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# Bidirectional interactions between neuronal and hemodynamic responses to transcranial direct current stimulation (tDCS): challenges for brain-state dependent tDCS

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1           **Bidirectional interactions between neuronal and hemodynamic**  
2           **responses to transcranial direct current stimulation (tDCS): challenges**  
3           **for brain-state dependent tDCS**

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12           **Abstract**

13           Transcranial direct current stimulation (tDCS) has been shown to modulate cortical neural activity.  
14           During neural activity, the electric currents from excitable membranes of brain tissue superimpose in  
15           the extracellular medium and generate a potential at scalp, which is referred as the  
16           electroencephalogram (EEG). Respective neural activity (energy demand) has been shown to be  
17           closely related, spatially and temporally, to cerebral blood flow (CBF) that supplies glucose (energy  
18           supply) via neurovascular coupling. The hemodynamic response can be captured by near-infrared  
19           spectroscopy (NIRS), which enables continuous monitoring of cerebral oxygenation and blood  
20           volume. This neurovascular coupling phenomenon led to the concept of neurovascular unit (NVU)  
21           that consists of the endothelium, glia, neurons, pericytes, and the basal lamina. Here, recent works  
22           suggest NVU as an integrated system working in concert using feedback mechanisms to enable  
23           proper brain homeostasis and function where the challenge remains in capturing these mostly  
24           nonlinear spatiotemporal interactions within NVU for brain-state dependent tDCS. In principal  
25           accordance, we propose EEG-NIRS-based whole-head monitoring of tDCS-induced neuronal and  
26           hemodynamic alterations during tDCS.

27           **Challenges in clinical translation of transcranial brain stimulation - an introduction**

28           Transcranial direct current stimulation (tDCS) - an electrically based intervention directed at the  
29           central nervous system level - is a promising tool to alter cortical excitability and facilitate  
30           neuroplasticity (Nitsche and Paulus, 2011). However, inter-subject variability and intra-subject  
31           reliability currently limits clinical translation (Horvath et al., 2014). Indeed, a recent meta-analysis  
32           showed that the treatment effects of transcranial brain stimulation in patients with stroke are rather  
33           inconsistent across studies and the evidence for therapeutic efficacy is still uncertain (Raffin and  
34           Siebner, 2014). Here, it may be possible to reduce inter-subject variability and improve intra-subject  
35           reliability using simultaneous neuroimaging that can objectively quantify the individual brain-state  
36           before and during tDCS. Non-invasive neuroimaging techniques that have previously been combined  
37           with tDCS include electrophysiological, e.g., EEG (Schestatsky et al., 2013) and haemodynamic,  
38           e.g., functional magnetic resonance imaging (fMRI) (Meinzer et al., 2014) and NIRS (McKendrick et  
39           al., 2015) approaches. Here, NIRS presents several advantages relative to fMRI, such as  
40           measurement of concentration changes in both oxygenated (HbO<sub>2</sub>) and deoxygenated (HHb)  
41           hemoglobin, finer temporal resolution, ease of administration and relative insensitivity to movement

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42 artefacts. Although fMRI has become the benchmark for in-vivo imaging of the human brain, in  
43 practice, NIRS and EEG are more convenient and less expensive technology than fMRI for  
44 simultaneous neuroimaging for brain-state dependent tDCS. However, the challenge remains in  
45 modeling whole-head spatiotemporal coupling of neuronal and hemodynamic alterations induced by  
46 tDCS where such brain-state dependent tDCS needs not only to consider the brain as a dynamical  
47 system but also need to consider that its parameters will be inter-individually heterogeneous,  
48 dependent on brain injury (and maladaptive plasticity, e.g., reactive gliosis (Buffo et al., 2008)), task  
49 characteristics (e.g., attention issues) and other factors (Raffin and Siebner, 2014).

## 50 Biophysical models for capturing hemodynamic alterations induced by tDCS

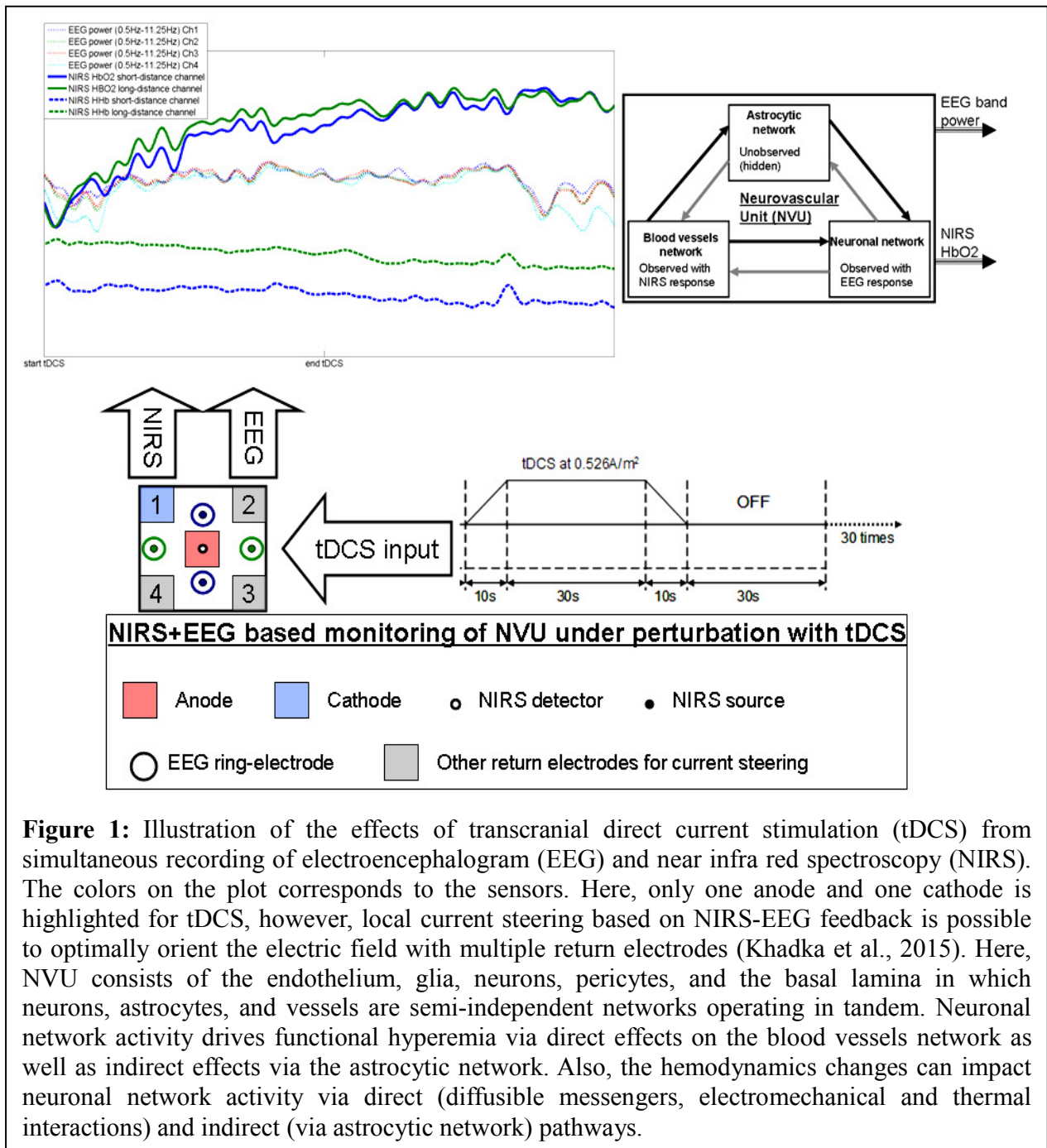
51 Neural activity has been shown to be closely related, spatially and temporally, to cerebral blood flow  
52 (CBF) that supplies glucose via neurovascular coupling (Girouard and Iadecola, 2006). The  
53 hemodynamic response to neural activity can be captured by near-infrared spectroscopy (NIRS),  
54 which enables continuous monitoring of cerebral oxygenation and blood volume (Siesler et al.,  
55 2008). The regulation of CBF and its spatiotemporal dynamics may be probed with short-duration  
56 anodal tDCS which challenges the system with a vasoactive stimulus in order to observe the system  
57 response. Based on prior works (Nitsche and Paulus, 2000)(Dutta et al., 2015), such short-duration  
58 (<1min) anodal tDCS is postulated to cause no aftereffects and may be used to probe neurovascular  
59 coupling (and NVU) (Jindal et al., 2015b). Here, CBF is increased in brain regions with enhanced  
60 neural activity via metabolic coupling mechanisms (Attwell et al., 2010) while cerebral  
61 autoregulation mechanisms ensure that the blood flow is maintained during changes of perfusion  
62 pressure (Lucas et al., 2010). During such a short-duration anodal tDCS experiment, cerebrovascular  
63 reactivity (CVR) can be measured as the change in CBF per unit change in relation to anodal tDCS  
64 intensity. Moreover, the rate of change of hemodynamic responses to same tDCS intensity may  
65 explain inter-individual differences in tDCS after-effects (Han et al., 2014). Also, phenomenological  
66 model for metabolic coupling mechanisms (Attwell et al., 2010) can be used to capture CVR that  
67 represents the capacity of blood vessels to dilate during anodal tDCS due to neuronal activity-related  
68 increased demands of oxygen (Dutta et al., 2013). Here, CVR reflects the capacity of blood vessels to  
69 dilate, and is an important marker for brain vascular reserve (Markus and Cullinane, 2001). Indeed  
70 pressure-perfusion-cognition relationships may be monitored with the brain vascular reserve  
71 (Novak, 2012) where the CVR distributes CBF toward the brain areas in need of increased perfusion  
72 due to enhanced neural activity.

73  
74 Prior work has shown a significant correlation between tDCS current strength and increase in  
75 regional CBF in the on-period relative to the pre-stimulation baseline (Zheng et al., 2011). We  
76 investigated regional CVR during anodal tDCS by adapting an arteriolar compliance model of the  
77 cerebral blood flow response to a neural stimulus (Behzadi and Liu, 2005). Regional CVR was  
78 defined as the coupling between changes in CBF and cerebral metabolic rate of oxygen (CMRO<sub>2</sub>)  
79 during anodal tDCS-induced local brain activation (Leontiev and Buxton, 2007). The complex path  
80 from the tDCS-induced change of the synaptic transmembrane current,  $u(t)$  (only excitatory effects  
81 considered) (Molaei-Ardekani et al., 2013) to a change in the concentration of multiple vasoactive  
82 agents (such as NO, potassium ions, adenosine), represented by a single vascular flow-inducing  
83 vasoactive signal,  $s$ , was captured by a first-order Friston's model (Friston et al., 2000). Chander and  
84 Chakravarthy (Chander and Chakravarthy, 2012) presented a computational model that studied the  
85 effect of metabolic feedback on neuronal activity to bridge the gap between measured hemodynamic  
86 response and ongoing neural activity. Here, the NVU (see Figure 1) consists of the endothelium, glia,  
87 neurons, pericytes, and the basal lamina that has been proposed to maintain the homeostasis of the  
88 brain microenvironment (Iadecola, 2004). In this connection, the role of lactate as a signaling

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89 molecule was described recently (Yang et al., 2014), which supports a (delayed) “reverse” influence  
90 in the NVU from the vessel back to neuron via lactate (Chander and Chakravarthy, 2012). Recently, a  
91 detailed biophysical model of the brain’s metabolic interactions was presented by Jolivet et al.  
92 (Jolivet et al., 2015). This not only supported the astrocyte-neuron lactate shuttle (ANLS) hypothesis  
93 that the lactate produced in astrocytes (a type of glial cell) can also fuel neuronal activity but it also  
94 provided a quantitative mathematical description of the metabolic activation in neurons and glial  
95 cells, as well as of the macroscopic measurements obtained during brain imaging. Indeed, this model  
96 captured the pattern of neurovascular responses observed in rodents in response to sustained sensory  
97 stimulation where CBF only starts to increase above its baseline ~0.5–1 sec after the onset of  
98 stimulation (Jolivet et al., 2015). We also found such onset effects (called "initial dip") of anodal  
99 tDCS in stroke patients (Dutta et al., 2015). Moreover, Jolivet et al. (Jolivet et al., 2015) highlighted  
100 the neuron-astrocyte cross-talk during oscillations linked to blood oxygenation levels (DiNuzzo et al.,  
101 2011) where such oscillations also occurred after anodal tDCS-based perturbation of the neuroglial  
102 networks in our EEG-NIRS stroke study (Dutta et al., 2015). We therefore postulate that short-  
103 duration anodal tDCS can be used to perturb neuroglial networks in health and disease to probe the  
104 spatiotemporal dynamics of the NVU based on simultaneous EEG-NIRS neuroimaging (Dutta, 2014)  
105 (Dutta et al., 2015) and biophysical model (Jolivet et al., 2015) based analysis.

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106

### 107 Neural mass or field models for capturing neuronal alterations induced by tDCS

108 During neural activity, the electric currents from excitable membranes of brain tissue superimpose at  
 109 a given location in the extracellular medium and generate a potential, which is referred to as the EEG  
 110 (Nunez and Srinivasan, 2006). Here, neural mass models (NMM) can provide insights into the  
 111 neuromodulatory mechanisms underlying alterations of cortical activity induced via tDCS (Molaei-  
 112 Ardekani et al., 2013). Specifically, the origin of tDCS-induced alterations in the EEG power  
 113 spectrum was captured using a thalamocortical NMM (Dutta and Nitsche, 2013). The NMM for a  
 114 single cortical source comprises of 4 neuronal subpopulations, excitatory pyramidal neurons (ePN),  
 115 excitatory interneurons (eIN), slow inhibitory interneurons (siIN), and fast inhibitory interneurons

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116 (fiIN) (Zavaglia et al., 2006). The NMM for the cortical source was coupled with another  
117 representing the thalamus (Sotero et al., 2007), which comprises of 2 neuronal subpopulations - an  
118 excitatory thalamocortical (eTCN) and an inhibitory reticular-thalamic (iRT). The basis of our  
119 cortical NMM is the Friston model (Moran et al., 2007) that emulates the activity of a cortical area  
120 using three neuronal subpopulations, ePN, eIN, and siIN. A population of ePN (output) cells receives  
121 inputs from inhibitory and excitatory populations of interneurons via intrinsic connections (intrinsic  
122 connections are confined to the cortical sheet). An extrinsic thalamo-cortico-thalamic loop consists  
123 of eTCN and iRT in the thalamic NMM (Ursino et al., 2010). Our lumped thalamo-cortico-thalamic  
124 network model can be used to simulate the subject-specific EEG power spectral density changes  
125 during/following tDCS (Dutta and Nitsche, 2013) by modifying the model parameters (e.g., average  
126 gain of synapses, their time constants) (Zavaglia et al., 2006). We found that anodal tDCS enhances  
127 activity and excitability of the excitatory pyramidal neuron at a population level in a non-specific  
128 manner and mu-rhythm desynchronization is generated (Dutta and Nitsche, 2013). The tDCS effects  
129 on the population kinetics depend on the direction of cortical current flow determining the relative  
130 influence of acute tDCS on the cellular targets responsible for modulation of synaptic efficacy, which  
131 are primarily somata and axon terminals (Rahman et al., 2013). Basal and apical dendrites can be  
132 concomitantly polarized in opposite directions, and Layer V pyramidal neurons exhibit the highest  
133 measured somatic sensitivities to subthreshold fields (Rahman et al., 2013). Therefore, not all neural  
134 tissue will be equally affected by a given stimulation protocol which may distinctly affect neuronal  
135 populations/neuronal compartments. Indeed, a recent computational modeling study suggested that  
136 tDCS may induce opposing effects on different types of interneurons (Molae-Ardekani et al., 2013).  
137 Here, the excitation versus inhibition effects (Krause et al., 2013) of tDCS on the population kinetics  
138 can produce a whole spectrum of EEG signals within the oscillatory regime of a neural mass model  
139 (David and Friston, 2003).

140 There are several prior works that have shown both "online" effects of tDCS on EEG with EEG  
141 performed during tDCS as well as "offline" effects with EEG performed after tDCS. Here, it is  
142 important to separate studies where tDCS is applied during a rest state (Ardolino et al., 2005) (Zaehle  
143 et al., 2011) (Spitoni et al., 2013) or an active task state (Matsumoto et al., 2010) (Mangia et al.,  
144 2014). We computationally found (Dutta and Nitsche, 2013) in concordance with the experimental  
145 results of Matsumoto et al. (Matsumoto et al., 2010) that tDCS effects on mu-rhythm  
146 desynchronization depend on the direction of cortical current flow determining the relative influence  
147 of acute tDCS on the cellular targets. Matsumoto et al. (Matsumoto et al., 2010) found that tDCS  
148 applied over the left primary motor area for 10min at 1mA with a 35cm<sup>2</sup> electrode influenced event-  
149 related desynchronization (ERD) during right hand grasping where the mu ERD increased after  
150 anodal tDCS and decreased after cathodal tDCS. Here, not only the "local" effects but the "distant"  
151 effects of tDCS are also relevant where Polanía et al. (Polanía et al., 2012) reported that the  
152 functional connectivity patterns significantly increased after anodal tDCS (i.e., "offline" effects) over  
153 the primary motor cortex where tDCS modulated functional connectivity of cortico-striatal and  
154 thalamo-cortical circuits. Notturmo et al. (Notturmo et al., 2014) showed spatial diffusion of anodal  
155 tDCS (during a motor task) effects where an increment of low alpha band power over the course of  
156 pre- and post-stimulation recording sessions was found during motor task that was localized in the  
157 sensorimotor and parieto-occipital regions. Indeed, not only the "offline" effects, but changes in  
158 functional connectivity patterns may start evolving during tDCS (i.e., "online" effects) as shown by  
159 our modeling study (Dutta and Nitsche, 2013). tDCS/EEG co-registration studies have shown that  
160 anodal tDCS mostly modulate spontaneous cortical activity in the alpha band where alpha-rhythm  
161 states have a significant effect on perceptual learning (Sigala et al., 2014). In fact, more than 60% of  
162 the observed inter-subject variability in perceptual learning can be ascribed to ongoing alpha activity  
163 where Sigala et al. (Sigala et al., 2014) highlighted the need for multidisciplinary approaches

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164 combining assessment of behavior and multi-scale neuronal activity, active modulation of ongoing  
165 brain states and computational modeling to reveal the mathematical principles of the complex  
166 neuronal interactions. We therefore postulate that concurrent EEG-NIRS-based neuroimaging of the  
167 short-duration tDCS-induced modulation can be analyzed by combining a biophysical model (Jolivet  
168 et al., 2015) of the NVU with the computational model (neural mass or field model) of multi-scale  
169 neuronal activity of the whole brain (Sigala et al., 2014) to capture the spatiotemporal dynamics of  
170 the interactions between the neuronal and hemodynamic responses in health and disease. Here, the  
171 challenges remain in ensuring the observability of the NVU with intelligent placement of EEG-NIRS  
172 sensors since presence of symmetry in the nonlinear network of NVU (see Figure 1) may decrease  
173 observability (although networks containing only rotational symmetries remain observable) (Whalen  
174 et al., 2015).

### 175 **Bidirectional interactions between neuronal and hemodynamic responses to tDCS - a discussion**

176 In our prior work (Dutta et al., 2015), we found an initial dip in the oxy-haemoglobin concentration  
177 and concomitant increase in the mean power spectral density within lower (<12Hz) EEG frequency  
178 band. It was postulated that the immediate need to fuel neuronal energy recovery was via the lactate  
179 shuttle (Pellerin and Magistretti, 1994) where blood glucose supply has a longer delay (Gruetter et  
180 al., 1996). A detailed biophysical model of the brain's metabolic interactions by Jolivet et al. (Jolivet  
181 et al., 2015) also supported the ANLS hypothesis. Moreover, recent works showed that lactate can  
182 modulate the activity of primary cortical neurons through a receptor-mediated pathway (Bozzo et al.,  
183 2013) and vasomotion rhythms can influence neural firing patterns (Nikulin et al., 2014). Also,  
184 lactate promotes plasticity gene expression by potentiating NMDA signaling in neurons, and the  
185 action of lactate is mediated by the modulation of NMDA receptor activity (Yang et al., 2014). These  
186 dynamic ANLS interactions leave us to question its role in tDCS facilitated neuroplasticity and  
187 learning (Suzuki et al., 2011). Also, the spatiotemporal dynamics of the millisecond-to-second-range  
188 direct (diffusible messengers, electromechanical and thermal interactions) and seconds-to-tens-of-  
189 seconds-range indirect interaction in the NVU following tDCS, i.e. the hemo-neural hypothesis  
190 (Moore and Cao, 2008), may at least partially explain the time course of the induction of homeostatic  
191 plasticity generated by repeated tDCS of the human motor cortex (Fricke et al., 2011). Fricke and  
192 coworkers (Fricke et al., 2011) hypothesized a role of L-type voltage-gated Ca<sup>2+</sup> channels (L-  
193 VGCC) in short-term homeostatic plasticity, since tDCS has been shown to induce a long-lasting  
194 disturbance of Ca<sup>2+</sup> homeostasis (Islam et al., 1995) and induce calcium-dependent plasticity  
195 (Nitsche et al., 2003). Here, the glial network may have an important role (i.e., spatial buffering) in  
196 regulating neural activity by distributing ions (Halmes et al., 2013) in seconds-to-tens-of-seconds-  
197 range where an influence of long-lasting disturbance of Ca<sup>2+</sup> homeostasis via tDCS on the myogenic  
198 and the metabolic control of cerebral circulation cannot be excluded. In fact, astrocytes, a sub-type of  
199 glia in the central nervous system, can integrate a large number of synapses and can respond to  
200 neuronal activity via neurotransmitter-evoked activation of astrocytic receptors (Araque et al., 2001).  
201 Indeed, neuronal activity can mobilize internal calcium in astrocytes and the calcium wave in  
202 different spatial-temporal dimensions can result in a higher level of brain integration (Volterra et al.,  
203 2014) where the evidence for tDCS-induced large scale changes in brain synchronization and  
204 topological functional organization has been shown after acute stimulation (Polanía et al., 2011).

205  
206 Based on these prior works, we recently proposed EEG-NIRS-based monitoring of neurovascular  
207 coupling functionality under perturbation with tDCS (Jindal et al., 2015b). Here, neuronal and  
208 hemodynamic responses measured with EEG-NIRS neuroimaging can be represented abstractly as  
209 the system response of the NVU to tDCS perturbation (see Figure 1) where presence of symmetry in

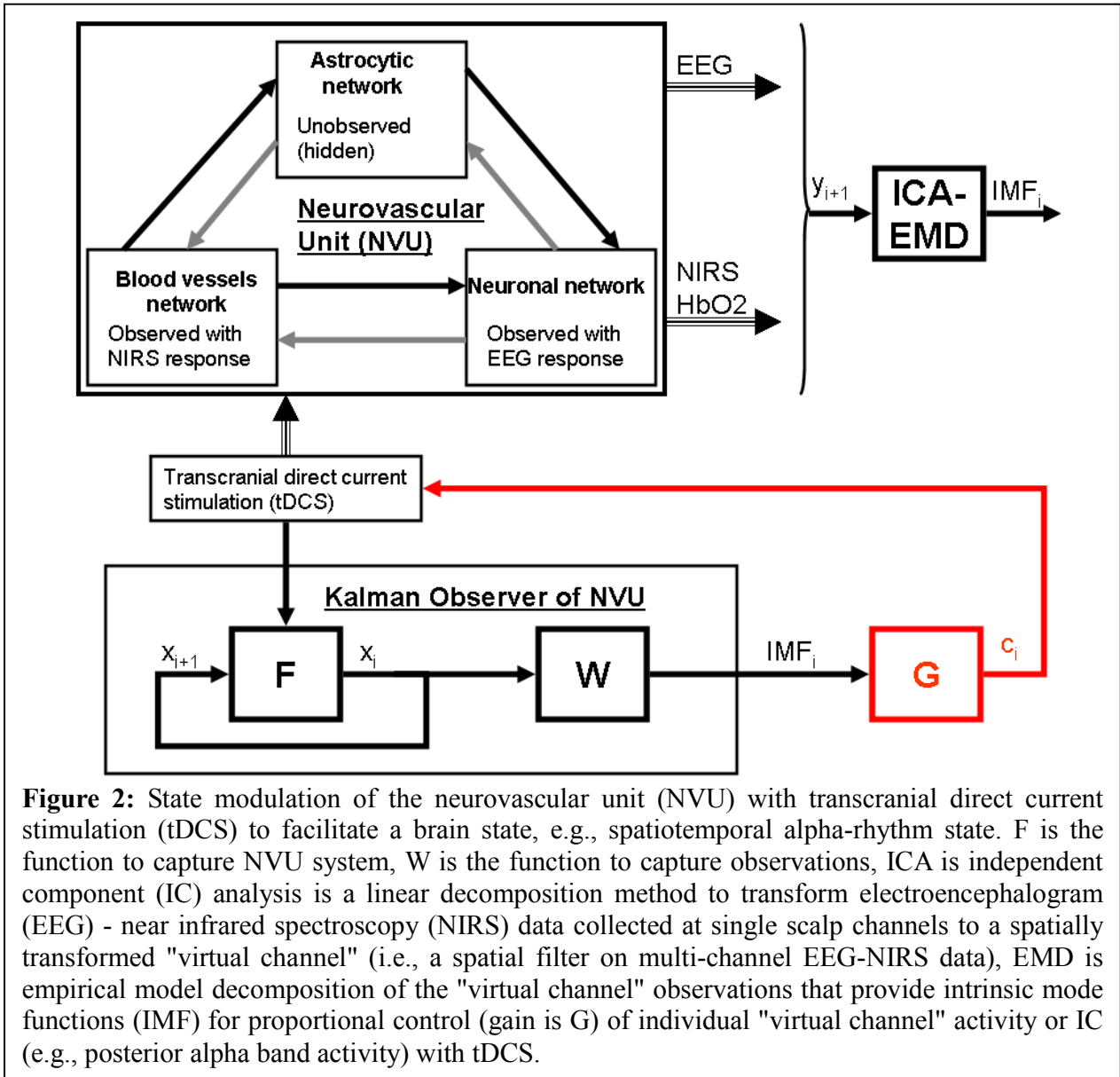
### Hemo-neural hypothesis for brain-state dependent tDCS

210 the nonlinear network of NVU (see Figure 1) may decrease observability (Whalen et al., 2015). Since  
211 no real-world network has exact symmetries so with intelligent placement of EEG-NIRS sensors (e.g.  
212 to avoid systemic interference (Sood et al., 2015)) along with system identification and parameter  
213 estimation techniques, it may be possible to track the spatiotemporal change of the states of the NVU.  
214 This observer model can then be used to drive multi-electrode tDCS (Dmochowski et al., 2011) for  
215 active spatiotemporal modulation of the brain states (e.g., posterior alpha-rhythm). Here, we base our  
216 discussions on the recent advances in Kalman filtering approaches to spatiotemporal nonlinear  
217 systems (Schiff and Sauer, 2008) and an understanding from group representation theory in controller  
218 or observer design by obtaining a modal decomposition into decoupled controllable and  
219 uncontrollable (observable and unobservable) subspaces (Whalen et al., 2015). Specifically, Schiff  
220 and Sauer (Schiff and Sauer, 2008) showed the feasibility of unscented Kalman filter (UKF) for  
221 recursive estimation of system state for nonlinear systems, including unobserved variables and  
222 parameter tracking, in a spatiotemporal model of cortex where such a nonlinear system is controllable  
223 using an adaptive feedback electrical field. Here, discretization of the whole-brain detailed  
224 biophysical model of NVU (Jolivet et al., 2015), for example with Galerkin methods that are used  
225 quite robustly in fluid dynamics, will be necessary where each discrete element corresponds to a  
226 volume of tissue imaged as well as stimulated with the EEG-NIRS/tDCS unit (see Figure 1). As an  
227 alternative to a fundamental NVU model (Jolivet et al., 2015) for the volume of tissue imaged and  
228 stimulated with EEG-NIRS/tDCS unit, we tried (Dutta et al., 2015) to find an empirical model where  
229 we performed empirical mode decomposition (EMD) and the Hilbert spectrum (Huang et al., 1998)  
230 to model the system dynamics and found a negative cross-correlation between one of the intrinsic  
231 mode function (IMF) of the HbO<sub>2</sub> time-series and log-transformed mean-power time-course of EEG  
232 primarily within 0.5Hz-11.25Hz frequency band (i.e., one of the EEG IMFs). In principal accordance,  
233 for whole-head monitoring, we propose independent component analysis (ICA) to transform multi-  
234 channel EEG-NIRS/tDCS unit imaging data to a spatially transformed "virtual channel" (i.e., a  
235 spatial filter) (Jung et al., 2001). Then, the "virtual channel" activity (e.g., posterior alpha band  
236 activity) can be subjected to EMD (i.e., a temporal filter) to reduce the dimension of the observable  
237 dynamics (i.e., further observer model reduction) before developing the Kalman filter observer  
238 (Schiff and Sauer, 2008) using the IMFs. For EEG-NIRS-based monitoring of NVU under  
239 perturbation with tDCS, as shown in the Figure 2, the NVU dynamics is captured by the function  $F$   
240 and the IMF observations by the function  $W$ . The UKF approach should match the nonlinear IMF  
241 dynamics up to the second order statistics where the feasibility remains to be tested experimentally in  
242 future studies. Furthermore, it may be possible to use the Kalman observer to calculate proportional  
243 control (see Figure 2) of the brain-state (e.g., cortical excitability (Jindal et al., 2015a)) with tDCS.  
244 Here, intelligent placement of EEG-NIRS sensors and tDCS effectors is necessary to ensure  
245 observability and controllability (Whalen et al., 2015) where Whalen et al. (Whalen et al., 2015)  
246 suggested in general that more direct incoming connections into an observed node lead to higher  
247 observability and more direct outgoing connections from a controlled node lead to higher  
248 controllability. Furthermore, controllability may be enhanced with multi-modal non-invasive brain  
249 stimulation (NIBS), e.g. with direct electrical stimulation (Pulgar, 2015) and photobiostimulation  
250 (Gonzalez-Lima and Barrett, 2014), which needs to be investigated.



## Hemo-neural hypothesis for brain-state dependent tDCS

251 Towards such brain-state dependent tDCS, the challenges include the nature of observability and  
 252 controllability in whole-brain complex NVU networks as well as the subtleties of the tDCS  
 253 interaction with the whole-brain NVU (e.g., based on heterogeneous geometrical characteristics  
 254 (Molae-Ardekani et al., 2013)) that can also have multi-timescale cross-talk and resulting complex  
 255 non-linear dynamics (Jolivet et al., 2015) where the spatiotemporal observability and controllability  
 256 remains to be verified in future studies.  
 257



258

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### 470 **Figure legends**

471 **Figure 1:** Illustration of the effects of transcranial direct current stimulation (tDCS) from  
472 simultaneous recording of electroencephalogram (EEG) and near infra red spectroscopy (NIRS). The  
473 colors on the plot corresponds to the sensors. Here, only one anode and one cathode is highlighted for  
474 tDCS, however, local current steering based on NIRS-EEG feedback is possible to optimally orient  
475 the electric field with multiple return electrodes (Khadka et al., 2015). NVU consists of the  
476 endothelium, glia, neurons, pericytes, and the basal lamina in which neurons, astrocytes, and vessels  
477 are semi-independent networks operating in tandem. Neuronal network activity drives functional  
478 hyperemia via direct effects on the blood vessels network as well as indirect effects via the astrocytic  
479 network. Also, the hemodynamics changes can impact neuronal network activity via direct (diffusible  
480 messengers, electromechanical and thermal interactions) and indirect (via astrocytic network)  
481 pathways.

482  
483 **Figure 2:** State modulation of the neurovascular unit (NVU) with transcranial direct current  
484 stimulation (tDCS) to facilitate a brain state, e.g., spatiotemporal alpha-rhythm state.  $F$  is the function  
485 to capture NVU system,  $W$  is the function to capture observations, ICA is independent component  
486 (IC) analysis is a linear decomposition method to transform electroencephalogram (EEG) - near  
487 infrared spectroscopy (NIRS) data collected at single scalp channels to a spatially transformed  
488 "virtual channel" (i.e., a spatial filter on multi-channel EEG-NIRS data), EMD is empirical model  
489 decomposition of the "virtual channel" observations that provide intrinsic mode functions (IMF) for  
490 proportional control (gain is  $G$ ) of individual "virtual channel" activity or IC (e.g., posterior alpha  
491 band activity) with tDCS.