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Brain Stimulation in Drug Addiction

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INTRODUCTION

Drug dependence is known to be associated with structural and functional damage to the Prefrontal Cortex **(PFC)** culminating in the reduction of frontal activity. Besides, the PFC is critically involved in processing the craving of smoking [1,2] and drugs such as alcohol [3]; opiates [4] and cocaine [5,6]. Specifically, craving is associated with enhanced activity of this cortical area during drug cue presentation. Once PFC is broadly related to executive functions and to the brain's reward circuitry [7-9], this imbalance indicates that the cognitive ability to regulate drug-seeking behaviour is decreased, and the risk of consuming the drug increases. Reducing craving and improving cognitive functions constitute great challenges in the treatment of drug addiction and, unfortunately, pharmacological and non-pharmacological approaches have not fully addressed these issues so far.

PFC activation during the exposure of drug-related cues may be specifically related to addiction and associated with an enhanced desire for the drug [10]. Furthermore, activity enhancement of PFC areas involved in drug-related processes, including emotional responses (medial OFC and ventromedial PFC in craving), automatic behaviors (OFC in drug expectation and ACC inattention bias) and also higher-order executive responses involved in drug-related working memory (DLPFC) [11] may constitute prominent factors preceding relapses.

The mesocorticolimbic dopamine system and the nigrostriatal dopamine system both contribute to cue-induced drug seeking [12-14] and other behavioral effects of drug use, including reward [15,16]. Several evidences suggest that an action in dopaminergic neurons may be the mechanism responsible for the reward caused by cocaine consume, or else, the blockade in the dopamine reuptake (Figure 1) and subsequent increase of the activity of this neurotransmitter over dopaminergic receptors may be the responsible for the "high" associated with cocaine use [17]. It is well known that some areas from the prefrontal cortex that are involved in these drug-related processes are activated when drug addicted is exposed to either the drug or some drug-cue [1,2,5,6,18-21]. Volkow et al (2002) postulated that this enhanced activity of PFC could contribute to the compulsive self-administration and the lack of control (impaired inhibition) in addicted subjects and also contribute to disruptive cognitive operations that impair judgment and favor relapse [22].

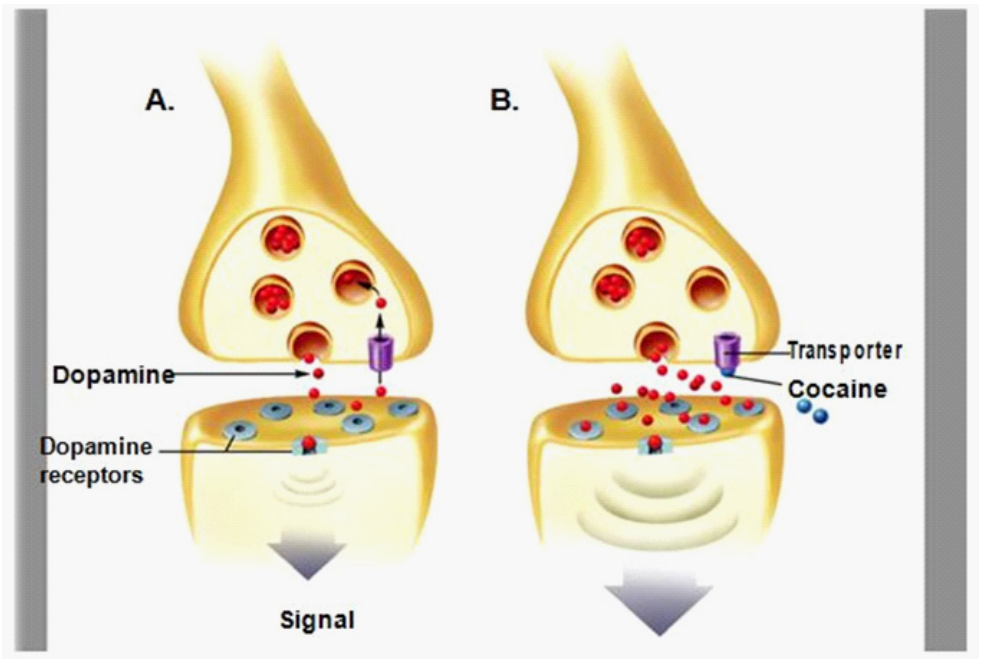

Figure 1: (From: Fowler et al, 2007).

COCAINE, SMOKED COCAINE AND ALCOHOL

Cocaine is a highly devastating drug. When smoked, the cerebral effects are immediate, intense and fleeting, leading to compulsive use and subsequently to increased risk of abuse and dependence. Patients addicted to crack-cocaine are routinely observed to have difficulties in adhering the treatment and this can be, at least in part, due to the structural and functional damage associated to the prefrontal cortex [23]. This frontal cerebral area is broadly related to executive functions and the brain's reward circuitry [24-26] strengthening the evidence that once this area is impaired in drug users (Figure 2), the cognitive ability to regulate drug-seeking/taking behaviour is decreased, increasing the risk of consuming the drug.

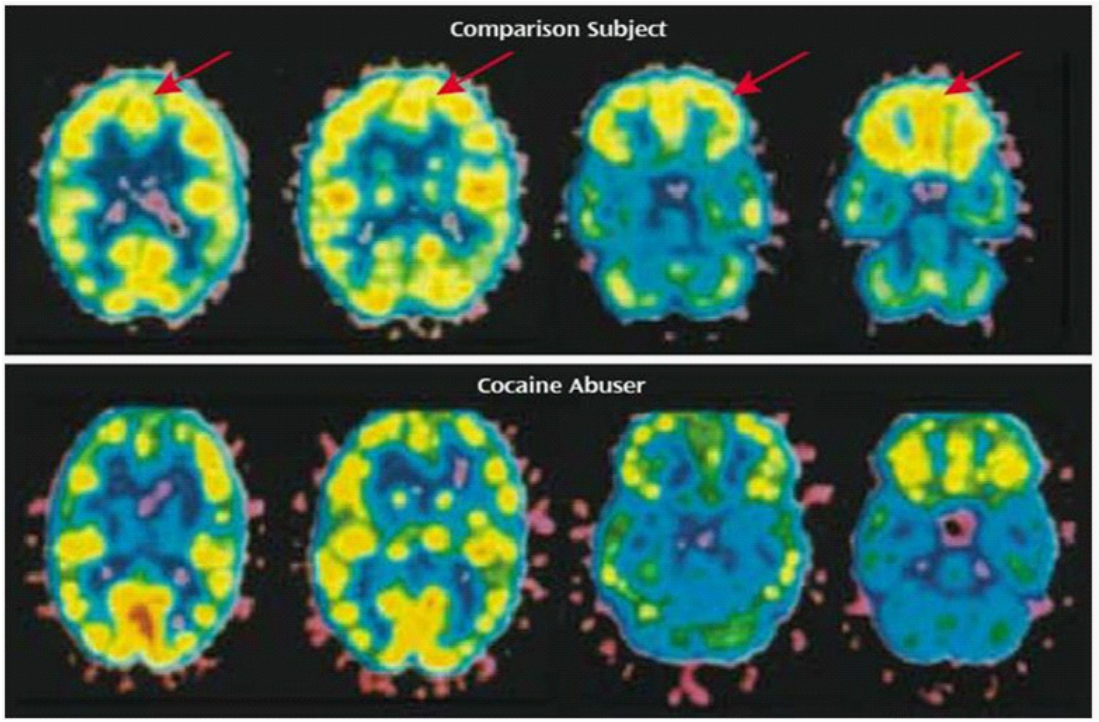

Figure 2: Lower Relative Glucose Metabolism in the Prefrontal Cortex and Anterior Cingulate Gyrus of a Cocaine Abuser Than in a Normal Comparison Subject (From: Goldstein & Volkow, 2002).

Alcohol and crack-cocaine share some similarities as they are both drugs of abuse that have increasingly burdening our society around the world [27-33].

These drugs depend on the mediation of the brain reward circuitry, including PFC areas, to produce highly addictive effects [11,34], and also strongly impair frontal functions [23,35-38]. However, they belong to different classes of psychotropic drugs. Alcohol is a typically depressant drug whereas crack-cocaine is typically a stimulant drug, even more harmful when compared to cocaine [39].

EVENT-RELATED POTENTIALS

Experimental investigations of addictive phenomena by using a cue-reactivity paradigm have been performed extensively [40-43] and a growing amount of evidence suggests that electroencephalographic activity of frontal-central areas increases when cocaine users are exposed to pictures of cocaine compared to neutral images [44-46]. Using scalp surface electrodes, the Event-Related Potential **(ERP)** can be recorded in response to a variety of sensory stimuli, and much information can be obtained from these electrodes after a given task with a high temporal resolution.

ERPs can be recorded with excellent temporal resolution by using scalp surface electrodes. Two major potentials studied are the time-locked components named N2 and P3. Studies on source analysis of the N2 indicate a cortical generator consistent with the position of the Anterior Cingulate Cortex **(ACC)** [47-49] and this area is shown to be associated with the timing of action-monitoring processes [50] and directed attention in situations that require response control or conflict resolution [51,52]. The P3 component is also observed in more anterior brain areas [53] and is sensitive to general and specific arousal, contributing to attention and information processing [54].

The P3 and also P3-related Late Positive Potential **(LPP)** have been related with enhanced motivated attention for the stimuli presented [55-57] and it is assumed that the enlargement of these late ERP components in substance users reflects their motivated attention for drug-related stimuli. A meta-analytic investigation by Field et al (2009) described that attentional bias and craving are related phenomena, i.e., in most studies of drug addiction, P3 and LPP

amplitudes are correlated with subjective craving [58].

Although experimental studies have shown that exposure to drug-related stimuli increase cravings in drug-dependent individuals, the most commonly used measures are subjective self-reports, which assess the 'desire' for a particular substance as we have measured with the questionnaire mentioned above. However, more objective physiological and behavioral responses can provide us more accurate measurement of brain activity under certain conditions. ERPs studies have been increasingly used for a more objective measurement of the motivational attribute of drug-related stimuli in human. In spite of its low spatial resolution, ERPs have an excellent temporal resolution, allowing the investigation of the time-course of emotional processing and drug cue reactivity.

NEUROMODULATION

Transcranial Direct Current Stimulation **(tDCS)** is technically a simple method of noninvasive brain stimulation that has been used to modulate neuronal resting membrane potential leading to changes of cortical excitability and other functional parameters [59-61]. It is well established that cathodal current decreases cortical excitability and anodal current increases excitability

[62-65]. The potential benefit of this neuromodulation induced by tDCS has been increasingly investigated in neuropsychiatric disorders, such as depression [66-70] and substance abuse and craving including alcohol [71,72], tobacco [73], Marijuana [74] and also foods disorders [75].

The potential use of tDCS in the treatment of drug addiction can be more explored. Assuming that tDCS has been associated with working memory enhancement and improvement in other cognitive domains [76-84], brain stimulation over Dorsolateral Prefrontal Cortex **(DLPFC)** can enhance executive function, providing improved cognitive control over relapsing on drug use.

On the other hand, tDCS has demonstrated an important effect in the reduction of craving when applied over the DLPFC. Anodal tDCS over the left and right DLPFC was beneficial for reducing cue-provoked smoking craving

[73]. In patients with alcohol dependence while being exposed to alcohol cues, both left anodal/right cathodal and right anodal/left cathodal significantly decreased alcohol craving compared to sham stimulation [71]. When tDCS was studied in chronic marijuana smokers, it was observed that right anodal/left cathodal tDCS over the DLPFC (the electrode montage of the present study) was significantly associated with a diminished craving for marijuana [74].

It has been proposed that cognitive intervention would attenuate the increased cue-induced response in the PFC during drug abstinence [11]. For example, when cocaine abusers purposefully inhibit craving when exposed to conditioned drug-cues, specific changes in brain regions that process reward and prediction of reward occur, or else, regions involved in processing conditioned responses decrease their activities. Interestingly, the increasing of the left DLPFC activity in the P3 segment under crack-related cue presentation observed in crack-cocaine users from non-stimulated group (sham-tDCS) was prevented by the cathodal tDCS applied over the left DLPFC in crack-cocaine users from real tDCS group, suggesting that cathodal tDCS over the DLPFC could be helpful to control the processing of drug-conditioned responses and subsequently the craving response [85,86]. In fact, according to Volkow et al (2010) "The frontal mediation of a neural circuit involved in the craving response provides a target for top-down cognitive interventions that may be therapeutically beneficial. Interventions that strengthen a weakened but still functional fronto-accumbal circuit may increase the ability of cocaine abusers to block or reduce the drug craving response" [87].

Transcranial electric activity has been shown to be associated with frontal-related cognitive changes in healthy subjects and several psychiatric conditions [76-84]. Previous study from our lab showed specific clinical and electrophysiological (as indexed by P3) effects of tDCS on patients with alcohol dependence in which we demonstrated that anodal tDCS over left

DLPFC resulted in an improved cognitive function [72]. Not only transcranial, but also epidural stimulation was already used to study emotion regulation and the impact of cognitive control on neural response to visual stimuli. Hajcak et al (2010) studied five patients with treatment-resistant

mood disorders stereotactically implanted with stimulating paddles over DLPFC bilaterally and this study corroborated the role of DLPCF in regulating measures of neural activity that have been linked to emotional arousal and attention [88]. Though the number of studies on frontal neuromodulation has been growing in psychiatric disorders, efforts are needed to propose this technique as an effective repetitive therapy in the treatment of such conditions.

Interestingly, we have observed that the effect of anodal tDCS stimulation over the left DLPFC is restricted to the left DLPFC. Besides, when left cathodal tDCS was coupled with right anodal tDCS over the DLPFC, the effect was still restricted to the left DLPFC [85]. These facts bring the issue about interhemispheric interaction which occurs via transcallosal fibers that transmit inhibitory influences between the homologous areas of both hemispheres [89]. These fibers are thought to be glutamatergic and to project onto inhibitory GABAergic interneurons [90]. This interaction had already been demonstrated for motor response after stroke through noninvasive brain stimulation over primary Motor Cortex **(M1)** [91-93]. The improved motor function after brain stimulation may be attributed to a suppression of interhemispheric inhibition (down-regulation of the excitability in the intact hemisphere) resulting in an improvement of the damaged function. In subjects with major depressive disorder, 1 Hz rTMS (applied to the left M1) decreased corticospinal excitability in the left hemisphere; however, it induced no significant changes in corticospinal excitability in the contralateral, right hemisphere. In this case, the authors observed a decreased interhemispheric modulation at M1 level contrary to those findings from stroke studies [94]. Knoch et al (2006) used cortical stimulation over PFC and they described the asymmetric role of the PFC in decision-making showing that risk-taking behavior was induced by disruption of the right, but not the left, PFC [95]. Using concurrent tDCS over the PFC, it was demonstrated that left cathodal/right anodal decreases risk-taking behavior compared with left anodal/right cathodal or sham stimulation supporting the idea that differential modulation of DLPFC activity, increasing the right while decreasing the left, might lead to decreased risk taking behaviors [96]. Our findings does not seem to corroborate the interaction between left and right DLPFC after tDCS, at least for P3 analysis, however, we are accordingly encouraged to focus on decreasing the left DLPFC activity for future perspectives in the treatment of addiction through cortical modulation.

FINAL CONSIDERATIONS

It has to be considered that many pharmacological and non-pharmacological treatments for drug dependence are available, but these treatments have failed to successfully manage the addiction, notably for strong addictive drugs, such as crack-cocaine. Reducing craving and improving cognitive functions constitute great challenges in the treatment of drug addiction and we suggest that approaches targeted for intervention on the prefrontal cortex would be of great success. Though the number of studies on brain stimulation has been growing in psychiatric disorders involving drug abuse, efforts are needed to propose this technique as an effective repetitive therapy in the treatment of such conditions.

References

1. McBride D, Barrett SP, Kelly JT, Aw A, Dagher A. Effects of expectancy and abstinence on the neural response to smoking cues in cigarette smokers: an fMRI study. Neuropsychopharmacology. 2006; 31: 2728-2738.
2. Wilson SJ, Sayette MA, Fiez JA. Prefrontal responses to drug cues: a neurocognitive analysis. Nat Neurosci. 2004; 7: 211-214.
3. Tapert SF, Cheung EH, Brown GG, Frank LR, Paulus MP. Neural response to alcohol stimuli in adolescents with alcohol use disorder. Arch Gen Psychiatry. 2003; 60: 727-735.
4. Sell LA1, Morris JS, Bearn J, Frackowiak RS, Friston KJ. Neural responses associated with cue evoked emotional states and heroin in opiate addicts. Drug Alcohol Depend. 2000; 60: 207-216.
5. Grant S, London ED, Newlin DB, Villemagne VL, Liu X. Activation of memory circuits during cue-elicited cocaine craving. Proc Natl Acad Sci U S A. 1996; 93: 12040-12045.
6. Grant S, London ED, Newlin DB, Villemagne VL, Liu X. Activation of memory circuits during cue-elicited cocaine craving. Proc Natl Acad Sci U S A. 1996; 93: 12040-12045.
7. Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am J Psychiatry. 2000; 157: 1789-1798.
8. Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. Annu Rev Neurosci. 2006; 29: 565-598.
9. Fuster JM. Executive frontal functions. Exp Brain Res. 2000; 133: 66-70.
10. D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S. The neural basis of the central executive system of working memory. Nature. 1995; 378: 279-281.
11. Goldstein RZ and ND Volkow.Oral methylphenidate normalizes cingulate activity and decreases impulsivity in cocaine addiction during an emotionally salient cognitive task. Neuropsychopharmacology. 2011; 36: 366-367.
12. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci. 2011; 12: 652-669.
13. Shalev U, Grimm JW, Shaham Y. Neurobiology of relapse to heroin and cocaine seeking: a review. Pharmacol Rev. 2002; 54: 1-42.
14. Feltenstein MW, See RE. The neurocircuitry of addiction: an overview. Br J Pharmacol. 2008; 154: 261-274.
15. Belin D, Jonkman S, Dickinson A, Robbins TW, Everitt BJ. Parallel and interactive learning processes within the basal ganglia: relevance for the understanding of addiction. Behav Brain Res. 2009; 199: 89-102.
16. Pierce RC, Kumaresan V. The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? Neurosci Biobehav Rev. 2006; 30: 215-238.
17. Wise RA. Roles for nigrostriatal--not just mesocorticolimbic--dopamine in reward and addiction. Trends Neurosci. 2009; 32: 517-524.
18. Volkow ND, Fowler JS, Wang GJ, Swanson JM. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. Mol Psychiatry. 2004; 9: 557-569.
19. Daglish MR, Nutt DJ. Brain imaging studies in human addicts. Eur Neuropsychopharmacol. 2003; 13: 453-458.
20. Volkow ND, Wang GJ, Fowler JS, Hitzemann R, et al. Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: implications in addiction. Am J Psychiatry. 1999; 156: 19-26.
21. Sell LA, Morris JS, Bearn J, Frackowiak RS, Friston KJ. Neural responses associated with cue evoked emotional states and heroin in opiate addicts. Drug Alcohol Depend. 2000; 60: 207-216.
22. Tapert SF, Cheung EH, Brown GG, Frank LR, Paulus MP. Neural response to alcohol stimuli in adolescents with alcohol use disorder. Arch Gen Psychiatry. 2003; 60: 727-735.
23. Volkow ND, Fowler JS, Wang GJ, Goldstein RZ. Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. Neurobiol Learn Mem. 2002; 78: 610-624.
24. Fein G, V Di Sclafani, and DJ Meyerhoff. Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men. Drug Alcohol Depend. 2002; 68: 87-93.
25. Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. Annu Rev Neurosci. 2006; 29: 565-598.

26. Fuster JM. Executive frontal functions. Exp Brain Res. 2000; 133: 66-70.

27. Stuss DT, Alexander MP. Executive functions and the frontal lobes: a conceptual view. Psychol Res. 2000; 63: 289-298.

28. Hannan DJ, Adler AG. Crack abuse. Do you know enough about it? Postgrad Med. 1990; 88: 141-143, 146-7.

29. Cornish JW, O'Brien CP. Crack cocaine abuse: an epidemic with many public health consequences. Annu Rev Public Health. 1996; 17: 259-273.

30. Pomara C, Cassano T, D'Errico S, Bello S, Romano AD. Data available on the extent of cocaine use and dependence: biochemistry, pharmacologic effects and global burden of disease of cocaine abusers. Curr Med Chem. 2012; 19: 5647-5657.

31. Proescholdt M, Walter M, Wiesbeck GA. [Alcohol and violence: a current review]. Fortschr Neurol Psychiatr. 2012; 80: 441-449.

32. Navarro HJ, Doran CM, Shakeshaft AP. Measuring costs of alcohol harm to others: a review of the literature. Drug Alcohol Depend. 2011; 114: 87-99.

33. Ribeiro M, Dunn J, Laranjeira R, Sesso R. High mortality among young crack cocaine users in Brazil: a 5-year follow-up study. Addiction. 2004; 99: 1133-1135.

34. Dias AC, Araújo MR, Dunn J, Sesso RC, de Castro V. Mortality rate among crack/cocaine-dependent patients: a 12-year prospective cohort study conducted in Brazil. J Subst Abuse Treat. 2011; 41: 273-278.

35. Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am J Psychiatry. 2002; 159: 1642-1652.

36. Moselhy HF, Georgiou G, Kahn A. Frontal lobe changes in alcoholism: a review of the literature. Alcohol Alcohol. 2001; 36: 357-368.

37. Zago-Gomes Mda P and EM Nakamura-Palacios. Cognitive components of frontal lobe function in alcoholics classified according to Lesch's typology. Alcohol Alcohol. 2009; 44: 449-457.

38. Hoff AL, Riordan H, Morris L, Cestaro V, Wieneke M. Effects of crack cocaine on neurocognitive function. Psychiatry Res. 1996; 60: 167-176.

39. Volkow ND, Hitzemann R, Wang GJ, Fowler JS, Wolf AP. Long-term frontal brain metabolic changes in cocaine abusers. Synapse. 1992; 11: 184-190.

40. Volkow ND, Hitzemann R, Wang GJ, Fowler JS, Wolf AP. Long-term frontal brain metabolic changes in cocaine abusers. Synapse. 1992; 11: 184-190.

41. Ringwalt CL, Palmer JH. Cocaine and crack users compared. Adolescence. 1989; 24: 851-859.

42. Hester R, V Dixon, and H Garavan. A consistent attentional bias for drug-related material in active cocaine users across word and picture versions of the emotional Stroop task. Drug Alcohol Depend. 2006; 81: 251-257.

43. Sokhadze E, Singh S, Stewart C, Hollifield M, El-Baz A. Attentional Bias to Drug and Stress-Related Pictorial Cues in Cocaine Addiction Comorbid with PTSD. J Neurother. 2008; 12: 205-225.

44. Carter BL, Tiffany ST. Meta-analysis of cue-reactivity in addiction research. Addiction. 1999; 94: 327-340.

45. Modesto-Lowe V, Kranzler HR. Using cue reactivity to evaluate medications for treatment of cocaine dependence: a critical review. Addiction. 1999; 94: 1639-1651.

46. Dunning JP, Parvaz MA, Hajcak G, Maloney T, Alia-Klein N. Motivated attention to cocaine and emotional cues in abstinent and current cocaine users-an ERP study. Eur J Neurosci. 2011; 33: 1716-1723.

47. van de Laar MC, Licht R, Franken IH, Hendriks VM. Event-related potentials indicate motivational relevance of cocaine cues in abstinent cocaine addicts. Psychopharmacology (Berl). 2004; 177: 121-129.

48. Bauer LO, Kranzler HR. Electroencephalographic activity and mood in cocaine-dependent outpatients: effects of cocaine cue exposure. Biol Psychiatry. 1994; 36: 189-197.

49. Bokura H, Yamaguchi S, Kobayashi S. Electrophysiological correlates for response inhibition in a Go/NoGo task. Clin Neurophysiol. 2001; 112: 2224-2232.

50. Nieuwenhuis S, Yeung N, Cohen JD. Stimulus modality, perceptual overlap, and the go/no-go N2. Psychophysiology. 2004; 41: 157-160.

51. Van Veen V, Carter CS. The anterior cingulate as a conflict monitor: fMRI and ERP studies. Physiol Behav. 2002; 77: 477-482.

52. Van Veen V, Carter CS. The timing of action-monitoring processes in the anterior cingulate cortex. J Cogn Neurosci. 2002; 14: 593-602.

53. Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD. Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature. 1999; 402: 179-181.

54. Botvinick MM, Cohen JD, Carter CS. Conflict monitoring and anterior cingulate cortex: an update. Trends Cogn Sci. 2004; 8: 539-546.

55. Katayama J, Polich J. Stimulus context determines P3a and P3b. Psychophysiology. 1998; 35: 23-33.

56. Polich J. Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol. 2007; 118: 2128-2148.

57. Hajcak G, MacNamara A, Olvet DM. Event-related potentials, emotion, and emotion regulation: an integrative review. Dev Neuropsychol. 2010; 35: 129-155.

58. Schupp HT, Cuthbert BN, Bradley MM, Cacioppo JT, Ito T. Affective picture processing: the late positive potential is modulated by motivational relevance. Psychophysiology. 2000; 37: 257-261.

59. Olofsson JK, Nordin S, Sequeira H, Polich J. Affective picture processing: an integrative review of ERP findings. Biol Psychol. 2008; 77: 247-265.

60. Field M, Munafò MR, Franken IH. A meta-analytic investigation of the relationship between attentional bias and subjective craving in substance abuse. Psychol Bull. 2009; 135: 589-607.

61. Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N. Transcranial direct current stimulation: State of the art 2008. Brain Stimul. 2008; 1: 206-223.

62. Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol. 2003; 553: 293-301.

63. Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F. Modulation of cortical excitability by weak direct current stimulation--technical, safety and functional aspects. Suppl Clin Neurophysiol. 2003; 56: 255-276.

64. Bay SM, Zeng EY, Lorenson TD, Tran K, Alexander C. Temporal and spatial distributions of contaminants in sediments of Santa Monica Bay, California. Mar Environ Res. 2003; 56: 255-276.

65. Nitsche MA and W Paulus. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000; 527: 633-639.

66. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology. 2001; 57: 1899-1901.

67. Nitsche MA, Liebetanz D, Tergau F, Paulus W. [Modulation of cortical excitability by transcranial direct current stimulation]. Nervenarzt. 2002; 73: 332-335.

68. Wassermann EM, Grafman J. Recharging cognition with DC brain polarization. Trends Cogn Sci. 2005; 9: 503-505.

69. Nitsche MA. Transcranial direct current stimulation: a new treatment for depression? Bipolar Disord. 2002; 4: 98-99.

70. Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord. 2006; 8: 203-204.

71. Fregni F, Boggio PS, Nitsche MA, Rigonatti SP, Pascual-Leone A. Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. Depress Anxiety. 2006; 23: 482-484.

72. Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int J Neuropsychopharmacol. 2008; 11: 249-254.

73. Bikson M, Bulow P, Stiller JW, Datta A, Battaglia F, et al. Transcranial direct current stimulation for major depression: a general system for quantifying transcranial electrotherapy dosage. Curr Treat Options Neurol. 2008; 10: 377-385.

74. Boggio PS, Sultani N, Fecteau S, Merabet L, Mecca T, et al. Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: A double-blind, sham-controlled study. Drug and Alcohol Dependence. 2008; 92: 55-60.

75. Nakamura-Palacios EM, de Almeida Benevides MC, da Penha Zago-Gomes M, de Oliveira RW, de Vasconcellos VF, et al. Auditory event-related potentials (P3) and cognitive changes induced by frontal direct current stimulation in alcoholics according to Lesch alcoholism typology. Int J Neuropsychopharmacol. 2012; 15: 601-616.

76. Fregni F, Liguori P, Fecteau S, Nitsche MA, Pascual-Leone A, et al. Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue-provoked smoking craving: A randomized, sham-controlled study. Journal of Clinical Psychiatry. 2008; 69: 32-40.

77. Boggio PS, Zaghi S, Villani AB, Fecteau S, Pascual-Leone A, et al. Modulation of risk--taking in marijuana users by transcranial Direct Current Stimulation (tDCS) of the Dorsolateral Prefrontal Cortex (DLPFC). Drug Alcohol Depend. 2010; 112: 220-205.

78. Fregni F, Orsati F, Pedrosa W, Fecteau S, Tome FA. Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. Appetite. 2008; 51: 34-41.

79. Kuo MF, Nitsche MA. Effects of transcranial electrical stimulation on cognition. Clin EEG Neurosci. 2012; 43: 192-199.

80. Jeon SY, Han SJ. Improvement of the working memory and naming by transcranial direct current stimulation. Ann Rehabil Med. 2012; 36: 585-595.

81. Fertonani A, Rosini S, Cotelli M, Rossini PM, Miniussi C. Naming facilitation induced by transcranial direct current stimulation. Behav Brain Res. 2010; 208: 311-318.

82. Fiori V, Coccia M, Marinelli CV, Vecchi V, Bonifazi S, et al. Transcranial Direct Current Stimulation Improves Word Retrieval in Healthy and Nonfluent Aphasic Subjects. Journal of Cognitive Neuroscience. 2011; 23: 2309-2323.

83. Dockery CA, Hueckel-Weng R, Birbaumer N, Plewnia C. Enhancement of planning ability by transcranial direct current stimulation. J Neurosci. 2009; 29: 7271-7277.

84. Jo JM, Kim YH, Ko MH, Ohn SH, Joen B. Enhancing the working memory of stroke patients using tDCS. Am J Phys Med Rehabil. 2009; 88: 404-409.

85. Boggio PS, Ferrucci R, Rigonatti SP, Covre P, Nitsche M. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J Neurol Sci. 2006; 249: 31-38.

86. Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Experimental Brain Research. 2005; 166: 23-30.

87. Marshall L, Mölle M, Hallschmid M, Born J. Transcranial direct current stimulation during sleep improves declarative memory. J Neurosci. 2004; 24: 9985-9992.

88. Conti CL, Moscon JA, Fregni F, Nitsche MA, Nakamura-Palacios EM. Cognitive related electrophysiological changes induced by non-invasive cortical electrical stimulation in crack-cocaine addiction. Int J Neuropsychopharmacol. 2014; 17: 1465-1475.

89. Conti CL and EM Nakamura-Palacios. Bilateral transcranial direct current stimulation over dorsolateral prefrontal cortex changes the drug-cued reactivity in the anterior cingulate cortex of crack-cocaine addicts. Brain Stimul. 2014; 7: 130-132.

90. Volkow ND, Fowler JS, Wang GJ, Telang F, Logan J. Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. Neuroimage. 2010; 49: 2536-2543.

91. Hajcak G, Anderson BS, Arana A, Borckardt J, Takacs I, et al. Dorsolateral prefrontal cortex stimulation modulates electrocortical measures of visual attention: evidence from direct bilateral epidural cortical stimulation in treatment-resistant mood disorder. Neuroscience. 2010; 170: 281-288.

92. Meyer BU, Röricht S, Gräfin von Einsiedel H, Kruggel F, Weindl A. Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. Brain. 1995; 118: 429-440.

93. Chen R. Interactions between inhibitory and excitatory circuits in the human motor cortex. Exp Brain Res. 2004; 154: 1-10.

94. Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. Ann Neurol. 2004; 55: 400-409.

95. Fregni F, Boggio PS, Valle AC, Rocha RR, Duarte J, et al. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. Stroke. 2006; 37: 2115-2122.

96. Fregni F, Boggio PS, Mansur CG, Wagner T, Ferreira MJ. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. Neuroreport. 2005; 16: 1551-1555.

97. Bajwa S, Bermpohl F, Rigonatti SP, Pascual-Leone A, Boggio PS. Impaired interhemispheric interactions in patients with major depression. J Nerv Ment Dis. 2008; 196: 671-677.

98. Knoch D. Disruption of right prefrontal cortex by low--frequency repetitive transcranial magnetic stimulation induces risk-taking behavior. J Neurosci. 2006.

99. Knoch D, Gianotti LR, Pascual-Leone A, Treyer V, Regard M. Disruption of right prefrontal cortex by low-frequency repetitive transcranial magnetic stimulation induces risk-taking behavior. J Neurosci. 2006; 26: 6469-6472.

100. Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. J Neurosci. 2007; 27: 12500-12505.