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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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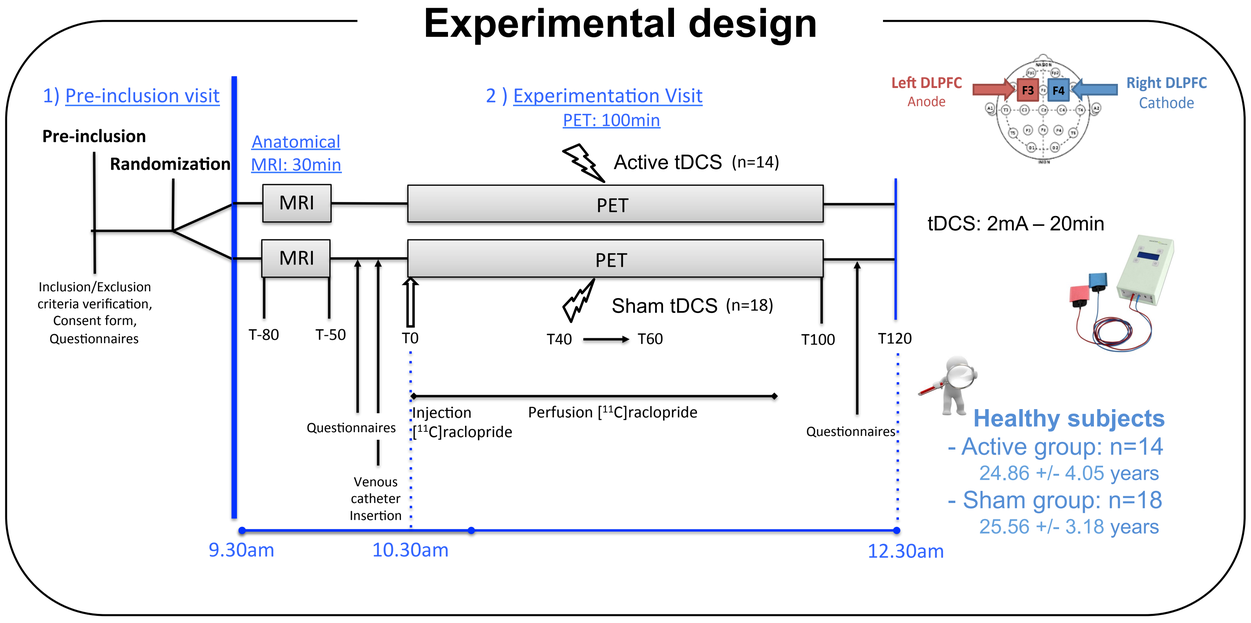
Background

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. However, despite an increasing use in clinical settings, spatial and temporal neurobiological effects of tDCS are far from being completely understood. Some imaging reports reveal that tDCS neurobiological effects are not restricted to the brain areas located under the electrodes and may reach subcortical dopaminergic areas. Moreover, some offline studies suggest that cortical stimulation by other approaches, such as transcranial magnetic stimulation may evoke a subcortical dopamine release following a single session applied over the left dorso-lateral prefrontal cortex (DLPFC) (Brunelin et al, 2011, Strafella et al, 2001). Thus, we hypothesize that bifrontal tDCS can modulate dopaminergic transmission, specifically in the ventral striatum, during and after the stimulation.

Objectives

The aim of this study was to test, in healthy subjects, the effects of a single-session of bifrontal tDCS with the anode over the left DLPFC and the cathode over the right DLPFC on the subcortical dopaminergic transmission. These effects were explored online by positron emission tomography (PET) using dopaminergic D2 subtype receptor availability via [^{11}C]raclopride binding.

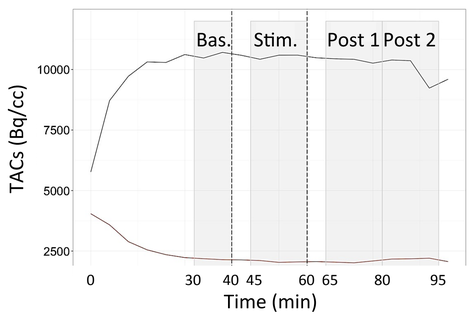
Experimental design



Subcortical dopamine analysis - Example

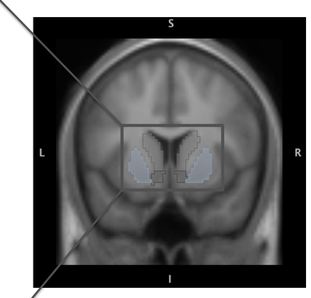
1) Kinetic Analysis (1 timepoint per 5 minutes)

- **Extraction of time activity curve (TACs)**
  In the region of interest (**striatum**) and reference region (**cerebellum**)



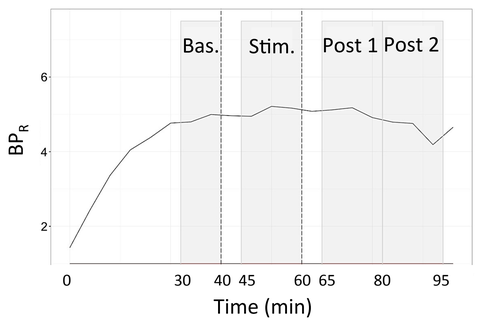
Striatum (subcortical dopaminergic region)

Cerebellum (reference region)



Regions of interest Atlas on MRI

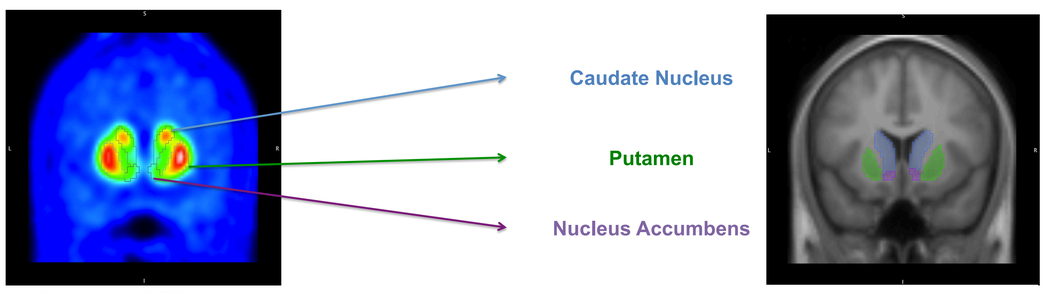
- **Binding potential (BP_R) → Extracellular Dopamine**
  Ratio of region of interest / cerebellum activities



Striatum (subcortical dopaminergic region)

2) Voxel-based analysis

- **Parametric Ratio Images for each time period (baseline, stimulation, post 1, post 2)**



Parametric PET image Example: Baseline period

Subregions of the striatum Atlas on MRI

Preprocessing (movement correction, coregistration, smoothing-8mm and normalization) were performed using an in-house script combining SPM12, Turku and minc tools.
Regions were determined based on the adult brain atlas developed by A. Hammers et al. (2003)

Dopamine transmission is increased in the striatum after bifrontal tDCS

Parametric Analysis - Significant clusters (Group * Time period)

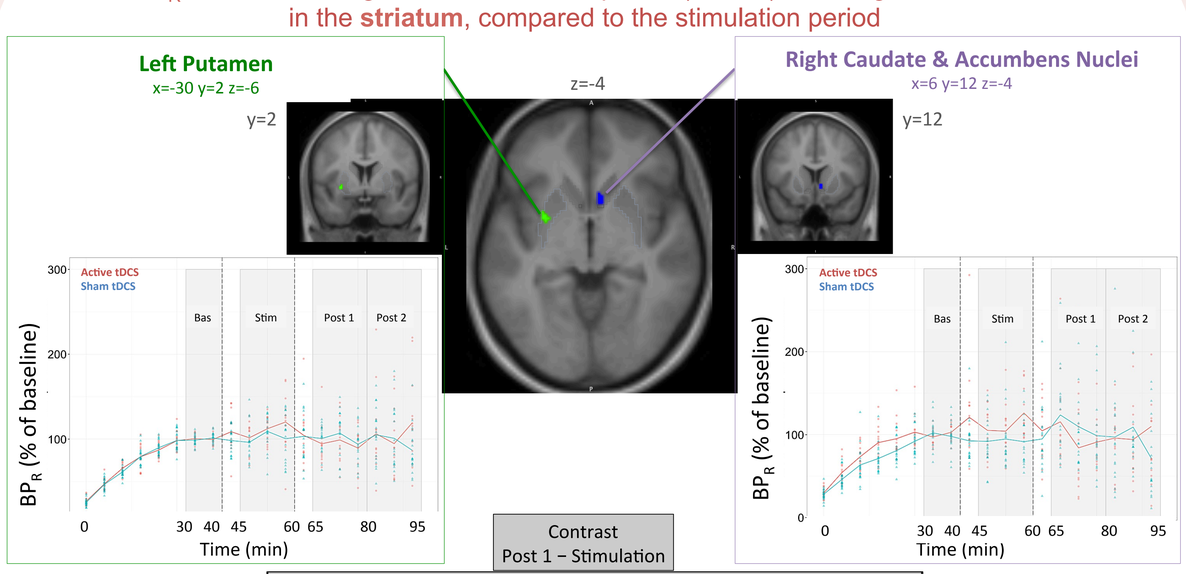
LEFT HEMISPHERE Activity curve — RIGHT HEMISPHERE Activity curve

1) Effects during stimulation

➢ No difference between the stimulation and baseline period

2) Acute after-effects (Post 1)

➢ BP_R decrease during the 5 to 20 minute period (**Post 1**) following the stimulation in the **striatum**, compared to the stimulation period

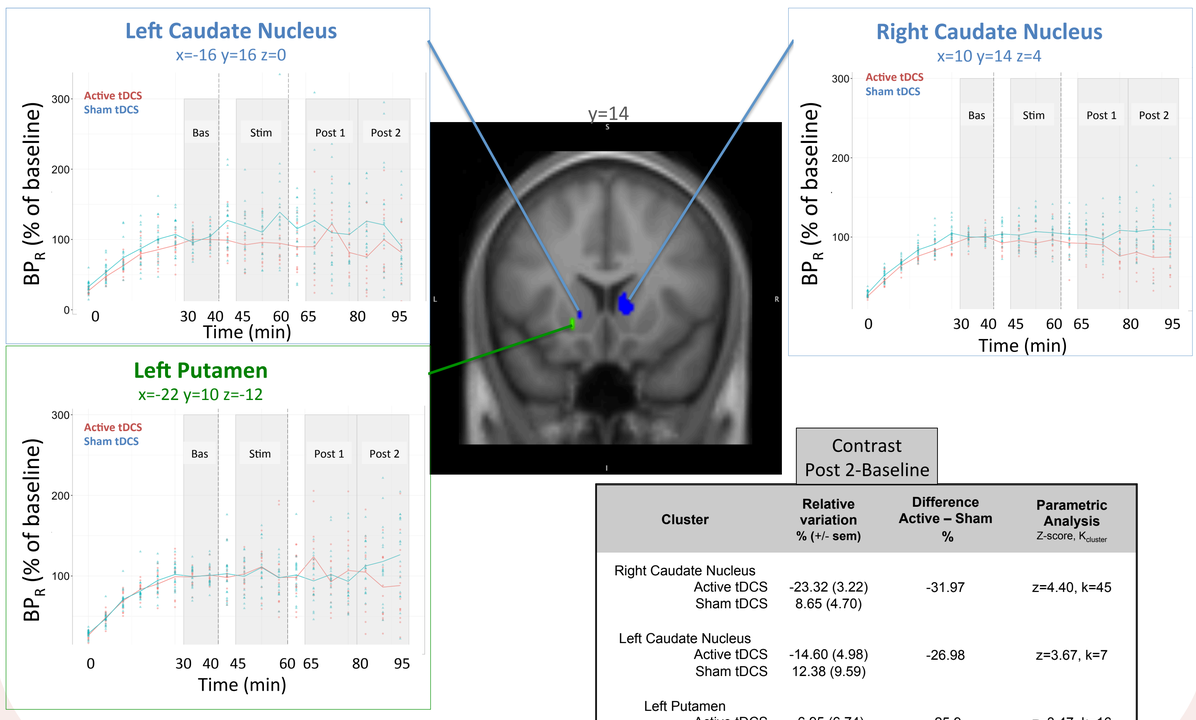


Contrast Post 1 − Stimulation

Cluster	Relative variation % (+/- sem)	Difference Active – Sham %	Parametric Analysis Z-score, $K_{cluster}$
Right Caudate and Accumbens Nuclei			
Active tDCS	-13.34 (5.00)	-33.82	z=4.17, k=18
Sham tDCS	20.48 (6.14)		
Left Putamen			
Active tDCS	-13.99 (5.82)	-13.989	z=3.53, k=24
Sham tDCS	-0.001 (4.25)		

3) Subsequent after-effects (Post 2)

➢ BP_R decrease during the 20 to 35 minutes period (**Post 2**) following the stimulation in the **striatum**, compared to the baseline and stimulation period



Contrast Post 2-Baseline

Cluster	Relative variation % (+/- sem)	Difference Active – Sham %	Parametric Analysis Z-score, $K_{cluster}$
Right Caudate Nucleus			
Active tDCS	-23.32 (3.22)	-31.97	z=4.40, k=45
Sham tDCS	8.65 (4.70)		
Left Caudate Nucleus			
Active tDCS	-14.60 (4.98)	-26.98	z=3.67, k=7
Sham tDCS	12.38 (9.59)		
Left Putamen			
Active tDCS	-6.95 (6.74)	-25.9	z=3.47, k=16
Sham tDCS	18.95 (5.59)		

Analysis were performed on SPM12 with a flexible factorial design (Group * Time period), in the striatum.
Significant clusters from the parametric analysis ($P_{uncorrected} < 0.001$, k>4) were selected then a TAC extraction was done for each cluster. The BP_R relative variations were calculated for each contrast.

Discussion

Areas of significant changes showed BP_R decreases in striatal subregions and specifically the ventral parts of the striatum (left and right ventral caudate nucleus, left ventral rostral putamen, right nucleus accumbens) when comparing the acute and subsequent effects of active and sham tDCS groups. However, no effects during bifrontal tDCS were observed.
These results suggest that tDCS induces subcortical dopamine release specifically in the limbic and executive parts of the striatum (areas delimited by Martinez et al, 2003).

Further studies are needed to study the impact of repeated bifrontal tDCS on dopaminergic transmission in psychiatric conditions.

Brunelin, J et al (2011) Theta burst stimulation in the negative symptoms of schizophrenia and striatal dopamine release. An iTBS- 11C raclopride PET case study. *Schizophrenia research*, **131**, 264--265.
Strafella AP, Paus T, Barrett J, Dagher A (2001) Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus, J Neurosci. 2001; 21:RC157.
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A. Hammers et al (2003) "Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe," *Hum. Brain Mapp.*, vol. 19, no. 4, pp. 224–247.

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