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REVIEW

The value of neuronavigated rTMS for the treatment of depression

L’intérêt de la stimulation magnétique transcrânienne répétitive neuronaviguée pour le traitement de la dépression

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Summary

Repetitive transcranial magnetic stimulation (rTMS) has been increasingly evaluated as a therapeutic tool for the treatment of depression, using various stimulation parameters and protocols. Heterogeneous results have been reported with regard to clinical outcome, at least partly due to the variety of procedures for coil placement above the desired site of stimulation. This article reviews the strategies for coil positioning in the treatment of depression. Considering preliminary clinical evidence, neuronavigated rTMS appears desirable to treat depression, compared to the standard targeting procedure (5 cm anterior to the motor cortex). Coil positioning strategy might improve in the future by taking into consideration the individual abnormalities revealed by functional neuroimaging data.

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MOTS CLÉS

Ciblage ; Dépression ; Imagerie par resonance magnétique ;

Résumé

La stimulation magnétique transcrânienne répétitive (SMTr) est de plus en plus étudiée comme outil thérapeutique dans le traitement de la dépression, utilisant divers paramètres ou protocoles de stimulation. L’hétérogénéité des résultats cliniques rapportés pourrait être due, au moins en partie, aux différentes stratégies utilisées pour placer la bobine au niveau du site de stimulation désiré. Cet article décrit et compare l’intérêt de ces différentes stratégies dans le traitement de la dépression. Selon les premiers résultats obtenus, l’utilisation de la navigation apparaît préférable à la procédure standard de SMTr (ciblage effectué 5 cm en avant du cortex moteur). La stratégie de placement de la bobine

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Introduction

Transcranial magnetic stimulation (TMS) was developed by Barker et al. in the early 1980s [4] and was rapidly introduced as a valuable tool in clinical neurology [5, 49]. TMS enables a non-invasive depolarization of cortical networks and does not need local anesthesia or narcosis during its application. Advances in the field of electronics in the early 90s made repetitive transcranial magnetic stimulation (rTMS) possible. This technical development made magnetic stimulation able to induce changes in cortical excitability for several minutes to hours. In analogy to experimental models [33], these after-effects likely correspond to long-term potentiation (LTP)- and long-term depression (LTD)-like mechanisms. Pioneering studies on motor cortex (M1) showed that rTMS delivered at low frequencies (≤ 1 Hz) for several minutes was able to transiently reduce the amplitude of motor evoked potentials (MEP), thus reflecting a transitory decrease in cortical excitability [7], whereas short trains at high frequencies (≥ 5 Hz) increased MEP size [39]. Neuromodulatory effects of rTMS appear to depend on the type of coil, pulse waveform, current direction, orientation and position of the coil over the scalp, intensity and frequency of stimulation, train length, intertrain interval, and total number of magnetic pulses delivered in the stimulation session. In the last 15 years, rTMS has been used in psychiatry and neurology to explore pathophysiological aspects and neurobiological dynamics of mental processes and to modulate neuronal activity in intracortical circuitry in order to treat brain disorders. In particular, the therapeutic value of rTMS has been evaluated in depression. The aims were to “normalize” the activity of the left DLPFC by means of high-frequency excitatory rTMS, or to reduce the activity of the right DLPFC by means of low-frequency inhibitory rTMS in order to restore the interhemispheric balance of DLPFC activity. The site of stimulation for antidepressant rTMS was targeted over anatomical landmarks, e.g. the vertex [23, 26], without taking into account the functional neuroanatomy of depression. Subsequent positron emission tomography (PET) and single photon emission tomography (SPECT) studies revealed a correlation between the depressive state and a reduction of glucose uptake (rCMRGlu) and regional cerebral blood flow (rCBF) in a region of the left DLPFC (reviews: [9, 31]). This area became a candidate target for rTMS in the treatment of depression. The aims were to “normalize” the activity of the left DLPFC by means of high-frequency excitatory rTMS, or to reduce the activity of the right DLPFC by means of low-frequency inhibitory rTMS in order to restore the interhemispheric balance of DLPFC activity. The site of stimulation for antidepressant rTMS was defined on the assumption that the DLPFC is situated 5 cm anterior to M1hand (so called “5-cm rule”), according to Talairach atlas coordinates [47]. In rTMS practice, the location of M1hand is determined by visual inspection or electromyographic recording of the greatest motor response of the abductor pollicis brevis muscle. This coil positioning strategy, used in the very first studies that reported beneficial effects of rTMS [13, 38], became the standard procedure for reaching the DLPFC in almost all rTMS trials. However, this method does not take into account inter-individual anatomical variability, and was demonstrated to lack anatomical precision [20]. It has been therefore hypothesized that the anatomical imprecision of the individual rTMS target site in therapeutic...
studies using the "5-cm rule" could partly explain the considerable heterogeneity of antidepressant efficacy of rTMS that was reported.

In order to overcome the inaccuracy of anatomical rTMS targeting, various strategies of coil positioning were introduced [22]. A simple method was to use the international 10–20 system for EEG electrode positioning. For instance, Grossheinrich et al. studied the effects of a new rTMS paradigm called theta-burst stimulation (TBS) delivered to medial and dorsolateral regions of the PFC with this approach [16]. It was shown that this strategy reached the DLPFC more reliably than the "5-cm rule" [21], but no clinical data have been yet provided to support this procedure in the treatment of depression. Other original strategies in coil positioning paralleled the increasing use of magnetic resonance imaging (MRI) techniques. For instance, scalp sites corresponding to specific cortical areas were identified by placing magnetic contrast-giving markers (e.g. vitamin E, nifedipine tbs.) for MRI examination [48]. However, this did not achieve broader implementation in clinical trials. Finally, frameless stereotaxic neuronavigation (FSN), according to various modalities, has been proven to offer an accurate and comfortable alternative for coil positioning.

**FSN in real time**

In 1997, the Massachusetts Institute of technology (MIT) developed a new modality of FSN to be used for focusing TMS to perform functional mapping of motor cortical areas [10]. FSN is based on classical stereotaxy, i.e., defined according to anatomical landmarks of the head's surface. This method allows the magnetic coil to be placed over a chosen cortical area in the virtual space of MRI data. A decisive advantage of this method is that the subject's head and the coil are not attached to a rigid stereotactic frame while navigating. Furthermore, FSN can be used during stimulation, thus providing a real-time monitoring of the coil position with respect to the head. During the stimulation, the stimulated brain area can be visualized on a computer screen. Two coordinate systems in the 3D space are transferred to a common reference system. These coordinate systems are:

- the brain coordinates in the MRI scans and;
- the head and coil coordinates monitored by a detector (e.g. camera/video) system.

MRI scans register the brain and the head surface with their coordinates in one reference system. FSN allows the visualization of high-resolution T1-weighted MRI slices in all three axes together with a 3D reconstruction of the head's surface (Fig. 1). The second registration system — the optical tracker — comprises two or three cameras or detectors which are mounted aligned on a bar. They detect the positions of several emitters (e.g. infrared light emitting diodes [LED] or reflectors) and calculate their spatial relationships. When at least three emitters are fixed to the head, the tracking system calculates the actual head position in space in all six degrees of freedom. These are the translations in the directions x, y, z and the rotations around these axes.

Three more emitters are fixed to a reference frame on the magnetic coil in order to detect its position by the same detectors in all six degrees of freedom. Accordingly, the head’s surface coordinates and the coil coordinates are registered in a common reference system. The head’s surface coordinates, measured by the optical tracking system, and defined in the MRI picture, serve as the interface for both reference systems. Both reference systems have to be coregistered by a referencing procedure. Several anatomical landmarks, e.g. nose rims, nasion or tragus, are defined on the surface of the 3D reconstruction of the head. The same points are registered on the subject’s head with an optically tracked pointer (Fig. 2). Both coordinate systems are aligned to each other using a transformation matrix that is generated by this referencing procedure. In the resulting common reference system, the coil position is determined in relation to the cortex and visualized on the computer screen. The relative positions of the head and the coil are registered in real-time during the stimulation. The spatial resolution of this method is limited by the precision of the matching procedure by approximately 1 to 3 mm and the MRI voxel size by 1 mm³ [45]. When used in a standard TMS-experimental setting, the accuracy of FSN is in the range of a few millimeters [45]. The peak of the electric field, as calculated for the magnetic coil, is below the center of the coil in the case of the figure-of-eight coil. In a protocol including iterative rTMS sessions, such as for the treatment of depression, it is crucial to monitor the position of the coil (including orientation and angle) to stimulate the same site during and between the sessions, because the head is not fixed and can move. The preparation of a navigated rTMS session, including the referencing procedure, takes about 10 minutes for a trained investigator.

**Navigated- vs non-navigated rTMS in depression**

Only a few studies have investigated whether neuronavigated rTMS would yield better clinical results compared to the standard procedure using the "5-cm rule". The first PET- and MRI-guided rTMS study using a FSN system was performed in a series of 25 depressed patients [19]. The DLPFC was localized on individual MRI data, according to structural brain anatomy. Then, the active rTMS was targeted over the right or left DLPFC area if PET scan showed lateralized hypometabolism within this region. In the absence of asymmetry in prefrontal metabolism, rTMS was performed above the left DLPFC according to neuronavigation. A third group of patients underwent a sham procedure. The patients who received active navigated rTMS delivered at high frequency (15 Hz) for 15 days over the hypometabolic DLPFC improved better than the patients who received sham rTMS (above the parietal-occipital transition). However, antidepressant effects were similar in all the patients who received active rTMS, and these positive effects (i.e. symptom amelioration of about 30% compared to baseline ratings) were independent of the metabolic state. Concerning antidepressant properties, an advantage of rTMS navigated above the PET-detected hypometabolic area of the DLPFC was not observed compared to an FSN-guided, anatomically oriented rTMS above the left DLPFC. This study showed that navigated rTMS could improve depressive symptoms but failed to demonstrate the superiority of a navigated procedure based
on PET assessment. However, the sample size was small, and the study did not assess navigated versus non-navigated active rTMS in the same patients.

A recent study with a similar design reported somewhat different results. Forty-eight patients with medication-resistant major depression were randomized to active rTMS over the most hypometabolic prefrontal area as determined on PET assessment, to active rTMS using the standard procedure, or to sham rTMS [36]. One session of 10 Hz navigated rTMS was daily administered for two weeks. The treatment had antidepressant efficacy (as rated by the Montgomery Asberg Rating Scale for Depression [MADRS]) only in patients who received active rTMS over the left DLPFC (defined as Brodmann areas [BA] 9 and 46), whatever the randomization group (PET-guided or standard). When the active stimulation (either PET-guided or standard rTMS) was delivered outside left BA 9 and 46, the patients did not benefit from the treatment. The sham procedure was also inefficacious. This study confirmed that the site of stimulation for antidepressant rTMS did not correspond to the prefrontal region of predominant hypometabolism. Although rTMS was not reliably guided by PET data, this study strongly supported the value of navigated rTMS to stimulate left BA 9 and 46 defined on individual MRI, because this region was not always accurately targeted by the standard procedure using the “5-cm rule”.

This was also demonstrated by Lefaucheur et al. using FSN in a depressed patient [30]. In this patient, the standard procedure failed to reach the left DLPFC, but targeted the anterior part of the Broca’s area (BA 45). After stimulating this target at high frequency (10 Hz), antidepressant effects were obtained, but less pronounced than after positioning the coil using FSN over the left BA 46. This optimal site of stimulation was located 8.3 cm (and not 5 cm) anterior to M1Hand.

The value of navigated rTMS was also recently assessed in a series of 51 patients with medication-resistant major depression who were randomized to MRI-guided versus standard rTMS [12]. Navigated rTMS was delivered at high frequency (10 Hz) over a cortical area anatomically defined between the center of the left BA 9 and the junction of the left BA 9 and 46 (i.e. the DLPFC [41], corresponding to the coordinates $x = -45$, $y = 45$, $z = 35$ in the Talairach atlas [47]). The stimulated area mainly included the anterior portion of BA 9 and the dorsal part of BA 46. After 4 weeks of stimulation, MRI-guided rTMS produced greater antidepressant effects (reduction in MADRS score) than the standard procedure using the “5-cm rule”.

Figure 1 Screen shot from the neuronavigator obtained while performing neuronavigated frameless stereotaxic repetitive transcranial magnetic stimulation (rTMS). It shows a real-time visualization during rTMS in the three axes (axial, coronal, sagittal). The right inferior image is a 3D-surface rendered MRI of the subject’s head, which is created by the navigator from the MRI data set. The dotted line represents a perpendicular line through the center of the figure-eight coil, where the peak of the magnetic field is estimated. The stimulation focus is located in this case above the left dorsolateral prefrontal cortex.
Figure 2 A. Subject’s nasion is tipped with an optically tracked pointer (1) in order to perform the co-registration between MRI landmarks and the same landmarks in the real head prior to running the referencing procedure. (2) optical-tracking-system, based on two or three cameras or detectors that are mounted aligned on a bar. This system detects the positions of several emitters and calculates their spatial relationship. (3) Workstation which allows the visualization of high resolution T1-weighted MRI slices (in all three axes together with a 3D reconstruction) and of the peak magnetic field of the coil in the MRI space. B. The examiner can visually control the precision of the referencing (matching) procedure using the optically tracked pointer and can target online the desired stimulation site. A dynamic reference frame with three emitters (light emitting diodes [LED]) is attached to the subject’s head (4). C. Stimulation of the left dorsolateral prefrontal cortex (DLPFC) using a figure-of-eight coil with three LED mounted on it (5).

Finally, the efficacy of navigated rTMS, delivered at low frequency (1 Hz) for 3 weeks over the right DLPFC, was assessed in an open study of 11 patients with drug-resistant bipolar depression [8]. A statistically significant improvement was observed on various depression scales (including MADRS), including six responders (reduction of the Hamilton Depression Rating Scale [HAM-D] score of more than 50%). No switch to mania was observed. However, this study lacked a controlled group.

Outlook

At present, the use of FSN for rTMS studies in cognitive neuroscience is gaining relevance, since it allows rTMS effects to be investigated on specifically targeted brain regions according to individual anatomy. Examples include rTMS effects on temporoparietal regions involved in language [2,3] and prefrontoparietal regions involved in working memory processing [17] or social functions [25]. In particular, FSN can help to investigate non-motor cortical regions on which rTMS effects could differ from those reported on motor cortex.

Preliminary clinical results, as well as theoretical considerations, also support the use of navigation systems to guide rTMS targeting for the treatment of depression. Antidepressant rTMS benefited from structural MRI rather than from PET guidance in the first published studies, but other functional imaging procedures, like functional MRI (fMRI), have not been yet tested in this domain. Several studies reported activation changes in medial and dorsolateral regions of the PFC in depressed patients [9,11,14,31,50]. Actually, therapeutic efficacy of rTMS can result from two mechanisms, either restoring a normal processing or interfering with an aberrant processing in altered brain regions. To identify these regions of abnormal brain activation in individuals and then to use this information for rTMS targeting may be a valuable strategy of which the feasibility was previously demonstrated in schizophrenic patients [44].

Navigated rTMS likely has advantage compared to the standard procedure ("5-cm rule") to target the relevant cortical area to treat depression on an individual basis. Navigation offers the possibility to position the coil precisely over a specific cortical region, defined anatomically or functionally and to ensure that the coil is maintained over this region with constant orientation and angle during the session and with an optimal reproducibility between the sessions. The main disadvantage of a navigated procedure is the cost of the FSN systems. In addition, validated criteria are lacking to define the dysfunctional brain regions or circuitry in indi-
viduals, and eventually promising candidate cortical site(s) over which the rTMS coil should be positioned. Finally, other aspects, such as genetic factors, may affect the individual response to rTMS, as recently demonstrated regarding the influence of the polymorphism of neurotrophic factors on the motor effects of rTMS [6]. The superiority of neuronavigated antidepressant rTMS still remains to be demonstrated in large-scale clinical studies. Nevertheless, it seems mandatory that future antidepressant rTMS trials should be based on image-guided cortical stimulation using dedicated navigation systems.

Conflicts of interest

None.

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