Brain Connectivity

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Results obtained by combining different estimators of EEG connectivity become uninterpretable if the underlying models are incompatible

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Running head: Limited combinability of EEG connectivity models

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Abstract

We comment on a recent paper published in Brain Connectivity (Hatz et al. 2016) that combined EEG microstate analysis with the phase locking index and found that the test-retest reliability of connectivity patterns as obtained by the phase locking index increased when the data had been previously parcellated into microstates. While we acknowledge the need to parcellate the continuous data into periods that supposedly correspond to transiently stable patterns of connectivity, we believe that the approach chosen by the authors is seriously mistaken. In particular, their approach disregards the particular a-priori assumptions contained in each of the two methods that define connectivity in specific terms. Unfortunately, for microstate analyses and the phase locking index, these definitions are mutually exclusive, which makes attempts to draw any coherent conclusion in terms of comprehensibly interlinked biological processes meaningless. The occurrence of this type of problems should draw the attention to the importance of the particular methodological and conceptual features and limitations that come with the specific a-priori assumptions contained in any quantifier of brain functional connectivity.

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Dear Editor,

It was with great interest that we read the recently published paper by Hatz and colleagues in Brain Connectivity (Hatz et al. 2016) entitled "Reliability of functional connectivity of EEG applying microstates-segmented versus classical calculation of phase lag index". The paper rightfully argues that measures of brain connectivity based on frequency domain indices of connectivity may be problematic, because these measures assume the signals to be stationary during the usually arbitrarily selected analysis windows. For the analysis of connectivity, it may thus be more appropriate to apply data-driven parcellation procedures that identify time periods that assumingly consist of singular and transiently stable patterns of connectivity before these patterns of connectivity are further quantified. This point is well taken, and it certainly worthwhile and timely to address. At the same time, any decomposition of the EEG, and thus also any analysis of connectivity among EEG subcomponents, requires specific a-priori models that define what constitutes a component, and how different components can be uniquely isolated. Departing from very different choices of how such separations may be obtained and justified, the currently available methodology offers several methods to quantify brain functional connectivity based on resting-state EEG data. When combining methods that assess brain connectivity, it is thus essential that we are aware of these a-priori choices, because they imply very different definitions of what constitutes "being connected".

The paper we are commenting on used a combination of two methods to investigate brain connectivity, namely so called microstate analysis (Pascual-Marqui et al. 1995) and the phase locking index (PLI, Stam et al. 2007). The authors reported that when EEG data was parcellated into time periods that correspond to the presence of particular microstates, i.e. time periods of quasi-stable scalp field configuration, the test-retest reliability of connectivity patterns as obtained by the analysis of lagged coherence increased. If this increase is to be meaningful, there must thus be a systematic relationship between what is contained in the two formal definitions of microstates and lagged coherence. And here is where we think that the mentioned paper runs into a contradiction, because the definition

of what constitutes "being connected" in the microstate model is by definition incompatible with the definition of connectivity in based on the PLI measure. Let us briefly review what the a-priori assumptions of the two methods contain:

- The microstate model, as developed by Pascual-Marqui (Pascual-Marqui et al. 1995) and as employed in the criticized publication, is a particular solution to the general mixing problem of the EEG, where the observed voltage distribution is accounted for by a weighted sum of voltage vectors that each represents a putative brain functional state (Koenig and Wackermann 2009):

$$V_t = \sum_{k=1}^{N_\mu} a_{kt}\Gamma_k + E_t$$

where V_t is the voltage vector of measurements at time t, Γ_k is the normalized voltage vector representing the spatial distribution of the k – th microstate, a_{kt} is the intensity of the k – th state at time t and E_t is the residual variance. Since this problem is underdetermined, further a – priori objectives need to be introduced. The microstate model of Pascual – Marqui achieves uniqueness of the solution to the above mixing problem by minimizing the residual variance E_t under the constraint that all but one a_{kt} are zero. Microstates of class k are then defined as continuous periods of time where for a given k, a_{kt} is non-zero. Thus, what defines a particular microstate in voltage vector V_t is solely determined by the constant voltage vector Γ_k and the modulation of the length of that vector by the non-zero time-varying scaling factor a_{kt}. Data that cannot be accommodated into such a framework is accounted for by an unspecific noise term, and does not contribute to the definition of microstates. Thus, the model divides the data into two subspaces: The typically larger of these subspaces defines a microstate, and implies at the same time that all scalp signals have the same time course, and thus the same phase, because all channels are commonly and solely modulated by the dynamics of a_{kt}, and is to be maximized. The second subspace does not contribute to the definition of a microstate, and allows for any kind of dynamics across channels. Importantly, on the source level, the microstate model implies that what defines a microstate is either a single source that drives all electrodes thru volume conduction and thus produces scalp signals with the same time courses, or a

set of sources that share, in a non-lagged fashion, a common dynamics in time that is observable on the scalp as a spatially constant mixture of the forward solution of these sources. Thus, the definition of a microstate does not allow for significant phase differences (except 180˚), neither in source not in scalp signal space. And as the explanation of a microstate by a single point source is not very plausible in normal resting states, the microstates model entails the existence of a form of connectivity that is defined by common, non-lagged dynamics of assumingly extended sets of brain electric sources (Michel and Koenig 2017).

- **The phase lagged connectivity model:** Contrary to microstate analysis that packs a not necessarily known number of sources into a transient state of synchronization that becomes manifest thru volume conduction on the scalp, other measures attempt to assess brain connectivity in EEG data by quantifying the communality among pre-selected pairs of EEG signals. However, volume conduction introduces interdependencies among EEG signals also in the absence of any functional interaction. To overcome this problem, it has been proposed that phase lagged connectivity measures such as the PLI may be used to quantify the relation between two EEG signals while excluding potential confounds by volume conduction. Since volume conduction is instantaneous, it has been argued that this can be achieved by excluding any relation between the dynamics of two putative components that can be explained by instantaneous correlations (Stam et al. 2007). In frequency-domain analyses, this effectively limits the analysis of lagged connectivity to consider only those part of the communality between two dynamics that have a lag of 90 degree, or as indicated by the formula for the PLI provided by the authors, by establishing the relationship between the two signals of interest thru a sinus function.

It now becomes obvious that for any set of active regions, the definition of what defined “being connected” in the microstate methodology is a-priori excluding what defines “being connected” as it is obtained when using indices of lagged phase locking or lagged coherence: The dynamics of sources conforming to the definition of a microstate have among them a non-lagged correlation of 1, whereas the dynamics of sources conforming to the PLI definition of connectivity have a non-lagged correlation of 0, whereas both of

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these source dynamics mix and become observable on the scalp thru the same volume conductor. The two definitions of "being connected" that the authors have used are thus from a formal point of view mutually exclusive, and their combination is contradictory: The claim that the reliability of the PLI index increases after parcellation of the data into microstates translates into the statement that the reliability of an estimator of lagged connectivity increases after selecting analysis periods that minimize the very same estimator.

The contradiction may however be resolved by the claim that there are two functionally connected systems that form a kind of meta-states: During such a meta-state, one of these systems may be assumed to operate in a way that can reasonably be accounted for by the microstate model, whereas during the same meta-state, the connectivity of the other system can be reasonably accounted for by lagged coherence. This is what the authors seem to suggest when they argue in the discussion that microstate-type network processes may be bound to deeper brain regions, whereas the lagged-coherence-type network processes take place in direct proximity of the electrodes, i.e. in superficial regions of the brain.

However, for this argument to work, it would be essential that the analysis of the microstate-type connectivity pattern was conducted solely based on a set of sources that excluded those sources interacting thru lagged oscillation, and that the analysis of lagged connectivity was conducted on signals that are not stemming from microstate-type network activity. Given the obvious issues with volume conduction on the scalp signal level, and given the low resolution of inverse solutions, it remains elusive how this problem can be solved in a mathematically rigorous way. Also the authors' proposal that such a separation may just coincide with a spatial separation in depth does not solve this issue, because the mixing of source signals on the scalp applies to all sources, such that the data recorded at each scalp electrode may contain information of both superficial and deep sources. Similarly, one may argue that the microstate parcellation would be a mere technical tool that is not meant to be understood literally as connectivity. However, while such an instrumentalist view can avoid the contradictory understandings of connectivity that we have pointed out, it then provides no reason why the measures of lagged

connectivity should be viewed any different, and be informative about connectivity beyond what we attribute to the microstate model.

In our opinion, it thus remains elusive what the results the authors reported might represent and how they may be explained.

Author Disclosure Statement

The authors declare that no competing financial interests exist.

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