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Accelerated repetitive transcranial magnetic stimulation does not influence grey matter volumes in regions related to alcohol relapse: An open-label exploratory study

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ABSTRACT

The application of repetitive transcranial magnetic stimulation (rTMS) to prevent relapse in alcohol addiction is currently being evaluated. However, how rTMS may influence the related brain processes is far from clear. Here we wanted to investigate whether baseline grey matter volume (GMV) can predict relapse and whether 15 accelerated high-frequency (HF)- rTMS sessions may influence GMV in areas related to relapse. Voxel-based morphometric (VBM) measurements were used to compare baseline GMV of 22 detoxified, hospitalized, alcohol-dependent patients with 22 age and gender matched healthy control subjects. Only patients received 15 accelerated HF-rTMS sessions at the right dorsolateral prefrontal cortex (DLPFC) followed by VBM measurements. Relapse rates were assessed four weeks after the end of the stimulation protocol. At baseline, alcohol-dependent patients overall showed less GMV in diffuse brain areas compared to healthy controls. Relapsers compared to abstainers displayed larger GMV decreases, especially in brain midline structures, insular, hippocampal, and amygdalar areas. Accelerated HF-rTMS treatment had no significant effect on GMV in alcohol-dependent patients, regardless of the relapse state. Although an accelerated HF-rTMS treatment protocol did not influence GMV in alcohol-dependent patients, baseline GMV predicted future relapse.

1. Introduction

Alcohol addiction is a chronic relapsing disorder having a well-known devastating impact on health and mortality rate (World Health Organization (WHO, 2014). According to the Global Status Report On Alcohol And Health (World Health Organization (WHO, 2014), 5.9% of all global deaths were attributable to the (ab)use of alcohol. More than 60% of alcohol-dependent patients will experience at least one drinking episode (= “lapse”) in the first year following alcohol detoxification (Witkiewitz, 2011).

Over the last decades researchers have gained more insight in the pathogenesis and pathophysiology of alcohol dependence (Koob and Volkow, 2010; Zahr et al., 2011). At the brain level, tissue loss, aberrant metabolism, and abnormal functioning of reward, motivational and cognitive control pathways have been identified (Xiao et al., 2015). Additionally, the neurotoxic effects of alcohol have long been established (Thayer et al., 2016; Xiao et al., 2015); compared to the healthy state, volume deficits have been observed in the thalamus, insula, cerebellum, anterior cingulate, and prefrontal cortex (Bullock et al., 2017; Mechtcheriakov et al., 2007).

In an effort to understand why dependent patients who successfully stopped their alcohol use started problematic drinking again, previous research already focused on the detection of neurobiological predictors of relapse. Beck et al. (2012) showed that relapsing and abstaining patients showed similar patterns of atrophy; however, lower levels of (sub) cortical atrophy could be observed in abstaining patients. Therefore, how these neurobiological substrates can be positively influenced to decrease relapse rate is important.

Currently, the application of transcranial magnetic stimulation (TMS) is being evaluated in the treatment of alcohol addiction (Trojak et al., 2017). Although efficacy and mechanisms of action are not yet clarified, previous research indicates a beneficial effect on craving

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(Nardone et al., 2012). In healthy volunteers, May et al. (2007) found that daily low frequency (LF) repetitive (r) TMS treatment for 5 days applied to the left superior temporal gyrus immediately increased grey matter volumes at the stimulation region. Also, in major depression, one group found increased grey matter volumes (GMV) at insula, anterior cingulate, angular gyrus and the superior temporal gyrus after twenty-five rTMS sessions delivered on the left dorsolateral prefrontal cortex (DLPFC) (Lan et al., 2016). Boes et al. (2018) found that increased GMV at the left rostral anterior cingulate cortex after daily left DLPFC HF-rTMS was associated with clinical improvement in depressed patients. However, one of the latest developments in stimulation protocols regarding depression research is the use of accelerated treatment paradigms, where multiple sessions per day are administered. This technique may have the potential to result in faster clinical responses and was not associated with any adverse events (Baeken et al., 2013; Holtzheimer et al., 2010). Importantly, neurobiological changes related to clinical outcome have been found after four days of accelerated stimulation on functional connectivity (Baeken et al., 2014), brain glucose metabolism (Baeken et al., 2015), and on the GABA system (Baeken et al., 2017). Also, no studies have yet investigated the effect of accelerated rTMS on GMV in either depressed or alcohol-dependent patients. Previously, we reported on the neural effects of accelerated HF-rTMS at the right DLPFC on baseline brain activation during an fMRI cue-exposure and consecutive relapse (Herremans et al., 2016). We found that, during an alcohol-related cue-exposure, baseline dACC activation served as a predictor for future relapse. However, we could not demonstrate a beneficial effect on relapse in contrast to a classical daily right DLPFC HF-rTMS protocol (Mishra et al., 2015) or to pharmacological treatment (Laaksonen et al., 2008). The rationale of stimulating the DLPFC originates from the fact that the DLPFC is involved in top-down inhibitory control mechanisms and is known to be dysfunctional in addiction. Concerning the hemispheric prefrontal stimulation target, rTMS studies are inconclusive regarding lateralization and outcome effects in these populations (Lefaucheur et al., 2014).

Building on our earlier research, we investigated how right-sided accelerated HF-rTMS may affect GMV in alcohol-dependent patients. We used voxel-based morphometry (VBM), a neuroimaging method that quantifies the amount of grey matter existing in a voxel (Ashburner and Friston, 2000).

Compared to healthy controls, we expected grey matter abnormalities in brain areas frequently reported in alcohol addiction. In line with previous literature (Beck et al., 2012; Rando et al., 2011), we hypothesized that baseline differences would be present between abstainers and relapsers. We expected that accelerated HF-rTMS treatment would positively affect GMV most prominently in the abstainers, in particular in regions related to relapse.

2. Material and methods

The study was performed at the University hospital UZBrussel. The ethical committee of UZBrussel approved the study. Written informed consent was obtained from all participants. The study was part of a larger project examining the neurobiological effects of HF-rTMS on alcohol craving in alcohol-dependent patients (during which the effect of 1 sham-controlled and 15 accelerated HF-rTMS sessions on alcohol craving and the corresponding craving neurocircuit is evaluated; published as Herremans et al., 2016, 2015).

2.1. Subjects

In total, 29 alcohol-dependent patients underwent the accelerated stimulation protocol. For more information about detoxification, in- and exclusion criteria, and post stimulation treatment/follow up, we refer to Herremans et al. (2015, 2016). We had relapse information about 22 detoxified alcohol-dependent patients.

Twenty-two healthy controls were included, closely matched for age and gender.

To be included, the right-handed healthy controls had to be medication free (except for birth-control medication), free of any psychiatric disorder as assessed with the Dutch version of the Mini-International Neuropsychiatric Interview (MINI, Sheehan et al., 1998). All healthy controls were financially compensated (50 euros).

2.2. Procedure

Patients started the study on Monday with a 3D MRI. First, all patients participated in a single randomized, placebo-controlled HF-rTMS session that was spread over two consecutive days (on Monday and Tuesday). These results are published elsewhere (Herremans et al., 2015). The remaining 14 sessions were administered as an accelerated stimulation protocol: four sessions on Wednesday, five on Thursday, and five on Friday, with an intersession interval of 15 min. In total, patients received 15 active HF-rTMS sessions (23,400 pulses), which are evaluated in this study. The following Monday, patients underwent the third and final 3D MRI. Since it was an open-label study, after the stimulation, all patients received treatment as usual. Four weeks after the HF-rTMS stimulation protocol, all patients were contacted by phone and were asked whether they had already consumed any amount of alcohol since.

2.3. HF-rTMS

We used a Magstim high-speed magnetic stimulator (Magstim Company Limited, Wales, UK), connected to a figure-of-eight formed double 70 mm coil held tangentially to the skull. To accurately target the middle of the right DLPFC individually (Brodmann area 9/46), the precise stimulation site and position of the coil was determined using MRI non-stereotactic guidance (Peleman et al., 2010). Perpendicular to this point, the precise stimulation site on the skull was marked and stimulated. The individual resting motor threshold (MT) for the right abductor pollicis brevis muscle was determined using single pulse TMS in combination with motor evoked potentials (MEP). The MT was considered as the lowest intensity to induce a visual MEP on electromyography. A stimulation intensity of 110% of the subject's MT was used for the study. In each HF (20 Hz) rTMS session, subjects received 40 trains of 1.9 s duration, separated by an intertrain interval of 12 s (1.560 pulses per session).

2.4. Imaging protocol and preprocessing

For each participant, we collected the 3D T1-TFE anatomical scan data (TI/TR/TE = 940.4/7.6/3.7 ms, flip angle = 8°, FOV = 240 × 240 × 200 mm, resolution = 1 × 1 × 2 mm and 100 axial slices) acquired at our 3 T Achieva MRI system (Philips, Best, The Netherlands) with a quadrature transmit-receive head coil.

The longitudinal VBM analysis was performed using the Computational Anatomy Toolbox (CAT12, http://dbm.neuro.uni-jena.de/cat/). After intra-subject realignment, the mean map of the realigned images was created for each subject. Bias correction and spatial segmentation were then performed on all time points and mean maps. The spatial normalization parameters estimated from the segmentations of the mean image were applied to the images of all time points and were finally modulated. The modulated gray matter images reflect the tissue volumes. The total intracranial volume (TIV) was calculated and used as a covariate for further statistical analyses. Finally, the normalized gray matter images (voxel size: 1.5 × 1.5 × 1.5 mm^3) were smoothed using 8-mm full-width half-maximum Gaussian filter.

2.5. Statistical analysis

2.5.1. Demographic data

All collected demographic data were analyzed with SPSS 24