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► **To cite this version:**

L. Lavallé, A. Aleman. rTMS for treatment of negative symptoms in schizophrenia: Clinical effects and neural basis. *L'Encéphale*, 2019, 45, pp.S50 - S51. 10.1016/j.encep.2019.04.002 . hal-03486816

**HAL Id: hal-03486816**

**<https://hal.science/hal-03486816>**

Submitted on 20 Dec 2021

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## Opening lecture

### **rTMS for treatment of negative symptoms in schizophrenia: clinical effects and neural basis**

Traitement des symptômes négatifs de la schizophrénie par rTMS : effets cliniques et fondement neurologique

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Symptoms of schizophrenia, a frequent chronic psychiatric disease, are commonly divided into 2 major categories, positive and negative. Negative symptoms are characterized by marked reductions in goal-directed behavior, which can include reduced initiative, social withdrawal, anhedonia, affective flattening and poverty of speech. No medications have emerged yet to treat effectively negative symptoms [1]. Facing the lack of available efficacious treatment, novel therapeutic solutions are warranted.

Advances in neuroimaging studies have identified that schizophrenia is associated with some impairments in dopamine-dependent frontostriatal interactions implicated in motor, cognitive and motivational control [2]. Indeed, models about apathy involve a lack decision value transmission from ventromedial prefrontal cortex, amygdala and nucleus accubens to the midbrain dopaminergic ascending pathways, resulting in a deficient modulation of goal-directed behavior by the frontostriatal circuits [3]. In a systematic review, Kos et al. [4] revealed similar neural basis of apathy across neurodegenerative disorders, acquired brain injury and psychiatric disorders and confirmed its association with abnormalities in frontal and striatal areas. The ventral tegmental area (VTA) dopaminergic connectivity with prefrontal regions and striatum has been negatively correlated with apathy's level, highlighting its association with deficits in mesocortical dopamine reward pathways [5]. Thus, models about apathy and other negative symptoms showed that frontal-striatal stimulation could normalize neuroplasticity in emotion regulation networks to restore motivated behavior in patients with schizophrenia. One can thus hypothesized that modulating DA subcortical would lead to reduce negative symptoms in schizophrenia. In patients with major depression, it has been reported that repetitive Transcranial Magnetic Stimulation (rTMS) applied over the dorso-lateral prefrontal cortex (DLPFC) inducing dopamine release in the striatum can lead to beneficial clinical outcomes [6]. TMS is a non-invasive brain stimulation technique in which a changing magnetic

field generates a brain electric field, resulting in neural activity or changes in resting potentials. A capacitor charged to a high voltage (up to 8kA) is discharged into the stimulating coil, which in turn produces a magnetic pulse of up to 2 Tesla. Applied over a specific brain region, TMS can modulate the excitability of the stimulated area but also modulated its connectivity within interconnected networks. Altogether, these results suggest that applying rTMS over the DLPFC would reduce apathy and negative symptoms in patients with schizophrenia by modulating subcortical DA release.

Several studies have thus investigated the clinical interest of DLPFC rTMS in patients with negative symptoms of schizophrenia but have produced mixed results. In a meta-analysis including nine randomized sham-controlled trials, Dlabac-de Lange et al 2010 reported a significant superiority of active rTMS over sham to reduce negative symptoms of schizophrenia [7]. In these studies, rTMS was mainly applied over the left DLPFC with high frequencies. In 2015, in a 32-patients double-blind study, a significant improvement of negative symptoms, that remained stable 3 months post-treatment, was observed following 10-Hz rTMS of the bilateral DLPFC during 3 weeks with 2 sessions per day (1 session per side, separated by a 5 hours interval). As observed during pharmacological trials [8], the significant clinical effect was observed when negative symptoms were measured by the Scale for the Assessment of Negative Symptoms (SANS) while no significant effect were reported with the Positive and Negative Syndrome Scale (PANSS) negative symptom subscale. In another study published the same year, 10 Hz rTMS over 3 weeks to the left DLPFC didn't reveal any significant benefits in the treatment of negative symptoms compared to sham stimulation [9]. These latter results could perhaps be explained, in part, by the exclusive use of the PANSS negative symptom subscale as outcome measure and the only left-DLPFC stimulation whereas neuroimaging studies suggest bilateral impairments in negative symptoms. Furthermore, a 3-weeks course of bilateral daily rTMS failed to reveal either substantial improvements in neither the negative symptoms measured by SANS and PANSS nor on depressive symptoms measured by the Calgary Depression Scale for Schizophrenia (CDSS) [10]. The alternating stimulation of the left and the right DLPFC within a same session, in which one brain region can inhibit the activation of the contralateral brain area, provides a potential explanation for this result. More recently, a meta-analysis including 18 studies and taking into account recent negative findings showed a significant beneficial effect (effect size of 0.31) of active frontal cortex rTMS to reduce negative symptoms of schizophrenia [11].

It was suggested that a better understanding of rTMS mechanisms of action and of negative symptoms pathophysiology may help optimize stimulation parameters and explain discrepancies observed between previous clinical studies. In line with this, after 3 weeks of 10-Hz treatment of the bilateral DLPFC, an fMRI analysis during the Tower of London (ToL) task showed a significant increase in both the left posterior cingular cortex (PCC) and the medial PFC (mPFC) activities as well as a significant decrease in the right DLPFC activity. Schizophrenia has been associated with a reduction of the anti-correlation interaction between the default mode network (DMN, including PCC and mPFC) and the DLPFC (which is involved in task-processing) during cognitive tasks. This study highlighted that bilateral DLPFC rTMS reduce the altered interaction between DMN and task-positive network [8] during a planning task. Using <sup>1</sup>H-Magnetic Resonance Spectroscopy (MRS) revealed that bilateral prefrontal TMS induced an increased glutamate and glutamine (Glx) concentration in the left DLPFC, providing a potential explanation for rTMS-induced plasticity by increasing prefrontal cortex metabolism [12]. Immediate effects of one session of non-invasive transcranial stimulation through tDCS or iTBS over the right DLPFC has been studied in a total of 110 healthy participants and measured by MRS in the dorsal striatum (DS), a brain region known to receive glutamatergic

efferece from the DLPFC [13]. This study suggested that DLPFC stimulation can enhance dopaminergic activity in distal brain regions involved in reward and motivation, including DS, VTA, substantia nigra (SN), and nucleus accubens (Nacc) [14]. These results are in line with animal models reporting that prelimbic cortex optogenetic stimulation decreased cocaine-seeking behavior by modulating activity in subcortical reward midbrain circuitry [15] and with studies in patients with cocaine use disorder showing that rTMS over the left DLPFC decreased cocaine-seeking behavior [16]. Based on this observed major contribution of the DLPFC on DA release and goal-oriented behavior, Aleman et al developed a new double-blind sham-controlled study to investigate the clinical effect (Apathy Evaluating Scale) and biological effect (MRS and rs-fMRI) of both right DLPFC intermittent Theta Burst Stimulation (iTBS) and prefrontal tDCS (another noninvasive brain stimulation technique). Future studies may also investigate the effect of brain-derived neurotrophic factor (BDNF) gene polymorphism because it has been suggested that it could influence response to rTMS in schizophrenia [17].

In sum, despite meta-analyses highlighted the superiority of active DLPFC rTMS over sham to decrease negative symptoms of schizophrenia, controversies remain regarding the clinical interest of this intervention. Until now, studies have measured negative symptoms using exclusively the SANS and the PANSS negative symptoms subscale. It would be of interest to conduct studies using other standardized clinical scales to individualize different kind of negative symptoms. In addition, large multicenter trials are needed to better understand the translational neurobiology of rTMS. Future research is needed to investigate and optimize rTMS parameters, especially in evaluating the iTBS use, which seems to be more relevant in medical practice because of its shorter administration duration. Furthermore, future studies should probe the combination of noninvasive neurostimulation (such as rTMS and tDCS) with psychosocial approaches (e.g. behavioral activation). Lastly, combining TMS with brain imaging is an exciting new area of research, promising to help uncover how TMS acts in the brain.

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