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ORIGINAL ARTICLE / ARTICLE ORIGINAL

Therapeutic and neurophysiologic aspects of transcranial magnetic stimulation in schizophrenia

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Abstract The use of repetitive transcranial magnetic stimulation (rTMS) in psychiatry provides the therapeutic field with a new tool. Since its introduction in the mid 1980s, the vast majority of studies have focussed on depression. A growing body of evidence suggests that rTMS is effective in the treatment of depression if dorsolateral prefrontal cortex is stimulated. Less is known about its efficacy in schizophrenia. Neuroimaging investigations in schizophrenia suggest abnormalities in the prefrontal and temporoparietal cortex (TPC), which are correlated with psychopathological dimensions. Based on its modulatory effect, rTMS seems to be a promising tool in exploring cortical excitability and reducing auditory hallucinations (AH) and negative symptoms. Neurophysiologic studies of patients suffering from schizophrenia using rTMS indicate high cortical excitability and a lack of transcallosal inhibition. In the therapeutic field, researches provide encouraging results, even though some studies indicate limited benefits. The most promising therapeutic effect seems to be the capability of rTMS to reduce AH if TPC is targeted using slow-frequency. The current paper aims to provide a review of the literature of the use of rTMS in schizophrenia.

MOTS CLÉS
rTMS ;
Schizophrénie ;
Neurophysiologie ;
Hallucinations auditives ;
Symptômes négatifs

Résumé Depuis le début des années 1990, la stimulation magnétique transcrânienne (TMS) est venue élargir l'arsenal thérapeutique dans le traitement des troubles psychiatriques. De nombreuses études ont montré que des stimulations répétitives (rTMS) de certaines structures corticales modifient la fonction dépendant de ces structures. Sur le plan thérapeutique, la majorité des études se sont focalisées sur la dépression montrant un effet antidépresseur en stimulant le cortex préfrontal dorsolatéral. Cependant, moins d'études se sont intéressées à l'efficacité de la rTMS dans le traitement des troubles schizophréniques. Les études en imagerie de la schizophrénie ont montré l'existence d'anomalies frontales et temporopariétales corrélées à certaines dimensions psychopathologiques. Ainsi, couplé à l'effet modulateur de la rTMS, ces deux structures constituent les principales cibles dans le traitement des symptômes positifs et négatifs. Les études neurophysiologiques de la schizophrénie ont mis en évidence une excitabilité corticale élevée, un déficit de l'inhibition intracorticale et transcallosale. Dans le champ thérapeutique, les résultats actuels montrent que la rTMS a des effets antihallucinatoires en stimulant le cortex pariétotemporal à basse fréquence et des effets sur les symptômes négatifs en stimulant à haute fréquence le cortex préfrontal dorsolatéral. Le but

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de cet article est de faire une revue de la littérature sur l'efficacité de la rTMS dans le traitement des symptômes schizophréniques.

Introduction

Transcranial magnetic stimulation (TMS) was introduced in the mid 1980s as a safe and non-invasive tool to explore neurophysiologic functioning of the brain [4]. In this approach, a coil is held on the scalp; a brief and powerful magnetic current passes undistorted through scalp and skull and produces a secondary electrical field, which induces neural depolarisation. TMS can be applied as a single-pulse or as repetitive pulses (rTMS). Repeated pulses of more than 1 per s (> 1 Hz) correspond to fast TMS while a stimulation frequency of 1 Hz or less is called slow TMS. A major hypothesis in the TMS field is that fast TMS would result in excitatory physiological changes, while slow TMS would have an inhibitory effect [23,42].

During the last decade, rTMS has been widely used as a therapeutic tool in depression. Indeed, there are numerous data indicating that rTMS is effective in the treatment of depression [39,43,44] even though meta analyses do not indicate high rates of response because of small-size effects [7,45]. Moreover, some studies showed that rTMS has antidepressant properties that may be as potent as electroconvulsive therapy in non-delusional depressive disorders [12,29]. Fewer studies have investigated the therapeutic effect of rTMS in mania [26,38,48,61], post traumatic stress disorders [10,27,59], and obsessive compulsive disorders [2,25,63].

In the field of schizophrenia, the experience is still limited and the efficacy of rTMS remains matter of debate. This article will review rTMS application as a neurophysiologic and therapeutic tool in schizophrenia.

Cortical excitability in schizophrenia

Methodological considerations: a reminder

Recently, a number of TMS techniques have been used to explore cortical excitability in psychiatric diseases. Three main paradigms are useful for this purpose:

- single-pulse can be applied to the motor cortex to determine the motor threshold (MT), which is defined as the lowest TMS single-pulse intensity that produces a motor evoked potential (MEP) from the target muscle;
- if single-pulse TMS is applied to the primary motor cortex at supra-threshold intensity, it produces a silent period (SP), which corresponds to the suppression of EMG activity of the target muscle after MEP induction;
- single TMS pulses of increased intensity applied to the motor cortex can be used to generate input–output curves that provide a measure of excitatory feedback to corticospinal efferent output.

Two other paradigms have been developed to assess inhibitory function in the brain. Both use paired-pulseTMS (ppTMS) with two different stimulus characteristics:

- the first paradigm is labelled on as long-interval cortical inhibition (LICI) and involves two successive supra-threshold stimuli. The first stimulus inhibits the MEP to the second stimulus if the latter is applied within a 50-200 ms interval. This paradigm allows the study of intracortical inhibition when two supra-threshold stimuli are applied with a long interstimulus interval (ISI);
- the second paradigm aims at evaluating intracortical excitability. A first conditioning sub-threshold stimulus is followed at a variable interval by a second supra-threshold stimulus. The results are highly dependent on both the intensity of the conditioning stimulus and the ISI. Short ISIs (1–4 ms) have an inhibitory effect on intracortical activity while large ISIs (> 4 ms) have an excitatory effect. Paired-pulse stimulation of the human motor cortex results in discharges in the corticospinal pathway. These consist of two components: the earlier component ("Direct-" or "D-wave") is produced by direct axonal stimulation; the second component consists of several waves ("Indirect-" or "I-waves") that follow the D-wave. These result from cortical interneuronal activation and depend on GABA activity.

Using these paradigms, it has been demonstrated that the modulatory effects of rTMS on cortical excitability depend on stimulation frequency. Low frequency (1 Hz) produces a decrease in cortical excitability, while high-frequency (> 1 Hz) produces the opposite effect [52,56,58].

Cortical excitability in schizophrenia

Motor deficits are frequently encountered in schizophrenics. A number of studies have suggested that schizophrenia might involve functional abnormalities of cortical inhibitory networks. Recent studies demonstrated a lack of cortical inhibition in schizophrenics but other studies failed to replicate these results.

The first study of cortical excitability using rTMS in schizophrenics [54] found a shorter MEP latency without any MT alteration in nine medication-free schizophrenic subjects who were compared to nine healthy controls. This suggests that schizophrenics would have a lack of cortical inhibition of motor response. In contrast, Abanabel et al. [1] reported significantly lower MTs but normal MEP latencies in 10 medicated schizophrenics who were compared with depressed patients and healthy controls. Eichhammer et al. [15] studied the cortical excitability using paired-pulse and single-pulse TMS to determine MTs in 21 drug-naïve first-episode schizophrenics compared to 21 sex- and age-matched healthy controls. They found significantly lower MTs but no