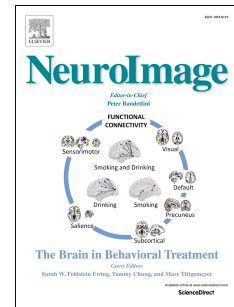


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EEG microstates as a tool for studying the temporal dynamics of whole-brain neuronal networks: a review

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Summary

The present review discusses a well-established method for characterizing resting-state activity of the human brain using multichannel electroencephalography (EEG). This method involves the examination of electrical microstates in the brain, which are defined as successive short time periods during which the configuration of the scalp potential field remains semi-stable, suggesting quasi-simultaneity of activity among the nodes of large-scale networks. A few prototypic microstates, which occur in a repetitive sequence across time, can be reliably identified across participants. Researchers have proposed that these microstates represent the basic building blocks of the chain of spontaneous conscious mental processes, and that their occurrence and temporal dynamics determine the quality of mentation. Several studies have further demonstrated that disturbances of mental processes associated with neurological and psychiatric conditions manifest as changes in the temporal dynamics of specific microstates. Combined EEG-fMRI studies and EEG source imaging studies have indicated that EEG microstates are closely associated with resting-state networks as identified using fMRI. The scale-free properties of the time series of EEG microstates explain why similar networks can be observed at such different time scales. The present review will provide an overview of these EEG microstates, available methods for analysis, the functional interpretations of findings regarding these microstates, and their behavioral and clinical correlates.

Keywords: EEG microstates, resting state networks, consciousness, psychiatric disease, state-dependent information processing, metastability

1. Introduction

Recent research using whole-brain imaging methods has led to important paradigm shifts in the understanding of higher cognitive functions, and of how such functions are affected by different brain pathologies. While previous research supported the notions that brain functions are localized in hierarchically distinct areas and information is processed in a feed-forward manner (Posner et al., 1988; Price, 2000), more recent studies have indicated that individual brain functions involve massive parallel processing in distributed brain networks (see reviews by (Bressler and Menon, 2010; Fries, 2005; He et al., 2007; Meehan and Bressler, 2012; Mesulam, 2008)). In addition, a radical shift has occurred in the understanding of brain states at rest: The prevailing hypothesis states that, rather than simply remaining inactive until incoming stimuli prompt a reaction, the brain is inherently active in an organized manner at rest to be optimally prepared for stimulus processing (Fox and Raichle, 2007; Fox et al., 2005; Greicius et al., 2003).

This new view of how the brain processes information led to a vast amount of studies that investigated large-scale brain networks at rest: their spatial organization, temporal dynamics, associations with cognitive states, and alterations due to different cognitive disorders and neurological diseases (Cabral et al., 2014; Foster et al., 2016; Fox and Greicius, 2010; Mitra and Raichle, 2016). Various methods are used to reveal these networks, leading to different interpretations regarding their spatial and temporal organization. Functional magnetic resonance imaging studies of brain networks aim to demonstrate correlations among BOLD fluctuations in different brain regions (Biswal et al., 1995), while those involving electro- or magnetoencephalography (EEG/MEG) typically evaluate correlations among fluctuations in the amplitude of oscillatory activity in different brain regions (de Pasquale et al., 2010; Fries, 2015). Researchers have proposed that the resting-state networks (RSNs) measured using fMRI (rsfMRI) reflect a sort of “constant inner state of exploration” that optimizes the system for a given impending input, thus influencing perception and cognitive processing (Deco et al., 2011). While this idea appears intuitive, the fluctuations observed using rsfMRI occur too slowly to be associated with preparation for a given unpredictable input and allow for a fast and adequate reaction. In order to mediate complex mental activities and optimally respond to rapidly changing input, networks must undergo reorganization into different spatial patterns on a sub-second time scale (Bressler, 1995). EEG/MEG can record fluctuations on this time scale and are

thus better suited for investigated the temporal dynamics of resting states and their influence on stimulus processing.

In this review, we discuss an increasingly utilized method for investigating the spatial and temporal properties of RSNs using multichannel EEG. The method is based on the concept of EEG microstates, which are defined as global patterns of scalp potential topographies recorded using multichannel EEG arrays that dynamically vary over time in an organized manner (Lehmann et al., 1987). More concretely, broad-band spontaneous EEG activity at rest can be described by a limited number of scalp potential topographies (maps) that remain stable for a certain period of time (60-120 ms) before rapidly transitioning to a different topography that remains stable again. These discrete epochs of topographic stability have been referred to as “microstates”, highlighting the notion that the scalp potential field reflects the momentary state of global neuronal activity, and that changes in the topography of this field indicate changes in the global coordination of neuronal activity over time. The present review will provide an overview of the “look and feel” of electromagnetic microstates in the brain, available procedures for the analysis of these microstates, functional interpretations of recent findings, similarities between conclusions derived via investigation of EEG microstates and other concepts associated with brain dynamics, and the known behavioral correlates of EEG microstates.

2. The phenomenology and history of EEG microstates

EEG directly measures the dynamic, synchronous polarization of spatially aligned neurons in extended gray matter networks, with post-synaptic excitatory or inhibitory potentials being the main sources of the signal (Lopes da Silva and Van Rotterdam, 2012). Other types of membrane potentials, such as action potentials or displacement currents, do not or to a much lower extent contribute to EEG signals in the most commonly analyzed frequency range (Gratny et al., 2017; Pettersen and Einevoll, 2008). Based on the far-field theory, such neuronal currents are usually modeled as an electrical current dipole composed of a current source and sink, separated by a small distance relative to that between the source and the scalp electrodes¹. By means of volume conduction, these potentials induce

¹ While the current dipole is the most popular (albeit simplified) model of the EEG source and is used in most source localization approaches, higher-order source models such as the quadrupole have also been proposed to represent neural electric sources (Jerbi et al. (2004). Additional evidence has indicated that monopolar components also contribute to field potentials (Riera et al. (2012).

passive current flow, which eventually passes through the skull and reaches the scalp to produce instantaneous scalp electric potentials. Any electrode on the scalp measures a portion of this field. This effect of volume conduction has two important consequences: First, an electrode at a given scalp location not only detects neuronal activity in areas directly below, but may also simultaneously record activity from potentially remote sources. Second, the activity of a single source will simultaneously affect all scalp electrodes, resulting in an intrinsic correlation among the signals recorded at these electrodes. While these are trivial notions based on Helmholtz' theorem, they are often ignored, leading to over-interpretation of the spatial location of neuronal activity underlying an observed phenomenon.

Using multi-channel recording arrays with electrodes distributed across the scalp, the spatial distribution of the potential field can be determined and plotted as three-dimensional (3D) potential maps. As demonstrated by Helmholtz (Helmholtz, 1853), many different current density distributions in a 3D volume can produce a given electric potential distribution on a surface enclosing this volume. This implies that any EEG map (even those produced using a large number of electrodes) can be explained by many different distributions of generators, leading to the so-called inverse problem. However, differences in the spatial configuration (i.e., topography) of the potential maps imply by the same physical laws that different distributions of neuronal generators are active in the brain (Lehmann, 1987; Vaughan, 1982). Thus, the present review highlights the need to examine *differences* in the topography of the scalp potential fields, which indicate changes in global network activity.

At first glance, the temporal series of scalp potential maps for spontaneous EEG activity gives the impression of a rather unorganized succession of maps with variable topography. However, when short time segments are analyzed, one can observe that a few topographic configurations dominate. This concept was discussed in a seminal paper by Dietrich Lehmann and colleagues in 1987 (Lehmann et al., 1987): By examining the time series of potential maps for alpha-filtered EEG and determining the positions of the maximal and minimal potentials on the electrode array, they noted that these extreme points remain at the same electrode location for a certain period of time and then rapidly switch to a new electrode location, where they remain stable again. However, during each stable period, shifts in the polarity of these extreme values (i.e., the sign of the maximum/minimum) can be observed. This polarity inversion follows the dominant frequency of the EEG oscillation. Since neuroelectric oscillations reflect rhythmic fluctuations of excitation and

inhibition in neuronal ensembles (Lopes da Silva, 1991), oscillations of the same generators in the brain lead to inversions of the polarity of the scalp potential field². When ignoring the polarity inversion, it becomes clear that periods of stable spatial configuration within the potential field not only exceed a full cycle of oscillation but can last for several oscillations and, conversely, can change within an ongoing oscillation (Figure 1). Such findings indicate that the duration of these stable periods is independent of the power of the frequency at which the generators of the brain operate, a fact later discussed by (Britz et al., 2010).

Most of the initial studies in the 1990's used these global map descriptors to parameterize the topography of each momentary map (i.e., the location of the negative and positive extremes or the location of the negative and positive centroids in 2D or 3D electrode space). By defining certain spatial windows around the descriptors, moments during which one such descriptor significantly changed position were detected and defined as significant changes in topography (Lehmann et al., 1993; Strik and Lehmann, 1993; Wackermann et al., 1993). These studies consistently confirmed that, even in broad-band EEG, segments during which these map extrema remain stable are observed, separated by fast transitions. On average, the duration of these segments is approximately 60-150 ms. Random permutation of the data destroyed these epochs of stability, indicating that the segmentation procedure revealed real properties of the EEG data and were not artifacts associated with the methods of investigation (Wackermann et al., 1993). Interestingly, by applying an agglomerative clustering procedure to determine the most dominant classes of centroid locations, previous studies revealed that most segments belonged to a small number of classes (range: 2-6 classes; mean: 3.7 classes for 90% of analysis time) (Wackermann et al., 1993). This finding was the first indication that only a few dominant topographies characterize the ongoing broad-band EEG.

The map extrema positions used to parametrize the potential field in these initial studies work rather well with dipolar fields but fail in cases of more complex fields with more than

² Because these stable maps often exhibit a dipolar shape (i.e., one maximal and one minimal potential at certain sites that invert every half-cycle of the alpha-frequency), Lehmann attributed this antiphase condition between the two extrema positions to a dipolar configuration of neuronal activity at a given area in the brain (Lehmann, 1971). Hebert et al. (Hebert et al., 2005) interpreted such patterns as fixed-end standing waves. Standing waves are zero-lag oscillations that have been proposed to be a fundamental characteristic of the EEG (Nunez and Srinivasan, 2006). Sivakumar et al. (Sivakumar et al., 2016) demonstrated that principal component analysis of standing waves over a sphere leads to spherical harmonics with multiple poles exhibiting maximal amplitude, partly resembling the typical microstate patterns. The relationships among standing waves, zero-phase oscillations, and microstates are discussed in (Hebert et al., 2005).

one positive and/or negative potential maximum. In addition, the definition of the window size around the extrema positions remained a controversial issue (Strik and Lehmann, 1993).

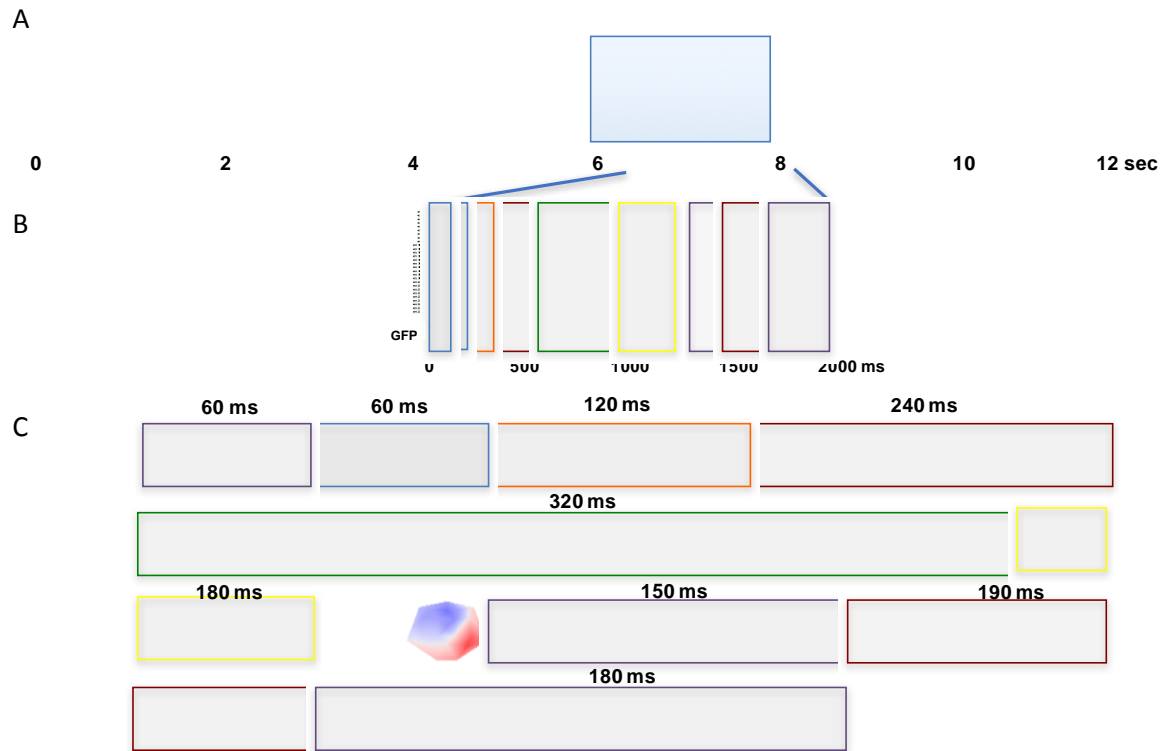


Figure 1: Map stability over time. **A.** A 12-s resting-state EEG with eyes closed showing periods of strong alpha activity lasting roughly 1 s. **B.** Close-up of EEG activity during an alpha burst. **C.** Potential maps at successive time points of global field power peak during the 2-s EEG shown in B. Polarities were inverted in each second map since polarity is ignored in the microstate analysis: Periods of stable map topography with different durations become apparent. They are marked in different colors, which are also superimposed on the EEG in B.

3. Computation of microstates and temporal descriptors

3.1. Spatial Cluster Analysis

In 1995, Pascual-Marqui and colleagues (Pascual-Marqui et al., 1995) proposed a statistical approach that directly considers the topography of the whole map, rather than reducing it to the position of the extrema. This method is based on a k -mean cluster analysis that groups maps with high spatial correlation in a nested iterative fashion and

determines the representative topography that best explains the variance in each cluster (Figure 2). Thereby, polarity of the map is ignored. In contrast to the sequential approaches described above, this global approach does not directly define microstates, it merely assigns all maps in the data to a few classes (clusters). Microstates are determined post hoc by fitting the cluster maps back to the data (see below). Several alternative methods for cluster or factor analysis can be used to determine the most dominant spatial components in map series, such as agglomerative hierarchical clustering (Murray et al., 2008), principal component analysis (Pourtois et al., 2008; Skrandies, 1989; Spencer et al., 2001), independent component analysis (Makeig et al., 2004; Makeig et al., 1999), a mixture of Gaussian algorithms (De Lucia et al., 2007), or decomposition based on Markov processes (Hadriche et al., 2013). These methods all aim to identify subcomponents of the data that are considered to be unrelated, but they differ with regard to the mathematical definitions of “unrelated.” Whereas a lack of association is defined as the absence of first-order associations in principal component analysis, independent component analysis eliminates also higher-order associations. Clustering algorithms such as *k*-means or agglomerative hierarchical clustering impose an even stronger criterion of non-relatedness between factors by allowing only one factor to differ from zero at any moment in time, making them mutually exclusive. Several tools are freely available for computing and quantifying microstates, such as Cartool (<https://sites.google.com/site/cartoolcommunity/>), a plugin for the BrainVision Analyzer (available upon request to thomas.koenig@puk.unibe.ch), and a plugin for EEGLAB.

3.2. Defining the number of clusters

The crucial question of all these spatial decomposition methods is the number of clusters necessary for capturing the informative features of the data and avoid over- or underfitting, a question that is similarly debated in fMRI resting state research using independent component analysis (e.g. (Li et al., 2007)). Originally, Pascual-Marqui and colleagues (Pascual-Marqui et al., 1995) proposed a cross-validation criterion for selecting the optimal number of cluster maps, which optimizes the ratio between the global explained variance and the degrees of freedom for a given set of cluster maps. However, this criterion is influenced by the dimensionality of the data (i.e., the number of electrodes and time points). Murray and colleagues (Murray et al., 2008) introduced a criterion based on a suggestion by (Krzanowski and Lai, 1988) that works well in evoked potential segmentation but often results in several prominent peaks for spontaneous EEG data. Many

other criteria exist, such as those described by (Milligan and Cooper, 1985) and (Charrad et al., 2014). In our own current method for EEG microstate segmentation (freely available software Cartool (<https://sites.google.com/site/cartoolcommunity/>)), we propose a meta-criterion based on several different criteria taken from the literature. First, each criterion is individually ranked from lowest to highest based on the relative positions of the values. The meta-criterion is then calculated by maximizing the average ranking and favoring unanimity (i.e., the highest signal-to-noise ratio of all criteria) (for details see (Custo et al., in press)).

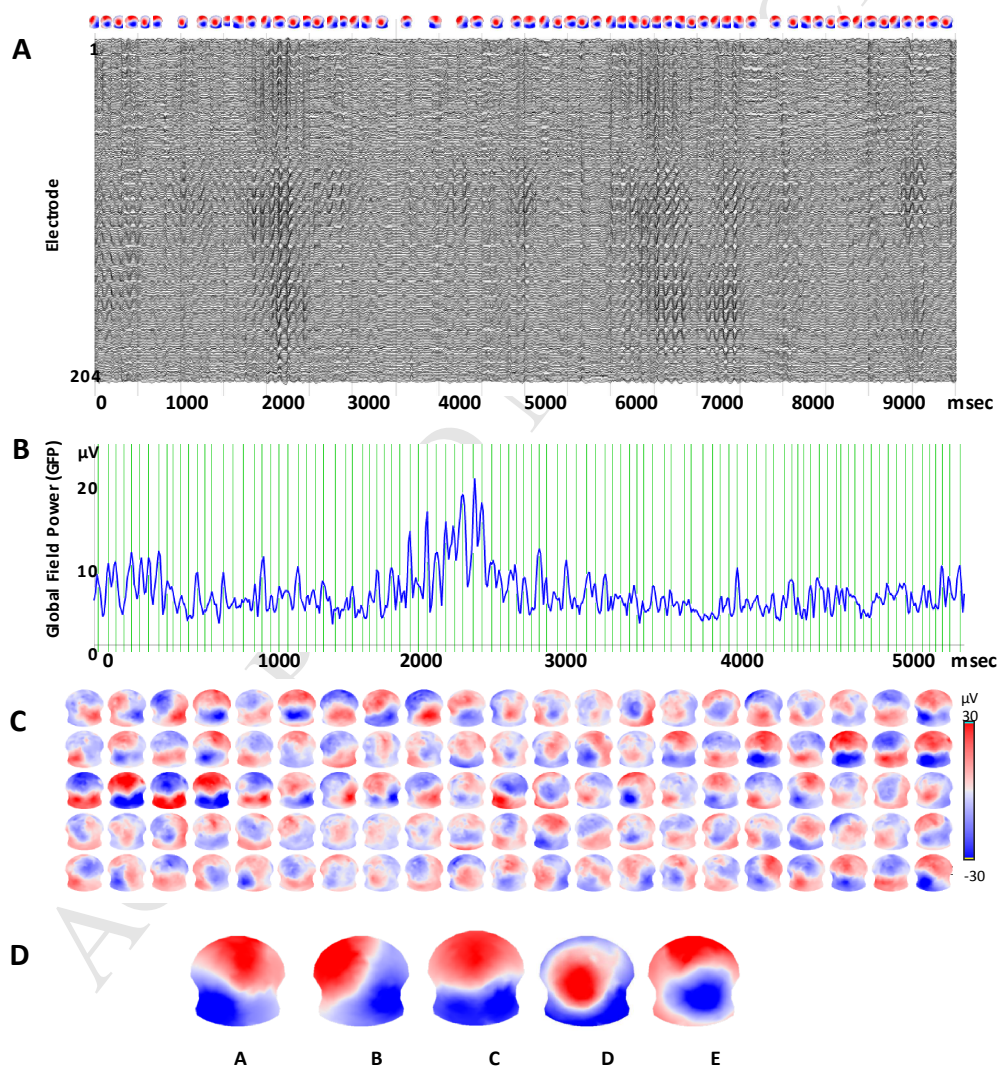


Figure 2. Illustration of the EEG microstate segmentation method: *A.* 10-sec eyes-closed EEG recording from 204 electrodes. *B.* Global Field Power (GFP) curve of the first 5 sec of this EEG file. The GFP peaks are marked by vertical lines. *C.* Topographic maps at consecutive GFP peaks. *D.* Spatial k -means cluster analysis of the maps at GFP peaks of the whole EEG file (30 sec duration). A meta-criterion (see text) revealed that 5 cluster

maps optimally explained this data. These maps are then fitted to the original EEG in A and each time point is labeled with the cluster map that correlated best. The time period that each of the cluster maps covered is indicated in A by color bars.

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Several initial studies that used the k-mean clustering approach and determined the optimal number of clusters by the cross-validation criterion revealed that the optimal number of maps across subjects is four (Britz et al., 2010; Brodbeck et al., 2012; Koenig et al., 1999). The amount of global variance that these four cluster maps explain varies between different reports, ranging from 65 to 84% (see figure 3). Seitzmann and colleagues (Seitzman et al., 2017) performed a systematic analysis of the explained variance of the cluster maps under different conditions, revealing that four cluster maps in their dataset explained only 69% and 62% of the variance in eyes-closed and eyes-open conditions, respectively. Fifteen clusters were required to explain approximately 80% of the variance. On the other hand, Tomescu et al. (Tomescu et al., 2014) found that only four cluster maps explained 80% of the variance. In our recent study that included 164 subjects recorded with 204-channel EEG during 3-7 minutes eyes-closed, a meta-criterion consisting of 11 individual optimization criteria was used to define the number of clusters. It revealed seven cluster maps as optimally explaining the data (shown in Figure 7). They explained 84.4% of the variance across all subjects (Custo et al., in press).

In our opinion, the optimal number of clusters should be estimated for each dataset individually using robust optimization criteria, rather than determining a fixed number. However, this becomes complicated if one aims to compare the temporal characteristics of microstates between groups. In such a case, one ideally wants to have a set of cluster maps that represent the recordings of all subjects and then fit these common maps to the individual data to test for differences in the presence and temporal dynamics of these maps. A straight forward way to achieve this goal is to apply the cluster analysis to the data of both groups and determine the global optimal cluster maps. This entails that the definition of particular microstate classes must be precise enough to separate functionally different states, yet allow enough leeway for accommodating interindividual differences of no interest. Thus, the most appropriate choice for the number of cluster maps may not necessarily correspond to the “true” number of clusters, but may instead result from a pragmatic compromise between the needs for specificity—which typically benefits from increasing the number of maps—and generalizability, which typically benefits from a relatively low number of maps. Such a compromise is likely to depend on the amount of

interindividual variance, and on the structure of the systematic variance that must be taken into account. Cross-validation methods for optimizing the compromise between specificity and generalizability within a study have been proposed for event-related potential microstate analyses (Koenig et al., 2014). In addition, a beta version of such a cross-validation procedure to identify this optimal compromise is currently implemented in an EEGLAB plugin available from the second author.

Besides comparing the temporal dynamics of the “same” microstates between groups or conditions, one might also want to know whether there are microstate maps that are specific for a certain group or condition. In order to do so, the cluster analysis needs to be performed separately and the number of optimal maps needs to be defined independently for each group. Statistical topographic correlation analysis can then be applied to distinguish maps that belong to the same class from those that are specific for a certain group or condition (Koenig et al., 1999; Koenig and Melie-Garcia, 2010; Lehmann et al., 2005; Nishida et al., 2013; Strelets et al., 2003).

Another issue concerns the comparison of the microstate analysis between studies. Many experimental and clinical studies fixed the number of clusters to the four initially determined (Koenig et al., 1999), arguing that four clusters were used to remain consistent with the majority of previous studies. While such an argument is justifiable and allows for comparisons among studies, it is obvious that this low number of clusters leaves a good part of the data unexplained (up to 30%) and may therefore eliminate a good portion of significant differences between experimental conditions or groups.

Study	N. Elect.	N. Subj.	Filter (Hz)	GEV (%)	A	B	C	D
König 1999	19	18	1-30	NR				
König 2002	19	496	2-20	79				
Lehmann 2005	16-21	27	2-20	84				
Britz 2010	64	9	1-40	66				
Kindler 2011	74	9	2-20	79				
Schlegel 2012	33	19	2-20	NR				
Brodbeck 2012	30	32	1-40	NR				
Andreou 2013	64	22	2-20	NR				
Nishida 2013	19	8	2-20	NR				
Tomescu 2014	204	28	1-40	80				
Tomescu 2015	64	27	1-40	84				
Khanna 2014	32	10	1-50	70				
Diaz 2016	32	20	2-20	71				
Pascual-Marqui 2014	109	61	2-20	NR				
Pipinis 2016	94	64	NR	NR				
Milz 2016	64	70	2-20	77				
Katayama 2007	19	12	2-20	NR				
Corradini 2014	19	26	NR	58				
Gschwind 2016	204	49	1-40	NR				
Drissi 2016	64	16	1-40	NR				
Seitzman 2017	61	24	2-20	68				
Santarnecchi 2017	20	74	1-30	NR				

Figure 3. Illustration of the topography of the four canonical microstate maps determined in several independent studies with different numbers of electrodes, participants, and filter settings. While the four microstate maps are very distinct from one another, they are highly reproducible across studies. Nevertheless, the similarities of the maps labeled with the same class (and consequently interpreted to exhibit similar functional significance) are not always obvious, particularly for maps C and D. In addition, the global variance (GEV) that these four maps explain varies substantially across studies (NR= not reported). References not in the text:(Corradini and Persinger, 2014; Pipinis et al., 2017; Schlegel et al., 2012).

Nevertheless, it is impressive that the four cluster maps retained in most previous studies exhibited highly similar topography, strongly resembling the maps initially described by Koenig and colleagues (Koenig et al., 1999). Figure 3 shows the four mean cluster maps from a series of studies. Koenig labeled these maps as class A, B, C, and D, and all subsequent studies retained this labeling, based on spatial similarity with the original cluster maps. Microstate map A exhibits a left-right orientation, map B exhibits a right-left orientation, map C exhibits an anterior-posterior orientation, and map D exhibits a fronto-central maximum. Even if more cluster maps are selected, these four maps seem to consistently dominate the data across different age ranges, conditions (e.g., sleep and hypnosis), and pathological states (Khanna et al., 2015).

However, Figure 3 also indicates that the maps assigned to a given class differ to a certain extent among studies, particularly with respect to microstate classes C and D, questioning the validity of the label that were assigned to them. This issue is explicitly demonstrated in (Custo et al., in press) where a split of microstate map C in two distinct maps is proposed, besides adding two more maps (Figure 6). If only four maps are retained in order to allow comparison with the literature, it may be necessary to examine both spatial and temporal characteristics to determine the most appropriate class of a given cluster map. For example, many studies have demonstrated that microstate map C is significantly more present than all other maps.

3.3. Determining microstates: Fitting the cluster maps to the data

Once the cluster maps have been determined, they are fitted to the individual participant's EEG data to define the microstates, extract the different temporal parameters for each of them, and comparing these parameters between experimental conditions or between participant groups. Usually, the following temporal parameters of microstates are calculated: (1) the average duration that a given microstate remains stable, (2) the frequency of occurrence for each microstate independent of its individual duration, (3) the fraction of total recording time for which a given microstate is dominant (i.e., coverage), (4) the global variance explained by each microstate, and (5) the transition probabilities of a given microstate to any other microstate (see reviews by (Khanna et al., 2015; Michel et al., 2009). If the cluster analysis is performed separately for conditions or groups, the topographical shape of the different microstate maps can also be compared across

conditions or groups (Nishida et al., 2013; Santarnecchi et al., 2017; Zappasodi et al., 2017). The boxplot in Figure 4 illustrates the different steps of microstate analysis.

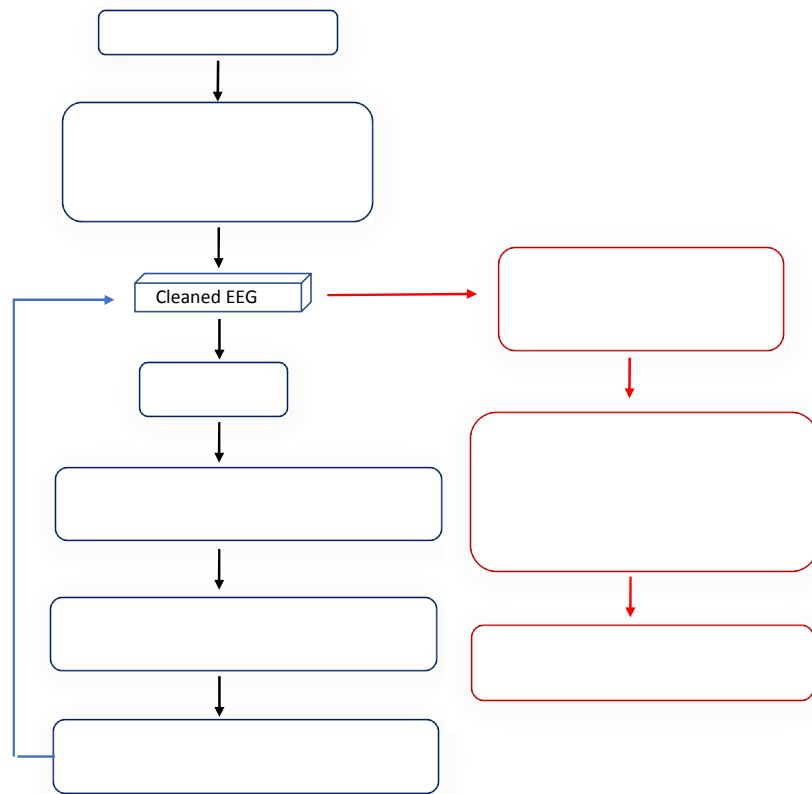


Figure 4. Boxplot detailing the different steps of microstate analysis.

Unsurprisingly, different pre-processing strategies, data selection methods, and smoothing parameters used in different studies may also influence the results of microstate analysis. However, a test-retest reliability study by Khanna and colleagues (Khanna et al., 2014) revealed that the results remain highly stable, independent of the methods used to determine the cluster maps and the number of recording electrodes. Naturally, maps at the moment of phase inversion exhibit low amplitude and high noise, leading to frequent segment changes if no smoothing parameters are introduced, and thus to shorter global durations of the microstates. Many studies have therefore been solely based on data observed at momentary GFP peaks, where the signal-to-noise ratio is optimal. In such studies, class assignments are often interpolated between these peaks, which may also affect microstate duration. However, how this influences the results when comparing temporal parameters between conditions or groups remains to be systematically

investigated. Importantly, it should be noted that the transition probabilities between microstate class assignments of maps at GFP peaks cannot simply be taken as proxies for the transition probabilities among microstate assignments in general. This remains a topic of controversy in current research (Gartner et al., 2015; Gschwind et al., 2015; Koenig and Brandeis, 2016).

4. Basic assumptions of the EEG microstate model

Any scientific analysis of EEG data requires an a priori rationale for decomposing the data into uniquely defined entities that can then be quantified (Koenig and Wackermann, 2009). In the aforementioned microstate analysis procedure, the crucial *a priori* assumption is that only one spatial map configuration entirely defines the relevant global state of the brain at each moment in time. This important *a priori* constraint is applied when fitting the representative cluster maps back to the recorded data: A spatial correlation is calculated between each cluster map, and the momentary recorded map and time points are assigned (labeled) based on the highest correlation. Thus, while the measured voltage distribution may in principle be accounted for by a weighted sum of different voltage vectors, the microstate model assumes that all but one of these vectors is zero (Koenig and Wackermann, 2009; Pascual-Marqui et al., 1995) and considers the residuals as noise. A series of arguments are typically employed to justify this assumption:

- a) Some researchers have argued that, if the object of investigation is the global brain state, there is one such global state that includes, by definition, all of its sub-states. Any sufficient change in one of these sub-states will thus simply result in a new global state, both in terms of its potential functional significance and physiological manifestation. This argument corresponds to functional theories that assume that only one global functional state occurs at any given moment in time (Baars, 2002a; Efron, 1970). Similar arguments are used to justify spatial clustering procedures in other brain imaging modalities such as fMRI (Cordes et al., 2002), in intracranial animal studies (Stopfer et al., 2003), and even *in vitro* (Wagenaar et al., 2006), embedding the application of the microstate methodology into an overarching framework used to explain particular functional features of brain activity (discussed in detail in Section 5).

- b) The most intriguing observation when applying this winner-take-all strategy to the data is that the cluster maps do not appear randomly in time. Each map remains dominant during a short time period, rapidly shifting to a new topography that again remains dominant for a certain duration. Pragmatically, since comprehensive statistics effectively reduce the dimensionality of the data, time periods with sufficiently similar, spatially defined clusters can be packaged together, following which the properties of these clusters can be quantified.
- c) While the primary advantage of brain electromagnetic data is its excellent temporal resolution, this feature has not been used to temporally resolve resting-state data into elements that have the potential to represent basic steps of information processing. However, these elements can be achieved by modeling the data using a sequence of non-overlapping, quasi-stable states. This global, extremely simple, and data-driven method can be used to extract unique features such as the duration of these states.
- d) Scalp field maps that remain stable over a certain duration entail important conclusions with regard to the temporal organization of functional brain networks: If we assume that brain activity accounting for a particular microstate is generated by a network of approximately simultaneously active sources, these different sources must have exhibited the approximately same temporal dynamics during the microstate, as differences in the time course of these sources would result in continuous changes of the scalp field generated. This observation can be expressed in the frequency domain as an assumption of approximately zero (or 180 degree)-phase differences among the sources during the microstate. The microstate model implies that the dynamics of the involved sources differ only by a scaling factor. If we express these dynamics in the frequency domain in terms of a set of amplitudes and phases, this scaling factor can only affect the amplitude of the dynamics, but cannot introduce any differences in phase, other than phase reversals when the scaling factor is negative³. This notion is in accordance with prevailing theories regarding standing waves, and discussed earlier. An important body of empirical data in animals (Fries et al., 2002; Singer and Gray, 1995) and humans (Engel et al., 1999; Kottlow et al., 2012) indicates that important cognitive functions such as feature binding are mediated by oscillatory patterns of the involved brain regions, among which a similar close alignment of

³ Note that, at the level of scalp measurements, the issue of phase reversals between electrodes also depends on the lead-field matrix, which defines how the activity of each source manifests at the scalp as a function of the location and orientation of the sources.

phase among neuronal groups can be observed. While such synchronization phenomena have predominantly been described in the gamma range, additional studies have reported similar phenomena in lower frequency bands (e.g., theta, alpha, and beta) (O'Neill et al., 2013; Palva and Palva, 2007). Thus, the microstate model shares an important property with empirically well-established frequency domain correlates of such cognitive functions. Moreover, the microstate model also assumes that, if the frequency domain representation of the microstate dynamics is based on more than one oscillatory element, the weights through which these elements define the dynamics of each of the involved sources do not change between these elements. In other words, a microstate is composed of a bundle of temporally overlapping and spatially synchronized oscillatory events that putatively originate from the same sources. We further discuss the relationships between microstates and frequency domain EEG models in Section 7.

- e) Beyond these technical and phenomenological arguments, the microstate model receives at least partial support from an important current model of neuronal communication (Fries, 2005). While this model argues that because the existence of conduction delays necessarily implies that there must be phase differences in the firing of neuronal groups, these delays are typically much smaller than the length of the typical, “spontaneous” cycles of excitability of these neuronal groups. For different neuronal groups to effectively transmit signals, it is thus important that these cycles of excitability are sufficiently time locked if the input of one neuronal group shall not fail to affect another neuronal group because that group happens to be in a transient trough of excitability (Fries, 2005). From this perspective, the phase locking of scalp EEG data as accounted for by microstates and related models may probably better be considered as signatures of transient large-scale processes that organize neuronal excitability rather than the signatures of neuronal communication within these cycles of excitability itself. One may further argue that these latter processes that implement communication itself may take place on spatial scales that are mostly below the resolution of scalp EEG data and typically need to be resolved by recording local field potentials (van Kerkoerle et al., 2014). The fact that combined EEG-fMRI data has shown that the topographic appearance of specific transient states of EEG synchronization (that are assumingly cortical) covaried with the spatial distribution of thalamic activity (Schwab et al., 2015) may further support this view, since the thalamus is a well-known pace-maker for cortical cycles of

excitability (Hughes et al., 2004) and may thus have the capacity to cause that a series of local cortical cycles align in phase.

In summary, the functional microstate model contains no constraints on the spatial distribution of brain activity for which it accounts, and does without implying that only one area in the brain is active at a given moment in time. However, the microstate model constrains the activity of all the sources contributing to a single microstate to a common time-course. Thus, many different areas can be active during each microstate, but all simultaneously active neuronal populations in the brain during each microstate generate one and only one global potential map on the scalp surface. Admittedly, only sources that produce sufficiently large fields that can propagate to the scalp surface contribute to the microstate. Accordingly, during the life-time of a microstate only increases/decreases in strength and polarity reversals of this global potential map are accounted for by a particular microstate, whereas the definition of microstates does not allow for the neural subsystems that contribute to the microstate to exhibit temporal shifts in dynamics. Consequently, approaches that attempt to explain functional brain interactions that yield the observed microstates based on phase-lagged connectivity during the microstate (Hatz et al., 2016) are fundamentally incompatible with the basic assumption used for the determination of EEG microstates. However, the microstate model does explicitly account for lawful temporal sequences of events as systematic biases in the transitions between microstates.

5. Microstates and the phenomenon of discrete epochs of cognition

The microstate concept arose from a purely phenomenological description of EEG map series, along with the observations that microstates can be chunked into segments of quasi-stable topographies—each lasting for a certain amount of time in the sub-second range—and that fast transitions occur between stable states. Interestingly, such a description of the temporal dynamics of brain processes aligns well with several theoretical concepts that suggest that conscious cognition is temporally discontinuous and parsed into series of stable intervals or “perceptual frames” (Efron, 1970). This concept is further supported by the results of numerous electrophysiological and imaging studies, although counter-

examples of continuity exist (see reviews by (Fingelkurts and Fingelkurts, 2006; Grossberg, 2000).

In 1980, William James postulated that the stream of consciousness is not continuous, but parsed in a series of states of mind—or “pulses of consciousness”. He claimed that each such state represents a certain thought with uniform content, however complex it may be. That is, the theory suggests that only one conscious thought occurs during each state, and that this thought is distinctly different from the thought in the previous or following mind state (James, 1890).

Based on the concept of series of conscious states, Dehaene and Changeux formulated the neuronal workspace model (Dehaene and Changeux, 2004; Dehaene et al., 1998; Dehaene et al., 2003), which posits that so-called workspace neurons from multiple brain areas become spontaneously co-activated and form discrete spatio-temporal patterns of global activity. Only one such episode of coherent activity is thought to occur at any given time, and episodes are separated by sharp transitions. Similar models were proposed by Baars and colleagues (Baars, 1997; Baars, 2002a), who concluded the following: “If conscious events are associated with global states of the dynamic core, such that only one such event can prevail at any one time, it follows that global states of the core appear serially” (Seth and Baars, 2005). In accordance with the neuronal workspace model—and with Dietrich Lehmann’s theory that EEG microstates represent the basic building blocks of consciousness (“atoms of thoughts”) (Koukkou and Lehmann, 1987; Lehmann, 1992; Lehmann et al., 1998)—we proposed that EEG microstates are the “electrophysiological correlates of a process of global, ‘conscious’ integration at the brain scale level”. That is, EEG microstates represent the neural correlates or elementary building blocks of the contents of consciousness (Changeux and Michel, 2004). A similar analogy between microstates and William James’ theory regarding the stream of consciousness has been discussed by Baars (Baars, 2002b).

Additional researchers have suggested that consciousness itself can be parceled into sequential episodes. For example, Rabinovich and colleagues proposed the concept of “heteroclinic channels” based on the chunking principle (Rabinovich et al., 2001; Rabinovich et al., 2015), which refers to the division of mental activity and cognition into a chain of transient, metastable states that are reflected in the brain as quasi-stable patterns of spatio-temporal activity. From a neurophysiological perspective, the stability of such patterns is due to phase-locked synchronization of activity, which has been regarded as a key mechanism of information integration in the brain (Fries, 2005; Singer, 1999; Varela et

al., 2001). At the sensor level, such phase-locked activity leads to stable topography (Tognoli and Kelso, 2014). As explained earlier, phase-locked synchrony produces a stable microstate over time. Therefore, the phenomenological observation of microstates aligns well with the concept of chunking dynamics proposed by Rabinovich and colleagues. This intriguing similarity has been discussed in detail by (Meehan and Bressler, 2012).

Intense discussion has surrounded the topic of how transitions between states occur, and what prevents states of sustained synchronization in the brain. Researchers have proposed the concept of metastability to account for such transition dynamics (Bressler and Kelso, 2001; Friston, 1997; Haken, 1988; Kelso and Fuchs, 1995). Based on this concept, a theory of “coordination dynamics” has been developed, which states that systems can flexibly switch from one coordination state to another (Fuchs and Jirsa, 2007; Kelso, 2010; Tognoli and Kelso, 2014). Transitions can be evoked by external stimulation (Jirsa et al., 1998; Schoner et al., 1986) or by noise (during resting conditions) (Deco and Jirsa, 2012) (Ghosh et al., 2008). Importantly, metastable coordination dynamics enable a system to change itself even in the absence of input or noise. As Tognoli and Kelso stated, “For a brain that is not purely reflexive and stimulus driven but endowed with temporally structured intrinsic activity, this is an important property to have: Changes in brain spatiotemporal patterns that occur spontaneously at rest naturally belong to the intrinsic dynamical repertoire of the metastable brain.” (Tognoli and Kelso, 2014).

A fundamental principle of such transition behavior is criticality, which reflects the border between stability and instability. Criticality is a fundamental property of dynamical systems that display scale-free temporal dynamics, also referred to as fractal dynamics. Scale-free dynamics is an organizing mechanism in which the system is constantly close to the critical state that allows it to flexibly control the incessant information flow from multiple sources with a high degree of responsiveness (Peng et al., 2000). Fractal behavior has been observed in many physiological systems and has been hypothesized to aid systems in coping with a constantly changing environment (Goldberger et al., 2002). Interestingly, mono-fractal behavior has been observed in EEG microstate time series (Dinov et al., 2016; Gschwind et al., 2015; van de Ville et al., 2010) (see further details in Section 6). Van de Ville and colleagues (van de Ville et al., 2010) utilized wavelet-based fractal analysis and Hurst-index calculations of the microstate time-series to demonstrate that microstate sequences are scale-free over six dyadic scales covering a range between 256 ms and 16 s. It remains an open question whether and how these scale-free properties of EEG microstate

time courses are related to the well-known 1/f spectral properties of EEG that are indicative of scale invariance (He, 2014)⁴.

Jirsa and colleagues have proposed a model that explicitly discusses the different time scales of brain network organization (Huys et al., 2014; Perdikis et al., 2011). Acknowledging the parcellation of brain functional dynamics in discrete states, they propose that elementary units be modeled as “structured flows on manifolds,” which are influenced on a faster time scale by instantaneous inputs to the system, and on a lower time scale by a mechanism that selects the dominant elementary unit. While the EEG microstates in such a model represent the “structured flows on manifolds”, it remains unclear which system is responsible for the dominance of a certain microstate over all others within a given period, and which mechanisms underlie the abrupt end of a microstate and the beginning of the next microstate. Thus, further studies are required to elucidate the association between EEG microstate dynamics to activities in different (e.g., very fast and very slow) frequency bands (Koenig et al., 2005) (see Section 7 for further details).

Previous studies have consistently reported that EEG microstates range in duration from 60-120 ms (Koenig et al., 2002); for a review see (Khanna et al., 2015), in accordance with previous findings regarding the duration required for conscious experience. For example, sequentially presented stimuli are not perceived as separate when they follow each other within less than 80 ms (Efron, 1970). Furthermore, masking a stimulus is efficient when presented with a latency of less than 100 ms (Libet, 1981); see also (Dehaene et al., 2003). Additional studies have reported similar durations for episodes of synchronous thalamo-cortical activity (Llinas and Ribary, 1998), sequences of alpha bursts (Williamson et al., 1996), and EPSP-IPSP sequences in mammalian forebrain neurons (Purpura, 1972) reviewed in (John, 2001). Using multivariate autoregressive modeling of multisite cortical ERPs recorded in a monkey during a visuomotor pattern discrimination task, Ding et al. (Ding et al., 2000) discriminated three different coordination states, each lasting around 100 ms, with short transitions of 25-50 ms between states. Coordination patterns lasting approximately 200 ms have been observed during EEG face-recognition tasks in humans (Rodriguez et al., 1999). In addition, spontaneous MEG and laminar studies have demonstrated that transient beta bursts typically last for approximately 150 ms

⁴ While 1/f power-law properties appear ubiquitous in a large number of natural phenomena including EEG and ECoG signals and local field potentials, the question whether 1/f scaling property is evidence for the existence of neuronal critical states still remains controversial (Bedard et al., 2006; He, 2014).

in animals (Lundqvist et al., 2016), and that such bursts are associated with memory encoding and decoding (Sherman et al., 2016). Overall, such findings indicate that there is ample evidence that brain activity is parceled into blocks of stable activity patterns that last roughly 100 ms, similar to EEG microstates.

6. The temporal structure of EEG microstates

Given that there are only a few microstate topographies and that they alternate in discrete chunks of approximately 100 ms in duration, it is then necessary to discuss whether the temporal structure of such alternations follows certain rules. More metaphorically, if the microstates represent the atoms of thought, does the sequence of microstates (“microstate syntax”) determine the content of the momentary daydream. That is, does the manner in which the words (the microstates) are organized yield something akin to a sentence that contains more information than its elements in isolation, and does the way these “sentences” are organized determine the story? The principal question is thus not only whether the transitions of microstates are non-random, but also whether this non-randomness is observable on different time scales. Several previous studies have investigated transition probabilities (Lehmann et al., 2005; Wackerman et al., 1993), clearly demonstrating that these probabilities are non-random. Interestingly, these transition preferences are altered in patients with schizophrenia (Lehmann et al., 2005) ((Tomescu et al., 2015). To date, only patients with Alzheimer-type dementia have exhibited transition probabilities indistinguishable from a random process (Nishida et al., 2013). As Koenig et al. stated, “There are not only connectivity structures that facilitate the coactivation of brain regions within a microstate, but there is another sequential connectivity where one type of brain state or mental operation facilitates the appearance of another” ((Koenig et al., 2005), page 1,019). Therefore, the time-course of the information flow between different brain states is crucial for ensuring the perception of incoming stimuli, proper cognitive processing, and adequate action in a conscious manner. As discussed earlier, microstates follow one another on a sub-second time scale, resulting in the formation of a well-organized (though not yet understood) syntax. Several research groups have aimed to determine whether the time series of these microstates are random or completely predetermined (Gschwind et al., 2015; van de Ville et al., 2010). Such studies have demonstrated that EEG microstate sequences exhibit scale-free mono-fractal dynamics over

six dyadic scales (from milliseconds to several seconds), indicating that EEG microstate time series are perfectly self-similar in the sense that observing them at various time scales reveals the same information. Microstate time series thus have a clearly structured temporal organization that is neither random nor predetermined, but cannot be predicted. As explained earlier, such scale-free dynamics can only emerge when a system operates near a critical point, indicating that the brain operates under conditions far from homeostasis at rest to ensure a high degree of responsiveness and the flexible management of continuous information flow from multiple sources. Notably, previous studies have revealed that the long-range dependency of the microstate sequence crucially depends on the variability of the individual microstate duration and not on the microstate sequence itself: Shuffling the microstate sequence does not destroy the fractal properties, while fixing the duration of the microstates does (van de Ville et al., 2010). These findings highlight the importance of the temporal dynamics of EEG microstates. Interestingly, changes in the duration of specific microstates represent critical markers for several neuropsychiatric diseases, indicating that changes in microstate duration and eventually changes of the scale-free properties of the microstate sequences may characterize changes in mental processes associated with neurological and psychiatric conditions (see Section 10 for further details).

In summary, analysis of the temporal sequence of microstates provides an ideal macroscopic window for observing the temporal dynamics of spontaneous brain activity. In the light of the evidence for scale-free properties of microstate sequences, further modeling of microstate sequences must extend beyond step-by-step, short-term interactions of the states using hidden Markov models (Gschwind et al., 2015).

7. EEG microstates and oscillatory brain states

As previously noted, the microstate model allows for any type of temporal dynamics within a particular microstate, as long as these dynamics are the same for all sub-processes contributing to that microstate. Accordingly, microstates have typically been regarded as broad-band phenomena. Microstates may thus take into account the broad range of frequency components observable in the human brain (Groppe et al., 2013). Furthermore, the typical features extracted from microstate analyses, such as mean durations and percentages of time covered, are independent of signal amplitudes. Thus, it is not surprising that some studies have reported no associations between inter-individual variance of EEG

spectral amplitudes and inter-individual variance in microstates (Britz et al., 2010; Koenig et al., 2002). However, within-subject fluctuations in the spatial and temporal distribution of dominant EEG spectral power have been systematically associated with the momentary presence of particular microstates (Milz et al., 2017).

The presence of within-subject but not between-subjects spectral correlates for microstates highlights a major concern in EEG research: the non-stationarity of EEG data. In the context of microstate analyses, the effects of non-stationarities in the EEG data should be discussed on two levels. At the microscopic level, the microstate model makes no particular assumptions regarding the dynamics of brain activity within a particular microstate. Non-stationarity of the data is thus by definition unproblematic. However, at the broader level, the often rapid and systematic changes in the frequency domain of EEG data—as observed for extraction using Kalman smoothers (Tarvainen et al., 2004)—are likely to be accompanied by similar systematic changes in microstate features (e.g., duration or transition probabilities). Thus, the spontaneous variance of these microstate features may be smaller within periods with fixed dynamical parameters, which can be identified using segmentation procedures that detect sudden changes in these parameters (Latchoumane and Jeong, 2011).

Conceptually, the discussion of microstates in the context of non-stationarities thus emphasizes two very different and mathematically independent ways of defining the term “state”:

- a) The microstate understanding defines “state” in a spatial manner. Each state is regarded as an *in toto* activation of a particular set of sources with temporally similar dynamics. As argued in the rsfMRI literature, the spatial specificity of this definition emphasizes the modality (sensory, motor, verbal, etc.) and thus the content of what mental processes the state may represent.
- b) The dynamic understanding defines “state” in a temporal manner, as the period of time during which EEG dynamics meet certain criteria of stationarity. Traditionally, this definition conveys information regarding the mode (awake, drowsy, sleeping, etc.) of access to some mental contents, whereby the spectral distribution of the activity may determine whether a particular state may activate or block information processing (Klimesch, 2012).

Unsurprisingly, several methodological developments have aimed to unify these two very different aspects of “state” definitions into a common framework. This is particularly important for clarifying the issue of inhibitory vs. activating roles of the functional

networks represented by microstates or similar models. The topographic time frequency decomposition of the EEG (Koenig et al., 2001) parses the data into brief transient oscillatory events. Each of these events is again constrained to a single spatial field configuration, and thus to a stable network of brain sources. Thus, the spatial and dynamic criteria are considered for each state. A recent study by Schwab et al. provided empirical evidence for the functional significance of both spatially and dynamically defined brain states (Schwab et al., 2015), indicating that different classes of states of synchronized cortical oscillation exhibited BOLD correlates in partially separate sub-regions of the thalamus. However, other researchers have criticized this approach, as the use of wavelets may alleviate but not eliminate non-stationarities in the data. Based on such criticisms, the methodology has been extended to include dictionary learning algorithms, which tailor the oscillatory elements used to decompose the data such that they optimally cover time-frequency ranges that are quasi-stationary (Studer et al., 2006).

Many EEG studies have employed frequency domain measures of lagged interactions to assess brain connectivity (Pascual-Marqui et al., 2011), and there is good electrophysiological evidence that these lags exist and play a functional role (van Kerkoerle et al., 2014). However, the microstate model contains a strong and *a priori* constraint on simultaneity, which excludes the existence of significant lags within a microstate. We believe that this is conceptually unproblematic because (a) the sequential aspects of electrical brain activity can be accounted for using sequences of microstates and the laws that govern the transitions between them, and because (b) lagged activity may be accounted for by the portion of the data for which the microstate model cannot account. Finally, the time frequency analyses mentioned above achieve decomposition of the data by postulating that each component complies with simultaneity, and that all components are separated by time, frequency, or phase. Figure 2 of (Koenig et al., 2001) shows one component (the final component) that overlaps with the other components in time and frequency but exhibits differences in phase. Such accounts may also be useful for explaining the phenomenon of traveling waves.

8. Brain sources underlying EEG microstates

As both fMRI and EEG can be used to identify RSNs, several studies have aimed to determine the association between the two measures. The most direct method for

investigating such associations involves the use of simultaneous EEG-fMRI (Laufs et al., 2008; Michel and He, 2011; Mulert, 2013; Rosenkranz and Lemieux, 2010). Using such methods, several studies have examined the association between fluctuations in the frequency power of spontaneous EEG activity and BOLD signals obtained using fMRI (Goldman et al., 2002; Jann et al., 2009; Laufs et al., 2003; Mantini et al., 2007; Tyvaert et al., 2008). These studies have revealed that oscillations in the different frequency bands contribute differentially to the BOLD signal. However, strong positive cross-correlations were observed between the different frequency bands, indicating that the neuronal assemblies of the different nodes of the fMRI RSNs oscillate at different frequencies (Bruns et al., 2000; Mantini et al., 2007).

Simultaneous EEG-fMRI has also been used to investigate correlations between EEG microstates and fMRI resting states. Two independent studies regarding this matter were published in the same issue of *Neuroimage* (Britz et al., 2010; Musso et al., 2010) and accompanied by two editorial comments (Laufs, 2010; Lehmann, 2010). Unfortunately, the methodological approaches of the two studies were very different, making it difficult to compare the results. Musso and colleagues (Musso et al., 2010) performed *k*-means cluster analysis of the EEG data for each participant, identifying a fixed number of 10 clusters (microstate maps) per participant with individually different topographies. The presence of each of these 10 maps in the individual EEG was then marked and convolved with the hemodynamic response function (HRF) in an event-related, generalized linear model (GLM) design. This analysis revealed significant correlations between BOLD fluctuations and spatial patterns for approximately half of the microstate maps in each participant. Factor analysis was used to identify similar topographies across all participants. Seven aggregation factors were identified at the group level, although only one of these factors was able to elicit significant BOLD activation in brain regions within the visual and default mode networks.

Britz and colleagues (Britz et al., 2010) utilized a different approach more closely related to the conventional method for EEG microstate analysis (Section 2). Using a cluster analysis, four EEG microstates were identified for each participant. A second cross-validation cluster analysis of all individual clusters identified four microstate maps across participants that were very similar to the four maps reported in previous studies. A spatial correlation analysis of these group template maps allowed the researchers to label each individual map with the most appropriate group template. These individual maps were then fitted to the corresponding EEG data, and the spatial correlation was calculated for each map at each time point, resulting in a time course for the goodness-of-

fit of each microstate. These time courses were convolved with the HRF in single-participant and multi-participant GLM analyses. The multi-participant GLM revealed distinct brain areas exhibiting significant correlations with the time-courses for each of the four microstates (Figure 5): Microstate A was correlated with negative BOLD activation in the bilateral superior and middle temporal lobe, while microstate B was correlated with negative BOLD activation in the bilateral occipital cortex. Microstate C was correlated with positive BOLD activation in the dorsal anterior cingulate cortex, the bilateral inferior frontal cortices, and the right insular area. Microstate D was correlated with negative BOLD activation in right-lateralized dorsal and ventral areas of the frontal and parietal cortices. Comparison with 15 components defined by traditional independent component analysis of the fMRI data revealed that each of these GLM maps best correlated with one of these components, which have been attributed as follows in the fMRI literature: auditory network (microstate A), visual network (microstate B), saliency network (microstate C), attention network (microstate D).

Subsequently, Yuan and colleagues (Yuan et al., 2012) reported a third approach for identifying BOLD correlates of EEG resting-state scalp topographies. They identified EEG resting state maps using a temporal independent component analysis, rather than a spatial cluster analysis. A subset of independent EEG components was compared with those estimated from fMRI independent component analysis. Among the 13 selected EEG components, six were associated with one or two fMRI RSNs, while the remaining seven were associated with more than two fMRI networks.

In conclusion, the three studies that utilized combined EEG-fMRI to identify fMRI correlates of EEG microstates produced different findings. However, due to fundamental differences in methodological approaches, it is difficult to compare the results among the three studies. Nevertheless, the findings of these studies strongly indicate that EEG microstates are closely associated with RSNs as defined using fMRI. The scale-free properties of microstate time series, which span the timescales characteristic of EEG microstate changes and fMRI BOLD oscillations, explain how information that can be observed at such different timescales is intertwined. Several studies have referred to (Britz et al., 2010), who utilized a more conventional approach, when interpreting the significance of specific microstate changes in different states and pathologies (see review by (Khanna et al., 2015)). However, given recent discussions regarding the anatomical overlap of various fMRI RSNs in time and space (Karahanoğlu and Van De Ville, 2015; Smith et al., 2012) and the subdivisions of these networks (particularly the default mode network) (Andrews-

Hanna et al., 2010; Andrews-Hanna, 2012), such one-to-one attributions of microstates to brain functions based on fMRI-correlations must be made with caution.

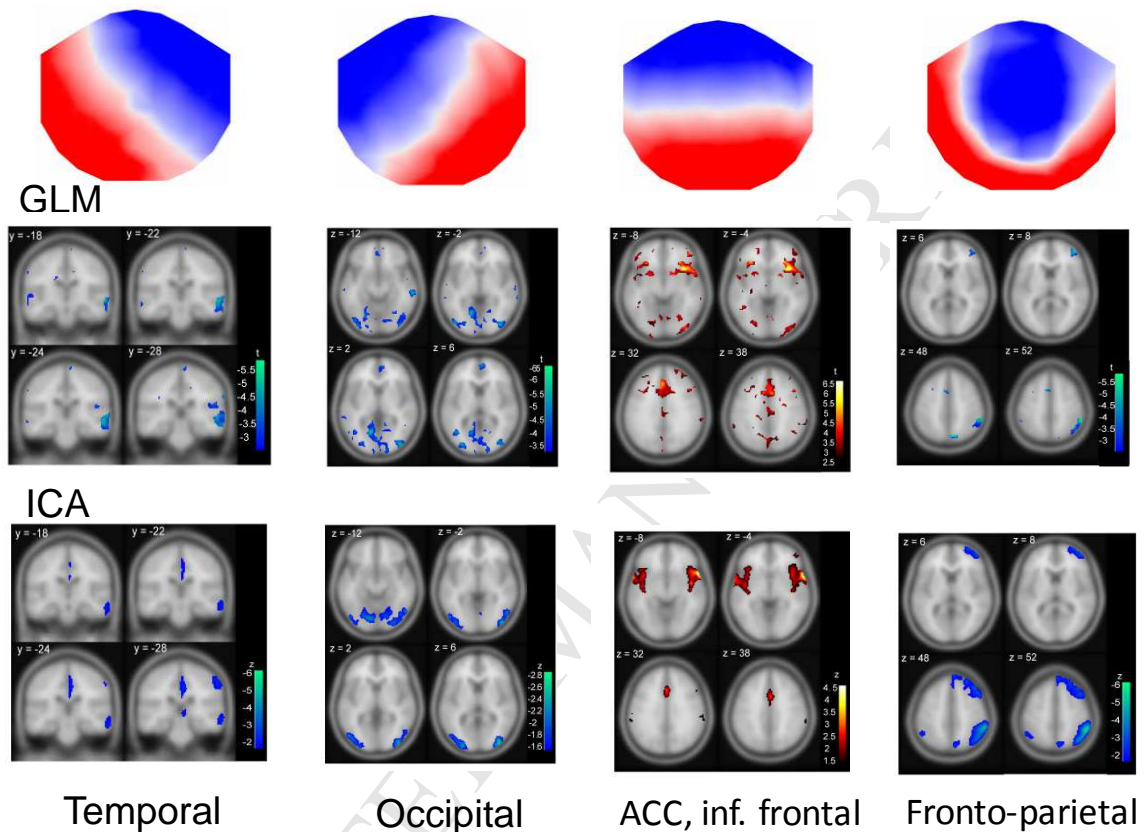


Figure 5. Combined EEG-fMRI recording of resting-state activity. The EEG data were analyzed using the EEG microstate approach (*k*-means clustering), resulting in four cluster maps that best explained the data across participants. The time course of the correlation of these four maps with the individual EEG data was convolved with the fMRI BOLD time course at each voxel using a generalized linear model (GLM). The group GLM revealed distinct BOLD activation patterns for each microstate. These activation patterns were then spatially correlated with the fMRI resting state networks of each participant, which were determined using independent component analysis. This comparison revealed that each of the four canonical microstates is best correlated with one of the known fMRI resting states. Figure modified from (Britz et al., 2010).

While the networks underlying EEG microstates can be indirectly determined based on correlations with BOLD fluctuations, it is in principle also possible to directly estimate the (electrophysiological) neural networks that generate resting-state scalp topographies by applying source localization methods to the multichannel data. To date, only two groups have utilized this direct approach (Custo et al., in press; Milz et al., 2017; Pascual-Marqui

et al., 2014). Using *k*-means clustering, (Pascual-Marqui et al., 2014) determined the four microstate maps of narrowly filtered (2-20 Hz) EEG data across a group of 109 participants. The individual labels were used to compute the microstate topography for each participant, following which the source distributions of the individual maps were computed using a distributed inverse solution (eLORETA) and tested for non-zero means at each solution point across participants. This analysis revealed that the source distributions of the four microstates exhibited a high degree of overlap, primarily for the anterior and posterior cingulate cortices and the left and right occipital/parietal areas. The posterior cingulate was active in all four microstates. The authors concluded that the four microstates represent different aspects of the default mode network, and that the resolution of EEG allows for temporal separation of these microstates.

In a recent study (Milz et al., 2017), the same group demonstrated that such activation primarily occurred within the alpha frequency range. However, in contrast to the EEG-fMRI studies described earlier, (Pascual-Marqui et al., 2014) and (Milz et al., 2017) did not distinguish the microstate networks based on their temporal signature, but rather focused on the spatial characteristics of the potential fields. Custo and colleagues (Custo et al., 2014) utilized a source localization approach that more closely resembled the GLM approach used in the EEG-fMRI study by Britz and colleagues (Britz et al., 2010). This method, known as topographic electrophysiological state source-imaging (TESS) uses a set of map topographies in a design matrix that has been fitted to each participant's EEG data using a GLM, which results in a time course of coefficients for each map topography for each participant. In parallel, a distributed linear inverse solution is applied to each time point of the individual EEG to estimate the time course of the source activity. A second temporal GLM fits these two time-courses, resulting in a set of active voxels for each map. Thus, similarly to combined EEG-fMRI analysis, the time courses of the maps are correlated with the time courses of the sources. However, the times courses of estimated current density rather than those of BOLD changes are used for this analysis, which preserves the temporal resolution of EEG. Custo and colleagues (Custo et al., in press) used this method to estimate the sources of the microstates, which were determined via *k*-means clustering of 256-channel EEG data for 164 participants. As described in Section 3 a meta-criterion applied to the *k*-means clustering revealed an optimum at seven cluster maps, which explained 84.8% of the global variance (Custo et al., in press). While the four canonical maps were among these seven maps, microstate C was divided into two maps, and two additional maps were included. TESS analysis of these seven microstates revealed a set of

brain regions active in the majority of microstate networks: These common areas corresponded to the main hubs described in several studies regarding structural and functional brain networks (e.g., anterior and posterior cingulate cortices, precuneus, superior frontal cortex, supramarginal gyrus, dorsal superior prefrontal cortex, and insula) (Hagmann et al., 2008; van den Heuvel et al., 2012; Collin et al., 2014). In addition to these common hubs, areas specific to each of the seven microstates were found, partly resembling the BOLD correlates described by (Britz et al., 2010) (Figure 6).

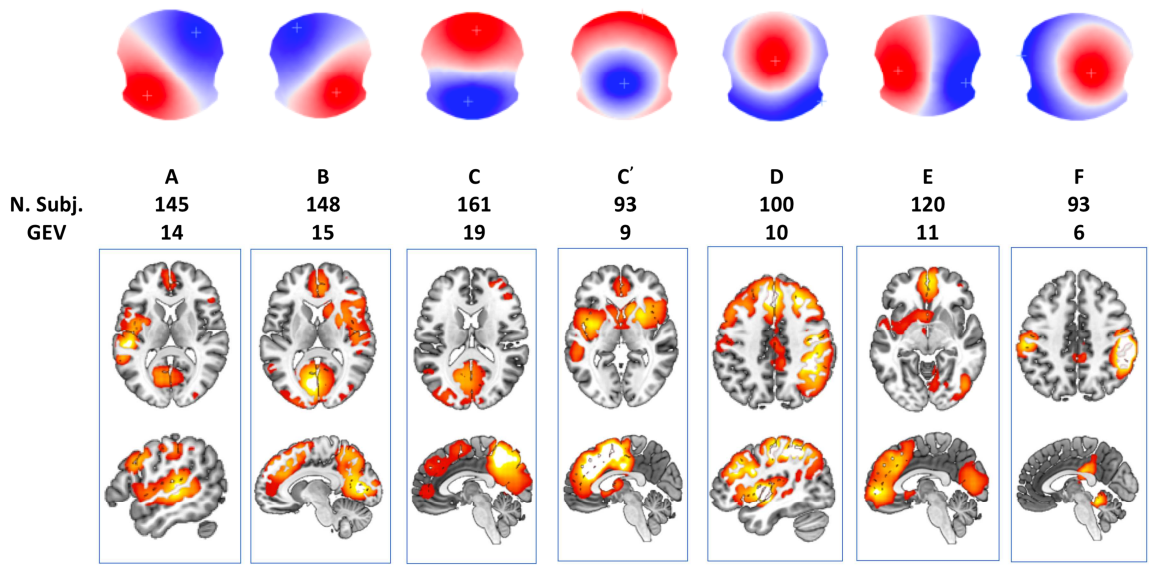


Figure 6: Source localization of seven EEG microstates based on correlations between the time course of EEG microstates and the time course of the current densities estimated using a generalized linear model (Custo et al., 2014). Note the split of microstate C in two separate microstates (see Figure 3). In addition to several areas of activation common to each microstate (common hubs), each of the seven microstates was reliably associated with state-specific brain areas. Data were obtained from 164 participants using 256-channel EEG. For details see (Custo et al., in press).

N. Subj. = Number of participants (out of 164) in which the microstate was observed.

GEV= Global variance explained by each microstate across participants.

9. The functional significance of EEG microstates

If EEG microstates indeed reflect the elementary building blocks of consciousness or the “atoms of thought” (Section 6), one would expect that such states are modulated by the content of the thoughts. Evidence in support of this notion was provided by Lehmann and colleagues (Lehmann et al., 1998), who investigated spontaneous, conscious experience in healthy participants under task-free conditions. Participants were placed in a dark room and

asked to keep their eyes closed and let their minds wander. In a random interval between 20 s and 2 minutes, a tone prompt was presented, and participants were asked to report what went through their minds just prior to the cue. These verbal responses were recorded on an audio tape, transcribed off-line, and then classified by two independent raters as either visual imagery or abstract thoughts. Microstate analysis of the 2-s EEG data revealed significant differences in microstate topographies between the two classes of spontaneous thought immediately preceding the reports, but not 2 s earlier. Interestingly, the topography related to imagery thoughts resembled the second of the four canonical microstates (microstate B), which has been suggested to reflect the visual resting state network (Britz et al., 2010).

Seitzman and colleagues (Seitzman et al., 2017) attempted to alter the temporal features of the four canonical microstates via behavioral manipulation. They hypothesized that the temporal parameters of microstate B would change when participants transition from an eyes-closed state to an eyes-open state, due to increased visual input. Indeed, they observed significant increases in the coverage and occurrence of microstate B, supporting the assumption that microstate B is associated with the visual system. However, Milz and colleagues (Milz et al., 2016) observed no such increases for microstate B when participants were asked to visualize images that had been presented on the screen during eyes-closed conditions. Rather, the coverage and occurrence of microstate B increased when participants were asked to define a visually presented noun to an imaginary partner, which was designed to represent the least visual condition of their study. In contrast, the occurrence of microstate C decreased during the visualization conditions when compared to levels observed during resting conditions. Britz and colleagues (Britz et al., 2010) associated microstate C with activity in cognitive control networks, primarily the salience network, and with activation of the anterior cingulate and insula (Seeley et al., 2007). Previous studies have referred to this network as the cingulo-opercular system (Coste and Kleinschmidt, 2016), which is thought to be associated with task performance. Thus, decreases in this microstate during visualization tasks appear to be counter-intuitive. Seitzman and colleagues (Seitzman et al., 2017) also reported decreases in the duration and occurrence of microstate C during a serial subtraction task relative to the resting condition, which also contradicts the notion that microstate C supports cognitive control.

These authors proposed that microstate C rather reflects a portion of the default mode network, a task-negative network in which activity decreases during the performance of cognitive tasks. The anterior cingulate is indeed a prominent hub of the default mode

network, and fMRI studies of episodic memory retrieval have reported robust functional dissociation within the default mode network: Posterior regions (angular gyrus, posterior cingulate/precuneus) were active during memory retrieval, whereas anterior regions (prefrontal cortex) were inactive (Sestieri et al., 2011). Additional fMRI studies provided further evidence in support of these findings regarding the default mode network (Damoiseaux et al., 2008; Lei et al., 2014). Xu and colleagues (Xu et al., 2016) demonstrated that the anterior regions of the default mode network are associated with self-referential mental thoughts, while the posterior regions are associated with episodic memory retrieval. Similarly, Andrews-Hanna and colleagues reported that the dorsal medial cortex subsystem of the default mode network is responsible for internally guided cognition, while the medial temporal subsystem is responsible for memory-guided imagery (Andrews-Hanna, 2012; Andrews-Hanna et al., 2010). These findings suggest that, if such a distinction of the default mode network had been used in (Britz et al., 2010), microstate C would have been associated with the anterior default mode network, rather than the salience network. Further studies are required to determine the association between microstate C and underlying functional networks. Such work is critical for determining whether alterations in microstates are associated with psychiatric conditions such as schizophrenia.

The last of the four canonical microstates (microstate D) increased in duration and occurrence relative to levels observed under resting conditions when participants were asked to perform a serial subtraction task, independent of whether their eyes were open or closed (Seitzman et al., 2017). In accordance with the findings of (Britz et al., 2010), these findings indicate that microstate D is associated with the dorsal attention network. However, in the behavioral manipulation study by Milz and colleagues (Milz et al., 2016), the duration and occurrence of microstate D increased during rest when compared to levels observed during goal-directed tasks (object-visualization, spatial-visualization, verbalization). The authors suggested that microstate D reflects reflexive aspects of attention, focus switching, and reorientation that occur more frequently during rest than during single-goal-directed tasks. As changes in microstates C and D are often observed in patients with schizophrenia, further studies regarding the functional significance of this network are required.

Researchers have also examined changes in EEG microstates during different states of consciousness. Brodbeck and colleagues (Brodbeck et al., 2012) compared EEG microstates during different sleep stages with those observed in waking states. Using the

conventional clustering approach and cross-validation, they identified the four canonical microstate maps in all stages (awake, N1, N2, N3). They then examined the temporal characteristics of these microstates, observing that microstate map C was most dominant in waking states and sleep stages N1 and N3, but that microstate B dominated in sleep stage N2. In contrast, the duration of all microstates increased in sleep stage N3, which can be partly explained by the incidence of slow waves in the EEG data. Notably, even if the optimal number of microstates for explaining the EEG data was identified as four, the topography of some microstate maps was rather dissimilar. Katayama and colleagues (Katayama et al., 2007) evaluated changes in EEG microstates in participants undergoing hypnosis. An experienced hypnotist induced hypnotic states in seven volunteers during 19-channel EEG. EEG microstates were compared among rest, light hypnosis, deep hypnosis, and recovery. The study revealed strikingly similar topographies of the four canonical microstates across conditions. Analysis of the temporal characteristics of the four microstates revealed decreases in the duration and occurrence of microstates B and D during hypnosis relative to rest, as well as increased in these parameters for microstates A and C. These results support the notion that microstate D is associated with attention and decreases in cognitive control during hypnosis, while microstate C is associated with the anterior default mode network (i.e., self-referential mental thoughts) (Xu et al., 2016)—activity in which may increase during hypnosis. However, this is highly speculative, and further studies are required to determine the association between various mental activities and microstates. Taken together, these findings indicate that EEG microstates may be necessary yet individually insufficient for the presence of conscious experiences, and that these microstates may result from evolutionary determined, brain-intrinsic biases toward particular patterns of co-activation particularly suited to represent environmentally relevant information. This assumption corresponds to observations in fMRI resting state studies, which have indicated that spontaneous brain connectivity is altered but not eliminated in patients with no signs of consciousness (Boly et al., 2008).

10. Modulation of EEG microstates by disease

Numerous studies have investigated changes in EEG microstates in patients with neuropsychiatric disorders (see review by Khanna et al., 2014). Figure 7 summarizes these studies and their main findings with regard to the temporal properties of the four

microstates. In the present review, we focus on those studies that used *k*-mean cluster analysis to determine the number of microstates and those that fixed the number of states to the canonical four maps. Earlier studies using different approaches for analysis (Dierks et al., 1997; Kinoshita et al., 1995; Strik et al., 1997; Strik et al., 1995) are not listed. The most prominent pathology studied using this approach is schizophrenia. Eight studies have examined EEG microstates in drug-free patients with schizophrenia or those experiencing their first episodes (Irisawa et al., 2006; Kikuchi et al., 2007; Koenig et al., 1999; Lehmann et al., 2005; Nishida et al., 2013; Strelets et al., 2003), while two studies have investigated microstates in patients receiving medication (Andreou et al., 2014; Tomescu et al., 2015). Two studies have also investigated patients at high risk for developing schizophrenia (Andreou et al., 2014; Tomescu et al., 2014), while an additional study examined differences in EEG microstates in patients with schizophrenia who reported hallucinations (Kindler et al., 2011) (discussed in (Lehmann and Michel, 2011)). Seven of these studies were included in a recent meta-analysis by Rieger and colleagues (Rieger et al., 2016). This analysis revealed medium-sized effects for microstate C and D, reporting that microstate C occurred more frequently in patients with schizophrenia, while microstate D was consistently shorter in duration. Notably, the effect sizes were larger than those typically reported in frequency domain resting-state studies, suggesting that the particular decomposition of the EEG data as obtained using microstate analyses may indeed isolate brain networks that exhibit psychiatric relevance. Microstate B was also often reported to decrease in duration, although this effect was not significant in the meta-analysis.

Based on the findings of microstate studies regarding altered states of consciousness (e.g., sleep, hypnosis, and meditation), the authors of these previous studies argued that there may be a functionally relevant balance between microstates C and D, and that a preponderance of microstate C may result in a progressive detachment of mental states from environmental input. Such an interpretation was also put forward in a study describing negative correlations of microstate C occurrence and fluid intelligence (Santarnecchi et al., 2017). Tomescu and colleagues (Tomescu et al., 2015; Tomescu et al., 2014) examined patients with 22q11 deletion syndrome, who have a 30% increase in the risk of developing schizophrenia relative to healthy controls. Similar alterations were observed for microstates C and D, indicating that these microstates may represent early markers for the risk of developing schizophrenia. In addition, Kikuchi et al. (Kikuchi et al., 2007) showed that successful antipsychotic treatment normalizes the patterns of microstates C and D in patients with schizophrenia, and Sverak et al., (Sverak et al., 2017)

showed that intensive repetitive TMS over the left dorsolateral prefrontal cortex decreased the occurrence of microstate C in those schizophrenic patients who responded positively to the treatment. These EEG microstate parameters may thus not only be relevant for monitoring the vulnerability of patients at risk for schizophrenia and the effects of treatment, but also for examining the efficacy of treatment in patients with schizophrenia. Diaz and colleagues (Diaz Hernandez et al., 2016) recently proposed that EEG microstate neurofeedback can be used to up-regulate the duration of microstate D in patients with schizophrenia. In a feasibility study involving healthy volunteers, the authors reported that participants successfully increased the duration of microstate D when this parameter when feedback regarding this parameter was provided in a close-loop system.

The microstate approach has also been used to investigate conditions such as dementia (Nishida et al., 2013), narcolepsy (Drissi et al., 2016), panic disorder (Kikuchi et al., 2011), multiple sclerosis (Gschwind et al., 2016), head injury (Corradini and Persinger, 2014), diplegia (Gao et al., 2017), and stroke (Zappasodi et al., 2017). In contrast to schizophrenia, decreased occurrence of microstate C and changes in microstate A and B have been observed in patients with most of these other conditions, indicating that imbalances in microstate C and D may be specific to schizophrenia. Gschwind and colleagues (Gschwind et al., 2016) investigated 53 patients with relapsing-remitting multiple sclerosis using high-density EEG, observing increases in the duration and appearance of microstate A and B. Using stepwise multiple linear regression models, the authors demonstrated that these two microstate changes predicted several clinical variables such as disease duration, and annual relapse rate as well as disability, depression, and cognitive fatigue scores. These findings suggest that multiple sclerosis affects the “sensory” networks (visual, auditory) rather than the higher-order functional networks, as observed in schizophrenia.

Study König	Year	Patients	Medication	Number	Microstate			
					A	B	C	D
	1999	Schizophrenia	No	9				↓ Dur, Topo
Strelets	2003	Schizophrenia	No	14		↓ Dur, Topo		
Lehmann	2004	Schizophrenia	No	27	↑ Occ, Cov	↓ Dur	↑ Occ	↓ Dur
Kikuchi	2007	Schizophrenia	No	21		↑ Occ	↑ Occ	↓ Dur, Cov
Nishida	2013	Schizophrenia	No	21	↓ Dur ↑ Occ	↓ Dur	↑ Occ	↓ Dur
Andreaou	2013	Schizophrenia	Yes	18		↑ Cov		
Tomescu	2015	Schizophrenia	Yes	27			↑ Dur, Occ, Cov, GEV	↓ Occ, Cov, GEV
Irisawa	2006	Schizophrenia	No	24		↓ Dur		
Kindler	2011	Hallucination	Yes	9				↓ Dur
Andreou	2013	High-risk Schizo	Yes	18	↑ Cov, Occ			
Tomescu	2014	22q11DS	Yes	30			↑ Dur, Occ, Cov, GEV	↓ Dur, Occ, Cov, GEV
Nishida	2013	Dementia	No	18			↓ Dur	
Kikuchi	2011	Panic disorder	No	18	↑ Cov, Occ		↓ Occ	
Gschwind	2016	Multiple sclerosis	No	53	↑ Dur	↑ Dur		
Corradini	2014	Head injury	No	26	↓ Dur		↓ Dur	↓ Dur
Drissi	2016	Narcolepsy	No	16	↑ Dur, Cov, GEV	↓ Dur, Cov, GEV	↓ Dur, Cov, GEV	
Gao	2016	Spastic diplegia	No	15	↑ Occ	↓ Dur	↑ Occ	
Zappasodi	2017	Stroke	No	47			↓ Occ & Topo in left stroke	↓ Cov & Topo in right stroke

Dur= Duration, Occ=Occurrence, Cov=Coverage, GEV=Global Explained Variance, Topo=Topography

Figure 7. Summary of published studies regarding EEG microstate changes in neuropsychiatric diseases using the conventional *k*-means clustering approach and restricting the analysis to the four canonical microstate maps.

11. Open questions and outlook

Microstate analysis has typically been presented as an alternative and independent approach for analyzing resting-state EEG data, although recent evidence indicates that microstate features and more classical quantifiers of EEG resting state activity exhibit some associations and similarities. Topographic time-frequency decomposition is based on wavelet-transformed multichannel data (Koenig et al., 2001), which assumes that all processes contributing to a particular state share the same temporal dynamics. In addition, this method replaces the constraint that prohibits temporal overlap with the constraint that prohibits overlap in time, phase, or frequency. In this case, EEG is regarded as the superposition and sequence of synchronous oscillations of potentially widespread networks at specific frequencies. When such methods are augmented by dictionary-learning

procedures, one may again obtain a discrete set of transiently active functional brain states, which are now defined in time, frequency, and phase (Koenig et al., 2005; Studer et al., 2006). Interestingly, a recent study based on combined EEG and fMRI measurements indicated that the activity of particular transient networks integrated by synchronous oscillations of cortical neurons was correlated with the BOLD signal in particular sub-regions of the thalamus in a frequency-specific manner (Schwab et al., 2015). The involvement of thalamo-cortical loops (Lopes da Silva, 1991) may thus be an important link between the typical oscillations observed using EEG, the overarching pattern of synchronization as assessed via microstate analyses, and the cognitive correlates of spectral and microstate features of resting-state EEG data.

In addition, different assumptions underlying the quantification of brain connectivity must be clarified to improve the analysis of resting-state connectivity based on EEG data. Some of these assumptions are incompatible and should not simply be combined, while studies to date have proposed incomplete solutions to the issue of volume conduction by regarding the signals obtained using particular electrodes as proxies for the activity of underlying brain regions, or by taking instantaneous correlations of signals as a direct index of connectivity among two regions without taking potential confounders of volume conduction into account. Even if such issues are fully considered (e.g., by basing connectivity analyses solely on the imaginary part of the coherence of source estimates), “microstate-type connectivity” remains incompatible with such lagged measures of connectivity, as the former assumes simultaneity of activity among the involved nodes, whereas the later excludes such simultaneity. However, this difference in methodology leads to the interesting question of whether such time delays exhibit functional or dysfunctional roles with regard to neuronal interactions. In addition, analyses of lagged connectivity become difficult if more than two nodes interact with one another, as one node (i.e., in the thalamus) simultaneously affecting two other nodes is likely to induce approximately simultaneous oscillations in these two target nodes. The activity of these two target nodes would thereby be non-lagged, and not be considered in measures of lagged connectivity, regardless of its potential functional significance. Our proposal for integrating both lagged and non-lagged connectivity into a common framework is thus to first collapse all variance of the signal that can reasonably be explained by a common phase, which captures all instantaneous interactions, and all effects of volume conduction. Following this initial step, it is then possible to study the time-delayed interactions among these states. In the classical microstate analysis, this involves examining transition probabilities. If

microstate-type time-frequency analyses are applied, the classical measures of lagged interactions, such as coherence or measures of causality, can be also be used.

12. Conclusion

The present review has attempted to show that EEG microstate analysis is based on observable phenomena that correspond well with a series of theoretical arguments and experimental evidence that suggest that ongoing mental activity can reasonably be parsed into series of stable intervals in time in the sub-second range. We suggest that the EEG microstates are the currently best available electrophysiological manifestations of these intervals. Whether or not each microstate reflects a distinct conscious mental brain state in the sense of William James' posit awaits further experimental evidence. The challenge will be to design experiments that are capable to establish direct causal relations of the EEG microstates to certain contents of thoughts.

EEG microstate methodology is increasingly used in experimental and clinical studies. It is therefore important that the analysis procedures and objective quantifiers are well defined so that studies can be compared. While we offer a standard analysis pipeline in this review, we also discuss some key issues are still not fully solved, in particular the number of microstates and the way to define them. Fixing the number of microstates to the 4 canonical map topographies can make sense, particularly in group comparisons. However, the attribution of these 4 maps to the canonical maps simply based on visually identified topographic similarities is rather problematic and can lead to misinterpretation of the results. We made clear in this review that the optimal number of clusters should be defined in each dataset individually and we proposed global criteria to define this number. In addition, rigorous statistical topographic correlation analysis has to be applied if a fixed number is used in order to compare conditions or groups.

Another issue concerns the sources underlying the different microstates. Several studies interpreted their findings of changes in the temporal dynamics of a certain microstate on the basis of the combined EEG-fMRI study by Britz and colleagues (Britz et al., 2010). This might be problematic given the still open issue of the relation between broad-band EEG activity and BOLD fluctuations, the different time-scale in which these phenomena are observed, and the ongoing debate about the subdivision and the functional significance of fMRI resting state networks. Direct EEG source imaging methods are more

promising but work still needs to be done to establish a stable, replicable and externally validated attribution of brain networks to the microstates.

Finally, an open question concerns the relation between functional connectivity analysis and the concept of EEG microstates. Since a stable topography over a certain amount of time excludes phase-lagged activity, connectivity analysis methods that look for time-lagged connections are incompatible with the definition of connectivity within a microstate, but may have systematic links to microstate transitions. Methods that explicitly and separately encompass both instantaneous and lagged manifestations of network dynamics in EEG are in principle available, but will certainly benefit from further developments, and still await to be systematically put to work and validated in relevant experimental data.

In sum, EEG microstate analysis is a promising tool to study the temporal dynamic of ongoing mental activity in health and disease. We are confident that future studies will establish a more stable methodological approach to define these states and will reveal the relation between these electrophysiological phenomena and the underlying mental activity of the human brain.

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