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Original article

Orbitofrontal structural markers of negative affect in alcohol dependence and their associations with heavy relapse-risk at 6 months post-treatment

E. Zois [a,*], S. Vollstädt-Klein [a], S. Hoffmann [a], I. Reinhard [c], K. Charlet [b], A. Beck [b], A. Jorde [a], M. Kirsch [a], H. Walter [b], A. Heinz [b], F. Kiefer [a]

[a] Department of addictive behaviour and addiction medicine, central institute of mental health, Mannheim, university of Heidelberg, Mannheim, Germany
[b] Department of psychiatry and psychotherapy, Charité-Universitätsmedizin Berlin, Berlin, Germany
[c] Department of biostatistics, central institute of mental health, Mannheim, university of Heidelberg, Mannheim, Germany

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ABSTRACT

Background: Alcohol relapse is often occurring to regulate negative affect during withdrawal. On the neurobiological level, alcoholism is associated with gray matter (GM) abnormalities in regions that regulate emotional experience such as the orbitofrontal cortex (OFC). However, no study to our knowledge has investigated the neurobiological unpinning of affect in alcoholism at early withdrawal and the associations of OFC volume with long-term relapse risk.
Methods: One hundred and eighty-two participants were included, 95 recently detoxified alcohol dependent patients (ADP) and 87 healthy controls (HC). We measured affective states using the positive and negative affect schedule (PANAS). We collected *T1*-weighted brain structural images and performed Voxel-based morphometry (VBM).
Results: Findings revealed GM volume decrease in alcoholics in the prefrontal cortex (including medial OFC), anterior cingulate gyrus, and insula. GM volume in the medial OFC was positively associated with NA in the ADP group. Cox regression analysis predicted that risk to heavy relapse at 6 months increases with decreased GM volume in the medial OFC.
Conclusions: Negative affect during alcohol withdrawal was positively associated with OFC volume. What is more, increased GM volume in the OFC also moderated risk to heavy relapse at 6 months. Reduced GM in the OFC poses as risk to recovery from alcohol dependence and provides valuable insights into transient negative affect states during withdrawal that can trigger relapse. Implications exist for therapeutic interventions signifying the OFC as a neurobiological marker to relapse and could explain the inability of ADP to regulate internal negative affective states.

1. Introduction

'*Affect*' refers to short emotional states that emerge when interacting with environmental stimuli. It's a two-dimensional formation, namely negative affect (NA) and positive affect (PA) [1]. People throughout life learn strategies to influence or evaluate emotional states to enable adaptive decision-making [2]. Failure to regulate emotions and feelings can result in maladaptive behaviors that increase the risk for the development and maintenance of a range of disorders including alcohol dependence (AD) [3]. AD is associated with severe mental, physical, and social functioning complications [4]. Increased alcohol consumption usually initiates to regulate negative affective stages especially in withdrawal [5–7]. During that phase, alcohol dependent patients (ADP) seek to improve internal negative affect states due to withdrawal related neuroadaptations, that make them susceptible to relapse [8,9].

On the neurobiological level, prolonged heavy alcohol consumption induces neuronal adaptations [10] in brain circuits

Abbreviations: ADP, alcohol dependent patients; AD, alcohol dependence; HC, healthy controls; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PA, positive affect; NA, negative affect; PANAS, positive and negative affect schedule; GM, gray matter; VBM, Voxel-based morphometry; MPRAGE, Magnetization-prepared Rapid Acquisition Gradient Echo.

* Corresponding author at: Department of addictive and addiction medicine, central institute of mental health, medical faculty Mannheim/Heidelberg university, square J5, 68159 Mannheim, Germany.
E-mail address: evangelos.zois@zi-mannheim.de (E. Zois).

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responsible for emotion regulation and decision-making [11]. The PFC plays an important role in regulating negative affect states as shown by evidence on GABA (gamma-amino butyric acid) projections from orbital and medial regions of the PFC to subcortical regions associated with negative emotion such as the amygdala [12]. Evidence suggests that the medial orbitofrontal (OFC) facilitates emotion, motivation, affective experience and executive function [13]. Emerging findings from lesion studies with neurological patients with medial OFC damage indicate that such patients show compromised decision-making abilities and abnormal autonomic responses to socially and emotionally meaningful stimuli [13–15]. Their subjective affective states are altered with impaired ability to foresee future risks [14], incapable to predict the negative long-term consequences of their decisions [14]. To formally test this, a neuropsychological paradigm was developed that assesses decision-making abilities [14]. The Iowa gambling task (IGT) resembles real life decision-making suggesting that emotions are integral in the decision-making process [14]. Unlike patients with medial OFC damage, neurologically normal individuals learn the contingencies involved in the task, demonstrating advantageous decision-making [16]. The paradigm has been employed not only in studies with neurological patients but also addiction suffers such as ADP [17,18]. Performance of ADP mimics that of medial OFC patients. ADP also show decision-making impairments such as that they tend to choose immediate reward gratification at the expense of the negative future outcome [17,18].

Functional neuroimaging (fMRI) studies employing tasks that tap emotion and motivation processing suggest that OFC neuronal activity is compromised in ADP compared to HC. Using alcohol cue reactivity Bach and colleagues (2015) found altered brain activation to alcohol related cues in the OFC that positively predicted alcohol craving in *GR1K1* risk allele carries of the glutamate neurotransmitter [19]. Moreover, in a resting-state fMRI investigation, ADP who relapsed 6 months following treatment compared to those who remained abstinent displayed attenuated resting-state synchrony in OFC [20]. Also, in a study examining emotional facial expression reactivity, neural activation differences were found during task performance [21]. Specifically, Charlet et al. (2014) found decreased brain activation in ADP compared to HC during processing of aversive faces in OFC adjacent regions [21].

Furthermore, structural neuroimaging investigations examining brain tissue deficits and gray matter (GM), have offered evidence in relation to medial OFC damage in ADP [17,22]. Studies have examined brain tissue damage inflicted in ADP due to long-term alcohol abuse and have employed voxel-based morphometry (VBM) or similar analysis techniques to investigate the whole brain in ADP compared to HC. Results suggest reduced GM volume especially in the frontal cortex including the OFC [17,22–26]. In line with the above, a recently published meta-analysis on ADP and brain structure, authors combined brain structural data from 8 different studies and found that amongst the brain regions that yielded effect sizes with confidence intervals below zero was the medial OFC [27].

Research suggests that the medial OFC is a crucial neural substrate involved in emotion regulation [11,13]. Its function [20,21] and structure [17,22,23,28] in ADP is alternated compared to controls showing either altered activation (hypoactivation/hyperactivation) or GM volume reduction compared to HC. Additionally, in neuropsychological tasks tapping medial OFC function, ADP exhibit compromised performance [17,18] suggesting that apart from decision-making dysfunction, emotion regulation could also be compromised. Literature suggests that during early stages of withdrawal negative affect escalates often resulting in alcohol lapses [6]. Considering the above, we are interested in investigating the neurobiological correlates of subjective affective states during withdrawal (3–28 days). Specifically, if GM volume in the medial OFC, predicts subjective negative affective states and consequently relapse in ADP. Considering that almost 60% of ADP will relapse within 6 months after treatment [29,30] and that alcohol relapse studies using GM volume as a relapse predictor are scarce to our knowledge, we will examine relapse risk in ADP patients. In detail, we aim at extending current findings using a big patient cohort ($n = 95$) of recently detoxified alcohol dependent individuals and investigate GM tissue compared to an equally large group of age matched healthy controls (HC; $n = 87$). All patients included in the current investigation, participated in a follow-up relapse assessment schedule to establish drinking status at 6 months [20,30] after inpatient treatment. Hence, we hypothesized that decreased GM volume in the OFC will predict increased subjective affect states and that increased GM volume in the same region will predict relapse to heavy drinking at 6 months. In addition, we hypothesize that alcohol dependence will have reduced GM volume compared to healthy controls.

2. Methods

2.1. Sample

The original sample of ADP comprised of 119. We have however excluded 24 patients from any analysis, as we were not able to obtain any data since their discharge. Therefore, 95 was the final patient sample included in this report. They were recruited from the day clinic and inpatient wards of the Department of Addictive Behavior and Addiction Medicine at the Central Institute of Mental Health in Mannheim, Germany.

In addition, we included 87 HC in the study. Participants were eligible for participation in the study if they were between 18 and 65 years of age, fulfilled the diagnostic criteria for alcohol dependence (ADP only) according to the 4th edition of the Diagnostic Statistical Manual of Mental Disorders (DSM-IV), were right-handed, had completed medically assisted withdrawal (ADP only) and had stayed abstinent for at least 3 and at most 28 days respectively (ADP only). Exclusion criteria were the occurrence of an Axis-I disorder within the previous 12 months [aside alcohol (ADP only) and nicotine dependence], positive urine drug-test, present use of psychotropic or anticonvulsive medications, epilepsy, suicidal ideation, pregnancy, neurological or severe physiological illness, MRI contraindications. Prior to study inclusion, all participants provided written informed consent (Declaration of Helsinki). The study was approved by the ethics committee of Heidelberg University.

2.2. Procedure

2.2.1. PANAS, additional clinical tools & relapse data

Participants completed the 20-item Positive and Negative Affect Schedule [PANAS, [31]]. They responded to each item on a 5-point Likert-scale with scores ranging from 10 to 50 for both dimensions. PANAS was administered once to the ADP with the instruction '*Think how you have felt in the past 12 months*'. The items of the PANAS are: interested, distressed, excited, upset, strong, guilty, scared, hostile, enthusiastic, proud, irritable, alert, ashamed, inspired, nervous, determined, attentive, jittery, active and afraid. Although the total number of ADP included in this investigation was 95, we have only managed to obtain data on PANAS that we could use in the analysis for only 72 of them. The Beck Depression Inventory [BDI, [32]], the Spielberger State-Trait-Anxiety Inventory [STAI, [33]] were also used. Follow-up relapse data was available for all 95 ADP patients (brief telephone based interview assessing alcohol use) with outcome criterion time to relapse to heavy drinking [48 g/day for women and 60 g/day for men ($4 \geq$ drinks per