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Transcranial Magnetic Stimulation (TMS) in tinnitus patients

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Abstract. *Transcranial Magnetic Stimulation (TMS) in tinnitus patients.* The objective of this paper is to present Transcranial Magnetic Stimulation (TMS), a new and highly promising technique in tinnitus modulation. We conducted a Pubmed and Web of Science search using the words 'Tinnitus', 'TMS' and 'Transcranial Magnetic Stimulation'. We report on the most relevant studies relating to the effects and stimulation parameters of TMS in tinnitus patients.
It has already proved possible to reduce tinnitus using TMS and rTMS in selected patient populations with specific stimulation parameters. Intrinsic and extrinsic factors were shown to determine the amount of tinnitus reduction. Though many studies point out that tinnitus reduction can be obtained using TMS, a lot of questions still remain concerning stimulation parameters and optimal patient selection.

Introduction

Presentation of the TMS unit

a) General facts

During Transcranial Magnetic Stimulation (TMS), strong impulses of magnetic fields up to 4 Tesla are applied to cortical tissues by means of a coil placed on the patient's skull (Figure 1).

TMS was introduced in neuroscientific studies to investigate physiological functions of the brain. The possibility of modulating abnormal cortical excitability using repetitive TMS (rTMS) has already been demonstrated in several pathologies, including writer's cramp,[1] auditory hallucinations,[2,3] depression[4-8] and obsessive compulsive disorders.[9,10]

Figure 1
Hand-held coil on patient's skull

b) The TMS device

The TMS device consists of two components: a high-voltage, high-current discharge system (Figure 2) and a current-carrying coil (Figures 3,4) that enables the delivery of magnetic pulsed fields. The maximal magnetic intensity that can be produced by the device is 4 Tesla.

The coils consist of a wound copper cord contained in a plastic coating. The two most widely used coils are the circular loop (Figure 3) and the figure-eight-shaped coil (Figure 4). The shape of the coils directly influences the current distribution. Computer models were used to define the optimal coil properties to ensure focal stimulation.[11] A circular coil parallel to the head has been shown to deliver rather non-focal stimuli, while a circular coil perpendicular to the head could provide more focal stimulation. The localisation of the stimulation was

Figure 2
High-voltage current discharge

shown to be even more precise using a figure-eight coil parallel to the head, and this figure-eight shape appeared to be the best choice for general focal purposes. Focality increased as coil diameter decreased. On the other hand, the current necessary to stimulate was shown to be negatively related to the coil diameter, resulting in very inefficient stimulations when the figure-eight coils were too small.

c) Sham stimulation

Sham stimulation in tinnitus can be performed in five different ways: 1) using a sham coil, 2) using a real coil with stimulation of non-auditory brain areas, 3) using a real coil tilted 45° to the skull surface, 4) using a real coil tilted 90° to the skull surface and 5) using two coils simultaneously: a sham coil applied to the patient's skull and a real coil tilted 90° to the sham coil. All five sham procedures are questionable.

A sham coil produces click sounds without any scalp sensations, and patients can therefore easily differentiate between verum and sham stimulation. The stimulation of non-auditory brain areas involves the potential modulation of other cortical tinnitus pathways and this detracts from the adequacy of this method. The tilted positioning of the coil could decrease the induced magnetic field in the brain, but no complete absence of electric currents in the cortex could be measured using this method.[12] The 45° procedure ensures a remaining tingling sensation on the patient's skin but probably still induces an intracranial magnetic current. The 90° procedure, on the other hand, prevents magnetic stimulation but also fails to generate a tingling sensation. Moreover, patients could deduce from the tilted coil position that they are receiving sham stimulation. This problem can be overcome by the use of a real coil tilted 90° to a sham coil. The real coil would assure the generation of clicking sounds. The sham coil would guarantee a sensation of regular coil placement on the patient's skull and also stop the magnetic field induced by the real coil from reaching the brain. However, this method again fails to produce the tingling sensations on the skin which are characteristic of real stimulation.

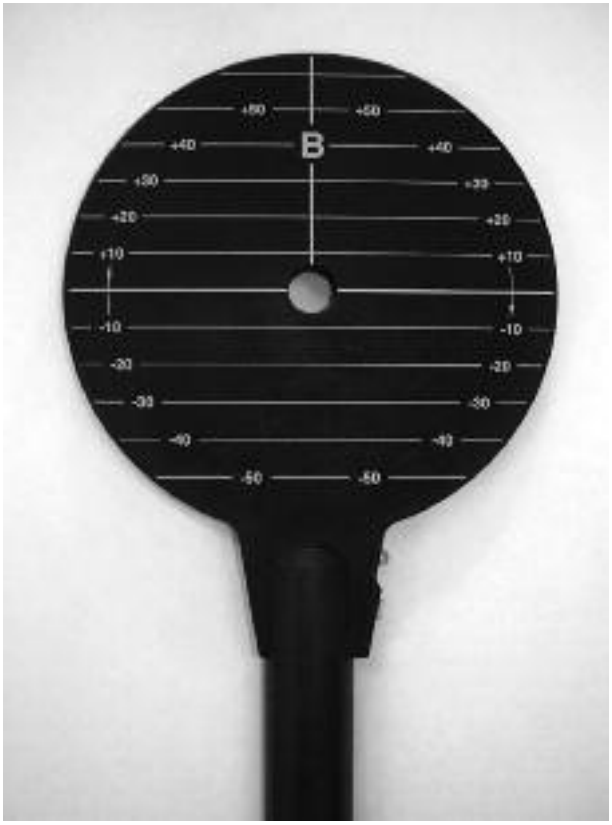

Figure 3
Circular coil

Figure 4
Figure-eight coil

d) Firing modulus

The pulses can be delivered in two different firing moduli: tonic and burst. In tonic stimulation (Figure 5), pulses are fired successively at fixed intervals. In other words, tonic stimulation is defined by the frequency and the intensity of the pulses. In burst stimulation (Figure 6), pulses are merged into "trains". Each train consists of a defined number of pulses separated by a fixed interval. In this way, more than by intensity and frequency alone, burst stimulation is defined by the number of trains, the number of pulses in each train, the time interval between the pulses in each train and the time interval between the separate trains.

Action mechanisms of TMS

When applied to the skull, the electric current provided by the coils generates a magnetic field that can induce an electric current in the brain.[13] Depending on the stimulation parameters, this induced electrical current can then temporarily excite or inhibit neuronal activity.[14]

One could imagine the vibrations or auditory clicks caused by the TMS coil to be responsible for the effects of TMS. However, subdural or epidural electrodes could provide benefits in tinnitus patients similar to those induced by TMS without any auditory stimulus or scalp sensory sensation.[15] Additionally, if the sound of the clicks were responsible for the experienced reduction in tinnitus, one would also expect tinnitus reduction when stimulating with a tilted coil. This would contradict the results previously cited. It is therefore improbable that skin vibrations or auditory clicks contribute to the effect resulting from TMS.

Physiology

The physiology underlying the effects of TMS has been investigated using felines, rodents and nonhuman primates, and is extensively discussed in a review by Wagner *et al*.[16]

In anaesthetised cats, 2-deoxyglucose uptake labelling

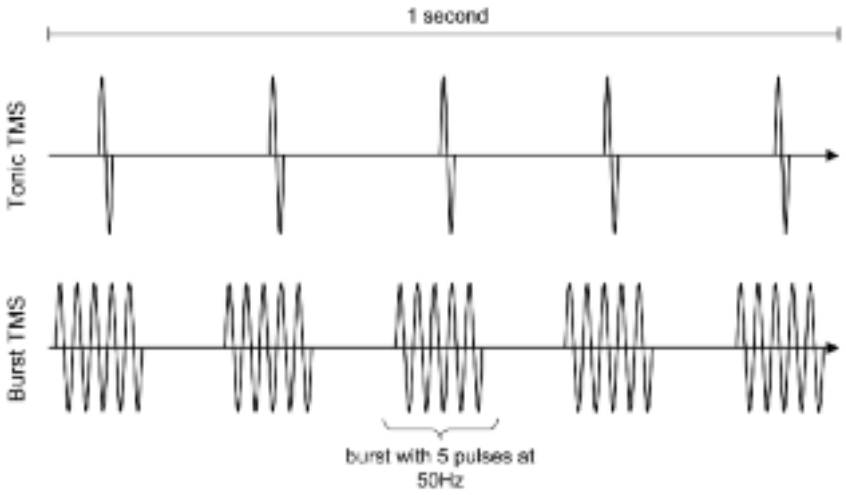

Figure 5
Schematic representation of tonic and burst TMS

Burst and tonic TMS: 5 Hz burst TMS consists of 5 bursts per second, each burst consisting of 5 rapid TMS pulses at, for example, 50 Hz. Five Hz tonic TMS consists of 5 tonic pulses per second.

Figure 6
Schematic representation of burst TMS

was used to image network effects of cortical rTMS stimulation.[17] In this way, the impact of rTMS was shown to reach a whole network of structures connected to the primary site of application. These remote effects were also demonstrated in the visual cortex in a study of rTMS in 6 volunteers.[18]

In addition to this connection to the primary site of application, the attenuating effect of the human skull and the rapid decline in magnetic field with increasing distance from the coil must be taken into account when considering the impact of the stimulation. In a study by Roth *et al*.,[19] the magnitude of the induced electric field was shown to decrease to about 75% of the maximum field within 10 mm.

2-deoxyglucose uptake labelling was also used to demonstrate neuromodulation induced by low or high frequency rTMS.[20] An increase and decrease in local glucose use was found after high- and low-frequency rTMS respectively. These effects were demonstrated in the anaesthetised animal, thereby ruling out behavioural and non-specific reasons for the differential impact of the stimulation.

However, the question has been raised of whether animal studies can be extrapolated for human application. Weissman *et al*.[21] succeeded in demonstrating a decline in the magnitude of the induced field by a ratio of at least 5 to 1 when using a small rodent brain instead of a human brain. One must therefore adopt a cautious approach to interpreting animal studies for human application. Moreover, the implementation of very small coils in animal studies has been advised in order to maintain the coil to skull ratio.[22]

Effects on neuronal activity

Wang *et al*.[23] demonstrated a non-linear increase in neuronal response to TMS at stimulation frequencies ranging from 1 to 10 Hz. Another animal study in guinea pigs found a decreased firing rate in the thalamus after low-frequency (1 Hz) electrical stimulation of the auditory cortex, with an inhibitory effect for stimulus frequencies up to 10 Hz.[24] Suppressive effects were found for both low (1Hz) and high (10Hz) frequencies, but 1 Hz stimulation was shown to be more suppressive than higher frequencies. The capacity of low- and high-frequency TMS to modulate cortical activity was again demonstrated by De Ridder *et al*.[25] in tinnitus patients. Tinnitus reduction after low- or high-frequency TMS was found to depend on the duration of the tinnitus.

Effects of TMS and rTMS in tinnitus

As mentioned above, the possibility of modulating abnormal cortical excitability with rTMS has already been studied for several pathologies, including writer's cramp,[1] auditory hallucinations,[2,3] major depressive disorders[4-8] and obsessive compulsive disorders.[9]

The stimulation of specific regions in the brain with implanted

Table 1

High-frequency TMS in tinnitus patients (MT = motor threshold)

Authors	Tinnitus side	Stimulation intensity & frequency	Stimulation site	Sham control	Total umber of stimulati	Results	Tinnitus assessment
Plewnia *et al.*[38]	14 (12 bilateral, 2 left-sided) 4 women, 10 men	10 Hz, 120% MT	various sites (10-20 EEG system)	coil tilted 90° and control position	5 × 30 stimuli	8 responders for left temporal / temporoparietal stimulation	reduction: score ≥ 1 on 0-4 scale
De Ridder *et al.*[25]	114 (8 bilateral, 106 unilateral)	1-20 Hz, 90% MT	left temporoparietal cortex (anatomical landmarks)	coil tilted 90°	5 × 200 stimuli	28 patients good suppression 32 partial suppression best suppression with tinnitus of > 3 y at 20 Hz	suppression on VAS: ≥80%: good 21-79%: partial
Londero *et al.*[39]	13 (10 left, 3 right)	10 Hz, 120% MT	various sites (fMRI)	not mentioned	1 × 30 stimuli	transient improvement in one patient	open questionnaire
Folmer *et al.*[40]	15 (8 right, 7 left)	10 Hz, 100% MT	left and right temporal cortex (10-20 EEG system)	sham coil with audio recording	5 × 30 stimuli	6 responders for active stimulation, 2 responders sham	VAS 1-10
Fregni *et al.*[41]	7 (bilateral) 3 women, 4 men	10 Hz, 120% MT	left temporoparietal and mesial parietal areas (10-20 EEG system)	sham coil	9 × 30 stimuli	3 responders left stimulation	score ≥1 on 0-4 scale
Khedr *et al.*[42]	14	1 Hz, 100% MT	left temporoparietal cortex (10-20 EEG system)	occipital stimulation, parallel group	10 × 1500 stimuli	1 patients good reduction, 5 partial reduction (after 12 months)	suppression on VAS: ≥80%: good 21-79%: partial

Table 2

Low-frequency TMS in tinnitus patients (MT = motor threshold)

Authors	Tinnitus side	Stimulation intensity & frequency	Stimulation site	Sham control	Total number of stimulati	results	Tinnitus assessment
Kleinjung *et al.*[43]	14 (bilateral) all right-handed 4 women, 10 men	1 Hz, 110% MT	auditory cortex (PET directed)	sham coil	5 × 2000 stimuli	8 responders, 5 non-responders, 1 worsened	tinnitus questionnaire[32,33]
Londero *et al.*[39]	13 (10 left, 3 right)	1 Hz, 120% MT	auditory cortex (fMRI)	not mentioned	1 × 1200 stimuli	5 responders, 1 sham responder	open questionnaire after 10 days
Langguth *et al.*[44]	28 (13 bilateral, 9 left, 6 right) 12 women, 16 male	1 Hz, 110% MT	left primary auditory cortex (new coil positioning method)	none	10 × 2000 stimuli	significant change tinnitus score until end of follow up (13w)	tinnitus questionnaire[32,33]
Plewnia *et al.*[37]	6 (bilateral) 1 woman, 5 men	1 Hz, 120% MT	auditory cortex (PET directed)	control position	20 × 1800 stimuli	5 responders, until 2 weeks after treatment	tinnitus questionnaire[32,33]
Kleinjung *et al.*[35]	45 (30 bilateral, 8 left, 7 right) 7 women, 38 men	1 Hz, 110% MT	left primary auditory cortex (MRI directed)	none	10 × 2000 stimuli	18 responders, all with shorter duration of tinnitus and less hearing loss	tinnitus questionnaire[32,33]
Plewnia *et al.*[36]	9 (8 bilateral, 1 right) 2 women, 7 men	1 Hz, 120%T	auditory cortex (PET directed)	control position	300 + 900 + 1800 stimuli	6 responders, up to 30 min less effect with longer tinnitus	VAS ranging from -5 to 5
Rossi *et al.*[45]	14 (7 bilateral, 4 left, 3 right) 3 women, 11 men	1 Hz, 120% MT	left temporoparietal region (10-20) EEG system)	coil tilted 90°	5 × 1200 stimuli	8 responders (-> 25% VAS) until 2 w after treatment	VAS, HAM-A, HAM-D
Khedr *et al.*[42]	16	10 Hz, 100% MT	left temporoparietal cortex (10-20 EEG system)	occipital stimulation, parallel group	10 × 1500 stimuli	4 patients good reduction, 8 partial reduction (after 12 months)	suppression on VAS: ≥80%: good 21-79%: partial

electrodes has already been shown to alter tinnitus in some patients.[26,27] Neural plasticity is believed to play an important role in tinnitus, and focal modulation of cortical activity can be achieved using TMS, and so tinnitus reduction can be expected after the stimulation of the auditory cortex with TMS.

Langguth *et al.*,[28] Londero *et al.*[29] and Pridmore *et al.*[30] have produced a review of the designs and results of studies investigating the effects of rTMS on tinnitus. An adapted summery is provided in Table 1 and Table 2.

Contrary to these findings, Marcondes *et al.*[31] reported a worsening of tinnitus in two patients following rTMS as a treatment for major depression. During rTMS, the patients experienced new or intensified tinnitus which diminished somewhat after treatment with clonazepam 1mg twice daily.

a) Assessing effects of TMS on tinnitus

The Tinnitus Questionnaire (TQ)[32-34] is a valuable measurement tool for tinnitus but it fails to determine transient tinnitus reductions lasting only a few seconds immediately after a single diagnostic TMS session. In such study protocols, patients are therefore asked to estimate the tinnitus reduction immediately following the TMS stimulation train on a visual analogue scale (VAS) ranging from 0 to 100. Nevertheless, tinnitus questionnaires can still be used in combination with VAS scores for long-term tinnitus follow-up in therapeutic rTMS protocols.

b) Patient factors influencing TMS results

Studies could identify patient-specific factors that influence the effects of TMS on tinnitus, with normal hearing and a short history of complaints being associated with better results after TMS.[25,35,36] Yet, to date, it has not proven possible to determine clear-cut criteria to predict which patients would benefit from either low- or high-frequency TMS. In a study involving 60 tinnitus patients,[25] a statistically significant correlation was found between the most effective TMS frequency and tinnitus duration. For acute types of tinnitus, the best tinnitus reduction was found after high-frequency TMS; in patients with a chronic type of tinnitus, the maximum reduction occurred after low-frequency TMS.

In a study performed on six patients with chronic tinnitus,[37] a high tinnitus-related neuronal activity in the anterior cingulate cortex (measured by increased cerebral blood flow with PET scan) correlated with a good response to rTMS. Inversely, in another study with 8 patients,[36] the 2 patients who failed to respond to rTMS showed an excessively higher tinnitus related cerebral blood flow during the tinnitus 'on' state compared to the tinnitus 'off' state. This increased cerebral blood flow was mainly located in the posterior cingulum.

This leads to the hypothesis that tinnitus-related cingulate cortex activation could predict the response to rTMS treatment. This idea needs to be investigated in a larger study population before further conclusions can be drawn.

Coil placement

Coil placement represents a crucial aspect of neurostimulation. The coil can be placed using conventional non-navigated or neuronavigated strategies. Sparing *et al.*[46] recently compared five different localisation methods for coil placement. Conventional non-navigated methods included 1: coil positioning according to the international 10-20 EEG system and 2: target positioning using a standardised function-guided procedure. This latter method assumes very similar interhemispheric position of TMS maps in the mediolateral axis.

Neuronavigated strategies included 1: coil placement by means of anatomical landmarks on patient specific MR images, 2: coil positioning by means of individual functional MRI (fMRI) data and 3: the "probabilistic approach" described by Paus.[47] This latter method uses group functional averages of PET or fMRI data to identify the target region.

Comparing these five strategies, Sparing *et al.*[46] concluded that the highest stimulation precision could be obtained when the coil was placed according to the patients' specific fMRI data. They also found very consistent results when the "probabilistic approach" was applied. Both methods require neuronavigation.

Langguth *et al.*[44] presented a frameless stereotactic EEG positioning system to compute the specific scalp coordinates within a range of about 20 mm diameter for stimulation of the primary auditory cortex. Nevertheless, further investigation will be needed to compare the precision of this procedure to the one obtained with neuronavigated coil placement approaches described above. Furthermore, additional studies are mandatory to investigate whether TMS or rTMS performed

with these more precise target localisations also leads to increased tinnitus reduction compared to non-stereotactic positioning strategies.

All the methods described above allow the localisation of patient-specific stimulation targets. This can be of particular importance in repetitive stimulation schemes since it allows for the cyclical stimulation of a patient's cortex at the exact same point.

TMS parameters influencing cortical excitability changes

Intrinsic and extrinsic factors determine the direction and magnitude of cortical excitability changes induced by TMS.[48]

Known intrinsic factors include the pre-stimulatory functional state of the cortex targeted by TMS. Extrinsic factors are represented by variables of TMS stimulation such as intensity, frequency, total number of stimuli and the type of coil used.

Intrinsic parameter: pre-stimulatory functional state of the cortex

a) Priming studies with TMS

The influence of the pre-stimulatory functional state of the cortex has already been demonstrated. In a study involving 25 healthy volunteers, 6 Hz TMS or placebo was performed to prime the motor cortex before 10 minutes of 1 Hz TMS. Motor-evoked potentials (MEP) were measured every 10 seconds for one hour after stimulation. Significant increases in cortical depression were found compared to placebo when the cortex had been primed with 6 Hz TMS.[49]

By contrast, in a study involving 32 chronic tinnitus patients, Langguth *et al*.[50] found no enhanced tinnitus reduction in patients receiving 1Hz rTMS primed with high 6 Hz TMS compared to patients receiving 1Hz rTMS alone.

Possible explanations given by the authors were 1: the lower number of applied stimuli in the priming group, 2: the amount of hearing loss and duration of tinnitus in their population, which are known to lead to poorer outcomes after rTMS[35] (see above), and 3: the fact that the enhanced effect of priming stimulation has, until now, been demonstrated only in healthy individuals, while their study population consisted of tinnitus patients.

b) Priming studies with tDCS (transcranial direct current stimulation)

In a study by Lang *et al*.,[51] the influence of the functional state of the cortex on TMS results was also demonstrated by priming TMS with tDCS.

In 10 healthy volunteers, 10 minutes of anodal, cathodal or sham tDCS were followed by a 20-second train of 5Hz TMS at an intensity of individual active MT (motor threshold) to the left primary motor hand cortex. Preconditioning with cathodal tDCS resulted in an increase in corticospinal excitability to levels above baseline, while preconditioning with anodal tDCS led to a decrease in corticospinal excitability to below baseline levels. No modulations in MEP magnitude were noted with sham tDCS. The same results were found in a study by Siebner *et al*.[52] involving 8 healthy male volunteers.

c) Light deprivation study

In a study involving TMS in healthy subjects undergoing light deprivation,[53] different modulations could be seen using the same TMS parameters, again suggesting that the pre-stimulation functional state of cortical inhibitory and facilitatory circuits determine the effects of TMS trains. Analogically, an altered state of cortical circuits between patients with acute or chronic tinnitus could explain why response to TMS or rTMS decreases with chronic tinnitus compared to acute tinnitus, as shown by De Ridder *et al*.[25] and Kleinjung *et al*.[35] Larger studies should be undertaken to investigate this hypothesis.

d) Implications of these studies for current views

In the past, low-frequency rTMS without preconditioning has been shown to lead to a decrease in corticospinal excitability, as opposed to the increased excitability found with high-frequency rTMS.[54-60]

Since preconditioning tDCS was found to alter the thresholds for TMS to induce lasting changes in corticospinal excitability, one might question the fact that TMS frequency alone is proposed as determinant factor for the inhibitory or facilitatory properties of TMS. In other words, in addition to TMS frequency and the pre-stimulatory functional state of the cortex, other factors could also contribute to the effects of TMS.

Another implication of priming studies can be derived from a study performed by Lang *et al*.[61] in which a relatively modest priming effect of tDCS on subsequent TMS stimulation of the visual cortex was shown, suggesting considerable disparity in the modulation of human motor and visual cortex excitability. This disparity should

probably be taken into account during threshold measurements in studies involving TMS and rTMS and tinnitus. In these studies, the patient's motor threshold is measured as a set point for TMS stimulation of the auditory cortex. In other words, the intensity at which TMS is given to the auditory cortex depends solely on the patient's specific motor cortex threshold as measured with a TMS device.

If an inconsistency can be seen between the thresholds measured for the motor cortex and the thresholds measured for the visual cortex, it seems highly plausible that similar differences exist between the motor cortex and the auditory cortex. Using the motor cortex to determine the motor threshold for auditory TMS might therefore not be an optimal choice.

In summary, the effects of TMS on cortical activity are influenced by several intrinsic parameters, including the baseline activity of the targeted cortical areas and stimulation frequency, but also the direction of the current induced in the brain.[62] It is probable that there are still many other influencing parameters remaining to be discovered.

Extrinsic parameters

a) Stimulation intensity

In a study of 15 healthy male patients, Lang demonstrated that both the stimulation intensity and the type of TMS coil have an impact on the after-effects of 1Hz TMS.[63] In line with previous findings by Fitzgerald *et al.*[64], longer and stronger reductions in MEP amplitude were found with suprathreshold 1 Hz TMS compared to subthreshold 1 Hz TMS. This finding indicated the superiority of suprathreshold low-frequency TMS in facilitating inhibitory circuits in the stimulated cortex compared to subthreshold low-frequency TMS.

A study by Lang *et al.*[61] of nine healthy subjects suggested a considerable disparity in the modulation of human motor and visual cortex excitability. The implication for TMS of the auditory cortex is discussed above.

b) Coils

Compared to round coils, figure-eight coils can produce more focal stimulation by creating a maximum current at the junction of the two circles.[14] Furthermore, the study by Lang *et al.*[63] referred to above, compared two different figure-eight coil types: the Medtronic coil and the Magstim coil. 1 Hz TMS with the Medtronic coil had a stronger inhibitory effect on corticospinal excitability than TMS with the Magstim coil. The authors attribute the differences in the after-effects after 1 Hz TMS with the Medtronic or Magstim coil to the substantial differences in the coil design. In summary, this study therefore found stronger decreases in MEP amplitude following TMS performed with the Medtronic coil and higher intensities of stimulation. However, one should keep in mind that this study was performed on the primary motor cortex of fifteen volunteers. To what extent these results can be extrapolated to auditory cortex TMS in tinnitus patients is therefore an issue that still requires investigation.

Imaging

Wagner *et al.*[16] conducted an extensive review of TMS imaging. This section summarises and comments on some properties of EEG, PET and fMRI during TMS. Thanks to new methods developed with a view to minimising EEG artefacts generated by TMS stimulation, it is now feasible to study EEG with TMS. The resulting data can show the effects of TMS on electrophysiological registration. Combining TMS with PET may throw up questions about the disturbance of the PET camera by the strong magnetic TMS field. Though experiments were undertaken with mu-metal shields,[47] another study denies that these protective measures are necessary.[65] In a study investigating PET-scan images following subthreshold rTMS in six healthy patients, cerebral blood flow was found to vary significantly and negatively in the sensory-motor cortex with the number of TMS stimulus trains.[66] This decreased blood flow could be interpreted as an inhibitory cortical effect of the stimulation. By contrast, another study by Paus *et al.*[18] found a positive correlation between cerebral blood flow and the number of TMS pulse trains with the intensity set at 70% of the maximum output of the stimulator. The correlation between suprathreshold TMS and increased cerebral blood flow at the site of stimulation was also reported by Fox *et al.*[67] Two other studies were performed using PET scans in order to neuronavigate TMS towards areas of hypermetabolism, with placebo-controlled response ratios of 75% (6 out of 8 patients)[36] and 83% (5 out of 8 patients).[37] This higher response rate compared to those in studies with rTMS performed without PET or fMRI neuronavigation[45] generates questions about the potential additional value of PET

guidance for rTMS in clinical practice. Arguments against routine PET guidance for TMS are radiation and a lack of spatial resolution combined with the time-consuming and expensive properties of this imaging technique. fMRI, on the other hand, has the advantage that it is safe and provides excellent spatial resolution. Temporal resolution is superior to PET, but nevertheless inferior to results obtained with EEG.

Conclusion

TMS is a new and very promising technique for tinnitus modulation. Several studies have already found tinnitus reduction following single or repetitive stimulation. Nevertheless, to date, a lot of questions still remain concerning patient selection and stimulation parameters. Further investigation of TMS in tinnitus patients is mandatory in order to answer those questions and consequently optimize its potential diagnostic and therapeutic properties.

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