Neurostimulation in alcohol dependence: The effect of repetitive transcranial magnetic stimulation on cognitive functioning and craving

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BRAIN FUNCTION DURING COGNITIVE FLEXIBILITY AND WHITE MATTER INTEGRITY IN ALCOHOL DEPENDENT PATIENTS, PROBLEMATIC DRINKERS, AND HEALTHY CONTROLS

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ABSTRACT

Cognitive flexibility has been associated with prefrontal white matter (WM) integrity in healthy controls, showing that lower WM integrity is associated with worse performance. Although both cognitive flexibility and WM integrity have found to be aberrant in alcohol dependent (AD) patients, the relationship between the two has never been tested. In this study we investigated the association between WM tract density and cognitive flexibility in patients with AD (n=26) and healthy controls (n=22). In order to assess the influence of AD severity, we also included a group of problematic drinkers (PrD; n=23) who did not meet AD criteria. Behavioral responses and brain activity during a cognitive flexibility task were measured during functional Magnetic Resonance Imaging (fMRI). Probabilistic fiber tracking was performed between the dorsolateral prefrontal cortex and basal ganglia; two crucial regions for task switching. Finally, the task related functional connectivity between these areas was assessed. There were no significant group differences in task performance. However, compared to healthy controls, AD patients and PrDs showed decreased WM integrity and increased prefrontal brain activation during task switching. Evidence is presented for a compensatory mechanism, involving recruitment of additional prefrontal resources in order to compensate for white matter and neural function impairments in alcohol dependent patients and problematic drinkers. Although present in both alcohol groups, the PrDs were more successful in invoking this compensatory mechanism when compared to the AD patients. We propose that this may therefore serve as a protective factor, precluding transition from problematic drinking into alcohol dependence.

1. INTRODUCTION

Alcohol and drug dependence are chronic relapsing brain disorders characterized by altered reward circuitry and weakened cognitive control systems that often lead to impairments in cognitive functioning, including impaired cognitive flexibility (Baler and Volkow, 2006; Koob and Volkow, 2010). Cognitive flexibility is a prerequisite for goal directed behavior and involves executive decision making preceding switching behavior (Lezak, 2004). It has been defined as the ability to adjust one’s thinking from old to new situations (Moore and Malinowski, 2009). Previous studies have shown impaired cognitive flexibility (Vanes et al., 2014) in almost all substance use disorders (for a review, see (Volkow et al., 2002)) and in problematic gamblers (for a review, see (van Holst et al., 2010)). These impairments in cognitive flexibility are related to the compulsive use of drugs and/or alcohol, which is one of the key elements in the development and persistence of substance dependence (Everitt and Robbins, 2005; Stalnaker et al., 2009).

Lesion and neuroimaging studies have shown that the dorsolateral prefrontal cortex (dIPFC) is essential for cognitive flexibility (Badre and Wagner, 2006; Nyhus and Barcelo, 2009). Neuroimaging studies on cognitive flexibility in healthy subjects using cognitive switching paradigms observed increased activation in dorsolateral prefrontal cortex (dIPFC), ventrolateral prefrontal cortex (vIPFC), including the inferior frontal gyrus (IFG), anterior cingulate cortex (ACC), posterior parietal cortex, and basal ganglia during
correct task switching (Ravizza and Carter, 2008; Smith et al., 2004; Sohn et al., 2000). In addition, many studies have reported on impaired prefrontal functioning during cognitive tasks in substance dependent patients (Baler and Volkow, 2006; Goldstein and Volkow, 2011). However neural processes underlying aberrant cognitive switching in alcohol use disorders are still not well examined.

Previous studies have also shown that prefrontal white matter (WM) integrity is related to cognitive functioning and cognitive flexibility (Bennett et al., 2011; van Schouwenburg et al., 2013). Alcohol is neurotoxic and inflicts damage to the brain, and WM in the prefrontal cortex in particular (Harper, 2007; Kril et al., 1997; Yeh et al., 2009). A decline in WM integrity in alcohol dependent (AD) patients has previously been linked to cognitive deficits, including (working) memory, attention and responsiveness to reward (Chanraud et al., 2009; Harris et al., 2008; Pfefferbaum et al., 2010; Schulte et al., 2010; Schulte et al., 2012). However, there are no studies that have investigated the relationship between prefrontal WM integrity and cognitive flexibility in a sample of AD subjects and problematic drinkers (PrD). Since previous studies strongly associate the dlPFC and basal ganglia with cognitive flexibility (van Schouwenburg et al., 2012), it is hypothesized that impaired switching behavior in substance dependence is related to damaged fiber bundles connecting the prefrontal cortex and basal ganglia, including ventral striatum and putamen (van Schouwenburg et al., 2013). WM integrity can be investigated non-invasively using diffusion tensor imaging (DTI) which provides fractional anisotropy (FA) and mean diffusivity (MD) values to describe the macroscopic characteristics of fiber bundles (Hagmann et al., 2006). Decreases in FA are thought to reflect a decline in fiber density and coherence, whereas increases in MD values mirror cell membrane damage (Beaulieu, 2002). In AD, decreases in FA and increases in MD values have been reported (Harper, 2007, 2009; Pfefferbaum et al., 2009; Pfefferbaum and Sullivan, 2004).

Similar to findings in substance dependence, there is a decrease in cognitive functioning and WM integrity in healthy aging of the brain (for a review, see (Goh and Park, 2009; Park and Reuter-Lorenz, 2009)). Neuroimaging studies have reliably reported increased prefrontal activation during cognitive tasks in elderly subjects (Cooper et al., 2013; Park and Reuter-Lorenz, 2009). High cognitive functioning elderly exhibit higher activations when compared to low cognitive functioning elderly (Park and Reuter-Lorenz, 2009). The scaffolding theory of aging and cognition (STAC) states that increased activation in cognitively demanding tasks in healthy aging is a compensatory mechanism for decreased WM integrity and neural functioning (Park and Reuter-Lorenz, 2009). Increased prefrontal activations are sometimes accompanied by decreases activity in more posterior parts of the brain (Davis et al., 2008). Higher activity during cognitive and emotional tasks has previously been reported and explained as a compensatory mechanism in substance dependent populations (Charlet et al., 2014b; Goldstein and Volkow, 2011; Yucel and Lubman, 2007). For example, higher activations during high working memory load and affective face recognition were associated with lower relapse risk (Charlet et al., 2014a; Charlet et al., 2014b). These higher activations are likely to be associated with alcohol induced WM damage and support the explanation that higher activations in cognitively demanding situations reflect a compensatory mechanism in patients with AD.
The aim of this study is to investigate cognitive flexibility and underlying neuronal mechanisms in a sample of AD patients, PrDs and healthy controls (HC). The inclusion of PrDs enables the assessment of WM integrity and cognitive flexibility across a broad range of alcohol related problems. On a behavioral level, we hypothesize that AD patients and PrDs perform worse compared to HC, as indicated by fewer correct switch trials and higher switch costs. In line with the STAC, we hypothesize that both the AD and the PrD group show a decline in WM integrity together with an increase in prefrontal neural activity during cognitive switching when compared to healthy controls. In analogy with high and low functioning elderly, it is expected that PrDs show higher compensatory activation of the prefrontal cortex than AD patients. To test our hypothesis we applied a cognitive switching task, while measuring the BOLD response in the brain, and performed diffusion tensor fiber tracking between the dlPFC and the basal ganglia.

2. MATERIALS & METHODS

2.1 Participants
AD subjects were recruited from Dutch addiction treatment centers where they received cognitive behavioral therapy. HCs and PrDs were recruited through advertisements in local newspapers. All participants were male, HC’s did not drink more than 21 standard units (10 g) of alcohol per week. The ethical review board of the Academic Medical Centre approved the study and all subjects provided written informed consent and were remunerated for their participation. The number of subjects varied per analysis due to missing data in either one or more modalities, the exact numbers per analysis can be found in Table 2.1 and are reported throughout the result section.

AD were diagnosed according to DSM-IV-TR alcohol dependence criteria with section J of the Dutch version of the Clinical International Diagnostic Inventory [CIDI, (World Health Organisation, 1997)]. A measure of alcohol problem severity was obtained for all participants by administering the Alcohol Use Disorders Identification Test [AUDIT;(Bush et al., 1998)]. Furthermore, to ensure that all participants were detoxified from alcohol, AD patients had to be abstinent for at least two weeks (range: 2 weeks to 12 months) to be included into the study. The PrDs were abstinent for at least 24 hours, which was confirmed with urine and breathing tests. For a more elaborative description of the PrD group, see (Starcke et al., 2013). Urine samples were analyzed by a clinical toxicology laboratory (ATAL Medical Diagnostics, Amsterdam, The Netherlands) and none of the tests were positive for alcohol.

Exclusion criteria for all groups included: lifetime diagnosis of schizophrenia or psychotic episodes, 12-month diagnosis of manic disorder, OCD, and post-traumatic stress disorder, other substance use disorders than alcohol dependence (except for nicotine), treatment for mental disorders in the past 12 months (except for alcohol dependence), use of psychotropic medication, difficulty reading Dutch, age under 18 years, IQ below 80 (measured by the Dutch Adult Reading Test;(Schmand et al., 1991)), positive urine screen for alcohol, amphetamines, benzodiazepines, opioids or cocaine, history or current treatment for neurological disorders, major internal disorders, brain trauma, or exposure to other neurotoxic factors than alcohol.
2.2 Assessments and statistical analyses

2.2.1 FMRI Paradigm
In order to test cognitive flexibility, we applied an fMRI compatible self-paced switch task adapted from Sohn et al. (Sohn et al., 2000). During each trial a stimulus consisting of one letter and one digit was shown, the color of which indicated the task to be performed: vowel/consonant (blue) or odd/even (red) judgments. Letters were taken from the set [a, e, i, u, b, c, d, f] and digits were taken from the set [2, 4, 6, 8, 3, 5, 7, 9]. Two consecutive trials never contained the same letter or digit. Color-task and stimulus-response associations were counterbalanced across subjects. Task switching (Color change) occurred randomly after 4-6 trials to avoid predictability. First trials immediately after a color switch were defined as ‘switch trials’, all other trials were defined as ‘repeat trials’. For example, on a switch trial the subject had to switch from making a number judgment to a letter judgment or vice versa. If the target was blue the criterion dimension was letter, and the criterion response was a left key press for a vowel and a right key press for a consonant. The task ended after 32 task switches and after 160 repeat trials, in a single run which took around 21 minutes to be completed. The task was self-paced with a maximum response window of 4000ms per trial and an inter-stimulus interval of 500ms. If the subject did not respond within 4000ms the trial was considered an error and the next trial appeared. In addition, the paradigm included six 30s baseline blocks during which a fixation cross was shown and in which the subject had to remain still and wait until the task resumed, i.e., a passive baseline condition. Subjects performed a training session outside the scanner. There was no provision of feedback during the task. Behavioral variables of interest included (1) percentage correct task switches, (2) percentage of correct task repeats, (3) switch cost [reaction times (RTs) of switch trials minus RTs of repeat trials].

2.2.2 Behavioral analysis
Demographic and behavioral data were analyzed using univariate analysis of variance (ANOVA and ANCOVAs) and Tukey’s post-hoc tests in SPSS 20.0 (IBM Corp. in Armonk, NY.). Non-normally distributed data (i.e. age, AUDIT scores, and number of drinks per week) were analyzed using Kruskal-Wallis Tests and post-hoc tests were conducted with Mann-Whitney tests. A paired-sample t-test was used to investigate differences between switch and repeat conditions across groups. Furthermore, an ANOVA test was used to assess group differences in task performance. Finally the effect of abstinence duration was assessed in a correlation analysis with task performance, brain activity and white matter integrity only in AD patients, because PrDs were mostly abstinent for less than two weeks. All analyses were performed two-tailed with alpha set at .05.

2.2.3 FMRI analysis
Imaging data were obtained using a 3.0 T Intera whole-body fMRI scanner (Philips Medical Systems, Best, The Netherlands) with a phased array SENSE RF eight-channel receiver head coil. Task stimuli were projected on a screen behind the subject’s head at the end of the scanner table. The screen was visible for the subject through a mirror mounted above the subject’s head. Two magnet-compatible response boxes were used to record the subject’s responses. A total of 35 axial slices (voxel size 2.29x2.29x3 mm) T2*-weighted echo planar images (EPIs) were obtained, without interslice gap, a matrix size of 96x96 mm2, TR/TE=2.3s/30ms, and a bandwidth of 90 kHz. These images are
sensitive to blood oxygenation level-dependent (BOLD) contrast and covered the entire brain except for the inferior regions of the cerebellum.

A T1-weighted structural scan was made for co-registration with the fMRI data (voxel size 1 x 1 x 1 mm; 170 slices). Functional imaging analyses were performed with SPM5 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK). Images were manually reoriented and subsequently slice-timed, and realigned and unwarped. Next, images were warped to MNI space using each subject's co-registered T1 image, and spatially smoothed using an 8 mm FWHM Gaussian kernel.

FMRI data were analyzed in the context of the general linear model, using delta functions convolved with a canonical hemodynamic response function to model responses to each type of stimulus (switch trials and repeat trials). Contrast images containing parameter estimates were entered into a second-level (random effects) analysis. Main effects across groups for each contrast were analyzed using one-sample t-test implemented in SPM5, and are reported at p<0.05 corrected for multiple comparisons at the voxel level across the whole brain, according to the family wise error (FWE) method. Peak significant voxels per group were extracted with Marsbar v0.43, in order to assess the relationship between activity levels, task performance and DTI measurements (Brett et al., 2002).

Group interactions were investigated using specific a priori regions of interest (ROIs) with a threshold set at p < .05, Family Wise Error (FWE) corrected for multiple comparisons (Friston et al., 1996). The dlPFC, vlPFC, ACC, posterior parietal cortex and basal ganglia were defined as a priori ROIs, given their role in cognitive switching (Ravizza and Carter, 2008; Smith et al., 2004; Sohn et al., 2000). The basal ganglia ROI, including the putamen was defined using the WFU PickAtlas Tool v2.4 (Maldjian et al., 2003) that incorporates the automatic anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Activity in the dlPFC, posterior parietal cortex and vlPFC was detected by using ROI templates of the dlPFC, parietal cortex, and the middle orbitofrontal cortex and inferior orbitofrontal cortex, respectively. These ROI’s were defined using the online Voxel of Interest Database (P.T. Fox and Lancaster, 1994). Secondly, for exploratory purposes we report brain regions which were not predicted a priori but which met a threshold of P < 0.001, uncorrected with a cluster size of 10 contiguous voxels (Supplement 1).

### 2.2.4 Functional Connectivity

Functional connectivity analyses were conducted with the Conn toolbox in Matlab (Whitfield-Gabrieli and Nieto-Castanon, 2012). Input for the functional connectivity analyses were the first level switch vs repeat contrasts for each subject. Per subject, the correlation coefficient between the dlPFC and basal ganglia ROIs was computed per hemisphere and analyzed in SPSS.

### 2.2.5 Diffusion Tensor Imaging: acquisition, pre-processing and fiber tracking

Diffusion weighted echo planar images were acquired along 32 directions with a b-value of 1000 s/mm$^2$ and one acquisition without diffusion weighting (b=0). All acquisitions were made with the following parameters: TR=4.862ms, TE=94ms, 38 axial interleaved slices with a 3mm slice thickness with no gap, with a 112x110 mm$^2$ matrix...
The pre-processing of the DTI data was performed using in-house developed software, written in Matlab (The MathWorks, Natick, MA) and was executed on the Dutch Grid using a web interface to the e-Bioinfra gateway (Olabarriaga et al., 2010; Shahand et al., 2011). We corrected for head motion and deformations induced by eddy currents by an affine registration of the Diffusion Weighted Images (DWIs) to the non-diffusion weighted image. The gradient directions were corrected by the rotation component of the transformation. The DWIs were resampled isotropically. Rician noise in the DWIs was reduced by an adaptive noise filtering method (Caan et al., 2010). Diffusion tensors were estimated with a non-linear least squares procedure. From the resulting tensors, fractional anisotropy and mean diffusivity maps were computed.

Additional processing was required to model crossing fibers (BEDPOSTX, Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques). Probabilistic fiber tracking was performed using (FMRIB’s Software Library (FSL) software (Behrens et al., 2007).). Seed regions for the fiber tracking were based on the functional MRI results by saving supra-threshold voxels in the dlPFC and basal ganglia masks as binary masks, reoriented and transformed back to single subject space with SPM8. These ROI-masks were resliced with the BedpostX output file and subsequently used as seed and waypoint masks in fiber tracking. Fiber tracking was performed bilaterally.

To improve inter-subject correspondence along the individually tracked fibers, we non-rigidly registered (Ashburner, 2007) the non-diffusion weighted images (b0) and warped the tracked fibers accordingly, with in-house written software in MATLAB (7.10.0; The MathWorks Inc., Natick, Massachusetts). The fiber with minimal distance to all fibers of all subjects was chosen as reference fiber. The normal plane along this fiber was used to define correspondence to the fibers of all subjects. The FA profiles with 2-mm distance sampling were generated on the bilateral dlPFC-basal ganglia tracts and resulted in 10 mean FA and MD points along the tracts. Subsequent analyses were performed in SPSS using a repeated measures ANCOVA test per tract to check for group differences in mean FA and MD values, and partial correlation analysis to assess the relationship with task performance.

In order to reduce the number of comparisons, the behavioral measurements of task switching were only correlated with those segments that differed most in FA and MD in the combined AD and PrD group, compared to the HC group. Greater differences are thought to reflect a higher degree of compromised white matter integrity and these segments are therefore of interest. The difference between the combined alcohol group compared to the HC group was greatest in the most prefrontal segments (corresponding to number 10) of the left (for MD) and right hemisphere (for FA); indicating that white matter integrity was mostly compromised in these areas. Partial correlation analysis between these areas and the task performance measurements were carried out. All DTI analyses were corrected for age, because age has a well-known negative effect on WM integrity (Bennett et al., 2011).
3. RESULTS

3.1 Demographics

Table 1 summarizes demographic and clinical characteristics for the three groups: AD, PrDs and HCs. There were no significant differences in age or IQ, but all groups significantly differed on their AUDIT scores and number of drinks per week. Post-hoc comparisons revealed that the AD group had significantly higher scores for the AUDIT and on the number of standard drinks per week compared to the PrD and the HC groups. Furthermore, the PrD group had higher AUDIT scores and more standard drinks per week compared to the HC group (AD>PrD>HC). Analysis for the effect of abstinence duration in AD patients revealed no significant effects on task performance, brain activity or white matter integrity.

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls N=22</th>
<th>Problem Drinkers N=21</th>
<th>Alcohol Dependent N=26</th>
<th>F (df)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>38.5 (10.3) [22 : 53]</td>
<td>42.1 (13.8) [22 : 61]</td>
<td>44.3 (9.2) [21 : 59]</td>
<td>3.08 (2)</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>IQ</strong></td>
<td>104.5 (12.5) [80 : 123]</td>
<td>106.7 (14.3) [73 : 128]</td>
<td>101.0 (15.1) [71 : 125]</td>
<td>2.12 (2)</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>AUDIT</strong></td>
<td>5.1 (4.4) [0 : 15]</td>
<td>18.5 (5.3) [11 : 33]</td>
<td>27.9 (5.1) [11 : 36]</td>
<td>51.83 (2)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>Number of standard drinks/week</strong></td>
<td>7.3(7.2) [0 : 25]</td>
<td>46.7(31.5) [0 : 144]</td>
<td>96.7(61.2) [0.5 : 264]</td>
<td>50.90 (2)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>DSM-IV criteria Alcohol Abuse</strong></td>
<td>0.14 (0.36) [0.0 : 1.0]</td>
<td>0.8 (0.95) [0.0 : 3.0]</td>
<td>1.9 (0.85) [1.0 : 3.0]</td>
<td>30.32 (2)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>DSM-criteria Alcohol Dependence</strong></td>
<td>0.05 (0.22) [0.0 : 1.0]</td>
<td>1.3 (1.46) [0.0 : 6.0]</td>
<td>6.65 (1.56) [3.0 : 9.0]</td>
<td>100.72 (2)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Table 1: Sample characteristics. Values for age, IQ, AUDIT, drinks per week, DSM-IV criteria for alcohol abuse and dependence are denoted as mean (standard deviation) and [min : max].

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls N=22</th>
<th>Problem Drinkers N=21</th>
<th>Alcohol Dependent N=26</th>
<th>F-value (df)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Percentage Correct Switches</strong></td>
<td>78.1 (19.6)</td>
<td>79.0(17.0)</td>
<td>74.2 (16.8)</td>
<td>.55 (2, 66)</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Switch Cost (RT)</strong>*</td>
<td>136.7 (20.8)</td>
<td>128.1 (27.2)</td>
<td>124 (29.3)</td>
<td>1.16 (2,61)</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Percentage Erroneous Repeats</strong></td>
<td>2.0 (1.2)</td>
<td>2.1 (1.3)</td>
<td>2.5 (0.8)</td>
<td>1.81(2, 66)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Table 2: Behavioral measurements of task switching. This table shows the results of the ANCOVA test with age as covariate. * The number of participants is smaller for the Switch Cost analysis, due to missing data (HC=19, PD=20, AD=25).
3.2 Behavioral performance on the Switch task
Across groups we found that subjects responded significantly faster during repeat trials (M=1118.7 SD=26.6) than to switch trials (M=1551.0 SD=316.9, t(66)=17.25 p<0.001). In addition, across groups, subjects made more correct responses during repeat trials (M=85.0% SD=13.4) than during switch trials (M=76.2% SD=16.7, t(68)=-10.12 p<0.001). There were no significant differences between groups in the percentage of correct task switches, percentage of erroneous task repeats or switch costs (see Table 2).

3.3 fMRI results

3.3.1 Main effect task switch vs. task repeat
Increased activity during switch versus repeat trials in all groups was found in the whole brain analysis for the bilateral basal ganglia, ventrolateral and dorsolateral PFC, right middle temporal cortex, left anterior cingulate cortex and right premotor cortex (see Supplement 1).

3.3.2 Group interactions task switch vs. repeats
Groups interactions were analyzed with ROIs and activity differed significantly between groups on their switch versus repeat brain activity, mainly in the dlPFC. Specifically, the PrD group particularly showed more activity in the left dlPFC than the HC group, and more activity in the left dlPFC than the AD group at a (trend) significant level (see Table 3). Task performance correlated with task performance only in HCs. Activity in the left dlPFC peak voxel was positively correlated with percentage correct switch trials (r=.48, n=18, p<0.05) and negatively correlated with erroneous repeats (r=-.49, n=17 P<0.05).

<table>
<thead>
<tr>
<th>Group Comparison</th>
<th>Brain Region</th>
<th>Hemisphere</th>
<th>Z-value</th>
<th>Number Voxels</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>P (FWE -corr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC &gt; AD</td>
<td>n.s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD&gt;HC</td>
<td>dlPFC</td>
<td>Left</td>
<td>3.51</td>
<td>4</td>
<td>-36</td>
<td>30</td>
<td>18</td>
<td>0.06</td>
</tr>
<tr>
<td>AD&gt;PD</td>
<td>n.s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD&gt;HC</td>
<td>dlPFC</td>
<td>Left</td>
<td>3.63</td>
<td>28</td>
<td>-33</td>
<td>36</td>
<td>27</td>
<td>0.04</td>
</tr>
<tr>
<td>PD&gt;AD</td>
<td>dlPFC</td>
<td>Left</td>
<td>3.52</td>
<td>27</td>
<td>-45</td>
<td>30</td>
<td>30</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>vlPFC</td>
<td>Left</td>
<td>2.90</td>
<td>3</td>
<td>-45</td>
<td>15</td>
<td>-6</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 3. Between group comparisons switch vs repeat functional MRI. This table reports the differential activations between the groups for the pre-selected ROIs. Significance levels are FWE-corrected, reported results with a p-value smaller than 0.05 are considered significant whereas a p-value of p=0.06 is considered trend significant. Legend: n.s = non-significant; hem. = hemisphere; FWE = Family wise error correction.
3.3.3 Functional connectivity
FMRI time courses were extracted from the bilateral dlPFC and basal ganglia masks and tested for correlational changes between the regions during switch and repeat trials. Both left \([t(45)=4.27, p<0.001]\) and right \([t(45)=4.85, p<0.001]\) hemisphere connectivity between these ROIs were significantly higher during switch trials compared to repeat trials (left; \(r=-.15, p<0.001\), right; \(r=-.15, p<0.001\)). Functional connectivity did not differ between groups and did not correlate with AUDIT scores or switch task performance.

3.3.4 Fiber tracking
The repeated measures ANCOVA revealed no significant interactions between group and segment for MD and FA values in either hemisphere. The FA and MD values in the left and right hemisphere all revealed significant effects for segment, except for left MD values. This indicates that MD and FA values differ along the fiber tract. Main effect of group was only significant for the left and right MD values (see Table 4). Post hoc analyses for these significant group effects in MD revealed that HCs had significantly lower MD values than AD (left; \(p<0.05\), right; \(p<0.01\)) and PD (left; \(p<0.05\), right; \(p<0.01\)), whereas AD and PrD did not significantly differ in MD values (see Figure 1: HC<PD=AD). Mean FA and MD values are reported in Supplement 2.

3.3.5 Relationship between FA values and task performance
The results of the correlation analyses revealed that for the overall group (HCs+PrDs+ADs), prefrontal white matter FA values correlated positively with the percentage correct switches and negatively with erroneous repeats (see Table 5), whereas MD values were not correlated with task performance. The results of the analysis per group indicate that the relationships between FA and task performance were restricted to the HC group (see Table 6). Moreover, in PrD MD values negatively correlated with percentage correct switches. FA or MD values were unrelated to functional connectivity. The MD and FA values did not correlate with activity levels in any of the groups.

<table>
<thead>
<tr>
<th>Left Hemisphere N=55</th>
<th>Right Hemisphere N=55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segment (repeated)</td>
<td>Group (Between Subjects)</td>
</tr>
<tr>
<td>FA</td>
<td>F(9)=10.94 p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>F(2)=.80 p=n.s.</td>
</tr>
<tr>
<td>MD</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Results for fiber tracking analysis for both left and right hemisphere. This table reports the results of the one-way repeated measures ANCOVA's that were conducted for FA and MD values in both hemispheres. Analyses are corrected for age.

<table>
<thead>
<tr>
<th>Correlations</th>
<th>Percentage Correct Switches N=51</th>
<th>RT Switch Cost N=47</th>
<th>Percentage Error Repeat* N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right FA segment 10</td>
<td>.35**</td>
<td>.17</td>
<td>-.37**</td>
</tr>
<tr>
<td>Left MD segment 10</td>
<td>.01</td>
<td>-.16</td>
<td>.11</td>
</tr>
</tbody>
</table>

Table 5. The results of the correlation analyses of the whole group. Results indicate that FA values are correlated with task performance. \(\gamma=\) log transformed. \(*=\) significant at \(p<0.01\), tested for 2-tailed significance.
Figure 1. FA and MD profiles for prefrontal white matter. The fiber tract is divided in ten segments, segment one is the most subcortical segment and segment 10 is the most prefrontal segment, as is depicted at the top of the figure. Different colors within the brain correspond to different segments. For the graphs, differently colored lines represent the different groups. MD-values are in mm²/s. Error bars denote standard error of the mean.
5. DISCUSSION

The current study reports on underlying functional and structural brain differences related to cognitive flexibility in HC, PrD and AD patients. Unexpectedly, no group differences in cognitive flexibility were found, but the results of this study confirmed the previously reported role of the dlPFC, vlPFC, ACC, posterior parietal cortex and basal ganglia in switching behavior (Ravizza and Carter, 2008; Smith et al., 2004; Sohn et al., 2000). Consistent with our hypotheses, PrD and AD groups revealed compromised WM integrity, especially mean diffusivity, and this was associated with increased dlPFC activity during task switching. These findings are in line with the scaffolding theory of aging and cognition (STAC) theory, which states that higher prefrontal activation in cognitive demanding tasks in the presence of neural damage reflects a compensatory mechanism. Our findings resonate with this compensatory hypothesis: PrDs showed higher activations compared to the AD and HC groups (PrD>AD>HC), whereas both AD patients and PrDs had significantly compromised WM integrity when compared to controls (Goldin et al., 2008). In healthy ageing some studies have found that increased prefrontal activation is accompanied by decreased activations in more posterior parts of the brain, these results were not found in this study (Davis et al., 2008). Possibly, the difference in results reflects differences between damage related to both healthy aging and the neurotoxic effects of alcohol. Based on the AUDIT scores, PrDs experienced less problems in daily life compared to AD patients and PrDs and AD patients may therefore be considered to represent high and low functioning phenotypes, respectively. The current results suggest a compensatory mechanism in alcohol use disorders, in which additional prefrontal resources are recruited in order to compensate for impaired WM integrity and neural functioning.

White matter integrity, especially MD values, differed between groups and indicate a loss of white matter integrity in PrDs and AD patients. FA values did not differ significantly between groups, but were only related to task performance in HC.
The absence of decreased FA values in AD compared to HCs is not in line with previous research which is however inconsistent, as both decreased (Pfefferbaum et al., 2009; Pfefferbaum et al., 2010; Pfefferbaum and Sullivan, 2004) and increased (Cardenas et al., 2013; De Bellis et al., 2008) in FA values compared to HCs have been reported. The association between WM integrity and cognitive flexibility is in line with a previous fiber tracking study on cognitive flexibility in healthy controls (van Schouwenburg et al., 2013).

The MD values correlated negatively with task performance only in PrDs, whereas MD values were not correlated with task performance in the AD group. The negative association between lower MD values and higher task performance indicates that those PrDs with less damage to prefrontal WM, show better switching performance. In AD patients no such relationship was apparent, since task performance did not correlate with any of the DTI measurements. This might indicate that WM damage in AD patients is too high to show an association with between DTI and functional performance, however, a similar pattern of WM damage and higher functional activity during the switch task was found. These results are likely to present a compensatory mechanism in AD patients and PrDs where decreased white matter integrity and related signal transfer is accompanied by increased neural recruitment. However, since the current study only assessed one specific fiber tract, it is not possible to make inferences on other WM tracts. Future studies should assess whether neural scaffolding is related to additional brain areas and other WM tracts.

These results should be viewed in light of some limitations. The non-significant difference between the groups on task performance might be related to practice effects, task design and/or sample sizes. Firstly, all subjects practiced outside the scanner, which may have obscured performance differences. Secondly, since the focus of our experiment was to assess the differential neural involvement in cognitive flexibility, the current version of the task was adapted for efficiently measuring the BOLD response while at the same time minimalizing the amount of trials to keep the paradigm as short as possible. The small amount of switch trials may therefore have been less suited to assess behavioral differences. Based on previous studies on diminished cognitive flexibility in substance dependence (Hildebrandt et al., 2006; Pitel et al., 2009; van der Plas et al., 2009) and combined with our reported differences regarding neural involvement during cognitive switching, we argue that these neural differences are indicative of subtle impairments in cognitive flexibility in both AD subjects and PrDs. However, future studies should consider using a different switch paradigm (for example as was used in de Ruiter et al., 2009), which is powerful enough to detect behavioral differences to assess cognitive flexibility, and relate those results to white matter integrity. Furthermore, there was no relationship between neural activity levels and DTI measurements. This would have underscored the results of this study, but this non-significant result does not dismiss the proposed compensatory mechanism in AD patients and PrDs. Although the non-significant result could be an indication that activity is unrelated to white matter integrity, it may also reflect some methodological issue. The fiber tracking was based on the whole dlPFC ROI, whereas we correlated the DTI measurements with the peak activation voxel and the location of the peak voxel was slightly different for the three groups. As mentioned in the method section, the PrDs and AD patients differed on their period of abstinence based on the inclusion
criteria of the study. We could therefore only perform correlation analyses for the AD group. Although abstinence did not have any relationship with task performance, fMRI or DTI measurements, the available data was not very specific and future studies should use a more precise way of determining abstinence duration. Furthermore, the AD patients all received CBT treatment which may have had an effect on brain function (Dichter et al., 2010; Zatorre et al., 2012). This may have influenced the results of the study, but unfortunately data on the exact period of treatment was not collected. Finally, sample sizes, although adequate for detecting BOLD differences, may have limited the possibility to detect significant differences in behavioral performance.

Conclusion

The current study reports on underlying functional and structural brain differences associated with cognitive flexibility between HCs, PrDs and AD patients. Evidence is reported for preserved cognitive flexibility in PrDs and AD patients by recruiting more prefrontal resources in order to compensate for reduced white matter integrity. Furthermore, PrDs showed more recruitment of compensatory prefrontal resources compared to AD patients. This compensatory mechanism could indicate a protective mechanism against a decline in cognitive functioning and/or transition into compulsive drug use, but future research should confirm these hypotheses.

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7. FINANCIAL DISCLOSURES
There are no conflicting financial interests to report.