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Title: **ONLINE TRANSCRANIAL DIRECT CURRENT STIMULATION OF THE FRONTAL CORTEX INDUCES DOPAMINE RELEASE IN THE STRIATUM – A SPATIAL AND TEMPORAL ANALYSIS IN HEALTHY HUMANS**

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Background: Bifrontal transcranial direct current stimulation (tDCS) applied over the dorsolateral prefrontal cortex (DLPFC) is associated with clinical improvements in several psychiatric conditions sharing disturbances in dopamine transmission. Some imaging reports reveal that tDCS effects spread through distributed cortical networks and suggest these effects may reach subcortical dopaminergic areas.

Objectives: The aim of this study is to investigate the effects of a single-session of bifrontal tDCS on subcortical dopaminergic transmission. These effects are explored online by positron emission tomography (PET) using dopaminergic D2 subtype receptor availability via [^{11}C]raclopride binding in healthy subjects.

Methods: In a double blind sham-controlled study, 32 healthy volunteers randomly assigned in two groups received a single-session of either active (n=14) or sham (n=18) bifrontal tDCS (20min, 2mA, anode over the left DLPFC, cathode over the right DLPFC) during a dynamic PET scan using a bolus-plus-continuous-infusion method for tracer administration. Extracellular dopamine concentration was assessed using simple pseudo-equilibrium 5-min ratios of ROI to cerebellum activities (B/F ratio). B/F ratios were calculated at baseline, during and after stimulation in the right and left nucleus accumbens, caudate nucleus and putamen. Variations from baseline in the active group were expressed relatively to variations in the placebo group (mean+/-sd).

Results: During active tDCS (online effects), the mean B/F ratio was reduced by around 7.7% (+/-10.5) in the left nucleus accumbens and 2.8% (+/-4.7) in the right putamen. No effects were observed in the opposite hemispheres and in both caudate nuclei. During the 20 minutes following the stimulation (offline effects), the mean B/F ratio decreased by 8.8% (+/-14.8) in the nucleus accumbens, 3.4% (+/-6.9) in the caudate nucleus and 2.8% (+/-7.0) in the putamen, in both hemispheres.

Conclusion: These results suggest temporally and spatially distributed effects of bifrontal tDCS on subcortical dopamine release.