Modulation of fronto-striatal connectivity by intermittent Theta Burst Stimulation (iTBS). A 18F-DesmethoxyFallypride Positron Emission Tomography (PET) study.

Usman jawed Shaikh[1], Antonello Pellicano[1], Andre Schüppen[1], Oliver Winz[2], Felix Mottaghy[2,3], Ferdinand Binkofski[1,4]

[1] Section Clinical Cognitive Sciences, Department of Neurology, Faculty of Medicine, RWTH Aachen University, Aachen,Germany,
[2] Department of Nuclear Medicine, Faculty of Medicine, RWTH Aachen University, Aachen, Germany
[3] Department of Radiology and Nuclear Medicine, Maastricht University Medical Center (MUMC+), Maastricht, Netherlands
[4]Juelich Aachen Research Alliance (JARA)—BRAIN, Juelich, Germany, Research Centre Juelich,

Presenter name: Usman Jawed, Shaikh **email: ushaik@ukaachen.de**

POSTER: A17

9th MBB SYMPOSIUM 2022 (VIRTUAL)

INTRODUCTION

Background : Frontostriatal networks are neural pathways that provides a connection between frontal lobe regions and the basal ganglia (striatum) that is involved in motor, cognitive, and behavioral processes such as decision making, working memory and emotion regulation. It has been shown that Transcranial Magnetic Stimulation (TMS) can modulate connectivity in the human brain[1].

Aim : The aim of the study is to investigate the fronto-striatal connectivity through a combined PET and TMS technique. We measured the release of dopamine in the striatum in response to an excitatory intermittent theta burst stimulation (iTBS) of the Left-Dorso Lateral Prefrontal Cortex (DLPFC). The18F-DesmethoxyFallypride(DMFP) radioligand was employed, that is a high affinity receptor-antagonist which competes with endogenous Dopamine neurotransmitters for D2/D3 receptor binding.

Question : To study the modulation of fronto-striatal connectivity by using PET to measure the changes in Dopamine concentration in vivo after repeated blocks of iTBS to the L-DLPFC.

METHODS

The study was conducted on 23 healthy participants, who underwent iTBS sham (control) and verum stimulations on separate days.

The PET scan lasted 120 mins, consisting of 4 iTBS stimulations delivered to the left-DLPFC at 30 mins interval. iTBS consisted of 600 pulses, delivered in bursts (10 burst in 2 secs with 8 secs pause), with a total duration of 180 secs. In **verum condition**, stimulation intensity was set to 90% of individual resting motor threshold (rMT) value.

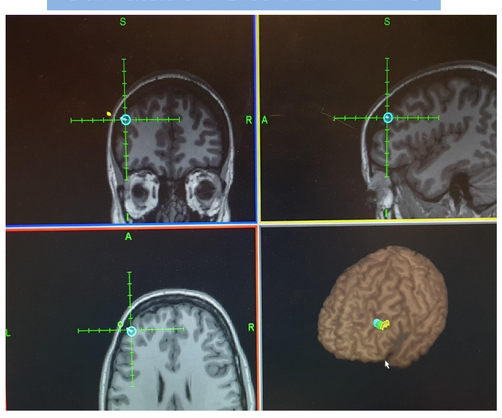
Anatomy T1-scan was collected with 3T Siemens Prisma system. PET dynamic dataset was obtained from Seimens HR+ ECAT scanner.

Image pre-processing procedures were performed using the PMOD brain tool (PMOD technologies, Zurich, Switzerland). Statistical analyses were conducted in SPSS (IBM SPSS Statistics version 25.0).

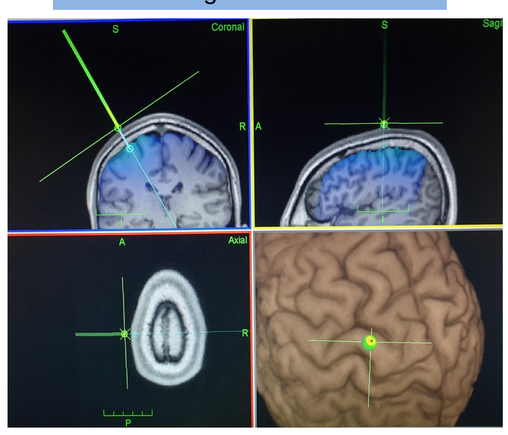
PET data was analyzed using reference methods in which cerebellum was used as the reference region providing distribution volume ratios (DVR) from which binding potentials (BP) was derived and used as a measure of concentration of receptors [3][4].

- A repeated-measure analysis of variance (ANOVA) was conducted on mean **Binding Potentials (BP)** with: *Area* (Nucleus Caudate vs. Putamen), *Sub-area* (left vs. right), *TMS condition* (sham vs. verum), and *Time frame* (1st to 28th) as within-subjects factors.

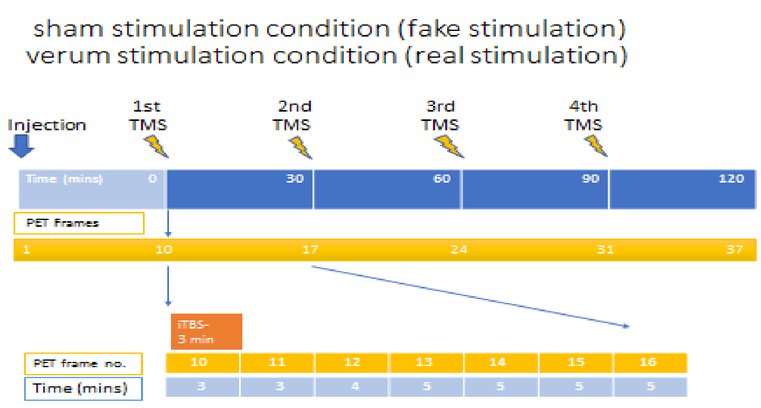
Stimulation Site : L-DLPFC

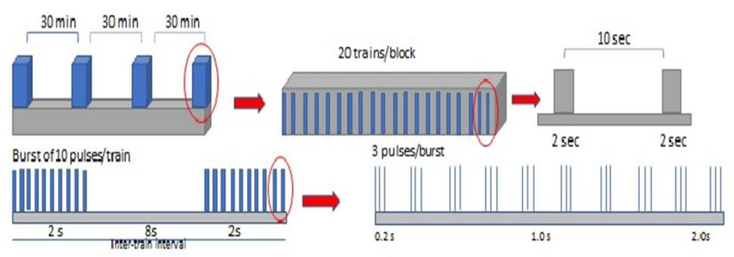


M1- Right hand area



Experiment

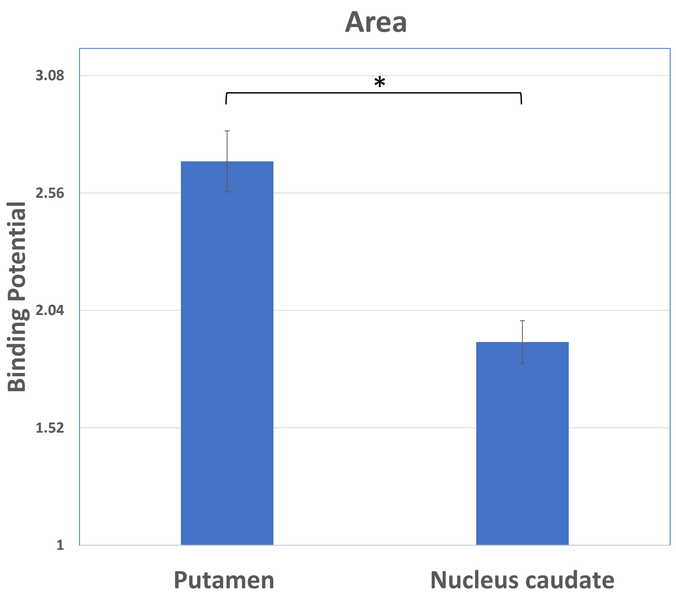


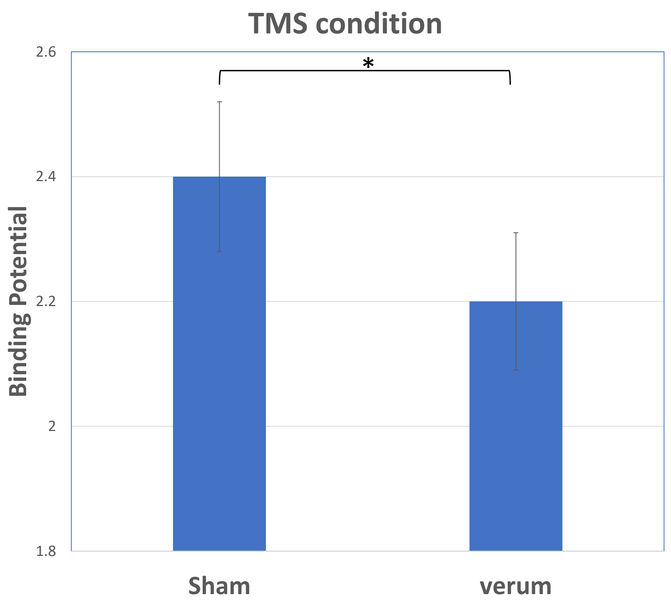


Each block of iTBS delivers 600 pulses in 3 mins, consisting of total 20 trains, with each train delivering burst of 10 pulses in 2 secs, inter train interval of 8 secs. Furthermore, each burst contains 3 pulses, which are delivered together in 0.2 secs,(i.e: 50 Hz stimulation).

RESULTS

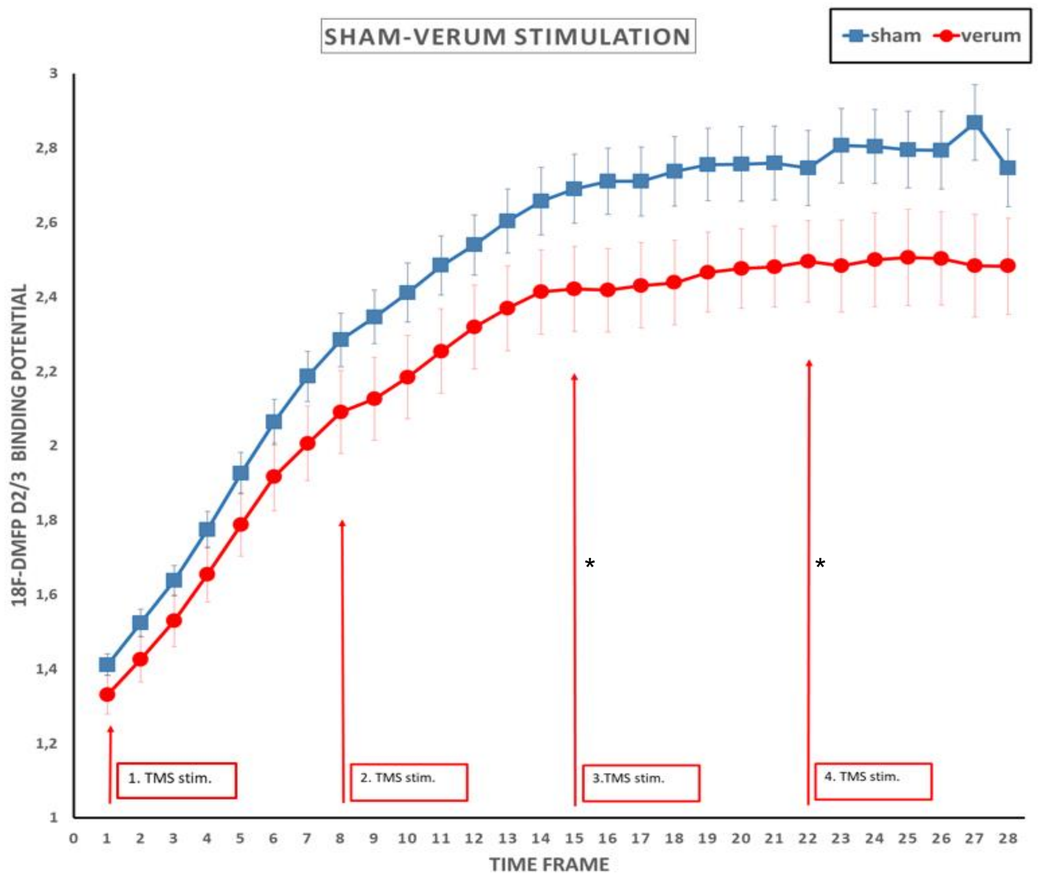
Significant Main effects : **Area**, **TMS condition (sham,verum)**





Significant TMS condition (*sham_verum) x time frame* interaction:

iTBS stimulation of the left DLPFC increased the dopamine release in the striatum areas in the **verum stimulation**, as compared to sham stimulation.



CONCLUSIONS

Results suggest that the short stimulation time iTBS protocol presented in the repeated blocks of short intervals can effectively increase dopaminergic fronto-striatal connectivity. This scheme could prevent the long stimulation protocols and be less painful.

Furthermore, our results demonstrate that repeated iTBS stimulations spaced by short time periods achieve larger effects than one single stimulation. This finding has implications for planning of therapeutic interventions, for example for treatment of major depression.

REFERENCES

Alkhasli I., (2019) 'Modulation of Fronto-Striatal Functional Connectivity Using Transcranial Magnetic Stimulation'. Front Hum Neurosci. 2019 Jun 13;13:190.

Huang, Y. Z., (2005).'Theta burst stimulation of the human motor cortex'. Neuron 45, 201–206.

Ji H. Ko., (2008).'Theta burst stimulation-induced inhibition of dorsolateral prefrontal cortex reveals hemispheric asymmetry in striatal dopamine release during a set-shifting task – a TMS–[11C]raclopride PET study'. Eur J Neurosci.; 28(10): 2147–2155.

Strafella, A. P., (2001). 'Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus'. J. Neurosci. 21, RC157–RC157.

Strafella, A. P.,(2003). 'Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex'. Brain 126, 2609–2615.

Email : ushaik@ukaachen.de