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DISSERTATION

Neurobiologische Korrelate von Selbstkontrolle und Belohnungsverarbeitung bei Alkoholabhängigkeit

Neurobiological correlates of self-control and reward processing in alcohol dependence

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List of abbreviations

ACC	Anterior cingulate cortex
AD	Alcohol dependence
ADS	Alcohol Dependence Scale
AI	Anterior insula
BIS	Barratt Impulsiveness Scale
FH+	Healthy first-degree relatives of alcohol-dependent patients
HC	Healthy controls
IFG	Inferior frontal gyrus
LDH	Lifetime Drinking History
MFG	Middle frontal gyrus
MIDT	Monetary incentive delay task
mPFC	Medial prefrontal gyrus
OFC	Orbitofrontal cortex
SSS-V	Form V of the Sensation Seeking Scale
VBM	Voxel-based morphometry
VS	Ventral striatum
VTA	Ventral tegmental area

Abstract

Alcohol dependence has been characterized by decreased self-control and altered reward processing. Both are independent but potentially interrelated factors, and have been associated with neurobiological changes related to addiction. To date, research on the neurobiological correlates of self-control and reward processing in alcohol dependence has yielded mixed results. Therefore, the aim of the present dissertation was to contribute to a further understanding of their neurobiological basis. On the one hand, we investigated structural changes in brain areas related to impulsivity and sensation seeking (behavioral tendency towards potentially risky experiences) as potential indicators of self-control in alcohol-dependent patients with high and low life-time alcohol consumption. On the other hand, we focused on the functional activation of brain areas associated with reward anticipation in alcohol-dependent patients and healthy individuals at high genetic risk in order to disentangle potential cause and consequence of reward processing in the context of alcohol dependence.

In the course of this: *(I)* Brain volumetric differences and correlates of self-control (operationalized as impulsivity and sensation-seeking) were investigated using voxel-based morphometry. *(II)* Neuronal gain anticipation was investigated using the "Monetary Incentive Delay" task. *(I)* Structural alterations in diverse regions of the frontal cortex were identified in patients with alcohol dependence.

In a subgroup characterized by comparatively low life-time consumption, a positive association between the volume of the grey matter in right middle frontal gyrus and sensation seeking was found. No other structural correlates of self-control were found. *(II)* At the neural level, anticipation of money gain did not differ between (rather long-term) abstinent subjects with alcohol-dependence, healthy controls and subjects with high genetic risk for alcohol dependence. However, anticipation of monetary loss was associated with a reduced functional response in the anterior insula in alcohol-dependent patients compared to healthy individuals.

Altogether, our results replicate findings of decreased prefrontal grey matter in AD, however, not correlated with self-report measures of self-control. Further, our findings might even attribute a protective effect regarding brain volume in the right middle frontal gyrus to sensation seeking. Finally, the lack of group differences in neural reward processing does not support common reward-processing theories of predisposition or disrupted function in prolonged abstinence.

Zusammenfassung

Alkoholabhängigkeit wird mit verminderter Selbstkontrolle und veränderter Belohnungsverarbeitung assoziiert. Beide sind unabhängige Faktoren, stehen jedoch in wechselseitiger Beziehung zueinander und werden mit neurobiologischen Veränderungen im Zusammenhang mit Suchterkrankungen definiert. Bislang zeigten sich in Bezug auf neurobiologische Korrelate von Selbstkontrolle und Belohnungsverarbeitung bei Alkoholabhängigkeit gemischte Ergebnisse. Ziel dieser Dissertation war es daher, zum weiteren Verständnis dieser neurobiologischen Grundlagen beizutragen. Einerseits untersuchten wir strukturelle Veränderungen in Hirnarealen, die mit Impulsivität und Sensation Seeking (Verhaltenstendenz zu vielfältigen, teils riskanten Erfahrungen) und damit Indikatoren für möglicherweise verminderte Selbstkontrolle bei alkoholabhängigen Patienten mit hohem und niedrigem Lebenszeitalkoholkonsum zusammenhängen. Andererseits untersuchten wir funktionelle Aktivierung von Hirnarealen, die mit Belohnungsantizipation bei alkoholabhängigen Patienten und gesunden Personen mit genetischem Risiko in Verbindung stehen, um mögliche Ursachen und Folgen der Belohnungsverarbeitung im Zusammenhang mit der Alkoholabhängigkeit zu entflechten. Dabei wurden: *(I)* Hirnvolumetrische Unterschiede und Korrelate der Selbstkontrolle (operationalisiert durch Impulsivität und Sensation Seeking) mittels Voxel-basierter Morphometrie untersucht. *(II)* Die neuronale Verstärkungsantizipation wurde mit Hilfe der "Monetary Incentive Delay"-Aufgabe untersucht. *(I)* Strukturelle Unterschiede in Subregionen des frontalen Kortex wurden bei Patienten mit Alkoholabhängigkeit festgestellt. In einer Untergruppe, ausgezeichnet durch vergleichsweise geringen Lebenszeitkonsum, wurde ein positiver Zusammenhang zwischen dem Volumen der grauen Substanz im rechten mittleren frontalen Gyrus und Sensation Seeking festgestellt. Andere strukturelle Korrelate der Selbstkontrolle wurden nicht gefunden. *(II)* Auf neuronaler Ebene unterschied sich die Antizipation von Geldgewinnen nicht zwischen (eher Langzeit-) abstinenten Patienten mit Alkoholabhängigkeit, gesunden Kontrollpersonen und Probanden mit hohem genetischem Risiko für Alkoholabhängigkeit. Allerdings war die Erwartung von Geldverlust bei alkoholabhängigen Patienten im Vergleich zu gesunden Personen mit verminderter funktionellen Reaktion in der vorderen Insula assoziiert. Zusammenfassend unterstützen unsere Ergebnisse Befunde über eine verringerte graue Substanz im präfrontalen Bereich bei Alkoholabhängigkeit, die jedoch nicht mit Selbsteinschätzungen zur Selbstkontrolle korreliert. Außerdem könn-

ten unsere Ergebnisse Sensation Seeking in Bezug auf graue Substanz im mittleren frontalen Gyrus sogar eine schützende Wirkung zuweisen. Schließlich stützt das Fehlen von Gruppenunterschieden in neuronaler Belohnungsverarbeitung nicht die gängigen Theorien zur Belohnungsverarbeitung, die von Veranlagung oder gestörter Funktion bei längerer Abstinenz ausgehen.

1 Introduction

Alcohol is one of the leading causes of preventable mortalities, with 3 million deaths per year resulting from harmful abuse[1]. Chronic consumption of alcohol can lead to a transition from recreational use to alcohol dependence (AD). AD is a disorder characterized by high relapse rates, which has been defined as a problematic alcohol use pattern „ *[…], leading to clinically significant impairment or distress*" by the *Diagnostic and Statistical Manual for Mental Disorders*, 4th edition (DSM-IV)[2] and requires presence of at least three symptoms including habitual alcohol seeking and intake, lack of control in limiting intake or the emergence of tolerance/withdrawal symptoms[3]*. In line with the progression of AD, alcohol exerts its' initial reinforcing effect by activating reward circuits in the brain, while continued harmful use is accompanied by alterations in structure and function of several brain regions. These impairments may have a negative impact on the interaction of motivational drive (enhanced reactivity towards alcohol-related stimuli) and of self-control (which is supposedly impaired)[4].

> *Volkow & Baler, 2013[4]: „ […], the implications derived from the current understanding of addiction could be easily misconstrued as advocating a sort of moral relativism at the expense of individual responsibility. Yet, nothing could be farther from the truth; for the addicted individual is responsible for the management and treatment of this disease. But at the same time, the fact that addiction is a brain disease that impacts the very neural fabric that enables self-monitoring, self-determination and complex social functioning indicates that a fundamental revisiting of society's conventional responses to the problem of substance use disorders is long overdue."*

1.1 Self-Control

In the context of AD, impaired self-control consists of sustained alcohol seeking and consumption despite negative and harmful outcomes[5]. Factors that potentially contribute to this lack of self-control are impulsivity and the tendency to seek out stimulation[6,7].

*By now, with the introduction of the current DSM version (DSM 5)[8], AD and alcohol abuse, former distinct diagnoses were merged into alcohol use disorder (AUD) and criteria were slightly adapted. As before, International Classification of Diseases (ICD-11) distinguishes between dependence disorders and harmful use[9].

Impulsivity is conceptualized as a multi-dimensional construct that describes various tendencies such as lack of inhibition, preference for immediate satisfaction or unplanned hasty reactions towards external stimuli[10]. The Barratt Impulsiveness Scale (BIS) has been widely used to assess impulsivity and divides it into sub traits comprised of attention-, motor-, and nonplanning-impulsiveness[11]. On the other hand, sensation seeking describes the predisposition to engage in stimulating and novel experiences and comprises of four factors assessed with the Sensation Seeking Scale (SSSV): “thrill and adventure seeking”, “experience seeking”, “disinhibition”, and “boredom susceptibility”[12]. While both concepts have been suggested to contribute to decreased self-control, a conceptual issue arising from the literature relates to the distinct characteristics of impulsivity and sensation seeking[13]. While sensation seeking could affect alcohol use by increasing approach tendencies, impulsivity and drinking might be associated through coping motivations[14,15]. Contrary to impulsivity, sensation seeking has also been ascribed a protective function in stress reactivity, which in light of the aggravating effect of stress in addiction, could paradoxically render this trait somewhat protective in the context of AD[16-18]. The protective role may be due to sensation seekers approaching alternative non-drug rewards. Interestingly, thrill and adventure seeking has been coined non-impulsive while the other SSSV traits are regarded as impulsive and harmful[19]. Despite these theoretical disparities, sensation seeking and impulsivity have been found to be increased in AD patients and both traits might be associated with neurobiological alterations in brain regions that play an important role in executive functioning[20,21]. Some research suggests that impulsivity and sensation seeking are associated with dysfunctional cortico-striatal pathways[21,22]. Specifically, reductions in function and grey matter volume in prefrontal cortical areas were linked with lack of self-control in AD patient cohorts [23,24]. Here, neuroimaging studies uncovered associations between impulsivity and sensation seeking and altered functionality and structure in the middle frontal gyrus (MFG) and anterior cingulate cortex (ACC) as well as the medial prefrontal cortex (mPFC) and inferior frontal gyrus (IFG)[25-30]. However, structural imaging studies in particular have produced inconclusive results and most studies have been performed in a healthy population[31-33]. Furthermore, the extent to which high impulsivity might form a predisposing factor that causes involvement in problematic alcohol use or whether neuroadaptations in consequence of alcohol use lead to deficient self-control is not clear, yet[13,34,35]. The initial use of drugs or alcohol seems to gradually shift from more goal-directed to cue-biased drug-seeking that is in turn enhanced by lack of self-control due to neuroadaptive processes associated with alcohol

intake[35]. In light of the significance of quantity of alcohol intake on structural and functional cortico-striatal alterations[36,37] as well as treatment outcome and relapse[38,39], it makes sense to consider baseline consumption severity as a factor when examining neurobiological correlates of self-control in AD.

1.2 Reward Processing

It has been postulated that the impact of an impaired ability to control behavior and repress alcohol seeking on AD progression is further aggravated by alterations in reward processing. Neuroimaging studies focusing on the reward system have found anticipatory neural responses to monetary rewards to be blunted in exchange for increased drug-related neural cue-reactivity in (recently detoxified) AD populations[40-42]. Interestingly, multiple studies have associated this dampened neural reaction to natural reward with higher scores of impulsivity in AD individuals[43,44]. This further stresses the importance of the interplay between self-control and reward processing. The most widely used task to examine neural incentive anticipation is the monetary incentive delay task (MIDT)[45]. It has been found to elicit functional activation within the mesocorticolimbic system associated with positive (gain anticipation) and negative (loss anticipation) affect[46]. Here, the ventral tegmental area (VTA), ventral striatum (VS), ACC and anterior insula (AI) have been shown to be implicated across numerous studies[40].
Similar to research on self-control, a consensus on whether sensitivity to alternative reward is a predisposing or maintenance factor in AD has not been reached. In this context, several theories have been proposed: the reward deficiency theory postulates a predisposing deficit in the reward system that leads to compensatory drug seeking in order to stimulate dysfunctional dopaminergic neurotransmission, which in turn renders individual vulnerable to the development of drug- and alcohol dependence[47,48]. Other theories suggest that substance induced neuroadaptive changes drive the transition from recreational consumption to dependence. The allostatic hypothesis proposes neuroplastic alterations that reflect counter adaptive neural response to drug- and alternative reward effects on neurotransmitter systems [35], whereas brain stress systems are increasingly activated opposing the rewarding, sensations elicited by drug abuse[49]. These neuroplastic adaptions have been indicated to persist into prolonged abstinence

and speed of recovery may predict treatment outcome[35,50]. Finally, the incentive salience hypothesis postulates a drug-induced sensitization of the dopaminergic mesocorticolimbic system that leads to increased incentive salience attribution to drugs of abuse such as alcohol[51,52]. This in turn has been hypothesized to enforce drug-seeking behavior over selection of natural rewards in AD populations[53]. To help disentangle the effects of predisposition and neuroplastic changes due to alcohol abuse, investigation of relatives of AD with high genetic risk has proven useful, but results so far have also been rather inconclusive and limited by small sample sizes[54,55].

1.3 Research Question and Hypotheses

While self-control and reward processing may be two separately contributing factors in AD, they may have a reciprocal relationship and both are supposedly associated with neurobiological alterations in the context of addiction disorders. To date, neuroimaging research of self-control and reward processing in AD has produced mixed results and various questions remain to be answered.

Therefore, the aim of the present dissertation was to contribute to the further understanding of the neurobiological basis of structural changes in brain areas related to impulsivity and sensation seeking in AD clusters of high and low lifetime alcohol consumption to also reflect a dose-dependent effect of alcohol intake. Furthermore, this work focuses on functional activation in brain areas related to reward anticipation in AD and high genetic risk subjects, in an effort to disentangle cause and consequence in reward processing in the context of AD.

The following guiding questions formed the object of investigation of the present publications:

1) What are the structural correlates of impulsivity as well as sensation seeking in the brain and how is this association linked to lifetime alcohol consumption in detoxified AD patients?
2) Do the neuronal responses to gain and loss anticipation differ between (rather long-term abstinent) AD patients with and healthy first-degree relatives of AD as well as healthy controls?

2 Methods

2.1. Background and Study Design

Both studies were part of sequential interdisciplinary consortia that aimed at investigating the underlying mechanisms of AD (e:Med-Systems Medicine Consortium: “Alcohol Addiction - A Systems-Oriented Approach” building on the “National Genome Research Project”, NGFN).

Study I [61]

In the first study, 62 recently detoxified AD patients (abstinence duration *mean* = 14.28 days; *SD* 1.92) and 62 HC, matched for age, sex, and IQ were examined, using structural MRI. Here, gray matter volume of *a priori* defined brain regions was compared between groups and correlations with questionnaire measures of self-control were assessed. Here, the Barratt Impulsiveness Scale (BIS 11)[10] as well as the updated form V of the Sensation Seeking Scale (SSSV)[56] were used. Severity of dependence was assessed with the Alcohol Dependence Scale (ADS)[57]. In addition, the individual lifetime alcohol consumption of all study participants was collected in a biographical interview (Lifetime Drinking History (LDH)[58]).

Study II [59]

In the second study, 75 rather long-term abstinent AD patients (abstinence duration *mean* = 957.66 days; *SD* = 1436.87), 76 HC and 62 healthy first-degree relatives of alcohol-dependent individuals (FH+) were studied using functional MRI. Neuronal activation patterns during a monetary incentive delay task (MIDT)[45] was used for group comparisons.

Both studies included participants diagnosed with AD according to DSM-IV criteria. Exclusion criteria for all participants of both studies were Axis I disorders according to DSM-IV (except for nicotine abuse or dependence for patients). The project was approved by the Ethics Committee of Charité — Universitätsmedizin Berlin and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Participants were given detailed information and provided fully informed written consent.

2.2. Neuroimaging

Structural MRI

In *study I*, the collection of T1-weighted anatomical image data was performed using standardized three-dimensional MR sequences (Magnetization Prepared Rapid Gradient Echo, MPRAGE) in a 3 Tesla MR tomograph (MAGNETOM Trio; Siemens, Germany).

Functional MRI

In *study II*, T2-weighted functional imaging data were collected in 3 Tesla MR tomographs (Berlin and Mannheim: MAGNETOM Trio, Siemens, Erlangen, Germany; Berlin: MAGNETOM Prisma, Siemens, Erlangen, Germany). FMRI data acquisition was performed with a Siemens product sequence (Echo Plenar Imaging, EPI, gradient echo) adapted to the MIDT paradigm.

Paradigm

The task that was used in *study II* was a modified version of the MIDT[45] that was presented in the scanner using the software Presentation (Neurobehavioral Systems, Albany, CA, USA).

During an anticipation phase, trials consisted of unpredictably appearing cues that predicted potential gains, losses or a neutral outcome**.** After a variable and brief delay, participants were instructed to react to a target cue by pressing a button. Success or failure of the response were indicated by direct feedback in an outcome phase. Here, monetary gain or loss were represented by +1€ or -1€ respectively, while neutral trials were followed by 0€ (Figure 1). The task lasted around 12 minutes and consisted of 75 trials in randomized order (25 in each condition). Successful learning of the cue-outcome association was ensured by participants' performing practice session, which was performed in the scanner prior to scanning. To ensure task engagement, an adaptive algorithm ensured individual success rates to approximate 70%.

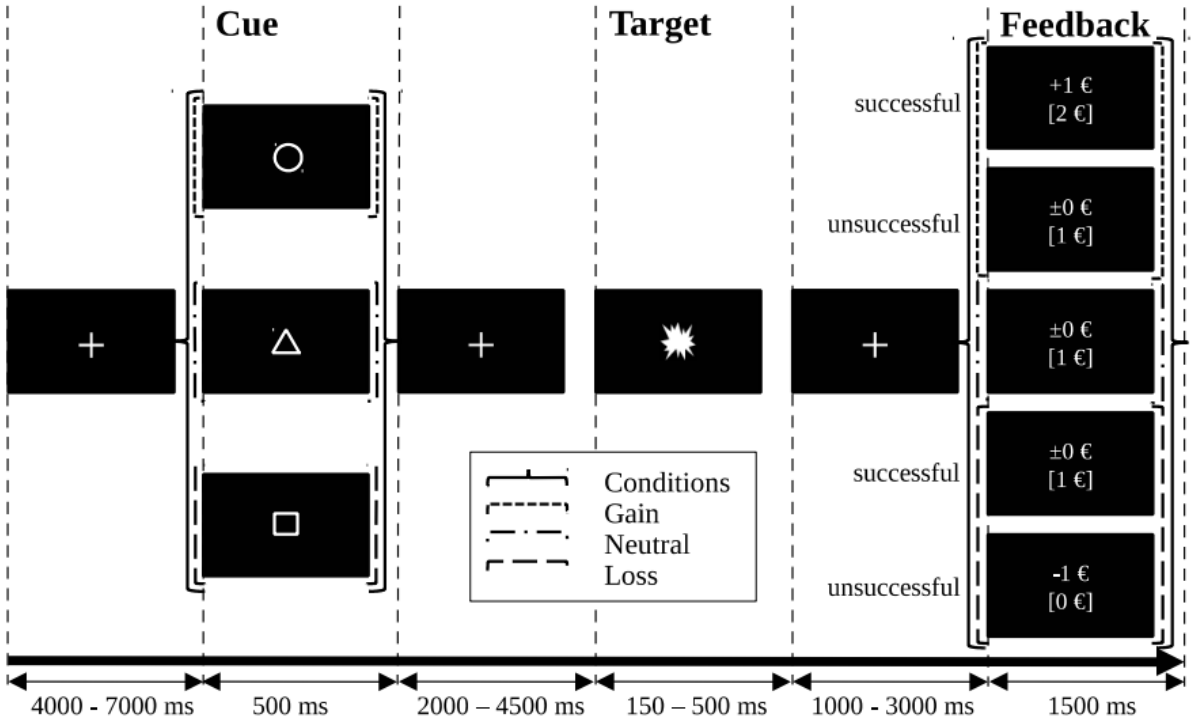

Figure 1: **Schematic representation of the monetary incentive delay task used in study II**. MIDT = monetary incentive delay task. Copied from Musial et al., 2022[59]

2.3 Statistical Analysis

With the Matlab-based software (Math-Works, Natick, MA, USA) "Statistical Parametric Mapping software package" (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) structural as well as functional MRI data were analyzed using the. All whole-brain and ROI analyses were performed with correcting for family-wise error (FWE) and a significance threshold of $p < 0.05$. Behavioral data were analyzed using IBM SPSS Statistics 23 and 28 for Windows (SPSS Inc., Chicago, IL, USA).

2.3.1. Specific Analyses

Study I

The main focus of this investigation was the analysis of neuroanatomical correlates in AD, with a voxel-based morphometry (VBM) approach. To this end, the computational anatomy toolbox (CAT12, Gaser and Dankhe, http://www.neuro.uni-jena.de/vbm) allowed

for automatic grey matter analysis to characterize differences between groups' regional brain volume based on structural MRI scans. The data went through preprocessing steps that comprised of tissue class segmentation, normalization, data quality checks and smoothing. Total intracranial volume estimates were applied as a covariate to control for individual brain size in the statistical analyses.

The preprocessed data was used to estimate a general linear model to 1. calculate group difference statistics by means of an analysis of covariance (ANCOVA) and 2. correlate measures of self-control, dependence severity and alcohol consumption with grey matter volume by multiple regression. All analyses were focused on a priori regions of interest (ROI), namely MFG, IFG, orbitofrontal cortex (OFC), mPFC and ACC. ROI masks were defined using the probabilistic Neuromorphometrics atlas (http://www.neuromorphometrics.com). To account for differences in alcohol consumption, analyses were repeated in AD high- and low-consumption groups, stratified by a k-means clustering algorithm based on LDH. Finally, results were further explored by mediation analysis that was performed with the PROCESS macro[60] implemented in SPSS.

Study II

In the second study, the processing of the functional images comprised of slice-timing and motion correction, co-registration, structural data segmentation and Montreal Neurological Institute (MNI) space normalization followed by smoothing (8 mm kernel). Preprocessed data were high-pass filtered with a cutoff of 128 s. As analysis focused on *a priori* ROIs, a binary mask of the VS, AI, ACC and VTA was created based on coordinates from previous MIDT studies. On a single-subject level, a model that included target presentation, anticipation (gain, loss, neutral) as well as feedback conditions (loss avoidance, failed loss avoidance attempt, neutral feedback, gain and failed gain attempt) was estimated, using head motion parameters as additional regressors. Linear contrasts images of interest were "gain > neutral anticipation" and "loss > neutral anticipation". Subsequently, activation maps for both contrasts within each subgroup (AD, HC, FH+) were calculated with one-sample t-tests. Activation differences between groups were computed with independent samples t-test. All models included MIDT success rate, handedness, location of MRI scanner, and smoking as nuisance variables.

3. Results

Study I

In line with our hypothesis, AD patients scored significantly higher than controls on the BIS total scale as well as attentional impulsivity and non-planning subscales, in contrast, no group differences in sensation seeking were found. Comparing high- to low consumers, AD patients with lower consumption displayed higher sensation seeking (total SSSV score) as well as Thrill and Adventure Seeking scores. Subgroups did not differ in impulsivity (BIS scores) but in age, as the high consumption group was significantly older. As expected, we found lower grey matter volume in AD patients compared to controls in bilateral MFG, right ACC and right mPFC. In addition, we found a positive association between right MFG volume of grey matter and the sensation seeking score (SSSV total score $r = 0.49$, $r^2 = 0.249$; $p_{FWE} = 0.05$; SSSV Thrill and Adventure Seeking $r = 0.53$, $r^2 = 0.280$; $p_{FWE} = 0.002$) in AD patients (*please see Figure 2*). This rather unexpected positive correlation was driven by the low-consumption cluster ($p_{Bonferroni} = 0.003$). In addition, addiction severity (ADS score) and right OFC volume were negatively correlated ($p_{FWE} = 0.03$). We found no significant associations between BIS impulsivity scores as well as LDH consumption quantity and grey matter volume.

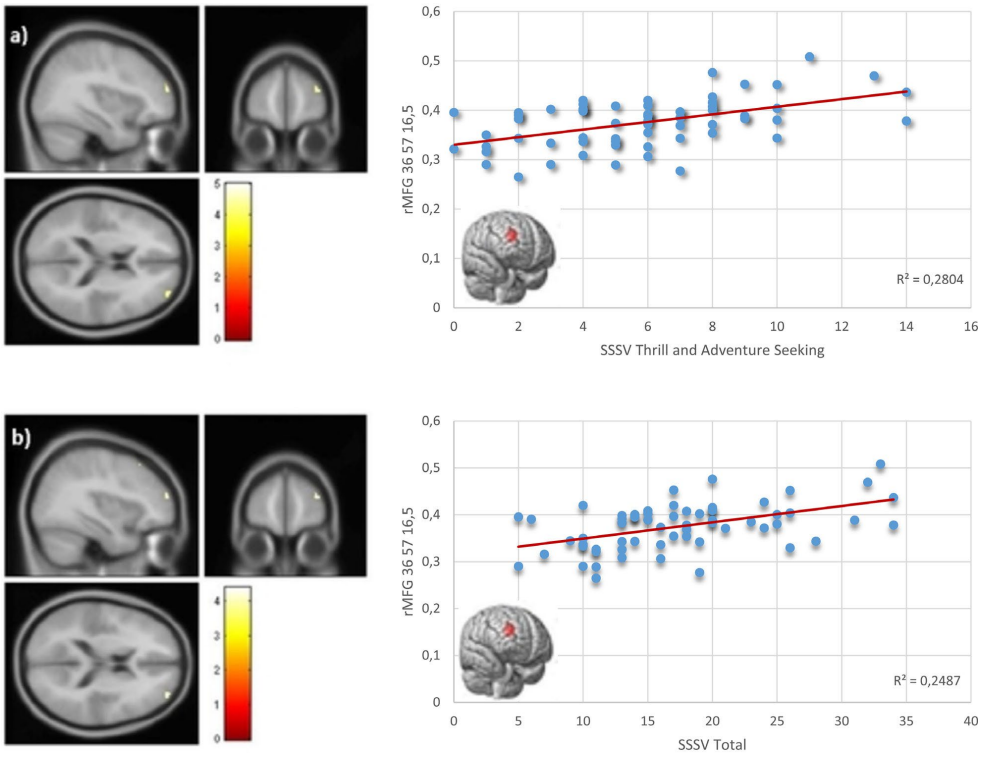

Figure 2. **Results of multiple regression analyses between sensation seeking and grey matter volume in alcohol-dependent patients.** The threshold of significance was set at $p < 0.05$ FWE-corrected. T-scores are represented by color scales. rMFG = right middle frontal gyrus; SSSV = sensation seeking scale updated form V. Copied from Rosenthal et al.[61]

Study II

We found robust activations during the anticipation of losses and gains in our predefined ROIs (VTA, VS, ACC and AI) in the MIDT (*please see Figure 3*). There were no group differences in activation between AD, FH+ and HC during the anticipation of gain. However, neural activation decreased with increasing age in the bilateral VS (right p_{FWE} = .003; left p_{FWE} = .013) and left AI (p_{FWE} = .043). In addition, AD subjects displayed decreased neural activation during the anticipation of loss in the left AI in comparison to HC subjects (p_{FWE} = .009) (*please see Figure 4*). Similar to gain anticipation, neural activation in response to loss anticipation decreased with increasing age in left putamen (p_{FWE} = .026), bilateral VS (left p_{FWE} = .002; right p_{FWE} = .024) and left AI (p_{FWE} = .014). Considering the substantial effect of age on MIDT brain activation, analysis was repeated in age-matched subgroups as well as with inclusion as age as a covariate. Here,

the only previously significant group difference in left AI activation during loss anticipation was rendered insignificant.

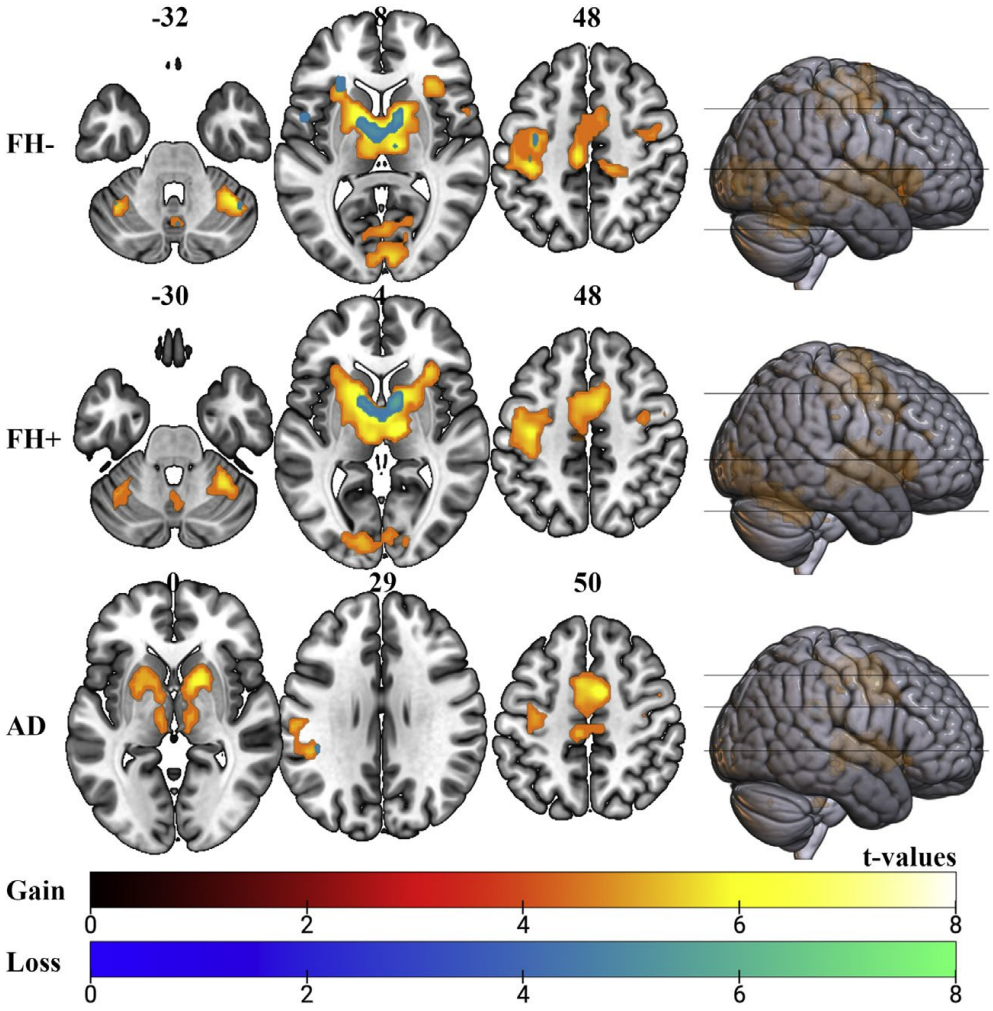

Figure 3. **Whole-brain activity during gain and loss anticipation**. FWE-corrected significance threshold was set at $p < 0.05$. Colors illustrate contrasts: gain (gain anticipation versus neutral; hot color scale) and loss (loss anticipation versus neutral; cool color scale) anticipation. Z coordinates are depicted above all layers. FH- = "healthy subjects without family history of alcohol dependence" (HC); FH+ = "healthy first-degree relatives of alcohol-dependent individuals"; AD = "alcohol dependent patients". Copied from Musial et al.[59]

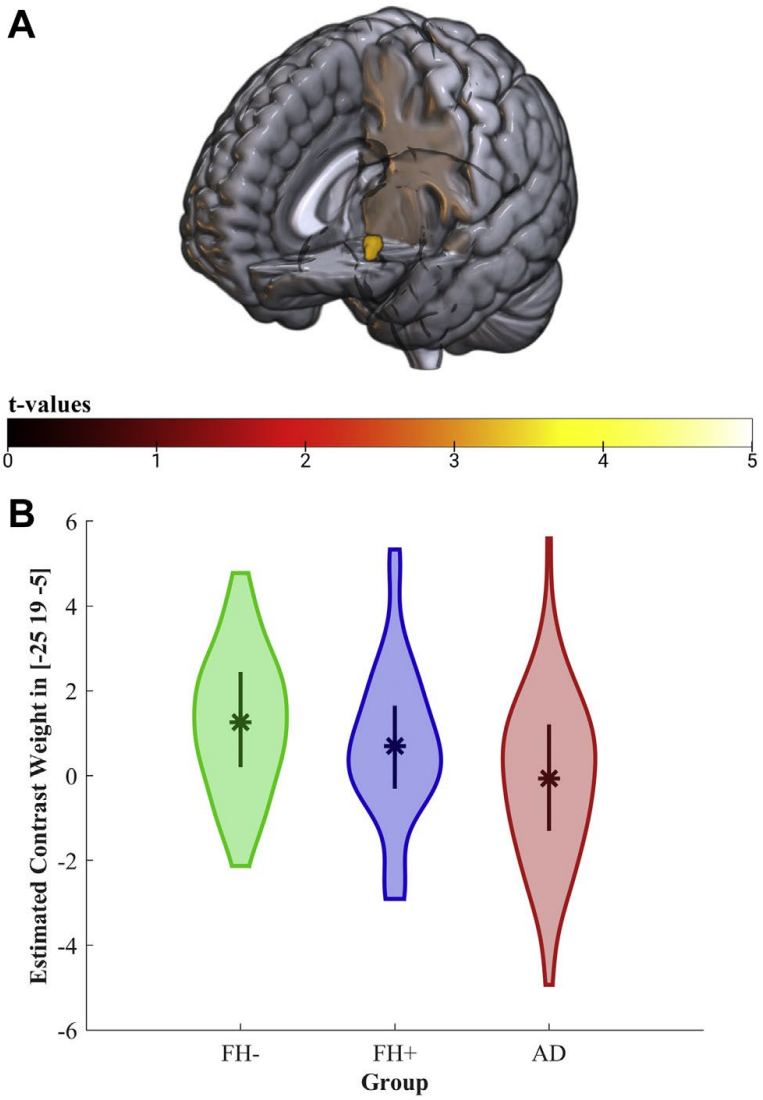

Figure 4. **Brain activation group differences in left anterior insula**. A. Activity difference between patients with alcohol dependence and healthy controls without family history of alcohol dependence. An uncorrected significance threshold of p< 0.001 was set. B. Group difference peak voxel estimated contrast weights. FH- = “healthy controls without family history of alcohol dependence” (HC); FH+ = “healthy first-degree relatives of alcohol-dependent individuals”; AD = “alcohol dependent patients”. Copied from Musial et al.[59]

4. Discussion

The following discussion elucidates the role of self-control and reward processing in AD. In the first study, we assessed grey matter volume in relation to impulsivity and sensation seeking as proxies of self-control in AD patients, while taking lifetime alcohol consumption into account.
In the second study, we examined mesocorticolimbic brain activation elicited by reward and loss anticipation, to study differences between AD patients, healthy first-degree relatives of AD patients and HC without family history of alcohol dependence.

4.1 Short summary of results

In comparison to healthy subjects, AD subjects displayed lower grey matter volume in areas related to self-control, including the bilateral MFG and right mPFC as well as in the right ACC. Remarkably, none of the impulsivity or sensation seeking scores negatively correlated with frontal lobe structure. Instead, sensation seeking - the thrill and adventure seeking subscale in particular – showed a positive association with right MFG volume. Additional analyses showed, that this association was prominent in the low consumption cluster only. The high and low consumption group significantly differed in age, as the high consumption group was older in comparison. Furthermore, severity of dependence as assessed by the ADS was negatively correlated with OFC volume but we found no negative association between grey matter and lifetime alcohol intake. Finally, we found no structural correlates of impulsivity assessed by the BIS. Regarding the investigation of natural reward-associated neural activation, we could not find any differences in neural response in anticipation of monetary gain between rather long-term abstinent AD subjects, high genetic AD risk participants, as well as HC. Only when anticipating monetary loss, the AD group displayed lower left AI activation compared to healthy subjects, which was not found in high genetic risk participants (FH+). However, inclusion of the effect of age diminished the significance of this group difference.

4.2 Interpretation of results

To a certain degree, findings of both studies were unexpected, as the results were in contrast with some of the neuroimaging research conducted on impulsivity, sensation

seeking and reward processing thus far. For instance, while AD subjects displayed lower grey matter volume across almost all prefrontal cortical areas of interest, we could not find an association between structure and severity of impulsivity and sensation seeking. On the one hand, this validates the findings of a large body of research that found AD patients to display grey matter volume loss, particularly in the PFC[62-64]. In our sample, this was not correlated with lifetime alcohol intake, while machine learning could successfully predict lifetime alcohol consumption from whole-brain grey matter data[65]. On the other hand, despite the neurotoxic effect of alcohol on brain structure, a correlation might have been undetected in our sample, as a result of a lack of a linear dose-response. This could be due to a variety of modifying factors such as neuromaturation, as well as individuals' frequency levels of drinking[66,67]. In addition, we also controlled for age as a confounding factor, which is associated with both grey matter shrinkage as well as longer periods of drinking and therefore increased lifetime alcohol intake. This could have masked potential effects[68]. In line with previous studies[69], we did find an association of structure loss and dependence severity in AD, namely the OFC. The OFC regulates motivation and next to its implication in AD, reduced volume of this region was found in prospectively relapsing patients[70,71]. While we found that consumption levels did not influence this association, structural volume reductions in the OFC has been shown to partially restore through abstinence[72,73].

Considering self-reported impulsivity, we found BIS scores to be higher in the AD population - validating a trend across studies[74]. Despite these differences, there was no association between impulsivity and the prefrontal structures we examined. So far, while some research pointed out structural volume decreases to be linked to impulsivity [32,34], some studies also showed a positive relationship between this construct and prefrontal grey matter[75]. This absent association, together with the lack of consumption-group differences in BIS scores, makes it difficult to draw conclusions on the influence of these proxies of decreased self-control on the course of AD: The increased impulsivity could not be attributed to the amount of alcohol consumed nor does it correlate with the grey matter decreases we found in AD.

Somewhat surprising, we could not detect any group differences in sensation seeking. In fact, the AD group with lower alcohol consumption showed higher sensation seeking scores, and in this subgroup, the right MFG displayed a positive association with Thrill and Adventure Seeking together with the total sensation seeking score. This finding is in

contrast to reports of a negative association between prefrontal brain structure and sensation seeking[22]. Sensation seeking is commonly perceived as a risk factor that contributes to the initiation and loss of control over alcohol intake[76,77]. In a study in adolescent populations, it predicted alcohol use[77], while another one found in-person variability in sensation seeking to be linked to alcohol use and other risky behaviors[78]. However, a consensus about the causal role of sensation seeking and its structural correlates in addictive disorders has not been reached. On the one hand, the positive relationship between prefrontal structure and sensation seeking might suggest a protective effect, at least of the Thrill and Adventure Seeking domain. This domain has been ascribed a social and unimpulsive character[79], and might be related to alternative, non-drug reward. On the other hand, sensation seeking has been shown to decrease with age, indeed supported by our results of a significant age differences between consumption groups. Here, probably attributed to the duration of drinking, high consumers were older compared to low consumers. Consequently, the positive association between MFG and sensation seeking might have been attributed to age, an influential factor in structural brain deterioration, especially in the PFC[80,81].

Aging not only plays a major part in brain structural development, it also impacts brain function. In our functional neuroimaging study, AD patients showed decreased loss anticipation in the left AI compared to HC, a finding that diminished with the inclusion of the age factor. Disrupted insula function has been indicated to play a role in addictive disorders, attributed to its functional relevance in the processing of salient stimuli and cue-induced craving[82]. In the context of loss anticipation, the insula has been proposed to process interoceptive information and is effectively connected to the VS to impact on decision-making[83]. While the decreased functional activation could indicate a certain impairment of loss avoidance in AD, it could also be solely attributed to age-related decreased function. Furthermore, for monetary loss anticipation, there were no group differences in function of any other ROIs, a finding that replicates the conclusions most other studies come to[44,84-86]. If MIDT-related loss anticipation is regarded in terms of anticipatory action for loss avoidance, the lack of group differences might contribute to the rejection of the reward deficiency syndrome hypothesis. In contrast to a large body of research [43,54,87], we detected no group differences in functional activation of key areas related to reward processing in anticipation of monetary gain in subjects with and without family history of AD. Here, the lack of disrupted functioning in first degree relatives

might also refute the “reward deficiency syndrome” hypothesis – and along with it, the premise of predisposing vulnerabilities in reward processing in the context of AD. Nevertheless, an increased concentration of D2 dopamine receptors has been found in the VS of subjects with high genetic AD risk, while abstinent AD showed reduced D2 receptor concentration[88]. This in turn might suggest a possible protective effect of high D2 receptor density from progression to problematic alcohol use or dependence. Neurobiologically this could be explained in light of the tight link between D2 receptors in the VS and prefrontal executive function and their potential effect on self-control[88]. Comparing AD and HC, anticipation of monetary gain did not elicit divergent neuronal responding in reward system regions. Again, this stands in contrast to various other studies that found an overall pattern of decreased activation in reward system areas[41,44,86,89,90] and reduced functioning of D2 receptors that recovers during abstinence[91]. Different from these studies, our cohort exhibited a rather long abstinence duration with an average of 3 years, while AD subjects are usually examined within the first weeks of abstinence. In line with that, we cannot exclude the possibility of restored dopaminergic function due to abstinence, which have been observed across some studies[41,44,89,90]. In addition, reward and loss magnitudes in the used MIDT were relatively low (+/- 1€), possibly limiting the reliability of the mesolimbic activation pattern we found[92]. Notwithstanding the variable abstinence duration in our sample, our findings likewise do not support the allostatic hypothesis that entails reduced neuronal responding to natural rewards that extents into long-term abstinence[49,50]. Although, increased mesocorticolimbic cue-reactivity to alcohol stimuli was found in AD patients and heavy drinkers, we cannot test the hypothesis of incentive salience [53,93]. That is, with the MIDT we cannot rule out the possibility of a hypersensitive reward system attributing increased incentive salience towards drugs of abuse at the cost of natural rewards.

4.3 Embedding the results into the current state of research

Our proxies of self-control (impulsivity, sensation seeking) and reward anticipation were not significantly associated with severity of AD, brain volume loss or functional activation differences. But the lack of correlation with lifetime alcohol consumption together with a predictive significance of impulsivity and risky drinking shown across studies[7,94], support the notion of reduced self-control contributing to AD vulnerability. However, the

lack of structural correlates with measures of self-control do not support the potential this factor to exerts an effect through prefrontal structural deficits. This questions the concept of a neurobiological self-control phenotype in the context of AD. In line with this, adverse experiences, such as early childhood trauma has been shown to exert effects on serotonergic functioning affecting levels of impulsivity and drinking[95]. In line with this, the expression of self-control highly depends on sociological and environmental factors. Higher socioeconomic status allows for sensation seeking to be channeled in stimulating activities such as extreme sports or traveling, while riskier outlets for these behavioral tendencies have to be found for those with lower income background. With regard to genetics, the lack of altered neuronal reward-processing in healthy AD relatives weakens the idea of predisposing deficits at least with regard to natural reward.
While we cannot exclude the possibility of an increased salience attribution to drug-related reinforcers, the absence of alterations in healthy subjects with a family history of AD refutes the idea of a large genetic component in non-drug reward processing. Furthermore, the comparable neuronal activation in long-term abstinent AD patients and healthy controls, importantly indicates a recovery or lack of impairment of natural reward processing.
Overall, our results support the notion that the investigated factors of AD are not “carved in stone” predispositions, but aggravating contributors of the disease. On the one hand, our findings favor the focus on prevention of environmental triggers of maladaptive behaviors through a vast offer of leisure and sports activities, such as the innovative Icelandic Prevention Model[96]. On the other hand, group differences in self-reported impulsivity warrant an importance of strengthening cognitive control through systematic rehabilitation in AD patients[97].

4.4 Strengths, limitations and future directions

Both studies have several limitations that warrant to be addressed. First of all, our samples differed in proportion of male and female subjects. This however, represents the prevalence of AD, with males being more commonly affected by the disease than females[98]. While we did take gender into account when analyzing our data, an even distribution of male (n = 46 in study *I*; n = 54 in study *II*) and female (n = 16 in study *I*; n = 21

in study *II*) participants could enable researchers to specifically address gender differences in patterns of reward processing and self-control and their neurobiological correlates[99].

Further, despite the effort to control for the confounding factor of age, we cannot rule out that some of our findings or the lack thereof could be attributed to this. For instance, trait sensation seeking has been shown to decrease with age, consequently we cannot rule out that reduced sensation seeking in high alcohol consuming AD is an age effect rather than a protective factor in low-consuming AD.

With regard to reward anticipation, inclusion of age as a covariate did not alter the results. In light of this, we assume comparable mesocorticolimbic functioning in all groups to be likely. Age not only affects neurobiological factors in AD, there is accumulating evidence that points to differential effects of risky neurobiological and psychosocial traits depending on age group and developmental stage[100,101]. In an effort to extricate the effect of age, a research consortium currently focuses on depiction of these moderating factors across the lifespan[102]. In contrast to this effort to describe longitudinal trajectories of alcohol use and its' contributing factors, our study design was cross-sectional, thus making it difficult to conclude how reward-processing and self-control develop, particularly over the course of abstinence. While cross-sectional studies cannot imply directionality from their results, the inclusion of baseline consumption severity contributes to partializing out some of the causal effect of alcohol on neurobiological and psychosocial functions. Furthermore, the inclusion of healthy first-degree relatives lent this study a robust design to test different hypotheses of reward processing in AD.

Finally, although disrupted reward-processing and self-control may interact with each other, we did not investigate these factors in the same cohort of individuals, excluding the possibility of examining the contribution of both factors or their interaction in this study. Overall, future research efforts could focus on the relationship between self-control and reward processing in cohorts of AD and at-risk populations, while taking different stages of addiction processes into account.

5. Conclusions

In conclusion, our findings indicated structural deficits in a priori defined prefrontal cortical regions such as the MFG, ACC and mPFC. However, we could not correlate grey matter volume in these regions to impulsivity. On the other hand, a contributing role of alcohol consumption levels on the association of rMFG volume and sensation seeking was found as the lower consumption group was characterized by a positive correlation between rMFG grey matter and total sensation seeking in addition to the thrill and adventure seeking scores. Furthermore, our findings could not support the reward deficiency syndrome or allostatic hypothesis in regard to permanent alterations in reward processing during protracted abstinence. Overall, future research on reward-processing and self-control in AD should focus on longitudinal trajectories across the lifespan to disentangle the directionality of these effects on the course of AD.

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Statutory Declaration

“I, Annika Rosenthal, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic “Neurobiologische Korrelate von Selbstkontrolle und Belohnungsverarbeitung bei Alkoholabhängigkeit” “Neurobiological correlates of self-control and reward processing in alcohol dependence” independently and without the support of third parties, and that I used no other sources and aids than those stated.
All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; http://www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

18.10.2022

Date Signature

Declaration of your own contribution to the publications

Annika Rosenthal contributed the following to the below listed publications:

Publication 1: **Annika Rosenthal**, Anne Beck, Evangelos Zois, Sabine Vollstadt-Klein, Henrik Walter, Falk Kiefer, Falk W. Lohoff, und Katrin Charlet, Volumetric Prefrontal Cortex Alterations in Patients With Alcohol Dependence and the Involvement of Self-Control, Alcoholism: Clinical and Experimental Research, 2019

Contribution (please set out in detail):

Ms. Rosenthal's contribution to this scientific publication equals up to 65%:

- ➔ data cleaning and editing
- ➔ Statistical analysis of behavioral and imaging data with SPSS and SPM12/CAT12
- ➔ Composing the first draft of the manuscript (she drafted the text and provided all figures and tables) and editing according to co-author feedback
- ➔ Submission of the manuscript
- ➔ Editing the manuscript according to peer-reviewer's comments and suggestions as well as answering the remarks on the first draft

Publication 2: Milena Philomena Maria Musial, Anne Beck, **Annika Rosenthal**, Katrin Charlet, Patrick Bach, Falk Kiefer, Sabine Vollstädt-Klein, Henrik Walter, Andreas Heinz, Marcus Rothkirch, Reward Processing in Alcohol-Dependent Patients and First-Degree Relatives: Functional Brain Activity during Anticipation of Monetary Gains and Losses, Biological Psychiatry, 2022

Contribution (please set out in detail):

Ms. Rosenthal's contribution to this scientific publication equals up to 35%:

- ➔ Aiding implementation of the study
- ➔ Recruitment and eligibility screening of participants
- ➔ Conducting neuropsychological testing and the majority of fMRI assessments
- ➔ Study project management
- ➔ Editing the first draft of the manuscript in terms of language and content
- ➔ Analysis for exploratory results (MIDT outcome phase reported in the supplements on pages 17 and 33)
- ➔ Finalizing manuscript editing for resubmission after peer-review

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Signature, date and stamp of first supervising university professor / lecturer

Signature of doctoral candidate

Excerpt from Journal Summary List

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI
Selected Categories: **"SUBSTANCE ABUSE"** Selected Category Scheme: WoS
Gesamtanzahl: 42 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1.	TOBACCO CONTROL	9,207	6.726	0.018580
2.	ADDICTION	19,861	6.343	0.030820
3.	ADDICTION	19,861	6.343	0.030820
4.	INTERNATIONAL JOURNAL OF DRUG POLICY	5,658	4.444	0.014970
5.	Alcohol Research-Current Reviews	899	4.214	0.002220
6.	ADDICTION BIOLOGY	4,329	4.121	0.008280
7.	NICOTINE & TOBACCO RESEARCH	10,026	4.079	0.020870
8.	DRUG AND ALCOHOL DEPENDENCE	20,269	3.951	0.040630
9.	Harm Reduction Journal	1,512	3.818	0.003540
10.	ADDICTIVE BEHAVIORS	13,899	3.645	0.022950
11.	ADDICTIVE BEHAVIORS	13,899	3.645	0.022950
12.	Addiction Science & Clinical Practice	646	3.088	0.001690
13.	JOURNAL OF SUBSTANCE ABUSE TREATMENT	5,696	3.083	0.010000
14.	ALCOHOLISM-CLINICAL AND EXPERIMENTAL RESEARCH	14,315	3.035	0.015690
15.	Journal of Addiction Medicine	1,672	3.014	0.005140
16.	AMERICAN JOURNAL OF DRUG AND ALCOHOL ABUSE	2,780	2.925	0.004250
17.	JOURNAL OF GAMBLING STUDIES	2,877	2.836	0.003710
18.	PSYCHOLOGY OF ADDICTIVE BEHAVIORS	5,301	2.780	0.007640
19.	Substance Abuse	1,595	2.652	0.004540

Printing copy(s) of the publication(s)

Rosenthal, A., Beck, A., Zois, E., Vollstädt-Klein, S., Walter, H., Kiefer, F., Lohoff, F. W. & Charlet, K. (2019). Volumetric Prefrontal Cortex Alterations in Patients With Alcohol Dependence and the Involvement of Self-Control. *Alcoholism: Clinical and Experimental Research* **43**, 2514-2524.

https://doi.org/10.1111/acer.14211

Excerpt from Journal Summary List

Journal Data Filtered By: **Selected JCR Year: 2020** Selected Editions: SCIE,SSCI
Selected Categories: **"NEUROSCIENCES"** Selected Category Scheme: WoS
Gesamtanzahl: 273 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NATURE REVIEWS NEUROSCIENCE	49,897	34.870	0.048890
2	NATURE NEUROSCIENCE	73,709	24.884	0.128020
3	TRENDS IN COGNITIVE SCIENCES	33,482	20.229	0.036270
4	NEURON	111,115	17.173	0.175220
5	ACTA NEUROPATHOLOGICA	28,031	17.088	0.036970
6	MOLECULAR PSYCHIATRY	28,622	15.992	0.046220
7	Molecular Neurodegeneration	6,772	14.195	0.011650
8	TRENDS IN NEUROSCIENCES	22,858	13.837	0.019470
9	Nature Human Behaviour	5,549	13.663	0.023120
10	BRAIN	64,627	13.501	0.061550
11	BIOLOGICAL PSYCHIATRY	50,155	13.382	0.045540
12	JOURNAL OF PINEAL RESEARCH	12,492	13.007	0.008170
13	BEHAVIORAL AND BRAIN SCIENCES	11,610	12.579	0.007760
14	Annual Review of Neuroscience	14,699	12.449	0.010490
15	PROGRESS IN NEUROBIOLOGY	15,161	11.685	0.010300
16	SLEEP MEDICINE REVIEWS	11,218	11.609	0.014840
17	ANNALS OF NEUROLOGY	43,728	10.422	0.039960
18	NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS	36,525	8.989	0.048970
19	Brain Stimulation	9,206	8.955	0.015960
20	npj Parkinsons Disease	1,093	8.651	0.003040
21	FRONTIERS IN NEUROENDOCRINOLOGY	5,338	8.606	0.005050

Printing copy(s) of the publication(s)

Musial, M. P. M., Beck, A., **Rosenthal, A.**, Charlet, K., Bach, P., Kiefer, F., Vollstädt-Klein, S., Walter, H., Heinz, A. & Rothkirch, M. (2022). Reward Processing in Alcohol-Dependent Patients and First-Degree Relatives: Functional Brain Activity during Anticipation of Monetary Gains and Losses. *Biological Psychiatry,* **93***,* 546-557.

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Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Publication list

Beck, A.*, **Rosenthal, A.***, Auriacombe, M., & Romanczuk-Seiferth, N. (2020). (Neuro) therapeutic approaches in the field of alcohol use disorders. *Current Addiction Reports*, *7*(3), 252-259.

Beck, A., **Rosenthal, A.**, Müller, C., Heinz, A., & Charlet, K. (2018). Alkohol. In *Handbuch Psychoaktive Substanzen* (pp. 609-629). Springer, Berlin, Heidelberg.

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**equal contribution*

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