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

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CHAPTER 6

RESTING STATE CONNECTIVITY IN ALCOHOL DEPENDENT PATIENTS AND THE EFFECT OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

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ABSTRACT

Alcohol dependence is thought to result from an overactive neural motivation system and a deficient cognitive control system, and rebalancing these systems may mitigate excessive alcohol use. This study examines the differences in functional connectivity of the fronto-parietal cognitive control network (FPn) and the motivational network (striatum and orbitofrontal cortex) between alcohol dependent patients (ADPs) and healthy controls (HCs), and the effect of repetitive transcranial magnetic stimulation (rTMS) on these networks. This randomized controlled trial included 38 ADPs and 37 HCs, matched on age, gender and education. Participants were randomly assigned to sham or right dorsolateral prefrontal cortex (dlPFC) stimulation with rTMS. A 3T resting state functional Magnetic Resonance Imaging (fMRI) scan was acquired before and after active or sham 10hz rTMS. Group differences of within and between network connectivity and the effect of rTMS on network connectivity was assessed using independent component analysis. Results showed higher connectivity within the left FPn ($p=.012$) and the left fronto-striatal motivational network ($p=.03$) in ADPs versus HCs, and a further increase in connectivity within the left FPn after active stimulation in ADPs. ADPs also showed higher connectivity between the left and the right FPns ($p=.025$), and this higher connectivity was related to fewer alcohol related problems ($r=.30$, $p=0.06$). The results show higher within and between network connectivity in ADPs and a further increase in fronto-parietal connectivity after right dlPFC rTMS in ADPs, suggesting that frontal rTMS may have a beneficial influence on cognitive control and may result in lower relapse rates.

1. INTRODUCTION

Substance dependence is a relapsing brain disorder characterized by compulsive drug seeking and consumption, despite adverse consequences (American Psychiatric Association, 2000). Neuroimaging studies have identified several brain regions that are related to substance dependence, including regions involved in reward (Volkow et al., 2011), motivation (Volkow et al., 2012) and cognitive control (Goldstein and Volkow, 2011). These studies constitute the basis for the dual-process theory of addiction, which describes two dysfunctional networks; the control network and the reward/motivation network (Kalivas & Volkow, 2005; Koob and Volkow, 2010). In the course of the development of addiction, motivational and reward processes become hypersensitive to substance related cues as a result of the repeated pleasurable drug effects resulting in increased motivation for drug use (Volkow et al., 2009), whereas the cognitive control mechanisms are weakened, together resulting in loss of control over the frequency and amount of drug use despite adverse consequences (Baler and Volkow, 2006).

These neural networks and their interactions can be detected by resting state fMRI (rsfMRI), which measures spontaneous fluctuations in brain activity at rest and identifies temporally correlated brain regions and brain networks (Laird et al., 2011; Smith et al., 2009; Van Den Heuvel and Hulshoff Pol, 2010). This technique has been used to identify the above mentioned control (Damoiseaux et al., 2006; Janes et al., 2010; Laird et al., 2011; Smith et al., 2009) and motivation networks (Damoiseaux et al., 2006; Janes et al., 2010; Laird et al., 2011; Müller-Oehring et al., 2014; Smith et al., 2009). The control

network is also referred to as the fronto-parietal control network (FPn), which can be separated into distinct left and right hemisphere fronto-parietal networks (left FPn and right FPn) (Damoiseaux et al., 2006). These networks consist of the Anterior Cingulate Cortex (ACC), Inferior Frontal Gyrus (IFG), the dorsolateral prefrontal cortex (dlPFC) and the posterior parietal cortex (PPC). The reward/motivation network mainly consists of the ventral striatum and the orbitofrontal cortex (Müller-Oehring et al., 2014).

So far, rsfMRI studies in alcohol dependent patients (ADPs) have produced inconsistent results. Two studies have shown that ADPs show higher connectivity within the control networks and lower connectivity in the reward network when compared to healthy controls (HCs) (Camchong et al., 2012, 2013a; Camchong et al., 2013b). Moreover, within the group of ADPs, higher resting state connectivity in the control network at baseline was associated with longer abstinence rates at follow-up (Camchong et al., 2012, 2013a; Camchong et al., 2013b). However, in a third study, ADPs showed weaker within network connectivity and expanded connectivity outside the executive control network and reward-motivational network compared to HCs (Müller-Oehring et al., 2014). Although the last study seems to contradict the first two studies, differences in seed location may explain the differences in results. These studies do show, however, that resting state connectivity within and between the reward/motivation network and the cognitive control network is compromised in ADPs.

Impaired functioning of these networks may be alleviated by brain stimulation techniques like repetitive transcranial magnetic stimulation (rTMS) (M.D. Fox et al., 2014; M.D. Fox et al., 2012). The use of rTMS over the dlPFC is an FDA approved treatment for major depressive disorder (Dell'Osso et al., 2011), enhances cognition in psychiatric patients and HCs (Guse et al., 2010), improves emotion regulation in HCs (Jansen et al., 2015b), and may reduce craving in ADPs (Jansen et al., 2013; Jansen et al., 2014). In rTMS, a magnetic field is used to alter brain activity, but the underlying effects on network connectivity remain unclear (George and Aston-Jones, 2010). Previous studies did show that stimulation effects are not restricted to the stimulation site, but spread throughout the brain (P.T. Fox et al., 1997; Kobayashi and Pascual-Leone, 2003; Paus et al., 1997). The dlPFC is a central hub in the FP networks, and therefore rTMS may change network dynamics in prefrontal networks as well as networks with anatomic connections to the dlPFC (M.D. Fox et al., 2012). A recent study indeed revealed that rTMS normalized elevated functional connectivity in the default mode network in patients with a major depressive disorder (Liston et al., 2014).

To date, there are no combined rsfMRI-rTMS studies in substance dependent populations. The current study first examines possible differences in functional connectivity between ADPs and HCs in prefrontal networks, including: the reward/motivation network, and the left and right FP control networks. Then the effect of high-frequency rTMS over the right dlPFC on these networks is evaluated. In the study, we examine both within and between network connectivity levels. Within network connectivity reflects how strong the spontaneous fluctuations are correlated within one network, whereas between network connectivity reflects the strength of the correlation between two networks. We hypothesize that ADPs show abnormal resting-state connectivity within and between the FP control networks and within the reward/motivational network, and that rTMS influences these resting state connectivity abnormalities.

2. EXPERIMENTAL PROCEDURES

2.1 Participants

A total of 38 ADPs and 37 HCs matched on age, sex and education were included. ADPs were recruited from addiction treatment centers in the larger city area of Amsterdam, the Netherlands. The presence of a DSM-IV diagnosis alcohol dependence was made by a clinician and confirmed with the Composite International Diagnostic Interview (CIDI) (World Health Organisation, 1990). ADPs were sober for at least three weeks. Current sobriety was confirmed with a urine test in the research lab and longer sobriety through self-report. HCs were recruited through internet and social media advertisements. All participants were screened for MRI suitability. Furthermore, participants with a (familial) history of epilepsy were excluded, in line with current TMS safety guidelines (Rossi et al., 2009). All subjects were screened for current psychiatric disorders, including anxiety disorders, major depressive disorder and, abuse and dependence of substances other than alcohol using the CIDI (World Health Organisation, 1990). Participants with current psychiatric comorbidities were excluded from the study.
The study was approved by the local Medical Ethical Committee of the Academic Medical Center of the University of Amsterdam and participants signed the informed consent form, consistent with the declaration of Helsinki, before participating in the study. Participants were remunerated for their participation.

2.2 Questionnaires

In addition to the CIDI interview, from which the abstinence duration was established, the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 2001), the Beck Depression Inventory (BDI) (Beck et al., 1988b) and Beck's Anxiety Inventory (BAI) (Beck et al., 1988a) were administered to assess levels of alcohol related problems, depression and anxiety, respectively.

2.3 Study design

This randomized controlled trial used a repeated measures design, containing two groups (between subjects; ADP/HC), two stimulation groups (between subjects; right/sham) and two sessions (within subjects; first/second) which were separated by at least two weeks (Mean=21.7, SD=23.2 days). The first session included the diagnostic interview, questionnaires and a baseline rsfMRI. In the second session, rTMS was applied directly followed by a second rsfMRI session. All subjects were randomly assigned to either sham or active right dlPFC stimulation. Randomization was concealed and took place before the first rsfMRI session. In both sessions the rsfMRI scan was preceded by an emotion regulation task (Jansen et al., 2015a, b).

2.4 rTMS

During the second session, participants received either sham or active right dlPFC rTMS using a MagStim Rapid2 Air-film coil with a 70mm-diameter (MagStim Co., UK). The active rTMS session consisted of 60 5-seconds trains of 10Hz at 110% motor threshold. These parameters are within the international safety limits for the use of rTMS (Rossi et al., 2009). The hotspot for stimulation was defined for each individual separately from an the emotion regulation task that was administered in the first session (for more information (Jansen et al., 2015), forthcoming). During this emotion regulation task, participants were shown negative images and were instructed to

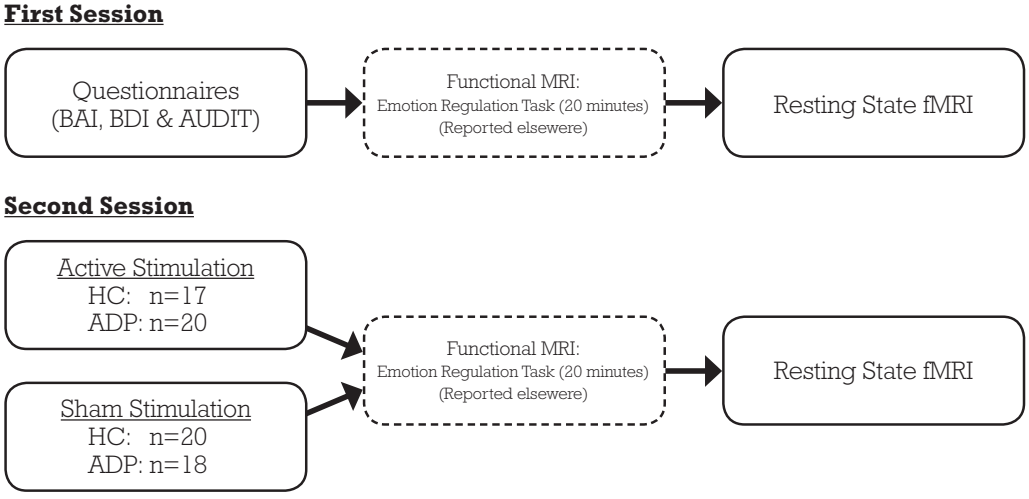


Figure 1. Study Design. This figure shows the design of the study. The resting state fMRI was preceded by an emotion regulation task in both sessions. The data of this task is published elsewhere [Jansen et al., forthcoming].

attend or regulate the emotions associated with these images. In the 'attend condition' participants had to experience emotions in a natural manner, whereas in the 'regulate condition' participants were instructed to reinterpret the emotions in a more neutral way (reappraisal). The hotspot was defined by contrasting the 'regulate condition' with the 'attend condition' and selecting the most significant voxel within the right dlPFC mask (as defined by the BrainMap database (P.T. Fox and Lancaster, 1994), see supplement 2). The coordinate of this peak voxel served as the functionally defined hotspot to stimulate the right dlPFC using neuro-navigation (Visor2, ANT). Sham stimulation was performed using identical parameters, but the rTMS coil was moved away from the (right-sided) scalp after the second train and tilted at 90° relative to the skull (Berlim et al., 2013). Data on blinding success was acquired for the majority of subjects and analysis shows that were blind to their stimulation group, see supplement 2.

2.5 Resting State fMRI

2.5.1 Data Acquisition

Scanning was performed on a Philips Achieva 3T scanner at the Spinoza Imaging Centre, Amsterdam, Netherlands. Participants were instructed to keep their eyes closed, not to think about anything in particular and not to fall asleep. The rsfMRI data acquisition was performed to acquire blood oxygenation level-dependent (BOLD) signals using a field-echo EPI sequence [210 Dynamics, Echo time (TE)=27.63ms; repetition time (TR)=2000ms; field of view (FOV)=240x240mm, 37 3mm slices, 0.3mm slice gap; 80x80 matrix; flip angle=76.1°]. These T2-weighted images were oriented axially along the anterior-commissure to the posterior-commissure (AC-PC) line and scanning time was 7 minutes. In addition to the rsFMRI, we acquired T1-weighted 3D datasets for anatomical reference; TR=8.196ms, TE=3.73ms, field of view (FOV)=140x188x220mm, matrix 240x187, flip angle=8°, slice thickness=1mm, number of slices=220.

2.5.2. Data Pre-processing

Resting state fMRI analysis was carried out using Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) toolbox from the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL)(Jenkinson et al., 2012). The first 5 time points were removed from analysis. Individual datasets were preprocessed using pre-statistical processing; motion correction with MCFLIRT (Jenkinson et al., 2002), brain extraction with BET (Smith, 2002), spatial smoothing using a Gaussian kernel of full-width at half maximum (FWHM) of 5mm, and a high-pass temporal filter of 100hz. In scanner motion did not differ between ADPs and HCs ($p=.26$) and remained below 2mm for all participants, which is below our criterion of one slice thickness (<3mm). Functional images were registered to subject specific, brain extracted high-resolution structural t1 scans using Boundary Based Registration (Jenkinson et al., 2002). Residual effects of motion and physiological (cardiorespiratory) noise were accounted for by the independent component analysis (MELODIC), see below.

2.5.3 Group ICA Analysis

Preprocessed functional data containing 205 time points for each subject were temporally concatenated across subjects to create a single 4D data set containing all data from the first session. The independent component analysis (ICA) algorithm was preset to 25 components and was performed with the MELODIC toolbox (Beckmann and Smith, 2005). Among these 25 networks, the intended reward/motivation network [based on a report by (Liard et al., 2011)] and the right and left FP networks [based on (Damoiseaux et al., 2006)] were identified. A comprehensive list of all 25 components can be found online in supplement 1.

2.5.4 Within Network Connectivity Analysis

For the group comparison (ADP vs. HC), a dual regression approach was used to identify subject-specific temporal dynamics and associated spatial maps during each subject's first session rsfMRI (Beckmann et al., 2009; Filippini et al., 2009). For the components of interest, non-parametric permutation testing (5,000 permutations) was used to test for between group differences in functional connectivity.

For the effect of rTMS on functional connectivity, a similar dual regression approach was used, but the subject-specific temporal dynamics and associated spatial maps were acquired for both the first and the second rsfMRI session. The spatial maps of the first session were subtracted from the second session for each subject. Non-parametric permutation testing (5,000 permutations) was used to test for interactions between Group (ADP/HC) and Stimulation (Active/Sham), based on the change in connectivity strength (second session – first session) for each component. We report the results based on a cluster-forming threshold of $z=2.5$. All group comparisons were masked with ICA group component maps and were thresholded using a bonferroni corrected p-value of $p=(0.05/3)=0.0167$. Given the limited sample size and the novelty of the parameters of interest, trend significant ($p<0.10$) results are also reported. The mean values were extracted from the clusters with significant group differences and were then used in the correlation analysis.

2.5.5 Between Network Analysis

In addition to the within network connectivity described above, we also report the between network connectivity differences between groups. For each participant, the

time courses for the different networks of interest were correlated using Matlab 2014a (The MathWorks Inc., Natick, MA, 2000). These individual correlation coefficients were used for group analyses in SPSS 20.0 (IBM Corp, 2011). Analyses on Group (ADP/HC) and Stimulation (Active/Sham) differences were conducted for the networks of interest which correlated significantly during the first session as determined by one-sample t-tests ($p < 0.05$). Group differences were assessed with an independent t-test, whereas the effect of rTMS was tested with a repeated measures ANOVA with the interaction effects for Group (ADP/HC) and Stimulation (Active/Sham) as between subject factors and the change in between network correlation coefficients (second session – first session) as dependent variables. Between network analyses are reported using a Bonferroni corrected significance level ($p=(0.05/3)=0.0167$) and as trend significant findings ($p<0.10$).

3. RESULTS

3.1 Sample characteristics

ADPs and HCs were successfully matched on age, gender and years of education. ADPs reported significantly more alcohol related problems, depression and anxiety. Abstinence in the ADP group ranged from 3 weeks to 6-12 months (standard outcome measures from the CIDI interview). Randomization of the APCs and HCs to either active or sham dlPFC rTMS was also successful with no significant differences between the intervention groups in age, gender and years of education, depression, anxiety and alcohol related problems ($p>0.2$ for all comparisons).

	ADP (n=38)	HC (n=37)	Significance
Age: mean (SD)	41.79 (8.40)	45.11 (9.94)	t(73)=1.56 p=.12
Gender: % males	65.8	56.8	x2(1,72)=.65 p=0.42
Education: mean (SD)	15.23 (3.07)	15.22 (2.74)	t(73)=.031 p=.98
AUDIT: mean (SD)	22.58 (9.91)	4.05 (2.37)	t(73)=11.06 p<0.001
Beck Depression Inventory mean (SD)	11.08 (9.31)	4.97 (6.21)	t(73)=3.33 p=0.001
Beck Anxiety Inventory mean (SD)	10.16 (9.40)	2.84 (6.07)	t(73)=4.00 p<0.001

Table1: Sample Characteristics. This table shows the sample characteristics for age, gender, years of education, and alcohol related problems (AUDIT), depression(BDI) and anxiety (BAI). All values are denoted as mean (standard deviation). BAI scores were recoded from 1 to 4, into 0–3 which is similar to the BDI scoring.

3.2 Group ICA Analysis

The ICA algorithm successfully identified the reward/motivation network, including orbitofrontal cortex and striatum, and left and right FPn control networks which included dorsolateral prefrontal, parietal and inferior frontal gyrus (Figure 2).

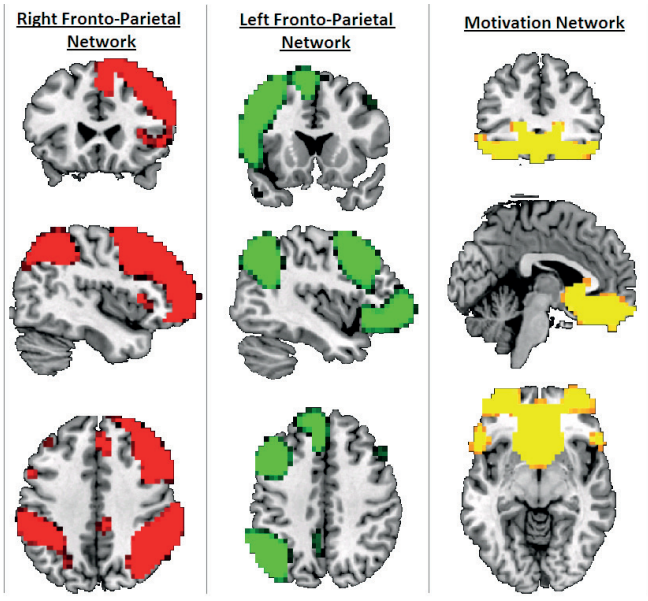
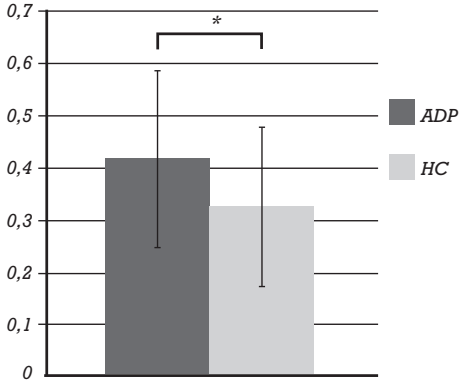


Figure 2. The group ICA networks. This figure shows the networks which were identified by the group ICA algorithm. The right FPn is shown in red, the left FPn is shown in green, and the reward/motivation network is shown in yellow. The reward/motivation network includes the orbitofrontal cortex and striatum, and the left and right FPns include the dorsolateral prefrontal cortex, the parietal cortex and inferior frontal gyrus

a Correlation coefficients between networks

	Right FPn	Left FPn	Motiva-tion
Right FPn	X	-	-
Left FPn	.37*	X	-
Motiva-tion	-.01	.11*	X

b Group Difference in Correlation between right and left FPn



c Correlation between Right and Left FPn with AUDIT

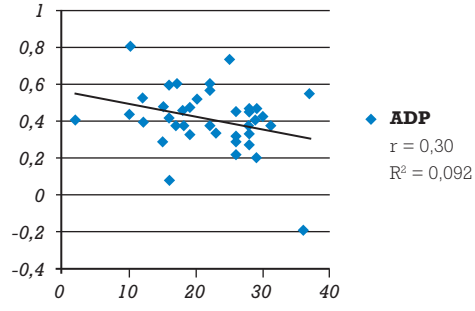


*Figure 3. Between network correlations, group difference and association with AUDIT scores. a. This table shows the correlation coefficients between the networks of interest. In the total group of ADPs and HCs, the left FPn correlated significantly with right FPn [r=.37, t(74)=18.90 p<0.001] and with the reward/motivation network [r=.11, t(74)=5.66 p<0.001], and these correlation coefficients were therefore used for group comparisons. b. The group comparison for the correlation between right and left FPn indicated that ADPs show higher between left and right FPn connectivity than HCs [t(73)=2.29 p=.025]. c. Trend significant negative association between network correlation (left vs right FPn) and AUDIT scores in ADPs [r(37)=.30, p=0.06]. FPn = Fronto-Parietal Network, * indicates statistical significance.*

3.3 Group differences

3.3.1 Within network analysis

ADPs showed elevated within network connectivity in the left FPn (p=0.012), and a trend significant elevation of within network connectivity in the reward/motivation network (p=0.03) (see Figure 4a). The connectivity values did not correlate with AUDIT, BAI or BDI scores within the ADP or within the HC group.

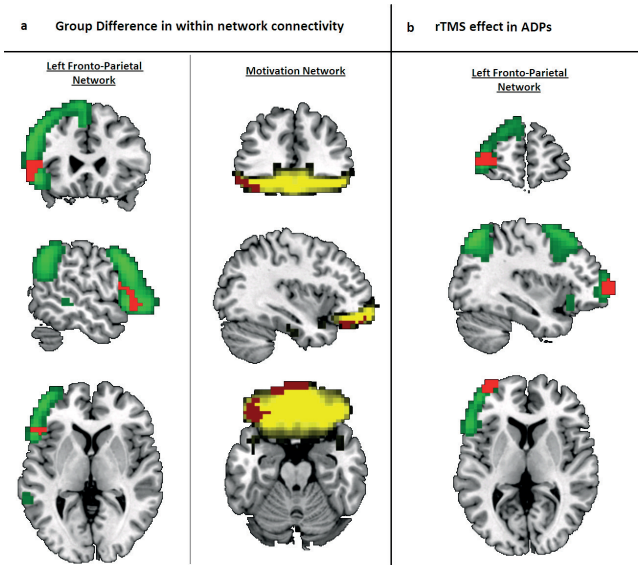


Figure 4. Within Network connectivity a. Group differences. The left side of this figure shows connectivity within the inferior fontal gyrus in the left FPn (in green) that was significantly higher (in red) in ADPs compared to HCs. The figure also shows that connectivity in the ventrolateral and ventromedial prefrontal cortex in the reward/motivation network (in yellow) was trend significantly higher (in red) in ADPs compared to HCs b. rTMS effect in ADPs. This figure shows (in red) that the ventral part of the medial frontal gyrus shows increased network connectivity in the left FPn (in green) due to active (vs sham) rTMS in ADPs (p=0.03) (Brodmann area 10, MNI coordinates [xyz]; -34, 58, 4).

3.3.2. Between network Analysis

The between network connectivity analysis showed that the correlation between left and right FPns [r=.37, t(74)=18.90 p<0.001], and between left FPn and reward/motivation network correlated significantly [r=.11, t(74)=5.66 p<0.001; see figure 3a]. Therefore, the effects of group and stimulation were assessed for these two between network correlations. ADPs showed a stronger connectivity between the left and right FP networks than HCs [Mean (M)=.41 (SD=.17) vs. M=.33 (SD=.16); t(73)=2.29 p=.025; see figure 3b]. This correlation showed a trend significant negative association with AUDIT scores in ADPs [r(37)=.30, p=0.06] (see Figure 3c), but no relation with BAI or BDI. No group differences were found in the correlation between left FPn and the reward/motivation network (p=.42).

3.4 TMS effect

3.4.1 Within network analysis

The interaction effect of stimulation (Active/Sham) and group (HC/ADP) for the change in network connectivity (second session – first session) was not significant (p>0.2), indicating that the effect of rTMS (active vs. sham) did not differ between ADPs and HCs. There was a trend significant (p=0.06) effect of rTMS in the left FPn, with active stimulation increasing within network connectivity compared to sham (Brodmann area 10, MNI coordinates [xyz]; -34, 58, 4). Despite the non-significant interaction between stimulation

and group and due to our specific interest in the effect of rTMS in the ADP group, separate exploratory analyses were performed for the ADP and HC groups. These post-hoc analyses showed that in ADPs, active stimulation trend significantly (p=.03; Figure 4b) increased network connectivity compared to sham, whereas no such effect was found in the HCs.

3.4.2 Between network Analysis

No (trend) significant between network connectivity changes due to rTMS were observed.

4. DISCUSSION

This is the first paper to report on resting state connectivity differences between ADPs and HCs and the ffect of high-frequency rTMS over the right dlPFC on ICA defined resting state networks. The study shows that, compared to HCs, ADPs display significantly higher resting state connectivity within the left FPn and a trend of higher connectivity within the reward/motivational network, as well as a significantly higher connectivity between the left and right FPns. Stimulation of the right dlPFC with active rTMS further increased connectivity within the left FPn at a trend level, especially in the ADP group (trend: p= .03). It is important to note that the rTMS effect was present even 20-27 minutes after the actual stimulation, which is much longer that the 9 minutes reported in a previous PET study (Eisenegger et al., 2008).

Based on these results one could argue that cognitive control processes are intact in ADPs, but that increased connectivity is required to deal with the increased demand for cognitive control, which is still insufficient for controlling alcohol related drives and urges. However, this in not in line with previous studies indicating deficient cognitive control in ADPs (for a meta-analysis see (Stavro et al., 2013)), nor with four seed-based rsfMRI studies in alcohol dependent patients (Camchong et al., 2012, 2013a; Camchong et al., 2013b; Müller-Oehring et al., 2014). Although differences in methodology may limit the comparison between these studies and our own, some similarities emerge. Higher connectivity in early abstinent (mean=72 days) ADPs compared to HCs was found in the executive control network (Camchong et al., 2013b), which is in line with our results and similar patterns have been found in long term abstinent (mean=7.9 years) ADPs (Camchong et al., 2013a). Interestingly, in another study, higher connectivity in the control network of short-term abstinent ADPs was predictive of lower relapse rates six months later (Camchong et al., 2012). Moreover, high connectivity within the control network was positively correlated with cognitive flexibility, indicating that higher connectivity in this network is related to better task performance within ADPs (Camchong et al., 2013a; Camchong et al., 2013b). The results from these studies therefore suggest that the increased resting state connectivity serves as a compensatory mechanism, possibly related to neuroplasticity (Cramer et al., 2011; Park and Reuter-Lorenz, 2009). The increased connectivity between the left and right FPns in ADPs was associated with less alcohol related problems, which supports the notion that higher between FPn connectivity may benefit ADPs. In short, the literature and our results suggests that increased connectivity may serve as a compensatory mechanism in ADPs

and that ADPs with severe problems are less successful in recruiting this mechanism. In contrast to the studies just mentioned and our own results, one other study reported decreased connectivity values within the reward/motivational network and FP control networks in ADPs (Müller-Oehring et al., 2014). Methodological issues may explain some of these contradicting findings. We used ICA to define the relevant networks, whereas Camchong et al. chose the subgenual ACC and nucleus accumbens (NcAcc) as their seed points based on the Talairach atlas (Camchong et al., 2011; Kelly et al., 2009) and Muller-Oehring et al. chose the Superior Frontal Gyrus (SFG) from the automated anatomical labeling (aal) template and the NcAcc using the MarsBaR toolbox. These seed-points differed in their location which has a substantial effect on connectivity patterns (e.g. (Kelly et al., 2009)), and hamper between study comparisons. In contrast, the use of data-driven independent component analyses may improve reproducibility since there is no (arbitrary) seed-selection. Nonetheless it points to the need for more studies on resting state connectivity in ADPs and HCs with standardized analysis techniques.

Interestingly, rTMS further increased resting state connectivity in ADPs. In line with our interpretation of increased connectivity representing a compensatory mechanism, these results may indicate that dlPFC rTMS has a beneficial influence on cognitive flexibility or control (Jansen et al., 2015a) and may result in lower relapse rates (Jansen et al., 2013). Previous studies have shown that rTMS has a positive effect on cognitive functioning in both healthy and patient populations (Guse et al., 2010) and may decrease craving levels (Jansen et al., 2013) and reduce cigarette consumption (Dinur-Klein et al., 2014). Together, these findings suggest that increased connectivity within and between networks may be beneficial for ADPs, and therefore increasing connectivity with rTMS may be clinically relevant. Future studies should assess the effects of stimulation related changes in resting state connectivity on cognitive functioning and clinical symptoms.

4.1 Strengths and Limitations

This study has several strengths. It is the first to assess and find differences in resting state networks in ADPs by using an ICA approach and it is also the first to assess and find positive effects of active versus sham rTMS on network connectivity (even after 20-27 minutes). There are also some limitations to consider. First, the resting state scan was preceded by an emotion regulation task which may have influenced resting state activity (Grigg and Grady, 2010). However, this would not have affected the rTMS effect, as the emotion regulation task was administered in both sessions. Furthermore, the rTMS effects were only trend-significant which may be related to the time between stimulation and the rsfMRI scan or due to the fact that we applied a single rTMS session. Previous studies in patients with major depressive disorder indicate that clinically significant effects of rTMS can only be expected after multiple stimulation sessions. The current study assessed the effects of a single rTMS session on network connectivity and provides valuable information on the immediate effects of rTMS, but generalizability to the clinical effects of multiple stimulation sessions is limited and should be established in future studies. In the absence of suitable data, the change in connectivity could not be related to changes in task performance or clinical symptoms. Replication studies are therefore needed, including indicators for cognitive functioning and alcohol use disorder symptoms (e.g. craving) before and after stimulation or resting state acquisition.

5. CONCLUSION

This study shows hyper connectivity within the left FPn and the reward/motivation network in ADPs compared to HCs and a further increase in connectivity within the left FPn after active versus sham dlPFC rTMS in ADPs, suggesting that dlPFC rTMS has a beneficial influence on cognitive flexibility and may thus result in lower relapse rates. Future studies should assess the effect of multiple sessions of rTMS on resting state connectivity, cognitive performance and specific substance use disorder symptoms (e.g. craving) and addiction severity.

6. ACKNOWLEDGEMENTS

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Supplementary information can be found online.