar behavioral patterns distinguished GD from HC in the current study. The classifier put most importance on the shift of acceptance rate by cue categories in the background and minor difference on loss aversion differences between groups.

2.6 | FMRI data

2.6.1 | Preprocessing and single-subject model of fMRI data

Imaging analyses were performed in SPM12 running on Matlab (R2014a). Please see Supplement S1.5 for description of preprocessing of MRI data. We modeled the preprocessed fMRI single-subject data based on the **laec** model[10,23,37] using three onset regressors (Cue, Cue plus gamble, and Cue plus gamble plus response option). The first and second onset regressors, each with their parametric modulators, modeled cue reactivity and PIT, respectively (Supplement S1.6).

2.6.2 | Extracting fMRI features for classifier building

We were interested whether PIT fMRI contrasts from certain brain regions (regions of interest, ROIs) could predict if a subject belongs to the HC or the GD group. We hence extracted the mean activity for cue reactivity (gambling, negative, positive; pmod(1–3) of onset regressor 1) and for the PIT contrasts (acceptXgambling, acceptXnegative, acceptXpositive; pmod(5–7) of onset regressor 2) using the within-subject means from the ROIs NAcc R/L and amygdala R/L. NAcc and amygdala ROIs were taken from the Neuromorphometrics SPM12 brain atlas.

To keep in line with accounts of PIT depending on NAcc–Amy connectivity[27,28] and on amygdala-OFC connectivity[29,30] (Figure S3), we also extracted functional connectivity (generalized psychophysiological interaction, gPPI)[41] for the PIT contrasts. We used the seeds amygdala R/L and NAcc R/L (see Supplement S1.7). For the seeds amygdala R/L, we extracted the mean from target ROIs OFC R/L (four subregions on either side) and from target ROIs NAcc R/L. For the seeds NAcc R/L, we extracted from the target ROIs Amy R/L. Information from left medial OFC was not available due to signal loss in that region. Collecting all the extracts per subject, we had at this point for each subject a vector representing his or her specific neural PIT pattern. We *z*-standardized this vector for each subject. We then reduced the dimensionality of this vector for each subject by computing within-subject means, collapsing for each ROI left and right (see Supplement S1.8).

To check for overall task signal, we checked for PIT effects in amygdala and NAcc across groups and for cue reactivity difference between groups in amygdala, NAcc, and OFC using years in school as a covariate of no interest in all cases.

2.6.3 | Building the classifier based on fMRI data

The neural PIT vectors per subject were stacked into a data set. Because HC and GD were not perfectly matched on years in school, we added this variable to the data set, which was then submitted to logistic elastic net regression, with group as dependent variable.

Elastic net regression is well suited for cases where there are few observations and many predictor variables that may contain groups of correlated variables[32,33,42] (see Supplement S1.9). Using tuning of its two hyperparameters,[42] it is also well suited to produce models that do not overfit but generalize well to new data. The algorithm tuned for optimal generalization performance on out-of-sample data using the AUC-ROC.[32,33] AUC-ROC ranges from 0.5 (chance) to 1 (perfect sensitivity and specificity).

We assessed the generalizability of the above algorithm 1000 times via 10-fold cross-validation, which yielded a distribution of classifiers and thus of AUC-ROCs. Note that the cross-validation to estimate generalizability led to the cross-validations used in the elastic net regression to become *nested*.[32] For a graphical illustration of the algorithm with cross-validation to estimate the generalization performance, see Figure 2. The data and R Code can be found here: https://github.com/pransito/PIT_GD_MRI_release. To compute a *p* value denoting the significance of classification improvement (full model vs. baseline model, i.e., model with only years of education as predictor), we compared the sampled distributions of classification performance under the full model versus under the baseline model[23] (Supplement S1.10).

After assessing the generalizability of the model by cross-validation, we fit the model to the entire data set (no splitting in training and test data) in order to build the final interpretable and reportable classifier. Because the modeling is probabilistic, we repeated this 1000 times. We plotted the ensuing distribution of regression weight vectors as per-parameter means with 95% percentile bounds.

2.6.4 | Inspecting the classifier based on fMRI data

In order to interpret the final classifier's regression weights as an *activation pattern* (*a*), that is, to know how greatly each predictor contributed to distinguishing GD from HC subjects in the classifier, we calculated

$$\boldsymbol{a} = \mathrm{cov}(X) * w, \tag{3}$$

[43]where w is the regression weight vector (a column vector), or in other words, the classifier. X is the matrix of predictors for all subjects, and cov(X) is the covariance matrix of X. Additionally, we calculated between-group *t* tests (HC vs. GD) for all predictors.

2.6.5 | Extending the inspection of classification performance

In order to assess the informational value of multiple classes of features, we explored the AUC-ROC on the test data when training on different combinations of features (Table S2). We especially explored an fMRI-only model with only the single-subject cue reactivity contrasts, and we used the behavior-only model as done in Genauck et al., [23] as well as an fMRI-behavior model to check whether the PIT-related fMRI signal holds additional classificatory value above and beyond behavioral features when distinguishing HC from GD subjects.

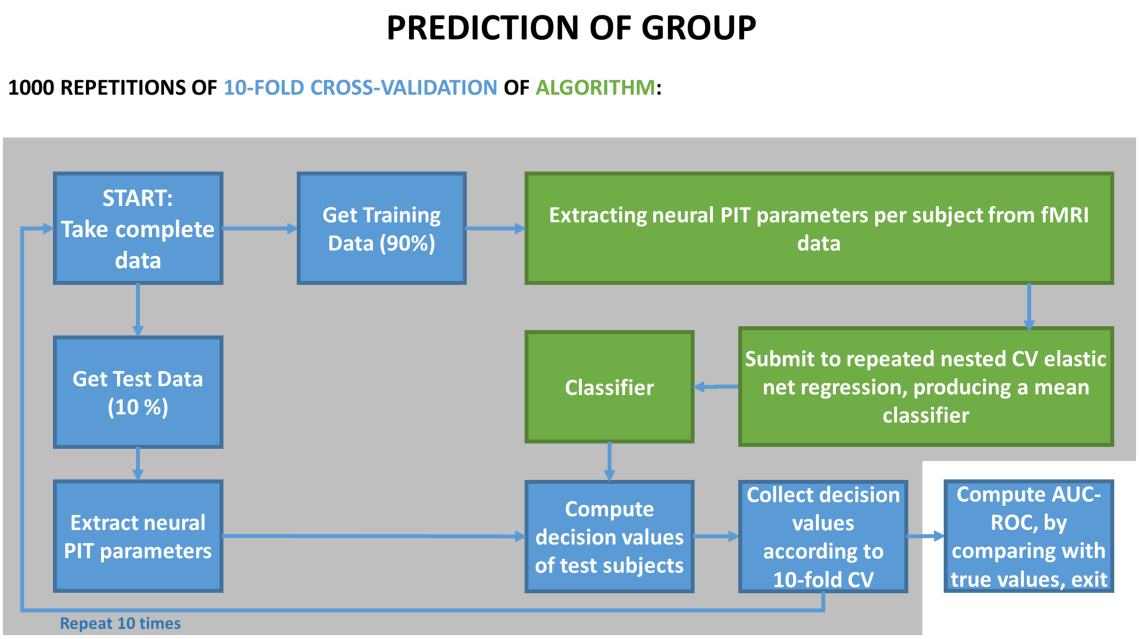

FIGURE 2 Classifier building algorithm with cross-validation (CV) to estimate generalization error. Nested CV was used for tuning the hyperparameters of the elastic net regression.[42] This was done repeatedly with different nested CV folds (10 times, 10-fold nested CV) to estimate a robust mean model within each repetition of classifier estimation

2.7 | Ethics

Subjects gave written informed consent. The study was conducted in accordance with the World Medical Association Declaration of Helsinki and approved by the ethics committee of Charité–Universitätsmedizin Berlin.

3 | RESULTS

3.1 | Cue ratings

Subjects perceived cues as intended and similar to a previous sample of HC and GD subjects[23] (Supplement S2.2). Gambling cues elicited more craving compared with neutral in GD subjects than in HC subjects (GD gambling > neutral: β = 1.749, HC gambling > neutral: β = 0.719, p(GD > HC) < 0.001).

3.2 | Behavioral choice data

Comparing the **laecg** to the **laec** models, we observed a significant χ^2 difference test result (χ^2 = 26.6, df = 7, p < 0.001; with ΔAIC = 12.6, ΔBIC = −39.0). The analogous comparison of the models without *ed*, **lac** versus **lacg** yielded a very similar result: χ^2 = 15.8, df = 6, p < 0.015; with ΔAIC = 3.7, ΔBIC = −40.0. Inspecting the estimated parameters of the **laecg** model, we observed that acceptance rate during neutral images with all other parameters at zero (i.e., at their mean, except for *ed*, actually zero) was for HC: 59.0% and for GD: 38.8%, p_{Wald} = 0.155. Gambling cues were associated with stronger increase in gamble acceptance in GD subjects (Δ% = 44) than in HC subjects (Δ% = −8, p_{Wald} = 0.003). The same was true for negative (GD: Δ% = 23, HC: Δ% = −16, p_{Wald} = 0.049) and positive cues (GD: Δ% = 23, HC: Δ% = 0, p_{Wald} = 0.030) (Figure 3). Groups did not differ in loss aversion (see Supplement S2.1). A group classifier estimated on external data[23] depending also largely on parameter group differences in acceptance rate per cue category (mainly driven by GD subjects accepting gambles more during presentation of gambling pictures in the background than HC subjects) and hardly on loss aversion differences yielded good performance on the current behavioral data set (AUC-ROC = 0.65, p = 0.47).[23]

3.3 | Neural effects and prediction of group using fMRI data

Exploring whole-group mass-univariate statistical maps, during the cue-only phase, we saw activity in medial prefrontal, anterior cingulum, insula, occipital cortex, precuneus, and fusiform gyrus in T-maps for the respective cue category contrasts against neutral images (Figure S8). Sensitivity to loss and gain contrasts in whole-group mass-univariate contrasts showed activity in inferior anterior cingulate cortex (ACC), medial prefrontal cortex, and occipital gyrus (Figure S9). Gamble acceptance X cue-category versus gamble acceptance X neutral category (i.e., PIT) contrasts showed no sub-threshold activity for gambling cues, only a small effect in superior frontal gyrus for HC > PG. For negative images, we saw, only for accXneg < accXneu, ventral medial prefrontal, inferior ACC activity and for positive cues (accXpos > accXneu) inferior occipital gyrus activity.

Using our ROIs relevant to the current study, across groups and in line with previous findings,[12,19,26,28] there was for gambling-cues PIT a significant effect in right amygdala: [15 −6 −15], p_{SVC} = 0.027, p_{uncor} = 0.003, k = 17. Further, there was for the cue reactivity contrast HC > GD (positive cues) a significant effect in left NAcc: [−6 6 −6], p_{SVC} = 0.033, p_{uncor} = 0.005, k = 4, and in right NAcc: [6 9 −6], p_{SVC} = 0.035, p_{uncor} = 0.007, k = 4.

The mean AUC-ROC of the full classifier using neural PIT signatures was 70.0% (mean for the baseline classifier, that is, covariate-only classifier: 61.5%, p = 0.013) (Figure S6).

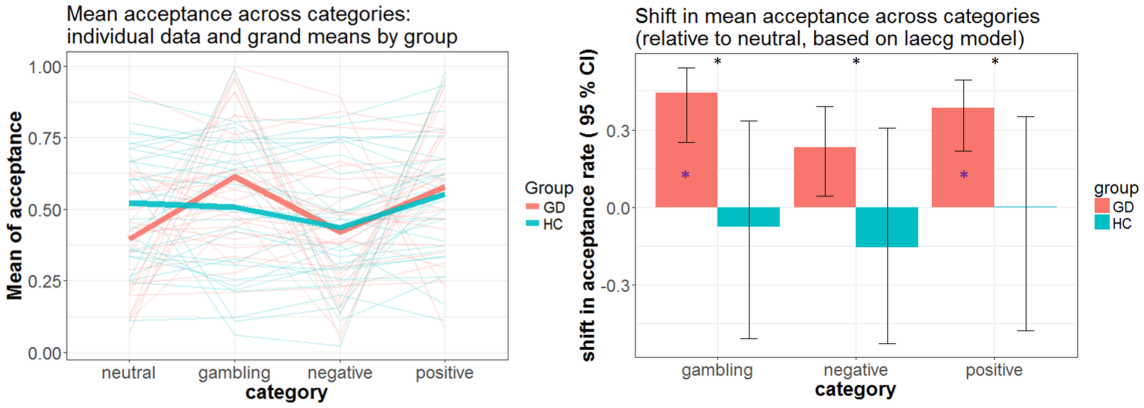

FIGURE 3 Shift in acceptance rate during gambles per category and group. Left: thick lines are mean acceptance rates of HC and GD. Thin lines are single-subject mean acceptance rates of HC and GD subjects. Right: Based on the **laecg** model. GD subjects show stronger increase in gamble acceptance (compared with neutral) in comparison with HC subjects during the presentation of all three cue categories in the background. Stars denote significant post hoc contrasts, where black stars indicate sig. group comparison and purple stars indicate significant difference from 0 within group. CIs based on standard errors of parameter estimates

Inspecting the final classifier's logistic regression weights (see Figure 4) (after transformation to predictor importance, see Equation 3, and according to *t* tests), we saw that the top predictor was negative-cues-PIT-related functional connectivity from amygdala to anterior OFC, with a negative sign (Figure 4). This means that the stronger not accepting a gamble was associated with increase in correlation between amygdala and anterior OFC, the *less* likely the subject was a GD person (and rather a HC subject). In other words, GD subjects showed lower such functional connectivity than HC. The next top three predictors were gambling-cues-related functional connectivity from NAcc to amygdala (positive sign), positive-cues-related functional connectivity from amygdala to lateral OFC (positive sign), and years in school (negative sign) (see Figure 4, Figure S7). Simple cue reactivity and simple PIT-related activity in NAcc and amygdala did not contribute significantly to the classifier's performance in distinguishing GD from HC.

3.4 | Extending the inspection of classification performance

In line with the fact that cue reactivity contrasts in the fMRI model were nonsignificant in predictor importance, we see that the cue-reactivity-only fMRI classification model performed worse than a full model. Note that the full fMRI-behavior model performed better than the behavior-only model on test data (AUC = 0.75 vs. AUC = 0.65, $p = 0.031$, Figure 5, Table S2).

4 | DISCUSSION

The influence of cues onto value-based decision making may be regarded as a form of PIT, the increase of which has been associated with addictive disorders in general.[17,19,20]

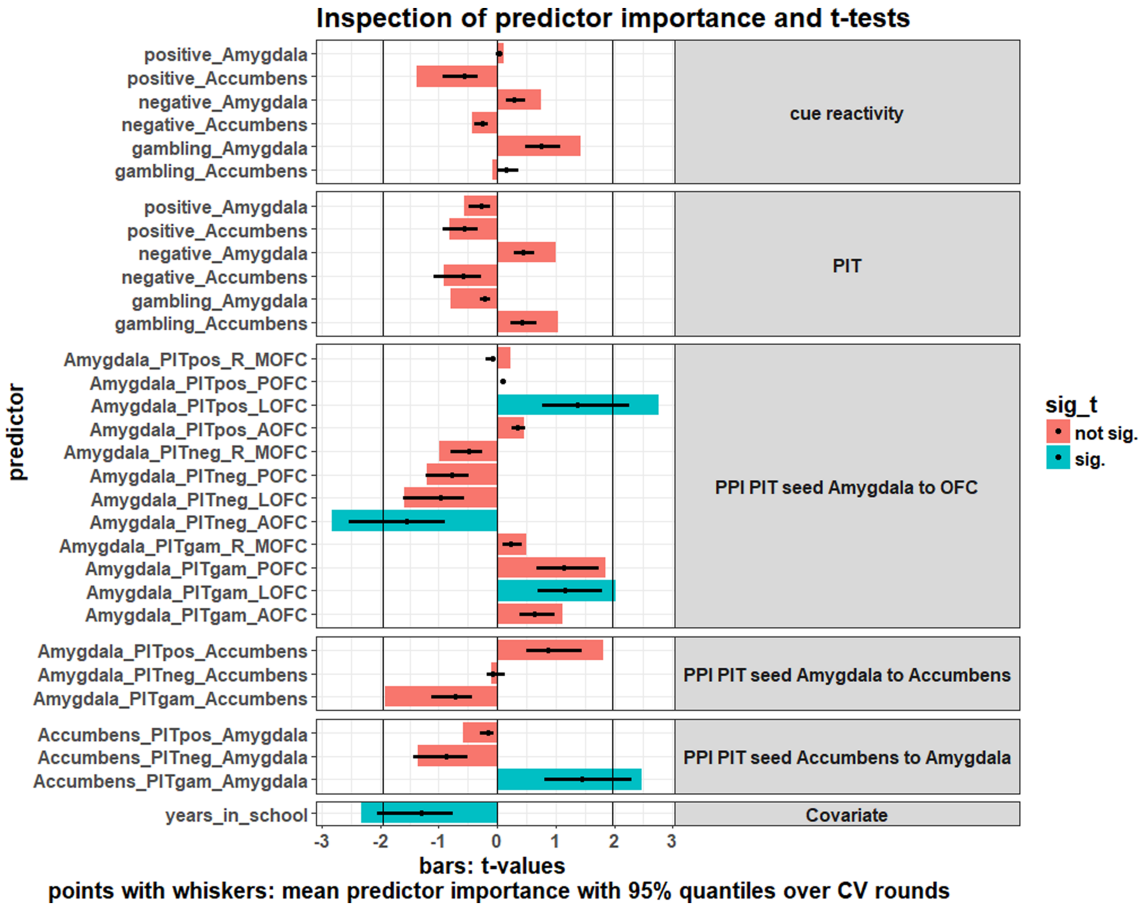

FIGURE 4 Estimated predictor importance. Points and quantiles are estimated predictor importance with 95% quantiles over 1000 classifier estimation rounds. The larger the absolute size of an importance value, the stronger the predictor adds to distinguishing HC from GD in the classifier. Positive predictor importance values mean that GD subjects showed stronger such activity than HC subjects and vice versa. Bars show *t* values of simple between-group *t* tests. Significant *t* tests are highlighted (Welch-test, $p < 0.05$, two-sided). Delimitations are at 1.96 and −1.96 to mark points of statistical significance for *t* test. Importance values/*t* values are grouped by the kind of fMRI predictor: cue reactivity related, PIT related, Psychological-physiological interaction (i.e., PPI) related. PPIs are further grouped by seed region and target extraction (e.g., "to OFC"). PIT: Pavlovian-to-instrumental transfer; OFC: orbital frontal cortex; AOFC, LOFC, POFC, MOFC: anterior, lateral, posterior, medial orbital frontal cortex; R: right; For graphical overview of results, see Fig. S7

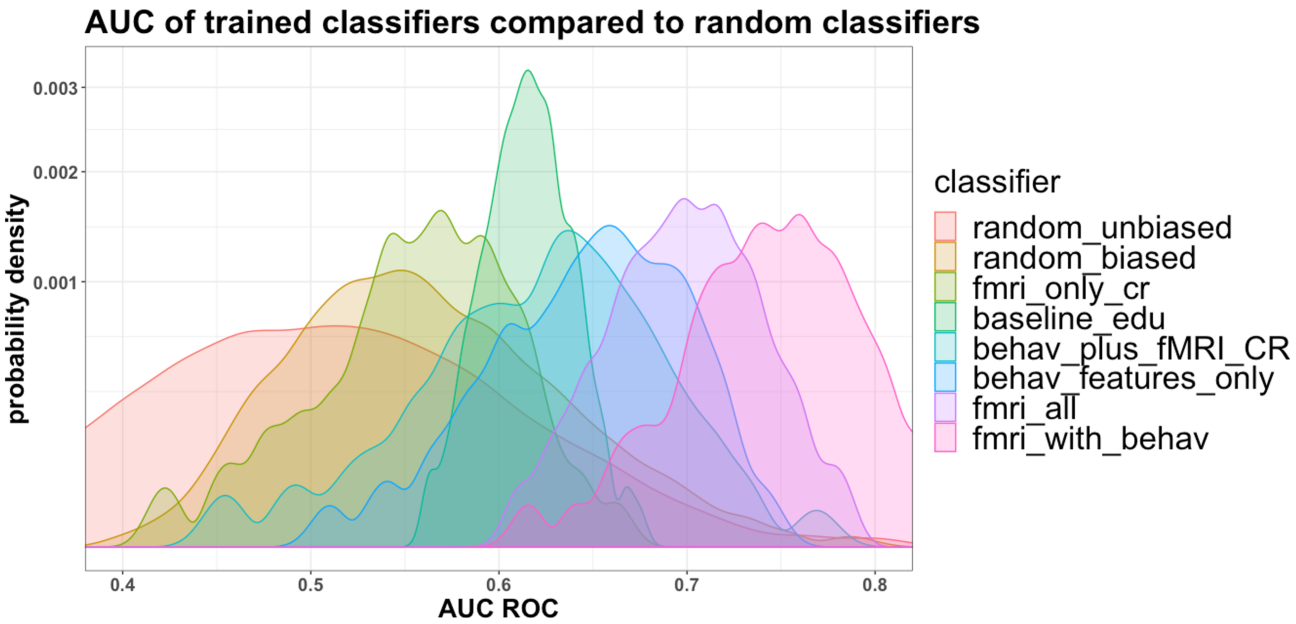

FIGURE 5 Multiple classifiers' performances against random and baseline classifiers. The classifier using all fMRI contrasts from the PIT neural search space performs better than all other classifiers, except for the classifier using all fMRI contrasts and the behavioral features. cr: cue-reactivity-related contrasts in amygdala and nucleus accumbens

We hypothesized that GD subjects should be distinguishable by neural PIT signatures based on fMRI contrasts recorded during an affective mixed-gambles task. We therefore built a classifier using fMRI PIT contrasts to distinguish GD from HC subjects focusing on brain structures known to be relevant in PIT, like amygdala and NAcc. We also incorporated amygdala's connectivity to OFC and amygdala's and NAcc's connectivity to each other. We further included neural cue reactivity contrasts as predictors. These predictors yielded a neural PIT signature per subject, which could be used to classify subjects into the GD or HC group.

Our results support our first hypothesis, showing that neural PIT signatures based on fMRI data gathered from the affective mixed-gambles task may successfully classify out-of-sample subjects into GD and HC, with a cross-validated mean AUC-ROC of 70.0% (p = 0.013). This performance on out-of-sample data is similar to other studies using MRI data for classification in the field of addictive disorders.[31,32,35] To our knowledge, however, the present study is the first one to use fMRI classification for investigating a behavioral addiction, namely, GD, and the neural basis of increased PIT. This means that it is possible to characterize a nonsubstance-related addiction to a considerable degree by a distinct neuro-functional signature, namely, a neural PIT signature in a network of amygdala, NAcc, and OFC, derived from PIT and SUD literature. This further implies that addictive disorders, in general, may be associated with PIT-related neural changes, independent of a substance of abuse, which means that neural PIT changes may be a product of addiction-related learning[44,113ff] and neural plasticity or even of an innate trait.[45]

Concerning the predictors in the classifier, we hypothesized that gambling-cue PIT-related functional connectivity from amygdala to OFC should be increased. We found that multiple PIT-related functional connectivities from amygdala to OFC were significant predictors in the classifier. For example, gambling-cues PIT-related functional connectivity from amygdala to OFC was increased in GD compared with HC subjects, in line with the above hypothesis and in line with the hypothesis that in GD subjects amygdala modulates the value computation in OFC, when addiction-related cues are presented in the background.[29,30] Furthermore, the top predictor in the classifier was PIT-related functional connectivity from amygdala to anterior OFC in trials with a *negative* cue, with a negative predictor weight. This means that the stronger the rejection of a gamble during the presentation of negative cues was associated with an increase in correlation between amygdala and anterior OFC, the *less* likely the subject was a GD person (and rather a HC subject). In other words, GD subjects showed weaker such functional connectivity than HC. GD subjects, compared with HC subjects, showed significantly more gambling during the presentation of negative cues than during the presentation of neutral cues. HC subjects may not show this effect because of stronger signal transmission related to negative cues from amygdala to OFC. Similarly, it has been found that reduced loss aversion in GD subjects was associated with reduced loss-related functional connectivity from amygdala to ventral medial prefrontal cortex in a pure mixed-gambles task.[10] This highlights that impaired decision making in GD during a pure mixed-gambles task, as well as during an affective mixed-gambles task, may draw from the same functional neural substrate.

Exploratively, we looked at the next two top predictors expecting that PIT-related (as opposed to purely cue reactivity related) neural predictors should be among these. Indeed, we found that the next top predictor was gambling-cues PIT-related functional connectivity from NAcc to amygdala (positive sign), a connectivity

important for cue-induced effects in mixed-gambles tasks.[27] This means that the more gamble acceptance during presentation of gambling cues was associated with an increase in correlation between NAcc and amygdala, the *more* likely the subject was a GD person. In other words, GD subjects showed stronger such functional connectivity than HC. NAcc is seen as encoding temporal difference prediction errors, that is, it fires when an unexpected reward signal is perceived from one moment to the next.[46] GD subjects rated gambling pictures as more craving-inducing and reacted with significantly stronger gamble acceptance increase than HC when gambling-associated cues were shown in the background. We also saw an important regression weight given to gambling-cues PIT-related functional connectivity from amygdala to OFC, in line with our initial hypothesis. Therefore, it may be that gambling cues elicit a prediction error in NAcc that modulates amygdala activity, which in turn modulates the value representation in OFC in such a way that GD subjects are more inclined than HC subjects to accept the gamble at hand. This is in line with a previous study, where it has been found that GD subjects display increased functional connectivity from amygdala to posterior OFC related to increasing possible gains in a pure mixed-gambles task.[10] This highlights again that impaired decision making in GD during a pure mixed-gambles task, as well as during an affective mixed-gambles task may draw from the same functional neural substrate. Also, it has been observed before that NAcc and amygdala seem to hold relevant signal related to PIT in healthy subjects[26] and to increased PIT in addicted subjects.[19] Interestingly, previous studies[19,20] have observed that in recently detoxified treatment-seeking AD patients, images of alcoholic beverages in the background have a suppressing effect on the instrumental task in the foreground. Contrarily, we have seen that gambling cues elicit a stronger gamble acceptance increase in GD than in HC. This may be because we have included only active non-treatment-seeking gamblers, who perhaps work less against their automated response toward addiction-related cues.

The third top predictor was also PIT related, in line with our hypothesis that PIT-related predictors should be more important than cue reactivity predictors. It was positive-cues PIT-related functional connectivity from amygdala to lateral OFC. This means that the stronger the acceptance of a gamble during the presentation of positive cues was associated with an increase in correlation between amygdala and OFC, the *more* likely the subject was a GD person. In other words, GD subjects showed stronger such functional connectivity than HC. This may be parallel to the finding on behavioral level that GD subjects react with more gambling increase to positive pictures than HC subjects. It seems that both positive cues and gambling cues lead to increased gambling and similarly increased connectivity between amygdala and OFC in GD subjects. Also, negative cues lead to increased gambling. This is surprising because one could have expected to see decreased gambling during negative and positive cues or no effect of those cue categories.[23] On the other hand, perhaps *all three* cue categories have special salience for GD subjects modulating the propensity to accept gambles. Future studies should further explore the effect of positive and negative stimuli on gambling in GD.

Considering the predictor importance of all fMRI contrasts, cue reactivity predictor importance values are relatively small, and the classifier draws more on PIT-related variables (the top-three predictors were PIT related). We also saw that the cue-reactivity-only fMRI classifier showed worse performance than the complete PIT fMRI classifier. This emphasizes the importance of PIT as a defining marker for addictive disorders beyond cue reactivity. Further, we saw that the complete PIT fMRI-behavior model performed better than the complete PIT fMRI model without behavioral parameters and better than the behavior-only model.[23] This suggests that PIT is not only behaviorally defined but may extend to multivariate neural signals enhancing the characterization of GD. The additional classificatory value of PIT-related neural signal should be explored in future studies. This is because different subjects may show different patterns/intensities related to the same PIT behavioral effect, and this in turn may be related to different levels of GD classification propensity. It may also mean that, in the long run, fMRI signal could enhance diagnostics in addictive and related disorders.[31,32,35]

We used the same cues as Genauck et al.[23] in a new sample of GD and HC subjects, and, in line with that study, we also observed that GD subjects rate the gambling cues as more craving inducing. Also in the other categories, cues were perceived as expected. The ratings and the result that neural PIT signatures successfully distinguish GD from HC subjects reinforce the notion that GD subjects' cue reactivity facilitates riskier decision making when addiction-related cues are presented in the background of a gamble task.

Changes in NAcc's structure[47] and function[22,25] related to GD have been observed in previous studies. The same is true for amygdala's structure[48] and function,[10] as well as for OFC's structure[49] and function.[5] Our study adds to these findings by considering the functions of these structures concurrently and in a network. Our results support the notion that GD, similar to SUD, is characterized by neural incentive sensitization[4,5] such that in GD a network of amygdala, NAcc and OFC facilitate gambling decisions in the face of gambling cues.

5 | STRENGTHS AND LIMITATIONS

The main strength of our study is that we have used a classification approach to assess the usefulness of known neural PIT contrasts to characterize GD in out-of-sample data. Using this approach, we have estimated the single-subject relevance of these fMRI signals. Our results therefore have not only explanatory value in elucidating the basis of increased PIT in GD, but also predictive value, given that they are likely to be found in new samples of GD and matched HC subjects.[34] Furthermore, we are to our knowledge the first to address the neural underpinnings of PIT in a behavioral addiction using a machine learning approach. Unfortunately, we have no independent validation sample to externally validate our results.[23,35] Further studies are needed to collect such data.

This study is driven by the question whether neural signatures related to addictive disorders (such as PIT-related neural signatures,

known from studies related to alcohol dependence) are dependent on a substance of abuse or perhaps on learning or even innate traits. We thus investigated an addictive disorder without a substance of abuse (GD) against HCs. However, a more direct test of this hypothesis would be to test directly against other substance-based addictive disorders.[10] This was not done in the current study but is an important perspective for future studies.

As we have laid out, there are multiple ways in which the brain may produce an overt PIT, involving at least amygdala, NAcc, and OFC. To increase statistical power, we have omitted other conceptualization of PIT, for example, as an interference task, and hence any limbic-dorso-lateral-prefrontal connectivity.[50] Future studies should explore this. In the current study, we did not address the distinction between outcome-specific and general PIT.[13,17,50] This would be a valuable next step for future studies in GD.

6 | CONCLUSION

We have observed that it is possible to classify HC and GD subjects on the basis of the neural correlates of PIT in a network of NAcc, amygdala, and OFC. Our findings further the understanding of GD and show that PIT is relevant for characterizing nonsubstance-related addictive disorders also on neural level. PIT alterations at the neural level related to an addictive disorder might thus not depend on the direct effect of a substance of abuse, but rather on related learning processes or even on innate traits.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

AG designed the experiment, collected the data, analyzed the data, and wrote the manuscript. CM reviewed the machine-learning algorithm and revised the manuscript. MA collected data and revised the manuscript. AH revised the manuscript and oversaw manuscript drafting. NK revised the manuscript and advised first author. LB collected and analyzed data. FC analyzed data and revised the manuscript. KD collected and analyzed data and revised the manuscript. NRS designed and supervised study and experiment and oversaw manuscript drafting and data analysis.

DATA AVAILABILITY STATEMENT

R code and data (stored in an RData file, which is loaded with the R code) to run the classifier estimation and cross-validation (i.e., extracted fMRI data and complete behavioral data) and the classical hierarchical regression analyses can be found in the following link. Further, you can find there also more detailed data concerning the MRI sequences, as well as the preprocessing of MRI data and the fMRI single subject design: http://doi.org/10.5281/zenodo.3966387 The complete raw and preprocessed fMRI data of this study are available from the corresponding author upon reasonable request.

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ORCID

Alexander Genauck https://orcid.org/0000-0002-9159-0709

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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