Towards Targeted Brain Stimulation in Stroke: Connectivity as a Biomarker of Response

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ABSTRACT: Stroke is a leading cause of adult disability. New treatments capable of assisting recovery hold significant potential to improve quality of life for many stroke survivors. Transcranial direct current stimulation is one technique that has received much attention due to its potential to promote neuroplasticity and enhance recovery. However, current evidence suggests this is not a one-size-fits-all treatment with indication that responses are highly variable. Using electroencephalography, Hordacre et al recently demonstrated that connectivity between the ipsilesional motor cortex, ipsilesional parietal cortex, and contralesional frontotemporal cortex was a strong predictor of the neurophysiological response to anodal transcranial direct current stimulation applied to the ipsilesional motor cortex in people with chronic ischemic stroke. Based on this outcome, we discuss the potential for connectivity to be used as a biomarker to target transcranial direct current stimulation. This includes identification of a connectivity threshold which could be used to select stroke survivors who are likely to respond to this potentially beneficial neuromodulatory treatment. Furthermore, we discuss treatment approaches for those identified as unlikely to benefit from ipsilesional anodal transcranial direct current stimulation based on connectivity profile. This represents an important progression towards targeting transcranial direct current stimulation for best treatment outcome based on individual connectivity characteristics.

KEYWORDS: Stroke, motor cortex, transcranial direct current stimulation, plasticity, electroencephalography, magnetic resonance imaging

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Stroke is a global leading cause of disability. In 2012, the World Health Organisation reported that there were 33 million stroke survivors living with persistent disability, requiring long-term care and secondary prevention measures.[1] Achieving independence in activities of daily living after stroke is, in-part, dependent on recovery of motor function, with restitution of function mediated by a process of functional or structural reorganisation in the brain known as neuroplasticity.[2] The current evidence indicates that most functional recovery happens within the first few months following stroke,[3] and this likely reflects spontaneous neurobiological processes occurring within days to weeks following stroke to create a critical period of enhanced neuroplasticity.[2] Identifying new approaches to deliver stroke rehabilitation is an area of research priority. Treatments capable of facilitating neuroplasticity in the brain have potential to accelerate sub-acute stroke recovery, or may be capable or re-establishing a period of enhanced neuroplasticity in chronic stroke survivors, similar to that seen early after stroke.[2]

Transcranial direct current stimulation (tDCS) is a technique thought to be capable of inducing neuroplasticity by non-invasively stimulating the brain and modulating cortical excitability. Transcranial direct current stimulation is thought to induce changes in postsynaptic activity, with effects of stimulation appearing to be polarity dependent. At the anode, tDCS depolarises the neuronal resting membrane potential which results in increased spontaneous firing rates and excitability.[4] At the cathode, tDCS hyperpolarises the resting membrane potential, resulting in decreased spontaneous firing rates and excitability.[4] Importantly, there is evidence to indicate that these changes in cortical activity can be observed beyond the period of stimulation with pharmacology studies demonstrating that the after-effects of tDCS are likely mediated by mechanism similar to long-term potentiation and long-term depression synaptic plasticity.[5] This ability to induce neuroplasticity and selectively modulate cortical function provides an opportunity to assist stroke recovery. For example, following stroke, the excitability of the ipsilesional hemisphere is reduced, and this is associated with greater impairment.[6] Non-invasive brain stimulation techniques, such as tDCS, have been used to increase excitability of the ipsilesional hemisphere, and there is some evidence that this results in improved motor function.[7] It may be that tDCS is a treatment that can greatly assist stroke recovery.

Despite the promising evidence suggesting that tDCS applied to the ipsilesional motor cortex may benefit stroke recovery, one issue that has limited potential for clinical translation is the substantial variability in responsiveness to this treatment. As a result, there is currently limited evidence to support the use of tDCS as an approach to facilitate neuroplasticity and improve response to rehabilitative training.[8] Further

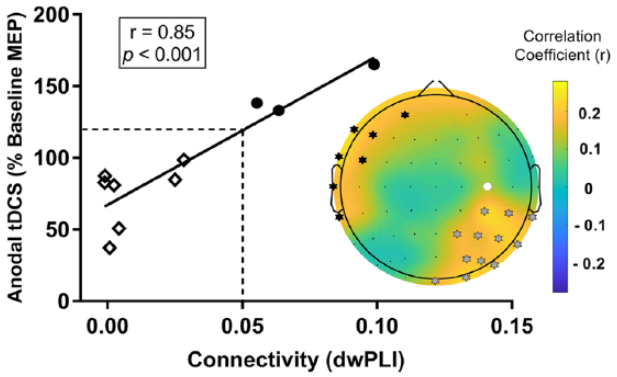

Figure 1. Connectivity with the ipsilesional motor cortex is greater in stroke participants who have an increase in MEP amplitude following anodal tDCS. The correlation analysis shows connectivity is positively correlated with increase in MEP amplitude. Cluster analysis identified two distinct groups with one demonstrating the anticipated increase in MEP amplitude following anodal tDCS (closed circles), while the other did not (open diamond). These two clusters can be separated using connectivity threshold of 0.05. Inset is the connectivity topographic plot model where connectivity between C4 (white circle) approximating the target lesioned M1, and two clusters of electrodes approximating the contralesional frontotemporal cortex (black stars) and ipsilesional parietal cortex (grey stars) in the alpha frequency band (8-13 Hz) predicted response to anodal tDCS.

understanding of dosage parameters, optimal electrode montages, and biomarkers to identify who is likely to benefit from tDCS is required. It may be that a biomarker could provide greater precision with which stimulation is applied by helping to individualise brain stimulation approaches to each participant.

Recently, it was shown that a measure of brain connectivity obtained using electroencephalography (EEG) was able to predict the neurophysiological response to anodal tDCS in chronic ischemic stroke survivors.[9] Participants who had stronger alpha band (8-13 Hz) connectivity, quantified with a conservative measure of connectivity (debiased weighted phase-lag index [dwPLI]) between the ipsilesional motor cortex, ipsilesional parietal cortex, and contralesional frontotemporal cortex prior to stimulation demonstrated the expected increase in motor cortical excitability following anodal tDCS applied to the ipsilesional motor cortex ($R^2 = 0.72$, leave-one-out and predict $R^2 = 0.58$; Figure 1). The addition of lesion volume, time since stroke, and age provided little improvement for predicting response to stimulation. Although performed in a relatively small sample of 10 chronic stroke survivors, this result provided a strong prediction of the neurophysiological response to anodal tDCS that appeared specific to this facilitatory stimulation as similar relationships were not observed for sham tDCS. This connectivity model was also robust across a range of thresholds used to generate the model. Therefore, it may be that this model of alpha band connectivity is an appropriate biomarker of response to anodal tDCS capable of identifying those likely to benefit most from this treatment.

This finding raises several questions for discussion. First, this result does not suggest that connectivity is a marker of improved motor function or reduced impairment but rather of the anodal tDCS-induced change in cortical excitability. The potential for connectivity to predict behavioural improvements to anodal tDCS is an area for further investigation.[10] However, this current result does provide some level of confidence to suggest that behavioural improvements may accompany tDCS-induced excitability change, at least, if the tDCS is applied in an appropriate way. That anodal tDCS can increase excitability of the ipsilesional motor cortex suggests that tDCS is able to induce long-term potentiation like synaptic plasticity in the post-stroke brain where connectivity profiles have a specific pattern to suggest potential benefit from stimulation. Previous studies have demonstrated that neuroplasticity underpins the restitution of function following stroke.[2] However, to observe behavioural improvements, it is probably critical that tDCS is paired with rehabilitative therapy to help establish new connections that are behaviourally beneficial and to ensure that meaningful movement patterns are reinforced. This is supported by a landmark study where rodents were found to have improved motor outcome following administration of a drug to promote neuroplasticity but only when drug dosing was paired with motor training.[11] For the rodents that were confined following administration of the drug, rate of recovery was reduced in comparison to those that received both the drug and training.[11] Since our previous study does suggest that tDCS can facilitate a period of enhanced neuroplasticity for people with specific patterns of EEG connectivity, it may be that behavioural improvements will be observed if this period of enhanced neuroplasticity is paired with training. Therefore, using measures of connectivity to identify stroke survivors likely to have the anticipated long-term potentiation like neuroplastic response to anodal tDCS may be the first step towards targeted brain stimulation to improve motor function.

A further point to consider is how a measure of connectivity obtained using EEG can be used as a biomarker to select stroke survivors who will benefit from tDCS in the future? While our previous study does provide a strong prediction of response to anodal tDCS using a leave-one-out and predict analysis, the EEG connectivity criteria that could be used to 'screen' stroke survivors to identify those likely to respond to this treatment are perhaps less clear. To help identify a potential threshold connectivity value, we performed a *k*-means cluster analysis to group responses to anodal tDCS. Further investigation of our data reveals two separate clusters for response to anodal tDCS. As expected, these two clusters separate participants who demonstrated the anticipated increase in motor evoked potential (MEP) amplitude following stimulation (145.5% ± 17.2% of baseline MEP amplitude) from those that did not (74.6% ± 22.0% of baseline MEP amplitude; Figure 1). A connectivity value that bisects between these two clusters is likely to be an appropriate initial approach to binarise connectivity values above or below a threshold to identify those likely to benefit for tDCS. In this case, an appropriate dwPLI threshold value may be 0.05, where values >0.05 indicate that a stroke

patient is likely to have the anticipated increase in cortical excitability following ipsilesional anodal tDCS, but if the values are <0.05, they may not (Figure 1). A threshold such as this could prove to be a valuable step towards targeting brain stimulation in people with stroke. However, we acknowledge that further work is required to validate a connectivity threshold, and it may be that additional biomarkers could be combined with this measure of connectivity to develop an algorithm to more accurately predict tDCS response on an individual basis.

Based on this observation, a dwPLI value >0.05 between the ipsilesional motor cortex, ipsilesional parietal cortex and contralesional frontotemporal cortex would indicate that anodal tDCS is likely to increase cortical excitability. While this result provides hope that tDCS can be targeted by using EEG functional connectivity as a biomarker to select stroke survivors likely to benefit from tDCS, the question remains whether tDCS can be of use for those with connectivity profiles suggesting they may not respond to stimulation. It is perhaps not surprising that lower connectivity with the ipsilesional motor cortex indicates that ipsilesional anodal tDCS may not be useful. Indeed, greater damage to the corticospinal tract after stroke is associated with greater movement-related activation of contralesional motor areas.[12] Reduced connectivity between the ipsilesional motor cortex, ipsilesional parietal cortex, and contralesional frontotemporal cortex may in-part reflect neural damage from the lesion. Therefore, it would appear plausible that applying stimulation to a different anatomical target could be appropriate in some stroke survivors. In support, alternative tDCS targets outside of the ipsilesional motor cortex have shown promise for improving motor function after stroke. For example, several studies have investigated contralesional motor cortex stimulation with both cathodal (inhibitory) and anodal (facilitatory) tDCS and reported gains in motor behaviour.[13,14] While the appropriate approach for stimulating the contralesional motor cortex (inhibitory vs facilitatory) is an area of active research, it may be that biomarkers such as functional connectivity can provide a foundation for individually selecting the most appropriate form of stimulation in this hemisphere. Furthermore, it has also been shown that tDCS applied to the cerebellum can modulate motor learning and cerebellar – motor cortex connectivity presumably via cerebella-thalamo-cortical pathways.[15] Although remote effects of the lesion may impact functional activity of different brain areas that are anatomically separate from the lesion site, it is likely that further characterisation of functional connectivity biomarkers for stimulation applied to either the contralesional motor cortex or cerebellum can help identify those likely to benefit from these alternative stimulation approaches. This outcome would represent a significant step towards tailoring tDCS treatments based on individual brain characteristics. It is likely that for treatments such as tDCS, clinical translation will require precision medicine–based approaches to tailor treatments to each individual to account for the heterogeneity observed in stroke.

It appears that ipsilesional anodal tDCS has the potential to induce neuroplasticity in people with stroke which may provide opportunity to achieve a more rapid and complete recovery of motor function. However, tDCS is not a one-size-fits-all treatment, and it appears that connectivity can provide a strong prediction of responsiveness to this treatment. Here, we have described how connectivity may be used as a biomarker to select those likely to benefit from ipsilesional anodal tDCS. Future studies should be conducted to explore the potential benefit of alternative stimulation targets for those unlikely to benefit from ipsilesional anodal tDCS.

Author Contributions

BH, BM, and MCR contributed to the paper and approved the final version.

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REFERENCES

1. Mendis S, Davis S, Norrving B. Organizational update: the World Health Organization global status report on noncommunicable diseases 2014; one more landmark step in the combat against stroke and vascular disease. *Stroke*. 2015;46:e121–e122.
2. Murphy TH, Corbett D. Plasticity during stroke recovery: from synapse to behaviour. *Nat Rev Neurosci*. 2009;10:861–872.
3. Prabhakaran S, Zarahn E, Riley C, et al. Inter-individual variability in the capacity for motor recovery after ischemic stroke. *Neurorehabil Neural Repair*. 2008;22:64–71.
4. Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: state of the art 2008. *Brain Stimul*. 2008;1:206–223.
5. Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain*. 2002;125:2238–2247.
6. Swayne OBC, Rothwell JC, Ward NS, Greenwood RJ. Stages of motor output reorganization after hemispheric stroke suggested by longitudinal studies of cortical physiology. *Cereb Cortex*. 2008;18:1909–1922.
7. Lindenberg R, Renga V, Zhu LL, Nair D, Schlaug G. Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. *Neurology*. 2010;75:2176–2184.
8. Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in people after stroke. *Cochrane Database Syst Rev*. 2016;3:CD009645.
9. Hordacre B, Moezzi B, Ridding MC. Neuroplasticity and network connectivity of the motor cortex following stroke: a transcranial direct current stimulation study. *Hum Brain Mapp*. 2018;39:3326–3339.
10. Welsby E, Ridding M, Hillier S, Hordacre B. Connectivity as a predictor of responsiveness to transcranial direct current stimulation in people with stroke: protocol for a double-blind randomized controlled trial. *JMIR Res Protoc*. 2018;7:e10848.
11. Feeney DM, Gonzalez A, Law WA. Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. *Science*. 1982;217:855–857.
12. Lotze M, Beutling W, Loibl M, et al. Contralesional motor cortex activation depends on ipsilesional corticospinal tract integrity in well-recovered subcortical stroke patients. *Neurorehabil Neural Repair*. 2012;26:594–603.
13. McCambridge AB, Stinear JW, Byblow WD. Revisiting interhemispheric imbalance in chronic stroke: a tDCS study. *Clin Neurophysiol*. 2018;129:42–50.
14. Khedr EM, Shawky OA, El-Hammady DH, et al. Effect of anodal versus cathodal transcranial direct current stimulation on stroke rehabilitation: a pilot randomized controlled trial. *Neurorehabil Neural Repair*. 2013;27:592–601.
15. Grimaldi G, Argyropoulos GP, Bastian A, et al. Cerebellar transcranial direct current stimulation (ctDCS): a novel approach to understanding cerebellar function in health and disease. *Neuroscientist*. 2016;22:83–97.