Non-invasive brain stimulation and fear extinction.

A systematic review

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Summary

Background: Despite the high prevalence of stress- and anxiety-related disorders, corresponding therapeutic measures have not yet reached their full potential. Recently, a number of studies have investigated the additional benefit of non-invasive brain stimulation (NIBS) in the psychotherapy of anxiety disorders. In order to further improve the effectiveness of brain stimulation in combination with psychotherapy, it is necessary to focus more on the modulation of therapy-relevant learning processes.

Methods: This systematic review presents the studies to date that have investigated modulation of fear extinction in humans using NIBS.

Results: A total of 7 studies were identified and analyzed using either repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) for fear extinction.

Conclusions: The review shows that NIBS can improve extinction learning. The transfer of these results into clinical trials has already begun and will provide clarity on the optimal stimulation parameters in the coming years.

Keywords: Non-invasive brain stimulation, tDCS, rTMS, anxiety disorders

With more than 15% (1), the lifetime prevalence of anxiety disorders is very high. To further improve the psycho-therapeutic approaches (such as cognitive behavioral therapy), non-invasive brain stimulation (NIBS) methods are currently being investigated. The idea is to improve therapy related processes, like extinction learning, via NIBS.

In this systematic review, we summarize all previous studies that investigate NIBS to improve fear learning.

Introduction

Anxiety Disorders

With more than 15% (1), the lifetime prevalence of anxiety disorders is very high and exceeds the incidence of affective disorders and substance use disorders. Also in the area of disease burden expressed in "Disability-adjusted life years" (dalys), patients with anxiety disorders show the second highest value after patients with depressive disorders (2).

The gold standard in the treatment of anxiety disorders is cognitive behavioral therapy (CBT; 3). However, not all patients benefit sufficiently from such treatment (4). Recently, a number of studies have investigated the benefits of non-invasive brain stimulation (NIBS) in the treatment of mental disorders. Two systematic reviews show that NIBS has a positive effect on symptoms both in the treatment of panic disorder (5) and in the treatment of post-traumatic stress

disorder (6). However, it remains to be seen what the optimal stimulation parameters are and whether activating or inhibitory brain stimulation is more beneficial. The initial studies aimed to normalize impaired prefrontal brain function through NIBS and thus achieve a positive therapeutic outcome. Marin and colleagues (7) alternatively suggest focusing more on the learning processes that are relevant in psychotherapy and optimizing them with NIBS. A systematic overview of the combination of NIBS with psychotherapy for anxiety disorders shows a positive additional effect of combined brain stimulation in the medium range (8), although not all studies explicitly refer to therapy-relevant learning processes. Extinction learning is an important learning process, which is essential in exposure therapy of anxiety disorders (9). In this systematic review, therefore, all work dealing with the modulation of fear extinction using NIBS will be compiled.

Non-invasive brain stimulation

NIBS includes transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS). In tDCS, weak electrical currents (1–2 mA) are transmitted by means of two electrodes (anode, cathode), which increase or decrease the spontaneous firing rate of the neurons by changing the resting membrane potential (neuromodulatory function (10)). In contrast, repetitive transcranial magnetic stimulation (rTMS) can induce a magnetic field

and focally modulate brain activity with the help of a magnetic coil applied tangentially to the skull. Depending on the frequency of the stimulation, the stimulation then has an inhibitory (< 1 Hz) or excitatory (5–20 Hz) effect on the underlying neurons and axons (11).

This systematic review integrates previous studies on the direct combination of brain stimulation procedures with fear extinction learning.

Review

Search strategy

The systematic literature search included the databases Pubmed, CENTRAL, Web of Science, Ovid MEDLINE and PsychINFO and was carried out in March 2019 with the following search terms: (tms or tdcS or rtms or NIBs) and ((extinction learning) or (fear extinction)). 75 literature references were identified. After removing the duplicates, 54 publications remained available for pre-selection (see flow chart in Figure 1). The following inclusion and exclusion criteria were used for the preselection:

Inclusion criteria:

1. written in English or German language
2. the study was carried out on humans
3. only adult participants were enrolled
4. a fear conditioning and fear extinction paradigm was performed.

Exclusion criteria

1. review, conference contributions, comments
2. therapy studies

Eleven papers were then tested for suitability in full text. Four publications had to be excluded, as only fear learning and not fear extinction was examined so that a total of seven studies could be included in this systematic review.

Results

Table 1 lists the work included in this review. Two papers use rTMS as non-invasive brain stimulation method, five use tDCS.

The first study investigating the modulation of the mPFC by rTMS was published by Guhn and colleagues (12). The authors first performed a differential fear conditioning with two faces (CS+, CS-) in healthy volunteers; a cry was used as unconditioned stimulus (UCS). The study was conducted as a randomized, single-blind study. Before the extinction

phase, the experimental group received a high-frequency rTMS above the mPFC (electrode position Fpz) and the control group received a sham stimulation. Immediately after the stimulation, both faces were presented again, this time without the aversive scream to enable extinction learning. On the following day, both faces were presented again without the aversive cry and without prior brain stimulation. Guhn et al. (12) found that the subjects of the experimental group had a significantly lower startle reflex and a significantly lower skin conductance response to the conditioned stimulus during extinction learning compared to the subjects of the control group. The subjects of the experimental group also rated their arousal lower than the subjects of the control group. When the faces were presented again on the second day, the experimental group still showed a significantly lower startle reflex than the control group. Overall, the results of Guhn et al. (12) indicate that after active stimulation of the mPFC (19) an extinction memory can be better acquired and retrieved than after sham stimulation. In a subsequent study, this stimulation protocol was successfully used to improve the exposure therapy of heights phobic patients (20). In the second work with the method rTMS (13) the mPFC was also selected as target region, but with a different stimulation approach. High-frequency rTMS was performed during extinction simultaneously with CS presentation (100 ms after onset). Two regions in the left prefrontal cortex were chosen as stimulation sites, but only one of

Table 1: Included studies

Author (year)	Number of probands real /sham	Paradigm	Stimulation			
			Methods	Localisation	Duration	Frequency /intensity
Guhn et al. (2014)	40/45	2-days	rTMS	FPz	20 minutes	10 Hz
Raij et al. (2018)	28	3-days	rTMS	left PFC	300 ms	20 Hz
Van't Wout et al. (2016)	44	2-days	tDCS	AF3, contralateral Mastoid	5 minutes	1.0 mA
Abend et al. (2016)	15/14	3-days	tDCS	FPz-Oz	20 minutes	1.5 mA
Dittert et al. (2018)	50/34	1-day	tDCS	F7-F8	20 minutes	1.5 mA
Van't Wout et al. (2017)	28	2- days	tDCS	AF3, contralateral Mastoid	10 minutes	1.5 mA
Ganho et al. (2019)	32/16	2-days Follow-up	tDCS	F4, contralateral Deltoid	20 minutes	1.0 mA

FPz, AF3, Oz, F7, F8, F4 = EEG electrode positions according to international 10-20 system; PFC = prefrontal cortex; mA= Milliampere; Hz = frequency in Hertz

them was functionally coupled to the ventromedial cortex, which was described as a neuronal correlate for extinction learning (9). The second region served as a control stimulation site. In this study, the subjects were conditioned on the first day; on the second day the extinction was combined with the TMS treatment. On the third day, the extinction recall showed a significantly reduced skin conductance response to CS+, but only in the group with stimulation above the region which has a functional coupling with the vmPFC.

The first work with the method of tDCS was published by Van 't Wout et al. (14) with a cross-over design. On day 1 a fear acquisition and extinction learning paradigm was performed, and on day 2 the extinction memory was retrieved. A special feature of this study was that two CSs+ were learned during the fear acquisition and deleted individually within two extinction blocks. In addition, the groups were divided so that one group received the tDCS (2 mA, 10 min) before and during block 1 (tDCS group 1) and the other group received it before and during block 2 (tDCS group 2). All

subjects went through the tDCS once and the sham condition once (within-subject design). In this study, a bilateral electrode arrangement (anode: AF3, cathode: contralateral mastoid) was chosen. There were group differences during extinction learning of the second CS+: compared to tDCS group 2, tDCS group 1 showed a smaller SCR in the late extinction in extinction block 2. A tDCS during extinction training could thus improve extinction learning in later extinction training for a second CS+. Since tDCS group 1 was stimulated before and during extinction block 1 and not 2, the SCR decrease in the second block could also have been caused by anxiolytic tDCS after-effects and thus not be an expression of improved extinction learning with tDCS.

In the same year, Abend et al. (15) published another randomized double-blind study. The subjects underwent a differential fear conditioning protocol (CS+, CS-) on the first day, and extinction was performed for 20 minutes on the second day. One group received a tDCS with 1.5 mA, a second group a transcranial alternating

electrical stimulation with 1 Hz and the third group a sham stimulation. To stimulate the mPFC, the authors chose an electrode arrangement with the anode between the EEG electrode positions Fpz and Fp1 above the frontal forehead and the cathode posterior below the occipital lobe. The results showed, however, that tDCS did not lead to a decreased skin conductance response to CS+ during extinction training; instead, an increased response to CS- was observed.

The next study was published in 2018 by Dittert et al. (16) and showed a positive effect of tDCS on fear extinction. This study was also conducted as a double-blind randomized study. The electrodes were placed bilaterally slightly below electrode positions F7 and F8. After a differential fear conditioning, the tDCS was initially performed at 1.5 mA for 10 minutes. With real stimulation, there was a significant reduction from acquisition to extinction for CS+ which was stronger than in the sham stimulated group. However, since in this study the extinction was performed on the same day as the fear conditioning, the effects could also be explained by a disturbance of the consolidation (22).

In the fourth study by van t'Wout et al. (17), patients with post-traumatic stress disorder (PTSD) underwent a two-day protocol. Fear conditioning and extinction were performed on the first day and extinction was repeated on the second day to measure extinction memory. On day 1, part of the patients received a 2 mA tDCS for

10 minutes during the extinction, another part after the extinction. The anode was placed over AF3. Since the study did not include a control group, the two stimulation groups were compared. On day 1 there were no significant effects in the extinction between the groups, but on day 2 there was a tendency to decrease the response to CS+ in patients receiving tDCS after extinction.

For the sake of completeness, a final paper, which has not yet undergone a peer review and can only be found on a preprint server (18), will also be presented. In the study, the right dorsolateral prefrontal cortex (dlPFC) was cathodically stimulated (against the left deltoid muscle). The skin conductance data show no effect of the stimulation on the extinction performance on day 2 of the experiment. In the follow-up after 1–3 months, a tDCS effect on avoidance behavior was observed when measured with a PC-based Approach-Avoidance Test (AAT).

Discussion

In summary, it can be stated that promising approaches have been published for both rTMS and tDCS which suggest that fear extinction learning can be improved by non-invasive brain stimulation. For rTMS, mPFC stimulation has already been translated into a therapy study. It has been shown that exposure therapy of heights phobic patients combined with rTMS leads to a significantly stronger reduction of symptoms compared to the control group (20). The approach

published by Raij et al. (23) to stimulate an area on the cortex surface with rTMS, which shows a functional coupling with the vmPFC, appears very promising. In future studies, individually defined regions could be used to further optimize the stimulation effects.

For the method tDCS, first studies show positive effects, but the results have to be replicated and extended. The work of van 't Wout et al. (14, 17) suggests that the arrangement of the stimulation electrodes used in these studies does not modulate the extinction power per se, but more likely modulates the consolidation of the extinction memory. The authors have shown in a feasibility study that the combination of tDCS with an exposure therapy is possible in virtual reality (24) so that in the future some new randomized and controlled therapy studies with this procedure will certainly be published. The stimulation protocol of Dittert (16) has to be replicated and, even with a consolidated fear memory, must effectively increase extinction before a positive effect in exposure therapy can be expected. The work of Abend et al. (15) shows no positive effect, the corresponding stimulation protocol should therefore rather not be pursued further. The results of the last study (18) are more aimed at avoidance behavior and show no effects on extinction learning. However, avoidance behavior is a relevant aspect for the therapy of anxiety disorders and should, therefore, be pursued further. Instead of an inhibition of the right dorsolateral

prefrontal cortex by cathodal stimulation as described in the above study (18), an improvement of the emotion regulation by anodic activation of the right inferior frontal cortex (25, 26) is also possible. Overall, the studies show first positive effects that extinction learning can be modified by brain stimulation procedures. However, future studies should increasingly consider the different processes involved in extinction (27). It would be useful to differentiate whether extinction learning or extinction consolidation should be modulated by brain stimulation (28).

Conclusion for the practice

- Laboratory experiments show that NIBS can improve fear extinction
- The first randomized controlled trials also showed a positive effect of NIBS in the psychotherapy of anxiety disorders.
- Further studies are needed to determine the optimal stimulation parameters.

Conflict of interest. The authors state that there is no conflict of interest.

This article does not include primary data from studies on humans or animals. The german version of this paper can be found here (29).

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