

Short communication

One session of high frequency repetitive transcranial magnetic stimulation (rTMS) to the right prefrontal cortex transiently reduces cocaine craving

Joan Albert Camprodon^a, José Martínez-Raga^b, Miguel Alonso-Alonso^a,
Mei-Chiung Shih^c, Alvaro Pascual-Leone^{a,*}

^a Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, KS 452, Boston, MA 02215, USA

^b Instituto de Drogas y Conductas Adictivas (IDYCA), Universidad Cardenal Herrera-CEU, Unidad de Conductas Adictivas Area 11, Agencia Valenciana de Salud, Spain

^c Department of Biostatistics, Harvard School of Public Health and Clinical Research Program, Children's Hospital Boston, 333 Longwood Avenue, Boston, MA 02115, USA

Received 26 March 2006; received in revised form 2 June 2006; accepted 7 June 2006

Abstract

Background: Cocaine dependence is a public health problem affecting 2 million individuals in USA. Craving is a predictor of subsequent cocaine use and is related to changes in brain activity in networks involving the prefrontal cortex.

Methods: We investigated the efficacy of one session of high frequency repetitive transcranial magnetic stimulation (rTMS) to reduce craving in cocaine addicted subjects. Six patients underwent two sessions of 10 Hz rTMS over left or right dorsolateral prefrontal cortex (DLPFC). Before, immediately after and 4 h after rTMS we measured craving using visual analogue scales.

Results: Right, but not left, DLPFC stimulation significantly reduced craving over time ($F(2,10) = 11.07$, $p = 0.0029$). The reduction was 19% (13.4–24.6%) from baseline and disappeared after 4 h. The interaction of time by site of stimulation for craving was also significant ($F(2,25) = 6.13$, $p = 0.0068$).

Conclusion: One session of 10 Hz rTMS over right, but not left, DLPFC transiently reduces craving in cocaine dependent individuals. These results highlight the potential of non-invasive neuromodulation as a therapeutic tool for cocaine addiction.

© 2006 Elsevier Ireland Ltd. All rights reserved.

Keywords: Cocaine; Addiction; Craving; Transcranial magnetic stimulation (TMS); Dorsolateral prefrontal cortex (DLPFC)

1. Introduction

Substance abuse is a chronically relapsing disorder that constitutes a grave threat to public health around the world. In 2002 in USA alone, an estimated 19.5 million Americans (8.3% of the population age 12 and older) were current users of illicit drugs and 0.9% were addicted to cocaine (Substance Abuse and Mental Health Services Administration, 2003). The estimated total cost of illicit drug abuse was approximately US\$ 200 billion (Office of National Drug Control Policy, 2001). These statistics stress the urgency and importance of developing effective therapies.

Over the last years, an increasing number of studies have advanced our understanding of the neurobiology of cocaine

addiction and efforts are being made towards the development of therapies based on molecular and cellular approaches (Nestler, 2004). Neuroimaging studies have provided insights into the neural networks affected by and involved in drug abuse (Goldstein and Volkow, 2002; Volkow et al., 2004). The modulation of these dysfunctional neural circuits through invasive and non-invasive brain stimulation may provide a valuable therapeutic approach. A growing number of studies implicate a distributed, bi-hemispheric neural network involving the nucleus accumbens, the amygdala, the anterior cingulate, the orbitofrontal and the dorsolateral prefrontal cortices (DLPFC) in the pathophysiology of craving (Wilson et al., 2004). The DLPFC is involved in reward, motivation and decision making circuits providing the substrate for integration of cognitive and motivationally relevant information and the inhibitory control over seductive options harboring the promise of immediate reward (Goldstein and Volkow, 2002; Bechara, 2005). In the

* Corresponding author. Tel.: +1 617 667 0203; fax: +1 617 975 5322.
E-mail address: apleone@bidmc.harvard.edu (A. Pascual-Leone).

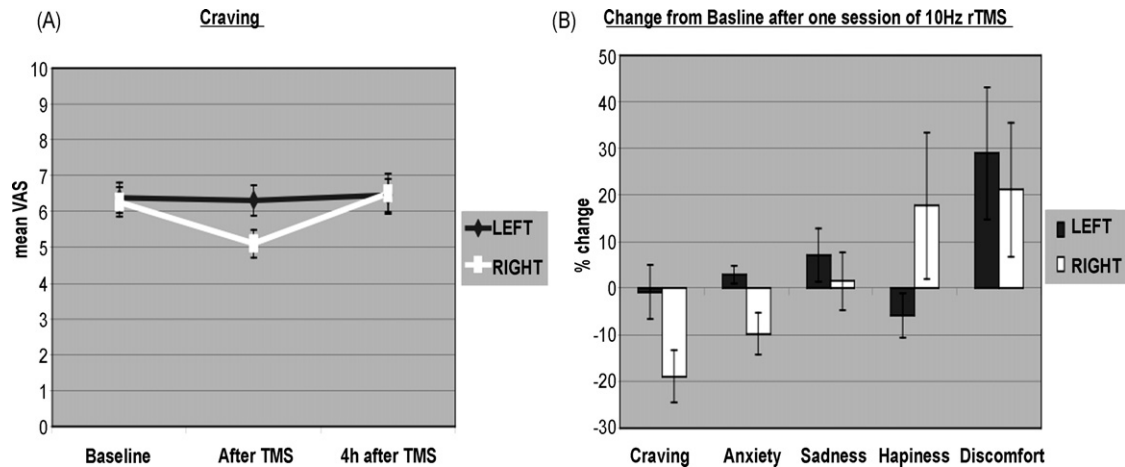


Fig. 1. Changes in cocaine craving after 10 Hz rTMS over the left and right dorsolateral prefrontal cortex (DLPFC). (A) Effect of rTMS of the right (white) or left (black) DLPFC on the subjective desire to consume cocaine (craving) in six cocaine dependent patients as indexed by subjective responses to visual analog scales (VAS). Mean \pm 95% confidence interval. (B) Bar histogram of the effects of rTMS on all measures (craving, anxiety, sadness, happiness, and discomfort) expressed as difference in the responses on visual analog scales before and after right (white) or left (black) rTMS to the DLPFC. Mean \pm 95% confidence interval.

present study we demonstrate that disruption of the right but not the left DLPFC by repetitive transcranial magnetic stimulation (rTMS) significantly reduces cocaine craving.

2. Methods

We studied six right-handed males (aged 19–23 years) fulfilling DSM-IV criteria for cocaine dependence. Smoking was the preferred route of administration for all patients. Participants completed an inpatient medically assisted withdrawal and were currently not dependent on other substances nor using any psychiatric medications. Patients with a history of neurologic disease, a medical disorder requiring chronic medication, a comorbid psychiatric disorder, an abnormal physical examination or those who failed to meet published criteria for TMS safety (Wassermann, 1998) were excluded from the study. Patients remained hospitalized throughout the study. Toxicological urine drug screens were performed prior to each TMS session and all tests were negative. Comorbid psychiatric conditions were ruled out using the SCID interview. After complete description of the study to the subjects, written informed consent was obtained.

In a randomized crossover study we investigated the efficacy of a single session of high frequency rTMS over left or right DLPFC to reduce craving. Secondary endpoints were changes in anxiety, happiness, sadness and discomfort. Patients underwent two sessions of rTMS, one to the left and one to the right DLPFC. The order of stimulation was randomized and counterbalanced across patients, and rTMS sessions were separated by at least 1 week. All patients were naïve to TMS. Each session consisted of 20 trains of 10 s duration, separated by 1 min pauses. The frequency of stimulation was 10 Hz and the intensity was 90% of the individual's motor threshold. The safety of these parameters has previously been described in other psychiatric populations (Pascual-Leone et al., 1996a).

Patients were asked to complete a set of 15 visual analogue scales (VAS) ranging from “not at all” to “more than ever”. Each VAS evaluated one of the primary or secondary endpoints on three occasions: 10 min before the intervention, immediately after, and 4 h after TMS. The outcome measures were analyzed using repeated measures analyses of variance (ANOVA) with fixed effect time and random subject effect, separately for left and right TMS. Subsequent post hoc pair-wise comparisons were performed when the Time effect was statistically significant using paired *t*-test and Bonferroni corrections for multiple comparisons. We also evaluated whether the effects of left and right prefrontal TMS were different from each other by testing the time by site of stimulation interaction in a repeated measures ANOVA model which included random effects for Subject and fixed effects for time and site of stimulation. Two-sided *p*-values were used to determine statistical significance.

3. Results

All patients tolerated the stimulation without complications or adverse effects.

As illustrated in Fig. 1A, “desire to consume cocaine” was significantly reduced after right prefrontal rTMS ($F(2,10) = 11.07$, $p = 0.0029$), but no effects were observed after left rTMS ($F(2,10) = 0.31$, $p = 0.7368$). Post hoc pair-wise comparisons for the effects of right DLPFC stimulation demonstrated a significant difference between the baseline and the post-TMS ratings of craving ($p = 0.002$) and the post-TMS and 4 h post-TMS ($p = 0.020$). The ratings at baseline and 4 h post-TMS showed no significant difference ($p = 0.463$). These results describe a transient effect of one single session of 10 Hz rTMS on craving that resolves within 4 h after stimulation: mean reduction (95% confidence interval) = 19.0% (13.4–24.6%). A single session of rTMS is thought to have a behavioral effect lasting somewhere between half and twice the duration of the actual rTMS train (i.e. for 20 min of rTMS one would expect a behavioral change from baseline lasting 10–40 min) (Robertson et al., 2003). Our results agree with this general rule. Longer-lasting clinical effects are usually the result of multiple daily sessions of rTMS, usually over the course of several weeks. Notice that the difference in the VAS ratings between post-TMS and 4 h post-TMS ($p = 0.020$) is only marginally significant after the Bonferroni correction, which establishes the significance threshold at $p = 0.017$ (0.003 below the described *p*-value). Still, the small difference, the conservative nature of the Bonferroni method and the fact that craving ratings at baseline and 4 h post-TMS show no significant difference lead us to consider the effects to be extinguished 4 h after stimulation.

For secondary outcomes (Fig. 1B), right DLPFC rTMS induced significant over time changes in anxiety ($F(2,10) = 10.57$, $p = 0.0034$) and happiness ($F(2,10) = 6.76$, $p = 0.0139$), while left stimulation induced significant over time changes in sadness ($F(2,10) = 4.92$, $p = 0.0325$). Discomfort was significantly affected by both left ($F(2,10) = 19.95$, $p = 0.0003$)

and right rTMS ($F(2,10) = 4.73, p = 0.0358$). Post hoc pair-wise comparisons revealed that for all these measures, the VAS ratings at post-TMS differed significantly from both baseline and 4 h post-TMS, while baseline and 4 h post-TMS did not significantly differ from each other.

The time by site of stimulation interaction term was significant for craving ($F(2,25) = 6.13, p = 0.0068$), demonstrating that the effects over the left and right prefrontal cortex are significantly different from each other, and highlighting the specificity of the intervention. The time by site of stimulation interactions for the secondary outcome measures were not significant, despite the strong trends for anxiety ($F(2,25) = 2.76, p = 0.0829$) and happiness ($F(2,25) = 3.12, p = 0.0615$).

4. Discussion

To the best of our knowledge, this is the first demonstration that a single session of high frequency rTMS can significantly reduce cocaine craving when applied to the right, but not the left prefrontal cortex. Anxiety was significantly reduced after right-sided stimulation. Happiness was increased after right- and sadness after left-sided stimulation. This is consistent with prior findings in healthy human subjects (Pascual-Leone et al., 1996b) but contrasted to findings in patients suffering from depression, who tend to show the opposite lateralization (Pascual-Leone et al., 1996a; Lisanby et al., 2002; Gershon et al., 2003). Discomfort was increased equally by left- and right-sided rTMS and the interaction term was clearly not significant ($F(2,25) = 2.25, p = 0.9286$), providing a useful control for the non-specific effects of the stimulation.

It has been described that DLPFC stimulation can induce subcortical dopamine release in the caudate nucleus, which may provide a possible mechanism of action for the present findings (Strafella et al., 2001). The dopaminergic mesocorticolimbic pathway, which arises in the ventral tegmental area (VTA) and connects brain structures involved with reward (nucleus accumbens) and cognitive control (prefrontal cortex), appears to be a critical substrate of drug craving and relapse. Imaging studies of cocaine abusers show that both cocaine and cocaine-elicited cues increase metabolic activity in this circuit (Goldstein and Volkow, 2002).

Two studies using functional Magnetic Resonance Imaging (fMRI) have correlated craving with left DLPFC activation (Maas et al., 1998; Garavan et al., 2000), while one study using Positron Emission Tomography (PET) showed right DLPFC increases in [^{18}F]fluorodeoxyglucose metabolism (Bonson et al., 2002). These contradictory findings could reflect methodological differences between neuroimaging techniques and their outcome measures (Blood Oxygen Level Dependent (BOLD) signal in fMRI versus neuronal glucose metabolism in PET) or other study design variations such as the approach used to induce craving or the subject selection criteria. Perceived drug abuse opportunity seems to be a critical variable on whether the DLPFC is activated or not in studies of craving using drug cue reactivity paradigms (Bonson et al., 2002). Our patients were trying to stop abusing cocaine and the results in actively abusing patients may be quite different.

In nicotine dependent individuals, Eichhammer et al. (2003) have reported reduction of cigarette smoking following 10 Hz rTMS to the left DLPFC as compared with sham stimulation. Similarly, in overweight individuals, Uher et al. (2005) found that the expected increase in food craving following repeated exposure to food was suppressed by real, but not by sham rTMS to the left DLPFC. However, neither one of these studies compared left- with right-sided rTMS. Our results describe that the reduction of cocaine craving is maximal after right prefrontal high frequency stimulation and non-significant after left stimulation. We hypothesize that increased right DLPFC activity might have resulted in even greater inhibitory capacity and suppressive control of superficially seductive options in these previous studies.

The effects of rTMS extend beyond the directly targeted brain structure to affect bi-hemispheric cortical and subcortical nodes of the neural network(s) connected with the stimulated region. George et al. (1999) demonstrated that high frequency rTMS to the left DLPFC with parameters similar to those employed in our study reduced activity in the right DLPFC as measured by PET. It is reasonable to assume that right high frequency rTMS has the same cross-hemispheric effects and thus results in suppression of left DLPFC activity. We hypothesize that high frequency rTMS to the right DLPFC leads to a transynaptic suppression of the left DLPFC, activated in the above-cited fMRI studies, via transcallosal connections. The degree of this suppression might be correlated with the reduction of craving.

Our data suggest that rTMS may provide a valuable therapeutic intervention for cocaine craving and dependency. Further studies using larger sample sizes are necessary to confirm the clinical potential of rTMS in cocaine craving, explore whether repeated daily sessions of rTMS (typically used for therapeutic purposes) may result in longer-lasting benefits, examine the mechanisms of action, and the applicability to other addictive behaviors.

Acknowledgements

The work on this article was partly supported by grants from the National Institutes of Health (K24 RR018875) and the Conselleria d'Educació i Ciència, Generalitat Valenciana (GV 2532/94) to A.P.L. and the Fundació "La Caixa" to J.A.C. The authors would like to thank Mark Thivierge for the invaluable administrative support and Dr. Zoe Woel for helpful comments on the manuscript. This manuscript is submitted in memory of M. Dolores Catalá who critically contributed to the study.

References

- Bechara, A., 2005. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nat. Neurosci.* 8, 1458–1463.
- Bonson, K.R., Grant, S.J., Contoreggi, C.S., Links, J.M., Metcalfe, J., Weyl, H.L., Kurian, V., Ernst, M., London, E.D., 2002. Neural systems and cue-induced cocaine craving. *Neuropsychopharmacology* 26 (3), 376–386.
- Eichhammer, P., Johann, M., Kharraz, A., Binder, H., Pittrow, D., Wodarz, N., Hajak, G., 2003. High-frequency repetitive transcranial magnetic stimulation decreases cigarette smoking. *J. Clin. Psychiatry* 64, 951–953.

- Garavan, H., Pankiewicz, J., Bloom, A., Cho, J.K., Sperry, L., Ross, T.J., Salmeron, B.J., Risinger, R., Kelley, D., Stein, E.A., 2000. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *Am. J. Psychiatry* 157, 1789–1798.
- George, M.S., Stallings, L.E., Speer, A.M., Nahas, Z., Spicer, K.M., Vincent, D.J., Bohning, D.E., Cheng, K.T., Molloy, M., Teneback, C.C., Risch, S.C., 1999. Prefrontal repetitive transcranial magnetic stimulation (rTMS) changes relative perfusion locally and remotely. *Hum. Psychopharmacol. Clin. Exp.* 14, 161–170.
- Gershon, A.A., Dannon, P.N., Grunhaus, L., 2003. Transcranial magnetic stimulation in the treatment of depression. *Am. J. Psychiatry* 160, 834–835.
- Goldstein, R.Z., Volkow, N.D., 2002. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am. J. Psychiatry* 159, 1642–1652.
- Lisanby, S.H., Kinnunen, L.H., Crupain, M.J., 2002. Applications of TMS to therapy in psychiatry. *J. Clin. Neurophysiol.* 19 (4), 344–360.
- Maas, L.C., Lukas, S.E., Kaufman, M.J., Weiss, R.D., Daniels, S.L., Rogers, V.W., Kukes, T.J., Renshaw, P.F., 1998. Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. *Am. J. Psychiatry* 155 (1), 124–126.
- Nestler, E.J., 2004. Historical review: molecular and cellular mechanisms of opiate and cocaine addiction. *Trends Pharmacol. Sci.* 25, 210–218.
- Office of National Drug Control Policy, 2001. *The Economic Costs of Drug Abuse in the United States, 1992–1998*. Executive Office of the President (Publication No. NCJ-190636), Washington, DC.
- Pascual-Leone, A., Rubio, B., Pallardó, F., Catalá, M.D., 1996a. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* 348, 233–237.
- Pascual-Leone, A., Catalá, M.D., Pascual-Leone Pascual, A., 1996b. Lateralized effect of rapid-rate transcranial magnetic stimulation of the prefrontal cortex on mood. *Neurology* 46, 499–502.
- Robertson, E.M., Theoret, H., Pascual-Leone, A., 2003. Studies in cognition: the problems solved and created by transcranial magnetic stimulation. *J. Cogn. Neurosci.* 15 (7), 948–960.
- Strafella, A.P., Paus, T., Barret, J., Dagher, A., 2001. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J. Neurosci.* 21, RC157.
- Substance Abuse and Mental Health Services Administration, 2003. *Overview of Findings from the 2002 National Survey on Drug Use and Health (Office of Applied Studies, NHSDA Series H-21, DHHS Publication No. SMA 03-3774)*, Rockville, MD.
- Uher, R., Yoganathan, D., Mogg, A., Eranti, S.V., Treasure, J., Campbell, I.C., McLoughlin, D.M., Schmidt, U., 2005. Effect of left prefrontal repetitive transcranial magnetic stimulation on food craving. *Biol. Psychiatry* 58, 840–842.
- Volkow, N.D., Fowler, J.S., Wang, G.J., 2004. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. *Neuropharmacology* 47 (Suppl. 1), 3–13.
- Wassermann, E.M., June 5–7, 1996. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the international workshop on the safety of repetitive transcranial magnetic stimulation. *Electroencephalogr. Clin. Neurophysiol.* 108, 1–16.
- Wilson, S.J., Sayette, M.A., Fiez, J.A., 2004. Prefrontal responses to drug cues: a neurocognitive analysis. *Nat. Neurosci.* 7, 211–214.