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A framework and practical guide for conducting double-blind randomized clinical trials combining transcranial electrical stimulation and psychotherapy

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Abstract

Transcranial electrical stimulation (tES) is a non-invasive technique for modulating neural activity with minimal side effects, making it ideal for delivery concurrent with evidence-based psychotherapy. However, combining these modalities introduces unique methodological challenges that should be carefully addressed to ensure rigorous clinical trials with interpretable results. This article provides a conceptual guide and initial framework for designing and conducting double-blind randomized controlled trials that combine tES with evidence-based psychotherapy. We present a conceptual model for understanding the bidirectional influences between tES and evidence-based psychotherapy, outline critical considerations for study design, and provide practical guidelines for trial implementation. Drawing from recent clinical trials and established best practices, we also address key issues including target identification, blinding procedures, regulatory considerations, personnel requirements, and equipment needs. This guide is intended for investigators planning to conduct tES-psychotherapy studies and aims to enhance the quality and interpretability of research in this emerging field.

Psychiatric disorders constitute a substantial global health burden and are among the leading causes of disability worldwide, with many individuals experiencing persistent symptoms despite available treatments [1, 2]. Both evidence-based psychotherapy and transcranial electrical stimulation (tES) approaches have individually demonstrated efficacy across a range of psychiatric conditions; however, each intervention shows critical limitations when delivered as standalone interventions [3–8]. As a result, it remains important for the development of novel interventions and reconsideration of implementation of current approaches. The safety profile, minimal side effects, and typical dose of time of approximately 40-60 min for tES provide a ready platform for integrating evidence-based psychotherapy with tES. Administering evidence-based psychotherapy concurrent with tES has therefore been proposed as a promising strategy to leverage complementary mechanisms of action, potentially yielding synergistic effects that improve clinical outcomes beyond those observed with either approach alone. While emphasis is placed on the concurrent tES-psychotherapy approach, this guide also explores sequential and complementary forms of combining tES with psychotherapy.

Psychotherapy targets cognitive, emotional, and behavioral processes through structured therapeutic interactions. Evidence-based approaches, such as cognitive-behavioral therapy (CBT), have demonstrated moderate efficacy across various psychiatric conditions [9, 10]. These interventions are theorized to operate primarily through changes

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in cognitive, emotional, and behavioral processes, which in turn may influence the neural systems that support symptom generation and persistence. However, these interventions only lead to a ~ 15% increase in skills use after one year of psychotherapy [11], a relatively small gain for the cost of the intervention [12]. Moreover, the effectiveness of psychotherapy can be limited by factors such as cognitive rigidity, impaired neuroplasticity, or dysregulated neural network activity [13]. Therefore, non-invasive brain stimulation, such as tES, may be effective at increasing psychotherapy engagement via increased cognitive control [14–17] or reward-responsive goal-directed behavior [18].

tES techniques, including transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS), offer complementary mechanisms of action [19, 20]. As Frohlich and Riddle [21] articulated in their framework for developing and implementing tACS clinical trials, tES can be conceptualized as a tool for restoring pathological alterations in brain network dynamics. tACS applies rhythmic electrical currents to entrain cortical oscillations at specific frequencies [22–25], while tDCS modulates cortical excitability through application of constant weak electrical currents [26]. By targeting specific neural circuits implicated in psychiatric disorders, tES may create an optimal neural state for psychotherapeutic interventions to take effect.

The rationale for combining tES with psychotherapy rests on the hypothesis that each modality can potentiate the effects of the other. tES may enhance immediate neural plasticity necessary for therapeutic learning in the moment [27], while psychotherapy may provide the structured experiences that guide plasticity toward adaptive long-term neural configurations. Early evidence provides partial supports for this hypothesis. For example, tDCS combined with exposure-based fear extinction experimental paradigms has shown that tDCS can, under some conditions, modulate fear extinction [28]. However, other studies have reported null effects of tDCS on fear extinction, underscoring the complexity of augmenting psychotherapy with tES and the sensitivity of outcomes to stimulation parameters, timing, and task context (see [29] for review). Within the tACS literature, our own work demonstrated that tACS paired with behavioral activation demonstrates improvements in depression, anhedonia, and well-being in depressed patients [30] using delta-beta cross-frequency tACS designed to increase prefrontal-motor coupling that was previously associated with reward-responsive goal-directed behavior [18, 31]. However, designing clinical trials to rigorously test combination approaches requires consideration of key methodological factors.

To date, relatively few studies have rigorously examined concurrent psychotherapy-tES in adequately powered, double-blind, sham-controlled randomized designs, and the available literature remains heterogeneous in targets, timing, dosing, and outcome selection [32, 33]. This paucity of high-quality trials likely reflects both the novelty of the approach and some methodological challenges inherent to combination research, such as aligning stimulation timing with active therapeutic mechanisms ("brain state"), ensuring blinding integrity, and demonstrating target engagement [32, 34]. Consistent with this complexity, results from larger sham-controlled trials have been mixed, including well-powered null findings for tDCS augmentation of CBT [35]. To carry out these studies, investigators need to navigate complexities in study design, blinding procedures, regulatory requirements, and mechanistic interpretation that extend beyond those encountered in single-modality trials.

Our team has published results from a trial of concurrent tACS with psychotherapy using a rigorous double-blind placebo-controlled design [30]. Using the experiences from running this trial as a frame of reference, in this article we aim to provide investigators with a guide for planning and executing high-quality clinical trials combining tES and evidence-based psychotherapy. We build upon the rational design framework for tES trials articulated by Kurmann and colleagues [36] as well as Frohlich and Riddle [21] and extend these principles to the unique context of studies combining tES and evidence-based psychotherapy. Our goal is to help researchers avoid common pitfalls, make informed design choices, and ultimately contribute to a robust evidence base for combination treatments.

Conceptual model considerations

Target identification

As a first step, investigators should identify a neural target, ideally a neural circuit dysfunction that correlates with a measurable change in cognitive, affective, or behavioral dysfunction that is related to symptom expression [37]. For concurrent tES-psychotherapy studies, an ideal neural target is a circuit that underlies a cognitive process which is targeted by psychotherapy and that has a clear electrical signature or anatomical localization that can be targeted with tES [37]. Researchers are encouraged to either conduct an experiment to verify their selection of neural targets or to motivate their decision based on a literature review, with a baseline session to verify the relationship between the neural circuit and the cognitive process of interest. Below we detail a few example approaches.

Psychotherapy selection

Developing effective concurrent tES-psychotherapy interventions requires understanding that different therapeutic modalities engage distinct neural circuits underlying specific symptom dimensions in psychiatric disorders. Practical guidance on implementation, fidelity, and delivery is addressed in the *Psychotherapy Implementation* section. Consistent with the Research Domain Criteria approach (RDoC), we recommend first focusing on specific psychiatric symptoms (e.g., anxious rumination or anhedonia) within diagnostic categories as these tend to have clearer neural targets [37, 38]. Next, researchers and clinicians aiming to combine tES into their practice should select therapeutic approaches based on what the supposed neural mechanisms involved in maintaining a patient's symptoms are. This mechanism-based selection then guides the choice of complementary tES targets.

Consider for example the selection of cognitive behavioral therapy (CBT) for depression for patients whose depressive symptoms are thought to arise from dysfunction in prefrontal-limbic circuits involved in emotion regulation [39]. CBT may target maladaptive cognitive processes by engaging dorsolateral and ventromedial prefrontal regions that exert top-down control over limbic emotional responses [40]. The therapeutic mechanism in this case may involve strengthening functional connectivity between these prefrontal control regions, which will in turn strengthen control over limbic structures. Neuroimaging studies support this mechanism-based rationale for CBT selection: meta-analyses demonstrate that successful CBT normalizes hyperactivity in the anterior cingulate cortex and insula (the putative salience network) in patients with anxiety and depression [41, 42]. Furthermore, individual differences in baseline prefrontal-amygdala connectivity predict treatment response, with stronger connectivity associated with better outcomes [43]. These findings indicate that CBT could be selected when the therapeutic target is dorsolateral prefrontal-amygdala dysregulation or ventromedial prefrontal to insula dysregulation, as the modality directly engages the circuits underlying cognitive and emotional control deficits. In this example, tES would be designed to increase prefrontal control signals (either dorsolateral or ventrolateral) with frequency specific targets selected from EEG studies of emotional control and cortical targets selected from fMRI studies. Further work is required to establish the specific circuits engaged be different skills within CBT; e.g., emotion regulation for dorsolateral prefrontal cortex or bodily awareness and regulation for ventrolateral prefrontal cortex.

In contrast, the therapeutic target of exposure therapy (broadly construed) may comprise the ventromedial prefrontal cortex (vmPFC), amygdala, and hippocampus [44]. Through repeated confrontation with feared stimuli in safe contexts, exposure therapy enhances vmPFC-mediated inhibition of amygdala fear responses while strengthening hippocampal contextual encoding of safety [45]. Indeed, individuals with greater vmPFC activation and reduced amygdala reactivity during laboratory extinction learning show better responses to subsequent exposure therapy [46]. Here, the vmPFC plays a critical role in the processing of subjective value [47, 48] and the type of regulation exerted is likely in the form of reappraisal (but see other evidence for ventrolateral PFC in reappraisal [49]). Following treatment, patients demonstrate increased resting-state connectivity between the vmPFC and amygdala, reflecting enhanced top-down fear regulation [50]. The selection of exposure therapy can be considered mechanism-driven, chosen specifically to retrain the extinction circuit in patients whose primary deficit involves conditioned fear instead

of cognitive dysregulation. Here, a tES montage can be designed to increase regulatory theta oscillations (associated with fear extinction [51]) in the vmPFC and rostro-medial PFC.

Behavioral activation (BA) exemplifies yet another mechanism-based selection, where it may be chosen for patients whose depressive symptoms are maintained by reduced engagement with rewarding activities and consequent hypoactivation of the ventral striatum and associated reward networks. The therapeutic mechanism involves systematically increasing behaviors that activate reward circuits, particularly the ventral striatum and its connections to the vmPFC. This mechanism-based rationale is also supported by neuroimaging findings: depression is characterized by blunted ventral striatal responses to reward anticipation and receipt [52, 53], and this hypoactivation is associated with anhedonia and reduced motivation. By increasing engagement in positively reinforcing activities, BA aims to enhance reward function. Thus, tES could target the processing of reward-value in the vmPFC or the planning and initiation of goal-directed behavior in the lateral prefrontal cortex that utilizes reward values computed in vmPFC. With tES targeted to the dorsolateral PFC, the construct of interest would be the planning and execution of goal-directed behaviors and may correspond to an anticipatory form of anhedonia localized to dlPFC, rather consummatory anhedonia localized to vmPFC [54–56].

In the examples above, it should be noted that even well-decomposed therapeutic techniques involve systems of co-occurring processes, including those that are not targeted explicitly by the therapy itself. For example, interactions among working memory, attention, semantic retrieval, and self-referential processing coactivate during a single reappraisal trial, making clean circuit attribution theoretically and practically difficult (e.g., [57]). Differences in the 'same' therapy, delivered across differing laboratory-based paradigms further complicates inference, as the same circuit likely operates under substantially different learning dynamics across contexts. Thus, in addition to identifying a psychotherapy or therapeutic component that engages a clear neural mechanism, selecting the appropriate psychotherapy also implies identifying an evidence-based manual to guide its implementation. Using formal exposure as an example, multiple manuals exist guiding broad exposure implementation principles as well as manuals that specifically apply exposure principles to a given DSM-5 disorder. Nevertheless, studies that examine the effects of exposure therapies may follow general guidelines, but typically not existing manualized approaches (e.g., [46]), making it unclear which therapeutic components are driving change and, moreover, whether observed effects are due to psychotherapy or other experimental variables. Ideal pairings would identify a therapy, a manual supported by at least two clinical trials, and an adherence scale to examine the fidelity of therapy implementation in the study, given emerging evidence that adherence guides treatment effectiveness. Failing to rigorously select a psychotherapy or to adhere to it means discarding the empirical groundwork that makes it effective—and exposes the combined intervention to pitfalls that may have been resolved within established therapeutic protocols.

tES type and parameter selection

Just as psychotherapeutic modalities should be selected based on evidence that a specific neural mechanism maintains a patient's symptoms, the selection of a tES montage and its parameters should be guided by the specific neural circuit or network dysfunction one aims to modulate [21]. Parameter selection therefore involves coordinated decisions about spatial targeting, frequency (when applicable), amplitude, and duration, each of which constrains how stimulation interacts with underlying neural activity. Rather than viewing tES as a nonspecific enhancer of treatment response, a mechanism-based rational design requires explicit consideration of how different stimulation modalities interact with neural activity. One class of mechanism-based selection involves frequency-specific modulation of neural oscillations, for which transcranial alternating current stimulation (tACS) is particularly well suited. tACS delivers sinusoidal electrical currents at specified frequencies, with the goal of interacting with and entraining endogenous neural oscillations when stimulation parameters are matched to intrinsic network dynamics [21, 22].

Computational and empirical work demonstrates that weak periodic stimulation can synchronize neuronal populations and that stimulation tends to entrain the dominant endogenous rhythm [22, 58]. For example, the Arnold tongue phenomenon states that a stronger electrical stimulus is required when misaligned with the endogenous oscillatory activity, e.g., stimulating in 10 Hz when the endogenous oscillation is at 12 Hz. Thus, attempts to

personalize the stimulation frequency based on individual neural activity is more likely to produce a meaningful change in cognition and symptoms (see [16, 54]). Empirical work demonstrates that tACS effects on neural synchrony and behavior are frequency specific and depend on the match between stimulation frequency and ongoing oscillatory dynamics [59]; as a result, measuring individual peak frequencies using EEG prior to stimulation is often recommended to enhance target engagement. This makes tACS an ideal choice when symptoms are hypothesized to arise from oscillatory abnormalities, such as altered frontal alpha activity in depression or disruptions in frontal theta rhythms supporting cognitive control [60–62]. In such cases, tACS can be selected to directly modulate the frequency band implicated in symptom maintenance, aligning stimulation parameters with the targeted network dysfunction in psychotherapy. In addition, tACS can target frequency-specific functional connectivity between two or more brain regions (see [15, 17]). By delivering synchronizing electric current to multiple brain regions, functional connectivity between those regions is increased [17]. Finally, tACS can target the interactions between multiple frequency bands, i.e., cross-frequency coupling. By delivering an electric current that mimics endogenous cross-frequency coupling rhythms, this coupling can be selectively increased by tACS [14, 16, 18, 63].

For each of these approaches, we recommend conducting electrophysiological analysis of activity during a cognitive task to reveal symptom-related behavior deficits to choose a neural target [37]. For example, in a recent series of studies, we identified that reduced reward-responsive goal-directed behavior correlated with a reduction of delta-beta cross-frequency coupling in people with symptoms of anhedonia [16, 18]. By delivering delta-beta tACS to restore coupling between the lateral prefrontal cortex and motor cortex, we found a restoration in levels of reward-responsive goal-directed behavior and a recovery of prefrontal-motor coupling [18]. This neural target was then leveraged for combination with behavioral activation in patients with anhedonia [30].

In contrast, transcranial direct current stimulation (tDCS) is conceptualized as a tool for modulating cortical excitability. tDCS applies constant, low-amplitude electrical currents that induce polarity-dependent shifts in neuronal membrane potentials, thereby influencing the likelihood of neural firing without directly eliciting action potentials [26]. Anodal stimulation is generally associated with increased excitability, whereas cathodal stimulation is associated with decreased excitability, though effects depend on stimulation intensity, duration, and underlying neural activity [64, 65]. Importantly, the effect of tDCS, like other forms of tES, on neural activity and behavior are critically state dependent, meaning that the behavioral and neural consequences of stimulation depend on the ongoing activity of the targeted circuit [27]. This property makes tES particularly well suited for combination with psychotherapy, as therapeutic tasks can be used to engage specific circuits while stimulation biases plasticity within those active networks.

A central implication of this mechanism-based framework is that nominal stimulation parameters (e.g., current intensity, electrode placement, or stimulation frequency) are insufficient proxies for neural target engagement unless the induced electric field (E-field) within the brain is explicitly considered. The magnitude, orientation, and spatial distribution of the E-field that actually reaches a cortical or network-level target depend on individual anatomy, tissue conductivity, cortical folding, and precise electrode placement, producing substantial inter-individual variability even under identical stimulation settings [66]. As a result, two participants receiving the same “dose” of stimulation may experience meaningfully different neural perturbations at the circuit level. Incorporating subject-specific E-field modeling therefore provides a critical link between stimulation parameters and the hypothesized neural mechanisms of change, enabling more precise targeting, improved mechanistic inference, and more interpretable combination trials [67]. Spatial targeting should further be guided by the anatomy and functional organization of the target circuit, as electrode montage determines the distribution of induced electric fields in ways that may not align directly with scalp location. Computational electric field modeling has become an important tool for optimizing montages to maximize current delivery to target regions while minimizing off-target effects [68, 69], and it is particularly valuable in combination studies where precise alignment with psychotherapy-relevant circuits is desired.

For tES, current amplitudes in the range of 1–2 mA are most commonly used in human studies and are generally well tolerated, though both efficacy and perceptibility vary as a function of intensity [26, 68]. Session duration (often 20–40 min) and the total number of sessions should be selected to align with the hypothesized therapeutic timeline and the plasticity mechanisms under investigation, rather than assuming that longer or stronger stimulation

necessarily yields greater benefit (although next generation approaches are typically applying higher amplitude tES for longer periods of time) [70].

With this mechanistic and target-specific framework in place, the next hurdles become how tES can functionally support psychotherapy at the level of learning and plasticity, and why these effects are expected to vary across individuals. Across specific targeting approaches, tES may support concurrent psychotherapy through several mechanisms: facilitating synaptic plasticity, biasing network dynamics toward adaptive states, and enhancing learning processes engaged during psychotherapy [27, 71]. However, as with psychotherapy selection, tES effects are not uniform across individuals. Variability in baseline neural function, anatomy, and plasticity-related factors can substantially influence stimulation outcomes [21]. Accordingly, rational tES selection requires matching the stimulation modality and parameters to the targeted neural mechanism, instead of applying a one-size-fits-all approach. Taken together, tES techniques should be chosen based on the specific circuits and neural dynamics implicated in symptom maintenance. When combined with psychotherapy, optimal treatment design suggests that stimulation targets align with, or complement, neural processes engaged by the therapeutic intervention, thereby maximizing the potential for synergistic and mechanism-driven change. Studies should additionally incorporate neuroimaging or neurophysiological measures capable of assessing whether stimulation modulates the intended neural process; demonstrating that changes in neural target engagement covary with clinical or behavioral improvement strengthens causal interpretation and distinguishes mechanism-based effects from nonspecific treatment responses (Frohlich & Riddle [21]).

Bidirectional influences: mapping mechanism and design

When combining tES with psychotherapy, bidirectional influences between these modalities warrant careful consideration during study design. A central consideration concerns the intended primary target of the intervention paradigm. Combination approaches may be designed to use psychotherapy to potentiate the effects of tES, or conversely to use tES to augment the efficacy of psychotherapy, or to synergize the effects of both the tES and psychotherapy. Although subtle, these distinctions carry important implications for study design, including intervention sequencing, outcome selection, and mechanistic inference. tES effects are not static but depend on the neural state at the time of stimulation, the learning demands imposed by therapy, and the temporal dynamics of plasticity; as a result, the timing of stimulation relative to therapeutic engagement may meaningfully shape both neural and clinical outcomes [21, 27]. Some illustrative examples of these are below:

Example 1: *Therapy to Enhance tES Effects—Therapy before tES*

In this approach, psychotherapy is conceptualized as creating an optimal brain state or engaging specific circuits to maximize tES efficacy. The primary therapeutic mechanism is attributed to tES, with therapy serving a preparatory or facilitating role. Sequential therapy-first designs may be particularly useful when the goal is to selectively bias stimulation toward circuits activated by recent therapeutic work, thereby enhancing specificity. This approach draws on evidence that neural activity immediately preceding stimulation can influence the direction and magnitude of stimulation effects [72]. For example, consider a study using tACS to modulate frontal alpha oscillations in depression. Behavioral activation might be administered before each tACS session to ensure that reward-processing circuits are active during tACS. The hypothesis would be that engaging these circuits through behavior prior to tACS enhances the efficacy of tACS-induced oscillatory modulation. In this paradigm, the critical outcome would be changes in neural oscillations and their correlation with symptom improvement, with therapy serving as a means to enhance target engagement. In this example, important considerations include the temporal alignment between therapy and tES, the specific therapeutic components most likely to engage the intended neural targets, and the feasibility of verifying therapy-induced brain states using neurophysiological measures such as EEG. These design considerations should be informed by existing empirical and mechanistic literature prior to study implementation.

Example 2: tES to Enhance Therapy Effects—tES before Therapy

In this approach, tES is conceptualized as creating optimal conditions for psychotherapeutic learning and consolidation. The primary therapeutic mechanism is attributed to therapy, with tES acting to set up enhanced engagement from therapy. In this framework, stimulation is used to enhance plasticity, normalize pathological

activity, or increase cortical excitability before therapy begins, creating a more receptive neural environment for therapeutic engagement. This design is commonly invoked in augmentation paradigms, where stimulation is conceptualized as lowering the threshold for therapeutic change rather than directly shaping learning content. Preclinical and human studies indicate that noninvasive stimulation can facilitate synaptic plasticity and learning processes when delivered prior to behavioral training [71]. For example, consider a study examining exposure therapy for post-traumatic stress disorder (PTSD). tDCS could be applied before exposure sessions with the aim of directly changing the neural activity of the vmPFC/rmPFC to adapt the patient to engage in exposure therapy. Under this framework, tDCS may facilitate the consolidation of extinction by altering cortical excitability prior to therapeutically relevant learning. In this paradigm, the critical outcomes would be behavioral measures of extinction learning and symptom reduction, with neural measures serving to confirm the hypothesized mechanism. This approach requires careful consideration of how tES timing relates to critical learning windows in therapy. Design decisions include whether stimulation should be applied during exposure, immediately following exposure, or during consolidation windows, as well as which stimulation parameters are most likely to enhance the specific form of plasticity engaged by therapy. It is also important to highlight, and relevant for design, that in order for sequential neuromodulation and psychotherapy to be effective, they need to happen immediately one after another [73].

Example 3: Synergistic Effects—Concurrent Therapy and tES

A third possibility is that tES and psychotherapy work synergistically, with each modality contributing essential but complementary mechanisms. In this case, neither alone would be expected to produce the full therapeutic effect. Concurrent designs maximize the likelihood that stimulation directly influences the same circuits recruited by psychotherapy. Empirical and theoretical work suggests that stimulation effects are strongly state-dependent, such that ongoing task-related activation determines how stimulation interacts with neural populations [27]. For example, stimulation delivered during cognitive restructuring, exposure exercises, or reward-based learning tasks may bias activity within engaged circuits, thereby amplifying or constraining learning-related neural dynamics. For instance, tACS might normalize pathological oscillations that maintain symptom states, while concurrent therapy provides the structured cognitive and behavioral experiences necessary to establish new, adaptive patterns. The combination would be expected to outperform either treatment alone because both the neural substrate ("normalized" through stimulation) and the therapeutic learning (provided by therapy) are necessary for sustained improvement. This paradigm is the most complex to study but potentially the most interesting. It requires demonstrating that the combination is superior to either modality alone, a more demanding statistical test but one that ultimately yields more compelling evidence.

Example 4: Separate-Track Designs—Therapy and tES on Different Days

Finally, separate-track designs, in which psychotherapy and tES are delivered on different days or in different sessions, allow investigators to examine cumulative or additive effects while minimizing immediate state-dependent interactions. Such designs may be appropriate when the hypothesized mechanisms involve slower changes in network organization or when logistical or tolerability considerations preclude concurrent delivery. Although separate-track approaches may sacrifice some mechanistic specificity, they provide a useful comparison for determining whether temporal coupling is necessary to achieve synergistic effects (Frohlich & Riddle [21]). These examples reflect distinct theoretical assumptions about how tES interacts with therapeutic learning and plasticity and illustrate that timing is not a logistical afterthought, but a core design decision with direct mechanistic implications. Timing should be explicitly aligned with the hypothesized neural mechanism; careful consideration of timing enhances interpretability, clarifies causal pathways, and strengthens conclusions regarding how combined psychotherapy-tES interventions exert their effects.

Population selection

The choice of study population is a critical component of mechanism-driven intervention design and should be guided by the same theoretical rationale that informs psychotherapy and tES selection. If combined interventions are intended to engage specific neural circuits or network dynamics, then the population under study needs to be selected

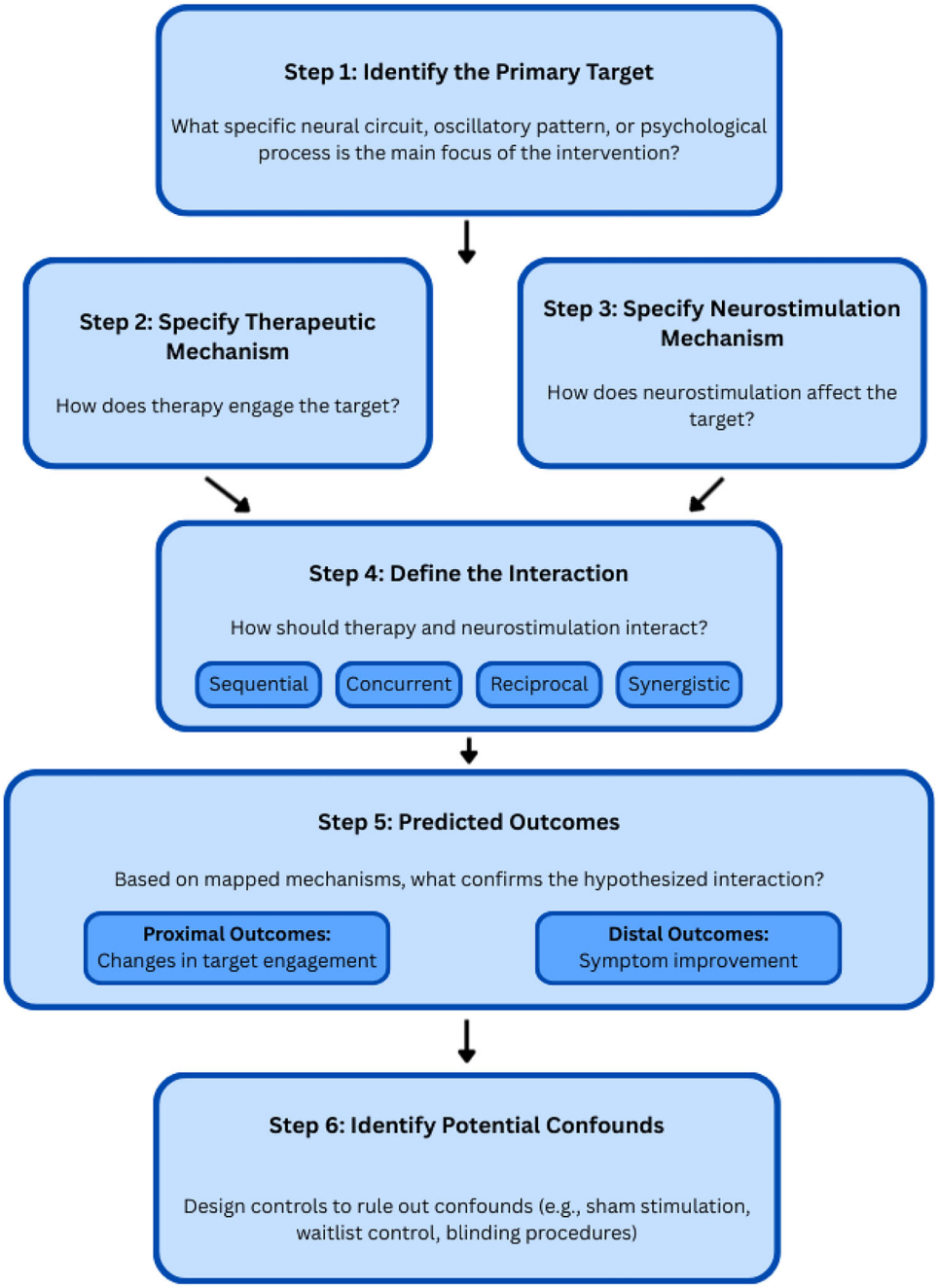

Fig. 1 Mapping Mechanisms: A Framework for Study Design.

such that the proposed mechanism is plausibly relevant and measurable. Contemporary frameworks in psychiatry emphasize that symptom expression, instead of diagnosis alone, reflects underlying neural dysfunction, reinforcing the importance of aligning population characteristics with mechanistic hypotheses [40, 74]. For example, this may mean considering targeting a symptom or symptom cluster with well-defined neural circuitry, such as reward responsiveness in depression or transdiagnostic emotion dysregulation meeting clinical thresholds [40, 75]. Failure to carefully define the clinical population and targeted phenomena risks obscuring treatment effects and limiting mechanistic interpretability, even when interventions are otherwise well specified.

Identification of key clinical profiles represents one important consideration. Although categorical diagnoses are heterogeneous, certain symptom dimensions show more consistent associations with particular neural circuits. For

example, emotion dysregulation, threat reactivity, and reward-processing impairments have been linked to partially distinct prefrontal-limbic, fear extinction, and cortico-striatal systems, respectively [40, 52]. Accordingly, population selection should prioritize individuals whose clinical profiles are most consistent with the circuit-level dysfunction the intervention is designed to modify, instead of relying exclusively on broad diagnostic labels.

Symptom severity and chronicity further influence population suitability. Neural abnormalities targeted by psychotherapy or tES may be more pronounced and stable in individuals with moderate to severe symptom presentations, potentially increasing sensitivity to circuit-level effects [75]. At the same time, greater severity and chronicity are often associated with treatment resistance and altered plasticity, which may limit responsiveness to certain interventions [76], and may thus show the most significant effects to these new treatments. These considerations are particularly relevant for early-phase or proof-of-concept studies, where demonstrating target engagement may be a primary objective. Accordingly, rigorous phenotyping is essential—many studies rely on self-identified symptoms or informal screening without standardized diagnostic evaluation or validated severity thresholds, limiting interpretability and reproducibility. Whenever possible, participants should be characterized using empirically supported diagnostic interviews and/or validated self-report measures with established cutoffs, whether targeting a full disorder or a transdiagnostic construct (e.g., anhedonia, emotion dysregulation), to ensure that observed effects, or lack thereof, can be meaningfully attributed to the proposed neural mechanisms.

With regard to participants on current psychotropic medications, it is also important to consider their seizure risk profile. Current safety guidelines highlight that neuromodulation while concurrently receiving psychotropics is unlikely to lead to a higher likelihood of seizures on its own, but that a combination of several medications, with neuromodulation, and with contextual factors such as alcohol use, or sleep deprivation, may need to be examined to reduce the risk for seizure ([77]). In our clinical trials, we collect careful information about current and past medications, including dose, frequency, and adherence, information about substance use, and information about sleep the night before neuromodulation, use of caffeine and other stimulants, and alcohol the night before tES. All this information is taken into account before administering tES to a new participant.

Taken together, these factors highlight that population selection is not merely a pragmatic recruitment issue but a central component of mechanism-based study design. Just as psychotherapy and tES modalities should be selected to engage specific neural targets, the study population should be chosen to ensure that those targets are meaningfully implicated. Aligning population characteristics with hypothesized neural mechanisms enhances interpretability, increases the likelihood of detecting target engagement, and strengthens causal inferences regarding how combined interventions exert their effects.

Mapping mechanisms: a framework for study design

Regardless of which paradigm guides a study, investigators should explicitly map out their theoretical model before finalizing the design. See Fig. 1 for a proposed framework.

We propose the following steps. First, identify the primary target: What specific neural circuit, oscillatory pattern, or psychological process is the primary focus of intervention? This target should be clearly defined and measurable. Second, specify therapy mechanisms: How is the chosen therapy expected to engage or modify the target? What are the critical therapeutic processes (e.g., extinction learning, cognitive restructuring, behavioral activation)? Third,

specify tES mechanisms: How is tES expected to affect the target? What are the neural mechanisms (e.g., entrainment of oscillations, modulation of excitability, enhancement of plasticity)? Fourth, define the interaction: How should therapy and neurostimulation interact? Is the interaction sequential (one prepares for the other), concurrent (both operate simultaneously), reciprocal (each enhances the other), or synergistic (combination produces unique effects)? Fifth, specify the predicted outcomes: Based on the mapped mechanisms, what specific outcomes would confirm the hypothesized interaction? These should include both proximal outcomes (e.g., changes in target engagement measures) and distal outcomes (e.g., clinical improvement). Finally, identify potential confounds: What alternative explanations could account for observed effects? How can the design rule out confounds such as placebo effects, time, attention, or expectancy? Explicitly articulating this framework clarifies testable hypotheses about

mechanism. It moves beyond simply combining treatments to understanding why and how the combination should work.

Practical guidelines

Administrative and regulatory considerations

Before initiating a combination trial, investigators must navigate several administrative and regulatory requirements.

Institutional review board (IRB) considerations

Combination studies sometimes require more extensive IRB review due to the involvement of investigational devices and the potential for unknown interactions between modalities. A few key considerations include investigation risk determination, informed consent, consent to record, safety monitoring, and data safety monitoring.

Investigation risk determination

In the United States, investigations involving medical devices are governed by the Title 21 Code of Federal Regulations (CFR), Part 812, Investigational Device Exemptions (IDE) which broadly indicate three types of device studies: significant risk (SR), nonsignificant risk (NSR), and device studies that are exempt from IDE regulations. There are many factors to be considered while navigating the regulatory/ethics approval process for combination investigations using neuromodulation techniques, such as the end goal of the investigation (e.g., in support of a marketing application, investigator-initiated trials, label expansion), whether neuromodulation techniques/devices used in the study are implanted or noninvasive, and predicate determinations of the risk classification of the tES device as it is proposed to be used in the trial that have been made by study Sponsors or the FDA. It is important to note that investigation risk determinations for medical devices are made based upon how the device is used in the study, not solely on the nature of the device itself. For studies investigating the combination of neuromodulation with psychotherapy, research teams most often seek a NSR determination to be made by the IRB of record and should work with study Sponsors and/or device manufacturers to present NSR rationale to the reviewing IRB based on the nature of the device, how it is intended to be used in the investigation, and any previously collected safety information about the device in the same or similar usage capacities. Importantly, a device study is considered NSR if it does not meet criteria for a SR device study (i.e., is intended as implant and presents potential for serious risk to health/safety/welfare of subjects, is used for supporting or sustaining human life and poses potential for serious risk to health/safety/welfare of subjects, etc.).

Provided the protocol does not include implantation, most neurostimulation device studies implementing non-invasive neuromodulation techniques (e.g., tACS, tDCS, tES) do not meet criteria for a SR device study as defined by FDA and CFR, placing the research under abbreviated IDE regulations and relieving the burden of FDA IDE submission. If, however, a reviewing IRB does not agree with a clinical investigator/Sponsor's NSR rationale and determines the device as used in the study represents a SR device study, the research cannot proceed until a submission is made to FDA and either a NSR determination has been made (FDA NSR determination is considered final and supersedes other determinations) or an IDE has been granted for a device study determined to be SR.

Informed consent

Consent documents must clearly describe both the psychotherapy and tES components, including potential risks and benefits of each modality and their combination. Because the interaction between modalities may not be well-characterized, consent should acknowledge uncertainty about how the combination might differ from individual

treatments. Additionally, in studies that involve sham control, there may need to be additional discussion with the institutional review board on how to best inform participants of the different types of intervention provided without breaking blinding procedures. One suggestion, depending on study design, is to say that participants may receive one of two types of neurostimulation (one under investigation and a control treatment), rather than describing the control as sham or fake stimulation.

Consent to record

In order to ensure proper adherence for psychotherapy, the research team must record psychotherapy sessions and inform participants about these visits being viewed and coded for adherence by an independent staff member. Because of the highly sensitive nature of these visits, proper encryption and training in data management safety is necessary to protect participant confidentiality.

Safety monitoring

Combination studies require robust adverse event monitoring systems. Standard tES side effects (e.g., scalp discomfort, phosphenes, headache) must be distinguished from therapy-related distress. Similarly, implementation of psychotherapy may come with disclosure of suicidality or violent behaviors and may increase distress temporarily. It is important to have a clear detailed plan to assess and intervene if suicide/homicide risk becomes apparent, and to involve in the study providers that are trained to assess and respond to risk or to increased distress.

Data safety monitoring

Depending on the study size and risk profile, a Data Safety Monitoring Board (DSMB) or, at a minimum, a Data Safety Monitor may be required. This is particularly important for longer-term studies, studies where the principal investigator is blinded to condition assignment, or those involving vulnerable populations.

Avoiding discriminatory practices

Because tES may come with additional risks and setup than traditional psychotherapy, it is important to carefully consider inclusion/exclusion criteria in combination trials, with an eye towards not inadvertently promoting discrimination. For example, pregnant women are often excluded from imaging and neuromodulation trials; nevertheless, there is no evidence to suggest adverse effects on the fetus from non-invasive brain stimulation (albeit more research is needed). While pregnancy in itself is a condition that should be investigated independently, the possibility of pregnancy may be an inadvertent way through which women of childbearing potential may be discriminated against. Following the guidelines and checklist described by [78] may be more appropriate than requiring a pregnancy test to protect against this risk.

Headwear, hairstyles, or hair textures should also be carefully considered when planning tES electrode placement. Participants should be informed during the informed consent process about exactly how tES will be placed on their head and the need to change their hairstyle or remove headwear for the visits. Participants should have the right to decline participation if these changes cannot be made but should be given the choice rather than being excluded automatically because of their cultural choices or natural hair type.

Additional study design considerations

In addition to the importance of an empirically-derived decision regarding what therapy and tES approaches to use, additional components of study design should be considered. Below, we discuss a few key elements that may be useful to consider when designing a combined therapy and tES trial.

Blinding procedures

Achieving adequate blinding in combined psychotherapy and tES studies presents distinct methodological challenges yet is essential for valid causal inference. Inadequate blinding can inflate effect sizes and obscure interpretation, particularly in trials involving noninvasive brain stimulation where sensory experiences may differ across conditions [21, 68]. Participant blinding typically relies on the use of active sham stimulation protocols designed to mimic the sensory experience of active stimulation while minimizing neuromodulatory effects. For tES, sham procedures commonly involve an initial ramp-up period (approximately 30–60 s) followed by ramp-down, which reproduces scalp sensations associated with stimulation onset without delivering sustained current [68, 79]. In tACS studies, additional steps may be required to manage phosphene perception, such as maintaining visual input during stimulation and selecting frequencies less likely to elicit retinal stimulation [80]. In addition to controlling for the effects of active neuromodulation, one should also consider a control for the psychotherapy condition, and a way to describe both active and sham interventions to participants in ways that do not break the blind. In some of our studies comparing the integration of cognitive restructuring with stimulation, we have designed a control for the behavioral intervention where participants are taught information about thoughts and emotions without being taught the actual skill of restructuring. Participants are told that they may receive one of two different skills to combine with neuromodulation to protect the blind.

Therapist blinding is also particularly important in combination studies, where expectancy effects could influence treatment delivery. To minimize bias, therapists should be blind to stimulation condition, with randomization of stimulation condition assignment managed by a separate, unblinded study coordinator who is not involved in the treatment portion of the trial. The use of highly structured and manualized psychotherapy protocols further reduces opportunities for differential therapist behavior across conditions [68]. Furthermore, separating the psychotherapy provider from the stimulation provider can also ensure additional blinding for both parties to further mitigate against bias.

Finally, assessor blinding remains a cornerstone of rigorous study design. Outcome assessments should be conducted by trained evaluators who are blind to treatment condition and independent of both psychotherapy delivery and tES administration.

Psychotherapy implementation

The following considerations address *how* to deliver the selected psychotherapy rigorously. Questions of modality selection and mechanistic rationale are addressed in the *Psychotherapy Selection* section above.

Selecting a manualized, evidence-based psychotherapy for the integration is essential because psychotherapy only improves outcomes when it is delivered as designed. Treatment manuals provide structure, define core components, and specify the therapeutic strategies that have been identified as mechanisms of change. When clinicians deviate from these components, treatment effects weaken and variability increases, making it difficult to attribute failure in a combined intervention to a faulty integration or a poorly executed behavioral treatment. Implementation science consistently shows that fidelity to an evidence-based model is a key determinant of clinical outcomes [81].

It is possible to select only one component of a psychotherapy, like we have done in our trials combining cognitive restructuring with stimulation ([82]). Nevertheless, when doing so, one must still rely on a manualized description of this component and on adherence measurement of its implementation. Designing a psychotherapeutic portion of a combined intervention that ‘sounds like’ an evidence-based treatment is not sufficient.

Evidence-based psychotherapies have at least two rigorous randomized controlled trials supporting their efficacy in specific populations ([91]). Any treatment without this type of evidence is unlikely to be a good choice for a combined intervention because we do not yet know if the behavioral treatment itself is successful. A list of psychotherapies and the status of their evidence-based status is maintained by the American Psychological Association (APA) Division 12. This list can be found here: societyofclinicalpsychology.org/resources/psychological-treatments. Alternatively, the study designer may examine the literature to determine whether sufficient rigorous evidence has been accumulated with the proposed treatment manual to warrant inclusion in a combined intervention.

Ensuring that the intervention is delivered competently is also critical and requires identifying providers who are already trained or establishing a clear plan for training them. Even well-trained clinicians drift from protocol over time [83], which is why fidelity monitoring is necessary to detect and correct deviations. Standard practice is to code approximately 10–20% of the psychotherapy sessions, randomly selected, to assess adherence to the protocol and competence using validated fidelity tools [84]. When adherence monitoring reveals drift, such as omission of core components or introduction of non-protocol elements, programs must have a predefined plan for retraining therapists to fidelity. Booster training, targeted supervision, and structured feedback are all recommended strategies for restoring fidelity to the model and should be included in a thorough experimental design. These steps ensure that the intervention being tested is the intervention actually delivered. We propose stringent adherence to evidence-based practice for rigorous trials and for the development of combined interventions. At the same time, combined treatments will need flexibility to accommodate both intervention approaches. One important design consideration in this treatment development space is the lack of alignment in timing between neuromodulation and psychotherapy. The timing of tES interventions can range from being delivered daily across multiple days to weeks [85, 86], to a brief one-time administration [30], to intensive multi-session administrations [87]. However, psychotherapies are traditionally delivered weekly, with homework assignments between sessions. Therefore, a combined intervention must carefully weigh the costs of departing from one of these timing models to accommodate the other. Based on evidence supporting that more frequent psychotherapy may be beneficial [88], we recommend compromising the spacing of therapy sessions rather than that of neuromodulation. Nevertheless, this decision should be made with the specific target, the interventions that need to be combined, and the population in mind. If spacing for psychotherapy sessions is reduced, it is important not to let go of homework assignments and at-home practice, as evidence strongly suggests that these components are instrumental to treatment success [89]. Rather, home practice can be adjusted to be doable in a shorter interval, while continuing to promote the application of skillful behavior in the person's naturalistic context.

Personnel requirements

Combination studies require a multidisciplinary team with clearly defined roles to ensure rigorous implementation and oversight, including the principal investigator, therapists/clinicians, tES technicians, research assessors, a study coordinator, and a safety monitor. Each role is briefly described here:

The principal investigator should have expertise in both domains involved in the intervention or, alternatively, include co-investigators whose expertise collectively covers both areas. The principal investigator is responsible for overall study design, scientific oversight, and ensuring adherence to the study protocol. Therapists should be clinicians trained in the specific therapeutic modality being delivered and in the study protocol to ensure standardized implementation of the intervention. Transcranial electrical stimulation (tES) technicians are trained personnel responsible for preparing and administering stimulation; they should have expertise in electroencephalography (EEG) electrode placement and in the operation of stimulation devices. Research assessors administer standardized clinical assessments and must remain blind to treatment condition to reduce potential assessment bias. A study coordinator oversees study logistics, including participant scheduling, regulatory compliance, and data management, and ensures smooth coordination among team members. Finally, a safety monitor—typically a clinician not directly involved in treatment delivery—is available to evaluate adverse events and address safety concerns that may arise during the study.

Equipment and infrastructure

Combined psychotherapy-tES studies impose specialized infrastructural requirements that may extend beyond those of standard clinical trials. Adequate equipment, physical space, and procedural separation are essential to ensure participant safety, maintain blinding, and support rigorous data collection [21, 68].

tES equipment should be selected to support double-blind, sham-controlled designs. Stimulation devices should allow remote or coded condition assignment, automated impedance monitoring, and secure data logging to prevent unblinding and enable quality control [21, 79]. Appropriate electrodes and supplies are required depending on the stimulation modality, along with conductive paste when EEG-based montages or concurrent recordings are used. When oscillatory targets are measured or individualized stimulation parameters are derived, access to EEG acquisition systems is necessary to support baseline assessment and target engagement verification [59]. Given the complexity of combined protocols, maintaining backup devices and consumables is critical to minimize study disruption and protocol deviations.

Therapy materials and physical space must likewise support both clinical and experimental rigor. Psychotherapy delivery requires standardized materials, such as workbooks and session handouts to ensure treatment fidelity across conditions. Therapy sessions should be conducted in private, comfortable rooms that can accommodate therapeutic activities as well as tES equipment when concurrent delivery is planned. Separate, dedicated spaces for clinical assessments are recommended to reinforce assessor blinding and reduce expectancy effects [68]. Finally, secure storage for equipment, paper materials, and electronic data is required to protect participant confidentiality and comply with institutional and regulatory standards, including HIPAA requirements. As mentioned before, psychotherapy should be administered in spaces that allow session recording for fidelity monitoring. In addition, for combined interventions, the length of time the participant is scheduled to be there may warrant considering drinks and snacks.

Reporting and reproducibility considerations

As research combining tES and psychotherapy continues to evolve, careful reporting of study methods will be essential to support replication and interpretation. Researchers should provide sufficient detail regarding stimulation procedures, including electrode montage, current intensity, stimulation duration, sham methods, impedance thresholds, and, when available, electric field modeling approaches and results. Reporting of the psychotherapy intervention should be equally thorough and include the treatment protocol, therapist training, procedures used to monitor treatment fidelity, adherence outcomes, and any deviations from the planned intervention. Studies should also describe randomization and blinding procedures, report assessments of blinding integrity when available, and document participant retention, adverse events, and protocol deviations. Including measures of target engagement alongside clinical outcomes can further strengthen mechanistic interpretation and facilitate comparisons across studies. Consistent reporting of both neuromodulation and psychotherapy methods will improve reproducibility and make it easier to synthesize findings across studies. Whenever feasible, investigators are encouraged to share study materials, stimulation protocols, analysis code, and other methodological resources through open repositories. Platforms such as the Open Science Framework and AsPredicted (ResearchBox) provide accessible mechanisms for sharing these materials and promoting transparency and reproducibility.

These infrastructural considerations underscore that combination studies are not simply additive extensions of psychotherapy or tES trials. Instead, they require integrated planning across equipment, personnel, and physical space to preserve methodological rigor and ensure that mechanistic hypotheses can be validly tested.

Discussion

Conducting rigorous clinical trials combining tES and psychotherapy represents a significant opportunity to extend the field and improve outcomes for individuals struggling with psychiatric symptoms. As we have outlined, success requires careful attention to conceptual foundations, methodological rigor, and practical implementation details. The conceptual model we have presented emphasizes the importance of explicitly mapping mechanisms and understanding bidirectional influences between modalities. Too often, studies are pursued with vague rationales about 'enhancing' treatment without clear specification of what is being enhanced and through what mechanisms. By requiring investigators to articulate whether they are using therapy to enhance tES effects, tES to enhance therapy effects, or pursuing true synergistic effects, we encourage more precise hypothesis generation, more interpretable outcomes, and enhanced replicability to examine durability of observed effects.

The practical guidelines we have provided address the reality that combination studies are complex undertakings. They require multidisciplinary expertise, sophisticated equipment, careful coordination of multiple intervention components, and meticulous attention to blinding. These requirements should not be underestimated. As has been observed across intervention literatures, underpowered or poorly executed studies can generate misleading findings that complicate interpretation and slow cumulative progress.

Several themes emerge from our recommendations that align with broader principles of intervention research. First is the importance of the mechanism. For tES and psychotherapy both, there is an emphasis that understanding mechanism of treatment is essential for rational treatment development. Combination studies offer unique opportunities to probe mechanism by examining how two mechanistically distinct interventions interact. Second is the critical importance of appropriate control conditions and blinding. In combination research, the question 'compared to what?' becomes complex. Is the goal to show that the combination is better than therapy alone, better than stimulation alone, or produces synergistic effects not attributable to either component? Each question requires different control conditions and analytic approaches. Third is the recognition that standardization and individualization need to be balanced. Rigorous trials require standardized protocols that can be replicated. However, both psychotherapy and tES may benefit from individualization, whether through tailoring therapeutic strategies to specific clinical presentations or tuning stimulation parameters to individual neural characteristics. Fidelity to the treatment model proposed is an essential tool to examine whether personalization stayed within the bounds of the evidence-based approach implemented.

Although substantial progress has been made in identifying candidate neural targets and developing mechanistically informed interventions, many questions (e.g., specific target engagement, individual variability, optimal intervention timing, and causal pathways linking neural and clinical change) remain unresolved. Accordingly, this initial framework should be viewed as a guide for hypothesis-driven study design rather than as a definitive set of best practices, as these best practices may evolve over time with the onset of new clinical trials. We anticipate that many recommendations will require refinement as the field accumulates additional mechanistic and clinical evidence. At the same time, we believe that articulating a structured framework is valuable precisely because the field remains in an early developmental phase. Mechanistically informed trial design may help accelerate knowledge generation, improve interpretability of findings, and reduce the risk of purely empirical "black-box" treatment development. Although the present article focuses on combined tES and psychotherapy interventions, many of the principles discussed—including target identification, target engagement, temporal alignment of interventions, and mechanistic outcome assessment—may ultimately prove useful for optimizing other multimodal treatment approaches.

Looking forward, the field of research assessing combined psychotherapy and tES is in its infancy. We have much to learn about how different forms of psychotherapy interact with different tES approaches. Key questions include optimal timing relationships, dose-response relationships, individual differences that predict response, mechanism specificity, long-term outcomes, and treatment optimization approaches. In sum, trials combining tES and psychotherapy, when done rigorously, offer the potential to significantly advance treatment of psychiatric and neurological disorders. By rationally integrating interventions that target complementary mechanisms, we may be able to help patients who do not respond adequately to existing approaches. However, this potential can only be realized

through rigorous research that prioritizes mechanistic understanding, methodological quality, and translational relevance.

Conclusion

The combination of tES and psychotherapy represents a promising frontier in psychiatric treatment development. This guide has provided a framework for conducting rigorous clinical trials examining these combinations. We have emphasized the importance of clearly articulating mechanistic hypotheses, mapping bidirectional influences, carefully selecting populations based on target presence, optimizing therapy delivery and timing, implementing robust blinding procedures, rationally choosing stimulation parameters and psychotherapy approaches, and ensuring adequate infrastructure. By following these guidelines and building on foundational work in tES trial methodology, investigators can design studies that not only test whether combinations are effective but also illuminate *why* and *for whom* they work. This understanding is essential for translating findings into clinical practice and for refining combination approaches. As the field matures, we anticipate that carefully designed trials will establish combination treatments as valuable tools for addressing substantial unmet needs in psychiatric care.

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