










Review Article

Boosting Psychotherapy With Noninvasive Brain Stimulation: The Whys and Wherefores of Modulating Neural Plasticity to Promote Therapeutic Change

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Received 3 May 2024; Accepted 4 December 2024

Academic Editor: Gabriele Sansevero

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The phenomenon of neural plasticity pertains to the intrinsic capacity of neurons to undergo structural and functional reconfiguration through learning and experiential interaction with the environment. These changes could manifest themselves not only as a consequence of various life experiences but also following therapeutic interventions, including the application of noninvasive brain stimulation (NIBS) and psychotherapy. As standalone therapies, both NIBS and psychotherapy have demonstrated their efficacy in the amelioration of psychiatric disorders' symptoms, with a certain variability in terms of effect sizes and duration. Consequently, scholars suggested the convenience of integrating the two interventions into a multimodal treatment to boost and prolong the therapeutic outcomes. Such an approach is still in its infancy, and the physiological underpinnings substantiating the effectiveness and utility of combined interventions are still to be clarified. Therefore, this opinion paper aims to provide a theoretical framework consisting of compelling arguments as to why adding NIBS to psychotherapy can promote therapeutic change. Namely, we will discuss the physiological effects of the two interventions, thus providing a rationale to explain the potential advantages of a combined approach.

Keywords: combined approach; neural plasticity; noninvasive brain stimulation; psychotherapy; transcranial direct current stimulation; transcranial magnetic stimulation

1. Introduction

Psychotherapy encompasses several interventions based on therapist–patient interaction aimed at producing cognitive, emotional, relational, and behavioral changes through novel experiences that trigger improvements in the patient's levels of functioning accompanied by a reduction in symptom severity [1]. Such positive modifications are commonly called “therapeutic change” and require (or promote) a sequence of

adaptive structural and functional changes in the brain, which fall under the umbrella term of “brain plasticity” [2, 3]. However, even when gold-standard psychotherapeutic interventions are employed, almost half of patients do not experience significant improvements [4], or encounter relapses within a year after a transient remission of their symptoms [5]. Therefore, alternative interventions or combined approaches should be developed to improve therapy outcomes, reduce individual response variability, and enhance effect duration. Previous

evidence highlights that combining psychotherapy with pharmacotherapy can be an effective strategy to counter psychiatric disorders' symptoms [6–8]. Nonetheless, drugs present relevant downsides, including a wide range of adverse effects and low compliance [9]. This observation has led researchers to explore other potential treatment strategies, especially for patients with refractory disorders or subjects experiencing intolerable aftermaths linked to medication. Among the currently available interventions, noninvasive brain stimulation (NIBS) emerges as a promising candidate to be combined with psychotherapy. Indeed, NIBS is designed to selectively target distinct brain circuits, causing long-lasting effects on neural excitability and synaptic transmission without sorting unbearable side effects in most cases [10, 11]. Scholars came up with such intuition since both psychotherapy and NIBS, as monotherapies, have proven their effectiveness in ameliorating the symptoms of numerous psychiatric populations [12–14]. Hence, combining the two interventions could have promoted faster and longer lasting improvements in patients' symptoms [15–19]. Another hypothesis is that NIBS enhances psychotherapeutic effects by tailoring the treatment to the patient's unique characteristics and therapeutic goals while allowing more direct control of therapy-induced neuronal changes [15]. However, the physiological rationale behind the effectiveness and usefulness of such integrated treatment is not yet fully understood. Therefore, this opinion paper aims to provide a theoretical framework of compelling arguments for why adding NIBS to psychotherapy can promote therapeutic change.

2. Principles of Neural Plasticity

To acknowledge the reasons behind coupling psychotherapy with NIBS, it is crucial to consider the brain as an ever-changing organ, that is, a “*plastic*” entity that constantly reshapes itself throughout its entire lifespan. In this framework, neural plasticity refers to the capacity of the nervous system to modify itself, functionally and structurally, in response to internal or external perturbations [20]. Among the different forms of neural plasticity currently discovered (e.g., spike-timing-dependent [21], anti-Hebbian [22], and homeostatic plasticity [23]), Hebbian plasticity results closely associated with memory and learning [24], and presumably to therapeutic change. Specifically, long-term potentiation (LTP) and long-term depression (LTD) are typical examples of Hebbian mechanisms [25]. These processes, brought to the forefront by the work of Bliss et al. [26–28], entail long-lasting changes in the pattern of synaptic weights, allowing neurons to strengthen, in the case of LTP, or weaken, in the case of LTD, their connections [29]. Such phenomena have been most observed in the hippocampus [30], but they also occur in other brain regions, such as basal ganglia [31], cerebellum [32], neocortex [33], and visual cortex [34]. Hebbian plasticity in the basolateral nucleus of the amygdala, especially, is required for the encoding and maintenance of fear-related memories, as well as for fear extinction [35]. In the most studied associative forms, LTP and LTD have been shown to involve different patterns of activation of N-methyl-D-aspartate (NMDA) receptors, thus leading to the rise of intracellular levels of calcium which in turn activates

signaling cascades involving protein kinases/phosphatases [36]. Also, presynaptic changes can support synaptic plasticity expression, driving both sub- and supra-threshold changes in neural transmission [37, 38]. Importantly, both LTP and LTD comprise functional and morphological changes detectable at the synapse level [39, 40].

In particular, LTP in the lateral and basolateral amygdala could be induced by applying high-frequency stimulation to the synaptic afferents in the external capsule [41], which causes a large NMDA-dependent increase in dendritic spine calcium concentrations [42, 43]. Such an increment leads to the activation of intracellular signaling cascades involving numerous protein kinases, such as calcium/calmodulin (CaM)-dependent protein kinase II (CaMKII), that is, a family of multifunctional serine/threonine protein kinases whose activation is known to induce potentiation of synaptic transmission and occlude further LTP phenomena [44, 45]. In turn, the activation of intracellular signaling cascades leads to an increase in the single-channel conductance of synaptic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and, more importantly, promotes the incorporation of additional AMPA receptors into the postsynaptic density [46, 47]. Notably, the novel synaptic AMPA receptors are stabilized through their interaction with so-called “slot proteins,” that is, a group of scaffold proteins capable of trapping AMPA receptors and reducing their lateral mobility [48, 49]. For example, postsynaptic density protein 95 (PSD-95), that is, a membrane-associated guanylate kinase found in the postsynaptic density, regulates the number of AMPA receptors at individual synapses [50]. Indeed, the overexpression of PSD-95 increases synaptic strength and occludes LTP [51], whereas the knockdown of PSD-95 decreases both the surface expression of AMPA receptors and synaptic strength [52]. Moreover, specific genes, whose expression is induced during the early LTP, encode plasticity-related proteins required for LTP maintenance and memory formation [53]. A subset of these plasticity-evoked genes, known as immediate-early genes (IEGs), has been implicated in the aforementioned molecular events because of their rapid and transient responsiveness to synaptic activation [54]. For instance, expression of IEGs such as *egr-1*, *c-fos*, and *Arc* results rapidly upregulated in the hippocampus and lateral amygdala following the neuronal activation associated with behavioral tasks [55, 56]. In parallel, structural changes within the synapse occur, such that the size of the postsynaptic density and dendritic spines are expanded [39]. Accordingly, the induction of LTP by either electrical or chemical stimulation causes an enlargement or increase in the number of dendritic spines [57–59], an increase in the number of bifurcated spines [60, 61], and the formation of spinules from the spine head [62]. These changes, in turn, drive an increase in the size of the presynaptic active zone such that the potentiated synapses are “permanently” enlarged [63]. The abovementioned modifications are possibly mediated by the action of neurotrophins, such as the brain-derived neurotrophic factor (BDNF), that is, activity-dependent modulators of neuronal structure and function known to support differentiation, maturation, and survival of neurons in the mammalian nervous system [64, 65].

Turning to LTD, such a process could be induced in the basolateral amygdala neurons by applying low-frequency stimulation to the lateral nucleus [66], which causes a modest NMDA-dependent increase in dendritic spine calcium concentrations [67, 68]. This leads to a preferential activation of calcium-dependent protein phosphatases instead of kinases [69]. The main signaling cascades include CaM-dependent phosphatase calcineurin, protein phosphatase 1 (PP1), and inhibitor-1, a phosphoprotein inhibiting PP1 until it is dephosphorylated by calcineurin [70]. Postsynaptic inhibition of these phosphatases consistently prevents LTD [71], whereas directly loading hippocampal pyramidal cells with PP1 enhances LTD [72]. In turn, the activation of protein phosphatase cascades leads to the dissociation of AMPA receptors from their molecular scaffolds and promotes their lateral movement to the periphery of the postsynaptic density, where they are endocytosed and potentially degraded [73, 74]. Furthermore, there is evidence that LTD is accompanied by a shrinkage or loss of dendritic spines [75–77], which could be reverted by a potentiation stimulus [78]. These structural changes have been associated with the loss of AMPA receptors [79]. The main hypothesis is that the activity-dependent trafficking of AMPA receptors into and out of synapses during LTP and LTD, respectively, constitutes the first step in the morphological growth or shrinkage of synapses, thus representing a potential mechanism by which bidirectional changes in synaptic strength are maintained [25]. Indeed, the size of individual synapses closely correlates with the number of AMPA receptors they contain [80, 81]. Besides the trafficking of AMPA receptors, other molecular mechanisms could be involved in the structural plasticity of dendritic spines. For instance, actin filaments play a crucial role in synaptic plasticity, given their propriety of changing the shape of the pre- and post-synaptic side and mediating the retraction and sprouting of synapses [82]. Accordingly, the pharmacological manipulation of actin polymerization and depolymerization effectively blocks LTP and simultaneously suppresses the structural enlargement of dendritic spines [83, 84]. Long-term plasticity and memory consolidation require, however, not only structural changes but also *de novo* protein synthesis. The gene expression pathway primarily implicated in these processes is activated by cyclic adenosine monophosphate (cAMP)-dependent mechanisms and mediated by members of the family known as cAMP-response element binding (CREB) proteins [85]. Specifically, cAMP activation initiates short-term synaptic changes that subsequently link—via nuclear translocation of protein kinase A and other kinases—to the activation and recruitment of CREB proteins and gene transcription [86]. Consistent with this assertion, overexpression of CREB promotes long-term memory storage from behavioral protocols that otherwise only induce short-term memory, indicating its pivotal role in the late phase of LTP and LTD [87, 88].

In addition to LTP and LTD, higher order dynamics have been shown to regulate synaptic plasticity, a phenomenon called metaplasticity [89]. The basic manifestation of metaplasticity is that the previous history of synaptic activity affects the direction and/or magnitude of activity-dependent synaptic plasticity in the

future [90]. Notably, metaplasticity regulates synaptic plasticity across space and time (see for a review [91]). The time of metaplasticity expression typically spans from minutes to hours but can last for days and even weeks [92, 93]. Moreover, metaplasticity can be expressed over a broad range of spatial extents of the postsynaptic neuron. Indeed, heterosynaptic metaplasticity can be global, that is, cell-wide, or confined to specific dendritic compartments [94–96], whereas homosynaptic metaplasticity is only expressed at those synapses that participated in the initial bout of priming activity [97–99]. Metaplasticity phenomena have been originally described in the Bienenstock–Cooper–Munro (BCM) theory of bidirectional synaptic plasticity, which postulates that the synaptic modification threshold (θ_M) is not stable but varies as a function of the integrated postsynaptic activity [100]. On one hand, θ_M decreases at a low level of previous postsynaptic activity, favoring the probability of subsequent LTP over LTD. On the other hand, θ_M increases at high levels of recent postsynaptic activity, thus favoring the induction of LTD over LTP [100]. Accordingly, in the hippocampus, repetitive activation of NMDA receptors can elicit a rapid shift in plasticity threshold such that LTP becomes difficult to elicit, and LTD induction is favored [101]. It has also been hypothesized that this sliding θ_M has an intrinsic homeostatic function, as it enables the maintenance of neuronal network activity within a physiological range [102]. Hebbian and homeostatic plasticity phenomena tend to interfere with each other if they are operating simultaneously at the same synapses [103]. Indeed, the latter is thought to represent a slow process that readjusts synaptic weights to stabilize circuit activity despite Hebbian plasticity [104, 105]. The induction of BCM-like metaplasticity involves multiple mechanisms, including NMDA receptor activation, and it is expressed by changes in NMDA receptor subunit composition [106].

All these synaptic plasticity phenomena occur constantly throughout the lifespan, although they appear influenced by age [107, 108]. In recent years, several tools, such as NIBS [109], have been proven effective in enhancing synaptic plasticity (and metaplasticity) even in mature brain structures and without significant external stimulation needed. In particular, NIBS has been shown to recruit activity-dependent synaptic plasticity and modulate both functional and structural plasticity processes [110–112]. For instance, high-frequency repetitive transcranial magnetic stimulation (TMS) protocols and theta-burst stimulation (TBS) induce LTP-like phenomena in the motor system of human subjects [113–115]. Similarly, transcranial direct current stimulation (tDCS) facilitates LTP induction and drives morphological changes at neuronal dendrites and spines in the animal model, thus suggesting its capability of enhancing plasticity in the human brain [116, 117]. Albeit we do not know if such interventions are effective on all brain circuits, it is plausible that NIBS can constructively interact with the natural processes of experience-dependent plasticity going on in the subject's brain during psychotherapy [118]. In the following paragraphs, we will outline the main neuromodulatory effects induced by psychotherapy and NIBS to explain how their action and combination could foster long-term learning and, therefore, enable consistent therapeutic changes.

3. Psychotherapy Effects on Neural Plasticity

According to the hypothesis put forward by Kandel [119], psychotherapy can produce enduring effects on human brain functioning and behavior, that is, the so-called therapeutic change. From a neurophysiological perspective, this process reflects long-lasting behavioral modifications achieved as a consequence of learning experiences involving the alteration of the strength and quality of synaptic connections [120]. Accordingly, neuroimaging studies conducted in the last decades have demonstrated that psychotherapeutic treatment produces durable changes in brain activity [3, 121–123]. Namely, investigations conducted on patients affected by major depressive disorder (MDD; [124–129]), anxiety disorders (ADs; [130–137]), obsessive–compulsive disorder (OCD; [138–143]), and posttraumatic stress disorder (PTSD; [144–148]) consistently highlighted psychotherapy-mediated modifications across several regions, including dorsolateral (dlPFC) and ventromedial (vmPFC) portions of the prefrontal cortex (PFC), cingulate cortex, insula, hippocampus, and amygdala. These brain areas, as well as the neuronal networks in which they are involved (e.g., limbic–cortical, prefrontal–striatal, and frontoparietal networks), play a pivotal role in the regulation of emotions, decision-making, and the encoding and retrieval of memories [149]. Among the most frequently observed changes in this research strand are the increased activity of prefrontal cortical areas (e.g., vmPFC and dlPFC [124, 130, 135, 136, 141]), the decreased activity of subcortical areas (e.g., amygdala and hippocampus [125, 129, 143]), and the enhanced functional connectivity between cortical and subcortical brain regions (e.g., vmPFC and amygdala [142]).

The aforementioned studies applied heterogeneous psychotherapeutic approaches, with cognitive–behavioral therapy (CBT) being the most employed. CBT is an evidence-based approach focusing on the interplay among patient's thoughts, feelings, and behaviors. Recognizing and understanding this interaction can help to modify maladaptive patterns and behaviors [150]. In particular, the cognitive model assumes that psychological disorders arise as a consequence of dysfunctional thinking [151]. Therefore, CBT aims first at recognizing and questioning patients' dysfunctional beliefs about themselves, the world, and other people and maladaptive coping strategies; and second to replace them with more functional beliefs and behaviors [150]. This process involves the application of techniques, such as daily logs, thought records, Socratic questioning, activity scheduling, graded task assignments, behavioral experiments, progressive relaxation training, and breathing exercises (see for review [152]). Due to its proven effectiveness, CBT is nowadays widely used across a variety of psychiatric disorders, including MDD, AD, OCD, eating disorders, and substance addiction [153]. Another psychotherapeutic approach widely applied in neuroimaging studies was prolonged exposure (PE), a specific type of CBT that teaches individuals to gradually approach their trauma-related memories, feelings, and situations instead of avoiding them [154]. This intervention is typically provided over a period of about 3 months with weekly individual sessions, encompassing the

understanding of the patient's traumatic experiences, the explanation of treatment rationale, psychoeducation, and teaching of breathing techniques [154]. After that, imaginal and in vivo exposure can promote habituation to the feared stimuli [155]. To date, PE is strongly recommended for the treatment of PTSD [156].

Given the observed relationship between diminished vmPFC activity, heightened amygdala activation, and alterations in the autonomic nervous system and hypothalamic–pituitary–adrenal axis activity, a similar conceptualization has been proposed for PTSD [157, 158], AD [159], and MDD [160]. In the case of PTSD, psychotherapeutic treatment alters the amygdala–vmPFC–hippocampus network, which is highly involved in fear extinction [161], a pivotal learning mechanism characterized by a decline in conditioned fear responses following nonreinforced exposure to a feared conditioned stimulus. In such a circuit, the vmPFC and amygdala are involved in emotion regulation, while the hippocampus, responsible for furnishing contextual information to the amygdala, assumes a critical role in extinction learning [162]. Among exposure-based psychotherapies, PE facilitates extinction recall by enhancing connectivity among the vmPFC, amygdala, and hippocampus. Indeed, successful PE treatment in PTSD is associated with increased left dlPFC activity, downregulated amygdala activity, heightened hippocampal function during traumatic memory retrieval, and augmented vmPFC activity during fear-related stimuli processing [163, 164]. Another psychotherapeutic intervention able to sort long-lasting effects on the neural circuitry underlying PTSD is eye movement desensitization and reprocessing (EMDR). EMDR is a structured therapy that encourages the patient to focus on trauma-related memories while simultaneously experiencing bilateral stimulation to reduce the vividness and distress linked to those memories [165]. Indeed, the application of alternating bilateral sensory stimulation, that is, a visual EMDR protocol, provides a steep reduction in fear-related responses and yields sustained increases in the activities of the superior colliculus and medio-dorsal thalamus [166, 167], attenuating the aftermath of traumatic memories.

Similarly, CBT induces heightened vmPFC, dlPFC, and vlPFC activation and diminished amygdala responsivity, leading to reduced depressive- and anxiety-related symptoms [168–173]. Efficacious psychotherapeutic interventions for MDD and AD elicit massive functional modifications within the limbic–cortical network [174, 175], which is involved in emotion regulation. Here, explicit modulation of emotions, that is, reappraisal processes involving a conscious endeavor to alter the interpretation of emotional stimuli, engages the dlPFC, dorsal anterior cingulate cortex (ACC), and parietal cortex [176]. Conversely, implicit emotion regulation, characterized by automatic processes devoid of introspective awareness, primarily hinges on the vlPFC and vmPFC [177, 178]. According to Mayberg's [174] model, psychotherapeutic approaches aimed at improving emotion regulation capacities enhance cognitive reappraisal mechanisms by augmenting top-down regulatory functions exerted by the PFC. Consequently, psychotherapy could fortify patients' adeptness in contending with negative affect, concomitantly regulating brain activity in

regions involved in emotional processing (e.g., amygdala and vmPFC), thereby mitigating maladaptive information elaboration and attentional bias [179]. Notwithstanding considerable support, the proposition positing heightened top-down control of the PFC over limbic regions through psychotherapy does not comprehensively account for all clinical manifestations of these disorders. For instance, research indicates that nonconscious processing of fear in PTSD is correlated with amygdala and vmPFC hyperactivity, thus presenting a nuanced perspective [180]. In light of these considerations, psychotherapeutic interventions for PTSD that enhance vmPFC activity are expected to influence conscious threat processing but leave the impact on nonconscious threat processing uncertain, necessitating exploration in future targeted investigations.

Psychotherapy has also been shown to restore aberrant neurocognitive processes implicated in OCD, for example, cognitive inflexibility, compulsive behaviors, and compromised response inhibition, which correlated with the overactive ventral–striatal circuitry and diminished regulatory influence from the prefrontal–striatal and frontoparietal networks [181]. For example, CBT ameliorates pathological hyperactivity in cortico–striato–thalamic regions while concurrently reinforcing functional connectivity in other brain areas supporting compensatory processes, that is, insula and cerebellum [182–184]. Furthermore, brain activation in the right insula predicts CBT outcomes, with lower activation predicting a higher symptom reduction [185].

Overall, it is evident that psychotherapeutic interventions operate, at least partially, by augmenting prefrontal control over subcortical regions [121, 186]. However, following psychotherapeutic treatment, psychiatric symptoms face remission in approximately half of the cases [4], suggesting that such an intervention does not consistently restore aberrant cortical connectivity. Nonetheless, the investigations also demonstrate that psychotherapeutic intervention targets dysfunctional circuits in various pathologies. It is only in these areas that structural and functional alterations can be observed. This consideration opens the possibility of combining new approaches, such as NIBS, with psychotherapy to focally induce neural plasticity in impaired brain areas and, thus, develop effective treatments for refractory disorders.

4. NIBS: An Overview

NIBS has been widely used to modulate neuronal activity and synaptic transmission in adults [115, 117, 187], without resulting in relevant side effects for the recipient [11, 188]. Among NIBS, the two most frequently applied techniques are TMS and tDCS [189].

TMS consists of administering strong brief focal electromagnetic pulses through a coil placed over the participant's head that penetrates the skull to stimulate target brain areas [190]. The pulse generates suprathreshold neuronal membrane depolarization, inducing neuronal firing of cortical neurons beneath the coil [191]. TMS pulses can be applied through different stimulation protocols, such as single pulses TMS, which is typically applied in the clinical field as a diagnostic tool in neurological disorders (e.g., [192]), or as repetitive trains

of stimulation, which can be either continuous at a specific frequency (rTMS) or patterned with specific interstimulus intervals, for example, intermittent theta-burst stimulation (iTBS) and continuous theta-burst stimulation (cTBS). Unlike single pulses TMS, rTMS, cTBS, and iTBS protocols are generally applied to induce long-term effects [193, 194]. Several stimulation parameters affect cortical activity, including frequency and intensity of the stimulation, shape of the magnetic pulse, duration of the stimulation period, and total number of pulses administered [195–197]. For instance, rTMS delivered at high frequencies (i.e., between 5 and 20 Hz and iTBS) causes excitatory effects and increases cortical excitability, whereas rTMS delivered at low frequencies (i.e., less than or equal to 1 Hz or cTBS) induces inhibitory effects and reduces cortical excitability [198, 199].

Conversely, tDCS involves delivering low-intensity electric currents through two (or more) rubber electrodes positioned in saline-soaked sponges or covered with conductive paste and placed over the scalp [200, 201]. One of the electrodes has a positive polarity (anode), and the other a negative (cathode). Unlike TMS, tDCS does not directly induce neuronal firing but modulates cortical excitability by a polarity-dependent shift of the neuronal membrane potential [202, 203]. The terminology anodal and cathodal tDCS reflect the placement of the anode and cathode electrodes over a target brain region [204]. Anodal tDCS is known to enhance cortical excitability, whereas cathodal tDCS has been shown to produce a reduction in cortical excitability [202, 203].

Although a detailed description of TMS and tDCS functioning goes beyond the aims of the current work, it seems crucial to highlight that NIBS outcomes in terms of cortical excitability and behavioral measures are difficult to predict in advance since they are the product of nonlinear interactions involving individuals' (anatomical, genetic, or hormonal) and contextual (functional, state-dependent, task, or activity-related) features, as well as stimulation parameters (frequency, polarity, intensity, number of sessions), leading to a high inter- and intra-individuals variability in NIBS responses [205–208]. Nonetheless, NIBS can yield significant cognitive and behavioral alterations [209–212] and reduced symptom severity among clinical populations. NIBS has been proven to be effective across many psychiatric disorders, for example, AD [213], MDD [214], OCD [215], PTSD [216, 217], eating disorders [218], and substance addiction [219, 220].

4.1. TMS Effects on Neural Plasticity. Converging evidence highlights that rTMS alters synaptic strength by facilitating LTP- and LTD-like mechanisms due to its ability to induce changes in cortical activity that exceed the period of pulse administration [114, 117, 221, 222]. Studies on corticospinal excitability suggested that high-frequency rTMS and iTBS applied over the primary motor cortex (M1) produce a long-lasting increase in motor-evoked potentials (MEPs) amplitude, indicating the occurrence of LTP phenomena and increased cortical excitability [223, 224]. Conversely, low-frequency rTMS and cTBS cause a decrease in the MEP amplitude, inducing, therefore, mechanisms comparable to LTD [113, 225]. A previous study suggests that the duration of rTMS-mediated

plasticity effects depends on the number of pulses within the stimulation protocol [221]. Indeed, it has been illustrated that 150 pulses of rTMS at 5 Hz over the motor cortex do not produce major physiological changes, whereas the administration of 900 and 1800 pulses of rTMS at 5 Hz on the same brain site increases MEPs amplitude over 20 and 40 min, respectively [226]. These results are consistent with the outcomes of animal models, in which the persistence of in vivo LTP-like mechanisms could be prolonged up to days, depending on the number of stimulation trains applied to the rodents [227, 228].

Neuroimaging studies also reveal similar effects. Long-term modifications have been detected following rTMS in the cerebral blood flow and the blood oxygenation level-dependent (BOLD) signal [229, 230]. Furthermore, high-frequency rTMS applied over M1 and PFC results in long-term cerebral blood flow and glucose metabolism increase [231–233]. In contrast, applying cTBS over frontal eye fields causes a reduction in BOLD signal originating from such brain regions [229]. Why high-frequency rTMS causes opposite physiological effects than low-frequency rTMS is still poorly understood. Nevertheless, it has been hypothesized that NMDA receptors are massively involved in plasticity phenomena [221, 234], as animals exposed to neurostimulation exhibited increased expression of such proteins at the ventromedial thalamus, amygdala, and parietal cortex [235]. Theoretically, when postsynaptic neurons are sufficiently depolarized, NMDA cation channels open, allowing Ca^{2+} and Na^{+} to enter the cell, triggering signaling mechanisms that lead to long-term modifications in synaptic efficacy [236–238]. In light of these considerations, there is evidence that high-frequency rTMS causes a steep increase in calcium concentration in postsynaptic dendrites, augmenting the likelihood that presynaptic axon and postsynaptic dendrite are simultaneously active and, consequently, synapses become strengthened [239]. This means high-frequency rTMS triggers a rapid and strong increase in postsynaptic calcium levels, inducing LTP-like mechanisms [194]. Conversely, low-frequency rTMS causes a prolonged and moderate increase in postsynaptic calcium levels, inducing LTD-like mechanisms [240].

Several cellular mechanisms regulate rTMS-induced plasticity. The abovementioned synaptic events involving NMDA cation channels trigger long-term changes by remodeling dendritic spines and regulating neurotransmitter release [241, 242]. Non-synaptic mechanisms could be involved as well, for example, neurotrophic factor release [243, 244], glial cell modulation [245], and epigenetic modifications [246]. Specifically, rTMS causes a significant increase in BDNF detectable in the hippocampus, parietal cortex, amygdala, and anterior parahippocampal gyrus [247, 248].

Despite significant advancements in understanding TMS mechanisms of action, much remains to learn about how these mechanisms relate to cognitive and behavioral effects observed in experimental subjects. Nevertheless, one established truth about TMS is that its effects are state-dependent, that is, the effects of TMS on brain networks are modulated by the initial activation state of the stimulated region [249]. The research strand on state dependency focused on various factors, including cognitive brain state, oscillatory brain state, and recent

brain state history [250]. These states play a crucial role in determining the effects of TMS at the moment of stimulation, and thus, they are expected to be linked to clinical outcomes of TMS therapy [251].

4.2. tDCS Effects on Neural Plasticity. TDCS causes a wide range of consequences at a molecular level, which has been demonstrated by in vitro studies reporting that direct current stimulation of cortical and hippocampal sections induces relatively long-lasting forms of synaptic potentiation [116]. In most cases, tDCS results in significant alterations in the postsynaptic excitatory potentials (EPSPs) generated by the brain tissues [252–254]. These in vitro investigations have been conducted to unravel the cellular mechanisms triggered by tDCS and have contributed to the identification of two neuronal pathways that could underlie the behavioral changes induced by its application [255]. The first is the alteration of intracellular calcium concentrations. In this regard, an experiment conducted by Khatib, Golan, and Cho [256] unveiled that applying a direct current produces a significant increase in calcium concentration within the biological units under examination. Furthermore, such an increase is completely abolished by inhibiting phospholipase C, an enzyme triggering the release of Ca^{2+} from intracellular calcium stores, including the endoplasmic reticulum [257]. In the mechanism of action of tDCS, the release of calcium from intracellular stores appears, therefore, to be involved. The second pathway modulated by tDCS relates to the expression of BDNF. Indeed, applying a direct current to acute slices prepared from the mouse brain has induced massive changes in brain tissue [258]. Specifically, the stimulation results in a marked increase in BDNF levels and activation of associated tropomyosin receptor kinases, leading to the conclusion that anodal tDCS promotes the expression of BDNF [258]. Despite inconsistent findings (e.g., [259–261]), in vivo studies show that tDCS interferes with BDNF-related signaling pathways. A summary of the current evidence is provided by a meta-analysis which reveals that following the application of tDCS at the PFC and hippocampus, experimental groups show a marked increase in BDNF levels compared to controls [116].

Several studies on rodent models have been conducted over the years, showing that applying a direct current via surgically implanted electrodes causes an increase in neuroplasticity (e.g., [259, 261–265]). However, these investigations report mixed results depending on the stimulation polarity. For instance, some research shows that the application of anodal stimulation at the hippocampus results in enhancing LTP phenomena [262], whereas the use of cathodal stimulation over the same brain site produces no significant synaptic changes [263]. Yet, this is refuted by a previously mentioned in vitro study in which it has been demonstrated that the application of a direct current stimulation effectively modulates LTP at *cornu ammonis* hippocampal synapses, in a polarity-specific manner: anodal stimulation markedly increases LTP, whereas cathodal stimulation significantly reduces it [254]. Overall, among animal models, it is anodal, not cathodal, stimulation of prefrontal and hippocampal regions that produces a statistically significant enhancement of LTP phenomena compared to unstimulated specimens [116]. The absence of a significant promotion of LTP following

the application of cathodal tDCS opens the hypothesis that the latter primarily modulates opposite forms of synaptic plasticity, namely LTD. This evidence is corroborated by an *in vitro* study conducted on neocortical sections taken from rats and humans in which a cathodal tDCS caused an increase in LTD-like phenomenon, that is, a marked decrease in the amplitude of EPSPs [266]. However, the literature suggests that cathodal tDCS selectively reduces LTP induction (e.g., [254]).

Additionally, synaptic changes induced by anodal tDCS are time-dependent. Indeed, in some cases, the first clear increases in LTP-like mechanisms are detected at a time immediately following treatment (i.e., within 60 min), while in others at a more prolonged time interval (i.e., after 60 min; [259, 262, 263, 265]). Nonetheless, the reasons why this occurs remain highly unknown and should be clarified in future research.

The effects of tDCS on neural plasticity entail changes in LTP induction and other synaptic modifications. As an example, Stafford et al. [267] observed a significant increase in AMPA receptor trafficking at the level of the hippocampus following the neurostimulation, while Jung et al. [268] demonstrated an increase in BDNF expression in synaptoneurosome (an *in vitro* preparation of isolated synaptic boutons including both pre- and post-synaptic compartments) derived from the hippocampal area after its treatment with anodal tDCS.

Experiments on humans revealed that glutamatergic receptors, particularly NMDA channels, are involved in tDCS-induced modulation of plasticity mechanisms (e.g., [269–273]). Especially NMDA receptor-mediated calcium flux represents a critical component of synaptic plasticity, suggesting that intracellular dynamics concerning such ions are largely involved in the physiological effects of tDCS. It is also possible to conclude that stimulation-induced effects on neuroplasticity depend on both intracellular calcium levels and NMDA receptor responses and, therefore, that the cellular mechanisms triggered by the intervention are comparable to those observed during LTP and LTD of glutamatergic synapses [40]. In addition, Stagg et al. [274] highlighted that the application of tDCS produces a decrease in GABA concentrations at the cortical level, an effect that was also found to be highly correlated with the degree of impairment of glutamatergic activity detected in the same brain areas. A consequent hypothesis is that tDCS heals potential imbalances between inhibitory (i.e., GABAergic) and excitatory (i.e., glutamatergic) neurotransmitter systems [255, 275].

As for TMS, the effects of tDCS are state-dependent [276–278]. Indeed, cognitive changes occurring in healthy humans during both anodal tDCS and cathodal tDCS are affected by ongoing brain activity, increasing and decreasing, respectively, cortical excitability of task-related brain networks [207, 279]. In addition to the cognitive activity [280, 281], the oscillatory brain state also affects the effects of tDCS [282]. Such states contribute to the high variability of cerebral and behavioral responses to tDCS [208], which still limits its application for clinical purposes as monotherapy.

5. Toward an Integrated Approach

This manuscript focused on synaptic and neuronal modifications induced by psychotherapeutic treatment and NIBS

application. These interventions have been associated not only with functional, physiological, and chemical changes but also with a decrease in the severity of patients' symptoms. However, only in a few cases psychotherapy and NIBS have been coupled, giving birth to a multimodal treatment aimed at achieving faster and longer lasting therapeutic changes [15, 16, 18]. Nonetheless, rTMS combined with CBT effectively improves the clinical conditions of patients affected by PTSD [283], AD [284], MDD [285], OCD [286], and substance addiction [287, 288]. Similar results have been observed when rTMS is coupled with PE, highlighting significant improvements in symptoms' severity reported by subjects with PTSD [289, 290], OCD [291], AD [292], and substance use disorders [293, 294]. Recently, rTMS has also been combined with mindfulness-based stress reduction (MBSR), highlighting a significant reduction in depressive symptoms' severity reported by subjects affected by poststroke depression [295]. TDCS has been coupled with psychotherapy as well, but currently, available evidence is highly heterogeneous. For instance, tDCS combined with cognitive training turned out to be effective in reducing craving among subjects with substance addiction in some cases [296], while it had no effect in others [297, 298]. Similarly, tDCS paired with cognitive psychotherapy results in clinical improvements in patients with MDD [299], but these results have not been confirmed by subsequent investigations [300]. Preliminary encouraging evidence on the efficacy of an integrated approach combining tDCS with psychotherapy has also been found for other psychiatric disorders, for example, PTSD [301], AD [302], and eating disorders [303].

In light of these data, we aim to provide a theoretical framework focusing on the rationale of combining psychotherapy and NIBS to boost therapeutic change. On one hand, psychotherapy could gain an advantage from NIBS application due to its ability to enhance synaptic plasticity phenomena recruited by cognitive and behavioral training and emotional processing. On the other hand, NIBS could benefit from psychotherapy because the latter might facilitate the efficacy of neuromodulation in a metaplastic manner. Additionally, neuronal modifications induced by psychotherapeutic interventions at specific or diffuse neural circuits could foster the following synaptic changes caused by NIBS, making them more likely and sustained.

We speculate that NIBS might play a pivotal role in enhancing metaplasticity, possibly enabling psychotherapy to induce further LTP- and LTD-like phenomena in the human brain. Indeed, consistent evidence for metaplasticity in the human cortex derives from NIBS investigations. For example, applying quadripulse stimulation with high-frequency priming over M1 causes a rightward shift of the threshold for the induction of LTP, that is, an enhanced probability of LTD-like plasticity and a decreased probability of LTP-like plasticity [304]. On the contrary, low-frequency stimulation priming causes the opposite effect, that is, a leftward shift of the threshold for the induction of LTP, suggesting an enhanced probability of LTP-like plasticity and a decreased probability of LTD-like plasticity [304]. Also, priming low-frequency rTMS over the motor cortex with high-frequency rTMS results in a stronger LTD-like MEPs decrease compared with low-frequency rTMS alone [305].

In this context, another important aspect relates to the metaplastic effects of neuromodulators and their role in psychiatric disorders. It is established that most forms of synaptic plasticity, including LTP, LTD, and spike-timing dependent plasticity, at almost all cortical and subcortical circuits (from the striatum to occipital and PFC), require the release of neuromodulators, such as dopamine and serotonin, at specific timing and dosages [306]. It was also shown that neuromodulator-dependent synaptic plasticity plays a role in the expression of psychopathological phenotypes, including depression and anxiety [307, 308]. Based on this, the observed changes in neuromodulator systems induced by psychotherapy (e.g., [309–311]) might further contribute to the efficacy of NIBS via a metaplastic route.

In addition, time-locking NIBS with a psychotherapeutic intervention can be a convenient approach, allowing clinicians to exploit the well-known state-dependent nature of NIBS. Namely, anodal tDCS elicits a widespread increase in cortical excitability at resting brain state [312], whereas cathodal tDCS fails to modulate cortical excitability, indistinguishable from sham stimulation [313]. Conversely, cathodal tDCS during a visuospatial attentional task reduced cortical excitability compared to the sham stimulation [279]. The possibility that the effects of neurostimulation depend on the brain state during stimulation is all the more significant. Consistently, in a study combining TMS and neuroimaging, it was observed that acute local and remote effects of TMS were influenced by the brain state during stimulation [314]. Since neurophysiological effects of neuromodulation could depend on the background cerebral activity, a pivotal question is how to combine NIBS with psychotherapy to maximize therapeutic effects. Unfortunately, when it comes to psychotherapeutic interventions, studies are typically heterogeneous considering the coupling of NIBS and psychotherapy, sometimes delivering neuromodulation before the psychotherapy session (as priming), sometimes during the psychotherapy session (as synergistic) and more rarely after the psychotherapy session (as consolidator) [15]. Hence, further investigations are needed to ascertain the optimal alignment between the two interventions.

6. A Transtheoretical Scheme for Implementing NIBS With Psychotherapy

During treatment, along with neuronal changes, cognition and behavior encounter the same fate, suggesting the existence of heterogeneous forms of plasticity that extend beyond the neural realm while remaining connected to it. In this framework, the notions of psychic and behavioral plasticity are introduced [315]. Psychic plasticity represents the ability to modify one's thoughts, evaluations, and beliefs, as well as to use endogenous and exogenous stimuli as input to modify one's point of view and to manage one's emotions functionally and adaptively [316, 317]. Psychic plasticity allows one to adapt to changes in context by modifying thoughts and emotions, thus enabling cognitive and emotional flexibility (i.e., the ability to shift attentional resources across environmental stimuli and manage one's emotional states according to experienced contingencies) [318, 319]. Behavioral plasticity refers instead to a change in

one's behavior that results from exposure to internal or external stimuli, that is, when individuals are confronted with novel environmental conditions [320, 321]. Behavioral plasticity allows individuals to adapt to the context by changing their behavior [322, 323].

Increasing psychic plasticity represents one of the main goals of psychotherapy, followed by a gradual reduction of the patient's maladaptive coping strategies and behaviors. Conversely, NIBS promotes neural plasticity and modulates a patient's cognition and behavior [324, 325], facilitating therapeutic change. It is worth mentioning that the induction of greater neuronal plasticity does not necessarily correspond to improvements in cognitive and behavioral flexibility. Consistently, in our previous works, TMS treatment significantly ameliorated patients' symptom severity scores, but no significant cognitive enhancement was observed [326, 327]. These results support the claim that cognitive remediation interventions should be incorporated into the clinical pathway, as they might facilitate TMS-induced synaptic plasticity. In other words, if NIBS promotes the onset of synaptic plasticity phenomena, these would probably be consolidated following psychotherapy.

Furthermore, in psychopathology, it is highly plausible that neural, psychic, and behavioral plasticity are compromised [328]. For example, MDD is characterized by synaptic loss in dlPFC circuits that underlie affective and cognitive processes [329]. Neuroimaging studies consistently show lower brain volume in the dlPFC, ACC, and hippocampus in MDD patients [330] and reduced functional connectivity between PFC and limbic areas [331]. These neurophysiological deficits are accompanied by cognitive, emotional, and behavioral rigidity, such as tunnel vision [332], persistence of sad mood, anhedonia, and suicidal tendencies [333, 334]. Besides MDD, other psychiatric disorders are characterized by dendritic and synaptic pathology, including abnormal spine density and morphology, synapse loss, and aberrant synaptic signaling and plasticity [335]. For instance, patients with bipolar disorder and schizophrenia show a significant reduction in the number of spines per dendrite, decreased spine density, and diminished dendrite length compared to healthy controls [336, 337]. Evidence linking the dysregulation of synaptic plasticity to psychiatric disorders highlights the potential role of synaptic homeostasis in psychopathology, suggesting that such deficits likely represent a core pathophysiological feature of these conditions.

Hence, time-locking NIBS with psychotherapeutic interventions could be an effective approach to consistently promote neural, psychic, and behavioral plasticity simultaneously. As previously mentioned, therapeutic change involves not only behavioral modifications but also psychic ones, requiring, therefore, a major "firepower" to be achieved. In light of this consideration, we propose a transtheoretical scheme for coupling NIBS with psychotherapy, accounting for neural, psychic, and behavioral modifications that occur during treatment. In our scheme, NIBS, including TMS and tDCS application, primarily facilitates neural plasticity and indirectly affects behavioral plasticity, causing a symptom reduction in the relatively short term. In turn, psychotherapeutic interventions, such as CBT, PE, MBSR, and EMDR, directly promote behavioral and cognitive plasticity based on the specifics of the treatment protocol. Psychotherapy also exerts an

indirect effect on neural plasticity in the long term. Metaplasticity and state dependency are pivotal in such an integrated approach since any neural, psychic, and behavioral change fosters further neural, psychic, and behavioral modifications. Also, considering the concept of synaptic homeostasis [338], the integration of psychotherapy with NIBS offers the advantage of physiologically “tuning” the plastic changes induced by neuro-modulation through the contextual efficacy of the therapy. Such an approach could help prevent overstimulation of neural circuits beyond clinical necessity or the potential dissipation of the stimulation’s ameliorative effects across broader brain networks.

Currently, our scheme is still a hypothesis that requires empirical validation, and it represents a mere simplification of the processes in place. Another limitation of our conceptualization is that it does not account for pharmacological interventions, which have been demonstrated to affect synaptic plasticity and, in turn, behavior, emotions, and cognition [339–341]. Moreover, we did not reserve the room for invasive stimulation strategies, for example, deep brain stimulation and epidural motor cortex stimulation, thus making our approach revisable for treating particularly refractory patients. Finally, although we argue that coupling NIBS and psychotherapy represents a potential approach for effectively counteracting psychiatric disorders, a gold-standard integrated protocol that facilitates plasticity induction and maximizes the effects of psychotherapy on patients’ cognition and behavior has yet to be identified.

7. Potential Targets for an Integrated Approach

Given that both NIBS and psychotherapy modulate cortical activity, an integrated approach combining the two could be particularly effective in treating patients suffering from psychiatric disorders with etiologies characterized by cortical abnormalities. Activity in ACC and dlPFC has been shown to be altered in MDD, with some consensus that activity of limbic regions (i.e., ACC and amygdala) is increased, whereas in frontal regions is decreased [342]. Furthermore, structural neuroimaging studies show widespread cortical alterations in MDD patients as compared to controls, for example, adults with MDD have thinner cortical gray matter than healthy subjects in the orbitofrontal cortex (OFC), anterior and posterior cingulate cortex, insula, and temporal lobes [343]. Similarly, compared to controls, subjects with PTSD and AD display a hypoactivation of the vmPFC, OFC, and ACC, and a hyperactivation of the amygdala, indicating a failure of the extinction to fearful stimuli [344, 345]. Here, the implementation of a multimodal approach combining NIBS with psychotherapy has the potential to restore balance in the activity of frontal cortical regions, thereby positively influencing patients’ symptomatology.

Aberrant functionality in cortical and subcortical brain regions has been also detected in OCD. Most notable are decreases in metabolism and perfusion of the ACC, caudate nucleus, thalamus, and multiple areas pertaining to the PFC, including OFC, dlPFC, vmPFC, and vlPFC [346]. Moreover, adults with OCD show a lower surface area for the transverse temporal cortex as well as a thinner inferior parietal cortex [347]. Thus, the application of integrated treatment protocols aimed at modulating the neural activity within regions of the

cortico–striato–thalamo–cortical circuit could produce significant therapeutic effects in this clinical population.

Turing to eating disorders, anorexia nervosa (AN) has been associated with hyperactivity in brain regions involved in motivational and emotional processing, such as the amygdala, insula, and hypothalamus, alongside hypoactivation in brain areas related to inhibitory control, including the vlPFC, vmPFC, middle frontal gyrus, and both the anterior and posterior cingulate cortex [348]. In addition, AN patients display a decreased gray matter volume in the bilateral median cingulate cortex (extending to the bilateral anterior and posterior cingulate cortex) and left middle occipital gyrus (extending to the left inferior parietal lobe) [349]. Bulimia nervosa (BN) has been characterized by reduced activation in vlPFC and vmPFC [350], and heightened activation in the insula and striatum, reflecting disruptions in impulsivity and emotion regulation [351]. Notably, even subjects with subthreshold BN exhibit abnormalities of the dlPFC and OFC in gray matter volume [352]. Binge eating disorder has been linked to weaker activation of the PFC, which could be improved by CBT [353], and hyperactivity in temporal cortex and striatum, highlighting links to dissociative strategies and addictive behaviors [351]. Augmenting psychotherapy with NIBS to precisely act on the altered activation in these brain regions belonging to the fronto-striato and limbic circuits, which are theorized to play a pivotal role in the pathophysiology of eating disorders, could be a way to consistently ameliorate patients’ clinical symptoms.

Functional neuroimaging studies on addictive behaviors have highlighted the key involvement of the PFC in modulating limbic reward regions and supporting higher order executive functions [354]. Impairments in PFC activity contribute not only to compulsive substance use but also to maladaptive behaviors characteristic of addiction, ultimately undermining autonomy and decision-making capacity [355]. Common to several addictive behavior is cue reactivity, in which exposure to stimuli induces craving as a consequence of Pavlovian conditioning [356]. Increased cue–reactivity converged in nicotine, alcohol, and cocaine addicts to the ACC, amygdala, and ventral striatum [357]. Moreover, a descriptive review of the literature suggests heightened activation in addicted individuals, particularly in prefrontal and orbitofrontal regions [358]. Cocaine addiction is associated with hyperactivity in the PFC, cingulate cortices, inferior frontal regions, and cerebellum during response inhibition, regardless of success [359]. Structural imaging reveals reduced volumes in the PFC, insula, inferior frontal gyrus, pregenual ACC, and anterior thalamus, with frontal gray matter declines correlating with addiction duration [360]. Furthermore, individuals with substance use disorders exhibit reduced cortical thickness in the insula and OFC compared to controls [361]. Therefore, addressing disturbances in frontostriatal circuitry through targeted modulation of PFC activity constitutes a preferential approach to alleviating symptom clusters specific to this clinical population, such as craving.

8. Conclusions

Considering that psychiatric disorders are characterized by the presence of pathologically altered neural plasticity and

connectivity, combining neurostimulation with concurrent psychotherapy could restore aberrant synaptic plasticity along with inducing psychic and behavioral modifications. Indeed, several works suggested the convenience of time-locking NIBS with psychotherapy interventions to alleviate patients' symptomatology [15, 17, 19], although research in this field is still in its infancy. Future studies should better clarify the neural underpinnings of the pathological and curative processes to optimize protocol interventions and, in turn, treatment effectiveness. Further investigations could also focus on testing this integrated approach among clinical and subclinical populations by monitoring symptom severity trends and changes in psychic, behavioral, and neuronal functioning.

Data Availability Statement

Data sharing is not applicable, no new data are generated, or the article describes entirely theoretical research.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Daniele Saccenti, Leonor J. Romero Lauro, Sofia A. Crespi, Andrea S. Moro, Alessandra Vergallito, Regina Gregori Grgič, Novella Pretti, Jacopo Lamanna, and Mattia Ferro: conceptualization. **Daniele Saccenti:** writing—original draft. **Daniele Saccenti, Andrea S. Moro, Alessandra Vergallito, Novella Pretti, and Jacopo Lamanna:** writing—review and editing. **Leonor J. Romero Lauro, Sofia A. Crespi, Alessandra Vergallito, Regina Gregori Grgič, Jacopo Lamanna, and Mattia Ferro:** supervision. Jacopo Lamanna and Mattia Ferro contributed equally to this work and shared the last authorship. Jacopo Lamanna and Mattia Ferro are corresponding authors.

Funding

No funding was received for this research.

References

- [1] C. Locher, S. Meier, and J. Gaab, "Psychotherapy: A World of Meanings," *Frontiers in Psychology* 10 (2019): 460.
- [2] I. M. Evans, "What Is Therapeutic Change?" in *How and Why People Change: Foundations of Psychological Therapy*, ed. I. M. Evans, (Oxford University Press, 2012): 25–52.
- [3] S. Malhotra and S. Sahoo, "Rebuilding the Brain With Psychotherapy," *Indian Journal of Psychiatry* 59, no. 4 (2017): 411–419.
- [4] E. A. Holmes, A. Ghaderi, C. J. Harmer, et al., "The Lancet Psychiatry Commission on Psychological Treatments Research in Tomorrow's Science," *The Lancet Psychiatry* 5, no. 3 (2018): 237–286.
- [5] S. Ali, L. Rhodes, O. Moreea, et al., "How Durable Is the Effect of Low Intensity CBT for Depression and Anxiety? Remission and Relapse in a Longitudinal Cohort Study," *Behaviour Research and Therapy* 94 (2017): 1–8.
- [6] M. Huhn, M. Tardy, L. M. Spinelli, et al., "Efficacy of Pharmacotherapy and Psychotherapy for Adult Psychiatric Disorders: A Systematic Overview of Meta-Analyses," *JAMA Psychiatry* 71, no. 6 (2014): 706–715.
- [7] E. Karyotaki, Y. Smit, K. H. Henningsen, et al., "Combining Pharmacotherapy and Psychotherapy or Monotherapy for Major Depression? A Meta-Analysis on the Long-Term Effects," *Journal of Affective Disorders* 194 (2016): 144–152.
- [8] F. Leichsenring, C. Steinert, S. Rabung, and J. P. A. Ioannidis, "The Efficacy of Psychotherapies and Pharmacotherapies for Mental Disorders in Adults: An Umbrella Review and Meta-Analytic Evaluation of Recent Meta-Analyses," *World Psychiatry* 21, no. 1 (2022): 133–145.
- [9] T. O. Aremu, O. E. Oluwole, K. O. Adeyinka, and J. C. Schommer, "Medication Adherence and Compliance: Recipe for Improving Patient Outcomes," *Pharmacy* 10, no. 5 (2022): 106.
- [10] W. Klomjai, R. Katz, and A. Lackmy-Vallée, "Basic Principles of Transcranial Magnetic Stimulation (TMS) and Repetitive TMS (rTMS)," *Annals of Physical and Rehabilitation Medicine* 58, no. 4 (2015): 208–213.
- [11] S. Rossi, A. Antal, S. Bestmann, et al., "Safety and Recommendations for TMS Use in Healthy Subjects and Patient Populations, With Updates on Training, Ethical and Regulatory Issues: Expert Guidelines," *Clinical Neurophysiology* 132, no. 1 (2021): 269–306.
- [12] A. R. Brunoni, B. Sampaio-Junior, A. H. Moffa, et al., "Noninvasive Brain Stimulation in Psychiatric Disorders: A Primer," *Brazilian Journal of Psychiatry* 41, no. 1 (2019): 70–81.
- [13] P. Cuijpers, E. Karyotaki, M. Reijnders, and D. D. Ebert, "Was Eysenck Right After All? A Reassessment of the Effects of Psychotherapy for Adult Depression," *Epidemiology and Psychiatric Sciences* 28, no. 1 (2019): 21–30.
- [14] J. Hyde, H. Carr, N. Kelley, et al., "Efficacy of Neurostimulation across Mental Disorders: Systematic Review and Meta-Analysis of 208 Randomized Controlled Trials," *Molecular Psychiatry* 27, no. 6 (2022): 2709–2719.
- [15] E. Tatti, A. L. Phillips, R. Paciorek, et al., "Boosting Psychological Change: Combining Non-Invasive Brain Stimulation With Psychotherapy," *Neuroscience & Biobehavioral Reviews* 142 (2022): 104867.
- [16] X. Xu, M. Xu, Y. Su, et al., "Efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) Combined With Psychological Interventions: A Systematic Review and Meta-Analysis of Randomized Controlled Trials," *Brain Sciences* 13, no. 12 (2023): 1665.
- [17] J. Dedoncker, C. Baeken, R. De Raedt, and M.-A. Vanderhasselt, "Combined Transcranial Direct Current Stimulation and Psychological Interventions: State of the Art and Promising Perspectives for Clinical Psychology," *Biological Psychology* 158 (2021): 107991.
- [18] J. He, Y. Tang, J. Lin, G. Faulkner, H. W. H. Tsang, and S. H. W. Chan, "Non-Invasive Brain Stimulation Combined With Psychosocial Intervention for Depression: A Systematic Review and Meta-Analysis," *BMC Psychiatry* 22, no. 1 (2022): 273.
- [19] A. V. Sathappan, B. M. Luber, and S. H. Lisanby, "The Dynamic Duo: Combining Noninvasive Brain Stimulation With Cognitive Interventions," *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 89 (2019), 347–360.
- [20] R. von Bernhardi, L. E. Bernhardi, and J. Eugeni, "What Is Neural Plasticity?" *Advances in Experimental Medicine and Biology* 1015 (2017): 1–15.
- [21] D. E. Feldman, "The Spike-Timing Dependence of Plasticity," *Neuron* 75, no. 4 (2012): 556–571.
- [22] G. Vignoud, L. Venance, and J. D. Touboul, "Anti-Hebbian Plasticity Drives Sequence Learning in Striatum," *Communications Biology* 7, no. 1 (2024): 555.

- [23] G. G. Turrigiano and S. B. Nelson, "Homeostatic Plasticity in the Developing Nervous System," *Nature Reviews Neuroscience* 5, no. 2 (2004): 97–107.
- [24] W. C. Abraham, O. D. Jones, and D. L. Glanzman, "Is Plasticity of Synapses the Mechanism of Long-Term Memory Storage?" *NPJ Science of Learning* 4, no. 1 (2019): 9.
- [25] A. Citri and R. C. Malenka, "Synaptic Plasticity: Multiple Forms, Functions, and Mechanisms," *Neuropsychopharmacology* 33, no. 1 (2008): 18–41.
- [26] T. V. P. Bliss and S. F. Cooke, "Long-Term Potentiation and Long-Term Depression: A Clinical Perspective," *Clinics* 1, no. Suppl 1 (2011): 3–17.
- [27] T. V. Bliss and T. Lomo, "Long-Lasting Potentiation of Synaptic Transmission in the Dentate Area of the Anaesthetized Rabbit Following Stimulation of the Perforant Path," *The Journal of Physiology* 232, no. 2 (1973): 331–356.
- [28] T. V. Bliss and A. R. Gardner-Medwin, "Long-Lasting Potentiation of Synaptic Transmission in the Dentate Area of the Unanaesthetized Rabbit Following Stimulation of the Perforant Path," *The Journal of Physiology* 232, no. 2 (1973): 357–374.
- [29] J. C. Magee and C. Grienberger, "Synaptic Plasticity Forms and Functions," *Annual Review of Neuroscience* 43, no. 1 (2020): 95–117.
- [30] J. R. Whitlock, A. J. Heynen, M. G. Shuler, and M. F. Bear, "Learning Induces Long-Term Potentiation in the Hippocampus," *Science* 313, no. 5790 (2006): 1093–1097.
- [31] J. R. Wickens, "Synaptic Plasticity in the Basal Ganglia," *Behavioural Brain Research* 199, no. 1 (2009): 119–128.
- [32] T. Hirano, "Long-Term Depression and Other Synaptic Plasticity in the Cerebellum," *Proceedings of the Japan Academy Series B, Physical and Biological Sciences* 89, no. 5 (2013): 183–195.
- [33] D. E. Feldman, "Synaptic Mechanisms for Plasticity in Neocortex," *Annual Review of Neuroscience* 32 (2009): 33–55.
- [34] F. M. Ribeiro, M. Castelo-Branco, J. Gonçalves, and J. Martins, "Visual Cortical Plasticity: Molecular Mechanisms as Revealed by Induction Paradigms in Rodents," *International Journal of Molecular Sciences* 24, no. 5 (2023): 4701.
- [35] A. L. Mahan and K. J. Ressler, "Fear Conditioning, Synaptic Plasticity and the Amygdala: Implications for Posttraumatic Stress Disorder," *Trends in Neurosciences* 35, no. 1 (2012): 24–35.
- [36] C. Lüscher and R. C. Malenka, "NMDA Receptor-Dependent Long-Term Potentiation and Long-Term Depression (LTP/LTD)," *Cold Spring Harbor Perspectives in Biology* 4, no. 6 (2012): a005710.
- [37] A. Malgaroli and R. W. Tsien, "Glutamate-Induced Long-Term Potentiation of the Frequency of Miniature Synaptic Currents in Cultured Hippocampal Neurons," *Nature* 357, no. 6374 (1992): 134–139.
- [38] A. Malgaroli, A. E. Ting, B. Wendland, et al., "Presynaptic Component of Long-Term Potentiation Visualized at Individual Hippocampal Synapses," *Science* 268, no. 5217 (1995): 1624–1628.
- [39] M. Bosch and Y. Hayashi, "Structural Plasticity of Dendritic Spines," *Current Opinion in Neurobiology* 22, no. 3 (2012): 383–388.
- [40] R. C. Malenka and M. F. Bear, "LTP and LTD: An Embarrassment of Riches," *Neuron* 44, no. 1 (2004): 5–21.
- [41] P. F. Chapman and L. L. Bellavance, "Induction of Long-Term Potentiation in the Basolateral Amygdala Does Not Depend on NMDA Receptor Activation," *Synapse* 11, no. 4 (1992): 310–318.
- [42] R. C. Malenka, "Postsynaptic Factors Control the Duration of Synaptic Enhancement in Area CA1 of the Hippocampus," *Neuron* 6, no. 1 (1991): 53–60.
- [43] R. C. Malenka and R. A. Nicoll, "NMDA-Receptor-Dependent Synaptic Plasticity: Multiple Forms and Mechanisms," *Trends in Neurosciences* 16, no. 12 (1993): 521–527.
- [44] R. C. Malenka, J. A. Kauer, D. J. Perkel, et al., "An Essential Role for Postsynaptic Calmodulin and Protein Kinase Activity in Long-Term Potentiation," *Nature* 340, no. 6234 (1989): 554–557.
- [45] D. L. Pettit, S. Perlman, and R. Malinow, "Potentiated Transmission and Prevention of Further LTP by Increased CaMKII Activity in Postsynaptic Hippocampal Slice Neurons," *Science* 266, no. 5192 (1994): 1881–1885.
- [46] V. A. Derkach, M. C. Oh, E. S. Guire, and T. R. Soderling, "Regulatory Mechanisms of AMPA Receptors in Synaptic Plasticity," *Nature Reviews Neuroscience* 8, no. 2 (2007): 101–113.
- [47] R. Malinow and R. C. Malenka, "AMPA Receptor Trafficking and Synaptic Plasticity," *Annual Review of Neuroscience* 25 (2002): 103–126.
- [48] I. Song and R. L. Huganir, "Regulation of AMPA Receptors During Synaptic Plasticity," *Trends in Neurosciences* 25, no. 11 (2002): 578–588.
- [49] E. Kim and M. Sheng, "PDZ Domain Proteins of Synapses," *Nature Reviews Neuroscience* 5, no. 10 (2004): 771–781.
- [50] I. Ehrlich and R. Malinow, "Postsynaptic Density 95 Controls AMPA Receptor Incorporation During Long-Term Potentiation and Experience-Driven Synaptic Plasticity," *The Journal of Neuroscience* 24, no. 4 (2004): 916–927.
- [51] V. Stein, D. R. C. House, D. S. Bredt, and R. A. Nicoll, "Postsynaptic Density-95 Mimics and Occludes Hippocampal Long-Term Potentiation and Enhances Long-Term Depression," *The Journal of Neuroscience* 23, no. 13 (2003): 5503–5506.
- [52] O. M. Schlüter, W. Xu, and R. C. Malenka, "Alternative N-Terminal Domains of PSD-95 and SAP97 Govern Activity-Dependent Regulation of Synaptic AMPA Receptor Function," *Neuron* 51, no. 1 (2006): 99–111.
- [53] K. Minatohara, M. Akiyoshi, and H. Okuno, "Role of Immediate-Early Genes in Synaptic Plasticity and Neuronal Ensembles Underlying the Memory Trace," *Frontiers in Molecular Neuroscience* 8 (2015): 78.
- [54] H. Okuno, "Regulation and Function of Immediate-Early Genes in the Brain: Beyond Neuronal Activity Markers," *Neuroscience Research* 69, no. 3 (2011): 175–186.
- [55] V. Ramírez-Amaya, A. Vazdarjanova, D. Mikhael, S. Rosi, P. F. Worley, and C. A. Barnes, "Spatial Exploration-Induced Arc mRNA and Protein Expression: Evidence for Selective, Network-Specific Reactivation," *The Journal of Neuroscience* 25, no. 7 (2005): 1761–1768.
- [56] J. E. Ploski, V. J. Pierre, J. Smucny, et al., "The Activity-Regulated Cytoskeletal-Associated Protein (Arc/Arg3.1) Is Required for Memory Consolidation of Pavlovian Fear Conditioning in the Lateral Amygdala," *The Journal of Neuroscience* 28, no. 47 (2008): 12383–12395.
- [57] E. Fifková and A. Van Harrevelde, "Long-Lasting Morphological Changes in Dendritic Spines of Dentate Granular Cells Following Stimulation of the Entorhinal Area," *Journal of Neurocytology* 6, no. 2 (1977): 211–230.

- [58] A. Van Harrevel and E. Fifkova, "Swelling of Dendritic Spines in the Fascia Dentata after Stimulation of the Perforant Fibers as a Mechanism of Post-Tetanic Potentiation," *Experimental Neurology* 49, no. 3 (1975): 736–749.
- [59] V. I. Popov, H. A. Davies, V. V. Rogachevsky, et al., "Remodelling of Synaptic Morphology but Unchanged Synaptic Density During Late Phase Long-Term Potentiation (LTP): A Serial Section Electron Micrograph Study in the Dentate Gyrus in the Anaesthetised Rat," *Neuroscience* 128, no. 2 (2004): 251–262.
- [60] N. Toni, P. A. Buchs, I. Nikonenko, C. R. Bron, and D. Muller, "LTP Promotes Formation of Multiple Spine Synapses Between a Single Axon Terminal and a Dendrite," *Nature* 402, no. 6760 (1999): 421–425.
- [61] J. C. Fiala, B. Allwardt, and K. M. Harris, "Dendritic Spines Do Not Split during Hippocampal LTP or Maturation," *Nature Neuroscience* 5, no. 4 (2002): 297–298.
- [62] D. A. Richards, J. M. Mateos, S. Hugel, et al., "Glutamate Induces the Rapid Formation of Spine Head Protrusions in Hippocampal Slice Cultures," *Proceedings of the National Academy of Sciences of the United States of America* 102, no. 17 (2005): 6166–6171.
- [63] J.-H. Tao-Cheng, A. Dosemeci, P. E. Gallant, et al., "Rapid Turnover of Spinules at Synaptic Terminals," *Neuroscience* 160, no. 1 (2009): 42–50.
- [64] C. R. Bramham and E. Messaoudi, "BDNF Function in Adult Synaptic Plasticity: The Synaptic Consolidation Hypothesis," *Progress in Neurobiology* 76, no. 2 (2005): 99–125.
- [65] S.-W. Ying, M. Futter, K. Rosenblum, et al., "Brain-Derived Neurotrophic Factor Induces Long-Term Potentiation in Intact Adult Hippocampus: Requirement for ERK Activation Coupled to CREB and Upregulation of *Arc* Synthesis," *The Journal of Neuroscience* 22, no. 5 (2002): 1532–1540.
- [66] S.-J. Wang and P.-W. Gean, "Long-Term Depression of Excitatory Synaptic Transmission in the Rat Amygdala," *The Journal of Neuroscience* 19, no. 24 (1999): 10656–10663.
- [67] S. M. Dudek and M. F. Bear, "Homosynaptic Long-Term Depression in Area CA1 of Hippocampus and Effects of N-Methyl-D-Aspartate Receptor Blockade," *Proceedings of the National Academy of Sciences of the United States of America* 89, no. 10 (1992): 4363–4367.
- [68] R. M. Mulkey and R. C. Malenka, "Mechanisms Underlying Induction of Homosynaptic Long-Term Depression in Area CA1 of the Hippocampus," *Neuron* 9, no. 5 (1992): 967–975.
- [69] R. M. Mulkey, C. E. Herron, and R. C. Malenka, "An Essential Role for Protein Phosphatases in Hippocampal Long-Term Depression," *Science* 261, no. 5124 (1993): 1051–1055.
- [70] R. M. Mulkey, S. Endo, S. Shenolikar, and R. C. Malenka, "Involvement of a Calcineurin/Inhibitor-1 Phosphatase Cascade in Hippocampal Long-Term Depression," *Nature* 369, no. 6480 (1994): 486–488.
- [71] A. Kirkwood and M. F. Bear, "Homosynaptic Long-Term Depression in the Visual Cortex," *The Journal of Neuroscience* 14, no. 5 (1994): 3404–3412.
- [72] W. Morishita, J. H. Connor, H. Xia, E. M. Quinlan, S. Shenolikar, and R. C. Malenka, "Regulation of Synaptic Strength by Protein Phosphatase 1," *Neuron* 32, no. 6 (2001): 1133–1148.
- [73] R. C. Carroll, E. C. Beattie, M. von Zastrow, and R. C. Malenka, "Role of AMPA Receptor Endocytosis in Synaptic Plasticity," *Nature Reviews Neuroscience* 2, no. 5 (2001): 315–324.
- [74] G. L. Collingridge, J. T. R. Isaac, and Y. T. Wang, "Receptor Trafficking and Synaptic Plasticity," *Nature Reviews Neuroscience* 5, no. 12 (2004): 952–962.
- [75] U. V. Nägerl, N. Eberhorn, S. B. Cambridge, and T. Bonhoeffer, "Bidirectional Activity-Dependent Morphological Plasticity in Hippocampal Neurons," *Neuron* 44, no. 5 (2004): 759–767.
- [76] K.-I. Okamoto, T. Nagai, A. Miyawaki, and Y. Hayashi, "Rapid and Persistent Modulation of Actin Dynamics Regulates Postsynaptic Reorganization Underlying Bidirectional Plasticity," *Nature Neuroscience* 7, no. 10 (2004): 1104–1112.
- [77] X. Wang, Y. Yang, and Q. Zhou, "Independent Expression of Synaptic and Morphological Plasticity Associated With Long-Term Depression," *The Journal of Neuroscience* 27, no. 45 (2007): 12419–12429.
- [78] Q. Zhou, K. J. Homma, and M.-M. Poo, "Shrinkage of Dendritic Spines Associated With Long-Term Depression of Hippocampal Synapses," *Neuron* 44, no. 5 (2004): 749–757.
- [79] H. Hsieh, J. Boehm, C. Sato, et al., "AMPA Removal Underlies $A\beta$ -Induced Synaptic Depression and Dendritic Spine Loss," *Neuron* 52, no. 5 (2006): 831–843.
- [80] Z. Nusser, R. Lujan, G. Laube, J. D. B. Roberts, E. Molnar, and P. Somogyi, "Cell Type and Pathway Dependence of Synaptic AMPA Receptor Number and Variability in the Hippocampus," *Neuron* 21, no. 3 (1998): 545–559.
- [81] Y. Takumi, V. Ramírez-León, P. Laake, E. Rinvik, and O. P. Ottersen, "Different Modes of Expression of AMPA and NMDA Receptors in Hippocampal Synapses," *Nature Neuroscience* 2, no. 7 (1999): 618–624.
- [82] E. Fifková, "Actin in the Nervous System," *Brain Research* 356, no. 2 (1985): 187–215.
- [83] T. Krucker, G. R. Siggins, and S. Halpain, "Dynamic Actin Filaments Are Required for Stable Long-Term Potentiation (LTP) in Area CA1 of the Hippocampus," *Proceedings of the National Academy of Sciences of the United States of America* 97, no. 12 (2000): 6856–6861.
- [84] M. Matsuzaki, N. Honkura, G. C. R. Ellis-Davies, and H. Kasai, "Structural Basis of Long-Term Potentiation in Single Dendritic Spines," *Nature* 429, no. 6993 (2004): 761–766.
- [85] C. M. Alberini and E. R. Kandel, "The Regulation of Transcription in Memory Consolidation," *Cold Spring Harbor Perspectives in Biology* 7, no. 1 (2014): a021741.
- [86] E. R. Kandel, "The Molecular Biology of Memory: cAMP, PKA, CRE, CREB-1, CREB-2, and C/EBP," *Molecular Brain* 5 (2012): 14.
- [87] J. Viosca, M. Lopez de Armentia, D. Jancic, and A. Barco, "Enhanced CREB-Dependent Gene Expression Increases the Excitability of Neurons in the Basal Amygdala and Primes the Consolidation of Contextual and Cued Fear Memory," *Learning & Memory* 16, no. 3 (2009): 193–197.
- [88] A. Gruart, E. Benito, J. M. Delgado-García, and A. Barco, "Enhanced cAMP Response Element-Binding Protein Activity Increases Neuronal Excitability, Hippocampal Long-Term Potentiation, and Classical Eyeblink Conditioning in Alert Behaving Mice," *The Journal of Neuroscience* 32, no. 48 (2012): 17431–17441.
- [89] W. C. Abraham and M. F. Bear, "Metaplasticity: The Plasticity of Synaptic Plasticity," *Trends in Neurosciences* 19, no. 4 (1996): 126–130.
- [90] F. Müller-Dahlhaus and U. Ziemann, "Metaplasticity in Human Cortex," *The Neuroscientist: A Review Journal*

- Bringing Neurobiology Neurology and Psychiatry* 21, no. 2 (2015): 185–202.
- [91] S. R. Hulme, O. D. Jones, C. R. Raymond, P. Sah, and W. C. Abraham, “Mechanisms of Heterosynaptic Metaplasticity,” *Philosophical Transactions of the Royal Society B: Biological Sciences* 369, no. 1633 (2014): 20130148.
- [92] W. C. Abraham, S. E. Mason-Parker, M. F. Bear, S. Webb, and W. P. Tate, “Heterosynaptic Metaplasticity in the Hippocampus *In Vivo*: A BCM-Like Modifiable Threshold for LTP,” *Proceedings of the National Academy of Sciences of the United States of America* 98, no. 19 (2001): 10924–10929.
- [93] A. Buschler and D. Manahan-Vaughan, “Brief Environmental Enrichment Elicits Metaplasticity of Hippocampal Synaptic Potentiation *In Vivo*,” *Frontiers in Behavioral Neuroscience* 6 (2012): 85.
- [94] C. D. Harvey and K. Svoboda, “Locally Dynamic Synaptic Learning Rules in Pyramidal Neuron Dendrites,” *Nature* 450, no. 7173 (2007): 1195–1200.
- [95] S. Sajikumar, Q. Li, W. C. Abraham, and Z. C. Xiao, “Priming of Short-Term Potentiation and Synaptic Tagging/Capture Mechanisms by Ryanodine Receptor Activation in Rat Hippocampal CA1,” *Learning & Memory* 16, no. 3 (2009): 178–186.
- [96] Q. Li, M. Rothkegel, Z. C. Xiao, W. C. Abraham, M. Korte, and S. Sajikumar, “Making Synapses Strong: Metaplasticity Prolongs Associativity of Long-Term Memory by Switching Synaptic Tag Mechanisms,” *Cerebral Cortex* 24, no. 2 (2014): 353–363.
- [97] B. R. Christie and W. C. Abraham, “Priming of Associative Long-Term Depression in the Dentate Gyrus by θ Frequency Synaptic Activity,” *Neuron* 9, no. 1 (1992): 79–84.
- [98] Y.-Y. Huang, A. Colino, D. K. Selig, and R. C. Malenka, “The Influence of Prior Synaptic Activity on the Induction of Long-Term Potentiation,” *Science* 255, no. 5045 (1992): 730–733.
- [99] C. R. Raymond, V. L. Thompson, W. P. Tate, and W. C. Abraham, “Metabotropic Glutamate Receptors Trigger Homosynaptic Protein Synthesis to Prolong Long-Term Potentiation,” *The Journal of Neuroscience* 20, no. 3 (2000): 969–976.
- [100] E. L. Bienenstock, L. N. Cooper, and P. W. Munro, “Theory for the Development of Neuron Selectivity: Orientation Specificity and Binocular Interaction in Visual Cortex,” *The Journal of Neuroscience* 2, no. 1 (1982): 32–48.
- [101] H. Wang and J. J. Wagner, “Priming-Induced Shift in Synaptic Plasticity in the Rat Hippocampus,” *Journal of Neurophysiology* 82, no. 4 (1999): 2024–2028.
- [102] W. C. Abraham, “Metaplasticity: Tuning Synapses and Networks for Plasticity,” *Nature Reviews Neuroscience* 9, no. 5 (2008): 387–387.
- [103] G. G. Turrigiano, “The Dialectic of Hebb and Homeostasis,” *Philosophical Transactions of the Royal Society of London Series B, Biological Sciences* 372, no. 1715 (2017): 20160258.
- [104] I. Pérez-Otaño and M. D. Ehlers, “Homeostatic Plasticity and NMDA Receptor Trafficking,” *Trends in Neurosciences* 28, no. 5 (2005): 229–238.
- [105] S. E. D. Sun, D. Levenstein, B. Li, et al., “Synaptic Homeostasis Transiently Leverages Hebbian Mechanisms for a Multiphasic Response to Inactivity,” *Cell Reports* 43, no. 4 (2024): 113839.
- [106] B. D. Philpot, K. K. A. Cho, and M. F. Bear, “Obligatory Role of NR2A for Metaplasticity in Visual Cortex,” *Neuron* 53, no. 4 (2007): 495–502.
- [107] G. Lynch, C. S. Rex, and C. M. Gall, “Synaptic Plasticity in Early Aging,” *Ageing Research Reviews* 5, no. 3 (2006): 255–280.
- [108] J. A. Bergado and W. Almaguer, “Aging and Synaptic Plasticity: A Review,” *Neural Plasticity* 9, no. 4 (2002): 738453, 16 pages.
- [109] C. Chisari, C. Fanciullacci, G. Lamola, B. Rossi, and L. G. Cohen, “NIBS-Driven Brain Plasticity,” *Archives Italiennes de Biologie* 152, no. 4 (2014): 247–258.
- [110] M. Ferro, J. Lamanna, S. Spadini, A. Nespoli, S. Sulpizio, and A. Malgaroli, “Synaptic Plasticity Mechanisms Behind TMS Efficacy: Insights From Its Application to Animal Models,” *Journal of Neural Transmission* 129, no. 1 (2022): 25–36.
- [111] S. A. Barbati, M. V. Podda, and C. Grassi, “Tuning Brain Networks: The Emerging Role of Transcranial Direct Current Stimulation on Structural Plasticity,” *Frontiers in Cellular Neuroscience* 16 (2022): 945777.
- [112] Y.-Z. Huang, M.-K. Lu, A. Antal, et al., “Plasticity Induced by Non-Invasive Transcranial Brain Stimulation: A Position Paper,” *Clinical Neurophysiology* 128, no. 11 (2017): 2318–2329.
- [113] L. Cárdenas-Morales, D. A. Nowak, T. Kammer, R. C. Wolf, and C. Schönfeldt-Lecuona, “Mechanisms and Applications of Theta-Burst rTMS on the Human Motor Cortex,” *Brain Topography* 22, no. 4 (2010): 294–306.
- [114] G. Cirillo, G. Di Pino, F. Capone, et al., “Neurobiological after-Effects of Non-Invasive Brain Stimulation,” *Brain Stimulation* 10, no. 1 (2017): 1–18.
- [115] U. Ziemann, “Thirty Years of Transcranial Magnetic Stimulation: Where Do We Stand?” *Experimental Brain Research* 235, no. 4 (2017): 973–984.
- [116] M. M. Y. Chan, S. S. Y. Yau, and Y. M. Y. Han, “The Neurobiology of Prefrontal Transcranial Direct Current Stimulation (tDCS) in Promoting Brain Plasticity: A Systematic Review and Meta-Analyses of Human and Rodent Studies,” *Neuroscience & Biobehavioral Reviews* 125 (2021): 392–416.
- [117] G. Kronberg, M. Bridi, T. Abel, M. Bikson, and L. C. Parra, “Direct Current Stimulation Modulates LTP and LTD: Activity Dependence and Dendritic Effects,” *Brain Stimulation* 10, no. 1 (2017): 51–58.
- [118] H. Sened, S. Zilcha-Mano, and S. Shamay-Tsoory, “Inter-Brain Plasticity as a Biological Mechanism of Change in Psychotherapy: A Review and Integrative Model,” *Frontiers in Human Neuroscience* 16 (2022): 955238.
- [119] E. R. Kandel, “A New Intellectual Framework for Psychiatry,” *American Journal of Psychiatry* 155, no. 4 (1998): 457–469.
- [120] E. R. Kandel, “Biology and the Future of Psychoanalysis: A New Intellectual Framework for Psychiatry Revisited,” *American Journal of Psychiatry* 156, no. 4 (1999): 505–524.
- [121] A. Barsaglini, G. Sartori, S. Benetti, W. Pettersson-Yeo, and A. Mechelli, “The Effects of Psychotherapy on Brain Function: A Systematic and Critical Review,” *Progress in Neurobiology* 114 (2014): 1–14.
- [122] D. E. J. Linden, “How Psychotherapy Changes the Brain—The Contribution of Functional Neuroimaging,” *Molecular Psychiatry* 11, no. 6 (2006): 528–538.
- [123] A. Manthey, A. Sierk, E.-L. Brakemeier, H. Walter, and J. K. Daniels, “Does Trauma-Focused Psychotherapy Change the Brain? A Systematic Review of Neural Correlates of Therapeutic Gains in PTSD,” *European Journal of Psychotraumatology* 12, no. 1 (2021): 1929025.
- [124] A. Buchheim, R. Viviani, H. Kessler, et al., “Changes in Prefrontal-Limbic Function in Major Depression After 15

- Months of Long-Term Psychotherapy,” *PLoS ONE* 7, no. 3 (2012): e33745.
- [125] G. S. Dichter, J. N. Felder, and M. J. Smoski, “Affective Context Interferes with Cognitive Control in Unipolar Depression: An fMRI Investigation,” *Journal of Affective Disorders* 114, no. 1–3 (2009): 131–142.
- [126] G. S. Dichter, J. N. Felder, and M. J. Smoski, “The Effects of Brief Behavioral Activation Therapy for Depression on Cognitive Control in Affective Contexts: An fMRI Investigation,” *Journal of Affective Disorders* 126, no. 1–2 (2010): 236–244.
- [127] C. H. Y. Fu, S. C. R. Williams, A. J. Cleare, et al., “Neural Responses to Sad Facial Expressions in Major Depression Following Cognitive Behavioral Therapy,” *Biological Psychiatry* 64, no. 6 (2008): 505–512.
- [128] G. J. Siegle, C. S. Carter, and M. E. Thase, “Use of fMRI to Predict Recovery From Unipolar Depression With Cognitive Behavior Therapy,” *American Journal of Psychiatry* 163, no. 4 (2006): 735–738.
- [129] S. Yoshimura, Y. Okamoto, K. Onoda, et al., “Cognitive Behavioral Therapy for Depression Changes Medial Prefrontal and Ventral Anterior Cingulate Cortex Activity Associated With Self-Referential Processing,” *Social Cognitive and Affective Neuroscience* 9, no. 4 (2014): 487–493.
- [130] M. E. Beutel, R. Stark, H. Pan, D. Silbersweig, and S. Dietrich, “Changes of Brain Activation Pre- Post Short-Term Psychodynamic Inpatient Psychotherapy: An fMRI Study of Panic Disorder Patients,” *Psychiatry Research: Neuroimaging* 184, no. 2 (2010): 96–104.
- [131] P. R. Goldin and J. J. Gross, “Effects of Mindfulness-Based Stress Reduction (MBSR) on Emotion Regulation in Social Anxiety Disorder,” *Emotion* 10, no. 1 (2010): 83–91.
- [132] T. Kircher, V. Arolt, A. Jansen, et al., “Effect of Cognitive-Behavioral Therapy on Neural Correlates of Fear Conditioning in Panic Disorder,” *Biological Psychiatry* 73, no. 1 (2013): 93–101.
- [133] V. Paquette, J. Lévesque, B. Mensour, et al., “Change the Mind and You Change the Brain: Effects of Cognitive-Behavioral Therapy on the Neural Correlates of Spider Phobia,” *NeuroImage* 18, no. 2 (2003): 401–409.
- [134] Y. Sakai, H. Kumano, M. Nishikawa, et al., “Changes in Cerebral Glucose Utilization in Patients With Panic Disorder Treated With Cognitive-Behavioral Therapy,” *NeuroImage* 33, no. 1 (2006): 218–226.
- [135] A. Schienle, A. Schäfer, A. Hermann, S. Rohrmann, and D. Vaitl, “Symptom Provocation and Reduction in Patients Suffering From Spider Phobia,” *European Archives of Psychiatry and Clinical Neuroscience* 257, no. 8 (2007): 486–493.
- [136] A. Schienle, A. Schäfer, R. Stark, and D. Vaitl, “Long-Term Effects of Cognitive Behavior Therapy on Brain Activation in Spider Phobia,” *Psychiatry Research: Neuroimaging* 172, no. 2 (2009): 99–102.
- [137] T. Straube, M. Glauer, S. Dilger, H.-J. Mentzel, and W. H. R. Miltner, “Effects of Cognitive-Behavioral Therapy on Brain Activation in Specific Phobia,” *NeuroImage* 29, no. 1 (2006): 125–135.
- [138] T. Freyer, S. Klöppel, O. Tüscher, et al., “Frontostriatal Activation in Patients With Obsessive-Compulsive Disorder Before and After Cognitive Behavioral Therapy,” *Psychological Medicine* 41, no. 1 (2011): 207–216.
- [139] E. Nakatani, A. Nakagawa, Y. Ohara, et al., “Effects of Behavior Therapy on Regional Cerebral Blood Flow in Obsessive-Compulsive Disorder,” *Psychiatry Research: Neuroimaging* 124, no. 2 (2003): 113–120.
- [140] J. O’Neill, E. Gorbis, J. D. Feusner, et al., “Effects of Intensive Cognitive-Behavioral Therapy on Cingulate Neurochemistry in Obsessive-Compulsive Disorder,” *Journal of Psychiatric Research* 47, no. 4 (2013): 494–504.
- [141] S. Saxena, E. Gorbis, J. O’Neill, et al., “Rapid Effects of Brief Intensive Cognitive-Behavioral Therapy on Brain Glucose Metabolism in Obsessive-Compulsive Disorder,” *Molecular Psychiatry* 14, no. 2 (2009): 197–205.
- [142] J. M. Schwartz, P. W. Stoessel, L. R. J. Baxter, K. M. Martin, and M. E. Phelps, “Systematic Changes in Cerebral Glucose Metabolic Rate After Successful Behavior Modification Treatment of Obsessive-Compulsive Disorder,” *Archives of General Psychiatry* 53, no. 2 (1996): 109–113.
- [143] T. Yamanishi, S. Nakaaki, I. M. Omori, et al., “Changes after Behavior Therapy Among Responsive and Nonresponsive Patients With Obsessive-Compulsive Disorder,” *Psychiatry Research: Neuroimaging* 172, no. 3 (2009): 242–250.
- [144] T. F. D. Farrow, M. D. Hunter, I. D. Wilkinson, et al., “Quantifiable Change in Functional Brain Response to Empathic and Forgivability Judgments With Resolution of Posttraumatic Stress Disorder,” *Psychiatry Research: Neuroimaging* 140, no. 1 (2005): 45–53.
- [145] K. Felmingham, A. Kemp, L. Williams, et al., “Changes in Anterior Cingulate and Amygdala After Cognitive Behavior Therapy of Posttraumatic Stress Disorder,” *Psychological Science* 18, no. 2 (2007): 127–129.
- [146] R. J. L. Lindauer, J. Booij, J. B. A. Habraken, et al., “Effects of Psychotherapy on Regional Cerebral Blood Flow During Trauma Imagery in Patients with Post-Traumatic Stress Disorder: A Randomized Clinical Trial,” *Psychological Medicine* 38, no. 4 (2008): 543–554.
- [147] J. F. P. Peres, A. B. Newberg, J. P. Mercante, et al., “Cerebral Blood Flow Changes During Retrieval of Traumatic Memories Before and After Psychotherapy: A SPECT Study,” *Psychological Medicine* 37, no. 10 (2007): 1481–1491.
- [148] M. J. Roy, J. Francis, J. Friedlander, et al., “Improvement in Cerebral Function With Treatment of Posttraumatic Stress Disorder,” *Annals of the New York Academy of Sciences* 1208 (2010): 142–149.
- [149] H. Barbas and M.Á. García-Cabezas, “Prefrontal Cortex Integration of Emotion and Cognition,” in *The Prefrontal Cortex as an Executive, Emotional, and Social Brain*, ed. M. Watanabe, (Springer Japan, Tokyo, 2017): 51–76.
- [150] J. S. Beck, *Cognitive Behavior Therapy: Basics and Beyond* (Guilford Publications, New York, 2020).
- [151] J. S. Beck and S. Fleming, “A Brief History of Aaron T. Beck, MD, and Cognitive Behavior Therapy,” *Clinical Psychology in Europe* 3, no. 2 (2021): e6701.
- [152] K. Fenn and M. Byrne, “The Key Principles of Cognitive Behavioural Therapy,” *InnovAiT: Education and Inspiration for General Practice* 6, no. 9 (2013): 579–585.
- [153] M. Nakao, K. Shirotaki, and N. Sugaya, “Cognitive-Behavioral Therapy for Management of Mental Health and Stress-Related Disorders: Recent Advances in Techniques and Technologies,” *BioPsychoSocial Medicine* 15, no. 1 (2021): 16.
- [154] C. P. McLean and E. B. Foa, “Prolonged Exposure Therapy,” in *Evidence Based Treatments for Trauma-Related Psychological Disorders: A Practical Guide for Clinicians*, eds. U. Schnyder and M. Cloitre, (Springer International Publishing, Cham, 2022): 161–179.

- [155] R. K. Sripada and S. A. M. Rauch, "Between-Session and Within-Session Habituation in Prolonged Exposure Therapy for Posttraumatic Stress Disorder: A Hierarchical Linear Modeling Approach," *Journal of Anxiety Disorders* 30 (2015): 81–87.
- [156] S. A. M. Rauch, A. Eftekhari, and J. I. Ruzek, "Review of Exposure Therapy: A Gold Standard for PTSD Treatment," *Journal of Rehabilitation Research and Development* 49, no. 5 (2012): 679–687.
- [157] J. P. Hayes, S. M. Hayes, and A. M. Mikedis, "Quantitative Meta-Analysis of Neural Activity in Posttraumatic Stress Disorder," *Biology of Mood & Anxiety Disorders* 2, no. 1 (2012): 9.
- [158] E. A. Phelps, M. R. Delgado, K. I. Nearing, and J. E. LeDoux, "Extinction Learning in Humans: Role of the Amygdala and vmPFC," *Neuron* 43, no. 6 (2004): 897–905.
- [159] A. L. Gold, T. Shechner, M. J. Farber, et al., "Amygdala-Cortical Connectivity: Associations with Anxiety, Development, and Threat," *Depression and Anxiety* 33, no. 10 (2016): 917–926.
- [160] C. G. Connolly, T. C. Ho, E. H. Blom, et al., "Resting-State Functional Connectivity of the Amygdala and Longitudinal Changes in Depression Severity in Adolescent Depression," *Journal of Affective Disorders* 207 (2017): 86–94.
- [161] A. Pittig, L. van den Berg, and B. Vervliet, "The Key Role of Extinction Learning in Anxiety Disorders: Behavioral Strategies to Enhance Exposure-Based Treatments," *Current Opinion in Psychiatry* 29, no. 1 (2016): 39–47.
- [162] K. M. Myers, K. J. Ressler, and M. Davis, "Different Mechanisms of Fear Extinction Dependent on Length of Time since Fear Acquisition," *Learning & Memory* 13, no. 2 (2006): 216–223.
- [163] L. Helpman, M.-F. Marin, S. Papini, et al., "Neural Changes in Extinction Recall Following Prolonged Exposure Treatment for PTSD: A Longitudinal fMRI Study," *NeuroImage: Clinical* 12 (2016): 715–723.
- [164] M. M. Stojek, L. B. McSweeney, and S. A. M. Rauch, "Neuroscience Informed Prolonged Exposure Practice: Increasing Efficiency and Efficacy Through Mechanisms," *Frontiers in Behavioral Neuroscience* 12 (2018): 281.
- [165] F. Shapiro, *Eye Movement Desensitization and Reprocessing (EMDR): Basic Principles, Protocols, and Procedures* (Guilford Press, 2001).
- [166] J. Baek, S. Lee, T. Cho, et al., "Neural Circuits Underlying a Psychotherapeutic Regimen for Fear Disorders," *Nature* 566, no. 7744 (2019): 339–343.
- [167] G. Montesano, M. Belfiore, M. Ripamonti, et al., "Effects of the Concomitant Activation of ON and OFF Retinal Ganglion Cells on the Visual Thalamus: Evidence for an Enhanced Recruitment of GABAergic Cells," *Frontiers in Neural Circuits* 9 (2015): 77.
- [168] G. A. Fonzo, H. J. Ramsawh, T. M. Flagan, et al., "Cognitive-Behavioral Therapy for Generalized Anxiety Disorder Is Associated With Attenuation of Limbic Activation to Threat-Related Facial Emotions," *Journal of Affective Disorders* 169 (2014): 76–85.
- [169] K. N. T. Månsson, A. Salami, A. Frick, et al., "Neuroplasticity in Response to Cognitive Behavior Therapy for Social Anxiety Disorder," *Translational Psychiatry* 6, no. 2 (2016): e727.
- [170] M. Ritchey, F. Dolcos, K. M. Eddington, T. J. Strauman, and R. Cabeza, "Neural Correlates of Emotional Processing in Depression: Changes with Cognitive Behavioral Therapy and Predictors of Treatment Response," *Journal of Psychiatric Research* 45, no. 5 (2011): 577–587.
- [171] C. F. Sandman, K. S. Young, L. J. Burklund, D. E. Saxbe, M. D. Lieberman, and M. G. Craske, "Changes in Functional Connectivity With Cognitive Behavioral Therapy for Social Anxiety Disorder Predict Outcomes at Follow-up," *Behaviour Research and Therapy* 129 (2020): 103612.
- [172] S. Shiota, Y. Okamoto, G. Okada, et al., "Effects of Behavioural Activation on the Neural Basis of Other Perspective Self-Referential Processing in Subthreshold Depression: A Functional Magnetic Resonance Imaging Study," *Psychological Medicine* 47, no. 5 (2017): 877–888.
- [173] Z. Yang, D. J. Oathes, K. A. Linn, et al., "Cognitive Behavioral Therapy Is Associated With Enhanced Cognitive Control Network Activity in Major Depression and Posttraumatic Stress Disorder," *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 3, no. 4 (2018): 311–319.
- [174] H. S. Mayberg, "Modulating Dysfunctional Limbic-Cortical Circuits in Depression: Towards Development of Brain-Based Algorithms for Diagnosis and Optimised Treatment," *British Medical Bulletin* 65, no. 1 (2003): 193–207.
- [175] L. M. Shin and I. Liberzon, "The Neurocircuitry of Fear, Stress, and Anxiety Disorders," *Neuropsychopharmacology* 35, no. 1 (2010): 169–191.
- [176] M. L. Phillips, C. D. Ladouceur, and W. C. Drevets, "A Neural Model of Voluntary and Automatic Emotion Regulation: Implications for Understanding the Pathophysiology and Neurodevelopment of Bipolar Disorder," *Molecular Psychiatry* 13, no. 9 (2008): 833–857.
- [177] L. M. Braunstein, J. J. Gross, and K. N. Ochsner, "Explicit and Implicit Emotion Regulation: A Multi-Level Framework," *Social Cognitive and Affective Neuroscience* 12, no. 10 (2017): 1545–1557.
- [178] A. Gyurak, J. J. Gross, and A. Etkin, "Explicit and Implicit Emotion Regulation: A Dual-Process Framework," *Cognition and Emotion* 25, no. 3 (2011): 400–412.
- [179] I. Messina, M. Sambin, A. Palmieri, and R. Viviani, "Neural Correlates of Psychotherapy in Anxiety and Depression: A Meta-Analysis," *PLoS ONE* 8, no. 9 (2013): e74657.
- [180] R. A. Bryant, A. H. Kemp, K. L. Felmingham, et al., "Enhanced Amygdala and Medial Prefrontal Activation During Nonconscious Processing of Fear in Posttraumatic Stress Disorder: An fMRI Study," *Human Brain Mapping* 29, no. 5 (2008): 517–523.
- [181] A. L. Thorsen, O. A. van den Heuvel, B. Hansen, and G. Kvale, "Neuroimaging of Psychotherapy for Obsessive-Compulsive Disorder: A Systematic Review," *Psychiatry Research: Neuroimaging* 233, no. 3 (2015): 306–313.
- [182] A. Baioui, J. Pilgramm, S. Kagerer, B. Walter, D. Vaitl, and R. Stark, "Neural Correlates of Symptom Reduction After CBT in Obsessive-Compulsive Washers—An fMRI Symptom Provocation Study," *Journal of Obsessive-Compulsive and Related Disorders* 2, no. 3 (2013): 322–330.
- [183] L. J. Norman, K. A. Mannella, H. Yang, et al., "Treatment-Specific Associations Between Brain Activation and Symptom Reduction in OCD Following CBT: A Randomized fMRI Trial," *American Journal of Psychiatry* 178, no. 1 (2021): 39–47.
- [184] X.-Y. Yang, J. Sun, J. Luo, et al., "Regional Homogeneity of Spontaneous Brain Activity in Adult Patients With Obsessive-Compulsive Disorder before and After Cognitive Behavioural Therapy," *Journal of Affective Disorders* 188 (2015): 243–251.

- [185] M. Cano, I. Martínez-Zalacaín, M. Giménez, et al., “Neural Correlates of Fear Conditioning and Fear Extinction and Its Association With Cognitive-Behavioral Therapy Outcome in Adults With Obsessive-Compulsive Disorder,” *Behaviour Research and Therapy* 144 (2021): 103927.
- [186] S. J. Brooks and D. J. Stein, “A Systematic Review of the Neural Bases of Psychotherapy for Anxiety and Related Disorders,” *Dialogues in Clinical Neuroscience* 17, no. 3 (2015): 261–279.
- [187] M. A. Nitsche, F. Müller-Dahlhaus, W. Paulus, and U. Ziemann, “The Pharmacology of Neuroplasticity Induced by Non-Invasive Brain Stimulation: Building Models for the Clinical use of CNS Active Drugs,” *The Journal of Physiology* 590, no. 19 (2012): 4641–4662.
- [188] A. Antal, I. Alekseichuk, M. Bikson, et al., “Low Intensity Transcranial Electric Stimulation: Safety, Ethical, Legal Regulatory and Application Guidelines,” *Clinical Neurophysiology* 128, no. 9 (2017): 1774–1809.
- [189] A. Bhattacharya, K. Mrudula, S. S. Sreepada, et al., “An Overview of Noninvasive Brain Stimulation: Basic Principles and Clinical Applications,” *the Canadian Journal of Neurological Sciences/Le Journal Canadien Des Sciences Neurologiques* 49, no. 4 (2022): 479–492.
- [190] Y. Terao and Y. Ugawa, “Basic Mechanisms of TMS,” *Journal of Clinical Neurophysiology* 19, no. 4 (2002): 322–343.
- [191] M. Kobayashi and A. Pascual-Leone, “Transcranial Magnetic Stimulation in Neurology,” *The Lancet Neurology* 2, no. 3 (2003): 145–156.
- [192] M. C. Eldaief, D. Z. Press, and A. Pascual-Leone, “Transcranial Magnetic Stimulation in Neurology: A Review of Established and Prospective Applications,” *Neurology Clinical Practice* 3, no. 6 (2013): 519–526.
- [193] F. Fregni and A. Pascual-Leone, “Technology Insight: Noninvasive Brain Stimulation in Neurology—Perspectives on the Therapeutic Potential of rTMS and tDCS,” *Nature Clinical Practice Neurology* 3, no. 7 (2007): 383–393.
- [194] M. Diana, T. Raji, M. Melis, A. Nummenmaa, L. Leggio, and A. Bonci, “Rehabilitating the Addicted Brain With Transcranial Magnetic Stimulation,” *Nature Reviews Neuroscience* 18, no. 11 (2017): 685–693.
- [195] N. Arai, S. Okabe, T. Furubayashi, Y. Terao, K. Yuasa, and Y. Ugawa, “Comparison Between Short Train, Monophasic and Biphasic Repetitive Transcranial Magnetic Stimulation (rTMS) of the Human Motor Cortex,” *Clinical Neurophysiology* 116, no. 3 (2005): 605–613.
- [196] J. Classen and K. Stefan, “Changes in TMS Measures Induced by Repetitive TMS,” in *The Oxford Handbook of Transcranial Stimulation*, eds. E. M. Wassermann, U. Ziemann, V. Walsh, T. Paus, and S. Lisanby, (Oxford University Press Inc, New York, 2008): 185–200.
- [197] J. L. Taylor and C. K. Loo, “Stimulus Waveform Influences the Efficacy of Repetitive Transcranial Magnetic Stimulation,” *Journal of Affective Disorders* 97, no. 1–3 (2007): 271–276.
- [198] E. Houdayer, A. Degardin, F. Cassim, P. Bocquillon, P. Derambure, and H. Devanne, “The Effects of Low- and High-Frequency Repetitive TMS on the Input/Output Properties of the Human Corticospinal Pathway,” *Experimental Brain Research* 187, no. 2 (2008): 207–217.
- [199] Y.-Z. Huang, M. J. Edwards, E. Rounis, K. P. Bhatia, and J. C. Rothwell, “Theta Burst Stimulation of the Human Motor Cortex,” *Neuron* 45, no. 2 (2005): 201–206.
- [200] M. A. Nitsche, L. G. Cohen, E. M. Wassermann, et al., “Transcranial Direct Current Stimulation: State of the Art 2008,” *Brain Stimulation* 1, no. 3 (2008): 206–223.
- [201] T. Reed and R. Cohen Kadosh, “Transcranial Electrical Stimulation (tES) Mechanisms and Its Effects on Cortical Excitability and Connectivity,” *Journal of Inherited Metabolic Disease* 41, no. 6 (2018): 1123–1130.
- [202] M. A. Nitsche and W. Paulus, “Excitability Changes Induced in the Human Motor Cortex by Weak Transcranial Direct Current Stimulation,” *The Journal of Physiology* 527, no. 3 (2000): 633–639.
- [203] M. A. Nitsche and W. Paulus, “Sustained Excitability Elevations Induced by Transcranial DC Motor Cortex Stimulation in Humans,” *Neurology* 57, no. 10 (2001): 1899–1901.
- [204] A. J. Woods, A. Antal, M. Bikson, et al., “A Technical Guide to tDCS, and Related Non-Invasive Brain Stimulation Tools,” *Clinical Neurophysiology* 127, no. 2 (2016): 1031–1048.
- [205] G. Castrillon, N. Sollmann, K. Kurcyus, A. Razi, S. M. Krieg, and V. Riedl, “The Physiological Effects of Noninvasive Brain Stimulation Fundamentally Differ Across the Human Cortex,” *Science Advances* 6, no. 5 (2020): eaay2739.
- [206] V. López-Alonso, B. Cheeran, D. Río-Rodríguez, and M. Fernández-del-Olmo, “Inter-Individual Variability in Response to Non-Invasive Brain Stimulation Paradigms,” *Brain Stimulation* 7, no. 3 (2014): 372–380.
- [207] A. Pisoni, G. Mattavelli, C. Papagno, M. Rosanova, A. G. Casali, and L. J. Romero Lauro, “Cognitive Enhancement Induced by Anodal tDCS Drives Circuit-Specific Cortical Plasticity,” *Cerebral Cortex* 28, no. 4 (2018): 1132–1140.
- [208] A. Vergallito, S. Feroldi, A. Pisoni, and L. J. Romero Lauro, “Inter-Individual Variability in tDCS Effects: A Narrative Review on the Contribution of Stable, Variable, and Contextual Factors,” *Brain sciences* 12, no. 5 (2022).
- [209] A. S. Moro, D. Saccenti, M. Ferro, S. Scaini, A. Malgaroli, and J. Lamanna, “Neural Correlates of Delay Discounting in the Light of Brain Imaging and Non-Invasive Brain Stimulation: What We Know and What Is Missed,” *Brain Sciences* 13, no. 3 (2023): 403.
- [210] A. S. Moro, D. Saccenti, A. Seccia, M. Ferro, A. Malgaroli, and J. Lamanna, “Poke and Delayed Drink Intertemporal Choice Task (POKE-ADDICT): An Open-Source Behavioral Apparatus for Intertemporal Choice Testing in Rodents,” *Animal Models and Experimental Medicine* 6: 619–626.
- [211] A. S. Moro, D. Saccenti, A. Vergallito, et al., “Transcranial Direct Current Stimulation (tDCS) Over the Orbitofrontal Cortex Reduces Delay Discounting,” *Frontiers in Behavioral Neuroscience* 17 (2023): 1239463.
- [212] D. Saccenti, A. S. Moro, S. Sassaroli, A. Malgaroli, M. Ferro, and J. Lamanna, “Neural Correlates of Metacognition: Disentangling the Brain Circuits Underlying Prospective and Retrospective Second-Order Judgments Through Noninvasive Brain Stimulation,” *Journal of Neuroscience Research* 102, no. 4 (2024): e25330.
- [213] A. Vergallito, A. Gallucci, A. Pisoni, et al., “Effectiveness of Noninvasive Brain Stimulation in the Treatment of Anxiety Disorders: A Meta-Analysis of Sham or Behaviour-Controlled Studies,” *Journal of Psychiatry and Neuroscience* 46, no. 6 (2021): E592–E614.
- [214] E. Piccoli, M. Cerioli, M. Castiglioni, L. Larini, C. Scarpa, and B. Dell’Osso, “Recent Innovations in Non-Invasive Brain Stimulation (NIBS) for the Treatment of Unipolar and Bipolar Depression: A Narrative Review,” *International Review of Psychiatry* 34, no. 7-8 (2022): 715–726.
- [215] S. Zhou and Y. Fang, “Efficacy of Non-Invasive Brain Stimulation for Refractory Obsessive-Compulsive Disorder:

- A Meta-Analysis of Randomized Controlled Trials,” *Brain Sciences* 12, no. 7 (2022): 943.
- [216] R. L. D. Kan, B. B. Zhang, J. J. Q. Zhang, and G. S. Kranz, “Non-Invasive Brain Stimulation for Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis,” *Translational Psychiatry* 10, no. 1 (2020): 168.
- [217] D. Saccenti, L. Lodi, A. S. Moro, et al., “Novel Approaches for the Treatment of Post-Traumatic Stress Disorder: A Systematic Review of Non-Invasive Brain Stimulation Interventions and Insights From Clinical Trials,” *Brain Sciences* 14, no. 3 (2024): 210.
- [218] P. A. Hall, C. M. Vincent, and A. M. Burhan, “Non-Invasive Brain Stimulation for Food Cravings, Consumption, and Disorders of Eating: A Review of Methods, Findings and Controversies,” *Appetite* 124 (2018): 78–88.
- [219] L. Del Mauro, A. Vergallito, and G. Gattavara, “Betting on Non-Invasive Brain Stimulation to Treat Gambling Disorder: A Systematic Review and Meta-Analysis,” *Brain Sciences* 13, no. 4 (2023): 698.
- [220] E. R. Stein, B. C. Gibson, V. R. Votaw, A. D. Wilson, V. P. Clark, and K. Witkiewitz, “Non-Invasive Brain Stimulation in Substance Use Disorders: Implications for Dissemination to Clinical Settings,” *Current Opinion in Psychology* 30 (2019): 6–10.
- [221] J. M. Hoogendam, G. M. J. Ramakers, and V. Di Lazzaro, “Physiology of Repetitive Transcranial Magnetic Stimulation of the Human Brain,” *Brain Stimulation* 3, no. 2 (2010): 95–118.
- [222] G. S. Pell, Y. Roth, and A. Zangen, “Modulation of Cortical Excitability Induced by Repetitive Transcranial Magnetic Stimulation: Influence of Timing and Geometrical Parameters and Underlying Mechanisms,” *Progress in Neurobiology* 93, no. 1 (2011): 59–98.
- [223] X. Diao, Q. Lu, L. Qiao, et al., “Cortical Inhibition State-Dependent iTBS Induced Neural Plasticity,” *Frontiers in Neuroscience* 16 (2022): 788538.
- [224] Y.-F. Hsu, K.-K. Liao, P.-L. Lee, et al., “Intermittent Theta Burst Stimulation Over Primary Motor Cortex Enhances Movement-Related Beta Synchronisation,” *Clinical Neurophysiology* 122, no. 11 (2011): 2260–2267.
- [225] A. Pascual-Leone, J. Valls-Solé, E. M. Wassermann, and M. Hallett, “Responses to Rapid-Rate Transcranial Magnetic Stimulation of the Human Motor Cortex,” *Brain: A Journal of Neurology* 117, no. Pt 4 (1994): 847–858.
- [226] A. Peinemann, B. Reimer, C. Løer, et al., “Long-Lasting Increase in Corticospinal Excitability After 1800 Pulses of Subthreshold 5 Hz Repetitive TMS to the Primary Motor Cortex,” *Clinical Neurophysiology* 115, no. 7 (2004): 1519–1526.
- [227] S. Chen, X. He, X. Wei, J. Huang, and J. Zhang, “After-Effects of Repetitive Transcranial Magnetic Stimulation With Parameter Dependence on Long-Term Potentiation-Like Plasticity and Object Recognition Memory in Rats,” *Frontiers in Neuroscience* 17 (2023): 1144480.
- [228] A. D. Tang, W. Bennett, C. Hadrill, et al., “Low Intensity Repetitive Transcranial Magnetic Stimulation Modulates Skilled Motor Learning in Adult Mice,” *Scientific Reports* 8, no. 1 (2018): 4016.
- [229] D. Hubl, T. Nyffeler, P. Wurtz, et al., “Time Course of Blood Oxygenation Level-Dependent Signal Response after Theta Burst Transcranial Magnetic Stimulation of the Frontal Eye Field,” *Neuroscience* 151, no. 3 (2008): 921–928.
- [230] E. Rounis, L. Lee, H. R. Siebner, et al., “Frequency Specific Changes in Regional Cerebral Blood Flow and Motor System Connectivity Following rTMS to the Primary Motor Cortex,” *NeuroImage* 26, no. 1 (2005): 164–176.
- [231] T. Paus, M. A. Castro-Alamancos, and M. Petrides, “Cortico-Cortical Connectivity of the Human Mid-Dorsolateral Frontal Cortex and Its Modulation by Repetitive Transcranial Magnetic Stimulation,” *European Journal of Neuroscience* 14, no. 8 (2001): 1405–1411.
- [232] H. R. Siebner, B. Takano, A. Peinemann, M. Schwaiger, B. Conrad, and A. Drzezga, “Continuous Transcranial Magnetic Stimulation During Positron Emission Tomography: A Suitable Tool for Imaging Regional Excitability of the Human Cortex,” *NeuroImage* 14, no. 4 (2001): 883–890.
- [233] B. Takano, A. Drzezga, M. Peller, et al., “Short-Term Modulation of Regional Excitability and Blood Flow in Human Motor Cortex Following Rapid-Rate Transcranial Magnetic Stimulation,” *NeuroImage* 23, no. 3 (2004): 849–859.
- [234] G. Madeo and A. Bonci, “Rewiring the Addicted Brain: Circuits-Based Treatment for Addiction,” *Cold Spring Harbor Symposia on Quantitative Biology* 83 (2018): 173–184.
- [235] S. H. Lisanby and R. H. Belmaker, “Animal Models of the Mechanisms of Action of Repetitive Transcranial Magnetic Stimulation (RTMS): Comparisons With Electroconvulsive Shock (ECS),” *Depression and Anxiety* 12, no. 3 (2000): 178–187.
- [236] S. F. Cooke and T. V. P. Bliss, “Plasticity in the Human Central Nervous System,” *Brain: A Journal of Neurology* 129, no. Pt 7 (2006): 1659–1673.
- [237] R. C. Malenka, J. A. Kauer, R. S. Zucker, and R. A. Nicoll, “Postsynaptic Calcium Is Sufficient for Potentiation of Hippocampal Synaptic Transmission,” *Science* 242, no. 4875 (1988): 81–84.
- [238] M. A. Sutton, H. T. Ito, P. Cressy, C. Kempf, J. C. Woo, and E. M. Schuman, “Miniature Neurotransmission Stabilizes Synaptic Function via Tonic Suppression of Local Dendritic Protein Synthesis,” *Cell* 125, no. 4 (2006): 785–799.
- [239] J. Banerjee, M. E. Sorrell, P. A. Celnik, and G. Pelled, “Immediate Effects of Repetitive Magnetic Stimulation on Single Cortical Pyramidal Neurons,” *PLOS ONE* 12, no. 1 (2017): e0170528.
- [240] D. Baur, D. Galevska, S. Hussain, L. G. Cohen, U. Ziemann, and C. Zrenner, “Induction of LTD-Like Corticospinal Plasticity by Low-Frequency rTMS Depends on Pre-Stimulus Phase of Sensorimotor μ -Rhythm,” *Brain Stimulation* 13, no. 6 (2020): 1580–1587.
- [241] A. V. Chervyakov, A. Y. Chernyavsky, D. O. Sinityn, and M. A. Piradov, “Possible Mechanisms Underlying the Therapeutic Effects of Transcranial Magnetic Stimulation,” *Frontiers in Human Neuroscience* 9 (2015): 303.
- [242] M. Lenz, C. Galanis, F. Müller-Dahlhaus, et al., “Repetitive Magnetic Stimulation Induces Plasticity of Inhibitory Synapses,” *Nature Communications* 7, no. 1 (2016): 10020.
- [243] B. Cheeran, P. Talelli, F. Mori, et al., “A Common Polymorphism in the Brain-Derived Neurotrophic Factor Gene (BDNF) Modulates Human Cortical Plasticity and the Response to rTMS,” *The Journal of Physiology* 586, no. 23 (2008): 5717–5725.
- [244] X. Zhang, Y. Mei, C. Liu, and S. Yu, “Effect of Transcranial Magnetic Stimulation on the Expression of c-Fos and Brain-Derived Neurotrophic Factor of the Cerebral Cortex in Rats with Cerebral Infarct,” *Journal of Huazhong University of Science and Technology* 27, no. 4 (2007): 415–418.
- [245] C. L. Cullen and K. M. Young, “How Does Transcranial Magnetic Stimulation Influence Glial Cells in the Central Nervous System?” *Frontiers in Neural Circuits* 10 (2016): 26.
- [246] A. Etiévant, S. Manta, C. Latapy, L. A. V. Magno, S. Fecteau, and J.-M. Beaulieu, “Repetitive Transcranial Magnetic

- Stimulation Induces Long-Lasting Changes in Protein Expression and Histone Acetylation," *Scientific Reports* 5 (2015): 16873.
- [247] Y. Chen, R. Zhang, F. Xue, et al., "Quetiapine and Repetitive Transcranial Magnetic Stimulation Ameliorate Depression-Like Behaviors and Up-Regulate the Proliferation of Hippocampal-Derived Neural Stem Cells in a Rat Model of Depression: The Involvement of the BDNF/ERK Signal Pathway," *Pharmacology Biochemistry, and Behavior* 136 (2015): 39–46.
- [248] M. B. Müller, N. Toschi, A. E. Kresse, A. Post, and M. E. Keck, "Long-Term Repetitive Transcranial Magnetic Stimulation Increases the Expression of Brain-Derived Neurotrophic Factor and Cholecystokinin mRNA, But Not Neuropeptide Tyrosine mRNA in Specific Areas of Rat Brain," *Neuropsychopharmacology* 23, no. 2 (2000): 205–215.
- [249] J. Silvanto, N. Muggleton, and V. Walsh, "State-Dependency in Brain Stimulation Studies of Perception and Cognition," *Trends in Cognitive Sciences* 12, no. 12 (2008): 447–454.
- [250] S. Borgomaneri, S. Battaglia, S. Garofalo, F. Tortora, A. Avenanti, and G. di Pellegrino, "State-Dependent TMS Over Prefrontal Cortex Disrupts Fear-Memory Reconsolidation and Prevents the Return of Fear," *Current Biology: CB* 30, no. 18 (2020): 3672–3679.e4.
- [251] A. T. Sack, J. Paneva, T. Kütke, et al., "Target Engagement and Brain State Dependence of Transcranial Magnetic Stimulation: Implications for Clinical Practice," *Biological Psychiatry* 95, no. 6 (2024): 536–544.
- [252] G. Kronberg, A. Rahman, M. Sharma, M. Bikson, and L. C. Parra, "Direct Current Stimulation Boosts Hebbian Plasticity in Vitro," *Brain Stimulation* 13, no. 2 (2020): 287–301.
- [253] A. Rahman, B. Lafon, L. C. Parra, and M. Bikson, "Direct Current Stimulation Boosts Synaptic Gain and Cooperativity In Vitro," *The Journal of Physiology* 595, no. 11 (2017): 3535–3547.
- [254] F. Ranieri, M. V. Podda, E. Riccardi, et al., "Modulation of LTP at Rat Hippocampal CA3-CA1 Synapses by Direct Current Stimulation," *Journal of Neurophysiology* 107, no. 7 (2012): 1868–1880.
- [255] L. F. Medeiros, I. C. C. de Souza, L. P. Vidor, et al., "Neurobiological Effects of Transcranial Direct Current Stimulation: A Review," *Frontiers in Psychiatry* 3 (2012): 110.
- [256] L. Khatib, D. E. Golan, and M. Cho, "Physiologic Electrical Stimulation Provokes Intracellular Calcium Increase Mediated by Phospholipase C Activation in Human Osteoblasts," *The FASEB Journal* 18, no. 15 (2004): 1903–1905.
- [257] C. A. Bill, C. M. Vines, and C. Phospholipase, "Phospholipase C," *Advances in Experimental Medicine and Biology* 1131 (2020): 215–242.
- [258] B. Fritsch, J. Reis, K. Martinowich, et al., "Direct Current Stimulation Promotes BDNF-Dependent Synaptic Plasticity: Potential Implications for Motor Learning," *Neuron* 66, no. 2 (2010): 198–204.
- [259] M. V. Podda, S. Cocco, A. Mastrodonato, et al., "Anodal Transcranial Direct Current Stimulation Boosts Synaptic Plasticity and Memory in Mice via Epigenetic Regulation of Bdnf Expression," *Scientific Reports* 6, no. 1 (2016): 22180.
- [260] P. R. M. Filho, R. Verdelino, S. G. Cioato, et al., "Transcranial Direct Current Stimulation (tDCS) Reverts Behavioral Alterations and Brainstem BDNF Level Increase Induced by Neuropathic Pain Model: Long-Lasting Effect," *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 64 (2016): 44–51.
- [261] D. T. Leffa, A. de Souza, V. L. Scarabelot, et al., "Transcranial Direct Current Stimulation Improves Short-Term Memory in an Animal Model of Attention-Deficit/Hyperactivity Disorder," *European Neuropsychopharmacology* 26, no. 2 (2016): 368–377.
- [262] J. G. Rohan, K. A. Carhuatanta, S. M. McInturf, M. K. Miklasevich, and R. Jankord, "Modulating Hippocampal Plasticity With In Vivo Brain Stimulation," *The Journal of Neuroscience* 35, no. 37 (2015): 12824–12832.
- [263] J. G. Rohan, M. K. Miklasevich, S. M. McInturf, et al., "Polarity and Subfield Specific Effects of Transcranial Direct Current Stimulation on Hippocampal Plasticity," *Neurobiology of Learning and Memory* 167 (2020): 107126.
- [264] Y.-J. Wu, C.-C. Lin, C.-M. Yeh, et al., "Repeated Transcranial Direct Current Stimulation Improves Cognitive Dysfunction and Synaptic Plasticity Deficit in the Prefrontal Cortex of Streptozotocin-Induced Diabetic Rats," *Brain Stimulation* 10, no. 6 (2017): 1079–1087.
- [265] T.-H. Yu, Y.-J. Wu, M.-E. Chien, and K.-S. Hsu, "Transcranial Direct Current Stimulation Induces Hippocampal Metaplasticity Mediated by Brain-Derived Neurotrophic Factor," *Neuropharmacology* 144 (2019): 358–367.
- [266] Y. Sun, J. O. Lipton, L. M. Boyle, et al., "Direct Current Stimulation Induces mGluR5-Dependent Neocortical Plasticity," *Annals of Neurology* 80, no. 2 (2016): 233–246.
- [267] J. Stafford, M. L. Brownlow, A. Qualley, and R. Jankord, "AMPA Receptor Translocation and Phosphorylation Are Induced by Transcranial Direct Current Stimulation in Rats," *Neurobiology of Learning and Memory* 150 (2018): 36–41.
- [268] S. H. Jung, C. Hatcher-Solis, R. Moore, et al., "Noninvasive Brain Stimulation Enhances Memory Acquisition and Is Associated With Synaptoneurosome Modification in the Rat Hippocampus," *eNeuro* 6, no. 6 (2019): 1–14.
- [269] D. Liebetanz, M. A. Nitsche, F. Tergau, and W. Paulus, "Pharmacological Approach to the Mechanisms of Transcranial DC-Stimulation-Induced After-Effects of Human Motor Cortex Excitability," *Brain: A Journal of Neurology* 125, no. Pt 10 (2002): 2238–2247.
- [270] K. Monte-Silva, M.-F. Kuo, S. Hentschler, et al., "Induction of Late LTP-Like Plasticity in the Human Motor Cortex by Repeated Non-Invasive Brain Stimulation," *Brain Stimulation* 6, no. 3 (2013): 424–432.
- [271] M. A. Nitsche, K. Fricke, U. Henschke, et al., "Pharmacological Modulation of Cortical Excitability Shifts Induced by Transcranial Direct Current Stimulation in Humans," *The Journal of Physiology* 553, no. 1 (2003): 293–301.
- [272] M. A. Nitsche, J. Grundev, D. Liebetanz, N. Lang, F. Tergau, and W. Paulus, "Catecholaminergic Consolidation of Motor Cortical Neuroplasticity in Humans," *Cerebral Cortex* 14, no. 11 (2004): 1240–1245.
- [273] M. A. Nitsche, W. Jaussi, D. Liebetanz, N. Lang, F. Tergau, and W. Paulus, "Consolidation of Human Motor Cortical Neuroplasticity by D-Cycloserine," *Neuropsychopharmacology* 29, no. 8 (2004): 1573–1578.
- [274] C. J. Stagg, J. G. Best, M. C. Stephenson, et al., "Polarity-Sensitive Modulation of Cortical Neurotransmitters by Transcranial Stimulation," *The Journal of Neuroscience* 29, no. 16 (2009): 5202–5206.
- [275] M. A. Nitsche, D. Liebetanz, A. Schlitterlau, et al., "GABAergic Modulation of DC Stimulation-Induced Motor Cortex Excitability Shifts in Humans," *European Journal of Neuroscience* 19, no. 10 (2004): 2720–2726.

- [276] M. Bikson and A. Rahman, "Origins of Specificity During tDCS: Anatomical, Activity-Selective, and Input-Bias Mechanisms," *Frontiers in Human Neuroscience* 7 (2013): 688.
- [277] C. Bradley, A. S. Nydam, P. E. Dux, and J. B. Mattingley, "State-Dependent Effects of Neural Stimulation on Brain Function and Cognition," *Nature Reviews Neuroscience* 23, no. 8 (2022): 459–475.
- [278] H. R. Siebner, G. Hartwigsen, T. Kassuba, and J. C. Rothwell, "How Does Transcranial Magnetic Stimulation Modify Neuronal Activity in the Brain? Implications for Studies of Cognition," *Cortex* 45, no. 9 (2009): 1035–1042.
- [279] A. Vergallito, E. Varoli, A. Pisoni, et al., "State-Dependent Effectiveness of Cathodal Transcranial Direct Current Stimulation on Cortical Excitability," *NeuroImage* 277 (2023): 120242.
- [280] L. Dubreuil-Vall, P. Chau, G. Ruffini, A. S. Widge, and J. A. Camprodon, "tDCS to the Left DLPFC Modulates Cognitive and Physiological Correlates of Executive Function in a State-Dependent Manner," *Brain Stimulation* 12, no. 6 (2019): 1456–1463.
- [281] G. Learmonth, G. Thut, C. S. Y. Benwell, and M. Harvey, "The Implications of State-Dependent tDCS Effects in Aging: Behavioural Response Is Determined by Baseline Performance," *Neuropsychologia* 74 (2015): 108–119.
- [282] F. Masina, S. Montemurro, M. Marino, N. Manzo, G. Pellegrino, and G. Arcara, "State-Dependent tDCS Modulation of the Somatomotor Network: A MEG Study," *Clinical Neurophysiology* 142 (2022): 133–142.
- [283] F. A. Kozel, M. A. Motes, N. Didehbani, et al., "Repetitive TMS to Augment Cognitive Processing Therapy in Combat Veterans of Recent Conflicts With PTSD: A Randomized Clinical Trial," *Journal of Affective Disorders* 229 (2018): 506–514.
- [284] S. Deppermann, N. Vennwald, J. Diemer, et al., "Neurobiological and Clinical Effects of fNIRS-Controlled rTMS in Patients With Panic Disorder/Agoraphobia During Cognitive-Behavioural Therapy," *NeuroImage: Clinical* 16 (2017): 668–677.
- [285] L. Donse, F. Padberg, A. T. Sack, A. J. Rush, and M. Arns, "Simultaneous rTMS and Psychotherapy in Major Depressive Disorder: Clinical Outcomes and Predictors From a Large Naturalistic Study," *Brain Stimulation* 11, no. 2 (2018): 337–345.
- [286] O. Tan, G. Hizli Sayar, B. Ünsalver, and M. Arat, "Combining Transcranial Magnetic Stimulation and Cognitive-Behavioral Therapy in Treatment Resistant Obsessive-Compulsive Disorder," *Anadolu Psikiyatri Dergisi* 16 (2014).
- [287] A. C. Dieler, T. Dresler, K. Joachim, J. C. Deckert, M. J. Herrmann, and A. J. Fallgatter, "Can Intermittent Theta Burst Stimulation as Add-On to Psychotherapy Improve Nicotine Abstinence? Results From a Pilot Study," *European Addiction Research* 20, no. 5 (2014): 248–253.
- [288] X. Hu, T. Zhang, H. Ma, et al., "Repetitive Transcranial Magnetic Stimulation Combined With Cognitive Behavioral Therapy Treatment in Alcohol-Dependent Patients: A Randomized, Double-Blind Sham-Controlled Multicenter Clinical Trial," *Frontiers in Psychiatry* 13 (2022): 935491.
- [289] M. Isserles, A. Y. Shalev, Y. Roth, et al., "Effectiveness of Deep Transcranial Magnetic Stimulation Combined With a Brief Exposure Procedure in Post-Traumatic Stress Disorder—A Pilot Study," *Brain Stimulation* 6, no. 3 (2013): 377–383.
- [290] M. Isserles, A. Tendler, Y. Roth, et al., "Deep Transcranial Magnetic Stimulation Combined With Brief Exposure for Posttraumatic Stress Disorder: A Prospective Multisite Randomized Trial," *Biological Psychiatry* 90, no. 10 (2021): 721–728.
- [291] L. Carmi, U. Alyagon, N. Barnea-Ygael, J. Zohar, R. Dar, and A. Zangen, "Clinical and Electrophysiological Outcomes of Deep TMS Over the Medial Prefrontal and Anterior Cingulate Cortices in OCD Patients," *Brain Stimulation* 11, no. 1 (2018): 158–165.
- [292] M. J. Herrmann, A. Katzorke, Y. Busch, et al., "Medial Prefrontal Cortex Stimulation Accelerates Therapy Response of Exposure Therapy in Acrophobia," *Brain Stimulation* 10, no. 2 (2017): 291–297.
- [293] R. Amiaz, D. Levy, D. Vainiger, L. Grunhaus, and A. Zangen, "Repeated High-Frequency Transcranial Magnetic Stimulation Over the Dorsolateral Prefrontal Cortex Reduces Cigarette Craving and Consumption," *Addiction* 104, no. 4 (2009): 653–660.
- [294] L. Dinur-Klein, P. Dannon, A. Hadar, et al., "Smoking Cessation Induced by Deep Repetitive Transcranial Magnetic Stimulation of the Prefrontal and Insular Cortices: A Prospective, Randomized Controlled Trial," *Biological Psychiatry* 76, no. 9 (2014): 742–749.
- [295] H. Duan, X. Yan, S. Meng, et al., "Effectiveness Evaluation of Repetitive Transcranial Magnetic Stimulation Therapy Combined With Mindfulness-Based Stress Reduction for People with Post-Stroke Depression: A Randomized Controlled Trial," *International Journal of Environmental Research and Public Health* 20, no. 2 (2023): 930.
- [296] B. R. Kooteh, B. Dolatshahi, M. Nosratabadi, N. M. Bakhshani, A. Mahdavi, and M. C. Hakami, "Combination Therapy and Opioids: Effectiveness of Transcranial Direct-Current Stimulation (tDCS) and Emotion Regulation Training in Reducing Current Drug Craving," *Maedica* 15, no. 1 (2020): 53–60.
- [297] E. D. Claus, S. D. Klimaj, R. Chavez, A. D. Martinez, and V. P. Clark, "A Randomized Trial of Combined tDCS Over Right Inferior Frontal Cortex and Cognitive Bias Modification: Null Effects on Drinking and Alcohol Approach Bias," *Alcoholism, Clinical and Experimental Research* 43, no. 7 (2019): 1591–1599.
- [298] T. E. den Uyl, T. E. Gladwin, J. Lindenmeyer, and R. W. Wiers, "A Clinical Trial With Combined Transcranial Direct Current Stimulation and Attentional Bias Modification in Alcohol-Dependent Patients," *Alcoholism: Clinical and Experimental Research* 42, no. 10 (2018): 1961–1969.
- [299] A. Monnart, M.-A. Vanderhasselt, E. Schroder, S. Campanella, P. Fontaine, and C. Kornreich, "Treatment of Resistant Depression: A Pilot Study Assessing the Efficacy of a tDCS-Mindfulness Program Compared With a tDCS-Relaxation Program," *Frontiers in Psychiatry* 10 (2019): 730.
- [300] C. L. Nord, D. C. Halahakoon, T. Limbachya, et al., "Neural Predictors of Treatment Response to Brain Stimulation and Psychological Therapy in Depression: A Double-Blind Randomized Controlled Trial," *Neuropsychopharmacology* 44, no. 9 (2019): 1613–1622.
- [301] M. van 't Wout-Frank, M. T. Shea, V. C. Larson, B. D. Greenberg, and N. S. Philip, "Combined Transcranial Direct Current Stimulation With Virtual Reality Exposure for Posttraumatic Stress Disorder: Feasibility and Pilot Results," *Brain Stimulation* 12, no. 1 (2019): 41–43.
- [302] F. Nasiri, A. Mashhadi, I. Bigdeli, A. G. Chamanabad, and K. K. Ellard, "Augmenting the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders With Transcranial Direct Current Stimulation in Individuals With Generalized Anxiety Disorder and Comorbid Depression: A Randomized Controlled Trial," *Journal of Affective Disorders* 262 (2020): 405–413.

- [303] G. Gordon, G. Williamson, V. Gkofa, U. Schmidt, T. Brockmeyer, and I. Campbell, "Participants' Experience of Approach Bias Modification Training With Transcranial Direct Current Stimulation as a Combination Treatment for Binge Eating Disorder," *European Eating Disorders Review* 29, no. 6 (2021): 969–984.
- [304] M. Hamada, Y. Terao, R. Hanajima, et al., "Bidirectional Long-Term Motor Cortical Plasticity and Metaplasticity Induced by Quadripulse Transcranial Magnetic Stimulation," *The Journal of Physiology* 586, no. 16 (2008): 3927–3947.
- [305] M. B. Iyer, N. Schleper, and E. M. Wassermann, "Priming Stimulation Enhances the Depressant Effect of Low-Frequency Repetitive Transcranial Magnetic Stimulation," *The Journal of Neuroscience* 23, no. 34 (2003): 10867–10872.
- [306] K. He, M. Huertas, S. Z. Hong, et al., "Distinct Eligibility Traces for LTP and LTD in Cortical Synapses," *Neuron* 88, no. 3 (2015): 528–538.
- [307] J. Lamanna, F. Isotti, M. Ferro, et al., "Facilitation of Dopamine-Dependent Long-Term Potentiation in the Medial Prefrontal Cortex of Male Rats Follows the Behavioral Effects of Stress," *Journal of Neuroscience Research* 99, no. 2 (2021): 662–678.
- [308] J. Lamanna, F. Isotti, M. Ferro, et al., "Occlusion of Dopamine-Dependent Synaptic Plasticity in the Prefrontal Cortex Mediates the Expression of Depressive-Like Behavior and Is Modulated by Ketamine," *Scientific Reports* 12, no. 1 (2022): 11055.
- [309] S. Cervenka, E. Hedman, Y. Ikoma, et al., "Changes in Dopamine D2-Receptor Binding Are Associated to Symptom Reduction after Psychotherapy in Social Anxiety Disorder," *Translational Psychiatry* 2, no. 5 (2012): e120.
- [310] H. Karlsson, J. Hirvonen, J. Kajander, et al., "Research Letter: Psychotherapy Increases Brain Serotonin 5-HT_{1A} Receptors in Patients With Major Depressive Disorder," *Psychological Medicine* 40, no. 3 (2010): 523–528.
- [311] S. Papalini, T. Beckers, and B. Vervliet, "Dopamine: From Prediction Error to Psychotherapy," *Translational Psychiatry* 10, no. 1 (2020): 164.
- [312] L. J. Romero Lauro, M. Rosanova, and G. Mattavelli, "TDCS Increases Cortical Excitability: Direct Evidence From TMS-EEG," *Cortex* 58 (2014): 99–111.
- [313] E. Varoli, A. Pisoni, G. C. Mattavelli, et al., "Tracking the Effect of Cathodal Transcranial Direct Current Stimulation on Cortical Excitability and Connectivity by Means of TMS-EEG," *Frontiers in Neuroscience* 12 (2018): 319.
- [314] S. Grosshagauer, M. Woletz, M. Vasileiadi, et al., "Chronometric TMS-fMRI of Personalized Left Dorsolateral Prefrontal Target Reveals State-Dependency of Subgenual Anterior Cingulate Cortex Effects," *Molecular Psychiatry* 29 (2024): 2678–2688.
- [315] L. Q. Uddin, "Cognitive and Behavioural Flexibility: Neural Mechanisms and Clinical Considerations," *Nature Reviews Neuroscience* 22, no. 3 (2021): 167–179.
- [316] J. J. Canas, I. Fajardo, and L. Salmeron, "Cognitive Flexibility," *International Encyclopedia of Ergonomics and Human Factors* 1, no. 3 (2006): 297–301.
- [317] D. R. Dajani and L. Q. Uddin, "Demystifying Cognitive Flexibility: Implications for Clinical and Developmental Neuroscience," *Trends in Neurosciences* 38, no. 9 (2015): 571–578.
- [318] S. Braem and T. Egner, "Getting a Grip on Cognitive Flexibility," *Current Directions in Psychological Science* 27, no. 6 (2018): 470–476.
- [319] S. Ghosh and S. Halder, "Emotional Regulation and Cognitive Flexibility in Young Adults," *Journal of Psychosocial Research* 15, no. 2 (2020): 609–617.
- [320] M. D. Binder, N. Hirokawa, and U. Windhorst, "Behavioral Plasticity," in *Encyclopedia of Neuroscience*, (Springer, Berlin Heidelberg, Berlin, Heidelberg, 2009): 372–372.
- [321] F. Mery and J. G. Burns, "Behavioural Plasticity: An Interaction between Evolution and Experience," *Evolutionary Ecology* 24, no. 3 (2010): 571–583.
- [322] E. C. Snell-Rood, "An Overview of the Evolutionary Causes and Consequences of Behavioural Plasticity," *Animal Behaviour* 85, no. 5 (2013): 1004–1011.
- [323] J. A. Stamps, "Individual Differences in Behavioural Plasticities," *Biological Reviews* 91, no. 2 (2016): 534–567.
- [324] A. Casula, B. M. Milazzo, G. Martino, et al., "Non-Invasive Brain Stimulation for the Modulation of Aggressive Behavior—A Systematic Review of Randomized Sham-Controlled Studies," *Life* 13, no. 5 (2023): 1220.
- [325] C. Miniussi and M. Ruzzoli, "Transcranial Stimulation and Cognition," in *Handbook of Clinical Neurology*, eds. A. M. Lozano and M. Hallett, 116, (Elsevier, 2013): 739–750.
- [326] A. S. Moro, D. Saccenti, A. Vergallito, et al., "Evaluating the Efficacy of Transcranial Magnetic Stimulation in Symptom Relief and Cognitive Function in Obsessive-Compulsive Disorder, Substance Use Disorder, and Depression: An Insight From a Naturalistic Observational Study," *Applied Sciences* 14, no. 14 (2024): 6178.
- [327] A. S. Moro, D. Saccenti, S. Scaini, et al., "Analisi Dei Processi Cognitivi Alla Base Del Craving Nelle Dipendenze," *Psicoterapia Cognitiva e Comportamentale* 30, no. 3 (2024): 269–288.
- [328] L. G. Appelbaum, M. A. Shenasa, L. Stolz, and Z. Daskalakis, "Synaptic Plasticity and Mental Health: Methods, Challenges and Opportunities," *Neuropsychopharmacology* 48, no. 1 (2023): 113–120.
- [329] R. S. Duman, G. K. Aghajanian, G. Sanacora, and J. H. Krystal, "Synaptic Plasticity and Depression: New Insights From Stress and Rapid-Acting Antidepressants," *Nature Medicine* 22, no. 3 (2016): 238–249.
- [330] J. L. Price and W. C. Drevets, "Neurocircuitry of Mood Disorders," *Neuropsychopharmacology* 35, no. 1 (2010): 192–216.
- [331] R. H. Kaiser, J. R. Andrews-Hanna, T. D. Wager, and D. A. Pizzagalli, "Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-Analysis of Resting-State Functional Connectivity," *JAMA Psychiatry* 72, no. 6 (2015): 603–611.
- [332] R. Miranda, J. Valderrama, A. Tsypes, E. Gadol, and M. Gallagher, "Cognitive Inflexibility and Suicidal Ideation: Mediating Role of Brooding and Hopelessness," *Psychiatry Research* 210, no. 1 (2013): 174–181.
- [333] L. Orsolini, R. Latini, M. Pompili, et al., "Understanding the Complex of Suicide in Depression: From Research to Clinics," *Psychiatry Investigation* 17, no. 3 (2020): 207–221.
- [334] G. Salvetti, D. Saccenti, A. S. Moro, J. Lamanna, and M. Ferro, "Comparison between Single-Dose and Two-Dose Psilocybin Administration in the Treatment of Major Depression: A Systematic Review and Meta-Analysis of Current Clinical Trials," *Brain Sciences* 14, no. 8 (2024): 829.
- [335] V. A. Kulkarni and B. L. Firestein, "The Dendritic Tree and Brain Disorders," *Molecular and Cellular Neuroscience* 50, no. 1 (2012): 10–20.
- [336] M. L. MacDonald, J. Alhassan, J. T. Newman, et al., "Selective Loss of Smaller Spines in Schizophrenia," *American Journal of Psychiatry* 174, no. 6 (2017): 586–594.

- [337] G. T. Konopaske, N. Lange, J. T. Coyle, and F. M. Benes, "Prefrontal Cortical Dendritic Spine Pathology in Schizophrenia and Bipolar Disorder," *JAMA Psychiatry* 71, no. 12 (2014): 1323–1331.
- [338] G. T. Macleod and K. E. Zinsmaier, "Synaptic Homeostasis on the Fast Track," *Neuron* 52, no. 4 (2006): 569–571.
- [339] J. F. M. Vetencourt, A. Sale, A. Viegi, et al., "The Antidepressant Fluoxetine Restores Plasticity in the Adult Visual Cortex," *Science* 320, no. 5874 (2008): 385–388.
- [340] D. Popova, E. Castrén, and T. Taira, "Chronic Fluoxetine Administration Enhances Synaptic Plasticity and Increases Functional Dynamics in Hippocampal CA3-CA1 Synapses," *Neuropharmacology* 126 (2017): 250–256.
- [341] A. Puścian, M. Winiarski, S. Łęski, et al., "Chronic Fluoxetine Treatment Impairs Motivation and Reward Learning by Affecting Neuronal Plasticity in the Central Amygdala," *British Journal of Pharmacology* 178, no. 3 (2021): 672–688.
- [342] J. Pilmeyer, W. Huijbers, R. Lamerichs, J. F. A. Jansen, M. Breeuwer, and S. Zinger, "Functional MRI in Major Depressive Disorder: A Review of Findings, Limitations, and Future Prospects," *Journal of Neuroimaging* 32, no. 4 (2022): 582–595.
- [343] L. Schmaal, D. P. Hibar, P. G. Sämann, et al., "Cortical Abnormalities in Adults and Adolescents With Major Depression Based on Brain Scans From 20 Cohorts Worldwide in the ENIGMA Major Depressive Disorder Working Group," *Molecular Psychiatry* 22, no. 6 (2017): 900–909.
- [344] A. Etkin and T. D. Wager, "Functional Neuroimaging of Anxiety: A Meta-Analysis of Emotional Processing in PTSD, Social Anxiety Disorder, and Specific Phobia," *American Journal of Psychiatry* 164, no. 10 (2007): 1476–1488.
- [345] V. Francati, E. Vermetten, and J. D. Bremner, "Functional Neuroimaging Studies in Posttraumatic Stress Disorder: Review of Current Methods and Findings," *Depression and Anxiety* 24, no. 3 (2007): 202–218.
- [346] K. R. Bijanki, Y. J. Pathak, R. A. Najera, et al., "Defining Functional Brain Networks Underlying Obsessive-Compulsive Disorder (OCD) Using Treatment-Induced Neuroimaging Changes: A Systematic Review of the Literature," *Journal of Neurology, Neurosurgery & Psychiatry* 92, no. 7 (2021): 776–786.
- [347] P. S. W. Boedhoe, L. Schmaal, Y. Abe, et al., "Cortical Abnormalities Associated With Pediatric and Adult Obsessive-Compulsive Disorder: Findings From the ENIGMA Obsessive-Compulsive Disorder Working Group," *American Journal of Psychiatry* 175, no. 5 (2018): 453–462.
- [348] T. S. Fuglset, N. I. Landrø, D. L. Reas, and Ø. Rø, "Functional Brain Alterations in Anorexia Nervosa: A Scoping Review," *Journal of Eating Disorders* 4, no. 1 (2016): 32.
- [349] T. Su, J. Gong, G. Tang, et al., "Structural and Functional Brain Alterations in Anorexia Nervosa: A Multimodal Meta-Analysis of Neuroimaging Studies," *Human Brain Mapping* 42, no. 15 (2021): 5154–5169.
- [350] L. A. Berner, S. R. Winter, H. Ayaz, et al., "Altered Prefrontal Activation during the Inhibition of Eating Responses in Women With Bulimia Nervosa," *Psychological Medicine* 53, no. 8 (2023): 3580–3590.
- [351] A. Celeghin, S. Palermo, R. Giampaolo, G. Di Fini, G. Gandino, and C. Civilotti, "Brain Correlates of Eating Disorders in Response to Food Visual Stimuli: A Systematic Narrative Review of fMRI Studies," *Brain sciences* 13, no. 3 (2023): 465.
- [352] L. Luo, Y. Luo, X. Chen, et al., "Structural and Functional Neural Patterns among Sub-Threshold Bulimia Nervosa: Abnormalities in Dorsolateral Prefrontal Cortex and Orbitofrontal Cortex," *Psychiatry Research: Neuroimaging* 342 (2024): 111825.
- [353] R. Veit, K. Schag, E. Schopf, et al., "Diminished Prefrontal Cortex Activation in Patients With Binge Eating Disorder Associates With Trait Impulsivity and Improves after Impulsivity-Focused Treatment Based on a Randomized Controlled IMPULS Trial," *NeuroImage: Clinical* 30 (2021): 102679.
- [354] R. Z. Goldstein and N. D. Volkow, "Dysfunction of the Prefrontal Cortex in Addiction: Neuroimaging Findings and Clinical Implications," *Nature Reviews Neuroscience* 12, no. 11 (2011): 652–669.
- [355] J. Suckling and L. J. Nestor, "The Neurobiology of Addiction: The Perspective From Magnetic Resonance Imaging Present and Future," *Addiction* 112, no. 2 (2017): 360–369.
- [356] B. L. Carter and S. T. Tiffany, "Meta-Analysis of Cue-Reactivity in Addiction Research," 94, no. 3 (1999).
- [357] S. Kühn and J. C. Gallinat, "Common Biology of Craving across Legal and Illegal Drugs—A Quantitative Meta-Analysis of Cue-Reactivity Brain Response," *European Journal of Neuroscience* 33, no. 7 (2011): 1318–1326.
- [358] S. J. Wilson, M. A. Sayette, and J. A. Fiez, "Prefrontal Responses to Drug Cues: A Neurocognitive Analysis," *Nature Neuroscience* 7, no. 3 (2004): 211–214.
- [359] C. G. Connolly, J. J. Foxe, J. Nierenberg, M. Shpaner, and H. Garavan, "The Neurobiology of Cognitive Control in Successful Cocaine Abstinence," *Drug and Alcohol Dependence* 121, no. 1–2 (2012): 45–53.
- [360] K. D. Ersche, G. B. Williams, T. W. Robbins, and E. T. Bullmore, "Meta-Analysis of Structural Brain Abnormalities Associated With Stimulant Drug Dependence and Neuroimaging of Addiction Vulnerability and Resilience," *Current Opinion in Neurobiology* 23, no. 4 (2013): 615–624.
- [361] H. F. Unterrainer, M. Hiebler-Ragger, K. Koschutnig, et al., "Brain Structure Alterations in Poly-Drug Use: Reduced Cortical Thickness and White Matter Impairments in Regions Associated With Affective, Cognitive, and Motor Functions," *Frontiers in Psychiatry* 10 (2019): 667.