New non-invasive transcranial stimulation techniques in neuroplasticity research

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Összefoglalás

Az elmúlt 20 évben számos nem-invazív transzkraniális stimulációs technika került bevezetésre az idegtudományok területét érintő alap- és klinikai kutatásban. A legismertebb neuroplaszticitás indukálása és fokozása céljából használt eszköz ezek közül a repetitív transzkraniális mágneses stimuláció (rTMS), valamint a transzkraniális egyenáram-ingerlés (tDCS).

Vizsgálatsorozatunk során új elektromos stimulációs technikákat teszteltünk, transzkraniális váltóáram stimulációt (tACS), valamint transzkraniális random zaj ingerlést (tRNS) vizsgáltunk elektrofiziológiai- és pszichofiziológiai módszerek segítségével. Kísérleteink első csoportjában 48 egészséges alany bevonásával a tDCS spektrumát terjesztettük a tACS felé. 10 Hz elsődleges motoros kérgen (M1) történő ingerlés a motoros kiváltott válaszok (MEP) amplitudóját csökkentette, emellett gyorsabb implicit motoros tanulást eredményezett a pszichofiziológiai tesztek használata során. Vizsgálataink egy részében a tACS-t anódális és katódális DC stimulációval kombináltuk. Ezekben a vizsgálatokban a MEP-ek amplitudója anódális 10- és 15 Hz-es ingerlést követően emelkedett.

Kísérleteink második csoportja 80 egészséges önkéntesen a tRNS technika utóhatásait vizsgálta. A tRNS a kortikális excitabilitás fokozódását eredményezte, mely emelkedés a stimulációt követően 60 percig szignifikáns mértékű volt. Az észlelt excitabilitás fokozódás mind az elektrofiziológiai-, mind pszichofiziológiai feladatok végzése során észlelhető volt. A kortikális ingerlékenység fokozódásáért eredményeink alapján elsősorban a magasabb frekvenciatartomány (100-640 Hz) tehető felelőssé.

Összegezve, a tACS és a tRNS hasznos eszközként szolgálhat neurofiziológiai alapkísérletek és klinikai kutatások során. Eredményeink alapján úgy tűnik, hogy a tRNS potenciális terápiás hatása az rTMS és tDCS terápiás hatásával mérhető. További vizsgálatok végzése azonban elengedhetetlen a biztonságos alkalmazási tartomány, illtve a potenciális klinikai használhatóság megállapítása végett.

Summary

For more than 20 years, non-invasive transcranial stimulation techniques like repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have been used to induce and potentiate neuroplastic-like effects in the human cortex, leading to synaptic alterations, namely the experience- and activity-dependent modification of synaptic transmission.

In our experiments we introduce novel methods of electrical stimulation, namely transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS). In the first group of our experiments we extended the tDCS technique to tACS. A marked decrease in motor evoked potential (MEP) amplitudes of about 20%, and improved implicit motor learning was observed after 10 Hz AC stimulation over the primary motor cortex (M1) in altogether 48 healthy subjects. If anodal or cathodal DC stimulation was superimposed on 5, 10 and 15 Hz AC stimulation, the MEP amplitudes were increased after anodal 10 and 15 Hz stimulation.

In the second group of studies, we introduce tRNS, whereby an alternating current with a random electrical oscillation-spectrum is applied over the M1. TRNS induced consistent excitability increases last 60 minutes post-stimulation. These effects have been observed in 80 subjects through both physiological measures (MEPs) and behavioural tasks (SRTT). Higher frequencies (100-640 Hz) appear to be responsible for generating this excitability increase.

Our results suggested that transcranial application of weak AC and RN currents may appear to be a tool for basic and clinical research in diseases with altered EEG activity. TRNS appears to possess at least the same therapeutic potential as rTMS or tDCS, while furthermore avoiding the constraint of current flow direction sensitivity characteristic of tDCS. Further studies are required to extend cautiously the safety range and uncover its influence on neuronal circuitries.

Introduction

Neuroplasticity is an ongoing, self-organizing, adaptive process widespread in cortical areas; it allows the brain to learn and adapt to new environmental situations. Several methods exist to influence excitability of the brain by external or transcranial stimulation. The most well-known methods to influence excitability of the brain by external means are transcranial magnetic stimulation (TMS) and weak transcranial direct current stimulation (tDCS).

Transcranial stimulation techniques in humans

Transcranial magnetic stimulation

One aim of developing external stimulation methods in humans was to modify cerebral excitability in a non-invasive, painless, reversible, and selective way. The most well-known method used to influence excitability of the brain by external means is TMS. Single pulse TMS is widely used in the routine diagnosis of pathological changes of the corticospinal tract and to estimate its integrity.

It was followed by various repetitive stimulation paradigms. RTMS is able to induce externally triggered alterations in the spiking pattern of neuronal populations, and interrupts or excites neuronal firing in a spatially and temporally restricted route. Recently another repetitive stimulation paradigm was introduced, namely theta burst stimulation (TBS). Although TBS increased the efficacy of rTMS by reducing stimulus intensity and the number of pulses required for achieving similar after-effects, its upper safety limits are still unclear due to the potential risk of rTMS inducing seizures.

Transcranial direct current stimulation

When compared to pulsed rTMS, tDCS represents the other end of the stimulation spectrum by delivering continuous electric current which leads to “brain polarization”. TDCS is able to induce long-lasting changes in cortical excitability in a reversible, relatively selective, painless and safe manner. Primarily, it causes polarity-dependent shifts of the resting membrane potential and consequently changes the firing rates of neurons under the electrodes, neuronal projections and subsequent connected cortical areas. Generally, M1 excitability is enhanced by anodal and decreased by cathodal stimulation. It allows for diagnostic and interventional applications, however, they also offer a potential therapeutic use in neurorehabilitation, chronic pain, focal epilepsy and neuropsychiatric disorders.

Aim of the studies

The aim of our experiments was to introduce novel methods of non-invasive electrical stimulation. In our first study we expand further the stimulation spectrum between DC and AC stimulation. To investigate the aftereffects of tACS we assayed a frequency spectrum between 1 and 45 Hz using transcranial electrical stimulation and analysed MEPs and EEG-spectra before and after AC stimulation, with and without an anodal and cathodal DC shift. Furthermore, on a behavioural level we studied AC-driven changes in performance during a variant of the serial reaction time task (SRTT), which is a standard paradigm to test implicit motor learning. In this task, subjects perform finger movements repetitively without being aware of a sequential order. We applied tACS or sham stimulation to the M1 during performance of the task.

In the second group of experiments we investigate the effect of tRNS. In our experiment we demonstrate this method of enhancing cortico-spinal and cortico-cortical excitability, as measured by TMS, by applying weak motor cortex tRNS for 10 minutes. Furthermore, a variant of the SRTT was used to study tRNS-driven changes in performance. In addition, we show how a mental or motor activity performed during stimulation can reduce the efficacy of tRNS, as previously described in the case of tDCS.

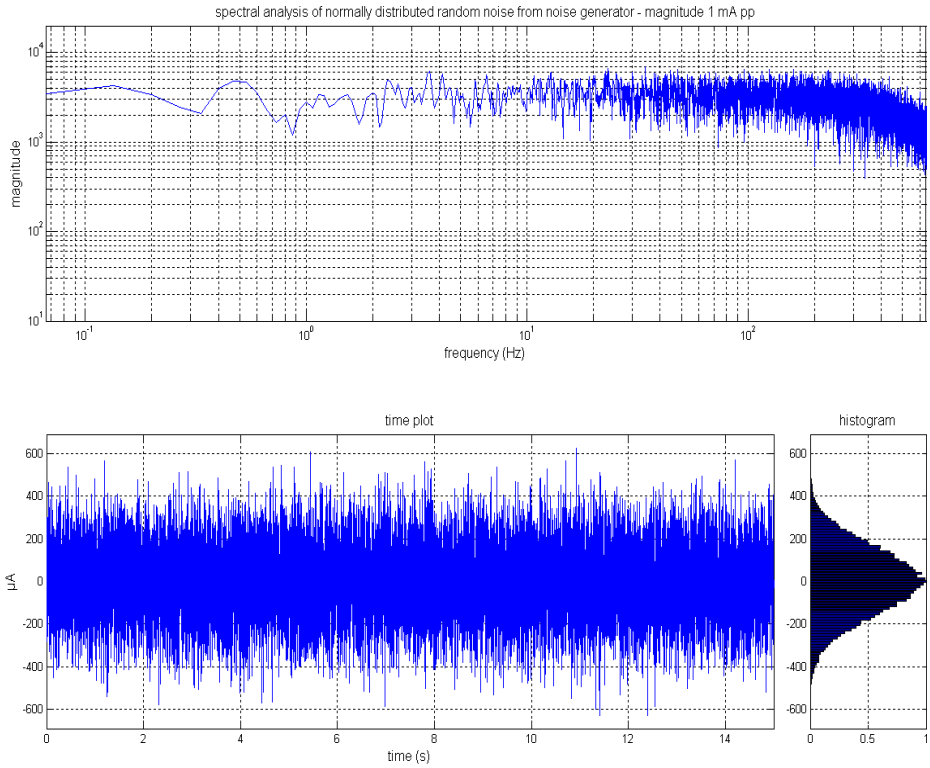
Methods and Materials

Subjects

Altogether 48 subjects participated in the tACS study, and 80 healthy volunteers were informed about all aspects of the tRNS experiment. None of the subjects suffered from any neurological and psychological disorders, and none had metallic implants/implanted electric devices, nor took any medication regularly. None of the subjects was on regular or acute medication. All subjects were right-handed, according to the Edinburgh handedness inventory. We conformed to the Declaration of Helsinki and the experimental protocol was approved by the Ethics Committee of the University of Göttingen.

tACS, tSDCS and tRNS

Electrical stimulation was delivered by a battery-driven constant-current stimulator (NeuroConn GmbH, Ilmenau, Germany) through conductive-rubber electrodes, encased in two saline-soaked sponges. In the stimulation mode “noise” there is a random level of current generated for every sample (sampling rate 1280 sps). The random numbers are normally distributed; the probability density function follows a bell-shaped curve. In the frequency spectrum all coefficients have a similar size (“white noise”). The noise signal contains all frequencies up to half of the sampling rate, i.e. a maximum of 640 Hz. In a second experiment this frequency spectrum was separated into a low (0.1 Hz – 100 Hz) and high (101 Hz – 640 Hz) frequency spectrum. Due to the statistical characteristics the signal has no DC offset, provided that the offset is set to zero.



The figure shows the output signal of the DC-Stimulator PLUS, as a frequency distribution of the signal; the time plot of the signal and as a histogram. The signal was generated by a computer. In the stimulation mode “noise“ there is a random level of current generated for every sample (sampling rate 1280 sps). The random numbers are normally distributed; the probability density function follows a bell-shaped curve. The amplitude of 1mA pp means that 99% of all generated amplitude values were between +500µA and -500µA

I. Electrophysiological studies

Transcranial magnetic stimulation (TMS)

To detect current-driven changes of excitability, motor evoked potentials (MEPs) of the right first dorsal interosseus muscle (FDI) were recorded following stimulation of its motor-cortical representational field by single-pulse TMS. These were induced using a Magstim 200 magnetic stimulator (Magstim Company, Whiteland, Wales, UK), with a figure-of-eight standard double magnetic coil. The coil was connected to two monophasic Magstim 200 stimulators via a bistim module (Magstim Co., Whiteland, Dyfed, UK) during the paired-pulse TMS study. Surface electromyogram (EMG) was recorded from the right FDI.

II. Behavioural studies

Serial Reaction Time Task (SRTT)

A behavioural task was used to study tRNS-driven changes in performance during a variant of the SRTT, which is a standard paradigm to test implicit motor learning. Subjects were seated in front of a computer screen at eye level behind a response pad with four buttons numbered 1-4 and were instructed to push each button with a different finger of the right hand. An asterisk appeared in one of four positions that were horizontally spaced on a computer screen and permanently marked by dots. The subjects were instructed to press the key corresponding to the position of the asterisk as fast as possible. After a button was pushed, the go signal disappeared. The test consisted of eight blocks of 120 trials. The test consisted of eight blocks of 120 trials. In blocks 1 and 6, the sequence of asterisks followed a pseudorandom order in that asterisks were presented with equal frequently in each position and never in the same position in two subsequent trials. In blocks 2 to 5 and 7 and 8, the same 12-trial sequence of asterisk positions repeated itself 10 times (abadbcdacbdc). Subjects were not informed about the repeating sequence. Whereas improved performance during the whole course of the task is due to implicit learning as well as to increasing task routine, differences in performance between block 5 and the random block 6 represent a measure of implicit learning only, as task routine is thought to be equivalent in both blocks, and thus any differences in performance should be due to implicit sequence learning.

Task-related modulation of tRNS

In this experiment we showed how a mental or motor activity performed during stimulation can reduce the efficacy of tRNS, as previously described in the case of tDCS.

III. Safety aspects

All of the subjects completed a questionnaire on the next day after the experimental sessions. The questionnaire contained rating scales for the presence and severity of headache, difficulties in concentrating, acute mood changes, visual perceptual changes, fatigue and discomforting sensations like pain, tingling, itching or burning under the electrodes during and after stimulation.

EEG recording

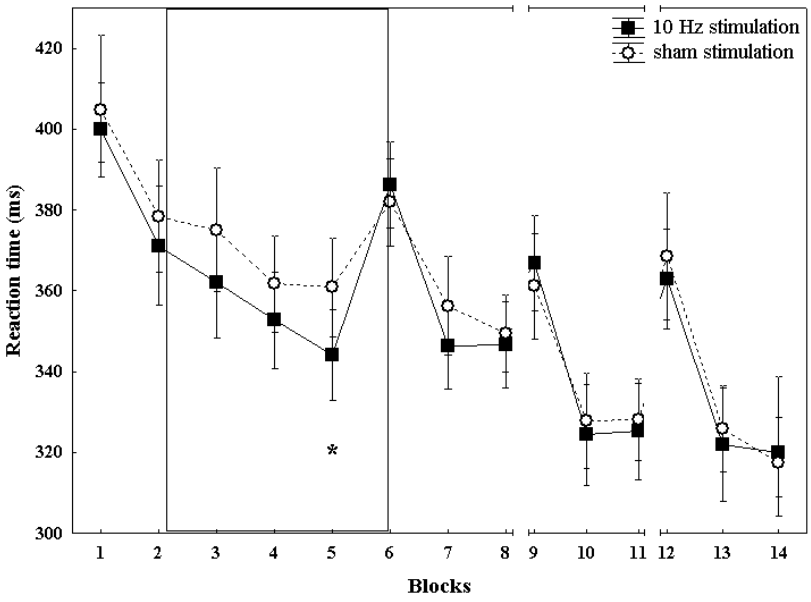
The EEG was recorded using a three channel montage. One electrode was placed over Oz and two laterally above the motor region (C3 and C4) in accordance with the international 10/20 system. Linked mastoids (RLm) were used as references; the ground electrode was positioned on the forehead.

Neuron-specific enolase (NSE) determination

To assess the safety of tRNS, we measured serum NSE, a sensitive marker of neuronal damage, evident in many neurological disorders, e.g. in epilepsy.

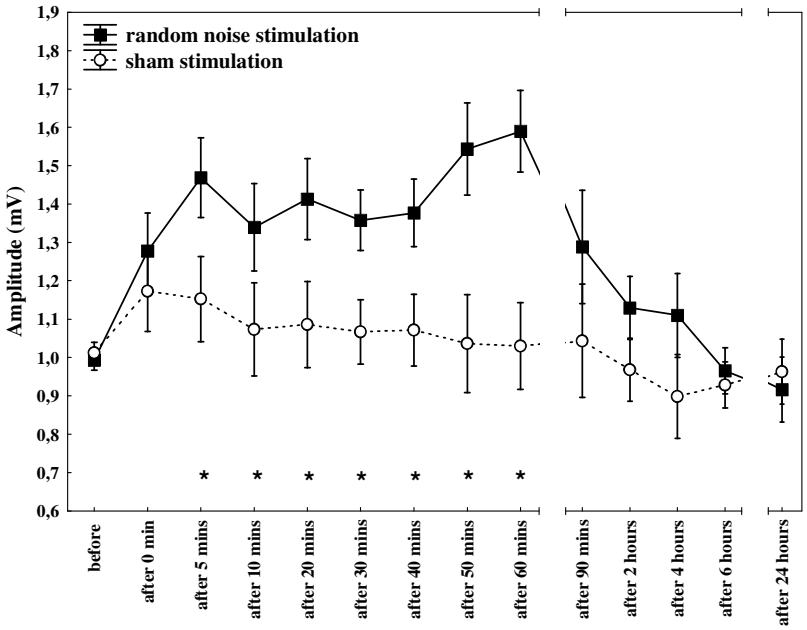
Main results

The aim of our present studies was to investigate new non-invasive transcranial stimulation techniques. We aimed to further expand the stimulation spectrum between DC and AC stimulation. For this we applied a frequency spectrum between 1 and 45 Hz using transcranial electrical stimulation and analysed MEPs, EEG-spectra and behavioural tasks, before and after AC stimulation, with and without an anodal and cathodal DC shift. The main result of this study was that 10 Hz tACS over the M1 using 7 min stimulation duration was able to improve implicit motor learning, and it modified motor cortical excitability that outlasted the stimulation duration itself. A marked decrease in MEP amplitude following 10 Hz AC stimulation was observed, compared to sham stimulation, without modifying EEG power.



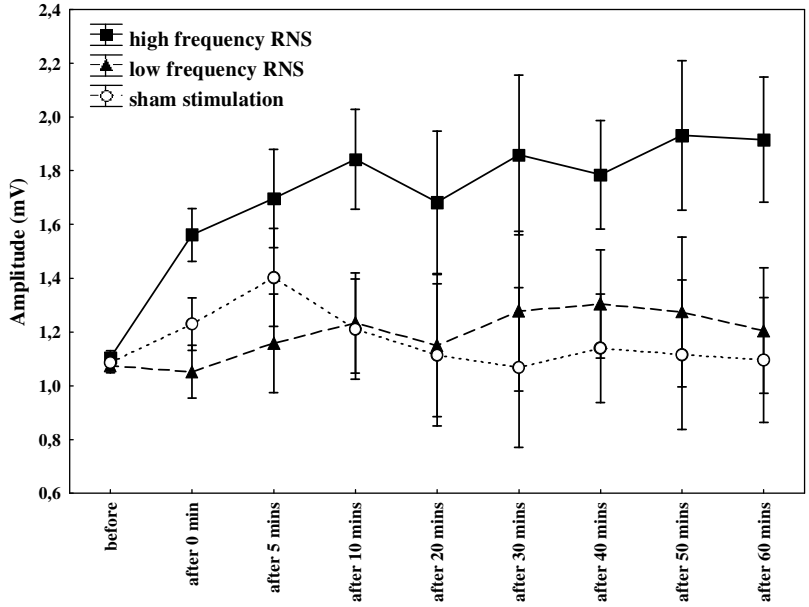
10 Hz tACS of the M1 improves implicit motor learning in its early phase. Reaction times decrease faster in the 10 Hz stimulation condition compared to the sham stimulation condition. Moreover, the RT difference comparing blocks 5 and 6, which indicates implicit sequence learning most purely, is bigger for the 10 Hz stimulation condition, when compared to the non-stimulation condition. The asterisk shows a significant difference regarding the reaction time differences between blocks 5 and 6, comparing 10 Hz and sham stimulation.

In our second experiment, we investigated a new stimulation technique, namely tRNS. In that study we demonstrated that weak tRNS over M1 enhances cortico-spinal excitability both during and after stimulation in the healthy human brain.



Effect of 10 min RN stimulation on motor evoked potentials. Time course of M1 excitability changes lasting for 60 minutes post-stimulation, shown after 10 min RN stimulation over M1 at 1mA, compared to sham stimulation. The figure shows mean amplitudes and their SEMs up to 60 min (including all subjects, n=17) and between 90 min and 24 hours (including eight subjects). Asterisks indicate significant differences between MEP amplitudes after 5, 10-60 min post-stimulation compared to baseline.

Furthermore, our results suggest that the high frequency subdivision of the whole tRNS spectrum between 100 and 640 Hz is functionally responsible for inducing excitability in the M1. The MEP declines observed after mental effort and motor activation are in agreement with previous studies using tDCS or paired associative stimulation (PAS).



Effect of 10 min low- (0.1 Hz-100 Hz) and high-frequency (101 Hz-640 Hz) RN stimulation on motor evoked potentials. Time course of M1 excitability changes lasting for 60 minutes post-stimulation, shown after 10 min high-frequency RN stimulation over M1 at 1mA, compared to low-frequency and sham stimulation. The figure shows mean amplitudes and their SEMs up to 60 min (including all subjects, n=12).

Summarizing table of our experiments

	Type of electrical stimulation	Study			Current intensity	Stimulation time	Main result of the experiment
Experiment 1 n=48	**tACS** 1, 10, 15, 30, 45 Hz	Electrophysiological studies	single-pulse TMS		400 µA	5 min	∅
		Behavioural studies	SRTT			~7 min	10 Hz: ↑ performance
		Safety aspects	EEG			4 min	∅
	tSDCS 5, 10, 15 Hz	Electrophysiological studies	TMS		250 µA	2, 4 min	∅
		Safety aspects	EEG			4 min	∅
Experiment 2 n=80	**tRNS**	Electrophysiological studies	single-pulse TMS	motor cortex	1000 µA	10 min	↑
				low frequency/high frequency			∅
				DC-shift induced excitability changes			∅
				premotor cortex			∅
				comparing to anodal tDCS			longer excitability changes after tRNS
			paired-pulse TMS				ICF: ↑
			iTBS				longer excitability changes after tRNS
		Behavioural studies	SRTT			~7 min	↑ performance
			task-related modulation			10 min	modified excitability increase
		Safety aspects	EEG			4 min	∅
			NSE				∅

Table 5. Summarizing table of our experiments.

Conclusion

In summary, the transcranial application of weak AC current and random noise may appear to be a promising tool for clinical neuroplasticity research. They allow for a selective, focal, non-invasive and reversible excitability modulation of the cortex. Furthermore, tRNS allows an unnoticeable and thus painless way to induce increases in cortical excitability. The main advantage of tRNS seems to be the direction insensitivity characteristic of the stimulation. It seems to provide a qualitatively new way of producing and interfering with brain plasticity. However, important research still has to be done, mainly in uncovering the mode of action, and in finding a way to prolong the aftereffects of weak current application further, as has already successfully been done in DC research.

Original papers listed in the thesis

I. Antal A, Boros K, Poreisz C, Chaieb L, **Terney D**, Paulus W. Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. *Brain Stimulation. 2008 Apr; 1(2):97-105.*

II. **Terney D,** Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. *The Journal of Neuroscience. 2008 Dec; 28(52):14147-14155.*

Other publications related to the dissertation

Antal A, **Terney D**, Poreisz C, Paulus W. Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. *European Journal of Neuroscience. 2007; 26:2687-2691.*

Terney D, Bergmann I, Poreisz C, Chaieb L, Boros K, Nitsche MA, Paulus W, Antal A. Pergolide increases the efficacy of cathodal direct current stimulation to reduce the amplitude of laser-evoked potentials in humans. *Journal of Pain and Symptom Management. 2008; 36(1):79-91.*

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