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Do tDCS and TMS influence tinnitus transiently via a direct cortical and indirect somatosensory modulating effect? A combined TMS-tDCS and TENS study

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Tinnitus is usually defined as an intrinsic sound percept that cannot be attributed to an external sound source that tinnitus can be suppressed by neuromodulation techniques such as transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and transcranial electrical nerve stimulation (TENS). It is thought that TMS and tDCS modulate tinnitus directly by targeting the frontal and/or auditory cortex of the brain, whereas TENS most likely influences tinnitus indirectly via cervical nerve-cochlear nucleus interactions. It is unknown whether part of the tinnitus modulating effect of tDCS and TMS also depends on a somatosensory modulating effect analogous to TENS, via the trigeminal and cervical nerves. We aimed to investigate this question by analyzing to which extent response to one neuromodulation technique predicts the response to another neuromodulation technique. We analyzed 153 patients with chronic tinnitus (> 1 year) who underwent all three neuromodulation techniques (C2 nerve TENS, auditory cortex TMS, and bifrontal tDCS). Our results show that TENS predicts tDCS and TMS better than the opposite, and tDCS predicts TMS response and vice versa. On the basis of these results, it is it is argued that TENS only modulates the tinnitus brain circuit indirectly, whereas TMS and tDCS have a dual working mechanism, a TENS-like mechanism plus a direct brain modulating mechanism.

Keywords tDCS; TMS; TENS; responders; nonresponders; tinnitus; neuromodulation; neurostimulation

Tinnitus is defined as an intrinsic sound sensation that cannot be attributed to an external sound source. This phantom perception is a common disorder. The American Tinnitus Association estimates that 50 million Americans are affected by it, and that 12 million of these people seek medical attention because of their tinnitus. In about 6 to 25% of the affected people, tinnitus causes a considerable amount of distress,[1-3] resulting in about 2-4 % of the population who are severely impaired in their quality of life by tinnitus.[4]

Animal models and neuroimaging studies in patients with tinnitus have demonstrated that tinnitus is related to

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changes in neuronal activity in both central auditory and nonauditory brain areas (eg, Moller 2007, Progress in Brain Research). The pathophysiologic relevance of these changes has been confirmed by the observation that tinnitus can be suppressed by neuromodulation techniques such as transcranial direct current stimulation (tDCS),[5] transcranial magnetic stimulation (TMS),[6-9] and transcranial electrical nerve stimulation (TENS).[10]

It is thought that TMS and tDCS modulate tinnitus directly by targeting the frontal[5,8] and/or auditory cortex[11,12] of the brain, whereas TENS most likely influences tinnitus indirectly via cervical nerve-cochlear nucleus interactions.[10] It is unknown whether part of the tinnitus modulating effect of tDCS and TMS also depends on a somatosensory modulating effect analogous to TENS, via the trigeminal and C2 nerve. Thus, TMS and tDCS could exert a double effect on the tinnitus intensity and tinnitus distress network, a direct effect via the cortex and an indirect effect via the trigeminal and cervical nerves, both of which modulate activity in the cochlear nucleus.[13-17]

In an attempt to elucidate whether this concept is correct we aimed to investigate to which extent response to one neuromodulation technique predicts the response to another neuromodulation technique. This is based on the idea that if TENS predicts tDCS and TMS better than the opposite, and both cortical modulating techniques predict each other equally well, it can be argued that TENS only modulates the tinnitus brain circuit indirectly, whereas TMS and tDCS have a dual working mechanism, a TENS like mechanism plus a direct brain modulating mechanism.

Materials and methods

Subjects

All patients presented at the TRI (Tinnitus Research Initiative) Tinnitus clinic Antwerp, Belgium. We retrospectively analyzed the data of 153 patients (male, 92; female, 61) with chronic tinnitus (> 1 year). Only patients were included in which the diagnostic workup (audiologic investigation including pure tone and speech audiometry, ENT investigation including tympanometry, neurological investigation, and magnetic resonance imaging [MRI] of the brain and posterior fossa) did not reveal a treatable cause of their tinnitus. Patients who responded either to sham TMS or to sham TENS were not included in the analysis. The mean age was 50.30 years (SD = 15.31) and the mean tinnitus duration was 5.81 years (SD = 8.45). Forty-five patients had pure tone tinnitus and 108 patients had narrow band noise tinnitus. Forty-six patients had unilateral tinnitus and 107 patients had bilateral tinnitus. On the basis of the tinnitus questionnaire (TQ), 11 patients had grade 1 tinnitus, 34 grade 2, 45 grade 3, and 63 grade 4 tinnitus.[18,19]

tDCS, TMS, and TENS are performed in the context of a diagnostic protocol for selection of candidates for specific therapeutic procedures (eg, implantation of permanent electrodes for electrical stimulation of the auditory cortex for treatment for tinnitus).[20,21] All patients underwent all three neuromodulation protocols, namely, bifrontal tDCS, auditory cortex TMS, and C2 TENS. Between each neuromodulation technique there was a washout period of at least 1 week. The real and sham stimulation was performed in the same session. The order of the different neuromodulation techniques was randomized over the patients.

tDCS

Direct current was transmitted by a saline-soaked pair of surface sponges (35 cm^2) and delivered by specially developed, battery-driven, constant current stimulator with a maximum output of 10 mA (Eldith; http://www.eldith.de). The dorsolateral prefrontal cortex (DLPFC) seems to play a specific role in auditory processing. That is, the DLPC has a bilateral facilitatory effect on auditory memory storage and contains auditory memory cells.[22] The DLPFC also exerts early inhibitory modulation of input to primary auditory cortex in humans[23] and has been found to be associated with auditory attention,[24-26] resulting in top-down modulation of auditory processing.[27] This was further confirmed by electrophysiologic data indicating that tinnitus might occur as the result of a dysfunction in the top-down inhibitory processes.[28] Previous research shows that bilateral single session tDCS of the DLPFC with the anode over the right DLPFC and the cathode over left DLPFC can decrease tinnitus in patients with chronic tinnitus, whereas bilateral tDCS with the anode over the left DLPFC and the cathode over right DLPFC has no influence on tinnitus.[5] Hence, tDCS was applied by placing the cathode over the left DLPFC and the anode over the right DLPFC as determined by the International 10/20 Electroencephalogram System corresponding to F3 and F4, respectively. A constant current of 1.5 mA intensity was applied for 20 minutes.[5] The stimulation amplitude is limited to 1.5 mA to prevent skin lesions,[29] and 1.5 mA is capable of modulating tinnitus activity. No sham condition was included because tDCS can have a delayed effect, interfering with the sham stimulation if performed on the same day.

TENS

TENS (Profile TENS, Body Clock Health Care Ltd., London, UK) can generate a constant current with a pulse rate of 1-200 Hz and an intensity of 0-100 mA. Two silver electrodes were respectively placed on the left and right C2 dermatomas. The positive electrode was placed ipsilateral to the tinnitus side. For bilateral tinnitus patients the positive electrode was placed on the right side. TENS consisted of 10 minutes of biphasic rectangular stimulation at 6 Hz, immediately followed by 10 minutes of stimulation at 40 Hz and sham stimulation. Both real stimulations were applying pulses of 250 μs pulse width. The intensity of the

TENS stimulation is slowly increased until a clear sensation of paresthesias was felt by the patient and was subsequently decreased to just below threshold. For sham stimulation, the electrodes were placed at the same positions as for the active stimulation, but the simulator was turned on for only 10 seconds. Thus, participants felt the initial itching/tingling sensation associated with TENS. This method was shown to be sufficient to keep participants blind to direct current stimulation,[30] the reason to also apply it in TENS. Each patient received a real and a sham TENS treatment.[10]

TMS

TMS is performed using a super rapid stimulator (Magstim Inc, Whitland, South Wales) with a figure-of-eight coil placed over the auditory cortex with the coil handle strictly upward. For unilateral tinnitus, this coil was placed contralateral to the tinnitus side, whereas for bilateral tinnitus, the coil was placed over the right auditory cortex. PET studies performed in tinnitus patients usually find increased metabolism on the left auditory cortex, irrespective of the side on which the tinnitus is perceived, and that left-sided TMS can suppress this metabolic activity.[31] In contrast, fMRI[32,33] and magnetoencephalography[34-36] studies suggest the neural generator might be located contralaterally to the tinnitus side. A recent study, which compares ipsilateral with contralateral stimulation, demonstrated that rTMS contralateral to the side of the tinnitus has a greater beneficial effect on symptoms than ipsilateral rTMS, and better suppression than left-sided stimulation.[37]

The motor threshold to TMS is first determined by placing the coil over the motor cortex. The coil was positioned tangentially to the scalp and oriented so that the induced electrical currents would flow approximately perpendicular to the central sulcus, at 45° angle from the midsagittal line. The intensity of the magnetic stimulation is slowly increased until a clear contraction is observed in the contralateral thenar muscle. Then the optimal position for eliciting this muscle contraction is determined. Then stimulator output is reduced to the stimulation intensity at which still a visible muscle contraction can be elicited in four of eight trials. This method has been shown to be reliable for determining motor threshold.[38]

The coil is then moved to a location over the auditory cortex contralaterally to the side to which the patients refer their unilateral tinnitus, and for bilateral tinnitus the coil was moved to right auditory cortex (5-6 cm above the auditory meatus on straight line to the vertex). The right side was elected for bilateral tinnitus patients for standardization purposes. With the intensity of the stimulation set at 90% of the motor threshold, the site of maximal tinnitus suppression is determined using 1 Hz stimulation consisting of 200 pulses. For diagnostic testing, 200 pulses seem enough as previous research abundantly showed.[5,39,40] The presence of a placebo effect is tested, by placing the coil perpendicular to the auditory cortex with the coil handle strictly upward. This sham TMS at 1 Hz was randomly performed before or after the real stimulation.

Evaluation

Before each session, patients grade their tinnitus on a numeric rating scale from 0-10 ("How loud is your tinnitus? 0 = no tinnitus and 10 = as loud as imaginable"). After tDCS and TENS, the patients are asked to estimate the decrease in tinnitus in percentage using a different numeric rating scale. When tinnitus suppression is induced by TMS, the patient is asked to notify when tinnitus has returned back to baseline, namely, when the tinnitus intensity is back to its initial VAS before the next TMS frequency (placebo or real) is applied.

Responders are defined as patients that respond transiently to treatment if they had a minimum of 10% suppression (equals suppression criterion of 10%) lasting seconds or longer, whereas nonresponders are defined as patients who do not respond to treatment nor had a suppression rate of less than 10%. However, calculations were also obtained when there was a suppression rate of minimum 20% (ie, responders with 20% suppression criterion) and nonresponders do not respond to treatment nor had a suppression rate of less than 20%.

Statistical analyses

A simple logistic regression analysis was conducted to verify whether the independent variables (ie, respectively response to tDCS, TMS, or TENS) could predict if a patient would respond or not, respectively, to TMS, TENS, and tDCS treatment. A multiple logistic regression analysis was conducted to verify whether two independent variables (ie, respectively, response to tDCS and TMS, TMS and TENS, tDCS, TMS) could predict if a patient would respond or not, respectively, to TENS, tDCS, TMS, or TENS treatment.

Probability was calculated:

Simple Logistic Regression

$$P = \frac{e^{(\beta_0 + \beta_1 X)}}{1 + e^{(\beta_0 + \beta_1 X)}}$$

Multiple Logistic Regression

$$P = \frac{e^{(\beta_0 + \beta_1 X_1 + \beta_2 X_2)}}{1 + e^{(\beta_0 + \beta_1 X_1 + \beta_2 X_2)}}$$

P is the probability that an event occurs (ie, that patient respond to a particular modulation technique, respectively, tDCS, TENS, or TMS), e is the base of the natural logarithm (about 2.718) and β_0 and β_1 (and β_2) are the parameters of the model. The value of β_0 yields P when X is zero, and β_1 (and β_2) adjusts how quickly the probability changes with changing X a single unit.[41]

Pearson correlations was calculated the amount of suppression patient perceived for, respectively, tDCS, TMS, and TENS.

Ordinal regression analysis was conducted with the sum of responses on the different neuromodulation techniques (tDCS + TMS + TENS) as dependent variables and tinnitus type (pure tone versus narrow band noise), tinnitus laterality (unilateral versus bilateral) and tinnitus grade. A Spearman Rang Correlation coefficient was calculated between sum of responses on the different neuromodulation techniques and tinnitus duration and controlled for multiple comparisons.

The same analyses were conducted when the suppression rate was defined as minimum 20%.

Results

The response rates for tDCS, TENS, and TMS were respectively 27%, 11%, and 38%. Table 1 gives an overview over mean suppression rates for all 153 patients for the three neuromodulation techniques as well as the mean suppression rates for the responders only.

Simple logistic regression analyses yield significant effects indicating that TMS, TENS, and tDCS could predict each other (Table 2). A similar effect was obtained when the suppression criterion was minimum 20% (Table 2). As Figure 1 shows that a patient responding to TMS has a probability of responding to tDCS of 51% and to TENS of 21% with a suppression criterion of minimum 10%. For a suppression criterion of 20% responding to TMS has a probability of responding to tDCS of 71% and to TENS of 20%. Patients responding to tDCS have a probability of 58% responding to TMS and to TENS of 21% for the response criterion of minimum 10% these numbers remained the same for the suppression rate of minimum 20% (Figure 1). Positive response to TENS predicts a tDCS response probability of 56% and a TMS response probability of 75% for the suppression criterion of minimum 10%. For a suppression criterion of 20% positive response to TENS predicts a tDCS response probability of 44% and a TMS response probability of 73%. Figure 2 also shows the probability a patient responds to a neuromodulation technique if the same patient does not respond to another neuromodulation technique. If a patient does not respond to TMS, this patient has a probability of 33% for the suppression criterion of 10% and 45% for the suppression criterion of 20% to respond to tDCS and 4% for both the suppression criterion of 10% and 20% for TENS. When not responding to tDCS, patients have a probability of responding to TMS of 33% for the suppression criterion of 10% and 31% for the suppression criterion of 20% and 6% for the suppression criterion of 10% and 7% for the suppression criterion of 20% to TENS. Not responding to TENS has a probability of 34% for the suppression criterion of 10% and 33% for the suppression criterion of 20% responding to TMS and a probability of 23% for the suppression criterion of 10% and 19% for the suppression criterion of 20% responding to tDCS.

Table 1 Response rate for respectively tDCS, TENS, and TMS

	Response rate (%)	Mean suppression (%)	Mean suppression responders (%)
tDCS	27	6.78	30.13
TENS	11	7.96	38.45
TMS	38	24.21	49.13

Multiple logistic regression analysis further reveals that TMS results are significantly predicted by TENS, whereas tDCS had no additional predictive value (Table 3). In parallel, TENS significantly predicts tDCS results, whereas TMS response had no significant additional predictive value (Table 3). When patients respond to both TENS and tDCS, there is a probability of 80% for the suppression criterion of 10% and 83% for the suppression criterion of 20% they will respond to TMS, whereas responders to TENS and TMS have a 60% probability for the suppression criterion of 10% and 62% probability for the suppression criterion of 20% to respond to tDCS. Patients who respond to both TMS and tDCS will respond to TENS with a probability of 34% for the suppression criterion of 10% and 26% for the suppression criterion of 20% (Figure 3). When patients do not respond to both TMS and TENS, there is a probability of 20% that they will respond to tDCS (Figure 4). However, if patients do not respond to both TMS and tDCS, only 3% will respond to TENS, whereas not responding to both tDCS and TENS has a probability of 31% of responding to TMS for the 10% suppression criterion (Figure 4). These results remain the same for the suppression criterion of 20%.

Correlations between the amounts of suppression between the three neuromodulation techniques revealed no significant effects for both the 10% and 20% suppression criterion, indicating that the amount of suppression for one neuromodulation technique is not related to the amount of suppression obtained in another neuromodulation technique.

An ordinal regression analysis revealed that tinnitus type, tinnitus laterality, and tinnitus grade do not predict whether tinnitus patients will respond to one or more neuromodulation techniques for both the suppression criterion of 10% or 20%. No correlation was found between the sum of responses on the different neuromodulation techniques and tinnitus duration and age for both the suppression criterion of 10% or 20%.

Discussion

In this study the aim was to investigate whether in tinnitus patients' response to one neuromodulation technique predicts a response to another technique as a means of elucidating the mechanisms of different neuromodulation techniques in tinnitus. The analyses performed show that responding to one noninvasive neuromodulation technique

Table 2 Logistic regression model: predicting responder for one noninvasive neuromodulation technique based on the responding to another tinnitus noninvasive neuromodulation technique

Suppression criterion minimum 10%	tDCS			TENS		
	B	*SE B*	e^B	*B*	*SE B*	e^B
TMS	0.76[a]	0.37	2.13	1.78[b]	0.61	5.94
Constant	−0.71			−3.13		
χ^2		4.14[a]			10.21[c]	
Nagelkerke R^2		0.04			0.13	
	TMS			TENS		
	B	*SE B*	e^B	*B*	*SE B*	e^B
tDCS	1.03[c]	0.21	2.79	1.44[b]	0.54	4.22
Constant	−0.71			−2.71		
χ^2		23.73[c]			6.99[b]	
Nagelkerke R^2		0.07			0.09	
	TMS			tDCS		
	B	*SE B*	e^B	*B*	*SE B*	e^B
TENS	1.78[b]	0.61	5.94	1.44[c]	0.54	4.22
Constant	−0.68			−1.19		
χ^2		10.21[c]			6.99[b]	
Nagelkerke R^2		0.13			0.07	
Suppression criterion minimum 20%	tDCS			TENS		
	B	*SE B*	e^B	*B*	*SE B*	e^B
TMS	1.09[b]	0.40	2.97	1.71[b]	0.61	5.50
Constant	−0.175			−3.11		
χ^2		7.38[b]			8.96[b]	
Nagelkerke R^2		0.07			0.12	
	TMS			TENS		
	B	*SE B*	e^B	*B*	*SE B*	e^B
tDCS	1.09[b]	0.40	2.97	1.18[a]	0.56	3.26
Constant	−0.78			−2.49		
χ^2		7.38[b]			4.35[a]	
Nagelkerke R^2		0.07			0.06	
	TMS			tDCS		
	B	*SE B*	e^B	*B*	*SE B*	e^B
TENS	1.71[b]	0.61	5.50	1.18[a]	0.55	3.26
Constant	−0.69			−1.43		
χ^2		8.96[b]			4.35[a]	
Nagelkerke R^2		0.08			0.04	

[a] $P < .05$.
[b] $P < .01$.
[c] $P < .001$.

(tDCS, TMS, TENS) predicts significantly that a patient will respond to another noninvasive technique (tDCS, TMS, TENS). Probability analysis further reveals that when a patient responds to TMS this patient has a change of 51% (for minimum 10% suppression criterion) or 71% (for minimum 20% suppression criterion) to respond to tDCS and 21% (for both minimum 10%) and or 20% (for minimum 20% suppression criterion) to TENS. When responding to tDCS, patients have a probability of 21% (for both minimum 10% or 20% suppression criterion) to respond to TENS and 58% (for both minimum 10% or 20% suppression criterion) to TMS. Probability analysis reveals further that patients responding to TENS have a probability of 75% (for minimum 10% suppression criterion) or 73% (for minimum 20% suppression criterion) to respond to TMS and 56% (for minimum 10% suppression criterion) or 44% (for minimum 20% suppression criterion) to tDCS. However, when not responding to a noninvasive neuromodulation technique analysis demonstrated changes reduce for responding to another neuromodulation technique. Combining techniques, it was demonstrated that when responding to TENS and tDCS a patient has a probability of 80% (for minimum 10% suppression criterion) or 83% (for minimum 20% suppression criterion) to respond

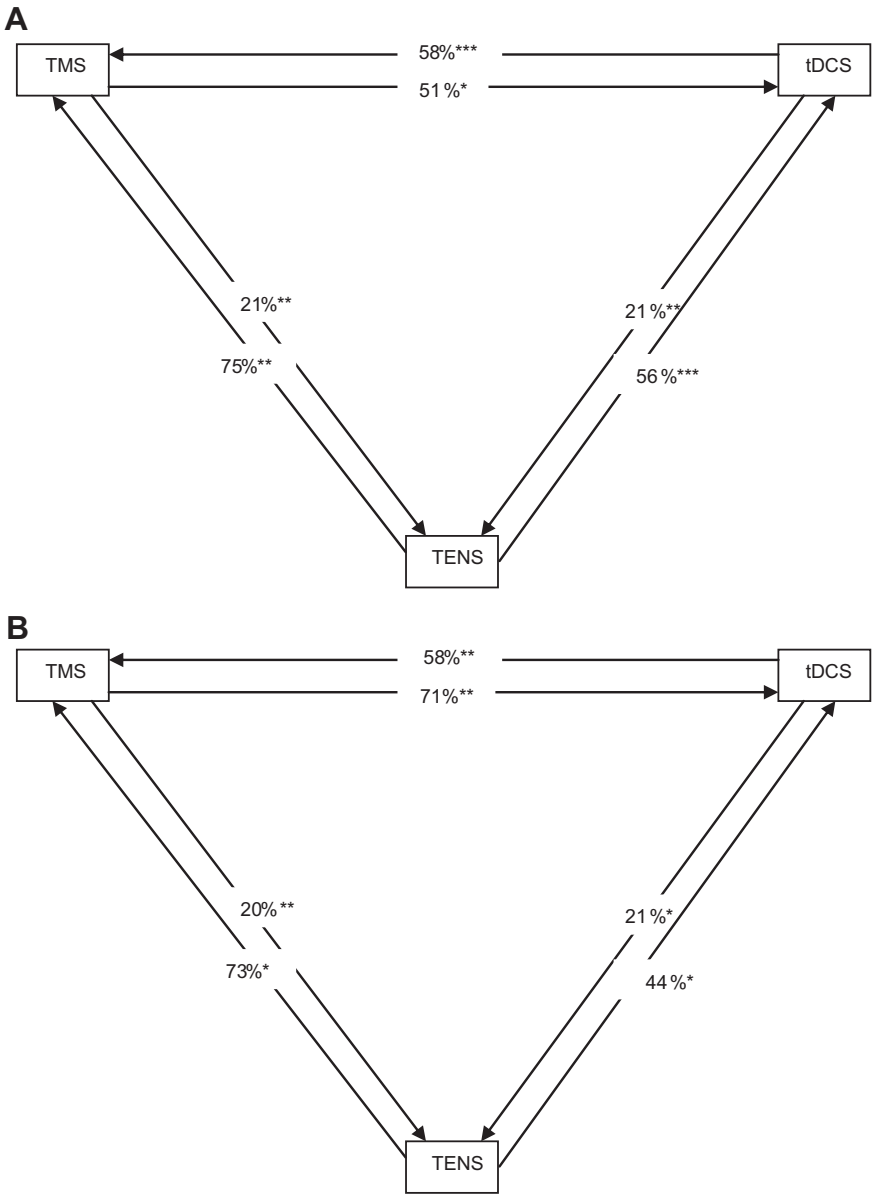

Figure 1 The probability to respond on, respectively, TMS, tDCS, and TENS base on the other neuromodulation technique (*$P < .05$; **$P < .01$; ***$P < .001$) (**A**) suppression criterion of minimum 10%; (**B**) suppression criterion of minimum 20%.

to TMS, whereas when responding both to TENS and TMS a patient has the probability of 60% (for minimum 10% suppression criterion) or 62% (for minimum 20% suppression criterion) responding to tDCS. Furthermore, it was shown that TMS and tDCS combined is not a good predictor for TENS, namely, 34% (for minimum 10% suppression criterion) or 26% (for minimum 20% suppression criterion). When not responding to two neuromodulation technique changes, the probability of responding to the other neuromodulation techniques are 20% for tDCS, 3% for TENS, and 31% for TMS for both 10% and 20% minimum suppression criterion. As such our data relatively remain the same for both the 10% and 20% suppression criterion. Further analysis revealed that there was no correlation between the amounts of suppression of the different noninvasive neuromodulation techniques. The different tinnitus characteristics (tinnitus type, tinnitus laterality, tinnitus grade) do not predict on how many neuromodulation techniques a patient will respond to and there is no correlation between how many neuromodulation techniques a patient will respond to and tinnitus duration.

During TMS a strong impulse of a magnetic field is produced by a coil that is placed over the skull. The magnetic pulse induces an electrical current in superficial brain areas and results in neuronal depolarization. Applied as repetitive TMS, it can induce alterations of neural excitability at the applied area and in functionally connected areas, which outlast the stimulation period. In tDCS,

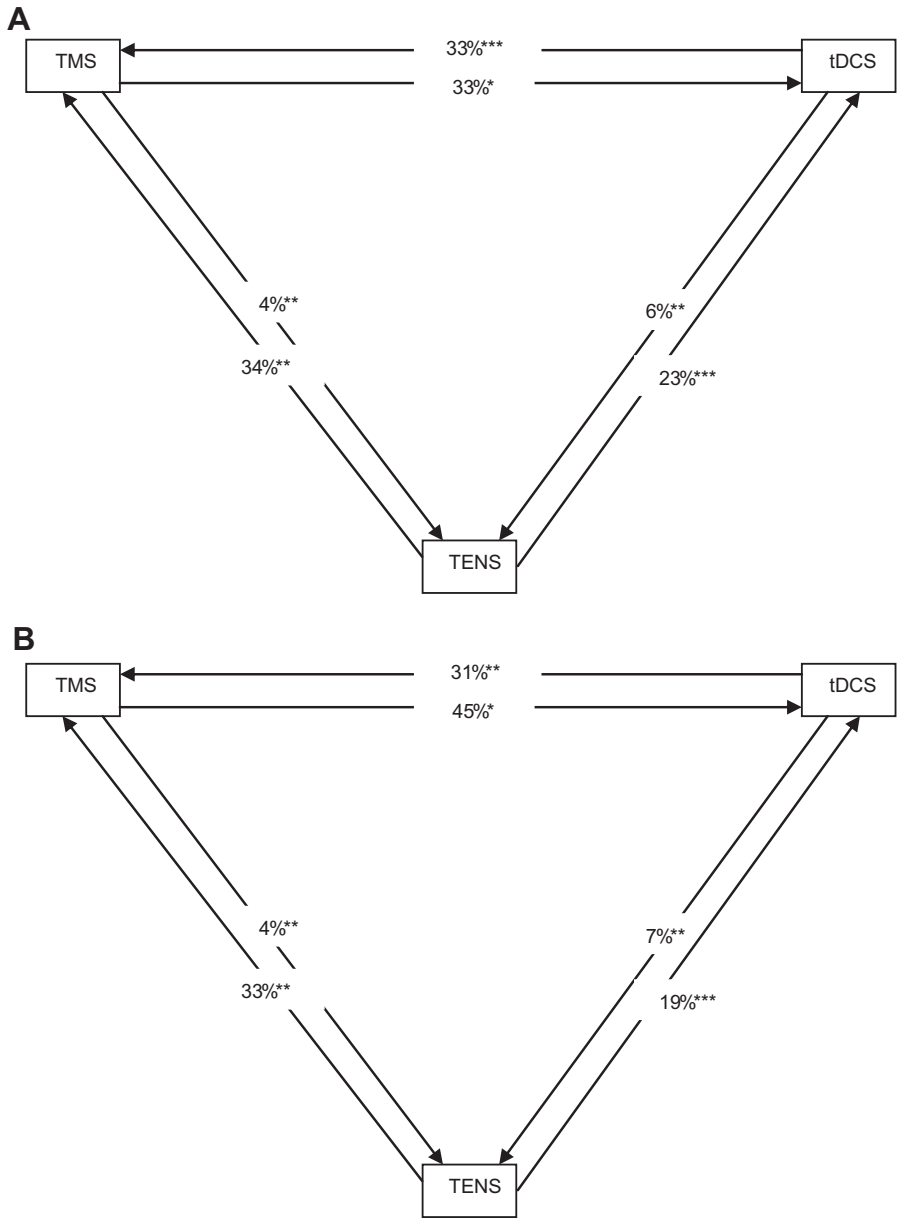

Figure 2 The probability to respond on, respectively, TMS, tDCS, and TENS base on not responding to the other neuromodulation technique (*$P < .05$; **$P < .01$; ***$P < .001$) (**A**) suppression criterion of minimum 10%; (**B**) suppression criterion of minimum 20%.

anodal and cathodal electrodes are placed on the skin over brain areas of interest. A weak direct current flow between the electrodes modulates cortical excitability by interfering with the neuronal membrane potential. There are fundamental differences in the mechanisms of action of these methods. Although TMS is thought to exert its effects by inducing action potentials in cortical neurons, tDCS modulates neuronal excitability by influencing the membrane potential but without inducing neuronal firing.[12,42] In TENS, a weak alternating electrical current is used for stimulating peripheral nerve fibers. By repetitive stimulation of afferent nerve fibers, TENS can also modulate neuronal excitability in specific areas of the central nervous system. Moreover, different brain areas are targeted by the different techniques, namely, the DLFLC for tDCS,[5] the auditory cortex for TMS,[11,43] and the upper cervical nerve (C2) for TENS.[10] In this context the observed high relationship between treatment responses to these different techniques is a surprising finding. A possible explanation for our finding may be that the different neuromodulation techniques might influence a final common network, even if their primary targets differ from each other.

However, we observed differences in the predictive value of the different techniques. TENS predicts better the other two techniques, namely, TMS and tDCS, than vice

Table 3 Logistic regression model: predicting responder for one noninvasive neuromodulation technique based on the responding to the other two noninvasive neuromodulation techniques

Suppression criterion minimum 10%	tDCS		
	B	*SE B*	e^B
TMS	0.55	0.39	1.72
TENS	1.23[a]	0.56	3.43
Constant	−1.39		
χ^2		8.92[b]	
Nagelkerke R^2		0.08	
	TMS		
	B	*SE B*	e^B
tDCS	0.55	0.39	1.73
TENS	1.63[a]	0.62	5.09
Constant	−0.82		
χ^2		12.14[b]	
Nagelkerke R^2		0.10	
	TENS		
	B	*SE B*	e^B
TMS	1.23[a]	0.56	3.43
tDCS	1.63[b]	0.62	5.09
Constant	−3.52		
χ^2		14.99[c]	
Nagelkerke R^2		0.19	
Suppression criterion minimum 20%	tDCS		
	B	*SE B*	e^B
TMS	0.92[a]	0.42	2.52
TENS	0.98[a]	0.59	2.66
Constant	−1.39		
χ^2		9.89[b]	
Nagelkerke R^2		0.10	
	TMS		
	B	*SE B*	e^B
tDCS	0.92[a]	0.42	2.52
TENS	1.52[a]	0.63	4.57
Constant	−0.82		
χ^2		13.79[c]	
Nagelkerke R^2		0.12	
	TENS		
	B	*SE B*	e^B
TMS	1.52[a]	0.63	4.57
tDCS	0.98[a]	0.59	2.66
Constant	−3.52		
χ^2		11.64[b]	
Nagelkerke R^2		0.11	

[a] $P < .05$.
[b] $P < .01$.
[c] $P < .001$.

versa. TMS and tDCS could predict each other equally good. This finding could be related to the hypothesized multimodal nature of TMS and tDCS effects. Besides stimulating the cortex, TMS also results in somatosensory and auditory stimulation. Similarly, tDCS affects somatosensory afferents. Thus, in addition to its direct effect on the frontal (tDCS) and auditory (TMS) cortex both TMS and tDCS exert an indirect effect on the tinnitus network via somatosensory modulation at the level of the trigeminal and C2 nerve, respectively. TENS, in contrast, exerts its effect only via C2 sensory pathways. TENS response thus indicates tinnitus modulation by somatosensory

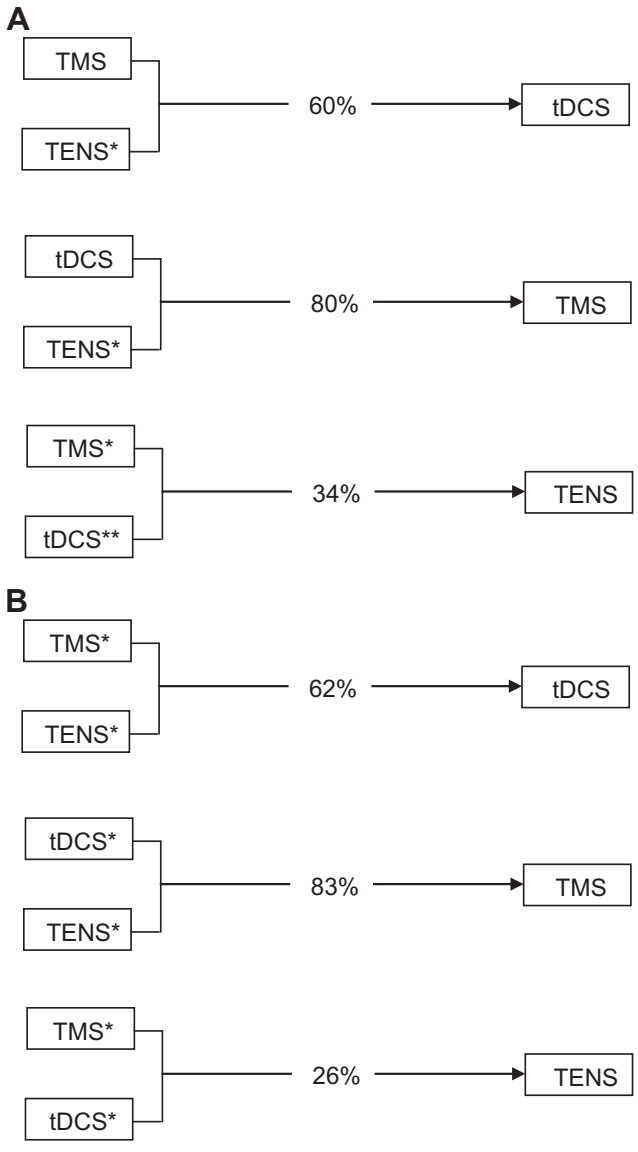

Figure 3 The probability to respond on respectively to a neuromodulation technique based on two other neuromodulation techniques (*$P < .05$; **$P < .01$; ***$P < .001$) (**A**) suppression criterion of minimum 10%; (**B**) suppression criterion of minimum 20%.

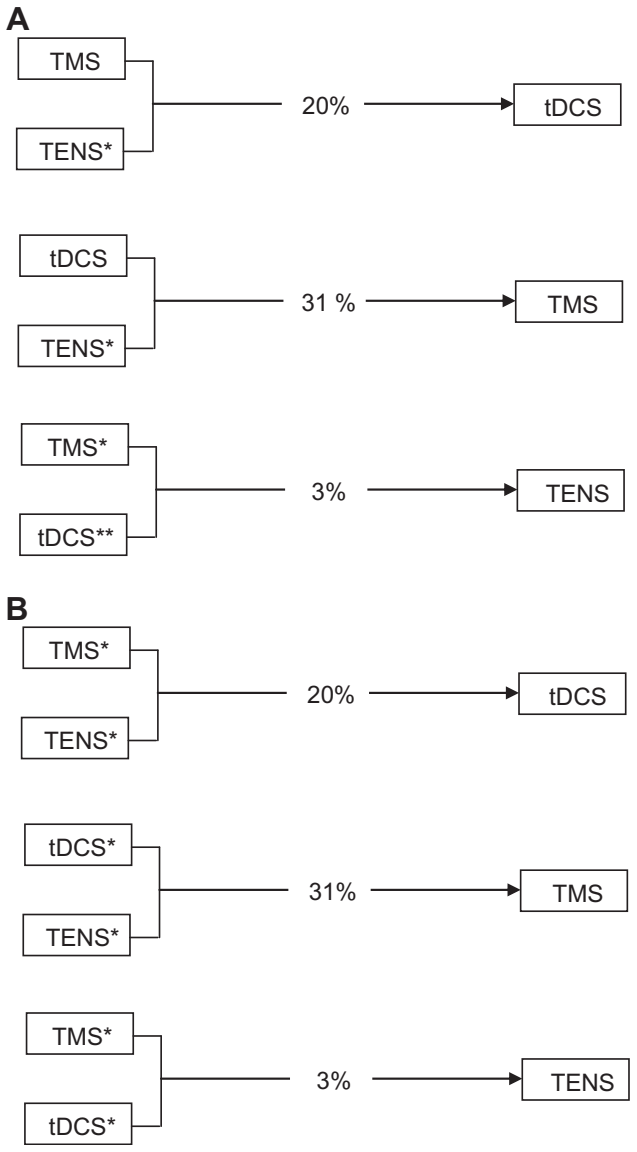

Figure 4 The probability to respond on respectively to a neuromodulation technique based on not responding to the two other neuromodulation techniques (*$P < .05$; **$P < .01$; ***$P < .001$) (**A**) suppression criterion of minimum 10%; (**B**) suppression criterion of minimum 20%.

stimulation. Because both TMS and tDCS exert also a somatosensory effect, one would expect that a positive response to TENS is a predictor for tDCS and TMS. In contrast, the response to tDCS and TMS may be due to the somatosensory effect or the modulatory effect on cortical activity or a combination of both. Therefore, one would expect that these neuromodulation techniques would be worse in predicting a response to TENS, which only has a somatosensory effect.

Somatosensory stimulation of the upper cervical nerve (C2) might be especially relevant in combination with auditory cortex stimulation. C2 stimulation increases the inhibitory role of the DCN on the central auditory nervous system.[15,44] The DCN receives auditory input from the 8th nerve (ie, vestibulocochlear nerve) and somatosenory input, directly from ipsilateral dorsal column and (spinal) trigeminal nuclei.[45-47] The upper cervical nerves C2 project to (spinal) trigeminal nuclei[48-50] and C2 electrical stimulation evokes large potentials in the DCN. Stimulation of C2 produces a pattern of inhibition of the DCN principal cells,[15] a hypothetical mechanism for suppressing tinnitus, which is in accordance with animal studies.[16,51] So when TMS of the auditory cortex is applied, the magnetic pulse reaches both directly the auditory cortex and indirectly via somatosensory afferents in the occipital branch of the C2 nerve.

The use of bifrontal tDCS for tinnitus treatment is based on the involvement of the DLPFC in processing aversive auditory stimuli and in tinnitus.[5,52] The effect on tinnitus intensity is thought to result mainly from the DLPFC's inhibitory modulation of the auditory cortex,[23] which is involved in tinnitus intensity coding.[53] However, bifrontal tDCS also activates somatosensory neurons in the trigeminal nerve, which send their input via trigeminal ganglion and spinal trigeminal nuclei directly to DCN.[54] It is further known that stimulating the origins of the trigeminal projections can excite or inhibit responses in the cochlear nucleus.[16,51,55] As such, tDCS could modulate the auditory nervous system indirectly via the supraorbital nerve of ophthalmic nerve to the trigeminal ganglion and from there directly to DCN. No correlations were found between the amounts of improvement between the different noninvasive neuromodulation techniques. This indicates that different neuronal mechanisms may be involved in determining whether a patient responds to stimulation and how much this patient responds to stimulation. Furthermore, tinnitus characteristics such as tinnitus type, tinnitus laterality and tinnitus grade did not predict whether patients would respond or not.

It is important to note that the classification of whether someone responds is obtained immediately after each neuromodulation technique. Some patients only respond to certain a neuromodulation technique after repetitive sessions. Therefore, our results can only be seen in the light of diagnostic measurements and not for therapeutic reasons. It is possible that repetitive sessions of the different neuromodulation techniques might have other predictive values. Therefore, future research is needed.

In conclusion, the results of this study show that there is variability in responding to tDCS, TMS, and TENS. The responsiveness to one technique predicts the response to another technique. As such the response variability in patients is related, but is not dependent on clinical characteristics. It is furthermore argued that TENS only modulates the tinnitus brain circuit indirectly, whereas TMS and tDCS very likely have a dual working mechanism, a TENS-like somatosensoriy mechanism plus a direct brain modulating mechanism. Further functional imaging studies should help elucidate whether this concept is indeed the explanation for the observed results.

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