Brain stimulation: Neuromodulation as a potential treatment for motor recovery following traumatic brain injury*

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Abstract

There is growing evidence that electrical and magnetic brain stimulation can improve motor function and motor learning following brain damage. Rodent and primate studies have strongly demonstrated that combining cortical stimulation (CS) with skilled motor rehabilitative training enhances functional motor recovery following stroke. Brain stimulation following traumatic brain injury (TBI) is less well studied, but early pre-clinical and human pilot studies suggest that it is a promising treatment for TBI-induced motor impairments as well. This review will first discuss the evidence supporting brain stimulation efficacy derived from the stroke research field as proof of principle and then will review the few studies exploring neuromodulation in experimental TBI studies.

Keywords

Epidural stimulation; Transcranial stimulation (TMS); Transcranial direct stimulation (tDCS); Motor cortex; Rehabilitative training

1. Introduction

An estimated 5.3 million traumatic brain injury (TBI) survivors are currently suffering long-term or life-long motor deficits (Langlois et al., 2006). While impairments in cognition, executive functions and mood regulation are more commonly reported and studied, motor deficits are prevalent but under investigated (Kozlowski et al., 2013; Langlois et al., 2006; Marshall et al., 2007; Pickett et al., 2007; Teasell et al., 2007; Walker and Pickett, 2007). Likely one of the best approaches to reduce injury-induced deficits would be to limit injury severity by reducing primary and secondary neuronal loss during the acute injury period.

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However, currently there are no effective neuroprotective treatments that clinically lead to better outcomes, although there are candidate treatments that have been shown to stabilize TBI acutely (Kabadi and Faden, 2014; Stocchetti et al., 2015). Even as safe and effective neuroprotective treatments become available, their effectiveness may be limited by the need for early administration (minutes, hours or days after injury) and there will be a continued need for rehabilitative therapy that can optimize recovery. Rehabilitative therapy and adjunctive post-acute treatments, such as cortical stimulation, aim to restore motor function by driving neural repair and remodeling. Augmentation of rehabilitation interventions provides a wider window of opportunity for effective treatment and is showing promise at improving behavioral outcomes.

Human and animal studies suggest that motor rehabilitative practice can improve motor function and drive brain remodeling following stroke (Dimyan and Cohen, 2011; Dobkin, 2004; Johansson, 2000; Jones and Adkins, 2010, 2015; Lang et al., 2015). Motor “relearning” and task-specific practice are considered essential in driving this neural plasticity (Johansson, 2000; Jones and Adkins, 2010; Kleim and Jones, 2008; Lang et al., 2015). Following an experimental stroke, animals that repeatedly practice with their impaired limb on a reach-to-grasp task, a skilled learning task, demonstrate enhanced forelimb motor recovery compared to non-trained controls (Castro-Alamancos and Borrel, 1995; Maldonado et al., 2008; Nudo et al., 1996; Tennant et al., 2014). Repeated practice drives neural network remodeling and induces synaptogenesis, axonal outgrowth, and angiogenesis (reviewed in: Jones and Adkins, 2015; Nudo, 2013; Overman and Carmichael, 2014). In squirrel monkeys, rats and mice impaired forelimb reaching practice has also been shown to spare motor cortical tissue around the lesion and prevent the loss of movement representation in the remaining motor cortex, measured with intracortical microstimulation mapping (Nudo et al., 1996) and results in enlarged forelimb motor representative maps compared to untrained controls (Conner et al., 2005; Tennant et al., 2014). Clinically, several studies also indicate that the more a movement is practiced the better people recover function; however, the duration and intensity of therapy may need to be titrated depending on time after stroke (Lang et al., 2015).

These studies in stroke suggest that skilled motor training after TBI could be equally as beneficial. However, we have recently reported that translation of effective treatments used in animal models of stroke may not be as effective in animal models of TBI. In the days and weeks after focal ischemic stroke to the motor cortex, the perilesional remaining motor cortex and contralateral cortex undergoes robust regenerative processes including upregulation of neurotrophic factors and other genes related to neural plasticity (Li and Carmichael, 2006), a reduction in growth limiting genes (Li and Carmichael, 2006) and extensive experience-dependent dendritic growth compared to non-stroke controls (Adkins et al., 2004; Jones and Schallert, 1992; Kozlowski et al., 1994). Although there is a similar pattern of up- and down-regulation of growth promoting and growth inhibiting genes following a unilateral controlled cortical impact (CCI) over the motor cortex (Harris et al., 2009), there is not the same robust structural plasticity response in the area surrounding the injury and in the contralateral homotopic motor cortex (Jones et al., 2012). These are regions that undergo dendritic growth and remodeling in the contralesional motor cortex that is linked to a stroke-induced hyper-reliance upon the non-impaired forelimb following infarcts.
Despite similar volume of injury and similar behavioral impairments, including a hyper-reliance upon the nonimpaired contralesional forelimb for postural support and exploration, there was not an increase in dendritic plasticity in the contralateral cortex following a CCI over the motor cortex (Jones et al., 2012). In the surrounding periinjury remaining motor cortex, there was also an increase in cells positive for growth inhibiting proteins and more dying neurons compared to sham controls (Jones et al., 2012). Thus, Jones et al. (2012) argue that compared to stroke induced injury there is a reduction in compensatory plasticity mechanisms following CCI induced motor cortical damage. Given the possibility that CCI resulted in an environment less supportive of experience dependent plasticity, we investigated whether behavioral treatments shown to be effective in stroke models would be as effective following CCI. We found that following a CCI over the motor cortex, reach training alone did not improve motor function compared to no training controls (Adkins et al., 2015), as it does in animal models of stroke (Alaverdashvili and Whishaw, 2010; Biernaskie and Corbett, 2001; Biernaskie et al., 2004; Johansson, 2000; Jones and Adkins, 2015). Instead, a combination of treatments was needed to improve forelimb function following CCI. Motor improvements required combining reach training with aerobic exercise (running wheel), with or without forced forelimb use, to improve function (Adkins et al., 2015). While the full explanation for these findings are incomplete, these data suggest that finding viable treatments for TBI recovery may require the combination of more robust treatments to drive neural remodeling and behavioral recovery. Thus, as we begin to investigate the potential utility of cortical electrical stimulation following TBI, we likely will not be able to simply apply previous stimulation parameters used successfully used in studies of stroke to TBI patients. Despite these limitations, we can still learn from stroke studies as a starting point to investigate potential effective treatments in a TBI model.

This review will focus on post-acute motor deficits and the nascent field of brain stimulation as a novel means to enhance the efficacy of motor task practice to improve functional motor recovery after TBI. We begin with a brief discussion of the different stimulation techniques currently under investigation and then discuss in more detail three of the most common techniques that are being used in conjunction with rehabilitative training in human stroke survivors.

2. Commonly studied motor cortical stimulation techniques

There are a growing number of brain stimulation techniques currently under development. The most common or most well studied stimulation approaches are transcranial direct cortical stimulation (tDCS), transcranial magnetic stimulation (TMS), and extradural or epidural cortical stimulation. We will briefly describe each technique and then describe how these neumodulatory approaches are being tested as adjuvant treatments following stroke and TBI.

3. Noninvasive cortical stimulation

Transcranial Magnetic Stimulation (TMS) uses a plastic handheld paddle that is most commonly in the shape of a figure of eight, circle, or cone. The paddle is held against the
head over the target brain region. A magnetic field is generated and produces a brief electrical current (electromagnetic induction) that passes through the skull and induces activity in cortical neurons below the current pulse. Single pulses of current can drive neurons to fire action potentials and thus when the motor cortex is the target, a TMS pulse of sufficient magnitude can produce specific muscle movements or motor evoked potentials. Repeated pulses of TMS (rTMS) can alter the excitability of neurons and the effects can last for hours after stimulation has ceased. Depending on the frequency in which the current pulses are delivered, TMS produces either neural excitability (>5 Hz) or inhibition (~1 Hz) (Rossi et al., 2009; Wassermann et al., 1996).

Transcranial Direct Stimulation (tDCS) delivers constant weak direct current that flows between a cathode and anode electrode that are placed on the skull in various positions depending upon the study design. tDCS does not deliver enough current through the skull to produce neuronal action potentials but can induce focal, prolonged shifts in cortical activity whether the activity is excitatory or inhibitory depends on which electrode is placed over the region of interest. Common electrode placements include placing one electrode over the site of interest, like the motor cortex, and the other electrode on the shoulder, then current flows between these two electrodes. If the anodal electrode is placed over the motor cortex, for example, there would be a shift towards excitation beneath the electrode; whereas if the cathodal electrode is placed on the motor cortex it would produce a reduction in excitation (Nitsche and Paulus, 2000, 2001).

3.1. Implanted stimulation devices
3.1.1. Extradural cortical stimulation—In general, extradural cortical stimulation consists of directly stimulating cortex through electrodes placed on dura. The specific waveform and frequency of stimulation are study dependent. Depending upon the configuration of the electrodes the current is considered primarily bipolar (cathodal and anodal electrodes are in close proximity and pass current through the brain) or monopolar (one electrode is on the cortex and the other is grounded outside of the brain). These electrodes are capable of directly driving motor evoked potentials and involuntary motor movements.

4. Transcranial cortical stimulation following stroke
In healthy controls, TMS and tDCS improve motor performance on tasks of motor imagery (Date et al., 2015), speed and (Vines et al., 2008), motor learning (Nitsche et al., 2003b; Reis et al., 2009; Tecchio et al., 2010) and general hand function (Boggio et al., 2006a, 2006b, 2007; Wassermann et al., 1993, 1998). Following stroke, excitatory anodal tDCS delivered over ipsilesion primary motor cortex (M1) or inhibitory cathodal tDCS delivered over the contralesion M1 improves motor performance on standardized tests of motor function (Fregni et al., 2006; Hummel et al., 2005, 2006; Hummel and Cohen, 2005, 2006; Kim et al., 2006). Repetitive TMS (rTMS) delivered at high frequency (5- to 20-Hz pulse trains) facilitates neural activation or lower frequencies (0.2-to 1-Hz pulse trains) inhibits neural activation. Low frequency rTMS reduces spasticity and hemiparesis in chronic subjects (Mally and Dinya, 2008) and improves grasping function after subcortical stroke (Nowak et
The size and design of current TMS coils make it challenging to deliver consistent CS to M1 during rehabilitation regimens, but it alters cortical excitation for a time period after stimulation ceases and facilitates learning and “re-learning” off-line at least for 90 min (Christova et al., 2015; Fregni and Pascual-Leone, 2007; Hummel and Cohen, 2006).

tDCS uses relatively weak electric currents (1–2 mA) that modulate neural activity via effects on ion channel activation (Floel, 2014; Nitsche et al., 2008). Excitatory tDCS (anodal) enhances motor learning, likely by strengthening synaptic connections through NMDA receptor-dependent long-term potentiation (LTP)-like effects and increases BDNF and TrkB activation (Fritsch et al., 2010; Monte-Silva et al., 2013; Nitsche et al., 2003a). tDCS delivered over the infarcted motor cortex or inhibitory tDCS delivered over the contralesional motor cortex improves motor functions (Fregni et al., 2005; Hummel et al., 2005; Hummel and Cohen, 2006; Kim et al., 2010).

Many transcranial stimulation studies have focused on restoring the balance of interhemispheric activity after stroke, based on findings of increased excitability of the contralesional hemisphere, which may overly inhibit activity in the injured hemisphere (Butefisch et al., 2008; Domann et al., 1993; Mittmann et al., 1994; Nair et al., 2007; Neumann-Haefelin and Witte, 2000; Shimizu et al., 2002) by increasing GABAergic activity in peri-lesion cortex (Carmichael, 2012; Zeiler et al., 2013). It follows that balancing interhemispheric activity, either by exciting the injured hemisphere or by inhibiting the contralesional cortex, might improve function. Consistent with this, facilitatory stimulation (high-frequency TMS or anodal tDCS) over the stroke-affected motor cortex or disruptive stimulation (low-frequency TMS or cathodal tDCS) can acutely improve performance of the paretic side (Di Lazzaro et al., 2008; Fregni et al., 2005, 2006; Hummel et al., 2005; Hummel and Cohen, 2006; Khedr et al., 2005, 2013; Kim et al., 2006; Mansur et al., 2005). However, the influence of excitability in the contralesional cortex, and hence the efficacy of disruptive stimulation in this hemisphere, is likely to vary with stroke severity and location e.g., cortical vs. subcortical (Butefisch et al., 2008; Gerloff et al., 2006; Grefkes and Ward, 2014).

Dhaliwal et al. (2015) and Li et al. (2015) have both recently reviewed the potential use of brain stimulation in TBI survivors. While most of the studies they review focus on non-motor impairments, they directly speak to the relative safety and potential benefit of brain stimulation in TBI individuals. Several studies demonstrate that rTMS and tDCS can reduce TBI related depression, tinnitus, neglect, and memory and attention disorders (see review: (Dhaliwal et al., 2015; Li et al., 2015)). Middleton et al. (2014) also report that bi-hemispheric tDCS in two TBI survivors (one individual had a stroke and TBI) improved upper-extremity Fugl-Meyer scores for up to 6 months post-treatment (Middleton et al., 2014). These studies demonstrate the potential benefit and safety of brain stimulation following TBI. However, as is discussed below the stimulation parameters may need to be altered to maximize benefit.
5. Epidural cortical stimulation (CS) following stroke

In rats and monkeys, combining daily motor rehabilitative training on a skilled reaching task with concurrent high frequency (50–250 Hz) sub- or epidural bipolar, cathodal or anodal cortical electrical stimulation (CS) of perilesion primary motor cortex (M1) improves forelimb function compared with training alone (Adkins et al., 2006, 2008; Adkins-Muir and Jones, 2003; Boychuk et al., 2011; Kleim et al., 2003; Moon et al., 2009; Plautz et al., 2003a; Teskey et al., 2003; Zheng et al., 2013; Zhou et al., 2010). Although there has not been an exhaustive comparison of potential effective CS combinations of frequencies and polarities following stroke, several studies do indicate that there is at least a range of effective combinations. Stimulation delivered between 50 and 250 Hz show behavioral benefit in most studies and CS delivered through each polarity shows benefit, but most robustly following cathodal stimulation compared to bipolar or anodal following ischemic damage (Adkins et al., 2006, 2008; Adkins-Muir and Jones, 2003; Boychuk et al., 2011; Kleim et al., 2003; Moon et al., 2009; Plautz et al., 2003a; Teskey et al., 2003; Zheng et al., 2013; Zhou et al., 2010). For example, Teskey et al. (2003) demonstrated that bipolar stimulation at frequencies between 50 and 250 Hz significantly improved reaching success after 10 days of CS+reach training compared to non-stimulated trained controls (Teskey et al., 2003). Although stimulation frequencies over 25 Hz reduced the amount of current needed to drive involuntary motor movements, indicating that stimulation was having a neuromodulatory effect, daily CS at 25 Hz combined with pasta reach training was insufficient to maintain or improve reaching accuracy above control levels. Reach training combined with 50 Hz cathodal stimulation also significantly increases reaching accuracy compared to 50 Hz bipolar, anodal or no stimulation; however, all stimulation polarities increased forelimb movement representations area, determined using intracortical microstimulation motor mapping, compared to no stimulation controls (Kleim et al., 2003). In primates, 50 Hz bipolar stimulation during a digit reach to grasp task improved reaching performance and increased distal arm representation compared to nonstimulated animals (Plautz et al., 2003b). In rats, 50 Hz bipolar stimulation combined with reach training increases dendritic growth (Adkins-Muir and Jones, 2003; Zheng et al., 2013) and reduces peri-injury gliosis (Zheng et al., 2013) and in some cases promotes anti-apoptotic signaling (Zhou et al., 2010). Cathodal 100 Hz CS increases synaptogenesis in periinfarc cortex and significantly improves reaching accuracy and a return to normalized reaching movements (Adkins et al., 2008). These cathodal 100 Hz CS improvements in rats are enduring, resulting in improvements lasting for 9–10 months post-treatment and are linked to a reduction in stroke related cortical atrophy (O’Bryant et al., 2014). Thus, following stroke there seems to be a large range of high frequencies that when used with either cathodal or bipolar electrodes significantly improve forelimb function and structural and functional plasticity in the remaining motor cortex.

CS was also most beneficial when paired concurrently with task-specific practice on reaching tasks, i.e., its effects did not generalize to other motor behaviors that were not practiced during CS delivery (Adkins et al., 2006, 2008; Adkins-Muir and Jones, 2003). The effects appear to be due in part to greater normalization of reaching movement practiced during CS delivery and to the promotion of functionally useful compensatory movement
patterns (Adkins et al., 2008; O’Bryant et al., 2014). CS effects are likely also time
dependent. Most of animal studies in conducted in stroke mentioned above tested the
benefits of treatments initiated within the first 3–14 days following infarct (Adkins et al.,
2006, 2008; Adkins-Muir and Jones, 2003; Boychuk et al., 2011; Kleim et al., 2003; Moon
et al., 2009; Plautz et al., 2003a; Teskey et al., 2003; Zheng et al., 2013; Zhou et al., 2010).
Following stroke, when 100 Hz cathodal CS and reach training were delayed 3 months,
rehabilitative reach training improved motor function but CS did not further enhance
reaching performance (O’Bryant et al., 2014). It is likely, but not fully studied, that CS is
more efficacious early after infarct because the brain is more plastic after injury within the
first month (Biernaskie et al., 2004; Carmichael et al., 2005; Carmichael, 2006). It is
possible, but untested, that different stimulation parameters or CS combined with a more
robust rehabilitative training regime may overcome this time-sensitive limitation.

Injury severity is also a major variable in the efficacy of epidural CS. Cathodal 100 Hz CS is
less effective in rats following large middle cerebral artery occlusions (MCAO) compared to
smaller lesion models (Boychuk). Cathodal 100 Hz CS also was not effective in severely
impaired motor cortical stroke animals (Adkins et al., 2008) or following white matter
ischemic lesion (Boychuk et al., 2015). Likely, a certain level of remaining motor system
integrity must exist in order for CS to be effective. Data from clinical trials also suggest that
there must be at least minimal capacity for the injured hemisphere to drive motor
movements in order for CS to enhance recovery. Despite two early Phase I and II trials that
demonstrated potential efficacy of CS in stroke survivors (Brown et al., 2006; Levy et al.,
2008a, 2015), a larger Phase III trial failed to show benefit when all study subjects were
included in the analysis (Levy et al., 2008b, 2015) although more CS treated subjects
maintained improvements at 24 weeks post-treatment compared to controls (Levy). Further,
follow-up analysis revealed major motor improvements in a subset of participants in whom
CS was delivered in a manner consistent with the parameters found to be effective in the
small clinical trials and animal studies (Levy et al., 2015; Plow et al., 2009). In the animal
studies, CS was delivered at 50–70% of the thresholds needed to evoke involuntary motor
movement. In the clinical trials, CS current was set at 50% of movement thresholds, and
when movements could not be evoked, subjects were stimulated at a predefined maximum
current of 6.5 mA, half the maximum current output. The main difference between the
earlier clinical trials and the Phase III study was in the proportion of subjects in which hand
movements could be evoked. In the Phase I and II studies, movement thresholds were
evoked in 75% and 42% of subjects, respectively. In the Phase III study, only 14% of
subjects had stimulation-evoked movements in the hand, and it was this subset that had
major improvements (Levy et al., 2015). These data suggest that a minimum level of
corticospinal integrity is necessary for CS to be effective.

6. Cortical stimulation following TBI

There is a growing interest in the potential use of brain stimulation to facilitate recovery of
motor function following TBI (Adkins, 2015; Dhaliwal et al., 2015; Li et al., 2015). Until
recently, CS was thought to be potentially unsafe for TBI survivors given that TBIs often
result in a lower threshold for seizures. However, across injury models brain stimulation
techniques have produced only a few documented seizures and the few reported may be
related to injury severity (Dhaliwal et al., 2015). As interest grows in testing the safety and efficacy of brain stimulation in TBI patients, we must recognize that the stimulation and rehabilitation paradigms that are beneficial following stroke may not be so following TBI.

As briefly discussed above, we have reported that the mechanisms of experience dependent regeneration following experimental TBI are muted compared to similarly sized and placed ischemic strokes and result in blunted behavioral improvements following rehabilitative training (Adkins et al., 2015; Combs et al., 2015; Jefferson et al., 2015). As discussed above, CS delivered concurrent with rehabilitative training following experimental stroke results in robust behavioral improvements and neural remodeling over a range of frequencies and polarities, although with 100 Hz cathodal and 50 Hz bipolar combinations are the most well-studied combinations. We have recently reported that despite repeated studies demonstrating the benefit of 100 Hz cathodal stimulation combined with reaching training greatly improves motor function following stroke, its application to TBI recovery is less impressive. Cathodal 100 Hz CS combined with daily reach training for 9 weeks after a CCI over the motor cortex significantly improved motor performance and resulted in a larger ipsi-injury wrist motor map representation compared to untrained animals (Jefferson et al., 2015). However, the level of motor recovery is not robust compared to similar stroke studies, despite tripling the number of days of CS and reach training. This is reminiscent of our findings that rehabilitative training alone was insufficient to drive motor recovery after motor cortical CCI and required the addition of aerobic exercise to improve function. Through a series of studies, we have found that higher frequencies and bipolar stimulation improve motor performance compared to 100 Hz cathodal CS following experimental TBI (Clayton et al., submitted). At this time, it is still unclear what the optimal stimulation parameters are, although they are currently under systematic investigation. Likely in both animal and human studies what is most effective in stroke may not be so in TBI. In addition to systematically examining the optimized frequency, polarity and current level we also need to address the dose and timing of treatment. It may be that CS combined with rehabilitation may be more effective if separated by time, as is seen with immunotherapy treatment and reach training (Wahl et al., 2014). It may be that CS treatments need to be longer, begin earlier or later after injury or may need to include aerobic or strength training. Many of these questions are straightforward, but their translation from human to animal or vise versa may not be and careful study designs are needed. Further, a better understanding of the mechanisms of action of CS alone and when combined with skilled training will help us design more optimized CS treatments for TBI survivors. The differences between stroke and TBI motor cortex in response to experience, CS and behavioral practice, also point to fundamentally different neural repair mechanisms that exist between these two injury models that are ripe for further exploration.

7. Conclusion

A growing number of studies support that brain stimulation enhances motor function following stroke. Preliminary studies also support that neuromodulation of the TBI brain can improve motor function and alter neural plasticity, but we are just at the beginning of uncovering an optimized treatment regime for chronic TBI survivors. Many further studies are needed to determine effective brain stimulation protocols and a greater understanding of
mechanisms are needed to move this field from pre-clinical experiments to clinical application.

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References


