Cognitive Rehabilitation and Modulating Neuroplasticity with Brain Stimulation: Promises and Challenges

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A substantial proportion of the severe functional disability observed in patients with schizophrenia is attributable to their persistent negative symptoms and cognitive deficits [1, 2]. Identifying these determinants of functional disability becomes even more crucial when patients remit from their florid hallucinations and delusions [3]. Indeed, there are very few evidence-guided interventions (e.g., cognitive remediation) that specifically target the neural systems underlying the persistent cognitive and volitional impairments. Despite showing promising results, the magnitude of benefits from cognitive remediation strategies could at best be described as modest [4]. It is therefore critical to explore and empirically examine alternative strategies to ameliorate cognitive deficits and improve functional outcome.

The core deficits in schizophrenia are increasingly being viewed as resulting from aberrant neuroplasticity, operating at multiple mechanistic levels of brain functioning—such as synapses, axons, glia and network plasticity. This maladaptive “dysplasticity” may involve both hypoplastic changes in strategic brain networks supporting cognitive functions and goal-directed behavior or volition, and hyperplastic changes in neural systems governing salience detection, emotion regulation as well as default mode systems [5].

A range of neurophysiological investigations probing plasticity at multiple levels supports these conclusions. For example, synchronous neural oscillations during spindle sleep, which have been considered, as markers of learning-related synaptic plasticity are reduced in schizophrenia. Moreover, they also predict deficits in attention, motor learning and executive functions [6, 7]. Similarly, pairing median nerve stimulation with transcranial magnetic stimulation (TMS) over the motor cortex produces lesser plasticity-dependent facilitation of motor potentials in schizophrenia when compared with healthy subjects; these plasticity-impairments were also significantly associated with the motor learning deficits observed in these patients [8].

One strategy that has promising therapeutic potential to adaptively modulate neuroplasticity is the use of non-invasive brain stimulation using TMS or transcranial direct current stimulation (tDCS). TMS is a non-convulsive method of modulating focal brain activity via induced electrical currents that result in neuronal depolarization. Repeated pulses (rTMS) administered at low (≤ 1 Hz) and high frequencies (≥ 5 Hz) can either inhibit or enhance the underlying cortical activity respectively [9]. The application of TMS in treating cognitive deficits, supported by advancing neurobiological evidence is only recently gaining momentum [10]. For instance, 4-weeks of 20-Hz rTMS delivered to bilateral dorsolateral prefrontal cortices resulted in significant improvement on working memory performance in schizophrenia patients, when compared to sham TMS [11]. Potentiation of task-evoked frontal gamma oscillatory activity may mediate this response [12]. However, another study using unilateral (left) 10-Hz rTMS to the dorsolateral prefrontal cortex did not find similar benefits [13]. Initial evidence suggests that social cognition deficits may also benefit from high frequency rTMS to the

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left dorsolateral prefrontal cortex as demonstrated in one pilot study [14]. Novel stimulation sites (e.g., the mirror neuron system and the cerebellum) are also promising avenues for further exploration [15, 16].

Transcranial direct current stimulation (tDCS) can also have effects on neuroplasticity by applying small monophasic electric currents (usually 1–2 mA) between anode and cathode electrodes placed over the scalp [17]. Anodal tDCS facilitates depolarization of the resting membrane potential and enables excitability of underlying cortical activity [18]. Cathodal tDCS facilitates hyperpolarization of the resting membrane potential and thus reduces cortical excitability [19]. Similar to TMS, tDCS is also a relatively safe procedure, with no major adverse events [20]. Being a portable device, tDCS can be used simultaneously with other cognitive or behavioral interventions. For example, anodal tDCS applied to the bilateral prefrontal cortices resulted in greater enhancement of working memory and attention in healthy individuals, especially if delivered “online”—during cognitive training, as opposed to “offline”—before cognitive training [21, 22]. This particular application of “online” tDCS could be a potential augmentation strategy to existing cognitive remediation programs. There is also data to suggest that these benefits are likely to be durable over 4-weeks [23].

Clearly, there is a growing body of evidence for the utility of the abovementioned non-invasive brain stimulation strategies to enhance cognition, more so in clinical populations [24]. However, future experiments need to build upon these preliminary findings and identify optimal stimulation parameters (e.g., site and laterality of stimulation, modality used, dose of magnetic/electrical currents, frequency and duration of sessions), before these techniques can be transferred to routine clinical applications.

Along with the promises of using non-invasive brain stimulation to harness neuroplasticity, several challenges need to be recognized and addressed. First, as alluded to earlier, apart from replicating these preliminary findings, efforts need to be made to optimize stimulation parameters and technique of delivery of the brain stimulation intervention. With respect to TMS, precise localization of dose delivery has been a constant challenge—more so because of the focal nature of TMS stimulation and the related difficulties in localizing specialized brain regions using scalp surface markings. A potential solution to this has been the emergence of MRI-guided neuronavigational delivery systems. These use either electromagnetic or optical infra-red techniques to guide TMS coil placement based on structural or functional MRI coordinates for that given individual [25]. This technique enhances the magnitude of TMS effects by several folds [26].

Second, it is accepted that complex brain disorders like schizophrenia, do not depend on functional lesions in

discrete neural regions; they are rather disorders of network connectivity, progressively being referred to as connectopathies. In this context, will stimulating one brain region suffice? Interestingly, TMS has trans-synaptic effects, i.e., it not only alters neuronal activity in the primarily stimulated neuronal region, but also its post-synaptic connections [27, 28], thus paving the way to study functional cortical network connectivity. Apart from informing the mechanisms of putative cognitive enhancement, these functional connectivity maps, often obtained through resting state functional neuroimaging can be used to predict who responds to the treatment and who remains symptomatic [29].

Third, non-invasive brain stimulation can penetrate only superficial cortical structures. However, several neuronal networks comprise of important subcortical nodes that need to be targeted. Wang and colleagues in their pioneering work have attempted to overcome this challenge by identifying strong resting state functional connectivity of deeper brain regions (e.g., left hippocampus) with more superficial cortical regions (e.g., left lateral parietal cortex). They delivered MRI-guided rTMS to the lateral parietal cortex in a subject-specific manner over 5 days to demonstrate strengthening of cortical-hippocampal networks, as well as, improvement in memory performance [30]. Deep rTMS is yet another avenue for exploring stimulation of deeper brain regions to facilitate cognitive enhancement [31]. This system uses a specialized array of coils to enable penetration of the magnetic fields to deeper regions; nevertheless this technique does not spare the superficial regions from being stimulated.

Yet another challenge is the durability of benefits. Even though these haven't been extensively tested, it is conceivable that the potential beneficial effects may not last beyond a few weeks of stopping treatment. Maintenance therapies have been documented in both TMS [32] and tDCS [33] literature for resistant auditory hallucinations. The feasibility of maintenance brain stimulation therapy is better with tDCS, given the portable nature of the device and its cost-effectiveness.

Lastly, dissemination of this novel technology to the end user is perhaps the biggest challenge. A strong evidence-base in terms of replicability of findings, durability of effects after treatment cessation, generalizability to real-world outcomes, magnitude and clinical relevance of the observed change, and its cost-effectiveness would determine how policy makers could support the use of these novel treatment approaches so that they are accessible to deserving patients.

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