

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

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## 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 <sup>18</sup>F-fallypride positron emission tomography (<sup>18</sup>F-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.<sup>1</sup> However, a categorical view of mental disease has recently been brought into question, in favor of a more dimensional and continuous approach.<sup>2–5</sup> This approach goes in line with an etiological model of mental disease, the diathesis–stress model.<sup>6</sup> 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.<sup>5</sup> In addition, during remission of symptoms following psychotherapeutic or somatic treatment, neurobiological alterations occur, which predict future remission.<sup>7–10</sup> 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.<sup>11</sup> 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.<sup>12</sup> 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.<sup>13,14</sup> For instance, acute alcohol consumption causes increased DA release in the striatum.<sup>15</sup> 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).<sup>13,15–17</sup> 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.<sup>18–20</sup> 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.<sup>19,21</sup> However, because radioligand binding competes with endogenous dopamine, reduced receptor availability could also be due to sensitized dopamine release.<sup>22,23</sup> 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.<sup>14</sup> 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.<sup>14</sup> Further, reduced D2/3 receptor availability in the putamen is associated with increased craving and frequency of alcohol intake.<sup>19,20</sup> Eventually, successful treatment of AUD also may lead to

beneficial changes in brain structure and function, including changes associated to dopaminergic neurotransmission.<sup>24,25</sup>

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](http://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]).<sup>26,27</sup> 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).<sup>28,29</sup> 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.<sup>28,30</sup> 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.<sup>26,27</sup> 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 criteria<sup>31</sup> 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 16<sup>32</sup> started simultaneously with intravenous injection of <sup>18</sup>F-fallypride. The injected dose of <sup>18</sup>F-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 <sup>18</sup>F-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 <sup>18</sup>F-fallypride mass as covariate did not show a mass effect on the <sup>18</sup>F-fallypride binding potential in bilateral PU ( $p = 0.926$ ). There was no difference between the groups in injected dose of <sup>18</sup>F-fallypride

**TABLE 1** Demographic variables and clinical questionnaires

Variable (N <sub>LR</sub> /N <sub>HR</sub> /N <sub>AUD</sub> )	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;  $p = 0.38$ ).<sup>33,34</sup> PET data were acquired for 4 h after FP administration in three successive blocks with a break between each block<sup>35</sup> 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.<sup>36</sup> 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.<sup>37</sup> 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.<sup>38</sup> For discussion with regard to application of the SLF as reference region, see our recently published study.<sup>39</sup> Individual T1 images were spatially normalized into the anatomical space of the Montreal Neurological Institute (MNI) using the unified segmentation approach.<sup>40</sup> 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 <sup>18</sup>F-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).<sup>41</sup> 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.<sup>42–45</sup> 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.

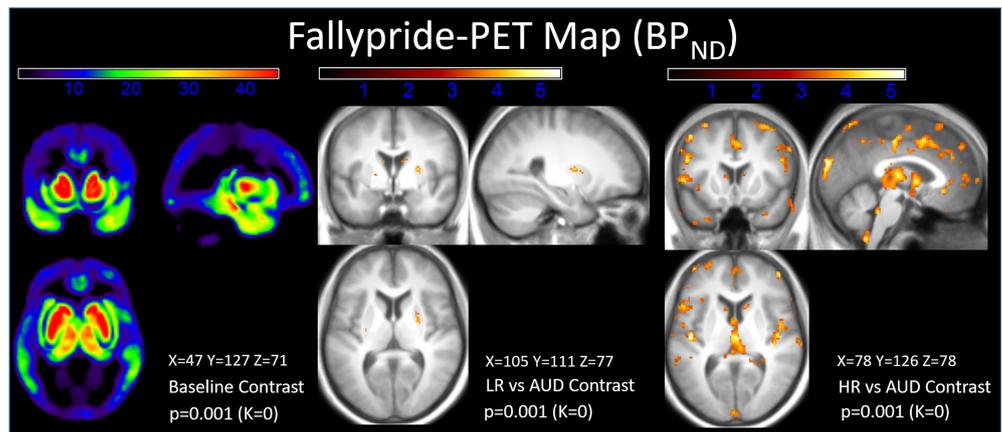
Additionally, post hoc group comparisons were conducted as two sample  $t$  tests. We further calculated Pearson correlation coefficients (partial correlations;  $\rho$ ) to investigate correlations between  $BP_{ND}$  with the ADS scale. Additionally, mainly for visual purposes, exploratory whole brain 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<sub>ND</sub>; 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<sub>ND</sub> in the CA, PU, and NA revealed global differences in mean BP<sub>ND</sub> between the groups ( $W = 0.77$ ,  $F(6,104) = 2.42$ ,  $p = 0.03$ , partial eta squared = 0.13).

**TABLE 2** Mean BP<sub>ND</sub> 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)

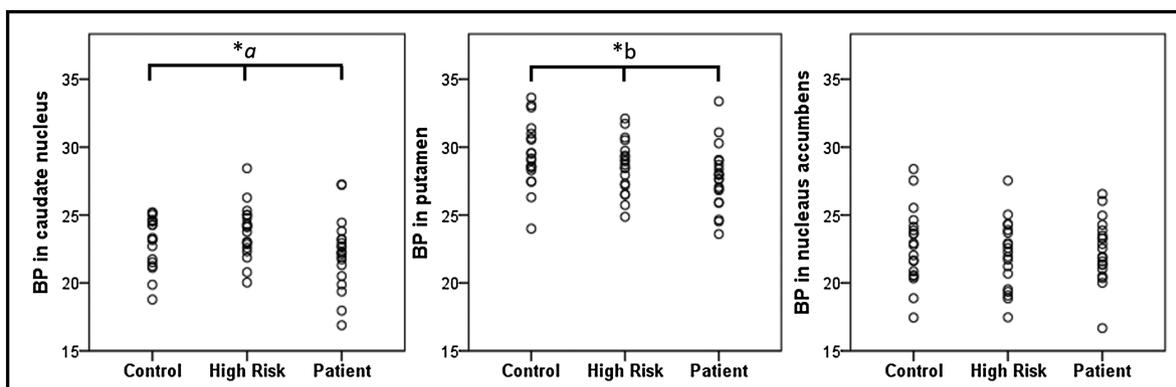
Abbreviations: AUD, alcohol disorder; HR, high risk; LR, low risk; N, number of participants per group; SD, standard deviation.

### 3.3 | Group differences of BP<sub>ND</sub> within striatal subdivisions

Univariate group effects showed a significant difference in BP<sub>ND</sub> 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<sub>ND</sub> (LR > HR > AUD), planned contrast weights were investigated with regard to linear/quadratic, negative relationships. A negative linear relationship between group and BP<sub>ND</sub> 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<sub>ND</sub> 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<sub>ND</sub> in the PU ( $d = 1.74$ ,  $p = 0.03$ ). AUD patients compared to HR subjects had lower BP<sub>ND</sub> 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<sub>ND</sub> 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<sub>ND</sub> 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

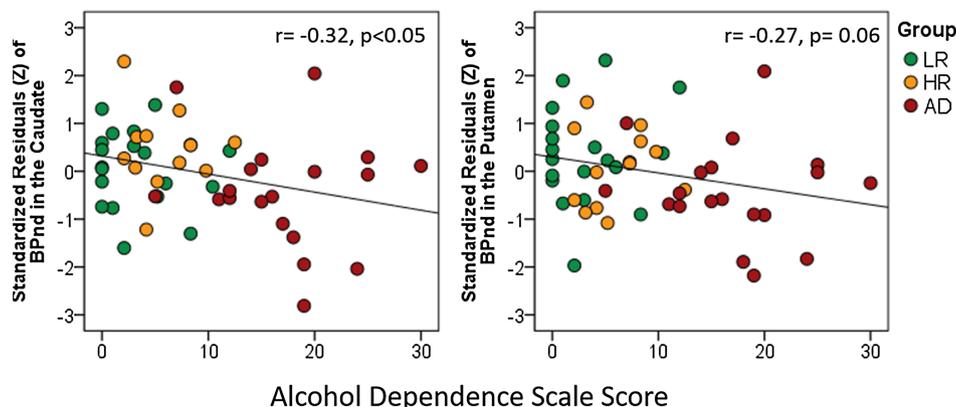
In the present study, we investigated striatal D2/3 receptor availability in recently abstinent alcohol addicted patients, subjects with increased risk for AUD and low alcohol consuming healthy controls. Differences in striatal D2/3 receptor availability between the three reference groups were observed 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<sub>ND</sub> measured by <sup>18</sup>F-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.<sup>19,20,46–50</sup> However, in earlier studies using [<sup>11</sup>C]raclopride-PET, decreased D2/3 receptor availability was observed in the NA of AUD patients,<sup>46,51,52</sup> in contrary to the present study. Still, in line with the present study, two studies that applied <sup>18</sup>Ffallypride-PET reported no significant baseline differences in striatal D2/3 receptor availability,<sup>53</sup> or no baseline difference, but increased striatal D2/3 receptor availability during detoxification.<sup>43</sup> Subsequently, it seems that in studies applying <sup>18</sup>Ffallypride-PET in AUD, ventral-striatal differences in D2/3 receptor availability are consistently absent, whereas in studies applying [<sup>11</sup>C]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).<sup>9,10,23</sup> In accordance, Koob and Volkow<sup>13</sup> argue that both the DS and NA contribute to the development and maintenance of AUD.<sup>13</sup> 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.<sup>54,55</sup> 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.<sup>19</sup> 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.<sup>19</sup> In contrast,



**FIGURE 3** Scatterplot for the relationship between the standardized residuals of BP<sub>ND</sub> 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.<sup>56,57</sup> 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.<sup>9,23</sup>

## 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.<sup>49</sup> 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.<sup>58</sup> In line with the present study, Volkow et al.<sup>49</sup> 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.<sup>43,49</sup> 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.<sup>13</sup> 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.<sup>59</sup> 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.<sup>58</sup>

## 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 <sup>18</sup>F-fallypride PET as in the present study, [<sup>11</sup>C]raclopride-PET<sup>46,48,49</sup> or [<sup>18</sup>F]desmethoxyfallypride-PET<sup>19,20</sup> was used. Additionally, among other studies, highly variable ROI approaches have been applied. For instance, the whole striatum,<sup>20,48</sup> anatomically defined structural subdivisions,<sup>19,49</sup> as well as functionally associated striatal subdivisions<sup>60</sup> 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.

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## 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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#### SUPPORTING INFORMATION

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

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