Combining Digital Therapeutics with Neuroplasticity-Inducing Agents: A Framework Modeled on MAT

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SUBMISSION DETAILS

Methodological Issue Being Addressed Neuroplasticity underlies the brain’s capacity to reorganize dysfunctional thoughts and behaviors, serving as a mechanistic foundation for therapeutic change in psychiatric disorders. A growing class of interventions, including pharmacologic agents, psychedelic compounds, and neuromodulatory devices, seek to induce neuroplastic states. However, outcomes remain highly variable due to inconsistent psychological and environmental contexts during treatment. In fact, it should be considered that neuroplasticity can induce vulnerability for detrimental experiences. The resulting variability limits both therapeutic reliability and the interpretability of clinical trials. Drawing from the Medication-Assisted Treatment (MAT) model in depression and posttraumatic stress disorder (PTSD) where pharmacologic and behavioral interventions are combined, we propose an alternative framework for the analysis of the effectiveness of these interventions: pairing neuroplasticity-inducing treatments with digitally delivered, standardized psychotherapeutic and neuromodulatory treatments to identify the relative contribution of each of the combined elements. A recent example is the development of MDMA in combination with psychotherapy for the treatment of PTSD (for example Mitchel et al., 2021). MDMA may support the action of psychotherapy, but the quantification of the effect is difficult to determine with the current trial design.

Introduction Neuroplasticity inducing interventions, including ketamine, psilocybin, MDMA as well as non-invasive neuromodulatory devices may promote neuroplasticity in conditions such as depression and PTSD. However, their clinical efficacy often hinges on the subjective experience during the neuroplastic window. Similar to how MAT combines medication with structured psychosocial support, neuroplasticity-enhancing interventions may require consistent, purposeful behavioral scaffolding. Without standardization variability threatens the identification of the benefit of these treatments. In addition, the effect of the psychotherapeutic intervention isolated from the pharmacological one or vice versa, the effect of the pharmacological innervation without the behavioral one is difficult to determine.

Methods We propose a methodological framework in which neuroplasticity-inducing treatments are coupled with a prescription digital therapeutic (PDT) that delivers two key components: (1) a structured psychotherapeutic intervention (e.g., emotional processing, cognitive restructuring, exposure tasks), and (2) digital neuroactivation and modulation (DiNaMo) techniques that engage neural circuits directly through algorithmically guided tasks, sensory stimuli, or affective computing. These DTx components can be personalized in real time using passive and active patient input. Efficacy can be evaluated through a 2×2 factorial trial design (factor “pharm”: active vs. placebo pharmacologic intervention; factor “PDT”: active vs. control PDT). This design allows three levels of comparison: 1. A comparison of the active vs placebo pharmacological intervention (factor: pharm), interpreting PDT as a covariate 2. The comparison of the effectiveness (efficacy) of the active vs. sham device (device), interpreting pharm as covariate; 3. To identify, whether a synergism exists, based on the presence of a statistically significant interaction term (pharm x PTD). A sample of 75 subjects per cell, i.e. 150 subjects per treatment group comparison would be adequate to detect moderate treatment effects across the targeted syndrome, but needs to be further specified based on the expected variability of the outcome variable. Such a design would be able to dissect the contribution and interaction of the interventions and provide arguments for or against a combination.

Results This approach is expected to yield insights into the timing, content, and personalization of interventions delivered during neuroplastic windows. Standardization via PDT could improve trial reproducibility and support regulatory alignment. Furthermore, the added benefit of combined interventions may be clearer identifiable. This may support the development of methods providing faster symptom relief, greater durability, and enhanced real-world applicability.

Conclusions Effective psychiatric treatment often requires both biological and experiential engagement. By aligning pharmacologic or device-based induction of neuroplasticity with digitally delivered behavioral and neuromodulatory input, this framework may address a central gap in our understanding of the contributions of biological vs. psychological/behavioral elements of a combined intervention.

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Guidelines I have read and understand the Poster Guidelines

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