



Short Commentary

# Not too late: Towards Personalized Treatment of Persistent Depression Using Neuromodulating Augmentation Strategies

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## Persistence of depression requires a personalized treatment approach

Depression is one of the most common psychiatric disorders affecting nearly 300 million people worldwide [1]. Not only is depression highly prevalent, it is also associated with chronicity, comorbidity, and suicidality, thereby greatly impacting quality of life. Although many effective treatment options are available for depression, up to 35% of patients do not respond to first-line treatment such as psychotherapy and antidepressant medication [2]. These patients suffer from persistent depression, which is most commonly operationalized as an inadequate response to at least two treatment trials of adequate dose and duration. A comprehensive reassessment of existing treatment approaches to depression is imperative, particularly those that allow a personalized approach and that account for the high prevalence of comorbidities we see in persistent depression. Accessible pharmacological and psychotherapeutic treatments remain central in the treatment of persistent depression. However, a way forward is adding or reorienting towards novel interventions that fit the patient's life and clinical profile, and that target transdiagnostic mental health mechanisms. We are therefore thrilled that there is increasing focus on personalized therapeutic (augmentation) strategies that are cost-effective, evidence-based, mechanism-oriented, safe, and scalable.

## Non-invasive brain stimulation (NIBS)

NIBS techniques have emerged as promising tools in this regard. NIBS aims at modulating brain activity without surgical

intervention or invasive procedures, using electrical, magnetic, or physical forces [3]. NIBS includes both convulsive and non-convulsive therapies and has a rich historical context within Europe. For example, electroconvulsive therapy (ECT) was introduced by the Italians Cerletti and Bini in 1938 and to date is still thought to be the most effective biological treatment option in depression [4].

Transcranial magnetic stimulation (TMS) technology advancements in the 80s were driven by the British neurophysiologist Anthony Barker and team [5]. Repetitive transcranial magnetic stimulation (rTMS) is a form of noninvasive neurostimulation that is increasingly being used in (persistent) depression with promising effects. The therapeutic effect of rTMS is achieved by delivering magnetic pulses through a coil that is positioned above the head. The magnetic field causes an electrical current in the underlying cortex that modulates neuronal activity also after the stimulation (for a recent review on rTMS in depression [6]).

Moreover, researchers from Germany have substantially contributed to the understanding of the mechanisms and applications of low intensity transcranial electrical stimulation [7,8]. Moreover, some NIBS techniques can be made widely available and can be implemented cost-effectively routine clinical care, in contrast to the invasive deep brain stimulation methods which require surgery and that are restricted to only a few specialist sites across Europe. An additional benefit of most NIBS is the potential for at-home and event long-term use, partly due to technical advances and tech-literacy improvement of the population.

### **Natural brain stimulation by means of physical exercise**

This potential for clinical and long-term at-home uptake of NIBS holds especially true for a natural form of brain stimulation: physical exercise (PA). PA - planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness [9] - has neuromodulating effects akin to other NIBS techniques which include the increase of neuroplasticity of the brain [10-12]. Ancient societies already used PA to improve mental health [13] and its potential as monotherapy of depression is widely supported [14-17]. PA's attractiveness is partly due to its general health benefits [18], personalization potential, and low-risk no-side-effect long-term use [14,19].

### **Brain-state dependency as augmentation strategy**

The effect of treatment for persistent depression needs to be interpreted as an interaction between treatment-induced and ongoing neural processing. This so-called *acute brain state* refers to the current physiological and neurological conditions of the brain, can indeed influence the effectiveness of brain stimulation and other forms of treatment. Factors such as mood, stress/arousal level, and cognitive functioning can all impact how the brain responds to any form of therapy. This brain-state dependency can be taken as an augmentation strategy by functionally engaging specific neural circuits that are relevant for therapy [20]. For example, the success of cognitive-behavioral therapy (CBT) may depend on the patient's cognitive state during therapy sessions which can be influenced in different ways. Below, we will briefly highlight the potential of augmenting therapy effects by influencing the brain state with mood-induction, NIBS and/or PA.

### **Mood-induction procedures**

Our brain favors processing information that is congruent with our current mood state. Due to mood-repair and emotion regulation strategies, sad mood states are generally only short-lived. However, emotional inertia holds that the sad mood state persists in depression, and influences how internal and external information is processed including what is presented during e.g., CBT sessions. Mood induction procedures yield physiological responses and affect brain activation [21-24] indicating their neuromodulation potential. To illustrate, some studies have demonstrated that inducing positive mood can lead to increased activity in brain regions associated with reward processing, such as the nucleus accumbens [25], and modulate the functioning of the amygdala [26,27], which is central to emotional processing. Additionally, positive mood induction has been linked to heightened activation in areas responsible for cognitive flexibility and problem-solving, such as the prefrontal cortex [28].

While newer paradigms include virtual reality to modify mood states [29], classically, music, emotional images, and imagery-based autobiographical memory retrieval techniques have been

implemented to alter mood and are relatively easily applied in clinical and at-home settings [30,31]. Implementing positive mood-induction procedures to augment depression treatment effects is still uncommon, but we do see that reactivity to such an experimental procedure is related to treatment response [32-35] facilitating personalized prescription and using mood induction procedures to enhance treatment effects.

### **Acute effect NIBS**

One of the primary targets for treating depression using repetitive transcranial magnetic stimulation (rTMS) is the dorsolateral prefrontal cortex (DLPFC). This brain area is a key player in cognitive control, which is crucial for regulating emotions. Stimulating the DLPFC with rTMS is believed to enhance cognitive control, potentially leading to improved mood regulation. Research has demonstrated that rTMS applied to the left DLPFC can increase its activity, benefiting both healthy individuals and those with depression by enhancing cognitive control (for example: [36]).

### **Acute effect PA**

Along the same line of thought, PA can be a personalized therapy for persistent depression by considering individual factors such as fitness level, preferences, and physical limitations. Tailoring the type, intensity, and duration of exercise to each person's needs and capacity can optimize its effectiveness [37]. Additionally, incorporating elements like social support, goal setting, and behavioral strategies can enhance adherence and outcomes. As a personalizable brain stimulation technique, PA's acute neuroplasticity and cognition enhancing effects are of importance. The impact of exercise on learning and memory is multifaceted, involving the release of neurotransmitters, heightened cerebral blood flow, and other neuroplastic mechanisms [38,39]. The learning and memory benefits have been observed both for 12-week exercise protocols in depressed patients [40] but are also already present directly after an exercise session [41,42], highlighting the acute effect on the individual's brain state. There is in fact growing recognition that providing PA with depression treatments, including CBT, can amplify treatment outcomes [43-47,39]. PA presents as a potent add-on to improve treatment effects for persistent depression by directly inducing a positive mood and plastic brain state.

### **Thinking modular: Enhancing treatment effects by combining interventions**

Especially if a patient is resistant to initial treatment steps, adding modules of evidence-based treatments should be considered. Based on patient preferences and personal and clinical profile, treatment augmentation strategies can be selected. By combining these strategies, individuals with depression can potentially experience a more holistic and personalized treatment approach.

Brain stimulation can target neural circuitry, physical activity can boost overall well-being, and mood induction can facilitate emotional regulation and resilience. When used in conjunction with traditional therapy modalities such as CBT or medication, these methods have the potential to enhance treatment outcomes and promote long-term mental health recovery. Of interest to this development, is the fact that there is emerging evidence for not only the enhancing effect of NIBS on common treatments such as CBT, but also for the combination of brain-and mood-enhancing strategies. To illustrate, both rTMS and PA may enhance the effect of mood-induction procedures, subscribing to its plasticity-, and mood- and stress-relieving mechanisms [48-50]. Interestingly and relying on the high potential for both update in routine clinical care and at-home use, also the combination of neuromodulation (e.g., rTMS) and PA is receiving attention with theoretical frameworks and empirical evidence supporting their augmenting neuroplasticity benefits [51]. Such approaches open up personalization and enhancement of treatment for patients with persistent depression...hopefully 'breaking' the depression's persistence to treatment.

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