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Using machine learning to resolve the neural basis of alcohol dependence

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Table of contents

Abbreviations

AUC	area under the receiver operating characteristic curve
BOLD	blood oxygenation level dependent
CI	confidence interval
DSM	diagnostic and statistical manual of mental disorders
DV	decision value
EEG	electroencephalography
fMRI	functional magnetic resonance imaging
FWHM	full-width-half-maximum
GNB	Gaussian Naïve Bayes
iRISA	syndrome of impaired response inhibition and salience attribution
LeAD	research program on "Learning and Habitisation as Predictors of the Development and Maintenance of Alcoholism"
LDA	linear discriminant analysis
MEG	magnetoencephalography
MVPA	multivariate pattern analysis
mPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
NGFN+	national genome research network plus
PET	positron emission tomography
PFC	prefrontal cortex
SNR	signal-to-noise ratio
SVM	support vector machine
WeiRD	weighted robust distance

1. INTRODUCTION

Alcohol dependence, the physical or psychological dependence on alcohol, is one of the most prevalent psychiatric disorders worldwide (Grant et al., 2004; Kessler et al., 2005; Rehm et al., 2015; Wittchen et al., 2011). It is a highly disabling mental disorder (Dawson et al., 2009; Hasin et al., 2007), impairs productivity (Rehm et al., 2009) and social functioning (Zeichner et al., 1994; Brismar and Bergman, 1998; Heinz et al., 2011), and contributes significantly to global morbidity and mortality (Lozano et al., 2012; Murray et al., 2012; Heinz et al., 2016). A better understanding of the underlying neurobiological disease mechanisms is thus a pressing societal issue.

To foster this understanding, the German Research Foundation (Deutsche Forschungs-gemeinschaft) funded a bicentric research unit (FOR 1617) at the Universitätsklinikum Dresden/Technische Universität Dresden and Charité Universitätsmedizin Berlin to investigate the neural basis of alcohol dependence ('Learning and Habitisation as Predictors of the Development and Maintenance of Alcoholism'; LeAD study). The LeAD study collected behavioural, functional and structural neuroimaging, psychosocial and genetic data in a number of cohorts, in particular a matched patient/control sample and an at-risk population of young adults to investigate the development of alcohol dependence.

The majority of works presented here are based on the matched patient/control sample of the LeAD study with a special emphasis on machine-learning approaches to neuroimaging data analysis. More specifically, the first part of this habilitation reviews works with a stronger focus on methodology in machine learning (2.1) and the second part describes works in which machine learning was applied to clinical research questions

based on neuroimaging data of the LeAD study (2.2). This introduction thus first provides a primer for machine learning in neuroimaging and then describes the specific research questions on alcohol dependence that were addressed through these techniques.

Machine learning in neuroimaging

In the early years of human neuroimaging, the analysis of brain data mostly followed a parsimonious approach: a statistical univariate comparison of activation levels between experimental conditions (within-subject) or between groups of participants (between-subject, e.g. patient-control studies). However, with the advent of higher computational power and the development of specialized data analysis toolboxes, a number of more advanced analysis techniques have emerged, which are collectively summarized as *multivariate pattern analyses* (MVPA).

The application of MVPA is driven by the assumption that valuable information is encoded beyond the univariate level of individual measurements (e.g., voxels, sensors or regions of interest) – in patterns of brain measurements. In other words, information in the brain about e.g. sensory representations or markers of psychiatric disease must not necessarily manifest as an overall difference in activation levels, but as an activation pattern 'fingerprint'. This approach was spearheaded in the beginning of the 2000s by functional magnetic resonance imaging (fMRI) studies which showed that the content of visual stimulation could be 'decoded' from low- and high-level visual cortex (Haxby et al., 2001; Haynes and Rees, 2005; Norman et al., 2006; Kamitani and Tong, 2005).

Here, the focus lies on a specific form of MVPA – machine learning. In general, the goal of machine learning is to 1) develop a statistical model of a given task on a training dataset

in order to 2) make predictions on an independent test dataset. This separation into training and testing is crucial to machine learning investigations, as models can otherwise easily overfit when applied to a single dataset at once. As full independent datasets are rare in the context of neuroimaging, this separation into training and test datasets is typically achieved through cross-validation procedures, in which the independence of training and testing is implemented by repeatedly splitting a single dataset into training and testing partitions. Each splitting corresponds to a cross-validation fold, and the performance of machine learning models is computed as an average of prediction accuracies across such folds.

The accuracy metric, often referred to as the *scoring metric*, depends on the type of predictions made by the machine learning model. While classification models label data patterns according to discrete classes (e.g. stimulus A or B, patient or control), regression models predict a continuous value for a given data pattern (e.g., reaction time, continuous disease severity score). In the works reviewed here, both classification (Guggenmos et al., 2018a; Sebold et al., 2017; Guggenmos et al., 2016, 2018b) and regression (Guggenmos et al., 2017, 2018a) models were used. The simplest scoring metric for classification is the raw accuracy, i.e. the percentage of correctly predicted samples. For imbalanced datasets (i.e. different number of samples per class), raw accuracy yields biased estimates and is therefore discouraged. For this reason, the present works either used the area under the receiver operating characteristic curve (AUC) (Sebold et al., 2017; Guggenmos et al., 2016) or the balanced accuracy (average of sensitivity and specificity; Guggenmos et al., 2018b, 2018a) as a scoring method. For continuous predictions, i.e. regression models, the Pearson correlation between predicted values and measured values was used (Guggenmos et al., 2017, 2018a).

A variety of machine learning models are available, but by far the most popular choice in the context of neuroimaging is a family of models referred to as support vector machines (SVMs) (Cortes and Vapnik, 1995). The main reason for this preference is that SVMs can robustly handle data with a relatively low number of samples but high dimensionality, both properties that are common to neuroimaging data. Yet, the preference for SVM and for many other analytic choices in machine learning investigations are often not informed by evidence. Instead, researchers often default to choices that were used in previous studies, regardless of whether they are fitting to the problem at hand. Here, two works are reviewed that address this issue. First, Guggenmos et al. (2016) introduces a novel classifier – the weighted robust distance (WeiRD), to demonstrate that a surprisingly simplistic and efficient distance-to-centroid classifier performs at a competitive level to canonical and often more complex classifiers. Second, Guggenmos et al. (2018b) systematically compares novel and established methods for preprocessing and classification with the aim to provide analytic guidance and default recommendations to the field.

Investigating the neural basis of alcohol dependence with machine learning

While machine learning was initially applied to fundamental research questions about the human brain, it is now increasingly used to investigate psychiatric research questions as well (Huys et al., 2016; Stephan et al., 2016). As machine learning models have led to breakthroughs in other domains such as object recognition (Ciresan et al., 2012), the hope is that these models will at some point be able to utilize the massive amount of data collected in neuroimaging measurements and make useful clinical predictions about diagnosis and treatment planning.

Despite its prevalence and impact on society, only a few studies have used machine learning to investigate the neural basis of alcohol dependence. Whelan et al. (2014) used machine learning to predict current and future adolescent binge drinking from a wide range of data of the IMAGEN project (Schumann et al., 2010), including structural and functional MRI data. While the combination of all data, including highly predictive variables such as smoking or conscientiousness, yielded notable accuracies for both current (91%) and future (70%) binge drinking, the contribution of brain imaging variables to these predictions was rather modest. Seo et al. (2015) compared a number of techniques for the prediction of relapse in alcohol-dependent patients from structural and functional MRI data. The predictive accuracy of the best approach based on robust soft learning vector quantization (Seo and Obermayer, 2003) was 79%. However, given the fact that a number of classification approaches were tested in combination with a small sample size (16 abstainers, 30 relapsers), this accuracy should be treated with caution until replicated.

Surprisingly, no study yet investigated whether machine learning can be used as a computer-based diagnostic tool for alcohol dependence. The most promising non-invasive neuroimaging modality for such a task is T1-weighted magnetic resonance imaging, as structural changes in alcohol dependence have been convincingly shown in many studies (for review, see Harper and Matsumoto, 2005). Here, structural brain changes associated with alcohol dependence were investigated from two conceptually different angles. Guggenmos et al. (2018a) investigated to what degree such structural changes were *predictive* of the diagnosis and the severity of alcohol dependence. By contrast, in Guggenmos et al. (2017) the focus was on the *meaning* of these structural changes against the background of the premature aging hypothesis (Oscar-Berman and

Schendan, 2000; Ellis and Oscar-Berman, 1989). Methodologically, in both studies machine learning was used to exploit the information contained in the *patterns* of regional grey-matter volume and density estimates.

Apart from diagnosis, there is a strong demand for models of alcohol dependence that make predictions about whether patients relapse after abstinence. Current estimates place the 1-year rate of relapse among abstinent alcohol-dependence subjects at 65-70% (Dawson et al., 2005; Anton and O'Malley, 2006), while neuro-behavioural predictors of relapse probability are largely unknown. From a theoretical view point it has been suggested that vulnerability to the development and maintenance of addiction can be explained as an imbalance between goal-directed and habitual or compulsive behaviour (Everitt and Robbins, 2016, 2005; McKim et al., 2016). According to this view, abstinence from conditioned stimuli such as alcohol requires goal-directed decision making, for which relapsing alcohol-dependent patients may show reduced capacity. In Sebold et al. (2017), this hypothesis was put to the test by means of a paradigm explicitly probing the balance between model-based and model-free (habitual) behaviour (Daw et al., 2011), functional magnetic resonance imaging and machine learning.

2. ORIGINAL WORKS

2.1 Works with a methodological focus on machine learning

The first part reviews works contributing methodological advancements in machine learning, which provided the basis for clinically more applied works in the second part.

2.1.1 WeiRD – a parameter-free and efficient machine-learning classifier

Guggenmos M, Schmack K, Sterzer P (2016). WeiRD - a fast and performant multivoxel pattern classifier. *6th International Workshop on Pattern Recognition in Neuroimaging (PRNI)*. doi:10.1109/prni.2016.7552349

The large majority of canonical machine-learning classifiers have one or more parameters that have to be optimized. The most common parameter is a regularization parameter, which determines the bias-variance trade-off. In brief, weak regularization leads to a precise fit of the classification model to training data, but comes with the risk of poor generalization. By contrast, strong regularization leads to a less precise fit on training data, but potentially better generalization. Examples for other parameters are the number of prototypes for k-nearest neighbor classifiers or the kernel coefficient for kernel-based methods such as SVM.

In the context of neuroimaging, two problems arise with the optimization of parameters. First, obtaining sensible estimates of these parameters for high-dimensional neuroimaging data often demands larger sample sizes than typically provided by neuroimaging studies. Second, parameter optimization procedures are computationally expensive, as they require nested cross-validation procedures to yield unbiased estimates.

Both issues were part of the motivation to devise a novel distance-to-centroid classifier termed weighted robust distance (WeiRD) with the goal to provide a parameter-free alternative to canonical parameter-based classifiers.

WeiRD is a distance-to-centroid classifier, which, in the training phase, 1) learns prototypes ("centroids") of two classes A and B as the arithmetic average feature vector, and 2) assigns importance scores to each feature based on a two-sample t-test between the samples of class A and class B. WeiRD thus utilizes the robustness of the t-test to effectively do a form of regularization, without requiring a dedicated regularization parameter. When presented with unseen samples during testing, WeiRD can be best understood as a voting scheme, where each feature receives a vote as to which of two classes a sample belongs. Votes are computed as the difference between the sample's Euclidean distances to prototypes A and B and thus reflect to which prototype a sample feature is closer (by ways of their sign) and by how much it is closer (by ways of their absolute value). The final classification is based on an ensemble vote, computed as the weighted sum of feature votes, where weights correspond to the importance scores estimated during training. Negative and positive signs of this weighted sum correspond to predictions of classes A or B, respectively.

To test whether WeiRD, despite its simplicity, performs competitive to other established classifiers, it was compared to SVM and a random forest classifier (Breiman, 2001) for a range of simulated and real-world neuroimaging classification problems. Simulated datasets mimicked a between-group design with 48 samples in each of two groups and a fictitious region of interest consisting of 100 voxels. Brain activation patterns were simulated by combining discriminative signal and normally distributed noise. The signal-to-noise-ratio and the allocation of signal to voxels varied between three different

"scenarios", each representing a characteristic challenge in neuroimaging classification problems: (1) a "Noise scenario", in which only few voxels contained discriminative signal information, while the majority of voxels was pure noise; (2) a "Dislocation scenario", in which a certain fraction of features was dislocated at a different position of the feature vector (mimicking an imperfect between-subject correspondence of voxels); and (3) a "Phenotype scenario", in which each class consisted of multiple subphenotypes. The goal of classification was to correctly predict group labels within a leave-one-sample-out cross-validation procedure.

The simulation results showed that WeiRD outperformed SVM and random forests in the Noise scenario and the Dislocation scenario across a percentage range of voxels containing signal and being dislocated, respectively. Thus, for these two characteristic challenges of neuroimaging, WeiRD yielded superior classification accuracies. In the Phenotype scenario, WeiRD was slightly inferior to SVM and random forests for more than two phenotypes, which can be explained by the fact that WeiRD estimates only a single prototype per class, and thus struggles when classes differentiate into multiple phenotypes. Nevertheless, overall WeiRD performed competitive to canonical classifiers for these simulated scenarios.

The real-world dataset consisted of whole-brain grey-matter maps estimated with voxel-based morphometry from 120 patients and 97 controls of the LeAD study. To assess the effect of resampling and smoothing on classification performance, grey-matter maps were additionally preprocessed with a range of resampling (3-12 mm) and smoothing (0-24 mm FWHM) choices. Classification accuracy was measured with the AUC to account for the class imbalance of the dataset. It was found that WeiRD slightly outperformed

both other classifiers across resampling and smoothing choices, thus reinforcing the result of the simulation.

Finally, the computational efficiency of WeiRD was tested on the simulated data and compared to SVM and random forests. On average, WeiRD was twice as fast as SVM and 200 times as fast as random forests. In general, while SVMs performance grows more than quadratically with the number of samples, WeiRD scales linearly and thus is well-behaved in cases with a large number of samples (Wilbertz et al., 2018).

Overall, WeiRD provides a parameter-free and computationally efficient alternative to canonical classifiers in the context of neuroimaging datasets. In terms of performance, WeiRD was en par – and in part superior – to canonical classifiers across a range of real-world and simulated neuroimaging datasets. WeiRD is particularly suited for datasets with a large number of samples and for exploratory machine learning analyses, enabling researchers to quickly asses the predictive accuracy of a given dataset for conditions of interest without expensive optimization schemes.

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Guggenmos M, Schmack K, Sterzer P (2016). WeiRD - a fast and performant multivoxel pattern classifier. *6th International Workshop on Pattern Recognition in Neuroimaging (PRNI)*.

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2.1.2 Comparing analytic choices for machine learning in neuroimaging

Guggenmos M, Sterzer P, Cichy RM (2018). Multivariate pattern analysis for MEG: a comparison of dissimilarity measures. *NeuroImage* 173, 434–447.

doi: 10.1016/j.neuroimage.2018.02.044

Machine learning work flows can be broadly divided into the preprocessing stage and the classification stages of training and prediction. To establish guidelines regarding optimal analytic choices for these stages, Guggenmos et al. (2018b) evaluated several established – and in part novel – methods for preprocessing and classification based on a high-powered neuroimaging (magnetoencephalography) dataset by Cichy et al. (2014).

During preprocessing, data are transformed and optimized in various ways before being submitted to machine learning models. Preprocessing methods include outlier removal, standardization (scaling to unit variance), mean centering, removal of the pattern means, more advanced noise normalization techniques and dimensionality reduction techniques (e.g. principal component analysis). Optimal preprocessing of neuroimaging data for machine learning is a challenging task due to a number of special properties: (1) highly varying signal-to-noise ratios (SNRs) across measurement channels, (2) strong unspecific components common to multiple experimental conditions, and (3) high spatial correlation. Addressing these properties for the case of electroencephalography (EEG) and magnetoencephalography (MEG) data, but with relevance for other neuroimaging modalities as well, was a major aspect of Guggenmos et al. (2018b).

Heterogenous SNR across measurement channels (e.g. voxels or channels) is a phenomenon common to nearly all neuroimaging modalities. Reasons for this heterogeneity are manifold and include varying quality of electrode contacts, local skull

thickness or head movement affecting different voxels to a different degree. In addition, given constant noise sources, different measurement channels may contain more or less informative signals about a condition of interest, thus affecting the nominator of the SNR. To address the issue of variable SNR across measurement channels, a common procedure is to weigh channels by an estimate of their error variance and thus to emphasize channels with high SNR and to deemphasize channels with low SNR. This procedure is known as univariate or variance-based noise normalization. In addition, it is possible to consider the covariance structure of measurement channels and thus to emphasize or deemphasize spatial frequencies across measurement channels. This procedure is known as multivariate noise normalization.

By systematically comparing established and newly developed noise normalization schemes, a number of important insights were achieved in Guggenmos et al. (2018b). First, it was shown that multivariate noise normalization indeed provided a benefit compared to univariate noise normalization. Thus, accounting for the full covariance structure of the data by normalizing with variance-covariance matrices yielded optimal classification accuracy. Second, a considerable boost of machine learning performance was observed when the variance-covariance matrix was regularized by means of a shrinkage operation (Ledoit and Wolf, 2004), which effectively biased the matrix towards the identity matrix. The benefit of such regularization suggests that the computation of the variance-covariance matrix was otherwise unstable, likely due to the low number of samples.

Third, a beneficial effect of estimating the variance-covariance matrix from task-related time periods was shown. This approach was contrary to established procedures, which typically estimated variance-covariance matrices from task- and stimulus-free baseline

periods in order to obtain an estimate of the error (co)variance that is not contaminated by the 'signal' (co)variance caused by different experimental conditions. In Guggenmos et al. (2018b), this issue was overcome by separately computing the error (co)variance *within* each condition (i.e. across samples within a given condition) and then averaging across conditions. The strong performance of this approach suggests that the noise structure in task and/or stimulus time periods differs from the noise structure during baseline periods, calling into question the established way of computing variance-covariance matrices from baseline data. Overall, estimating variance-covariance matrices from task-related data in combination with shrinkage yielded a substantial improvement in machine learning performance: compared to a previous publication on the same dataset which achieved a percentage of correct predictions slightly higher than 70% (Cichy et al., 2014), this new approach yielded an accuracy of over 90%.

At the classification stage, Guggenmos et al. (2018b) compared several different classifier types (SVM, WeiRD, linear discriminant analysis – LDA, Gaussian Naïve Bayes – GNB) with respect to classification accuracy. In brief, SVM, WeiRD and LDA were found to perform equally well, while GNB fell off by a large margin. Additional analyses suggested that the impaired performance of GNB was due to its implicit assumption about the conditional independence of features – an assumption that is heavily violated in nearly all neuroimaging data sets, as different features (e.g., voxels or sensors) typically show a strong shared unspecific component. Thus, while SVM, WeiRD and LDA were equally potent choices, GNB should only be used after decorrelating features, e.g. via principal component analysis (which, however, bears the risk of losing relevant information).

Finally, in Guggenmos et al. (2018b) a novel method to preserve gradual information from machine learning predictions was evaluated. Most applications of classification-based machine learning only consider categorical (often binary) predictions from classifiers, which are based on implicit criteria or thresholds imposed on decision values of the classifier. Yet, there is a number of applications where gradual decision values themselves could provide meaningful additional information in the, entertaining the notion that decision values reflect the *certainty* of predictions. One example is the application of machine-learning to multimodal neuroimaging data, where multiple modality-specific classifiers are combined to make an ensemble prediction. It is plausible that considering not only the predicted categorical labels, but also the certainty provided by each modality, improves overall multimodal classification performance. However, whether decision values (e.g. distance to the hyperplane in case of SVM) are well-behaved on neuroimaging data and provide reliable and systematic information about the certainty of predictions is currently unknown.

To this aim, Guggenmos et al. (2018b) developed the concept of decision-value(DV)-weighted classification accuracies – the correctness of individual predictions weighted by their certainty – to test the reliability of DV-augmented classification accuracies. Specifically, the reliability was computed as a test-retest reliability, as the dataset by Cichy et al. (2014) comprised two identical experimental sessions per participant. It was found that DV-weighted accuracy showed indeed substantially improved test-retest reliability compared to raw classification accuracy. This suggests that meaningful and well-behaved information is contained in continuous classifier decision values, which could be used to provide certainty estimates around classifier predictions or enable fine-grained ensemble predictions.

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Guggenmos M, Sterzer P, Cichy RM (2018). Multivariate pattern analysis for MEG: a comparison of dissimilarity measures. *NeuroImage* 173, 434–447.

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2.2 Works with a clinical focus on the neural basis of alcohol dependence

This second part reviews the application of machine learning to clinical research questions using data from the LeAD study.

2.2.1 Predicting diagnosis and lifetime consumption in alcohol dependence from grey-matter pattern information

Guggenmos M, Scheel M, Sekutowicz M, Garbusow M, Sebold M, Sommer C, Charlet K, Beck A, Wittchen H-U, Smolka MN, Zimmermann U, Heinz A, Sterzer P, Schmack K (2018). Decoding diagnosis and lifetime consumption in alcohol dependence from grey-matter pattern information. *Acta Psychiatrica Scandinavica* 137, 252–262.
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A common dilemma of machine learning applications to psychiatric disorders is the fact that their maximum performance is bounded by the *label noise* associated with training examples. As there are no objective markers for psychiatric illnesses, the certainty of a label for a given training sample (e.g., a brain scan of a patient) depends on the reliability of psychiatric diagnoses. However, even in the newest iteration of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) only a few psychiatric illnesses are diagnosed with "very good agreement" (kappa > 0.6) between raters and many show questionable or unacceptable agreement (Freedman et al., 2013). This state of affairs makes alcohol dependence, which typically shows excellent inter-rater reliabilities (Huang et al., 2009; Ruskin et al., 1998), an interesting test candidate for the development of machine learning applications in psychiatric neuroimaging. In addition, alcohol-induced grey-matter atrophy is well-established for alcohol dependence (Harper and

Matsumoto, 2005), making it a promising neuroimaging marker that could inform clinical diagnosis.

Thus, in Guggenmos et al. (2018a) a machine learning model was applied to structural brain scans from the LeAD study of 119 alcohol-dependent patients aged 20-65 (18 female) meeting criteria of alcohol dependence according to ICD-10 and DSM-4 (American Psychiatric Association 2000) and 97 controls matched according to age, gender and education. The goal was to predict both the diagnosis of alcohol dependence and a continuous marker of severity (lifetime consumption) using grey-matter pattern information estimated from structural brain scans with voxel-based morphometry (Ashburner and Friston, 2000; Mechelli et al., 2005). In addition, a number of recent concerns about machine learning applications in psychiatric neuroimaging were addressed, including (i) the opaqueness of many machine learning models impeding the interpretability of results (Brodersen et al., 2014), (ii) overfitting and lack of validation on independent datasets (Demirci et al., 2008; Whelan and Garavan, 2014; Schnack and Kahn, 2016) and (iii) a lack of comparison with human expert judgements (Klöppel et al., 2008).

As the key machine learning model the WeiRD algorithm (Guggenmos et al., 2016, 2018b) introduced in 2.1.1was used, for two reasons. First, the voting scheme of WeiRD makes explicitly transparent the contribution of each feature to classification, thus addressing (i). Second, as described in 2.1.1, WeiRD does not require the optimization of hyperparameters, which addresses (ii) by reducing the danger of overfitting. SVM was used as a reference classifier in order to compare the performance achieved through WeiRD to an established machine learning model.

Both classifiers were applied in four different classification schemes. In the first and simplest scheme, a single biomarker was computed as the whole-brain average of grey-matter concentration. The second scheme occupied the other extreme and submitted *all* voxels (around 700.000) to classification. The third and fourth scheme involved parcellation into 110 anatomically plausible brain regions and was based on either regional averages or on the voxel patterns of each brain region. The results showed that the classification based on anatomical parcellation and regional averages in combination with WeiRD performed best, yielding 74% accuracy (71% accuracy for SVM). In addition, these results demonstrated the value of multivariate machine learning methods (i.e. the pattern of 110 regional averages) over a classification scheme based on a univariate comparison of average grey-matter concentration. An inspection of WeiRD votes for these 110 regions revealed that classification was mainly based on inferior frontal, dorsal cingulate and insular regions, brain areas that are consistent with previously reported foci of grey-matter damage in alcohol dependence (Chanraud et al., 2007; Tanabe et al., 2009; Demirakca et al., 2011).

Through a collaboration with the NGFN+ project (Spanagel, 2009), the classification scheme could be applied to an independent dataset including structural MRI scans from 94 individuals with alcohol dependence and 83 controls. An interesting aspect of this generalization dataset was that it was acquired by a different research group and in a different scanning facility. Moreover, it differed in terms of gender balance from the original data set (36% female in the validation versus 16% female in the original data set). Thus, the validation dataset was different enough from the original dataset to probe the real-world generalizability of the machine-learning approach. Applying the WeiRD classifier after training on the original LeAD dataset on the NGFN+ dataset yielded 73%

accuracy, demonstrating excellent generalizability and robustness to differences between datasets.

Finally, the performance of computer-based classification was compared to the performance of a human expert. An experienced radiologist from the Charité was recruited to judge structural MRI scans as belonging to alcohol-dependent patients or controls. To ensure a fair comparison, the radiologist likewise was provided with information about age and gender of the subjects. However, to avoid strategic judgements, the radiologist did not receive information about the relative proportion of patients and controls in the sample. The radiologist achieved an accuracy of 66%, which was clearly above chance, but significantly below the accuracy of computer-based classification. The radiologist showed higher specificity than computer-based classification (81% versus 76%), but much lower sensitivity (51% versus 71%).

To assess how age and gender information was used by the radiologist, a logistic regression with judgement (control=0, patient=1) as the regressand was performed. The results showed that the judgements were significantly influenced by age (odds ratio [95% CI]: 1.05 [1.02; 1.08]) and gender (2.94 [1.18; 7.35]), such that being older and male increased the chances of a patient judgement. By contrast, computer-based classification, in which age and gender information was likewise accounted for, did not show equivalent biases. Interestingly however, when age and gender information was *not* accounted for, computer-based classification showed similar biases for age (1.15 [1.11; 1.20]) and gender (1.63 [0.64; 4.20]). This result suggests that these biases are data-driven (rather than being based on stereotypes) and were more efficiently taken into account by computer-based classification when provided with this demographic information.

For copyright reasons, the following work has been removed from this habilitation:

Guggenmos M, Scheel M, Sekutowicz M, Garbusow M, Sebold M, Sommer C, Charlet K, Beck A, Wittchen H-U, Smolka MN, Zimmermann U, Heinz A, Sterzer P, Schmack K (2018). Decoding diagnosis and lifetime consumption in alcohol dependence from grey-matter pattern information. *Acta Psychiatrica Scandinavica* 137, 252–262.

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2.2.2 Quantifying brain aging in alcohol dependence

Guggenmos M, Schmack K, Sekutowicz M, Garbusow M, Sebold M, Sommer C, Smolka MN, Wittchen H-U, Zimmermann US, Heinz A, Sterzer P (2017). Quantitative neurobiological evidence for accelerated brain aging in alcohol dependence. *Translational Psychiatry* 7, 1279. doi: 10.1038/s41398-017-0037-y

A long-standing hypothesis about the damaging effects of alcohol is the hypothesis of *premature brain aging* (Oscar-Berman and Schendan, 2000; Ellis and Oscar-Berman, 1989). This hypothesis suggests that the effects of alcohol both at the behavioural and the neurobiological level are akin to those observed in natural aging. On the neurobiological level, this hypothesis has received support from post mortem brain analyses (Courville, 1966) and magnetic resonance imaging (Pfefferbaum et al., 1998; Fein et al., 2002; Chanraud et al., 2007; Jernigan et al., 1991), which qualitatively noted similarities between atrophies of alcohol dependence and aging. Surprisingly, however, no study to date had systematically and quantitatively investigated the similarity of age-related and alcohol-related grey matter loss.

The goal of Guggenmos et al. (2017) was two-fold. First, to systematically compare grey-matter alterations due to alcohol- and age-related effects for a comprehensive set of anatomically plausible brain areas. And second, to quantify aging of alcoholic brains *in years* by means of a brain aging model. For both analysis goals, the brains of subjects were 1) segmented into grey matter, white matter and cerebral spinal fluid and 2) grey-matter volume was estimated by means of voxel-based morphometry (Ashburner and Friston, 2000; Mechelli et al., 2005).

To compare the effects of alcohol dependence with those of aging, two second-level group contrasts were estimated on the resulting whole-brain grey-matter volume maps: a contrast between patients and controls and a regression contrast on the control subjects with age as regressand. These whole-brain group contrasts were subsequently parcelled into 110 anatomical grey-matter brain areas. A correlation analysis across regions revealed a substantial similarity between the grey-matter effects of alcohol dependence and aging (r=0.54). Thus, nearly 30% of alcohol-related grey-matter loss variance across regions was explained by the effect of age-related grey-matter changes across regions. This result provided first quantitative neurobiological evidence for the premature aging hypothesis of alcohol dependence.

Given that alcohol-related grey-matter changes show characteristics of brain aging, the next question was by *how much* the brain age of alcohol-dependent patients increases. To investigate, a machine learning model was trained on regional grey-matter patterns of control subjects with chronological age as a continuous target variable. This trained model was then applied to the sample of alcohol-dependent patients in order to predict their 'brain age'. This analysis revealed that the brain age of patients was increased by 4.0 ± 0.7 years on average relative to their chronological age, indicating substantial brain aging. Moreover, relating brain aging to kilogram lifetime consumption, it was found that 1kg of pure alcohol intake corresponded to approximately half a day of brain aging.

From a theoretical perspective, two different versions of the premature brain aging hypothesis have been put forward. Whereas the *accelerated aging hypothesis* assumes that the damaging effects of alcohol dependence are largely independent of chronological age, the *vulnerability hypothesis* poses that these effects manifest mainly later in life (mid-40s and older). To distinguish between these two hypotheses, patients and controls were

grouped into five chronological age decades (20-29, 30-39, 40-49, 50-59, 60-69) and *relative* brain aging was determined as the difference of brain aging between patients and controls for each decade separately. This analysis showed that brain aging increased systematically with age, reaching 11.7 ± 2.4 years in the oldest age group (60-69). By contrast, the two youngest age groups (20-29 and 30-39) showed no significant effects of brain aging.

Thus, in accord with the accelerated aging hypothesis, brain aging was found throughout lifetime, except for the youngest patients. However, in line with the vulnerability hypothesis, brain aging was indeed strongest in the oldest age groups. Overall, these results thus resemble a hybrid of both accounts, indicating effects of accelerated brain aging in all but the youngest patients and an increasing vulnerability to brain aging with increasing age. Beyond these two hypotheses, the results provide evidence for protective factors in younger subjects against the damaging effects of alcohol and an elevated vulnerability in elderly individuals.

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Quantitative neurobiological evidence for accelerated brain aging in alcohol dependence

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Abstract

The premature aging hypothesis of alcohol dependence proposes that the neurobiological and behavioural deficits in individuals with alcohol dependence are analogous to those of chronological aging. However, to date no systematic neurobiological evidence for this hypothesis has been provided. To test the hypothesis, 119 alcohol-dependent subjects and 97 age- and gender-matched healthy control subjects underwent structural MRI. Whole-brain grey matter volume maps were computed from structural MRI scans using voxel-based morphometry and parcelled into a comprehensive set of anatomical brain regions. Regional grey matter volume averages served as the basis for cross-regional similarity analyses and a brain age model. We found a striking correspondence between regional patterns of alcohol- and age-related grey matter loss across 110 brain regions. The brain age model revealed that the brain age of age-matched AD subjects was increased by up to 11.7 years. Interestingly, while no brain aging was detected in the youngest AD subjects (20–30 years), we found that alcohol-related brain aging systematically increased in the following age decades controlling for lifetime alcohol consumption and general health status. Together, these results provide strong evidence for an accelerated aging model of AD and indicate an elevated risk of alcohol-related brain aging in elderly individuals.

Introduction

The premature aging hypothesis posits that alcohol dependence (AD) accelerates aging and that the brains of individuals with AD resemble those of chronologically older healthy individuals[1]. The first neuroanatomical report about a parallel between chronological aging and AD was based on post mortem analyses: Courville[2] noticed that the cerebral atrophy in brains of individuals with AD resembled the brain shrinkage that occurs with chronological aging. More recent studies have used magnetic resonance imaging (MRI) in individuals with AD and found cortical and subcortical grey matter loss (GML) throughout the brain as compared to healthy controls[3–6]. Here too, qualitative reports have noted that those areas that are particularly susceptible to GML in individuals with AD (in particular frontal regions) overlap with those found for chronological aging[7]. However, to date no study has systematically and quantitatively investigated the similarity of age-related and alcohol-related GML or quantified the extent of brain aging in AD.

To this aim, we developed and applied a novel whole-brain pattern-based approach to analyse grey matter volume information measured with MRI. We used data from a recent study in Germany, in which structural MRI scans were obtained from recently detoxified, abstinent individuals diagnosed with AD ($N = 119$) and a healthy control group ($N = 97$) (see Table 1 for sample

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Table 1 Sample characteristics for alcohol-dependent and healthy control subjects

	AD group (N=119)			Control group (N=97)					
	Mean	SD	%	Mean	SD	%	t or χ^2	df	p
Gender (female)			15.1			16.5	0.001	*N*=216	0.98
Age in years	45.0	10.7		43.7	10.8		0.9	214	0.38
SES	−0.4	1.9		0.7	2.1		−3.6	170	<0.001
Lifetime alcohol intake in kg (pure alcohol)	1805	1121		285	810		11.1	214	<0.001
Alcohol intake per drink year in kg (pure alcohol)	55.5	25.8		10.0	23.3		13.4	214	<0.001
Age of AD onset in years (DSM-IV)	32.0	12.0						*N*=111	
Duration of AD in years (DSM-IV)	11.7	9.9						*N*=110	
Abstinence before MRI in days	22.8	11.5						*N*=115	
ADS	14.8	6.9		2.0	3.0		17.0	213	<0.001
OCDS-G total score	11.9	8.5		2.8	2.8		10.1	207	<0.001
Smokers			76.5			67.0	1.9	*N*=216	0.16
FTND (sum score)	3.6	2.8		1.4	2.0		6.4	214	<0.001
WHODAS-II	19.9	6.8		13.5	8.4		8.4	204	<0.001
BIS-15 total score	31.6	6.5		29.1	5.5		2.9	205	0.004
TMT (percentile)	36.1	25.1		44.8	25.1		2.5	209	0.014
DSST	64.3	15.1		73.5	16.6		4.2	211	<0.001
DSB	6.5	1.9		7.4	2.0		3.4	214	0.001
MWT	104.7	9.4		104.5	8.9		−0.2	209	0.82

Socioeconomic status (SES): sum of *z*-transformed self-ratings of social status, household income and inverse personal debt scores[29]; Alcohol Dependence Scale (ADS): degree/level of AD[30]; Obsessive Compulsive Drinking Scale (OCDS-G): current craving for alcohol[31]; Fagerström test for nicotine dependence (FTND): intensity of physical addiction to nicotine; Disability Assessment Schedule 2.0 of the World Health Organization (WHODAS-II): generic assessment instrument for health and disability; Barratt Impulsiveness scale (BIS-15): impulsivity[32]; trail making test (TMT): visual attention and task switching; digit symbol substitution test (DSST): processing speed; digit span backwards (DSB): working memory; multiple-choice vocabulary intelligence test (Mehrfachwahl-Wortschatz-Intelligenztest, MWT): crystallized/verbal intelligence

characteristics). A parcellation scheme of cortical and subcortical brain regions[8] served to compare cross-regional GML patterns of AD with patterns of chronological aging. In addition, these patterns served as the basis for a brain aging model of AD.

The premature aging hypothesis has been outlined in two different versions[9]. According to the accelerated aging hypothesis[10], adverse effects of AD manifest relatively independent of chronological age and are thus to be found across all ages. By contrast, the increased vulnerability hypothesis[11, 12] places the timing of AD-related neurodegenerative effects and behavioural impairments later in life (mid-40s and older[11]). In addition to our general hypothesis of alcohol-related brain aging, we therefore aimed to answer the following questions arising from the above versions of the premature aging hypothesis: is the extent of putative brain aging stable across the lifespan, as predicted by the accelerated aging hypothesis? Or is the onset of brain aging relatively late in life, as predicted by the vulnerability hypothesis?

Subjects and methods

Participants

This study was conducted as part of the LeAD study, a bicentric (Berlin, Dresden) German program investigating the neurobiological basis of AD (www.lead-studie.de; clinical trial number: NCT01679145[13–15]). Pooled across the Berlin and Dresden sites, we assessed 119 individuals aged 20–65 (18 females) meeting criteria of AD according to ICD-10 and DSM-IV-TR and 97 healthy controls aged 21–65 (16 females) matched in terms of age, gender and education (highest school-leaving qualification).

We used the computer-assisted interview version Composite International Diagnostic Interview (CAPI-

CIDI[16, 17]) to verify diagnosis criteria of AD in the patient group. For inclusion, individuals with AD had to meet criteria for AD for at least 3 years and had to undergo an inpatient detoxification phase (average duration, ±SEM: 22.8 ± 1 days). Alcohol lifetime consumption (LC) was quantified by the standard drink section of the CAPI-CIDI. The instrument was also used to exclude the possibility of AD in healthy controls.

Exclusion criteria for all subjects were left-handedness (Edinburgh handedness index below 50[18]), contraindications for MRI, and a history of or current neurological or mental disorders (excluding nicotine dependence in both groups and alcohol abuse in individuals with AD, but including abuse of other drugs). Mental disorders were assessed according to DSM-IV axis one as verified by the computer-assisted interview version Composite International Diagnostic Interview, CAPI-CIDI[16, 17]. It was ensured that all subjects were free of psychotropic medication (including detoxification treatment) known to interact with the central nervous system for at least four half-lives. Current non-tobacco/non-alcohol drug abuse was confirmed by means of a dedicated urine test.

On a neuropsychological level, we assessed crystallized intelligence using a standardized vocabulary test in German (Mehrfachwahl-Wortschatztest-Intelligenztest[19]) and three facets of fluid intelligence: (i) working memory capacity by assessing the digit span backwards task (Digit Span[20]), (ii) executive functioning using the trail making test, TMT A and B[21], and (iii) processing speed by the digit symbol substitution task (DSST, from the Wechsler Adult Intelligence Scale[20]).

The study was conducted in accordance with the declaration of Helsinki and approved by local ethics committees of the Technische Universität Dresden and the Charité Universitätsmedizin Berlin. All participants provided written informed consent after receiving a complete description of the study.

MRI acquisition

High-resolution T1-weighted structural MRI scans were acquired on a 3-Tesla Siemens Trio scanner using a magnetization-prepared rapid gradient echo sequence (repetition time: 1900 ms; echo time: 5.25 ms; flip angle: 9°; field of view: 256 × 256 mm^2; 192 sagittal slices; voxel size: 1 mm isotropic).

Data analysis

Voxel-based morphometry

Data were preprocessed and analysed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and VBM 8 (http://dbm.neuro.uni-jena.de/vbm). Images were spatially normalized to a Montreal Neurological Institut (MNI) template, segmented (grey matter, white matter, cerebrospinal fluid) and resampled to 1.5 mm isotropic. To create volumetric grey matter partitions corrected for brain size, normalized grey matter images were modulated through a nonlinear-only transformation, resulting in relative grey matter volume maps[22]. This procedure allowed for analysing the relative differences in regional grey matter volume (ie, corrected for individual brain size). Modulated images were smoothed with an 8 mm isotropic Gaussian kernel.

Whole-brain univariate analysis

Three different second-level general linear models were computed to estimate whole-brain grey matter volume effects of (i) AD vs. control, (ii) aging and (iii) alcohol LC. Group differences were assessed by subjecting individual grey matter volume images to a second-level random-effects analysis with the factor group (AD, control), controlling for age, gender, site (Berlin, Dresden), smoking (FTND sum score) and general health status (WHODAS-II). Note that there were no significant whole-brain differences between the sites Berlin and Dresden. The effects of aging on grey matter volume was investigated in the healthy control group by regressing on age, while controlling for gender, site, smoking, general health status and mean yearly intake (kilogram pure alcohol) ingested since the first alcoholic drink. Finally, the relationship between grey matter volume and LC in the AD group was investigated with a regression analysis on LC, while controlling for age, gender, site, smoking and general health status.

Atlas-based parcellation and cross-regional correlation analysis

Contrast images of the whole-brain univariate analysis provided the basis for a cross-regional correlation analysis. In a first step, the brain was parcelled into 110 GM areas on the basis of an anatomical atlas (JHU atlas[8]), which included a comprehensive set of both cortical and subcortical brain areas. Next, within each brain region, average grey matter contrast estimates were computed for the three group-level models (group, age, LC): (i) controls > AD; (ii) age < 0 (ie, less grey matter volume with increasing age); (iii) LC < 0. Finally, to assess the cross-regional correspondence between AD diagnosis, age and LC, contrast estimates between these factors were correlated across regions.

Brain age model

The goal of the brain age model was to compute the biological brain age of participants on the basis of whole-brain grey matter volume patterns. Regional averages were extracted for the brain regions of the JHU atlas from the original grey matter volume map of each participant. To build the model, in each analysis a multilinear ridge

regression ($\lambda = 1.0$) with age as the dependent variable was trained on data of the control group. The regression model comprised 110 regressors based on the regional grey matter volume patterns and three regressors for gender, site and smoking (FTND sum score). For control subjects, brain age was predicted in a leave-one-sample-out procedure. To predict brain ages of AD subjects, the model was trained once on the entire set of control subjects.

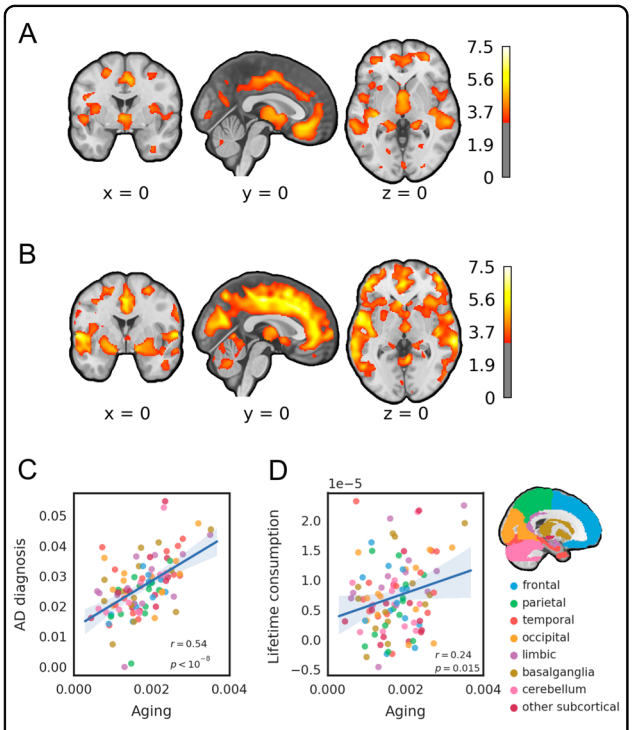

Fig. 1 Correspondence between AD-related and age-related grey matter loss (GML). **a** and **b** show t-maps for univariate whole-brain analyses, thresholded at $p < 0.001$ uncorrected, for illustration. **a** T-map for AD-related grey matter volume loss, based on a two-sample *t* test between AD subjects and control subjects, controlling for age, gender, site, smoking (FTND sum score) and general health status (WHODAS-II). **b** T-map for age-related grey matter volume loss in control subjects using a regression analysis controlling for gender, site, smoking, general health status and mean yearly intake (kilogram pure alcohol) ingested since the first alcoholic drink. **c** and **d** show the cross-regional similarity between AD-related and age-related GML. Each data point corresponds to one of 110 anatomical brain regions. Colours indicate regions pertaining to different parts of the brain, as indicated by the map on the right. Age-related GML was derived from the contrast estimates in **b**. **c** Cross-regional relationship between age-related GML and GML associated with the group contrast control > AD of **a**. **d** Cross-regional relationship between age- and consumption-related GML (lifetime consumption). Consumption-related GML was computed as the contrast estimate of a negative relationship between grey matter volume and kilogram lifetime consumption, controlling for age, gender, site, smoking and general health status

Results

Congruent patterns of age- and AD-related grey matter loss

In a first step, we computed whole-brain statistical maps for group- and age-related GML based on regional grey matter volume. Fig. 1a, b and Supplementary Tables 1 and 2 show that both AD group membership and chronological aging were associated with widespread and qualitatively similar patterns of GML across the brain, strongly affecting frontal (especially cingulate cortex and middle frontal gyrus), superior temporal and cerebellar areas. To quantitatively assess the cross-regional similarity between age- and AD-related GML, we extracted the average contrast estimates for both effects within each region of the JHU brain atlas[8] and correlated them across regions. This approach revealed a strong linear relationship between age-related and AD-related GML across 110 anatomical brain regions ($r_{\text{Pearson}} = 0.54$, $p_{214} < 10^{-8}$) (Fig. 1c).

A possible concern is that the correlation between age- and AD-related grey matter loss might be inflated by the fact that the magnitude of grey matter loss in different regions primarily depends on the size or the general variance of the region. To account for these possibilities, we approximated region size by counting the number of grey matter voxels in each region. Across-subject variance of grey matter volume was computed within the control group for each region individually. A partial correlation approach showed that the correlation also held when controlling for region size ($r_{\text{Pearson}} = 0.56$, $p_{214} < 10^{-9}$), variance ($r_{\text{Pearson}} = 0.36$, $p_{214} < 10^{-4}$) or both ($r_{\text{Pearson}} = 0.34$, $p_{214} < 10^{-3}$). Thus, aging and AD similarly affected regional GML across a comprehensive set of 110 anatomical brain regions even when controlling for region size and interindividual variance.

In a next step, we investigated whether individual LC within the AD group would likewise be reflected in an age-like cross-regional pattern. Using contrast estimates for a negative linear relationship between LC and grey matter volume, we found a clear correspondence between GML patterns of LC and age ($r_{\text{Pearson}} = 0.24$, $p_{214} = 0.015$) (Fig. 1d). Thus, age-related GML patterns were similar to alcohol-related GML patterns both in terms of a between-group diagnostic contrast and a within-group consumption-based contrast.

Increased brain age in AD subjects

While the above results hint at an accelerated aging process in brains of AD subjects, they leave open the extent of such an acceleration; in other words, by how much does the brain age of AD subjects increase? To answer this question, we trained a multilinear ridge regression model on the grey matter volume patterns of the control group with chronological age as the

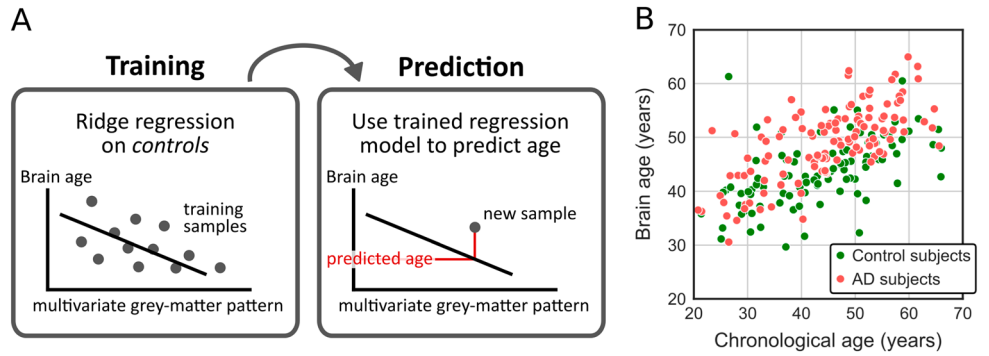

Fig. 2 Brain age. **a** Brain age model. A ridge regression model was trained on the grey matter patterns of control subjects and served to predict the brain age of AD subjects. **b** Chronological age vs. predicted brain age in AD and control subjects

dependent variable (Fig. 2a). For an initial verification, we first tested the age model within the control group. A leave-one-out cross-validation procedure was used, such that in each of N folds the model was trained on N−1 control subjects and predicted the age of the left-out control subject. We found that the predicted age was strongly related to the chronological age ($r_{\text{Pearson}} = 0.54$, $p < 10^{-7}$; average predicted age: mean ± SEM = 43.7 ± 1.1 years; average chronological age: 43.7 ± 0.6; mean absolute error: 6.9 years) (Fig. 2b), thus affirming the general validity of the model.

We then trained the brain age model on all control subjects and applied it to AD subjects. We found that the brain age of AD subjects was increased by 4.0 ± 0.7 years relative to their chronological age (predicted age: 49.0 ± 0.6; chronological age: 45.0 ± 1.0; mean absolute error: 6.7 years). This increase was significant (one-sample t test: $t_{118} = 5.6$, $p < 10^{-6}$). In an exploratory analysis, we investigated brain aging in AD subjects for different regions of the brain, which revealed that limbic, temporal and frontal were numerically most strongly affected (Fig. S1). To ensure that the model was generally suited for the AD group, we confirmed that, despite the predicted age gap, the predicted age and the chronological age of AD subjects were strongly correlated ($r_{\text{Pearson}} = 0.69$, $p_{214} < 10^{-17}$) (Fig. 2b). These results provide clear evidence for accelerated aging in the brains of AD subjects.

Brain aging increases with lifetime alcohol consumption and age

Finally, we assessed to which degree brain aging (predicted age minus chronological age) in AD subjects was affected by the amount of LC and chronological age.

First, we regressed brain aging on LC, accounting for age. We found that 1 kg (or 71 standard drinks of 14 g) of alcohol intake corresponded to approximately half a day of brain aging in AD subjects ($\beta = 0.56 \pm 0.25$, $p_{214} =$ 0.028). Thus, the degree of brain aging is predicted by the amount of alcohol consumed throughout life.

Second, we assessed the relationship between brain aging in AD and chronological age. Since brain age estimates were biased with respect to chronological age irrespective of group (controls: $r_{\text{Pearson}} = -0.82$, $p_{214} < 10^{-24}$; AD: $r_{\text{Pearson}} = -0.77$, $p_{214} < 10^{-23}$; see also Fig. 2b), we compared brain aging in AD subjects directly to age-matched control subjects. After regressing out gender, LC, smoking and general health status (WHODAS-II) from brain aging estimates, we sorted AD and control subjects into five chronological decades and submitted the brain aging estimates to a two-way (2 × 5) analysis of variance with factors group and decade. This analysis revealed main effects of group ($p < 10^{-6}$, $F_{1,43} = 27.8$) and age ($p < 10^{-15}$, $F_{1,68} = 60.0$) as well as an interaction of group and

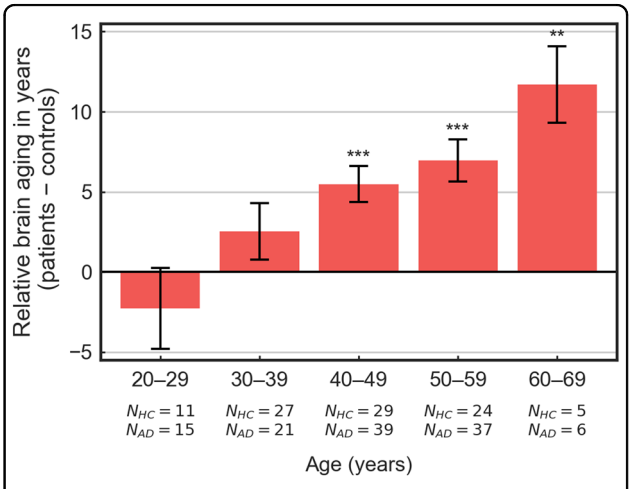

Fig. 3 Brain aging in dependence of chronological age. Brain aging of AD subjects in comparison to control subjects for five life decades. Mean values indicate the difference of the group means (AD group minus control group); error bars indicate the pooled standard error of the group differences; **: < 0.01; ***: < 0.001

age ($p < 0.001$, $F_{4,2} = 5.0$) (Fig. 3). A post hoc t test for the hypothesis of linearly increasing brain aging in AD subjects but not control subjects (contrast vector: [−2, −1, 0, 1, 2; 0, 0, 0, 0, 0]), was likewise significant ($p < 10^{-6}$, $t_{214} = 5.5$). Thus, brain aging in AD subjects increased with chronological age. While brain aging was not significant in the range 20–29, it was estimated as high as 11.7 ± 2.4 years in the ages 60–69.

Discussion

Our whole-brain analyses revealed that both AD and aging reduced grey matter volume in largely overlapping brain areas, in particular frontal (cingulate cortex and middle frontal gyrus), cerebellar and superior temporal regions. We quantitatively substantiated this parallel by showing a striking correlation between regional alcohol-related and age-related GML patterns. A brain age model built on grey matter patterns showed substantial brain aging in the AD group, which increased with LC and chronological age.

The strong similarity between AD- and age-related GML invites two possible, nonexclusive interpretations. First, it may be that the neurotoxic effects of excessive alcohol intake are, at a fundamental biological level, comparable to deteriorating effects of the aging brain. While the exact pathological molecular mechanisms of alcohol-related neuronal damage have not been revealed yet[23], prominent candidate mechanisms are processes that alter cell-integrity such as (chronic) oxidative stress[24]. Indeed, oxidative stress has been found to increase both with aging[25] and (in model organisms) with excessive ethanol exposure[26]. Crucially, if different brain regions vary in their vulnerability to such a common biological mechanism, similar regional patterns of age-related and AD-related GML as observed in the present study are the consequence.

Second, different brain areas might be generally more or less susceptible to grey matter loss irrespective of a specific neurodegenerative mechanism. In this case, one may expect to find similar cross-regional profiles across a variety of illnesses that affect grey matter. A potential avenue for future research is thus to investigate whether other factors that cause GML, such as chronic stress or psychiatric and neurodegenerative disorders, exhibit patterns of GML that are likewise comparable to the pattern of the aging brain. A recent study[27] provides initial evidence for this possibility, by showing aging-like changes in brain structure for a range of psychiatric disorders (schizophrenia, major depression and borderline personality disorder). Such future research would clarify whether the similarity to age-related GML is indeed specific to AD.

The similarity between age- and AD-related GML patterns provided motivation for a brain age model of AD. Our results revealed an average increase of the brain age of 4 years relative to chronological age, thus demonstrating that alcohol-related brain aging was substantial in relation to the human lifespan. Of note, despite its simplicity, the accuracy of the model with respect to the age prediction in control subjects was on a competitive basis with more complex approaches[28]. Our results thus confirm and quantify, for the first time, accelerated alcohol-related brain aging on a chronological scale. Moreover, relating brain aging to LC, we found that each kg of alcohol consumption corresponded to approximately half a day of brain aging. This result provides further validation for the brain aging model and may be particularly useful for psychoeducational purposes.

An analysis of brain aging as a function of chronological age revealed a systematic increase of brain aging over the lifespan. While brain aging was highest in the oldest AD subjects of our cohort (ages 60–69; 11.7 ± 2.4 years), no brain aging was detectable in the youngest AD subjects (ages 20–29). These results resonate with both the vulnerability hypothesis and the accelerated aging hypothesis. In line with the accelerated aging hypothesis (but contrary to the vulnerability hypothesis), brain aging was measurable throughout the lifetime, with the exception of only the youngest AD subjects tested. On the other hand, the results did show more pronounced alcohol-related brain aging with increasing chronological age. This pattern, as well as the indication of protective factors in the youngest AD subjects, are in accordance with the vulnerability hypothesis. Overall, our results thus suggest a middle ground between the accelerated aging hypothesis and the vulnerability hypothesis, evidencing accelerated brain aging in all but the youngest individuals with AD and a progressive vulnerability to brain aging with increasing chronological age.

Limits of the present study are the relatively small number of females (16%) in this study, potentially masking effects of gender, and possible side effects of physical or mental comorbidities on GML, that may have not been fully prevented by controlling for general health status (WHODAS-II) and by excluding participants with non-AD mental disorders.

In conclusion, the present study provides novel neurobiological evidence for accelerated aging in AD, casting the neurotoxic effects of alcohol as an effective increase of brain age. In addition, it demonstrates that over and above total grey matter volume, cross-regional grey matter patterns are a useful marker of AD.

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Competing interests
The authors declare that they have no competing financial interests.

Supplementary information
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2.2.3 Predicting relapse in alcohol dependence with model-based functional magnetic resonance imaging

Sebold M, Nebe S, Garbusow M, **Guggenmos M**, Schad DJ, Beck A, Kuitunen P-S, Sommer C, Neu P, Zimmermann US, Rapp MA, Smolka MN, Huys QJM, Schlagenhauf F, Heinz A (2017). When habits are dangerous - Alcohol expectancies and habitual decision-making predict relapse in alcohol dependence. *Biological Psychiatry* 82, 847–856. doi: 10.1016/j.biopsych.2017.04.019

A prominent theoretical account of addiction poses that drug consumption is initially *goal-directed* with respect to the anticipated positive effects of drugs, but progressively becomes more *habitual* and then compulsive (Everitt and Robbins, 2016, 2005; McKim et al., 2016). In line with this account impaired goal-directed behaviour has been found for a number of substance disorders, including methamphetamine (Voon et al., 2015), cocaine (Ersche et al., 2016), and alcohol dependence (Sebold et al., 2014; Sjoerds et al., 2013). The goal of Sebold et al. (2017) was to investigate differences in goal-directed (*model-based*) and habitual (*model-free*) control between alcohol-dependent relapsers and abstainers as well as healthy controls, both at the behavioural and the neurobiological level.

The two-step task was used as a behavioural paradigm to distinguish between model-based and model-free behaviour (Daw et al., 2011) and fMRI in combination with machine learning was used for group predictions (controls, abstainers, relapsers) based on the underlying neural correlates. In the two-step task, subjects first decide between two choices (first step), each one leading probabilistically to a second set of choices

(second step) which may or may not be rewarded. The assumption is that model-based agents consider the probabilistic transition structure between both steps, whereas model-free agents repeat choices at both stages that led to reward in previous trials. To capture such behavioural differences, a computational model was used which estimated the balance between model-free and model-based control (Daw et al., 2011; Deserno et al., 2015b, 2015a). Moreover, as positive alcohol expectancies have been linked to current (Leigh, 1989) and future (Reese et al., 1994; Goldman and Darkes, 2004) alcohol misuse, a possible interaction of model-free/based control with alcohol expectancy was considered.

Applying model-based analysis to the behavioural data it was found that model-free or model-based control per se did not distinguish between healthy controls, abstainers, or relapsers; by contrast, the interaction between model-based control and alcohol expectancies did indeed predict group membership, such that a tendency to expect positive alcohol effects combined with low model-based control was strongest in relapsers, followed by abstainers and healthy controls. Conversely, in healthy controls (and to a degree in abstainers), high alcohol expectancies were associated with stronger model-based control. Using machine learning and a cross-validation procedure, it was found that a logistic regression model predicted group membership with high accuracy (AUC=0.77).

In a next step, model-based control signals from the computational model were correlated to fMRI data to investigate potential differences between groups. In general, model-based control signals were found to be encoded in ventral striatum and medial prefrontal cortex (mPFC), confirming previous studies (Daw et al., 2011; Deserno et al., 2015b, 2015a). Crucially, in line with behavioural results, a significant difference was found in mPFC

between the group of relapsers and the group of abstainers and controls, such that relapsers showed the weakest signature of model-based control in mPFC. A control analysis using voxel-based morphometry showed that his result could not be explained by differences in individual grey-matter density.

Overall, these results suggest that impaired model-based control predicts relapse only in patients with high alcohol expectancies. Relapsers with high alcohol expectancies may thus be less likely to make informed decisions and more influenced by habitual responses possibly caused by interoceptive cues that induce positive alcohol expectancies. By contrast, the positive relationship between high alcohol expectancy and model-based control in abstainers and healthy controls might help these subjects to use alcohol within a framework of self-determined values and goals and to make more informed decisions about their drinking using model-based control mechanisms. At the neural level, model-based control signals and their influence on relapse probability may be mediated by the mPFC, which showed reduced activation in relapsers.

For copyright reasons, the following work has been removed from this habilitation:

Sebold M, Nebe S, Garbusow M, Guggenmos M, Schad DJ, Beck A, Kuitunen P-S, Sommer C, Neu P, Zimmermann US, Rapp MA, Smolka MN, Huys QJM, Schlagenhauf F, Heinz A (2017). When habits are dangerous - Alcohol expectancies and habitual decision-making predict relapse in alcohol dependence. *Biological Psychiatry* 82, 847–856.

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3. GENERAL DISCUSSION

Two broad conclusions emerge from the studies presented in this work. First, at a methodological level the findings of this work delineate the utility but also the challenges of machine learning approaches to psychiatric neuroimaging (Guggenmos et al., 2016, 2018b). Second, machine learning applied to the investigation of alcohol dependence yielded converging evidence for a role of structural and computational prefrontal dysfunction in alcohol dependence (Sebold et al., 2017; Guggenmos et al., 2017, 2018a). Here, both conclusions are discussed in the context of the empirical studies on the neural basis of alcohol dependence (Sebold et al., 2017; Guggenmos et al., 2017, 2018a).

A first question is whether machine learning indeed provides an advantage over conventional univariate data analysis. This question was explicitly investigated in Guggenmos et al. (2018a), where three multivariate classification schemes based on either voxels or regional averages were contrasted with univariate classification. The results were two-fold. On the one hand, classification using the full information of voxel-level patterns did not provide an advantage over patterns of regional averages based on anatomically plausible parcellation. Thus, regional averages appear to be the appropriate spatial scale for distinguishing alcohol-dependent patients and controls based on grey-matter information. On the other hand, patterns based on regional averages were superior to univariate classification, in which classification was based on the whole-brain average of grey-matter concentration. Thus, conditional on the appropriate spatial scale, machine-learning-based analysis of brain *patterns* can be more sensitive compared to traditional univariate approaches.

A general advantage of classification-based analyses is the fact that they can be evaluated by means of prediction accuracy metrics such as percent correct classification or balanced accuracy (Brodersen et al., 2010), i.e. quantities that describe the actual utility of a putative biomarker. As shown in Guggenmos et al. (2018a), evaluating differences between samples (here alcohol-dependent patients and controls) in terms of classification accuracy puts univariate statistical results into perspective. Here, a conventional two-sample t-test between whole-brain grey-matter maps of patients and controls yielded effects that would be judged as *very strong* in a neuroimaging context: family-wise-error corrected significance levels of $p<0.001$ in a number of peak voxels. Intuitively, one may have expected that such strong univariate differences should be reflected in a perfect or close-to-perfect classification accuracy score in a machine learning setting. However, the best classification scheme achieved 74% correct, which, although clearly above chance, was far from perfect.

To understand, two factors have to be considered. First, as one can show easily via simulation, even two-sample t-test statistics for a variable of interest that are considered extraordinarily strong evidence (t-values of 10 to 20, assuming typical samples in the range of 30-100 per group), are associated with classification accuracies of well below 100% in a cross-validated classification setting. The second point touches a common misconception in the psychiatric neuroimaging literature in that it has become routine to correct p-values for the massive multiple comparison problem in whole-brain analyses, while classification accuracies computed for peak voxels or individual regions are often taken at face value. However, these accuracies are mathematically meaningless, as they too are subject to the same multiple comparison problem and thus inflated. Nevertheless, it is a relatively widespread procedure to prominently report classification accuracy

metrics for individual searchlights (Uddin et al., 2011), individual clusters (Coutanche et al., 2011), individual regions of interest (Gowin et al., 2015; Schuckit et al., 2016), individual anatomical regions of atlas-based classification (Ball et al., 2014) or even voxels (Ahrens et al., 2014). These reported classification accuracies are often in the range of 80-90% percent correct and have contributed to an inflated expectation about the accuracy of neuroimaging-derived biomarkers for psychiatric disorders.

Two possible methods exist to compute mathematically meaningful classification accuracies in the context of these multiple comparison problems. Either, all voxels or regional averages under investigation are fed to a single classifier and a single accuracy is computed for all data (as e.g. in Guggenmos et al., 2018a). It is then left to the classifier to discard uninformative and to emphasize the most predictive voxels or regions. The alternative is a validation data set, such that the most predictive region, searchlight, or voxel is determined in a training data set, and its predictive accuracy is determined in an independent dataset. This approach requires more data, but allows to compute mathematically meaningful classification accuracies for single searchlights, voxels or regions and thus higher spatial specificity.

Methodological issues to quantify the accuracy of machine learning models aside, an important benchmark for any such model is the comparison to human expert judgements. After all, the great promise of machine learning methods is that they are more sensitive compared to human judgements. Nevertheless, such comparisons are rarely undertaken (see Klöppel et al., 2008, for an exception). In Guggenmos et al. (2018a), three findings emerged from the comparison of computer-based classification with the judgements of an experienced radiologist for the case of discriminating between alcohol-dependent patients and controls.

First, computer-based classification performance was overall more accurate than radiological judgements (74% versus 66%). This shows that, at least in principal, computer-based classification can provide an advantage over human performance. However, in the case of alcohol dependence it has to acknowledged that a clinical diagnosis would typically not be based on a brain scan, but on clinical anamnesis, and would have much higher accuracy. In this sense, this example of superior computer-based classification has to be qualified as a proof of principal and not a case of immediate clinical relevance. Nevertheless, as an anticipated machine learning revolution is still in its infancy, and promising new machine learning models based on deep learning (Lecun et al., 2015) have yet to be applied to psychiatric research questions in a large scale, it is likely that such proof of principals will soon translate to actual advancements in clinical diagnosis and treatment planning.

Second, computer-based classification showed higher sensitivity compared to human judgements (71% versus 51%), i.e. identified a larger proportion of alcohol-dependent patients. This result is in line with a previous study comparing support vector machine classification against human performance for the discrimination between patients with sporadic Alzheimer's disease from 1) controls or 2) patients with fronto-temporal lobar degeneration (Klöppel et al., 2008). Here, the sensitivity of computer-based classification was up to 100%. Together, these results suggest that currently machine learning may be particularly suited as a screening tool, identifying candidate cases with high sensitivity for a subsequent radiological assessment with high specificity.

Third, a specific advantage of computer-based classification identified in Guggenmos et al. (2018a) was the effective quantitative consideration of additional demographic data (age and gender) supplied with the brain scans. Not only did the correction of brain scan

data by demographic data improve overall classification performance, it also reduced biases that were found without such a correction (increased likelihood of patient predictions for being male and older). In contrast, although provided with the same demographic information, the radiologist showed these biases for both age and gender. This suggests that machine learning methods are better at accounting for additional quantitative information provided with primary neuroimaging data. As the development and trajectory of psychiatric disorders is likely influenced by a number of internal and external factors (e.g. demographic, social, psychological, educational or economic factors), this strength of machine learning will pay off even more off, when more comprehensive and larger data sets become available that include comprehensive quantitative information about these factors.

As an important step in this direction, Sebold et al. (2017) investigated a specific hypothesis about disturbed model-based learning signals in alcohol dependence and how those interact with positive alcohol expectancies. Behaviourally, it was found that reduced model-based learning signals in combination with high alcohol expectancies were predictive of relapse in alcohol-dependent patients. At the neural level, model-based learning signals encoded in the medial prefrontal cortex (mPFC) were found to distinguish between alcohol-dependent relapsers and abstainers as well as healthy controls.

Zooming out, the emerging theme across the three clinical studies reviewed here (Sebold et al., 2017; Guggenmos et al., 2018a, 2017) is a disturbance of frontal brain structure and function in alcohol dependence. Guggenmos et al. (2018a) showed that grey-matter concentration in dorsal cingulate and inferior frontal brain regions contributed most to the classification between alcohol-dependent patients and controls. Casting grey-matter

alterations in alcohol dependence as brain aging, Guggenmos et al. (2017) showed that frontal brain areas were among the regions that showed the most severe aging effects. Finally, using fMRI Sebold et al. (2017) found that prefrontal model-based learning signals were reduced in alcohol-dependent patients compared to controls and additionally distinguished within the patient group between relapsers and abstainers. Together, these results support the theory of frontal lobe pathology in alcohol dependence (Moselhy et al., 2001).

At the core of this theory is the assumption that the prefrontal cortex exerts top-down inhibitory control over compulsive behaviours (Abernathy et al., 2010). These executive functions, including attention, planning, and decision making, are thought to operate through the dynamic interaction of two parallel networks of the PFC – an 'executive' network at the top of the hierarchy with dorsolateral and dorsal cingulate divisions of the PFC and a 'limbic' network primarily contained in the orbitofrontal PFC (Abernathy et al., 2010). In particular, the limbic network is thought to relay the integrated and 'value-tagged' summary of sensory inputs to the executive network (Rolls, 1998).

The specific disturbances underlying addiction in this network model of the PFC are still debated. Top-down models pose that the executive control functions of the prefrontal cortex are attenuated in individuals that are vulnerable to alcohol addiction as well as through alcohol exposure itself. This loss of inhibitory control by the PFC has been conceptualized as a *syndrome of impaired response inhibition and salience attribution* (iRISA) (Goldstein and Volkow, 2002; Volkow et al., 2003). On the other hand, bottom-up models emphasize the role of the limbic system, which may be caused by disturbances in dopaminergic salience signalling. For instance, the *incentive sensitization theory* suggests that drug consumption leads to a sensitization of the dopamine system through

associative learning, which "causes excessive incentive salience to be attributed to the act of drug taking and to stimuli associated with drug taking" (Robinson and Berridge, 1993; Heinz et al., 2004). As a consequence, drug seeking and taking become a major motivational force, often occurring at the expense of social or professional obligations.

The structural and functional disturbances found in the clinical studies reviewed here largely support a top-down model. First, grey-matter concentration in the dorsal anterior cingulate cortex was most predictive for the distinction between alcohol-dependent patients and controls in the machine learning approach of Guggenmos et al. (2018a) and thus a regions that is thought to belong to the executive PFC network. It is conceivable that grey-matter atrophy in the executive PFC network may contribute to the loss of inhibitory control observed in alcohol dependence. Second, Sebold et al. (2017) found a reduction of model-based control signals in the medial PFC of patients relative to controls (and relapsers relative to abstainers), and thus signals that support goal-directed and strategic 'top-down' behaviours. Overall, the studies reviewed here therefore reinforce a transition in the literature over the past two decades, which increasingly emphasizes disturbed top-down control functions in the PFC, as opposed to a disruption of subcortical reward circuits centred around the neurotransmitter dopamine (Goldstein and Volkow, 2012).

Taken together, the works reviewed here demonstrate both the utility and the current limits of machine learning approaches to psychiatric neuroimaging. Clear advantages of machine learning are the exploitation of the full information contained in brain activation patterns, which are largely inaccessible to standard data analysis and human evaluation, as well as their ability to systematically and quantitatively account for additional information (demographic, psychosocial, etc.) provided with the subject data. However,

the accuracy of machine learning models is currently not sufficient to have a clear clinical benefit. At present, the most realistic application of these models is to serve as screenings tool with high sensitivity. A promising avenue for future research is the combination of machine learning with computational modelling (*generative embedding*; Stephan et al., 2016), such that computational modelling extracts meaningful mechanistic features from brain and behaviour which are subsequently processed by machine learning models to predict diagnoses or treatment outcomes in alcohol dependence and other psychiatric disorders.

4. SUMMARY

Alcohol dependence is a psychiatric disorder with a lifetime prevalence of over 10% and a leading cause of morbidity and premature death. A better understanding of the neural mechanisms underlying alcohol dependence to improve prevention, diagnosis and treatment is thus of great societal interest. Recent advancements in the analysis of neuroimaging data based on machine learning have opened new paths to a better quantitative understanding of the disorder. The present habilitation reviews both works with a focus on improving machine learning methodology and empirical works in which machine learning was applied to investigate the neural basis of alcohol dependence.

The methodological works advanced several aspects of machine learning in neuroimaging. In particular, they introduced i) a novel classifier (weighted robust distance – WeiRD), which operates parameter-free, computationally efficient and enables a transparent inspection of feature importances, ii) a method to preprocess neuroimaging data based on multivariate noise normalization, which yielded a substantial improvement in classification performance compared to previous the state-of-the-art, and iii) a novel method to reintroduce meaningful graded information into discretized classification accuracies by utilizing classifier decision values.

Drawing on a large neuroimaging dataset of alcohol-dependent patients and controls from the LeAD-study (www.lead-studie.de; clinical trial number: NCT01679145), machine learning methods were applied in empirical works to investigate structural and functional alterations in alcohol dependence. Structural damage associated with alcohol dependence were investigated from two conceptually different angles. A first study was aimed at providing the first quantitative evidence for a long-standing hypothesis about the

damaging effects of alcohol – the premature aging hypothesis. To this end, a machine learning model was trained on the relationship between grey-matter pattern information and chronological age in a healthy control group and then applied to the sample of alcohol-dependent patients. The predicted 'brain age' of patients was found to be was several years higher than their chronological age, thus not only providing quantitative evidence for brain aging in alcohol dependence, but also showing that these aging effects are indeed substantial in relation to the human lifespan. The second study used machine learning to quantify the predictive accuracy of grey-matter pattern information for the diagnosis and a severity measure (lifetime consumption) of alcohol dependence. On average, machine learning models correctly predicted the diagnosis in three of four subjects and accurately estimated the amount of lifetime alcohol consumption. Closer inspection of the prediction model indicated an important role of dorsal anterior cingulate cortex. Comparison with an experienced radiologist, who, like the classifier, was provided with the structural brain scans of the subjects, demonstrated superior performance of computer-based classification and in addition a more effective consideration of demographic information (age and gender). Finally, a third study used functional magnetic resonance imaging to investigate a specific hypothesis about reduced goal-directed learning in alcohol dependence as well as its relation to relapse after detoxification. Computational modelling in combination with machine learning revealed that the interaction of model-based learning and high alcohol expectancies was predictive of diagnosis (patients versus controls) and treatment outcome (abstainers versus relapsers). This finding was paralleled by a signature of model-based learning in medial prefrontal cortex, which was reduced in patients relative to controls and in relapsers relative to abstainers.

In sum, the works presented in this habilitation advance machine learning methods for neuroimaging and show that these methods yield novel insights into the neural basis of alcohol dependence. An emerging theme across the three empirical studies on alcohol dependence is the disturbance of executive frontal brain structure and function, supporting a top-down rather than bottom-up view for the aetiology of alcohol dependence.

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Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
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- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

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