Drug and Alcohol Dependence 158 (2016) 147–153

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Neurophysiological, psychological and behavioural correlates of rTMS treatment in alcohol dependence

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ARTICLE INFO

Article history:
Received 26 May 2015
Received in revised form
12 November 2015
Accepted 12 November 2015
Available online 22 November 2015

Keywords:
High-frequency transcranial magnetic stimulation
Alcohol detoxification
Brain oscillations
Thalamo-cortical dysrhythmias
Inhibitory control
Selective attention
Alcohol craving
Psychological symptoms

ABSTRACT

Background: Addiction is associated with dorso-lateral prefrontal cortex (DLPFC) dysfunction and altered brain-oscillations. High frequency repetitive transcranial magnetic stimulation (HFrTMS) over DLPFC reportedly reduces drug craving. Its effects on neuropsychological, behavioural and neurophysiological are unclear.

Methods: We assessed psychological, behavioural and neurophysiological effects of 4 sessions of 10-min adjunctive HFrTMS over the left DLPFC during two weeks during a residential programme for alcohol detoxification. Participants were randomized to active HFrTMS (10 Hz, 100% motor threshold) or sham. Immediately before the first and after the last session, 32-channels EEG was recorded and alcohol craving Visual Analogue Scale, Symptom Check List-90-R, Numeric Stroop task and Go/No-go task administered. Tests were repeated at 1-month follow-up.

Results: 17 subjects (mean age 44.7 years, 4 F) were assessed. Active rTMS subjects performed better at Stroop test at end of treatment ($p = 0.036$) and follow up ($p = 0.004$) and at Go-NoGo at end of treatment ($p = 0.05$) and follow up ($p = 0.015$). Depressive symptoms decreased at end of active treatment ($p = 0.036$). Active-TMS showed an overall decrease of fast EEG frequencies after treatment compared to sham ($p = 0.026$). No significant modifications over time or group emerged for craving and number of drinks at follow up.

Conclusion: 4 HFrTMS sessions over two weeks on the left DLPFC can improve inhibitory control task and selective attention and reduce depressive symptoms. An overall reduction of faster EEG frequencies was observed. Nonetheless, this schedule is ineffective in reducing craving and alcohol intake.

1. Introduction

Recurring drug intoxication can result in addiction (Goldstein and Volkow, 2002; Karoly et al., 2015), a devastating and chronic relapsing disorder with social, psychological and physical consequences. More effective treatment options are needed (O'Brien, 2008; Karoly et al., 2015; Zalewska-Kaszubska, 2015).

Recently, brain stimulation techniques, as transcranial Direct Current Stimulation (tDCS) and Transcranial Magnetic Stimulation (TMS), were suggested as potential treatments for reducing addictive behaviour (Bellamoli et al., 2014; Gorelick et al., 2014; Grall-Bronnec and Sauvaget, 2014). Repetitive TMS (rTMS) can modulate neuronal activity and induce acute effects on circuitries that mediate behaviour. Repeated sessions of rTMS of the dorsolateral part of the prefrontal cortex (DLPFC) are suggested to

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http://dx.doi.org/10.1016/j.drugalcdep.2015.11.018
0376-8716/

reduce drug craving, drug-seeking and eventually drug consumption (Amiaz et al., 2009; Mitchell, 2004). Addiction is associated with increased impulsivity and impaired decision-making (Knoch et al., 2006). rTMS on the DLPFC could modulate these decision-making processes and enhance inhibitory control, thus reducing craving (Amiaz et al., 2009; Eichhammer et al., 2003; Johann et al., 2003; Li et al., 2013; Hayashi et al., 2013; Pripfl et al., 2013; Prikryl et al., 2014; Politi et al., 2008).

DLPFC rTMS stimulation is indeed an approved treatment for major depression. Few studies on people with addiction took into consideration the effects on mood, with discordant results (Höppner et al., 2011; Camprodon et al., 2007; Rapinesi et al., 2013). In one study on cocaine addicted persons, positive mood was increased after right-sided rTMS, whereas left sided rTMS decreased it (Camprodon et al., 2007). These findings contrast with those on people with major depression, which show opposite lateralization (Fitzgerald and Daskalakis, 2012; Gershon et al., 2003). Other authors did not find significant differences in mood after active rTMS over the left DLPFC in individuals with alcohol dependence (Höppner et al., 2011).

The neural mechanisms underlying these rTMS effects are still not clear. Execution of complex cognitive functions requires coordination across many neurons in multiple areas. Brain rhythms link the activity of related ensembles of neurons (Başar et al., 1998; Klimesch, 1999; Palva and Palva, 2007; Harmony, 2013) in perceptual, sensorimotor, and cognitive operations. Different frequency bands have been hypothesized to play a role in cognition.

Delta activity (1–4 Hz) (Başar et al., 2001) seems implicated in the synchronization of brain rhythms with autonomic functions, in motivational processes associated with both reward and atavistic defensive mechanisms and behavioural inhibition (Kamarajan et al., 2004; Knyazev, 2007, 2012; Putman, 2011).

Theta rhythm (4–8 Hz) is associated with different cognitive processes, such as conscious awareness, episodic retrieval, recognition memory, and frontal inhibitory control (Klimesch et al., 2001, 1994; Klimesch, 1999; Kamarajan et al., 2004). Mid-frontal theta band activities reflect computation used for cognitive control and for the implementation of such control across disparate brain regions. Thus, frontal theta is a compelling candidate mechanism by which emergent processes, such as 'cognitive control', may be biophysically realized (Cavanagh and Frank, 2014).

Alpha band is supposed to influence sensory perception and memory (Van Rullen and Koch, 2003). It has been suggested that upper frequency alpha amplitude is associated with the inhibition of non-essential processing (Klimesch et al., 2007).

The potential functional role of beta-band oscillations is not yet well understood. Evidence from recent studies suggests that beta band activity is related to the maintenance of the current sensorimotor or cognitive state (Engel and Fries, 2010). It was hypothesized that beta oscillations and/or coupling in the beta-band are stronger expressed if the maintenance of the status quo is intended or predicted than if a change is expected. It was also suggested that pathological enhancement of beta band activity is likely to result in an abnormal persistence of the status quo and a deterioration of flexible behavioural and cognitive control. In the resting electroencephalogram (EEG) of individuals with alcohol dependence high beta predominates, suggesting hyper-arousal and diminished behavioural flexibility, whereas the decreased delta and theta oscillations suggest a cognitive disinhibition at a functional level (Campanella et al., 2009).

The aim of our study was to assess psychological, behavioural and neurophysiological modifications after adjunctive rTMS applied with a schedule of 4 sessions of 10 min over two weeks during a residential programme for the treatment of alcohol dependence. The hypothesis is that a relative reduction of fast EEG bands (beta/gamma) or an increase of slower ones (theta/alpha) should be the neurophysiological correlate of a boosting effect on control and inhibition in alcohol dependence, as demonstrated in other forms of addiction.

2. Materials and methods

This was a prospective, hospital-based, single-blinded, sham-controlled rTMS study. Subjects were admitted to a 3-week residential programme for the treatment of dependence. 10 Hz rTMS (2 weekly sessions over two weeks) was added to the standard protocol. Subjects were blinded to treatment; neuropsychologist was unaware of the treatment group; the laboratory technician, administering rTMS, was unblinded.

The recruitment was conducted from February 2012 to December 2013. The study was ethically approved by the Ethic Committee of the Verona Addiction Department. Participants provided written informed consent.

2.1. Participants

Recruitment occurred during the first week of admission at Addiction Unit. Inclusion criteria were: age 18–65 years, a diagnosis of alcohol dependence confirmed by a Structured Clinical Interview (SCID) for Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, expression of desire to achieve abstinence or significantly reduce the consumption, adequate mastering of the Italian language and ability to consent. Exclusion criteria were: people with major medical or neurological or psychiatric co-morbidity and/or contraindication to TMS (Rossi et al., 2009), i.e., pacemaker, hearing aids, metallic craniofacial implants, pregnancy.

A randomization list was generated, according to the random permuted blocks, which assigned subject to one of two treatments (active or sham) in the order of entry into the study. Subjects were equally likely to be assigned to active rTMS or sham rTMS (ratio between active rTMS and sham rTMS group 1:1).

2.2. rTMS procedure

Resting Motor Threshold (MT) is defined as the minimum stimulus intensity which is required to produce a motor evoked potential (MEP) of more than 50 μV in at least 5 of 10 consecutive trials at rest (Rossini et al., 1994). The MT was registered using electromyography (EMG). MEPs were recorded from the muscle abductor pollicis brevis of the right hand by surface electrodes. Single-pulse TMS was applied to the left motor cortex in order to find resting MT. rTMS were delivered using the Magstim Rapid 2 device (Magstim Company Ltd., Whitland, Wales, UK) with a 70 mm air-cooled figure-of-eight coil with the handle pointing backwards. Participants were administered 4 sessions (2 each week) of HF rTMS (10 Hz) at 100% of MT over the left DLPFC. Lateralization was based on previously published data on craving reduction by rTMS (Wing et al., 2013). The international 10–20 EEG system was used to target the site (F3). Induced currents were directed antero-posteriorly. Each session consists of 20 trains of 50 pulses at 10 Hz; inter-train interval was 20 s each. Sham TMS was obtained by placing a 3-cm thick wooden plate under the figure of eight coil to prevent induced current to penetrate.

2.3. EEG procedure

EEG data were acquired using a magnetic resonance (MR)-compatible EEG amplifier (BrainAmp 32MRplus, BrainProducts GmbH, Munich, Germany) and a cap providing 30 MR-compatible coated-electrodes positioned according to a 10/20 system (impedance was kept below 10 kΩ). Additional electrodes were used as ground (AFz) and reference (FCz); two surface electrodes