



Dopamine D2/3 receptor availability in alcohol use disorder and individuals at high risk: Towards a dimensional approach

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Funding information

Deutsche Forschungsgemeinschaft, Grant/Award Numbers: GA 707/6-1, HE 2597/14-1, HE 2597/14-2, HE 2597/15-1, HE 2597/15-2, RA 1047/2-1, RA 1047/2-2, SFB TRR 265

Abstract

Alcohol use disorder (AUD) is the most common substance use disorder worldwide. Although dopamine-related findings were often observed in AUD, associated neurobiological mechanisms are still poorly understood. Therefore, in the present study, we investigate D2/3 receptor availability in healthy participants, participants at high risk (HR) to develop addiction (not diagnosed with AUD), and AUD patients in a detoxified stage, applying ¹⁸F-fallypride positron emission tomography (¹⁸F-PET). Specifically, D2/3 receptor availability was investigated in (1) 19 low-risk (LR) controls, (2) 19 HR participants, and (3) 20 AUD patients after alcohol detoxification. Quality and severity of addiction were assessed with clinical questionnaires and (neuro)psychological tests. PET data were corrected for age of participants and smoking status. In the dorsal striatum, we observed significant reductions of D2/3 receptor availability in AUD patients compared with LR participants. Further, receptor availability in HR participants was observed to be intermediate between LR and AUD groups (linearly decreasing). Still, in direct comparison, no group difference was observed between LR and HR groups or between HR and AUD groups. Further, the score of the Alcohol Dependence Scale (ADS) was inversely correlated with D2/3 receptor availability in the combined sample. Thus, in line with a dimensional approach, striatal D2/3 receptor availability showed a linear decrease from LR participants to HR participants to AUD patients, which was paralleled by clinical measures. Our study shows that a core neurobiological feature in AUD seems to be detectable in an early, subclinical state, allowing more individualized alcohol prevention programs in the future.

KEYWORDS

alcohol, D2/3 receptors, dependence, dopamine, high risk, PET

T. Gleich and G. Spitta have contributed equally to this work.

[Correction added on 4 December 2020, after first online publication: Tobias Gleich was designated as co-corresponding author].

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1 | INTRODUCTION

Traditionally, mental diseases are diagnosed and treated based on discrete categories of symptom collections or patterns, observed to be present over a certain amount of time.¹ However, a categorical view of mental disease has recently been brought into question, in favor of a more dimensional and continuous approach.^{2–5} This approach goes in line with an etiological model of mental disease, the diathesis–stress model.⁶ Further support for a dimensional view comes from psychological and neurobiological studies, showing that severity of symptoms as well as temporal aspects of mental diseases are associated with rather continuous neurobiological changes in the brain.⁵ In addition, during remission of symptoms following psychotherapeutic or somatic treatment, neurobiological alterations occur, which predict future remission.^{7–10} Even though a large body of research on neurobiological changes in association with mental disease (e.g., depression and addiction) has been conducted, it is in general still poorly understood how neurobiological changes interact with psychological changes in the course of the development of mental diseases.

One of the major health related issues in modern society is addiction, especially related to alcohol. According to the World Health Organization (WHO), 3.3 million people worldwide are dying because of excessive alcohol consumption and its consequences every year.¹¹ With respect to the dimensional approach, boundaries of symptoms and consequences of moderate alcohol consumption, risky alcohol use, and alcohol dependence are fluent rather than categorical.¹² Although alcohol consumption broadly affects structural, functional, and neurochemical characteristics in the brain, specifically the dopamine (DA) system plays a key role in the development and maintenance of addiction.^{13,14} For instance, acute alcohol consumption causes increased DA release in the striatum.¹⁵ This increased DA release may further contribute to the rewarding effects of alcohol and seems to play an important role especially in early stages of alcohol use disorder (AUD).^{13,15–17} Additionally, in later stages of addiction, increased DA levels in the striatum have been found to be linked to cue-induced craving and further may predict relapse to a certain extent.^{18–20} Chronic alcohol consumption may lead to further long-lasting neurobiological changes, such as reduced dopamine receptor availability in the striatum, which seems to contribute to the maintenance of addictive behavior.^{19,21} However, because radioligand binding competes with endogenous dopamine, reduced receptor availability could also be due to sensitized dopamine release.^{22,23} Recently, the important role of decreased dopamine D2 receptor availability in addiction was described in a meta-analysis including mainly in vivo neuroimaging studies, showing that reduced dopamine D2/3 receptors in the striatum (particularly in the caudate and putamen) play a crucial role in the emergence and maintenance of AUD.¹⁴ This finding is further supported by a recent meta-analysis including mainly in vivo neuroimaging studies, showing reduced dopamine D2/3 receptors in the striatum, particularly in the caudate and putamen.¹⁴ Further, reduced D2/3 receptor availability in the putamen is associated with increased craving and frequency of alcohol intake.^{19,20} Eventually, successful treatment of AUD also may lead to

beneficial changes in brain structure and function, including changes associated to dopaminergic neurotransmission.^{24,25}

The dimensional approach towards mental disease predicts that dopamine receptors undergo progressive changes during the development of the disease. However, to our knowledge, dopamine D2/3 receptor availability and related clinical phenotypes have yet not been investigated in individuals at high risk (HR) to develop AUD. To gain more insight into the development of subclinical addiction, it is therefore important to investigate neurobiological trajectories of dopamine D2/3 receptor availability starting in preclinical states. Therefore, here we investigated D2/3 receptor availability in individuals with (1) low risk (LR) to develop AUD (healthy controls), (2) individuals at HR to develop AUD (HR participants), and (3) detoxified patients with a diagnosis of AUD. Further, we studied possible associations between drinking behavior (measured by clinical questionnaires) and D2/3 receptor availability.

In association with findings from earlier studies, we expect lower striatal D2/3 receptor availability in the HR and AUD groups compared with the LR group. We further hypothesize that D2/3 receptor availability in striatal subdivisions is different in HR participants compared with AUD patients. Additionally, we expect interactions between D2/3 receptor availability, region of interest (caudate nucleus and putamen nucleus accumbens), and group (LR/HR/AUD). Further, we expect clinical measures to be associated with changes in D2/3 availability.

2 | MATERIALS AND METHODS

2.1 | Participants

The present study is part of a multicenter project investigating neurobiological, reward-related deficiencies in AUD (see www.lead-studie.de; clinical trial number: NCT01679145; present sample contains data from subprojects “P2” and “P5”). Altogether, 58 participants were included in the final sample: 19 LR controls, 19 HR participants, and 20 AUD patients (see Supporting Information for more details on sample characteristics). HR participants compared with LR controls are considered to be at increased risk to develop AUD, owing to self-reported addiction-related symptoms. Thus, HR individuals experience addiction-related symptoms but however do not fulfill diagnostic criteria for addiction at time of diagnosis. AUD patients were recruited during detoxification treatment from hospitals in Berlin (see Supporting Information for recruitment locations; *Comment 1.*) and fulfilled DSM-IV-TR (American Psychiatric Association 2000) criteria for alcohol dependence for a duration of at least 3 years (diagnosed by a clinician in the respective facility). Additionally, diagnostic results were later confirmed during testing procedure (Composite International Diagnostic Interview [CIDI]).^{26,27} At the time of testing, participants were abstinent for at least 3 days (72 h). Only patients with low withdrawal symptom severity (score < 3 on the “Clinical Institute Withdrawal Assessment for Alcohol” [CIWA]) were included.

LR controls and HR participants were recruited via local online platforms and advertisements in supermarkets and newspapers. Participants were assigned to the LR/HR group based on the individual score in the Alcohol Use Disorders Identification Test (AUDIT).^{28,29} Subjects with an AUDIT score equal or below 8 were defined as LR control, a score above 8 was classified as HR control as described in the literature earlier.^{28,30} An advantage of the AUDIT is that it is widely used internationally for both clinical and research applications and is known for its validity and reliability. Mean AUDIT score was 4.67 (SD = 1.21) in the LR group and 12.32 (SD = 3.02) in the HR group. Also in LR/HR subjects, the CIDI was assessed to exclude alcohol dependency (as defined in DSM-IV). To exclude AUD in LR subjects, LR participants were selected based on the CIDI to exclude alcohol dependence and an alcohol abuse.^{26,27} And all LR subjects were free of AUD. Further, LR/HR participants were matched with AUD patients for gender, age, handedness, nicotine consumption, and education. Participants were instructed not to consume alcohol 24 h before positron emission tomography (PET) (which was verified using breath alcohol on the day of testing) and not to consume medication interacting with the central nervous system (CNS) 10 days prior to PET. Participants with substance dependence or current substance use (other than nicotine) were excluded, based on urine screening. Further, participants diagnosed with bipolar or psychotic disorders, major depressive disorder, generalized anxiety disorder, posttraumatic stress disorder (PTSD), borderline personality disorder, or obsessive-compulsive disorder based on DSM-IV criteria³¹ were excluded. Participants with neurological diseases, current pregnancy/nursing, or contraindications for magnetic resonance imaging (MRI) scanning were excluded. The study was approved by the Ethics Committee Charité – Universitätsmedizin Berlin (EA1/245/11). Experiments were carried out in accordance with the Declaration of Helsinki of 1975. More detailed information on recruitment and general procedure strategy is included in Figures S1, S2, and S4.

2.2 | Clinical assessment and psychological testing

At least 1 day before the MRI measurement and minimum 2 days before PET scanning, participants were informed and instructed on the background and procedures of the experiment. After signing written informed consent, participants underwent a standardized clinical

assessment (neuropsychological testing and questionnaires). In AUD patients, additional clinical information was collected from patient history files (see Tables 1 and S2 for details). The groups did not statistically differ in terms of gender (LR = 3/16; HR = 2/17; AUD = 3/17; female/male, respectively), smoking status (LR = 10/9; HR = 17/2; AUD = 16/3; smokers/nonsmokers, respectively), or age. One participant in the AUD group was left-handed; all other participants were right-handed (based on EHI). In AUD, the mean abstinence duration was 36.5 days (min. = 9; max. = 96; median = 29; SD = 20.1). One patient was measured delayed (after 96 days) owing to technical difficulties and an electricity failure at the PET scanner. For more detailed demographic and addiction related variables, see Tables 1 and S2. For a list of assessed questionnaires and clinically relevant information, see Tables S1 and S2.

2.3 | Magnetic resonance tomography

MRI was conducted at “Physikalisch-Technische Bundesanstalt” (PTB) in Berlin using a 3-Tesla scanner (Siemens Verio). Among other (functional) MRI sequences, T1-weighted MR images (MPRAGE, isotropic resolution 1.0 mm, TR = 2.3 s, TE = 3.03 ms, TI = 900 ms, flip angle 9°) were utilized for spatial normalization of the PET images.

2.4 | Positron emission tomography

2.4.1 | Acquisition

Dynamic PET imaging with a time-of-flight PET/CT system Philips Gemini TF 16³² started simultaneously with intravenous injection of ¹⁸F-fallypride. The injected dose of ¹⁸F-fallypride was 198.73 ± 14.0 MBq in the LR group, 194.38 ± 6.9 MBq in the HR group, and 197.49 ± 7.18 MBq in the AUD group. Injected ¹⁸F-fallypride mass was 3.7 ± 1.4, 3.1 ± 1.2, and 3.7 ± 1.4 µg in the LR group, in the HR group, and in the AUD group, respectively (ANOVA; $p = 0.351$). ANOVA with group as fixed factor and injected ¹⁸F-fallypride mass as covariate did not show a mass effect on the ¹⁸F-fallypride binding potential in bilateral PU ($p = 0.926$). There was no difference between the groups in injected dose of ¹⁸F-fallypride

TABLE 1 Demographic variables and clinical questionnaires

Variable (N _{LR} /N _{HR} /N _{AUD})	LR		HR		AUD		ANOVA	
	Mean (range)	SD	Mean (range)	SD	Mean (range)	SD	F	p
Age in years (19/19/20)	45.2 (30.8–1.8)	8.7	42.9 (26.8–7.6)	9.1	45.4 (29.4–58.3)	8.4	0.49	0.61
Education in years (19/17/20)	14.6 (8–21)	3.2	17.5 (12–31)	5.4	15.1 (10–23)	3.3	0.21	0.81
BMI (19/19/20)	25.6 (20.6–34.7)	4.1	27.26 (20.7–38)	4.5	26.77 (19.7–32.9)	26.8	0.90	0.41
ADS score (19/13/19)	3.2 (0–12)	3.8	5.97 (2–12)	3.2	17.05 (5–30)	6.3	43.37	0.01

Abbreviations: ADS, Alcohol Dependence Scale (ADS); AUD, alcohol use disorder group; BMI, body mass index; F/p, test value for test statistics of univariate analyses of variance (ANOVA); HR, high-risk group; LR, low-risk group; SD, standard deviation.

($F(2,55)$ (factor group) = 0.98; $p = 0.38$).^{33,34} PET data were acquired for 4 h after FP administration in three successive blocks with a break between each block³⁵ and in three successive blocks each of 30-min duration (Figure S3). The first block (3 × 20 s, 3 × 1 min, 3 × 2 min, 2 × 5 min, 1 × 10 min) started with the intravenous tracer injection. The second and third blocks (both 3 × 10 min) started 60 and 210 min after tracer injection, respectively. A low-dose CT for attenuation correction was performed before each block. Transaxial PET images were reconstructed using the iterative LOR-RAMLA algorithm of the scanner software with default parameter settings for brain (three iterations, 33 subsets, “normal” relaxation).

Spatial resolution in the reconstructed PET images was about 7-mm full width at half maximum. Head motion during an emission block was corrected by frame-wise realignment using the realign tool of the Statistical Parametric Mapping software package (SPM8, Wellcome Department of Imaging Neuroscience, Institute of Neurology, London; <http://www.fil.ion.ucl.ac.uk/spm/>). The second and third PET blocks were coregistered to the first block using the coregistration tool of SPM8. Then, all PET frames were coregistered to the subject's MPRAGE MRI using the sum of early PET frames (perfusion phase) as source image.

2.4.2 | Processing of PET data

Voxel-by-voxel parametric maps of the nondisplaceable FP binding potential (BP_{ND}) were obtained by the two-step simplified reference tissue method (SRTM) for noise reduction by use of a global rate constant of tracer clearance from the reference region.³⁶ The latter was obtained by conventional SRTM modeling of the FP time activity curve of the whole bilateral striatum. BP_{ND} is the ratio of specifically bound FP (to D2/D3 receptors) to that of nondisplaceable FP (by competition with dopamine) at equilibrium.³⁷ The bilateral superior longitudinal fasciculus (SLF) as defined by the white-matter tractography atlas provided by the Laboratory of Brain Anatomical MRI of Johns Hopkins University (Hua et al. 2008) was used as reference region, as it has been suggested that white matter regions increase statistical power of FP PET in comparison with grey matter structures.³⁸ For discussion with regard to application of the SLF as reference region, see our recently published study.³⁹ Individual T1 images were spatially normalized into the anatomical space of the Montreal Neurological Institute (MNI) using the unified segmentation approach.⁴⁰ The subject's BP_{ND} map and individual regions of interest (ROI; see next section) were normalized into MNI space by the same transformation routine.

2.4.3 | Statistical analyses of ¹⁸F-fallypride and clinical measures

We extracted BP_{ND} from striatal subregions (caudate nucleus [CA]; putamen [PU]; nucleus accumbens [NA]) in SPM8 using subject-specific ROIs based on anatomical landmarks, produced via automatic

segmentation algorithms in the FMRIB Software Library (FSL).⁴¹ We used bilateral instead of unilateral ROIs to enhance statistical power. Group comparisons and associations of BP_{ND} with clinical data were conducted using IBM SPSS Statistics Version 24.0 for Windows (IBM Corp., Armonk, NY). Normal distribution of clinical data and BP_{ND} was investigated via Shapiro–Wilk tests in SPSS; data were normally distributed.

For group comparisons, we conducted a multivariate analysis of variance (MANOVA), investigating BP_{ND} in bilateral subregions of the striatum (CA/PU/NA), comparing between the three groups (LR/HR/AUD). As test statistic, Wilks' lambda was used. We investigated differences in BP_{ND} in PU, CA, and NA via group effects. Age (in years) of participants and smoking status were included as covariates, as it has been shown that both factors independently influence the dopamine receptor status.^{42–45} Age was correlated with BP_{ND} in the CA ($r = -0.30$; $p = 0.02$) and PU ($r = -0.40$; $p = 0.01$). Additionally, in the “smoker” group, D2/3 receptor availability was lower than in the “nonsmokers” (CA: mean difference = 2.02, $t = 2.95$, $df = 56$, $p = 0.01$. PU: mean difference = 1.87, $t = 2.56$, $df = 56$, $p = 0.01$, $N = 15/43$; nonsmokers/smokers, respectively). To analyze the relationship between state of addiction and BP_{ND} , planned contrast weights were investigated for a (negative) quadratic (LR > HR < HR), as well as linear (negative) relationship between BP_{ND} and group (LR > HR > AUD). Whereas a negative quadratic effect would support a categorical approach, where neurobiological alterations only occur in the presence of the observed disorder (AUD), a linear relationship would support a dimensional, continuous approach, where neurobiological alterations correlate with symptom severity.

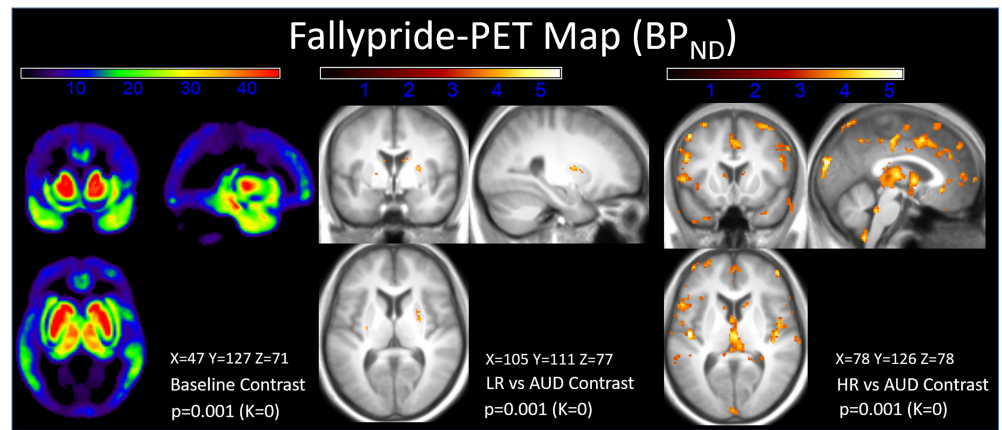
Additionally, post hoc group comparisons were conducted as two sample t tests. We further calculated Pearson correlation coefficients (partial correlations; ρ) to investigate correlations between BP_{ND} with the ADS scale. Additionally, mainly for visual purposes, exploratory whole brain analyses were conducted (voxel-wise, one-way, between-group ANOVA; factor: “group” [LR, HR, AUD]; covariates: age in years, smoking status), followed by post hoc tests (two-sample t tests).

3 | RESULTS

3.1 | Voxel-wise whole brain analysis of dopamine receptor availability

Voxel-wise, whole brain analyses throughout the sample (LR, HR, and AUD; baseline contrast and for group comparisons LR–AUD; HR–AUD) revealed the highest BP_{ND} in striatal areas as expected, alongside with broad but weaker BP_{ND} in cortical areas. Mainly striatal differences were observed between the LR and AUD group. Comparing HR with AUD subjects, again striatal differences were visible, but also differences in BP_{ND} in neocortical areas were observed (Figure 1). No differences were present between LR and HR groups (not shown).

FIGURE 1 Baseline contrast and main group comparisons of BP_{ND}; color bars represent *F* values for the baseline contrast and *t*-values for group comparisons (LR vs. AUD; HR vs. AUD); voxel-wise analysis was mainly performed for visual purposes and comparability with earlier studies



3.2 | Multivariate results

The MANOVA results regarding BP_{ND} in the CA, PU, and NA revealed global differences in mean BP_{ND} between the groups ($W = 0.77$, $F(6,104) = 2.42$, $p = 0.03$, partial eta squared = 0.13).

TABLE 2 Mean BP_{ND} in subregions of the striatum

Region	Group	N	Mean (SD)
Putamen (PU)	LR controls	19	28.43 (2.85)
	HR participants	19	27.43 (1.93)
	AUD patients	20	26.31 (2.45)
Caudate (CA)	LR controls	19	22.23 (2.26)
	HR participants	19	22.37 (1.98)
	AUD patients	20	20.70 (2.71)
Nc. Accumbens (NA)	LR controls	19	22.11 (2.69)
	HR participants	19	21.36 (2.66)
	AUD patients	20	21.64 (2.36)

Abbreviations: AUD, alcohol disorder; HR, high risk; LR, low risk; N, number of participants per group; SD, standard deviation.

3.3 | Group differences of BP_{ND} within striatal subdivisions

Univariate group effects showed a significant difference in BP_{ND} in the CA ($F(2,53) = 3.09$, $p = 0.05$) and marginally significant results in the PU ($F(2,53) = 3.68$, $p = 0.06$). No significant differences were found in the NA.

To analyze an assumed ranking of the groups with regard to the BP_{ND} (LR > HR > AUD), planned contrast weights were investigated with regard to linear/quadratic, negative relationships. A negative linear relationship between group and BP_{ND} was present in the PU ($d = -1.23$, $p = 0.02$), but not in the CA ($d = -1.68$, $p = 0.17$) or NA ($d = -1.28$, $p = 0.88$). Also, a marginally significant quadratic relationship was present in the CA ($d = -1.08$, $p = 0.06$), but not in the PU ($d = -1.17$, $p = 0.81$) or NA ($d = -0.94$, $p = 0.65$). Mean BP_{ND} per group is reported in Table 2; individual data are presented in Figure 2.

Post hoc contrasts revealed that AUD compared to LR subjects had significantly lower BP_{ND} in the PU ($d = 1.74$, $p = 0.03$). AUD patients compared to HR subjects had lower BP_{ND} in the CA ($d = 1.70$, $p = 0.03$). No further significant differences were observed between the groups.

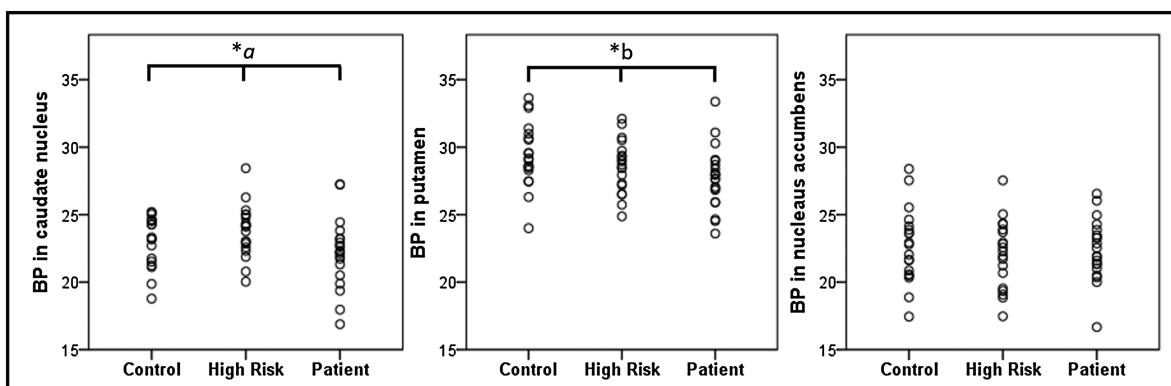


FIGURE 2 **a*: Marginally significant negative quadratic relationship ($p = 0.06$; quadratic contrast). **b*: Significant negative linear relationship (linear contrast; $p < 0.05$); further results of direct group comparisons are reported in the results section. Control = low-risk group; high risk = high-risk group; patient = AUD group. Shown data are corrected for age and smoking status

3.4 | BP_{ND} and ADS scale-related findings

The groups differed significantly from each other in terms of ADS score (see Table 1 for descriptives and ANOVA). The LR group had a lower mean ADS score compared to the HR group ($t = -2.16$, $df = 30$, $p = 0.04$), whereas the AUD group had a higher ADS mean score than had the HR group ($t = -5.80$, $df = 30$, $p = 0.01$). In the whole sample, we observed a significant negative correlation between the ADS score and BP_{ND} in the CA ($df = 47$, $r = -0.32$, $p = 0.03$, Figure 3) and a marginally significant correlation with the PU ($df = 47$, $r = -0.27$, $p = 0.06$, Figure 3). No significant correlations were observed within subgroups.

4 | DISCUSSION

In the present study, we investigated striatal D2/3 receptor availability in recently abstinent alcohol addicted patients, subjects with increased risk for AUD and low alcohol consuming healthy controls. Differences in striatal D2/3 receptor availability between the three reference groups were observed in the PU and CA subregions. Although, striatal D2/3 receptor availability in the PU and CA did not differ between the LR and HR group in direct comparison, a significant linear relationship was present between disease state and D2/3 availability in the PU throughout the whole sample. Those findings support the view of a continuous decrease of striatal D2/3 receptor availability during the development of AUD but may also reflect a predisposition to a differing extent in the subgroups. HR participants showed increased D2/3 receptor availability compared to LR and AUD groups in the CA (marginally significant). Further, D2/3 receptor availability was related to the sum score of the ADS scale in the whole sample.

4.1 | Group differences

Along with our hypotheses, we observed differences in the striatal postsynaptic dopaminergic neurotransmitter system between groups of subjects with different alcohol use behavior. Specifically, alterations in BP_{ND} measured by ¹⁸F-fallypride PET were shown in the PU and the CA. The present findings are in line with several recent PET studies, which found decreased D2-receptors in the striatum in AUD

patients compared with controls.^{19,20,46–50} However, in earlier studies using [¹¹C]raclopride-PET, decreased D2/3 receptor availability was observed in the NA of AUD patients,^{46,51,52} in contrary to the present study. Still, in line with the present study, two studies that applied ¹⁸Ffallypride-PET reported no significant baseline differences in striatal D2/3 receptor availability,⁵³ or no baseline difference, but increased striatal D2/3 receptor availability during detoxification.⁴³ Subsequently, it seems that in studies applying ¹⁸Ffallypride-PET in AUD, ventral-striatal differences in D2/3 receptor availability are consistently absent, whereas in studies applying [¹¹C]raclopride-PET, they are consistently present.

In general, dopamine neurotransmission (including receptor availability/density) in AUD may further depend on progress of addiction, as well as environmental, psychological, and biological factors (e.g., genetics).^{9,10,23} In accordance, Koob and Volkow¹³ argue that both the DS and NA contribute to the development and maintenance of AUD.¹³ The authors hypothesize that the transition towards alcohol dependence involves impairments of the NA, the DS, the orbitofrontal cortex, prefrontal cortex, cingulate gyrus, and the extended amygdala. Neurobiological mechanisms leading to the shift in signaling from NA to DS might be regulated via ascending spiral connections in the midbrain.^{54,55} Although, in earlier studies, differences in D2/3 availability were observed during detoxification, time-related factors were approached in a different way. For instance, delay between starting date of hospitalization for the detoxification therapy and time of PET measurement was more constraint in comparison with the present study.¹⁹ Receptor changes in AUD may further depend on stage of addiction, environment, and genetics. Further, dopaminergic changes may be specific with regard to subdivisions of the striatum (e.g., PU/CA/NA). Thus, we interpret our findings in the PU and CA as being specific to the disease state of AUD patients in our sample. Those changes may also relate to psychological symptoms (e.g., craving) during the course of detoxification. With regard to the NA, D2/3 receptors may recover as a result of the absence of ongoing acute effects of alcohol and may eventually return to a level comparable with LR controls and HR participants. As we did not find any relationship between duration of detoxification and D2/3 receptor availability, the time window of dopamine receptor levels in the NA returning to a preclinical stage might be relatively short, leading to differences compared with earlier studies.¹⁹ In contrast,

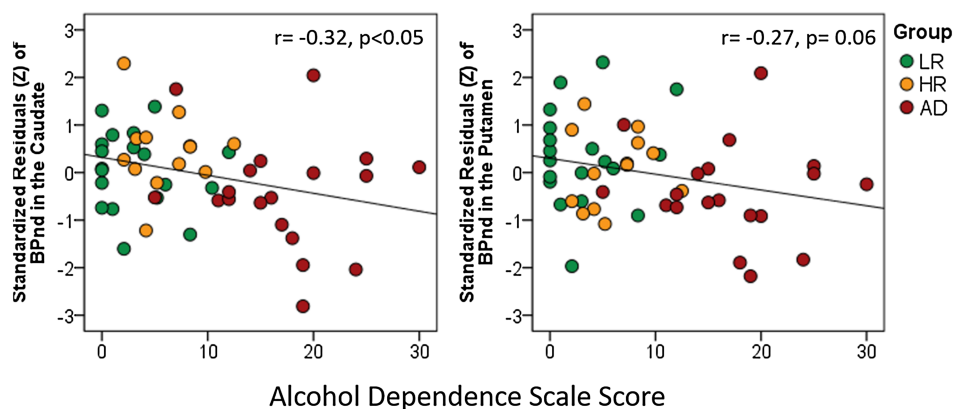


FIGURE 3 Scatterplot for the relationship between the standardized residuals of BP_{ND} in the caudate with the “Alcohol Dependence Scale” (ADS). Data are corrected for age and smoking status. AUD, alcohol use disorder group; HR, high-risk group; LR, low-risk group

differences in D2/3 receptor availability in PU and CA may be long lasting; however, future research is needed for clarification.

Further, the present findings not only may be due to alcohol effects on dopaminergic neurotransmission but also reflect a genetically or epigenetically determined predisposition.^{56,57} HR individuals may have an intermediately strong predisposition for alcoholism, compared with a strong predisposition in AUD patients. Further, we found a trend towards quadratic change in the CA. However, dopamine receptor sensitivity was found to quickly recover following detoxification, and density was unaltered post mortem, pointing towards more dynamic alterations.^{9,23}

4.2 | Differences specific to HR individuals

Although we did not observe a difference in D2/3 receptor availability between HR and LR participants in direct comparison, we observed a linear decrease (LR > HR > AUD) in D2/3 receptor availability in the PU. Thus, our findings support the proposed dimensional approach towards biological changes in AUD. Interestingly, the present results point to a quadratic change in the CA, which might reflect a rather categorical type of change (only trend-wise). Further, another study observed reduced dopamine D2 levels in the caudate and putamen of patients with alcohol dependence versus controls during early abstinence but no significant recovery.⁴⁹ In general, the negative relationship between the severity of alcohol dependence and striatal D2/3 receptor availability supports assumptions of a compensatory downregulation of D2/3 receptors due to chronic alcohol intake, notwithstanding the possibility of predispositions and alterations in dopamine receptor availability, density or sensitivity. In the framework of the proposed dimensional view, we believe that the relationship between the severity of alcohol dependence and lowered dorso-striatal D2/3 receptor availability may contribute to a gradual loss of control over drinking behavior.⁵⁸ In line with the present study, Volkow et al.⁴⁹ observed a striatal D2/3 receptor reduction in the CA and PU in an early state of detoxification. Interestingly, in a late stage of detoxification (4 months), reduction in striatal D2/3 receptors was limited to the CA. Additionally, other studies reported recovery of striatal D2/3 receptors in four out of 17 AUD subjects during detoxification, whereas mean receptor levels were not different.^{43,49} Thus, future studies should investigate more closely, whether decreased D2/3 receptor density in the CA during late detoxification may point to different involvement of the CA and PU during the course of AUD on and treatment.

It is important to note that HR participants had much broader and more variable D2/3 receptor availability in many different brain regions, including prefrontal, insular, and hippocampal areas (see Figure 1). This is in line with earlier studies, where it was proposed that transition towards addiction may involve dopaminergic factors in the orbitofrontal cortex, prefrontal cortex, cingulate gyrus, and the extended amygdala.¹³ We believe that extra-striatal changes in D2/3 receptor availability might be modulated via changes in cortico-striatal connectivity, involving additional

neurotransmitter systems (e.g., glutamate and GABA) as proposed in addiction and other mental diseases in earlier studies.⁵⁹ However, the discussion of those results is beyond the aim of the present study (manuscript in preparation).

4.3 | Dopamine receptor availability and alcohol dependence scale

Severity of alcohol dependence, measured with the ADS-Score, was related to DR2/3 availability in the CA in the whole sample. In general, the negative relationship between the severity of alcohol dependence and striatal D2/3 receptor availability underlines the theory of a compensatory downregulation of D2/3 receptors due to chronic alcohol intake but may also reflect lowered D2/3 receptor availability as a potential predisposition to developing an AUD. However, in the framework of the proposed dimensional view, we believe that the relationship between the severity of alcohol dependence and lowered dorso-striatal D2/3 receptor availability represents a gradual loss of control over drinking behavior and its possible neurobiological correlates.⁵⁸

5 | LIMITATIONS

We did not find differences in D2/3 receptor availability in the striatum between the LR and HR groups. Still, as described above, we found a negative correlation between addiction severity and D2/3 receptor availability in the PU.

Further, during voxel-based group comparisons of D2/3 receptor availability, we observed broad extrastriatal differences between the groups. The discussion of those results is beyond the scope of the present study.

It is important to note that in past research on D2/3 receptors in human individuals, highly variable methods of investigation and analysis were utilized. For instance, instead of rather than ¹⁸F-fallypride PET as in the present study, [¹¹C]raclopride-PET^{46,48,49} or [¹⁸F] desmethoxyfallypride-PET^{19,20} was used. Additionally, among other studies, highly variable ROI approaches have been applied. For instance, the whole striatum,^{20,48} anatomically defined structural subdivisions,^{19,49} as well as functionally associated striatal subdivisions⁶⁰ were applied. Further, due to the cross-sectional design in the present study, we cannot make any claims about causality. Future research should investigate larger samples to rule out those issues.

6 | CONCLUSION

In summary, our study confirmed previous reports suggesting reduced availability of dopamine D2 receptors in the dorsal striatum of detoxified patients and suggests that HR AUD patients are in between low-risk healthy controls and patients with alcohol dependence. Prospective studies with repeated measurements should capture the

dynamics and behavioral correlates of dopamine D2 receptor availability in alcohol use disorders.

ACKNOWLEDGEMENT

The present work was supported by grants from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, FOR 1617: grants HE 2597/14-1, HE 2597/15-1, HE 2597/14-2, HE 2597/15-2, GA 707/6-1, RA 1047/2-1, RA 1047/2-2; as well as DFG grant CRC TRR 265). The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

AUTHOR CONTRIBUTIONS

JG, MR, AH, and FS were responsible for the study concept and design. TG and GS analyzed and interpreted the data and wrote the draft. OB, KZ, MS, SA, RB, GS, and MG further designed the experimental procedures and collected the data. All authors critically reviewed the content and approved the final version of the manuscript for publication.

/CONFLICT OF INTEREST

TG, GS, OB, KZ, SA, MS, MG, MR, FS, RB, AH, and JG declare no potential conflict of interest.

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REFERENCES

- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC; 2013.
- Heinz A, Schmidt LG, Reischies FM. Anhedonia in schizophrenic, depressed, or alcohol-dependent patients—neurobiological correlates. *Pharmacopsychiatry*. 1994;27(Suppl 1):7-10. <https://doi.org/10.1055/s-2007-1014317>
- Krueger RF, Markon KE. The role of the DSM-5 personality trait model in moving toward a quantitative and empirically based approach to classifying personality and psychopathology. *Annu Rev Clin Psychol*. 2014;10:477-501. <https://doi.org/10.1146/annurev-clinpsy-032813-153732>
- Waszczuk MA, Zimmerman M, Ruggero C, et al. What do clinicians treat: diagnoses or symptoms? The incremental validity of a symptom-based, dimensional characterization of emotional disorders in predicting medication prescription patterns. *Compr Psychiatry*. 2017;79:80-88. <https://doi.org/10.1016/j.comppsy.2017.04.004>
- Krueger RF, Kotov R, Watson D, et al. Progress in achieving quantitative classification of psychopathology. *World Psychiatry*. 2018;17(3):282-293. <https://doi.org/10.1002/wps.20566>
- Tambis K, Czajkowsky N, Røysamb E, et al. Structure of genetic and environmental risk factors for dimensional representations of DSM-IV anxiety disorders. *Br J Psychiatry*. 2009;195(4):301-307. <https://doi.org/10.1192/bjp.bp.108.059485>
- Becker A, Gerchen MF, Kirsch M, Hoffmann S, Kiefer F, Kirsch P. Striatal reward sensitivity predicts therapy-related neural changes in alcohol addiction. *Eur Arch Psychiatry Clin Neurosci*. 2018;268(3):231-242. <https://doi.org/10.1007/s00406-017-0805-y>
- Ekhtiari H, Rezapour T, Aupperle RL, Paulus MP. Neuroscience-informed psychoeducation for addiction medicine: a neurocognitive perspective. *Prog Brain Res*. 2017;235:239-264. <https://doi.org/10.1016/bs.pbr.2017.08.013>
- Heinz A, Deserno L, Zimmermann US, Smolka MN, Beck A, Schlagenhauf F. Targeted intervention: computational approaches to elucidate and predict relapse in alcoholism. *Neuroimage*. 2017;151:33-44. <https://doi.org/10.1016/j.neuroimage.2016.07.055>
- Sebold M, Nebe S, Garbusow M, et al. When habits are dangerous: alcohol expectancies and habitual decision making predict relapse in alcohol dependence. *Biol Psychiatry*. 2017;82(11):847-856. <https://doi.org/10.1016/j.biopsych.2017.04.019>
- World Health Organisation. Global status report on alcohol and health. 2014.
- Saitz R. Unhealthy alcohol use. *New England Journal of Medicine*. 2005;352(6):596-607. <https://doi.org/10.1056/NEJMc042262>
- Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2010;35(1):217-238. <https://doi.org/10.1038/npp.2009.110>
- Kamp F, Proebstl L, Penzel N, Adorjan K, Ilankovic A, Pogarell O, Koller G, Soyka M, Falkai P, Koutsouleris N, Kambitz J. Effects of sedative drug use on the dopamine system: a systematic review and meta-analysis of in vivo neuroimaging studies. *Neuropsychopharmacology* August 2018. <https://doi.org/10.1038/s41386-018-0191-9>, 44, 4, 660, 667
- Di Chiara G. Alcohol and dopamine. *Alcohol Health Res World*. 1997;21(2):108-114.
- Boileau I, Assaad J-M, Pihl RO, et al. Alcohol promotes dopamine release in the human nucleus accumbens. *Synapse*. 2003;49(4):226-231. <https://doi.org/10.1002/syn.10226>
- Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science*. 1997;275(5306):1593-1599.
- Schuckit MA. Alcohol and Alcoholism. In: *Harrison's Principles of Internal Medicine*. 18th ed. New York, NY: McGraw-Hill; 2016.
- Heinz A, Siessmeier T, Wrase J, et al. Correlation between dopamine D2 receptors in the ventral striatum and central processing of alcohol cues and craving. *AJP*. 2004;161(10):1783-1789. <https://doi.org/10.1176/ajp.161.10.1783>
- Heinz A, Siessmeier T, Wrase J, et al. Correlation of alcohol craving with striatal dopamine synthesis capacity and D2/3 receptor availability: a combined [¹⁸F]DOPA and [¹⁸F]DMFP PET study in detoxified alcoholic patients. *AJP*. 2005;162(8):1515-1520. <https://doi.org/10.1176/appi.ajp.162.8.1515>
- Heinz A. Dopaminergic dysfunction in alcoholism and schizophrenia—psychopathological and behavioral correlates. *Eur Psychiatry*. 2002;17(1):9-16.
- Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev*. 1993;18(3):247-291.
- Hirth N, Meinhardt MW, Noori HR, et al. Convergent evidence from alcohol-dependent humans and rats for a hyperdopaminergic state in protracted abstinence. *Proc Natl Acad Sci U S A*. 2016;113(11):3024-3029. <https://doi.org/10.1073/pnas.1506012113>
- Barsaglini A, Sartori G, Benetti S, Pettersson-Yeo W, Mechelli A. The effects of psychotherapy on brain function: a systematic and critical review. *Prog Neurobiol*. 2014;114:1-14. <https://doi.org/10.1016/j.pneurobio.2013.10.006>
- Kühn S, Charlet K, Schubert F, et al. Plasticity of hippocampal subfield volume cornu ammonis 2+3 over the course of withdrawal in patients with alcohol dependence. *JAMA Psychiat*. 2014;71(7):806-811. <https://doi.org/10.1001/jamapsychiatry.2014.352>
- Jacobi F, Mack S, Gerschler A, et al. The design and methods of the mental health module in the German Health Interview and Examination Survey for Adults (DEGS1-MH). *Int J Methods Psychiatr Res*. 2013;22(2):83-99. <https://doi.org/10.1002/mpr.1387>
- Wittchen HU, Pfister H. *DIA-X-Interviews: Manual Fur Screening-Verfahren Und Interview; Interviewheft Langsschnittuntersuchung*

- (DIA-X-Lifetime); *Erganzungsheft (DIA-X-Lifetime)*; *Interviewheft Querschnittuntersuchung (DIA-X-12 Monate)*; *Erganzungsheft (DIA-X-12Monate)*; *PC-Programm Zur Durchföhrung Des Interviews (Langsund Querschnittuntersuchung)*; *Auswertungsprogramm*. Frankfurt: Swets & Zeitlinger; 1997.
28. Saunders JB, Aasland OG, Babor TF, De La Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction*. 1993;88(6):791-804. <https://doi.org/10.1111/j.1360-0443.1993.tb02093.x>
 29. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med*. 1998;158(16):1789-1795.
 30. Conigrave KM, Hall WD, Saunders JB. The AUDIT questionnaire: Choosing acut-off score. Alcohol Use Disorder Identification Test. *Addiction*. 1995;90(10):1349-1356.
 31. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. , Text Rev. Washington, DC; 2000.
 32. Surti S, Kuhn, A, Werner ME, Perkins AE, Kolthammer J, Karp JS. Performance of Philips Gemini TF PET/CT scanner with special consideration for its time-of-flight imaging capabilities. *J Nucl Med*. 2007; 48(3):471-480.
 33. Mukherjee J, Yang ZY, Das MK, Brown T. Fluorinated benzamide neuroleptics—III. Development of (S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-[¹⁸F]fluoropropyl)-2,3-dimethoxybenzamide as an improved dopamine D-2 receptor tracer. *Nucl Med Biol*. 1995;22(3):283-296.
 34. Slifstein M, Hwang D-R, Huang Y, et al. In vivo affinity of [¹⁸F] fallypride for striatal and extrastrialdopamine D2 receptors in non-human primates. *Psychopharmacology*. 2004;175(3):274-286. <https://doi.org/10.1007/s00213-004-1830-x>
 35. Slifstein M, Kegeles LS, Xu X, et al. Striatal and extrastrialdopamine release measured with PET and [(18)F] fallypride. *Synapse*. 2010; 64(5):350-362. <https://doi.org/10.1002/syn.20734>
 36. Wu Y, Carson RE. Noise reduction in the simplified reference tissue model for Neuroreceptor Functional Imaging. *J Cereb Blood Flow Metab*. 2002;22(12):1440-1452. <https://doi.org/10.1097/01.WCB.0000033967.83623.34>
 37. Innis RB, Cunningham VJ, Delforge J, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *Journal of Cerebral Blood Flow & Metabolism*. 2007;27(9):1533-1539. <https://doi.org/10.1038/sj.jcbfm.9600493>
 38. Ishibashi K, Robertson CL, Mandelkern MA, Morgan AT, London ED. The simplified reference tissue model with ¹⁸F-fallypride PET: Choice of reference region. *Mol Imaging*. 2013;12(8). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4103900/>
 39. Sebold M, Spitta G, Gleich T, et al. Stressful life events are associated with striatal dopamine receptor availability in alcohol dependence. *J Neural Transm (Vienna)*. February 2019;126(9):1127-1134. <https://doi.org/10.1007/s00702-019-01985-2>
 40. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage*. 2005; 26(3):839-851. <https://doi.org/10.1016/j.neuroimage.2005.02.018>
 41. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. *Neuroimage*. 2012;62(2):782-790. <https://doi.org/10.1016/j.neuroimage.2011.09.015>
 42. Fehr C, Yakushev I, Hohmann N, et al. Association of low striatal dopamine D2 receptor availability with nicotine dependence similar to that seen with other drugs of abuse. *AJP*. 2008;165(4):507-514. <https://doi.org/10.1176/appi.ajp.2007.07020352>
 43. Rominger A, Cumming P, Xiong G, et al. [¹⁸F]fallypride PET measurement of striatal and extrastriatal dopamine D_{2/3} receptor availability in recently abstinent alcoholics. *Addict Biol*. 2012;17(2):490-503. <https://doi.org/10.1111/j.1369-1600.2011.00355.x>
 44. Albrecht DS, Kareken DA, Yoder KK. Effects of smoking on D/D striatal receptor availability in alcoholics and social drinkers. *Brain Imaging Behav*. 2013;7(3):326-334. <https://doi.org/10.1007/s11682-013-9233-4>
 45. Wiers CE, Cabrera EA, Tomasi D, et al. Striatal dopamine D2/D3 receptor availability varies across smoking status. *Neuropsychopharmacology*. June 2017;42(12):2325-2332. <https://doi.org/10.1038/npp.2017.131>
 46. Martinez D, Gil R, Slifstein M, et al. Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. *Biol Psychiatry*. 2005;58(10):779-786. <https://doi.org/10.1016/j.biopsych.2005.04.044>
 47. Ravan S, Martinez D, Slifstein M, Abi-Dargham A. Molecular imaging in alcohol dependence. *Handb Clin Neurol*. 2014;125:293-311. <https://doi.org/10.1016/B978-0-444-62619-6.00018-5>
 48. Volkow ND, Wang G-J, Fowler JS, et al. Decreases in dopamine receptors but not in dopamine transporters in alcoholics. *Alcohol Clin Exp Res*. 1996;20(9):1594-1598. <https://doi.org/10.1111/j.1530-0277.1996.tb05936.x>
 49. Volkow ND, Wang G-J, Maynard L, et al. Effects of alcohol detoxification on dopamine D2 receptors in alcoholics: a preliminary study. *Psychiatry Res*. 2002;116(3):163-172.
 50. Volkow ND, Wang G-J, Telang F, et al. Profound decreases in dopamine release in striatum in detoxified alcoholics: possible orbitofrontal involvement. *J Neurosci*. 2007;27(46):12700-12706. <https://doi.org/10.1523/JNEUROSCI.3371-07.2007>
 51. Tupala E, Hall H, Bergström K, et al. Dopamine D(2)/D(3)-receptor and transporter densities in nucleus accumbens and amygdala of type 1 and 2 alcoholics. *Mol Psychiatry*. 2001;6(3):261-267. <https://doi.org/10.1038/sj.mp.4000859>
 52. Tupala E, Hall H, Bergström K, et al. Different effect of age on dopamine transporters in the dorsal and ventral striatum of controls and alcoholics. *Synapse*. 2003;48(4):205-211. <https://doi.org/10.1002/syn.10206>
 53. Spreckelmeyer KN, Paulzen M, Raptis M, et al. Opiate-induced dopamine release is modulated by severity of alcohol dependence: an [¹⁸F] fallypride positron emission tomography study. *Biol Psychiatry*. 2011; 70(8):770-776. <https://doi.org/10.1016/j.biopsych.2011.05.035>
 54. Haber SN, Fudge JL, McFarland NR. Striatonigrostriatal pathways in Primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci*. 2000;20(6):2369-2382. <https://doi.org/10.1523/JNEUROSCI.20-06-02369.2000>
 55. Ikemoto S. Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. *Brain Res Rev*. 2007;56(1):27-78. <https://doi.org/10.1016/j.brainresrev.2007.05.004>
 56. Comings DE, Blum K. Reward deficiency syndrome: genetic aspects of behavioral disorders. *Prog Brain Res*. 2000;126:325-341. [https://doi.org/10.1016/S0079-6123\(00\)26022-6](https://doi.org/10.1016/S0079-6123(00)26022-6)
 57. Schellekens AFA, Franke B, Ellenbroek B, et al. Reduced dopamine receptor sensitivity as an intermediate phenotype in alcohol dependence and the role of the COMT Val158Met and DRD2 Taq1A genotypes. *Arch Gen Psychiatry*. 2012;69(4):339-348. <https://doi.org/10.1001/archgenpsychiatry.2011.1335>
 58. Everitt BJ, Belin D, Economidou D, Pelloux Y, Dalley JW, Robbins TW. Review. Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. *Philos Trans R Soc Lond B Biol Sci*. 2008;363(1507):3125-3135. <https://doi.org/10.1098/rstb.2008.0089>
 59. Gleich T, Deserno L, Lorenz RC, et al. Prefrontal and striatal glutamate differently relate to striatal dopamine: potential regulatory mechanisms of striatal presynaptic dopamine function? *J Neurosci*. 2015; 35(26):9615-9621. <https://doi.org/10.1523/JNEUROSCI.0329-15.2015>

60. Martinez D, Gil R, Slifstein M, et al. Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. *Biol Psychiatry*. 2005;58(10):779-786.

SUPPORTING INFORMATION

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

How to cite this article: Gleich T, Spitta G, Butler O, et al. Dopamine D2/3 receptor availability in alcohol use disorder and individuals at high risk: Towards a dimensional approach. *Addiction Biology*. 2021;26:e12915. <https://doi.org/10.1111/adb.12915>