Scalp field dynamics in evoked and spontaneous EEG

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Introduction

This handout summarizes the educational course on the analysis of the temporal dynamics of scalp electromagnetic fields. The course demonstrates the advantages of scalp field analysis over conventional waveform analysis and illustrates its application in evoked and spontaneous EEG signals. The text follows chapter 6 in the book "Electrical Neuroimaging" (1). More details can be found in this chapter and in other review articles (2-6). The course focuses on EEG and ERP analysis but the methods can be applied to MEG as well.

Caveats of ERP waveform analysis

The conventional analysis of event-related potentials focuses on specific components that are defined in time and in space (7). Definition in time refers to the post-stimulus time period during which the component peak is expected to appear; definition in space refers to the electrode at which this peak is expected to be maximal. Latency and amplitude differences of this peak between stimulus conditions or between groups of subjects and patients is supposed to reflect alterations of stimulus processing at a certain sensory or cognitive stage. While this approach has certainly led to many important insights into human brain function, it suffers from several caveats that can lead to misinterpretations and to difficulties to replicate findings (8).

Most of the ERP studies are nowadays recorded with multichannel EEG systems and electrodes cover the whole head surface. Restricting the analysis to a few electrodes only is difficult to justify. In addition, it leads to high risk of Type 1 error if the selection of the electrodes and time windows of interest is based on screening of the dataset and is not pre-determined based on the literature (8). On the other hand, analysis of the multichannel data without à priori selection of electrodes or time windows leads to massively parallel significance testing that need to be treated appropriately. In addition, ERP waveforms completely depend on the reference and consequently results of significance tests of amplitudes between conditions change if the reference electrode changed (6). Finally, interpretation of such amplitude differences at a given electrode cannot directly be interpreted as changes in the neuronal activity underlying this electrode.

The three main problems of ERP waveform analysis are illustrated here:

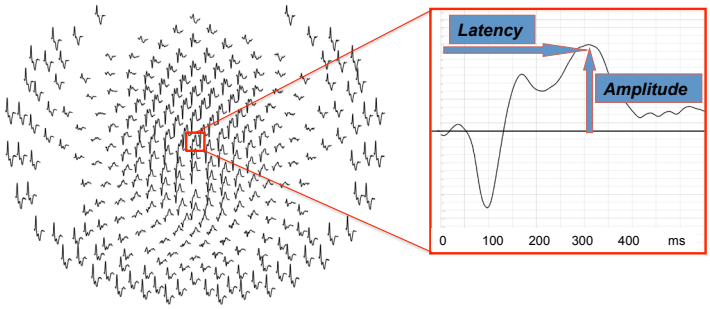

Fig. 1: Caveat 1: The choice of electrode site and time window is prone to **Type I error** if selected on the basis of the observed differences in the same data. Selection of one or a few electrodes and one specific latency window in multichannel ERP data must be well justified and ignores a wealth of information.

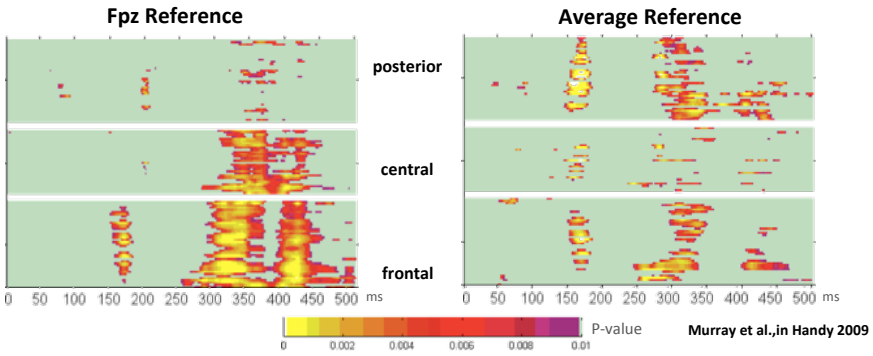

Fig.2: Caveat 2: ERP waveforms are **reference-dependent**. The choice of the reference determines the results and studies with different reference locations cannot be compared.

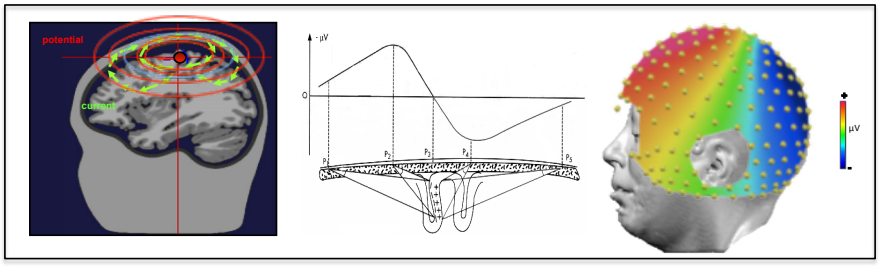

Fig.3: Caveat 3: The interpretation of the results is hampered by the fact that the scalp electrodes **not only record brain activity directly underlying them**. Interpreting an effect at a certain electrode as neuronal activity differences underneath the electrode it wrong.

Topographic analysis of the event-related potentials

Instead of looking at multichannel EEG and event-related potentials as multiple waveforms, one can view it as a series of scalp potential fields, i.e. as surface potential maps with a certain unique topography at any moment in time. This topography reflects the sum of the all momentary active neuronal populations in the brain whose potential fields propagates to the brain surface due to volume conduction. It is a physical law that whenever the topography of the scalp potential map changed, the distribution of the active neuronal populations in the brain changed. Note, however, that the opposite does not hold: the same topography can be generated by different configurations of active neurons in the brain (the inverse problem).

The main aim of the topographic analysis of EEG and ERPs is to look for such changes of the configuration of the potential field over time, between experimental conditions, or between groups. It directly reveals when different generators are being active in the brain.

The topographic analysis of the scalp potential field has several advantages over the waveform analysis:

1. It is **reference-independent**: changing the reference does not change the topography of the electric field (i.e. the potential distribution).

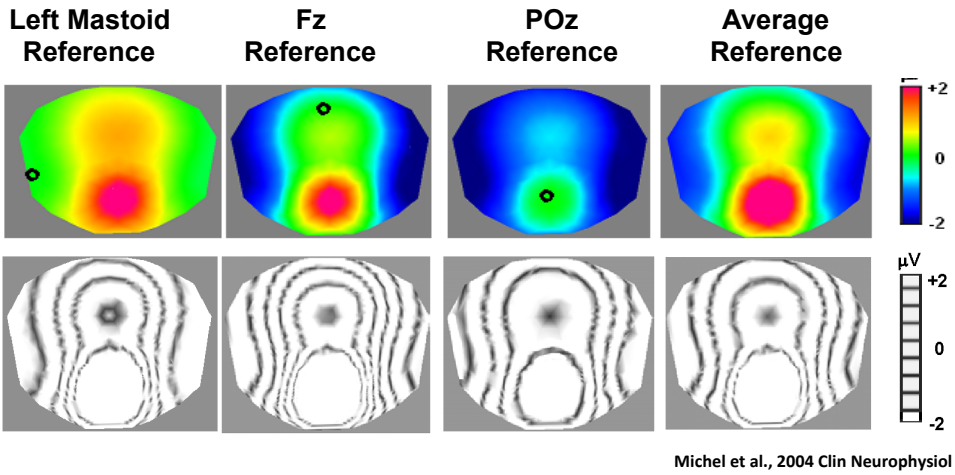

Fig. 4: *EEG maps referred to different references: the zero-level changes, but not the topography as illustrated with the equipotential maps below the color maps.*

2. The number of significance **tests is drastically reduced** when comparing topographies between conditions/groups as compared to the comparison of amplitudes at each electrode.

3. Differences in topography directly indicate differences in the configuration of the **underlying sources**.

Event-related potential microstates

Looking at event-related potentials as a series of potential maps makes clear that the time series are characterized by a limited number of map configurations, each of it staying stable for a certain period of time and just increasing and decreasing in strength. These different map configurations can be classified using data-driven spatial factor analysis approaches that describe the ERP as a being composed of a limited set of topographies (9). Fitting these maps back to the data by calculating the spatial correlation between the cluster map and each individual map of the time series results in sequential time periods that are each covered by one specific map. In most cases, these time periods include one specific ERP component known from the conventional waveform analysis (2). The time period during which the map is present has been called "ERP microstates" (10, 11) that Dietrich Lehmann initially described in the spontaneous EEG (see below).

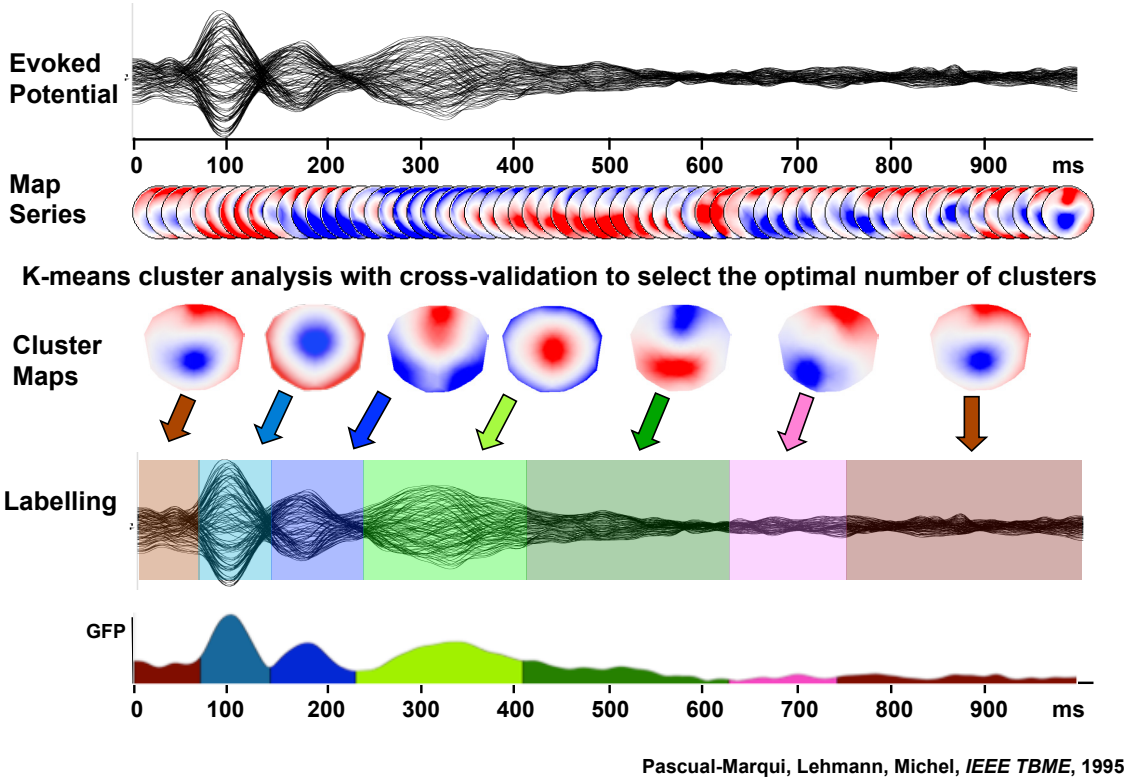

Fig. 5: *Illustration of the spatio-temporal factor analysis of ERPs: The ERP is described as a series of maps. These maps are submitted to a factor analysis, in this case to a k-means cluster analysis and a certain optimization criterion, (in this case cross-validation) determines the optimal number of dominant maps. These cluster maps are then fitted back to the data by spatial correlation and each time-point is labeled with the map it best correlated with. This fitting shows that each map covers a certain time period (microstate) that usually includes the well-known ERP components.*

Statistical analysis of ERP microstates

As described above multichannel ERPs can be compared by testing for significant difference between conditions or subject groups for each time-point and electrode. While this analysis can give some indication of when and where the conditions differ, it is prone to the problems described above (multiple testing, reference-dependency, limited interpretability).

One can directly test difference of the topography of the ERPs for each time point. This test is reference-independent and independent of the number of electrodes. It is based on bootstrapping methods with randomly shuffling maps between conditions and comparing the Global Map Dissimilarity between the shuffled and the original distribution (4, 5, 12). Significant differences in map topography between conditions directly indicate that the underlying generators were different at the tested time point.

A problem can arise with this test if the conditions that are compared shift in latency because of a prolongation of a certain processing step in one condition. Such a latency shift can lead to differences in topography at all latencies and to misinterpretations if not checked by other methods.

An alternative approach to test for differences of multichannel ERPs between conditions is to directly apply the above described spatial factor analysis to all ERPs of all conditions simultaneously and then test for factors (i.e maps) that are specific for a given condition (4, 13). For that the maps derived from the factor analysis, for example the k-means cluster analysis, are fitted back to each single subject's ERP of each condition. This individual assignment allows to extract several parameters for every single cluster (microstate) map:

- the variance explained by the map
- the time when the first or last assignment to the map was observed
- the total number of time points assigned to the map

These individual parameters can then entered into classical univariate test statistics such as t-tests or ANOVAs to test which of the maps with which parameter differs between conditions or groups. The following figure illustrates this approach. A similar approach has been applied to single-trial ERPs (14) and modifications in terms of determining the number of cluster and of performing group statistics have been proposed (4).

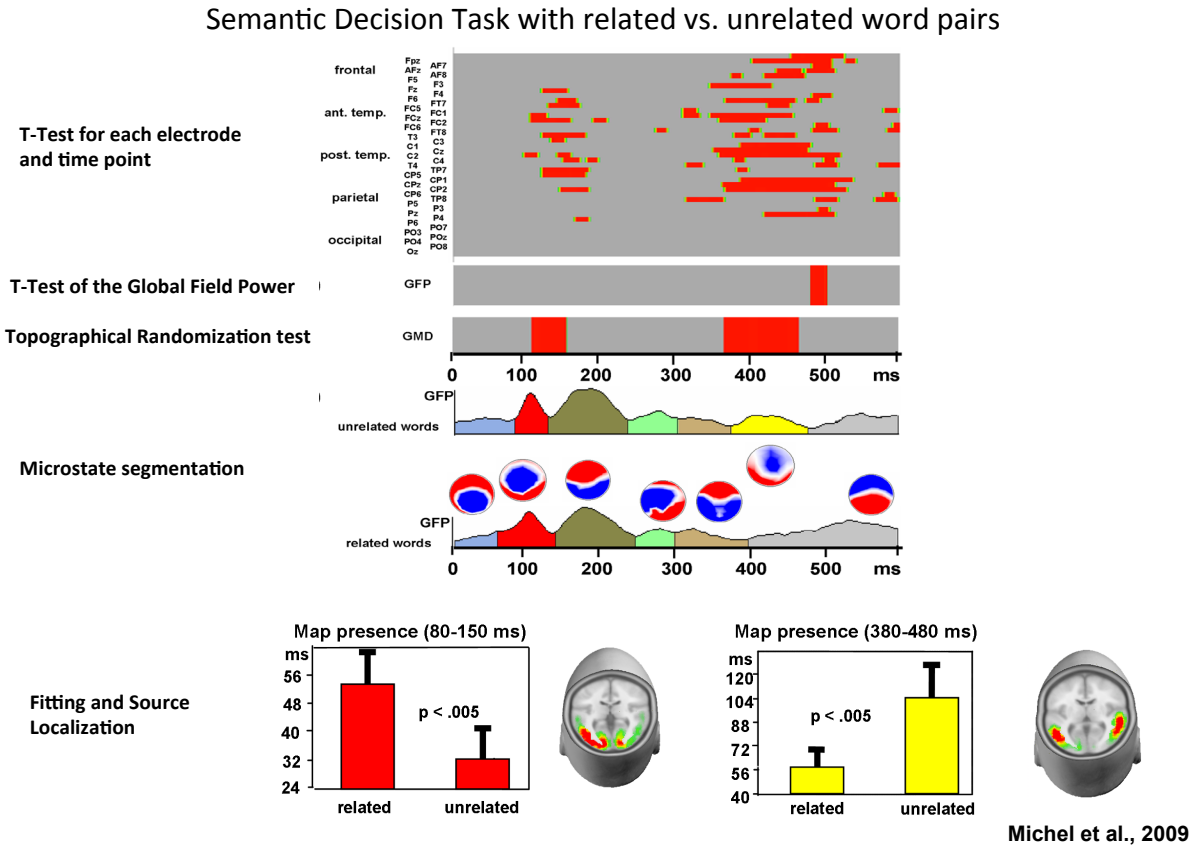

Fig.6. *Example of a comprehensive analysis of multichannel ERP. The data comes from a visual semantic decision task where subjects had to decide whether word pairs semantically correspond or not. The first ERP comparison was done on the level of the amplitude at the single electrodes (referred to the average reference) at each time points. It indicates differences in two time windows (around 150 at 400 ms). The second and third analysis concerns global measures across all electrodes for each time point. The first on global map strength (global field power, GFP), the second on field configuration (global field dissimilarity, GMD). They show that the previously observed effect in first time period is due to topographic changes only, while the second time period is it due to topographic and field strength changes. The third analysis used the clustering and fitting method. This "microstate analysis" revealed that the effect in the first time window was due to a strong prolongation of the microstate covering the P100 component (leading to a topographic difference at the transition between P100 and N150). The effect in the second time window, on the other hand, is due to the appearance of a new map in the semantically unrelated word pairs, the well-known N400 component. Statistically, these effects are confirmed by the increased presence of the maps in the corresponding condition in the individual subjects. Finally, a distributed inverse solution of these microstate maps allows to estimate the brain structures participating in these effects (from (1)).*

Spatio-temporal analysis of spontaneous EEG

Conventionally, spontaneous EEG is analyzed in the frequency domain by assessing time-series of spectral power in given frequency bands at certain electrodes and correlation of activity between electrodes. It is widely believed that brain rhythms are the basic parameter that define functioning and interaction within and between the modules of large-scale functional networks, and thus the basic mechanism of cognitive processing.

Almost three decades ago (15), Dietrich Lehmann introduced an alternative approach to analyze multichannel spontaneous EEG, namely in terms of time-series of scalp potential maps and in terms of the variations of their spatial properties across time. The same arguments as for the ERP described above speak in favor of this approach for the spontaneous EEG. Most importantly again, the spatial configuration of the scalp potential map is independent of the reference electrode, while power spectra and coherence measures of EEG waveforms are not.

When inspecting time-series of scalp potential maps of the spontaneous EEG it becomes obvious that like for the ERP, the topography of the map does not randomly and continuously change over time. The map topography remains stable for some tens of milliseconds and then very quickly changes into a new configuration in which it remains stable again. Thus, potential map series appear as discrete segments of electrical stability that last for about 100 ms, and are separated by sharp transitions. Within a given period of stable configuration, the strength of the field can vary, but the topography remains the same. Only polarity continuously alternates according to the dominant rhythm due to the intrinsic oscillation within the circuit, but without changing the topography.

After the initial description of this temporal behavior of spontaneous EEG maps, several studies explored the characteristics, rules, and functional significance of these segments of stable activity patterns, termed *"functional microstates"* (for recent reviews see (1, 11)). These studies revealed that the number of microstate classes in terms of topography is small. Many studies using different classification approaches, different number of electrodes and different filter settings, repeatedly demonstrated that only 4 microstate classes largely dominate the spontaneous EEG in awake, healthy adults (16-18). These four microstate classes have very typically topographies that are highly similar across subjects (1, 11, 17, 19) and are stable across the life span: one study with 496 subjects between 6 and 80 years showed that the mean durations of each of these four microstates is around 80–150 ms (18).

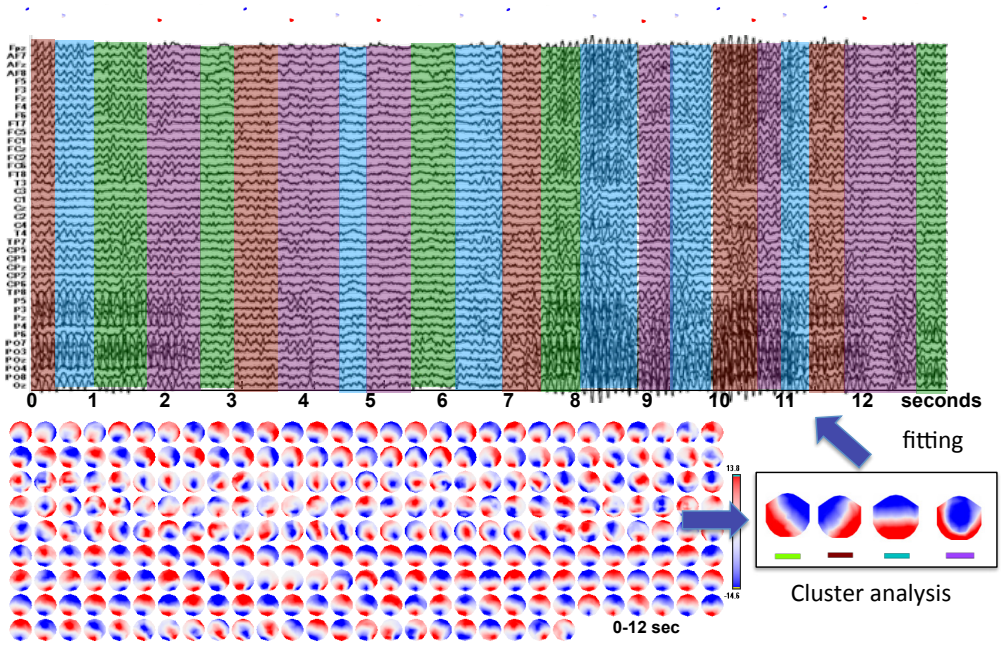

Fig.7. *The EEG microstates: The EEG is considered as a series of scalp potential maps. These maps are clustered using a spatial cluster analysis (ignoring polarity). Typically, 4 prototypical maps domain the eyes-closed resting EEG, explaining about 70-80% of the data. When fitting these 4 cluster maps to the data and labeling each time point with the best assigned cluster map, one observes sequential time periods that last in average about 100 ms, during which the same map is dominating, a so-called EEG microstate.*

The empirical observation of functional microstates of the brain that last for around 100 ms fits very well with models of discrete periods of coherent network activity (20). Lehmann repeatedly proposed that the EEG microstates reflect the different "steps" or "contents" of information processing, i.e. that they are the basic building blocks of the content of consciousness, the "atoms of thoughts" (19, 21, 22). Therefore, several researchers discussed the possibility that the functional microstates are the neural implementations of the elementary building blocks of consciousness, i.e. the electrophysiological correlates of a process of global "conscious" integration at the brain-scale level (20, 23, 24). BJ Baars concluded: "the possibility of brain microstates supporting conscious 'flights and perches' is intriguing. We may see a consensus emerging if the evidence holds up" ((25) , page 2).

The temporal structure of the EEG microstates

Given the fact that there are only a few microstate topographies and that they alternate in discrete chunks of around 100 ms duration, the most evident question is whether the temporal structure of this alternation follows certain rules. More metaphorically: if the microstates represent the atoms of thought, does the sequence of the microstates ("microstate syntax") determine the content of the momentary daydream. The principal question is thus not only whether the transitions of microstates are non-random, but also whether duration, appearance and frequency of the different microstates have a certain functional significance. Two studies directly examined the question of

microstate transition (17, 26). Both studies demonstrated that transition probabilities deviated clearly from a random process. Thus, as Koenig puts it, "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" ((27), page 1019).

In fact, several studies showed EEG microstate changes in different mental disorders. They showed that schizophrenic patients have a reduced number, a decreased duration, and an altered syntax of some microstates classes (26, 28-31), that reversed with medication (32). Microstate duration was also decreased in depression and some microstate were repeated more frequently (33). Patients with Alzheimer's disease also showed decreased duration and an increased number of microstates (34, 35). Antipsychotic and anxiolytic drugs as well as meditation and hypnosis can also alter microstate characteristics (36, 37).

Correlation between the functional microstates and the fMRI resting states

The reproducibility of the microstates and the fMRI-defined resting state networks across subjects indicates that they might be mediated by the same hard-wired large-scale neurocognitive networks (27). The obvious question is therefore whether and how the EEG microstates, and the fMRI-defined resting-state networks are related. The possibility to record the EEG inside the scanner and to adequately clean the artifacts induced in this environment allow for direct comparisons. Several such comparison studies were recently performed (38-40). Despite methodological differences, all of them showed clear relations between fMRI resting states and EEG microstates. In our own study we analyzed the EEG in the scanner with the same methods described above (38). We then submitted the cleaned EEG data of each subject to the global spatial k-means cluster analysis, and used the cross-validation criterion to determine the optimal number of maps. In virtually all runs of all subjects, the cross-validation criterion again identified 4 clusters as the best solution, and the maps of these 4 clusters corresponded very well to the four microstates previously described (see above). We then computed the spatial correlation between the 4 dominant microstate maps and the raw EEG, indicating how strongly a given microstate is represented at any given moment. We convolved these time courses with the canonical hemodynamic response function to obtain the regressors for subsequent fMRI general linear model estimation. In other words, we built a model of how well each microstate map could explain the BOLD fMRI activations in each subject. Group-level statistics revealed four resting state networks that were previously identified based on the fMRI signal alone using ICA: the auditory network, the visual network, a network implied in saliency-processing and the attention-reorientation network (Figure 8). The study also showed that there is no correlation between the time-course of power in certain EEG frequency bands and the EEG microstate time-courses, demonstrating that they measure different phenomena recorded with the EEG (Figure 9).

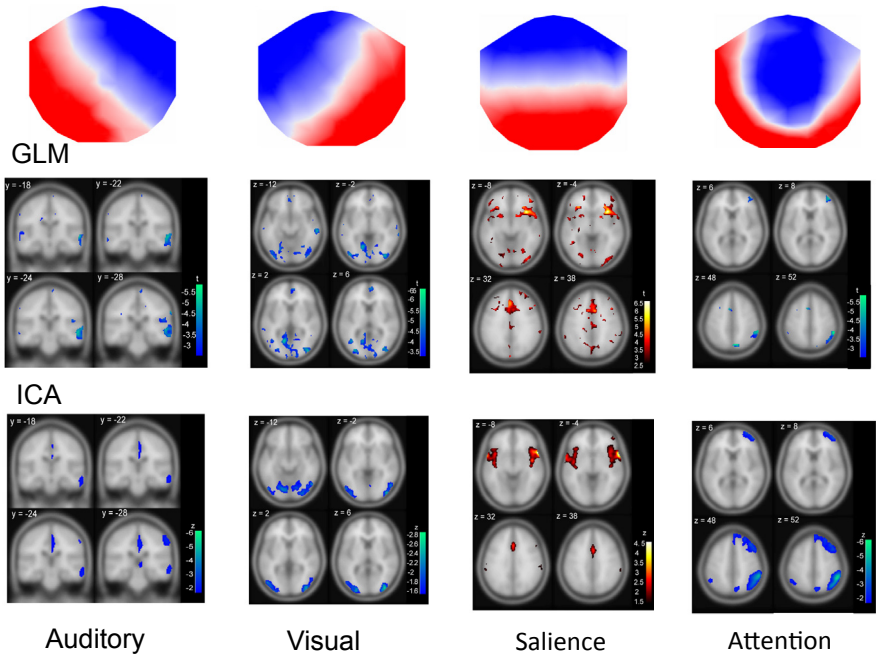

***Fig. 8**. Comparison of EEG microstates with fMRI resting states. The four EEG maps represent the dominant microstate maps identified at the group level (N=8) using cluster analysis of the EEG in the scanner. For each microstate map the BOLD activations revealed by GLM regression of its time course is shown. Bilateral temporal areas were found for microstate 1 (a), bilateral extrastriate visual areas for microstate 2 (b), ACC and bilateral inferior frontal areas for microstate 3 (c), and right superior and middle frontal gyrus as well as the right superio r and inferior parietal lobules for microstate 4 (c). These four networks strongly correlated with one specific fMRI network found by conventional ICA analysis of the fMRI of these subjects. Figure from (38).*

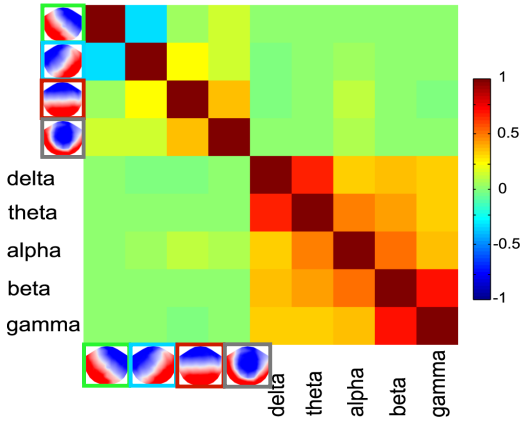

***Fig. 9**. Correlation between the time courses of the EEG microstate maps and the time courses of the power in different frequency bands (averaged over all electrodes). Note that the microstate maps are not or even anti-correlated, while the frequency power of the different frequency bands are highly correlated. No correlation is found between microstate time courses and frequency power, indicating two completely independent measures of spontaneous EEG. Figure from (38).*

A particularly interesting finding in this study was that the anti-correlated time courses of the EEG microstates, which fluctuate at the order of ~100 ms, remained anti-correlated after convolution with the canonical HRF, which acts like a huge temporal smoothing filter. In other words, this measure of momentary overall brain activity varies at a high frequency and is still meaningful after convolution with the HRF. This clearly indicates that the underlying dynamics of the resting state networks is much faster than analysis of the fMRI signal alone suggests. The result is also indicative of the presence of long-range dependencies in the time course of the microstate occurrence. Without such long-range dependencies, the temporal smoothing with the HRF would have removed any anti-correlation between the different microstate time-courses. In (41) we formally demonstrated this long-range dependency of EEG microstates.

Conclusion

This course demonstrated the advantages of spatio-temporal analysis of multichannel EEG and ERP as compared to conventional waveform analysis to study spontaneous, evoked, and pathological brain functions. The fact that the temporal progression of the brain electric activity can be described as sequence of microstates with stable map topographies makes it reasonable to consider these microstates as the neurophysiological manifestation of the basic building blocks of spontaneous or evoked mental activitiess. The spatial segmentation procedures adapted from pattern recognition algorithms permits to mathematically describe and efficiently differentiate these microstates in time and between experimental conditions. Together with powerful distributed source analysis methods that are nowadays available to estimate the sources that generated the scalp potential maps, the spatio-temporal EEG analysis allows to describe the active large-scale neuronal networks of the brain in the sub-second range.

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