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Review

Effects of non-invasive neurostimulation on craving: A meta-analysis

Jochem M. Jansen[a,b,*], Joost G. Daams[c], Maarten W.J. Koeter[a], Dick J. Veltman[a,d], Wim van den Brink[a,b], Anna E. Groudiaan[a,b,e]

[a] Academic Medical Centre, Department of Psychiatry, University of Amsterdam, Amsterdam, The Netherlands
[b] Amsterdam Institute for Addiction Research, University of Amsterdam, Amsterdam, The Netherlands
[c] Academic Medical Centre, Medical Library, University of Amsterdam, Amsterdam, The Netherlands
[d] VUmc, VrijeUniversiteitMedisch Centrum, Amsterdam, The Netherlands
[e] Arkin Mental Health, Amsterdam, The Netherlands

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ABSTRACT

This meta-analysis was conducted to evaluate the available evidence regarding the effects of non-invasive neurostimulation of the dorsolateral prefrontal cortex (DLPFC), on craving in substance dependence and craving for high palatable food. Non-invasive neurostimulation techniques were restricted to repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS). A total of 17 eligible studies were identified. Random effects analysis revealed a pooled standardized effect size (Hedge's *g*) of 0.476 (CI: 0.316–0.636), indicating a medium effect size favouring active non-invasive neurostimulation over sham stimulation in the reduction of craving ($z = 5.832$, $p < 0.001$). No significant differences were found between rTMS and tDCS, between the various substances of abuse and between substances of abuse and food, or between left and right DLPFC stimulation. In conclusion, this meta-analysis provides the first clear evidence that non-invasive neurostimulation of the DLPFC decreases craving levels in substance dependence.

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* Corresponding author at: Room PA3-220, AMC, Department of Psychiatry, 1100DD Amsterdam, The Netherlands. Tel.: +31 633692340.
E-mail addresses: j.m.jansen@amc.uva.nl, jochemjansen89@gmail.com (J.M. Jansen), j.g.daams@amc.uva.nl (J.G. Daams), m.w.j.koeter@amc.uva.nl (M.W.J. Koeter), d.j.veltman@vumc.nl (D.J. Veltman), w.vandenbrink@amc.uva.nl (W. van den Brink), a.e.goudriaan@amc.uva.nl (A.E. Groudiaan).

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1. Introduction

Substance dependence is a chronic relapsing brain disorder that inflicts great costs to affected patients and society in general (Kalivas, 2005). Alcohol dependence alone accounts for approximately 4% of the global mortality rate and substance dependence in general ranks as the 8th cause of death globally (Rehm et al., 2009; WHO, 2010). Furthermore, alcohol and other substance use disorders account for 5.4% of the total global burden of disease (WHO, 2010). During the development of substance dependence, incentive salience of drug related stimuli increases whereas the salience of natural reinforcers declines (Everitt and Robbins, 2005; Hyman, 2005). Impaired inhibitory control, increased salience and craving for the abused substance are related to the development, continuation, and relapse in addictive disorders (Perry and Carroll, 2008). These cognitive and motivational changes are associated with important changes in brain functions in addictive disorders (Kalivas, 2005; Koob and Volkow, 2010). Firstly, repeated drug or alcohol use has been found to lead to neuro-adaptations in the ventral striatum and ventral tegmental areas, which in turn result in decreased dopamine secretion (Volkow et al., 2009). Evidence from both human and rodent studies suggests that these changes are accompanied by increased saliency and craving for the abused substance, and the increased cue-reactivity related to increased salience has its neural basis in increased striatal and orbitofrontal responses to addiction-related cues (Baler and Volkow, 2006; Berridge, 2007; Everitt and Robbins, 2005; Koob and LeMoal, 2008). Secondly, diminished functioning of the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) is present in addictive disorders, presumably underlying diminished cognitive and behavioural control and a higher tendency to cue-induced relapse in alcohol or drug use (Garavan, 2007; van Holst and Schilt, 2011). Furthermore, diminished functioning of frontal brain circuits is related to a higher susceptibility to stress and stress-induced relapse, in the rat brain (Capriles et al., 2003). Together, these compromised brain activity patterns are associated with a higher chance to relapse in methamphetamine, nicotine and cocaine dependent subjects (Janes et al., 2010; Kosten et al., 2006; Paulus et al., 2005).

Drug craving is assumed to be an important risk factor for relapse in patients with substance dependence and, higher craving has indeed been found to be related to higher relapse rates (Oslin et al., 2009; Sinha et al., 2006). Although craving poses a risk for relapse, it can be counteracted by exerting cognitive and behavioural control over the increased motivational drive of craving. Therefore, craving for substances in persons with an addictive disorder presents a problem specifically when the ability to inhibit the drive to use the relevant substance is affected.

Craving for food has been, and often still is, a useful and adaptive process through which the body communicates its needs. For example, craving has been important from an evolutionary perspective for building food reserves during periods of food shortage, and one may crave meat when low on iron (Levin, 2007). However, with the current widespread availability of (processed) high sugar and fat foods in western countries, those previously beneficial cravings pose a risk for developing obesity or binge-eating disorder (May et al., 2012). There is a growing body of evidence suggesting a role for craving in the obesity epidemic (Pelchat, 2009a). Furthermore, there is an ongoing debate on whether there is something like 'food addiction' (Corsica and Pelchat, 2010; Ziauddeen and Fletcher, 2013) and if so whether this is mainly true for binge eating behaviour (Gearhardt et al., 2011; Smith and Robbins, 2013; Umberg et al., 2012). Independent of the debate on food *addiction*, craving for food is well documented (Hill, 2007; Sobik et al., 2005). Furthermore, deficient control processes are frequently reported in obese and binge eating people (Pelchat, 2009b; Volkow et al., 2011; Yanovski, 2003). The combination of loss of control in combination with higher food cravings – especially cravings for palatable or high caloric food, may lead to loss of control over food intake and therefore weight gain. Consistent with this, higher craving for food has been related to higher weight and lack of success in weight loss programmes (Lafay et al., 2001; Vander Wal et al., 2007; Wurtman and Wurtman, 1986).

The neurobiological correlates of craving are hypothesized to be shared between substance dependent patients and people who are craving for high palatable food (Volkow et al., 2013). In fact, there is considerable evidence from human neuroimaging studies implicating the same neural structures in both food and drug craving. The orbitofrontal cortex (OFC) is related to salience attribution to potentially rewarding stimuli, such as food or drugs (Volkow et al., 2013). Increased salience attribution to drugs is an important aspect of addiction (Dom et al., 2005). Increased OFC activity has also been linked to increased food craving in lean healthy controls (Wang et al., 2004). Other studies have also shown that dopamine is related to the desire for both drugs and food (Blum et al., 2011; Volkow et al., 2002). Furthermore, brain activations in amygdala, insula, bilateral orbitofrontal cortex and striatum overlap for food and smoking cues in normal weight individuals (Tang et al., 2012). Moreover, D2-dopamine receptor density in the striatum has been negatively correlated with BMI of obese people (Wang et al., 2001). Lower D2-dopamine receptor density in the striatum is also related cocaine dependence, heavy nicotine and alcohol use (Connor et al., 2007); nicotine craving (Connor et al., 2007; Erblich et al., 2005; Heinz et al., 2004; Volkow et al., 1993); and reduced frontal metabolism in cocaine dependence (Volkow et al., 1993).

Reduced (pre)frontal activation has been reported in obese patients, with and without binges, in reaction to food and food cues. Hypo-activation of the (pre)frontal cortex has been implicated in deficient inhibitory control and hyper-activation of DLPFC in reaction to food stimuli was related to craving for food (Karhunen et al., 2000; Wang et al., 2004). Obese patients show less activation in DLPFC compared to healthy controls after a meal, indicating reduced reactivity to ingestion of food, which may be related to satiation (Le et al., 2006). Also, decreased blood flow in the prefrontal cortex has been associated with higher weight in healthy subjects (Willeumier et al., 2011, 2012). Impaired executive control has been reported in obese women (Kishinevsky et al., 2012) whereas successful dieters activate their DLPFC/OFC while eating (DelParigi et al., 2007). Together, these findings implicate the presence of disrupted motivational neural processes and impulse control in obesity (Nijs et al., 2009).

Addiction and obesity are among the biggest health problems of the western world today (Hedley et al., 2004; WHO, 2010). Substance dependence is known for its high relapse rates (Dutra et al., 2008) and as noted before, craving is an important risk factor for relapse (Oslin et al., 2009; Sinha et al., 2006). In a review, McLellan et al. (2000) concluded that only 40–60% of all treatment seeking substance dependent patients were still abstinent at 1 year follow-up. Relapse rates for nicotine dependence are estimated to be around 85% for counselling therapy alone and 78% for counselling combined with medication (Fiore et al., 2008). Furthermore, weight loss programmes are often ineffective for obese patients, as 33% to 66% of patients regain all weight that was lost, or gain even more (Bacon and Aphramor, 2011; Mann et al., 2007). Therefore, the available treatment options are ineffective for a substantial proportion of these patients and new treatment options are clearly needed. Non-invasive neurostimulation such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are new intervention methods that may target the reduction of craving levels in substance dependence and obese or binge eating groups. By reducing craving levels, it would become

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