Eur Arch Psychiatry Clin Neurosci (2014) 264 (Suppl 1):S27–S33
DOI 10.1007/s00406-014-0540-6

REVIEW

A perfect match: noninvasive brain stimulation and psychotherapy

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Received: 17 August 2014 / Accepted: 8 September 2014 / Published online: 25 September 2014
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Abstract One out of four patients with a psychiatric disorder does not tolerate or sufficiently respond to standard treatments, leading to impaired quality of life, significant morbidity and mortality, as well as high socioeconomic costs. There is increasing evidence that—apart from psychopharmacologic and psychotherapeutic interventions—targeted modulation of neural networks by brain stimulation techniques might serve as a third treatment modality. In the whole spectrum of treatment modalities, combined approaches are often used for difficult-to-treat patients. They may be superior strategies compared to monotherapy and could possible also include brain stimulation interventions. However, systematic research is lacking for the latter issue. Particularly, noninvasive brain stimulation (NIBS), e.g., transcranial direct current stimulation (tDCS) can be easily combined with psychotherapy approaches. Here, we introduce NIBS techniques for priming and augmenting psychotherapy, review preliminary data and propose a future research strategy. Interestingly, this strategy parallels the promising development in neurology and neurorehabilitation where tDCS is currently combined with functional training tasks to enhance motor or cognitive performance.

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Keywords Non-invasive brain stimulation · Cognitive-behavioral therapy · Depression · Transcranial magnetic stimulation · Transcranial direct current stimulation

Introduction

Psychiatric disorders are leading the list of highly prevalent disorders, causing major individual burden of disease (clinical symptoms, impairment of social functioning and quality of life, mortality) and high direct and indirect economic costs (in Europe 2010, between 74 and 113 billion € for anxiety, psychotic and mood disorders, respectively) [70]. Despite the fact that for most psychiatric disorders, the majority of patients can be treated by either evidenced-based pharmacotherapy or psychotherapy, 20–30 % of patients with mood or anxiety disorders and up to 50 % of patients with schizophrenia do not sufficiently respond to standard therapeutic interventions [32, 57, 72]. Thus, there is need for novel effective treatment strategies in order to ameliorate the course of disease, to improve quality of life and to improve the level of individual psychosocial functioning. The classical research strategy for developing novel interventions is aimed at the development of a single effective intervention for a distinct psychiatric disorder. However, it appears questionable whether this can be achieved in psychiatric conditions with a considerable heterogeneity in their respective pathophysiology. Thus, personalized adjustment of interventions combing effective approaches would be another promising avenue of development. Here, we hypothesize that combining noninvasive brain stimulation (NIBS) and psychotherapy could constitute a promising novel approach for developing personalized interventions in psychiatry.

Based on a large body of neurobiological evidence, psychiatric disorders are conceptualized as system-level

disorders of the brain. The increasing understanding of the critical role of specific brain sites within distinct brain circuits has generated a broad interest in anatomy- and neurophysiology-based therapeutic interventions directly interacting with dysfunctional brain structures and associated networks. Promising research lines have provided sound preclinical and clinical data strongly supporting the application of NIBS as treatment for psychiatric disorders in order to overrule treatment resistance and chronicity. The increasing clinical use of NIBS techniques testifies the potential effectiveness of these treatment strategies.

Brain stimulation as "third pillar" of psychiatric treatment

Data from animal experimental, structural and functional imaging as well as neurophysiological studies converge to indicate that psychiatric disorders exhibit more or less reversible changes in neural networks [15, 29, 36, 43, 46, 47, 52, 56, 62]. Several key regions and hubs within networks involved in the pathophysiology of common psychiatric disorders are located in the prefrontal cortex (PFC) [36, 47, 52]. Targeted stimulation of PFC subregions and closely connected areas by NIBS, but also invasive brain stimulation, allows modulation within dependent networks that translate into functional and behavioral modifications [17, 39, 48, 50]. NIBS methods balancing dysregulated neural network connectivity may therefore provide a new causative therapeutic paradigm for the treatment of psychiatric disorders.

Strong preclinical and clinical evidence suggests that NIBS as well as convulsive or invasive brain stimulation is therapeutically effective in defined common psychiatric disorders [2, 7, 20, 27, 50, 51, 69]. For instance, in major depressive disorders (MDD), the clinical evidence includes the application of electroconvulsive therapy (ECT) [38, 65] which is still the most effective antidepressant intervention to date, three large randomized controlled trials (RCT) with prefrontal repetitive transcranial magnetic stimulation (rTMS) [22, 37, 49], one large RCT with prefrontal transcranial direct current stimulation (tDCS) [11] and deep brain stimulation (DBS) [39, 42, 44, 55] trials.

Particularly, NIBS techniques are promising for a wider application in different psychiatric settings based on their mode of action and their favorable side effect profile. Here, we distinguish NIBS from convulsive techniques, i.e., ECT and magnetic seizure therapy (MST) as well as from invasive methods, i.e., DBS and vagus nerve stimulation (VNS). The array of NIBS includes rTMS, tDCS, but also interventions which have been developed more recently, e.g., transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS) and transcutaneous vagus nerve stimulation (tVNS).

Why the combination of noninvasive brain stimulation and psychotherapy makes sense?

From a neuroscientist's point of view, NIBS and psychotherapy resemble each other in some respect, i.e., the mode of intermittent intervention leading to persistent changes in neuronal networks and their behavioral correlates outlasting the acute interventions. Both interventions are applied for a short period of time (10–60 min) on a single or several days during the week without treatment ongoing during intervals. This is in contrast to pharmacotherapy, where drug levels in blood and brain lead to a constant stimulation of neurotransmitter systems.

Functional neuroimaging studies of the effects of psychotherapy [1, 4] have generated preliminary knowledge of the effects of psychotherapy on neuronal networks which allow to relate these effects not only to the functional anatomy of pathological conditions, but also to specific effects NIBS exert. Moreover, enhancing implicit or explicit learning or cognitive control or just top-down control of emotional stimuli and reactions may lay the ground where NIBS and psychotherapy could interact.

Third, NIBS offers unique positive characteristics distinguishing this therapeutic approach from other currently available interventions:

- NIBS is well tolerated, especially if compared to other neuromodulatory interventions such as ECT as the best available antidepressant intervention that unfortunately still has relevant cognitive side effects in some patients as one the main limiting factors [8, 45]. Even more, NIBS has not only proven to be well tolerated, but also has shown that it has the potential to enhance basic neurocognitive functions [30]. This leads to recent discussions about ethical implications of "cosmetic neurology" [28].
- NIBS is easy to handle. Other neuromodulatory interventions need neurosurgeons or a complex setting with anesthesiologists. NIBS, and here especially tDCS, is so easy to apply that it even finds its way into life style applications far beyond FDA regulations and therapeutic indications (e.g., www.foc.us).
- NIBS is widely accepted among patients and health care professionals [5, 6].
- NIBS is assumed to be cost-effective. Although systematic studies are lacking, low cost for development, production, material and health care professionals especially for tDCS suggest that NIBS is more cost-effective as compared to other neuromodulatory

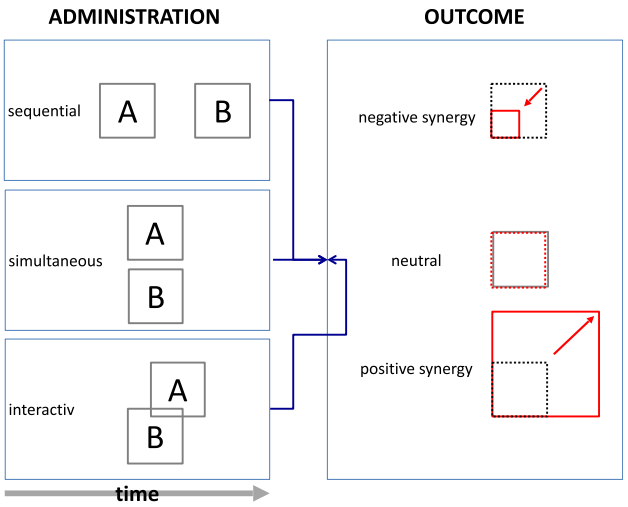

Fig. 1 Forms of interaction and effects of combining psychotherapy and brain stimulation. The two therapeutic interventions can be combined either in a sequential fashion, simultaneously without interdependencies or in an interactive synergistic way. Theoretically, the two therapeutic interventions can either have no effect (*neutral*), antagonize (*negative synergy*) or augment (*positive synergy*) each other

interventions such as DBS or pharmacological interventions.

- And finally, NIBS and cognitive-behavioral psychotherapy increase dorsolateral prefrontal cortex activity to convey their clinical effects.

Taken these arguments, it is therefore tempting to combine these two methods with the aim to increase efficacy while taking advantage of the four mentioned beneficial characteristics. This approach becomes even more meaningful since converging evidence indicates that synergistic effects can occur on a neurobiological, behavioral, as well as on a clinical level.

Possibilities of combining noninvasive brain stimulation and psychotherapy

If two therapeutic interventions A and B should be used together, three different combination patterns are possible: Interventions can be administered one after the other (sequential), in parallel independently (simultaneous) or in a way where the effect of one intervention has an impact and depends on the effect of another intervention (interactive). All of the three combination patterns may result in either no added value (*neutral*), or in reduced effects (*negative synergy*) or in a usually wished augmentative effect (i.e., *positive synergy*, see Fig. 1). In the case of NIBS and psychotherapy, examples for the three approaches would be: (1) Cognitive-behavioral therapy is being performed as a continuation treatment after successful BS (*sequential*); (2) A depressive patient receives prefrontal TMS and at the same time cognitive-behavioral therapy (*simultaneous*); (3) tDCS is used to facilitate the psychotherapeutic technique of cognitive control or the mechanism of emotional learning (*interactive)*. Along this line, neuromodulation and psychotherapy can interact on two different levels: First, NIBS can enhance processes by mechanisms involved with direct interaction with neural activity in a stimulated area needed for task performance. A second possible interaction would be the NIBS induced disruption of neuronal processing which competes or distracts from therapeutically relevant cognitive processes.

Pilot studies on the interaction between NIBS and emotions/cognition/behavior

Numerous studies in cognitive neurosciences have successfully used NIBS for modulation of cognitive functions, emotions and behavior e.g., [41]. Many of those studies have concluded that NIBS may finally serve to modulate such functions in a therapeutic manner leading to improved or normalized performance.

Direct cortical effects elicited by rTMS range from basic working memory tasks to more complex judgment tasks. Cattaneo and colleagues [13] performed a study in which they demonstrated that nonverbal working memory improved after NIBS. Along this line, rTMS has led to improvement in language [40] and spatial [66], as well as in emotional word dimensions of working memory [24, 25, 67, 68]. Of importance in the context of an approach aiming at the improvement of psychotherapeutic outcome, rTMS demonstrated to improve continuous performance [31] as well as attention [14].

Disruption of distracting activities is another mechanism (see above) by which rTMS exerts its efficacy. Again, effects were reported on different relevant neuropsychological domains. Kirschen et al. [33] were able to demonstrate that virtual lesions elicited by rTMS improved verbal working memory performance. Similarly, Sauseng and colleagues [54] increased working memory capacity by high-frequency rTMS and Schutter and van Honk [58] by low-frequency rTMS. Attention was improved by different potentially activity disrupting rTMS protocols such as low-frequency rTMS [64] and continuous theta burst stimulation, a novel variant of rTMS [21]. Along this line, tDCS has also demonstrated to improve a broad variety of different psychotherapeutically relevant cognitive functions such as the processing of emotional memory [67, 68], as well as emotion regulation [18].

Discussing the relevance of single observations for the issue of combined NIBS psychotherapy approaches

requires a definition of functions relevant for the principles of psychotherapy. This spectrum of functions reaches from (1) simple explicit learning to (2) implicit cognitive processes, e.g., implicit learning or processes involved in mentalization to (3) cognitive control over emotional content (top-down) or (4) regulation of emotions in order to allow improved cognitive performance (bottom-up) or (5) modulating social cognition and behavior including communication and bonding. In addition, there is a huge array of structural functions of the self: e.g., the interaction of self-perception x object-perception including theory of mind (ToM) functions.

Theoretically, each function or construct has its own neurocognitive underpinnings. Thus, augmentation of single functions by NIBS needs to be carefully based on specific neurocognitive concepts. One example of this idea is a research track starting at neurocognitive findings in major depression involving prefrontal cortex functions (3), running though studies on specific cognitive tasks which can also be used as therapeutic interventions, i.e., cognitive control therapy (CCT, 61) and ending so far at first evidence that CCT can be successfully combined with tDCS [61, 11 und/oder 13]. Segrave [61] and colleagues were able to demonstrate superior effects for the combination of CCT + 2 mA tDCS for 5 days over both CCT + placebo tDCS and placebo CCT + 2 mA tDCS during follow-up 3 weeks after the end of treatment. The other recent, randomized, double-blind, placebo-controlled trial investigated the combination of a CCT with 2 mA tDCS for 10 days [10, 12] demonstrating that CCT + tDCS was superior over CCT + placebo tDCS only if age and cognitive performance were taken into account. Both pilot trials represent explorative proof-of-principle studies, but do not allow generalizing their results for ready-to-use clinical applications in depression. However, this principle can be easily extended to interventions targeting other neurocognitive domains: e.g., other groups demonstrated that tDCS can be applied to enhance cognitive control over negative emotional content in major depression [10, 12, 72]. Similarly, tDCS could be similarly used in conjunction with specific neurocognitive training in depression (i.e., anti-rumination interventions), but may be also helpful for augmenting cognitive-behavioral therapy (CBT) in general.

Combined NIBS psychotherapy approaches may also be a valuable treatment options for other disorders, e.g., in addiction, both tDCS as well as intermittent theta burst stimulation combined with psychotherapy showed beneficial effects on intermediate tobacco abstinence [19, 53]. Rüther et al. also demonstrated that tDCS can be easily applied as simultaneous treatment in a group of 12 patients undergoing tDCS for priming of an immediately subsequent cognitive-behavioral group therapy. This novel NIBS "group therapy" approach also underlines the favorable profile of tDCS for wider clinical applications.

The issue of phenotypes and endophenotypes

At this stage, most studies investigating clinical effects of NIBS mainly focus on therapeutic outcomes such as the global improvement of symptoms in depression or schizophrenia often with modest clinical effects. Attempts to identify clinically defined subgroups in order to improve efficacy have only inconsistently been successful [7, 9]. Starting with the considerations on specifically augmenting neurocognitive performance, we also suggest that an alternative approach based on neurobiological findings and sharply defined endophenotypes [23] might be more promising. If endophenotypes relevant for successful cognitive-behavioral therapy are selected as targets for NIBS, they in addition open the opportunity for combining different approaches based on neurobiological knowledge and in a synergistic fashion. In theory, the way is clearly defined departing at findings in which NIBS have been proven to have neuroenhancement capabilities, via beneficial effects on an endophenotype level in clinical population, toward trials in which these findings are evaluated in larger clinical populations. As outlined above, there is a huge number of findings indicating that NIBS can improve cortical functions relevant for a successful psychotherapy in healthy volunteers; however, translation into clinical populations is rarely seen. Previous results indicate that NIBS techniques—if investigated at an endophenotype level—have profound effects on psychotherapeutically relevant cognitive functions such as memory, cognitive control, emotion regulation or attention. So far, only few studies have taken the next (translational) step and investigated how such modulation of cognitive endophenotypes can be used in a therapeutic setting.

Future directions

NIBS has the big advantage that the translational stretch of way is rather short as compared to other therapeutic interventions. Focusing on cognitive endophenotypes rather than on clinical disorders has the big advantage that augmented cognitive processes can be incorporated into psychotherapeutic settings. In addition, such augmented techniques have the potential to be used in many other conditions in which executive planning, the ability to direct and sustain attention, language and several types of memory are of importance [60]. In the neighboring disciplines of neurorehabilitation, NIBS as an augmentation for

cognitive [19, 64] and motor training [34] are already under investigation in larger clinical trials. Starting point for the development of mechanism-based therapies will always arise from very basic cognitive neuroscience findings such as the modulation of fear conditioning in a health population [26] or from clinical findings such as the improvement of working memory deficits in schizophrenia [36] or the reduction of craving by rTMS in alcohol use disorder [35]. The next step would be to evaluate whether NIBS effects are big and relevant enough for distinct disease entities. This could be carried out by model-based evaluation in proof-of-principle studies investigating whether sequential, simultaneous or interactive NIBS psychotherapy approaches are proposed by pilot data of clinical outcomes. The final step within this translational process would be large multicenter trials and upon success the implementation into therapeutic guidelines.

Conflict of interest Malek Bajbouj has received fundings from the Deutsche Forschungsgemeinschaft as well as unrestricted grants from Medtronic and Tonica. Frank Padberg has received grants and research support from Brainsway Inc., Israel, and NeuroConn GmbH, Ilmenau, Germany.

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