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The value of navigation-guided rTMS for the treatment of depression: An illustrative case

Un cas illustratif de l'intérêt de la SMTr guidée par neuronavigation dans le traitement de la dépression

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Summary Repetitive transcranial magnetic stimulation (rTMS) of the prefrontal cortex has been thought to have great potential to treat refractory depression since the first studies published ten years ago. However, one of the potential limitations of rTMS is the poor definition of the localization of the prefrontal cortical target, which is based on a rather simplistic anatomical approach, i.e., 5 cm anterior to the primary motor cortical representation of the hand. This "standard procedure" does not take into consideration interindividual variations in brain morphology. We report the case of a 40-year-old woman who underwent two weeks of 10 Hz-rTMS for the treatment of a major, drug-resistant depressive episode. The rTMS target was determined with the "standard procedure" for the first week and with a dedicated navigation system as the left Brodmann area 46 for the second week. The clinical assessment of antidepressant effects was performed before and after each week of stimulation. Following the first week of stimulation, the patient improved, in particular regarding speech production. Using the navigation system, the location of the target stimulated during the first week was found to correspond to Broca's area, and not to the prefrontal area as intended. Antidepressant effects were more marked after the second week of navigated rTMS. In the present case, the prefrontal target was situated 8.3 cm anterior to hand motor cortex. This illustrates that the

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“standard procedure” may inaccurately target the prefrontal cortex, although resulting in antidepressant-like effects. The use of navigation systems should limit the variability of the results reported so far in the treatment of depression by rTMS.

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Résumé Le potentiel de la stimulation magnétique transcrânienne répétitive (SMTr) du cortex préfrontal pour traiter les dépressions résistantes est connu depuis dix ans. Cependant, une des limites de la SMTr est la définition anatomique simpliste de la cible préfrontale, 5 cm en avant de la représentation corticale motrice de la main. En effet, cette « procédure standard » ne prend pas en compte les variations interindividuelles de la morphologie du cerveau. Nous rapportons le cas d’une femme de 40 ans qui bénéficia du traitement d’un épisode de dépression majeure résistante par deux semaines de séances quotidiennes de SMTr à 10 Hz. La cible préfrontale fut déterminée par la « procédure standard » pour la première semaine de traitement et dans l’aire 46 de Brodmann par un système de navigation pour la seconde semaine de traitement. Les effets antidépresseurs furent évalués cliniquement avant et après chaque semaine de stimulation. La patiente s’améliora à la fin de la première semaine, notamment sur le plan de la parole. Or la cible stimulée lors de cette première semaine fut localisée par le système de navigation dans l’aire de Broca et non dans le cortex préfrontal comme attendu. Les effets antidépresseurs furent encore plus marqués après la seconde semaine de stimulation. Chez cette patiente, la cible préfrontale était située 8,3 cm en avant du cortex moteur de la main. Ce cas illustre le fait que la « procédure standard » de localisation de la cible préfrontale peut être erronée, même si des effets possiblement antidépresseurs sont obtenus. Le guidage par navigation est susceptible de réduire la variabilité des résultats de la SMTr par rapport à ce qui a été publié à ce jour dans le traitement de la dépression.

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Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non invasive and painless technique of focal brain stimulation that was proposed for therapeutic application in major depression [8,33]. A number of functional neuroimaging studies suggested that a reduced activity of the left dorso-lateral prefrontal cortex (DLPFC), mostly corresponding to Brodmann areas (BAs) 9 and 46, was implicated in the pathophysiology of depression [2,28]. Therefore, reactivating this region by applying rTMS at excitatory frequencies (more than 1 Hz) was proposed as therapy for depressive disorders. The DLPFC was reported to be situated 5 cm anterior to the primary motor cortex [33]. This “standard procedure” was applied in nearly all rTMS studies performed in patients with depression for ten years. However, a previous study, using MRI-based neuronavigation, suggested that this “standard procedure” was not accurate, given important interindividual variations in cortex morphology and revealed that the 5 cm-measure was probably too short [12]. In this previous study, the stimulation site determined with the “standard procedure” was found to correspond to BA 6 (premotor cortex) or BA 8 (frontal eye field) in 68% of the cases and to BA 9 (DLPFC) in only 32% of the cases. The inaccuracy of coil placement, among other sources of variability (number of pulses, type of depressive disorder...), may have contributed to the wide range of rTMS responses reported so far in depressive patients [3,22,26,27,37]. In the present case, we confirm that the “standard procedure” can lead to the stimulation of an unexpected cortical region, i.e. the Broca’s area, instead of the DLPFC as intended. In addition, this case suggests that antidepressant effects or antidepressant-like

effects can result from the stimulation of the left inferior frontal gyrus.

Patient and methods

A 40-year-old right-handed woman was addressed to our laboratory for the treatment of a major, drug-resistant depressive episode, which was not in the context of a bipolar disorder and was not associated with comorbid anxiety disturbances. The diagnosis of a first single episode of major depression was established by a trained psychiatrist according to the DSM-IV criteria. The patient was first treated by venlafaxine up to 300 mg/day for four months and then she was treated with clomipramine with monitored plasma levels for four months. Lithium was associated with clomipramine during the last two months and fluoxetine was added during the last month. Both antidepressants and lithium were progressively stopped three weeks before starting the rTMS procedure. The rTMS procedure was performed with a MagPro X100 MagOption stimulator (Medtronic Functional Diagnostics, Skovlunde, Denmark). It consisted of 20 rTMS trains of 10 s (intertrain intervals: 50 s) with a frequency of 10 Hz and a total duration time of 20 min (2000 pulses per session) each weekday for two weeks. The intensity of stimulation was set at 90% of the rest motor threshold, which was defined as the minimal intensity that produced motor evoked potentials of at least 50 μ V in the *abductor pollicis brevis* (APB) muscle for five out of ten stimulations [41].

For the first week of stimulation, the location of the left prefrontal target was determined using the “standard procedure” of coil placement (5 cm anterior to the motor hot

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