Archival Report

Reward Processing in Alcohol-Dependent Patients and First-Degree Relatives: Functional Brain Activity During Anticipation of Monetary Gains and Losses

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ABSTRACT

BACKGROUND: According to the reward deficiency syndrome and allostatic hypotheses, hyposensitivity of mesocorticolimbic regions to non–alcohol-related stimuli predisposes to dependence or is long-lastingly enhanced by chronic substance use. To date, no study has directly compared mesocorticolimbic brain activity during non–drug reward anticipation between alcohol-dependent, at risk, and healthy subjects.

METHODS: Seventy-five abstinent alcohol-dependent human subjects (mean abstinence duration 957.66 days), 62 healthy first-degree relatives of alcohol-dependent individuals, and 76 healthy control subjects without family history of alcohol dependence performed a monetary incentive delay task. Functional magnetic resonance imaging data of the anticipation phase were analyzed, during which visual cues predicted that fast response to a target would result in monetary gain, avoidance of monetary loss, or a neutral outcome.

RESULTS: During gain anticipation, there were no significant group differences. During loss anticipation, abstinent alcohol-dependent subjects showed lower activity in the left anterior insula compared with healthy control subjects without family history of alcohol dependence only (Montreal Neurological Institute [MNI] −25 19 −5; t_{506} = 4.17, familywise error corrected p = .009). However, this effect was no longer significant when age was included as a covariate. There were no group differences between abstinent alcohol-dependent subjects and healthy first-degree relatives or between healthy first-degree relatives and healthy control subjects during loss anticipation, respectively.

CONCLUSIONS: Neither the neural reward deficiency syndrome nor the allostatic hypotheses are supported by the results. Future studies should investigate whether the incentive salience hypothesis allows for more accurate predictions regarding mesocorticolimbic brain activity of subjects with alcohol dependence and healthy individuals during reward and loss anticipation and further examine the neural substrates underlying a predisposition to dependence.

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Alcohol use disorders affect 5.1% of the world’s population (1) and account for substantial levels of disease burden and mortality (2,3), with a family history of alcohol dependence being a risk factor for the disorder’s occurrence (4,5).

Mesocorticolimbic brain regions play a key role in addiction development and maintenance (6,7). All drugs of abuse release dopamine in the nucleus accumbens in the ventral striatum (VS) (8), which reinforces drug consumption and salience attribution to drug-associated cues that can thus elicit drug wanting (9). It has been suggested that alcohol intake is originally rewarding and elicits hedonic liking, which may be associated with its effects on endorphin and serotonin systems rather than dopamine in the VS (8), while chronic drug seeking and intake can become gradually more habitual or even compulsive (10). Habitual drug seeking and consumption can then be upheld despite drug intake being no longer rewarding (or liked) (9). It has been suggested that this shift to habitual or even compulsive drug intake is associated with counter-regulatory downregulation of dopamine D2 receptor availability in the VS (11) and increased cue processing in the dorsal striatum (12). Furthermore, the insula has been implicated in the transition toward habitual or even compulsive behavior, including drug intake despite aversive consequences (13,14). The insula is closely functionally linked to the anterior cingulate cortex (ACC), ventral tegmental area (VTA), and VS (15,16) and is involved in the conscious representation of stimulus-induced craving and abstinence-induced dysphoria (17).

According to the incentive salience hypothesis (9,18,19), repeated substance use leads to a hijacking of the
mesocorticolimbic system persisting throughout abstinence, as repeated drug use sensitizes dopamine release in the VS and thus reinforces drug intake and salience attribution to drug-associated cues (29). While phasic dopamine release as elicited by drug cues cannot be measured in vivo in humans, some empirical support for this hypothesis is provided by studies in abstinent (20–23) individuals with alcohol dependence (23,24), reporting increased functional activity in the VS, related mesocorticolimbic regions, and the insula in response to alcohol-associated stimuli compared with healthy control subjects.

Alternatively, the reward deficiency hypothesis suggests that an at least partly heritable deficit in the brain reward system including its dopaminergic input predisposes subjects to consume drugs of abuse or excessively engage in other activities such as food consumption, gambling, or high-risk sports because they strongly stimulate otherwise impaired dopaminergic neurotransmission and thus temporally compensate for the deficit (25,26).

Conversely, the allostatic hypothesis (27–30) postulates that chronic substance use both decreases the sensitivity of the reward system to drug-related and natural rewards and recruits anti-reward networks in the sense of an opponent process (31,32). These neuropsychoetic changes are hypothesized to persist even during protracted abstinence (27–30), though some studies described rather fast recovery of dopaminergic neurotransmission within the first days of alcohol abstinence (11,33) or even a hyperdopaminergic state after protracted abstinence (34).

A paradigm widely used to study brain activity during non-substance reward processing is the monetary incentive delay task (MIDT) (35), allowing dissociation between reward anticipation and receipt (36). During gain and loss anticipation, healthy subjects show robust activations in the VS, an important receptor region of dopaminergic afferents from the midbrain, as well as in the ACC and anterior insula (AI) (36,37). MIDT studies comparing abstinent alcohol-dependent (AD) subjects to healthy control subjects during functional magnetic resonance imaging (fMRI) have provided contradictory findings (36). While some found no differences during the anticipation phase (38–40), most studies, including a meta-analysis (41), reported comparatively decreased activity in AD subjects in the VS, insula, and frontal brain regions, among others (5,20,42–44).

Whether neuronal differences are a consequence of chronic alcohol consumption or due to predisposition to alcohol dependence has been debated. One strategy to disentangle the contribution of underlying factors has been the examination of high-risk subjects, namely healthy first-degree relatives of alcohol-dependent individuals [family history-positive (FH+) subjects (45)]. For instance, according to the reward deficiency syndrome hypothesis (26), FH+ subjects, and (abstinent) individuals with alcohol dependence should exhibit similarly decreased neural activation to non-substance-related rewards, resulting in a chronic dysphoric state that can solely be reversed by substance use or other highly rewarding activities (26). While most MIDT studies in FH+ subjects (46–49) found no functional differences to healthy subjects during the anticipation phase, other studies showed comparatively increased (45,50,51) or decreased (52) activity in relatives. Differences existed in the VS, ACC, and insula, among others (45,51,52).

Findings from previous studies only allow for limited conclusions regarding the role of neural responses to non-drug reward cues as a risk factor for alcohol dependence as they 1) mainly had small sample sizes (5,20,39,42–46,49,51–53) and 2) did not directly compare neural responses between FH+ and AD subjects. It thus remains to be elucidated whether similar functional abnormalities occur in both groups.

To this end, AD subjects with alcohol dependence according to the DSM-IV (54), FH+ subjects, and healthy control subjects without a family history of alcohol dependence (family history-negative [FH−] subjects) were examined using fMRI during a MIDT. To our knowledge, this is the first direct comparison of AD, FH+, and FH− subjects during the anticipation of monetary gains and losses. In addition to whole-brain analyses, region of interest (ROI) analyses were also performed. Based on the theoretical importance of the mesocorticolimbic dopamine system and the insula in reward processing and on a recent meta-analysis on anticipatory functional activity in healthy subjects (37), the VTA, VS, ACC, and AI were defined as ROIs.

Departing from the reward deficiency syndrome (26) and the allostatic hypotheses (27–30), we expected that 1) AD subjects would show lower neuronal activity than FH− subjects, 2) FH+ subjects would show lower activity than FH− subjects, and 3) AD subjects would show lower activity than FH+ subjects in the ROIs during gain and loss anticipation, compared with anticipation of neutral outcomes, respectively.

METHODS AND MATERIALS

Subjects and Procedures

A total of 235 subjects (87 AD, 66 FH+, 82 FH−) participated in the study. Twenty-two subjects (12 AD, 4 FH+, 6 FH−) were excluded from data analyses due to missing or poor-quality MRI data. In total, we thus included data of 213 subjects (75 AD, 62 FH+, 76 FH−). Subjects gave written informed consent prior to participation, and the study was conducted in accordance with the Declaration of Helsinki and approved by all local ethics committees.

AD subjects reported a diagnosis of alcohol dependence according to DSM-IV (54) and at least 7 days of abstinence at the time of screening. With an average abstinence duration of 957.66 days (SD = 1436.87), the majority of the AD sample was in protracted abstinence. FH+ subjects reported not being affected by DSM-IV (54) alcohol dependence themselves but having at least one affected first-degree relative. In case of uncertainty about the relative’s diagnosis, we administered the Family History Assessment Module (55,56). FH− subjects reported the absence of alcohol dependence according to DSM-IV (54) in themselves and any first-degree relative.

Participants were excluded if they had any DSM-IV (54) Axis I psychiatric disorder other than alcohol dependence (AD group), nicotine dependence or abuse, single past depressive episodes, or anxiety and adjustment disorders, as assessed via the German screening version of the Structured Clinical Interview for DSM-IV Axis I (57). As verified by drug urine tests, subjects had not consumed psychotropic substances (cannabinoids, amphetamines, cocaine, opioids) within 1 month.
prior to participation. Further exclusion criteria were current antidepressant or neuroleptic medication, claustrophobia, physical diseases potentially interfering with the examinations or having an influence on the parameters of interest, MRI contraindications, insufficient knowledge of German language, and current breastfeeding or pregnancy. Significant age differences were present between AD and FH subjects and between AD and FH subjects, respectively (Table 1).

**Monetary Incentive Delay Task**

We administered a modified version of the MIDT (35) using Presentation (Neurobehavioral Systems) (Supplemental Methods and Figure S1). In each trial, subjects saw a cue indicating a potential gain, potential loss, or neutral trial, respectively (anticipation phase). After a variable delay, they had to respond to a target as quickly as possible. Subsequent feedback (outcome phase) indicated whether a trial was successful (i.e., +1€ in gain trials, 0€ in loss trials) or unsuccessful (i.e., 0€ in gain trials, −1€ in loss trials). The outcome for neutral trials was always 0€. The MIDT had a total duration of approximately 12 minutes and consisted of 25 gain, 25 loss, and 25 neutral trials presented in a pseudo-randomized order, with the same condition occurring maximally twice in succession.

To avoid decreased anticipatory activity at the beginning of the MIDT (36) and to ensure learning of the association between the cues and their respective outcomes, participants performed one practice session each outside and inside the scanner. An adaptive algorithm was applied in the in-scanner practice session and during the main task, leading to each subject being successful in approximately 70% of trials (Supplemental Methods).

**Functional Magnetic Resonance Imaging**

fMRI was performed in three 3T scanners (Berlin and Munich: MAGNETOM Trio, Siemens; Berlin: MAGNETOM Prisma, Siemens). T2-weighted images were obtained using echo-planar imaging (repetition time = 2.2 seconds, echo time = 30 ms, flip angle = 75°, matrix = 64 × 64, voxel size = 3.44 × 3.44 × 3.41 mm³, 40 slices, 323 or 360 images). A T1-weighted structural image was acquired as an anatomical reference (repetition time = 2.3 seconds, echo time = 3.03 ms, flip angle = 9°, matrix = 256 × 256, voxel size = 1 × 1 × 1 mm³, 192 slices).

**Data Analysis**

Demographic and behavioral MIDT data were analyzed using SPSS Statistics 23 and 28 (IBM Corp.), while fMRI analyses were performed with SPM12 (The Wellcome Centre for Human Neuroimaging) in MATLAB (versions 2013b and 2021a; The MathWorks, Inc.). Data analyses were preregistered in the Open Science Framework (https://osf.io/3gnk9) (68).

**Behavioral Data.** Group differences regarding sociodemographic and psychometric data were examined using χ² tests or analyses of variance, respectively. For MIDT reaction time (RT), success rate, and outcome analyses, we used univariate analyses of variance. Significant main effects of group were followed by post hoc independent-samples t tests or, in case of variance inequality, Welch tests. In case of significant main effects of anticipation condition, we performed post hoc t tests for dependent samples. For exploratory analyses including age as a covariate, see the Supplement.

**fMRI Data.** After preprocessing (Supplemental Methods), we performed first- and second-level analyses in the context of the general linear model. At the first level of the event-related design, 3 anticipation conditions (gain, loss, neutral), target presentation, and 5 feedback conditions (gain, unsuccessful gain attempt, neutral feedback, loss avoidance, unsuccessful loss avoidance attempt) were modeled using stick functions convolved with the hemodynamic response function implemented in SPM. In addition, we included 3 regressors each for translational and rotational head motion.

For each participant, the linear contrast images gain > neutral anticipation and loss > neutral anticipation were computed and subsequently used in the random-effects second-level analysis. Here, the 3 groups (AD, FH⁺, FH⁻) were included as regressors. MRI scanner, handedness, and smoking status were included as covariates of no interest (Supplemental Methods). To rule out the possibility that neural group differences were caused or masked by systematically different success rates (36) and thus by systematically different motivation to actively achieve a positive outcome, we included success rate in MIDT gain or loss trials as a covariate (Supplemental Discussion).

Besides whole-brain analyses, we conducted ROI analyses using small-volume correction for each group comparison (AD vs. FH⁻, FH⁺ vs. FH⁻, AD vs. FH⁺) for the contrasts gain > neutral anticipation and loss > neutral anticipation. Based on previous MIDT studies (37) and using an in-house tool (59), the VS, AI, ACC, and VTA were defined as ROIs (Supplemental Methods, Figure S2, and Tables S1 and S2).

A familywise error (FWE)-corrected significance level of p = .05 was used in all whole-brain and ROI analyses. Activations within AD, FH⁺, and FH⁻ groups during gain and loss anticipation were assessed using one-sample t tests, group differences (AD vs. FH⁻, FH⁺ vs. FH⁻, AD vs. FH⁺) for both contrasts (gain > neutral anticipation, loss > neutral anticipation) using independent-samples t tests. For exploratory analyses related to success rate, age, craving measures, abstinent duration, and the MIDT outcome phase, see the Supplement.

**RESULTS**

**Behavioral Data**

We found a main effect of anticipation condition on RT (Tables 2 and 3): consistent with a basic assumption underlying MIDT (36), participants responded faster in gain and loss compared with neutral trials, respectively. In addition, RT across groups was lower in gain than in loss trials. Moreover, the main effect of groups was significant (Figure 1A), with AD and FH⁺ subjects responding more slowly than FH⁻ subjects across anticipation conditions, respectively. AD and FH⁻ subjects did not differ regarding RT. The interaction between group and condition was not significant.

A similar pattern emerged regarding success rate (Tables 2 and 3): across groups, the success rate was higher in gain than...
Table 1. Sociodemographic and Psychometric Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Group Differences</th>
<th>Post Hoc Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment Site and Scanner, Berlin Trio/Berlin Prisma/Mannheim Trio, n^t</td>
<td>AD, n = 75</td>
<td>FH^t, n = 62</td>
<td>FH^t, n = 76</td>
</tr>
<tr>
<td>Sex, F/M, %</td>
<td>28.00%/72.00%</td>
<td>59.68%/40.32%</td>
<td>27.63%/72.37%</td>
</tr>
<tr>
<td>Age, Years, Mean ± SD</td>
<td>50.03 ± 10.85</td>
<td>38.89 ± 13.35</td>
<td>43.62 ± 12.58</td>
</tr>
<tr>
<td>Handedness, R/L/Bi, %</td>
<td>88.00%/6.67%/5.33%</td>
<td>98.67%/6.45%/0.50%</td>
<td>98.67%/6.45%</td>
</tr>
<tr>
<td>BMI, Mean ± SD</td>
<td>25.46 ± 4.87</td>
<td>24.43 ± 3.52</td>
<td>24.45 ± 3.73</td>
</tr>
<tr>
<td>German as Native Language, True/Not True, %</td>
<td>4.00%/96.00%</td>
<td>1.61%/96.77%</td>
<td>5.26%/94.74%</td>
</tr>
<tr>
<td>Birth or Pregnancy Complications, Present/Absent, %</td>
<td>17.33%/80.00%</td>
<td>17.74%/80.65%</td>
<td>11.84%/84.21%</td>
</tr>
<tr>
<td>Smoking Status, %</td>
<td>52.00%</td>
<td>24.19%</td>
<td>24.19%</td>
</tr>
<tr>
<td>Alcohol Dependence in Parents, %</td>
<td>32.00%</td>
<td>62.90%</td>
<td>62.90%</td>
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<tr>
<td>Number of Cigarettes/Day, Mean ± SD^d</td>
<td>18.79 ± 10.97</td>
<td>8.57 ± 4.3</td>
<td>12.53 ± 7.1</td>
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<td>AUQ Sum Score, Mean ± SD^e</td>
<td>12.03 ± 5.40</td>
<td>12.10 ± 5.30</td>
<td>10.88 ± 3.90</td>
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<tr>
<td>OCDS Sum Score, Mean ± SD^f</td>
<td>16.28 ± 11.22</td>
<td>12.24 ± 6.66</td>
<td>12.87 ± 2.22</td>
</tr>
<tr>
<td>Alcohol Dependence in Parents, %</td>
<td>9.33%</td>
<td>5.26%</td>
<td>6.58%</td>
</tr>
<tr>
<td>Father</td>
<td>57.33%</td>
<td>14.52%</td>
<td>100%</td>
</tr>
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</table>
in loss trials. In addition, we found a main effect of group (Figure 1B). Post hoc t tests revealed that AD subjects were less successful than FH− subjects, while AD and FH− subjects as well as FH+ and FH− subjects did not differ, respectively. The interaction between group and condition was not significant.

**fMRI Data**

As expected (37,60), confirming MIDT effectiveness, FH− subjects showed significant activation in the VTA, VS, ACC, and AI, among others, during both gain and loss anticipation contrasted against neutral trials, respectively (Figure 2; Tables S5 and S8).

**Gain Anticipation**

During gain anticipation (gain > neutral anticipation), we found no differences in activity between AD, FH+, and FH− subjects, neither within the ROIs (Figure 3) nor in whole-brain analyses (Figure 2; Tables S3–S5).

Exploratory ROI and whole-brain analyses 1) including age as covariate, with and without success rate as covariate, respectively, and 2) on subsamples of age-matched AD versus FH− subjects or AD versus FH− subjects, respectively, did not reveal any group differences. Instead, we found significant reductions in neural activity with increasing age in the VS ROI (right: MNI 9 15 −5; f205 = 4.46, pFWE < .003; left: MNI −11 12 −5; f205 = 4.02, pFWE = .013) and left AI ROI (MNI −29 26 −2; t205 = 3.64, pFWE = .043) in the full sample (Supplement).

When exploring the role of the substantial variation in abstinence duration in AD subjects, we found no significant correlation (r = 0.64, r2 = −0.19, p = .14) between mean activity in the bilateral VS ROI during gain anticipation and abstinence duration (Supplemental Results and Figure S4).

**Loss Anticipation**

During loss anticipation (loss > neutral anticipation), AD subjects exhibited significantly decreased neuronal activity in the left AI ROI compared with FH− subjects (MNI −29 19 −5; t205 = 4.17, pFWE = .009) (Figure 4). There were no significant differences in activity within the ROIs between AD and FH− subjects or between FH+ and FH− subjects, respectively. Whole-brain analyses did not reveal any significant group differences, although, descriptively, neural activity spanned fewer brain regions in AD than in FH+ and FH− subjects, respectively (Figure 2; Tables S6–S8).

When exploratorily 1) including age as covariate in whole-brain and ROI analyses, with and without success rate as covariate, respectively, and 2) repeating whole-brain and ROI analyses on subsamples of age-matched AD versus FH− subjects or AD versus FH− subjects, we neither found a difference between AD and FH− subjects in left AI nor any other group difference. Instead, with increasing age, BOLD signals decreased in left putamen (whole-brain, MNI −18 15 −5; t205 = 4.70, pFWE = .026) and in the ROIs of left VS (MNI −15 12 −5; t205 = 4.52, pFWE = .002), right VS (MNI 9 15 −9; t205 = 3.87, pFWE = .024) and left AI (MNI −25 19 −5; t205 = 4.03, pFWE = .014) (Supplemental Methods).

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>AD, n = 75</th>
<th>FH+, n = 62</th>
<th>FH−, n = 56</th>
<th>Post Hoc Tests p Value</th>
<th>Effect Test Statistic</th>
<th>Test Statistic</th>
<th>p Value</th>
<th>Effect Test Statistic</th>
<th>Test Statistic</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group Differences</td>
<td>Alcohol Dependence in Children, %</td>
<td>AD, 94/6; FH+, 91/8; FH−, 95/4</td>
<td>AD, 88.3/6; FH+, 83.4/3; FH−, 78.4/1</td>
<td>AD, 90/4; FH+, 79/5; FH−, 71/6</td>
<td>0.25</td>
<td>0.05</td>
<td>−0.017</td>
<td>.14</td>
<td>.003</td>
<td>.034</td>
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<tr>
<td>Group Differences</td>
<td>Verbal IQ, Mean (SD)</td>
<td>106.14 (9.86)</td>
<td>104.55 (10.81)</td>
<td>107.19 (11.01)</td>
<td>0.25</td>
<td>0.05</td>
<td>−0.017</td>
<td>.14</td>
<td>.003</td>
<td>.034</td>
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Reward Processing in Alcohol Dependence

Table 1. Continued

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>AD, n = 75</th>
<th>FH+, n = 62</th>
<th>FH−, n = 56</th>
<th>Post Hoc Tests p Value</th>
<th>Effect Test Statistic</th>
<th>Test Statistic</th>
<th>p Value</th>
<th>Effect Test Statistic</th>
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<td>AD, 90/4; FH+, 79/5; FH−, 71/6</td>
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<td>0.05</td>
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<td>−0.017</td>
<td>.14</td>
<td>.003</td>
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Table 2. Descriptive Behavioral Performance in the Monetary Incentive Delay Task

<table>
<thead>
<tr>
<th>Variable</th>
<th>AD, n = 75</th>
<th>FH⁺, n = 62</th>
<th>FH⁻, n = 76</th>
<th>All, N = 213</th>
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<tr>
<td>RT Gain, ms⁺</td>
<td>297.75 ± 89.13</td>
<td>283.82 ± 72.43</td>
<td>245.98 ± 68.99</td>
<td>275.00 ± 80.34</td>
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<tr>
<td>RT Neutral, ms⁺</td>
<td>319.31 ± 89.47</td>
<td>312.67 ± 86.32</td>
<td>264.86 ± 75.95</td>
<td>297.73 ± 87.10</td>
</tr>
<tr>
<td>RT Loss, ms⁺</td>
<td>303.33 ± 86.5</td>
<td>289.93 ± 80.8</td>
<td>248.34 ± 70.38</td>
<td>279.57 ± 82.53</td>
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<tr>
<td>Total RT, ms⁺</td>
<td>306.80 ± 85.12</td>
<td>295.47 ± 77.69</td>
<td>253.06 ± 70.46</td>
<td>284.10 ± 81.09</td>
</tr>
<tr>
<td>Success Rate Gain, %</td>
<td>63.31 ± 12.96</td>
<td>67.16 ± 14.54</td>
<td>67.11 ± 11.97</td>
<td>65.78 ± 13.17</td>
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<tr>
<td>Success Rate Loss, %</td>
<td>59.84 ± 16.42</td>
<td>63.42 ± 14.23</td>
<td>66.21 ± 11.75</td>
<td>63.15 ± 14.44</td>
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<td>Total Success Rate, %</td>
<td>61.57 ± 11.91</td>
<td>65.29 ± 12.21</td>
<td>66.66 ± 10.30</td>
<td>64.47 ± 11.61</td>
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<td>Total Outcome, €</td>
<td>7.65 ± 7.76</td>
<td>10.66 ± 8.36</td>
<td>12.86 ± 7.47</td>
<td>10.38 ± 8.10</td>
</tr>
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</table>

Values are presented as mean ± SD.
AD, abstinent alcohol-dependent subjects; FH⁺, healthy first-degree relatives of alcohol-dependent individuals; FH⁻, healthy control subjects without family history of alcohol dependence; Gain, in gain trials; Loss, in loss trials; Neutral, in neutral trials; RT, reaction time.

*pValues refer to a subsample of 208 subjects (72 AD, 61 FH⁺, 75 FH⁻) (Supplemental Methods).

DISCUSSION

During the anticipation of monetary gains or losses, FH⁺ subjects did not exhibit reduced or increased neural responses in mesocorticolimbic regions in comparison to FH⁻ and AD subjects, respectively. In contrast, AD subjects showed decreased activity in the left AI during loss anticipation compared with FH⁻ subjects. However, this finding was not significant when age was included as a covariate. Taken together, our findings are neither in accordance with the reward deficiency hypothesis (26) nor the allostatic hypothesis (27–30), at least when the latter refers to persistent hyporesponsivity of the reward system to non–drug-related stimuli during prolonged abstinence.

Gain Anticipation

We found no significant functional differences between FH⁺ and FH⁻ subjects in VTA, VS, ACC, or AI during gain anticipation. While this is in line with a number of previous studies (46–49), it stands in contrast to others reporting functional differences of inconsistent direction between FH⁺ and FH⁻ subjects during gain anticipation (45,50–52).

Reinforced by a comparatively large sample size, our finding questions the validity of the reward deficiency syndrome hypothesis (26) and the concomitant assumption that

Table 3. Behavioral Performance Differences in the Monetary Incentive Delay Task

<table>
<thead>
<tr>
<th>Behavioral Measure</th>
<th>Effect</th>
<th>F</th>
<th>p Value</th>
<th>Post Hoc Tests</th>
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<td></td>
<td></td>
<td>F</td>
<td>p</td>
<td>t</td>
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<tr>
<td>RT⁺</td>
<td>Group</td>
<td>F₂,205 = 9.66</td>
<td>&lt;.001ᵇ,c</td>
<td>AD vs. FH⁺</td>
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<td>AD vs. FH⁻</td>
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<td>FH⁺ vs. FH⁻</td>
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<tr>
<td></td>
<td>Anticipation condition</td>
<td>F₁,₂₄₄ = 54.62</td>
<td>&lt;.001ᵇ</td>
<td>Gain vs. neutral</td>
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<td>Loss vs. neutral</td>
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<td>Gain vs. loss</td>
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<td></td>
<td>Group × anticipation condition</td>
<td>F₂,₈₉ˌ₂₉₅ˌ₉₉ = 0.87</td>
<td>.452</td>
<td>AD vs. FH⁺</td>
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<td>AD vs. FH⁻</td>
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<td>FH⁺ vs. FH⁻</td>
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<tr>
<td>Success Rate</td>
<td>Group</td>
<td>F₂,₂₁₀ = 3.95</td>
<td>.021ᵈ</td>
<td>AD vs. FH⁺</td>
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<td></td>
<td>Anticipation condition</td>
<td>F₁,₁₂₀ = 6.85</td>
<td>.010ᵈ</td>
<td>AD vs. FH⁺</td>
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<td>Group × anticipation condition</td>
<td>F₂,₂₁₀ = 0.80</td>
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<td>AD vs. FH⁺</td>
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<td>FH⁺ vs. FH⁻</td>
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AD, abstinent alcohol-dependent subjects; FH⁺, healthy first-degree relatives of alcohol-dependent individuals; FH⁻, healthy control subjects without family history of alcohol dependence; Gain, in gain trials; Loss, in loss trials; Neutral, in neutral trials; RT, reaction time.

*pValues refer to a subsample of 208 subjects (72 AD, 61 FH⁺, 75 FH⁻) (Supplemental Methods).

ᵇSignificant when age was included as a covariate. See Supplemental Methods and Results for further information.
ᶜSignificant when age was included as a covariate. See Supplemental Methods and Results for further information.
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Reward Processing in Alcohol Dependence

Figure 1. Behavioral performance of healthy control subjects without family history of alcohol dependence (FH\(^-\)), healthy first-degree relatives of alcohol-dependent individuals (FH\(^+\)), and abstinent alcohol-dependent subjects (AD) in the monetary incentive delay task. (A) Reaction time (RT) across gain, loss, and neutral trials. (B) Success rate across gain and loss trials. Asterisks represent means, lines within violin plots represent interquartile range, and width of violin plots represents distribution density.

The AI has been linked to action initiation in response to subjectively salient stimuli (77) and impairments in insula, among others. Importantly, most previous studies reporting group differences assessed patients with rather short abstinence durations [1–3 weeks; e.g., (5,20,42,44)], while in the current study, average abstinence duration was about 3 years (Supplemental Results). Neuroadaptations elicited by chronic alcohol intake have, at least in subgroups (66,67), been shown to reverse within the first weeks or days of abstinence (33,68,69). Conversely, delayed recovery of dopaminergic neurotransmission following detoxification is associated with subsequent relapse (11,69). In our long-term abstinent sample, dopamine neurotransmission and dopamine-dependent reward anticipation (70) might thus long have recovered from such neuroadaptations, and we cannot rule out reduced mesolimbic responses in acutely abstinent individuals. Our finding that abstinence duration was not correlated with mean reward anticipatory activity in the VS does not stand in contrast to this hypothesis, as only 2 subjects with a known abstinence duration of <1 month were included (Supplement).

Conclusively, our findings in AD subjects support neither the reward deficiency syndrome hypothesis (26) nor the allostatic hypothesis (27–30) insofar as the latter postulates decreased reward network sensitivity to non–drug-related stimuli during protracted abstinence (28,71–73). Instead, AD subjects might rather be characterized by a hypersensitivity of mesocorticolimbic regions to alcohol-related cues (9,18,19). This would be consistent with the incentive salience hypothesis (5,9,18,19) and is supported by previous studies (20–22,34). It should be noted, however, that the allostatic hypothesis is more complex than portrayed here (72–74) and emphasizes anti-reward network activation during protracted abstinence (27–30,71,75). Currently lacking (76), longitudinal studies should assess trajectories of drug- and non–drug-related primary and secondary reward anticipation over the course of abstinence and among subsequently abstaining versus relapsing alcohol-dependent individuals.

Loss Anticipation

During loss anticipation, FH\(^+\) subjects did not show decreased activity in any ROI compared with FH\(^-\) subjects. This is inconsistent with 2 previous studies (51,52), but in line with most studies reporting no group differences in insula (46,48,52) or VS activation (46,48) between relatives and individuals without family history of alcohol dependence. As loss anticipation in the MIDT may be best understood as anticipation of potential loss avoidance, this finding, again, argues against the reward deficiency syndrome hypothesis.

However, AD subjects exhibited decreased activity in the left AI compared with FH\(^-\) subjects during loss anticipation. The AI has been linked to action initiation in response to subjectively salient stimuli (77) and impairments in insula.

consistent with the incentive salience hypothesis (9,13,18,19), increased alcohol cue–elicited activity in the insula, among other regions, has been found in heavy drinkers regardless of familial exposure (65).

For AD and FH\(^+\) subjects, we found comparable neuronal activation during the anticipation of monetary gains. While in line with 3 previous studies (38–40), this is inconsistent with the majority of MIDT research in AD subjects (5,20,42–44) and a meta-analysis (41) reporting decreased activity in the VS and insula, among others. Importantly, most previous studies reporting group differences assessed patients with rather short abstinence durations [1–3 weeks; e.g., (5,20,42,44)], while in the current study, average abstinence duration was about 3 years (Supplemental Results). Neuroadaptations elicited by chronic alcohol intake have, at least in subgroups (66,67), been shown to reverse within the first weeks or days of abstinence (33,68,69). Conversely, delayed recovery of dopaminergic neurotransmission following detoxification is associated with subsequent relapse (11,69). In our long-term abstinent sample, dopamine neurotransmission and dopamine-dependent reward anticipation (70) might thus long have recovered from such neuroadaptations, and we cannot rule out reduced mesolimbic responses in acutely abstinent individuals. Our finding that abstinence duration was not correlated with mean reward anticipatory activity in the VS does not stand in contrast to this hypothesis, as only 2 subjects with a known abstinence duration of <1 month were included (Supplement).

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hypersensitivity of the mesocorticolimbic reward system to non–substance-related rewards predisposes to alcohol dependence, at least when assuming a genetic contribution to reward deficiency shared between (subsequent) patients and relatives of alcohol-dependent patients. However, unaffected family history–positive individuals may differ from (subsequent) addicted individuals: Volkow et al. (61) observed increased dopamine D\(_2\) receptors in the VS of unaffected relatives of alcohol-dependent patients, who, in contrast, tended to display reduced dopamine D\(_2\) receptors at least during early abstinence (62–64). Whether, instead, a hypersensitivity of mesocorticolimbic regions to alcohol-related stimuli (8,18,19) plays a role in relatives remains to be elucidated. So far,
function have repeatedly been associated with addictive behavior (13,14,17). However, the decreased AI activation was most likely driven by AD subjects' being significantly older than FH subjects rather than by their diagnosis of alcohol dependence, as it was no longer significant when age was included as a covariate.

Apart from the AI, we found no significant differences in neural activation between AD and FH subjects in any other ROI. This is inconsistent with 2 previous findings (5,20), but in line with several MIDT studies in AD subjects (38,39,42,43) and suggests that the most robust finding is that of no group differences during loss anticipation.

Limitations

An important limitation of this study is that we cannot rule out the confounding influence of age. Indeed, exploratory analyses showed that activation in the VS and AI decreased with increasing age, which is in line with findings in healthy subjects (78). However, considering that older FH subjects who did not develop alcohol dependence are likely particularly resilient, we did not find any group differences in mesolimbic activation when comparing age-matched subsamples of FH and AD or FH and AD subjects, respectively. In addition, since ROI analyses including age as a covariate did not reveal any significant group differences during gain or loss anticipation, we deem it unlikely that age differences between groups could

Figure 2. Whole-brain activity \(p < .05\), familywise error [FWE] corrected) within healthy control subjects without family history of alcohol dependence (FH\(^{-}\)), healthy first-degree relatives of alcohol-dependent individuals (FH\(^{+}\)), and abstinent alcohol-dependent subjects (AD), respectively, during gain (gain > neutral anticipation; warm colors) and loss (loss > neutral anticipation; cold colors) anticipation in the monetary incentive delay task. The respective z coordinate is indicated above each layer.

Figure 3. Estimated contrast weights for mean activity in the bilateral ventral striatum (VS) region of interest during gain anticipation (gain > neutral anticipation) in the monetary incentive delay task for healthy control subjects without family history of alcohol dependence (FH\(^{-}\)), healthy first-degree relatives of alcohol-dependent individuals (FH\(^{+}\)), and abstinent alcohol-dependent subjects (AD), respectively. Asterisks represent means, lines within violin plots represent interquartile range, and width of violin plots represents distribution density.
alcohol use in association with certain personality traits and over, recent studies suggest that neural activation in the VS, decreased anticipatory activity in gain and loss trials in the VS among abstinent alcohol-dependent subjects (AD) and healthy control subjects (FH) during loss anticipation compared with FH subjects is likely due to group age differences and was no longer significant after controlling for age. Future research should investigate drug and non-drug reward cue processing over the course of abstinence and control for individual differences including sign-tracking behavior as a potential confound. This research could assess 1) whether the incentive salience hypothesis—compared with the reward deficiency syndrome and allostatic hypotheses—allows for more accurate predictions regarding mesocorticolimbic brain activity of AD and FH subjects during reward and loss anticipation, and 2) which neural substrates underlie a predisposition to dependence.

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