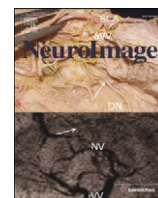




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Review

Towards the utilization of EEG as a brain imaging tool

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ABSTRACT

Recent advances in signal analysis have engendered EEG with the status of a true brain mapping and brain imaging method capable of providing spatio-temporal information regarding brain (dys)function. Because of the increasing interest in the temporal dynamics of brain networks, and because of the straightforward compatibility of the EEG with other brain imaging techniques, EEG is increasingly used in the neuroimaging community. However, the full capability of EEG is highly underestimated. Many combined EEG-fMRI studies use the EEG only as a spike-counter or an oscilloscope. Many cognitive and clinical EEG studies use the EEG still in its traditional way and analyze grapho-elements at certain electrodes and latencies. We here show that this way of using the EEG is not only dangerous because it leads to misinterpretations, but it is also largely ignoring the spatial aspects of the signals. In fact, EEG primarily measures the electric potential field at the scalp surface in the same way as MEG measures the magnetic field. By properly sampling and correctly analyzing this electric field, EEG can provide reliable information about the neuronal activity in the brain and the temporal dynamics of this activity in the millisecond range. This review explains some of these analysis methods and illustrates their potential in clinical and experimental applications.

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Introduction

Over 80 years ago the EEG was first described with the promise of it providing a “window into the brain” (Berger, 1929). However, the transparency of this window has been obscured in the sense that the sources in the brain that produced the signals on the scalp were not readily visible. Recent advances in EEG recording technology and EEG analysis methods made this window much more transparent, and the signal–source relationship has become clearer. In this review we overview some of the basic methods that render EEG a comprehensive and powerful brain-imaging tool that directly maps the brain neuronal activity with reasonable spatial and superb temporal resolution.

During the largest part of the 80 years of existence of EEG, and unfortunately to some extent still today, the analytic potential of EEG has not been fully exploited. On the contrary, several serious misunderstandings about the generation of the scalp potentials have led to wrong interpretations of the data and to claims about brain functions that were later falsified by intracranial recordings, lesion studies, or neuroimaging methods; thereby severely discrediting EEG.

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Such misinterpretations were mainly due to the ignorance of important physical principles that underlie the measurement of electric potentials at the scalp surface. Most important is the fact that a given electrode on the scalp does not record solely the neuronal activity directly underlying it. Rather, every electrode picks up signals from different sources that can eventually be quite distal. This is because the electric field of each active source in the brain spreads in all directions and is thus picked up to a variable extent by each electrode. This also holds for the reference electrode against which the potential at one scalp electrode is compared. Fluctuation of the voltage at the reference electrode will lead to changes of the potential at the active electrode even if the voltage at that point was actually stable. There is no point that is electrically silent and could be considered as true zero potential. Thus, changing the reference position will change the absolute potential at the active electrode because EEG forcibly entails recording potential differences. This reference-dependent feature of EEG potentials is often cited as a major drawback of EEG as compared for example to MEG (Hari, 2011).

However, it is important to note and to insist on the fact that the topography of the potential field is completely independent of the choice of the reference (Geselowitz, 1998). Because it is the topography of the electric or magnetic field that is the only relevant information used for electric or magnetic source imaging, the so-called “reference-problem” of the EEG effectively does not exist and a search for an optimal reference (Gencer et al., 1996) for source imaging is meaningless.

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In this article we overview EEG analysis methods that are based on the understanding of the biophysical principles that lead to the potential field on the scalp and that are quantifying the properties of this potential field in time and in space. Analysis methods that are based on single channel waveforms are not considered here, because such analyses are ambiguous with respect to 1) the underlying generators as well as more general neurophysiologic causes and 2) the statistical confidence that can be placed on them (Michel et al., 2009; Murray et al., 2008; Murray et al., 2009).

Principles of EEG spatial analysis

The EEG is traditionally analyzed in terms of temporal waveforms at certain channels, looking at power of rhythms in the spontaneous EEG, at amplitude and latency of the peaks and troughs in event-related potentials (ERPs), or at particular grapho-elements in pathological or sleep stages. There is no doubt that this type of analysis has provided many important insights regarding brain functioning in health and disease, but it has not been considered as an imaging method in the sense that one could infer active areas in the brain generating these waveform features.

From a biophysical point of view, a given active electrode on the scalp measures the electric field that is generated by the sum of the momentary post-synaptic potentials in the brain. Due to volume conduction these electric fields spread in the brain and reach in attenuated form the scalp surface. Each electrode measures a local part of this field. Accordingly and with a sufficient number of electrodes distributed all over the scalp, this electric field can be measured and reconstructed as a so-called scalp potential map. A new map is generated at every time instant in the millisecond range (whatever the sampling rate of the EEG amplifiers). It is a physical law that whenever the map topography has changed, the distribution and/or orientation of the active dipoles in the brain have changed (Vaughan, 1982) (Lehmann, 1987).

Since its inception, the MEG community uses this topographic framework for the analysis of the signals. Instead of waveforms, the MEG community generally looks at the properties of the magnetic field outside the head and infers the sources and the temporal dynamics of these sources in the brain (Salmelin and Baillet, 2009; Williamson et al., 1991). It has been recognized for a long time that the EEG can be analyzed in the same way as the MEG; namely using topographic maps and spatial pattern analysis methods as well as source localization techniques (Wong, 1991). While the traditional waveform-based analysis still dominates in the EEG community (Luck, 2005), the increasingly common use of high-density EEG systems with more than 100 electrodes (Tucker, 1993) both in experimental and clinical settings leads to an increasing request for such spatial analysis methods for the EEG as well (Fig. 1).

There are several reasons for basing analyses on topographic information and more generally for treating the data from the entire electrode montage as a multivariate vector. First, topographic measures are reference-independent. The shape of the electric field at the scalp will not change even if one chooses another reference (cf. Fig. 3 in Michel et al., 2004b). It only shifts the zero line without influencing any spatial characteristics of the field. Second, topographic information has a direct neurophysiologic interpretability. Physical laws dictate that topographic differences are indicative of changes in the configuration of the active cerebral sources (though the converse need not be true). Therefore, analysis methods that test for differences in the topography of the scalp potential field are directly revealing instants where the configuration of the neuronal generators changed or differed between conditions. Third, multivariate analyses allow for taking better advantage of the added information provided by high-density electrode montages while also retaining statistical rigor. Analyses can be formulated in a way that effects of strength and differences between conditions due to changes in sources'

configuration can be disentangled and treated independently (Murray et al., 2008). Fourth, EEG mapping is the precursor for EEG source imaging. Using sophisticated source and head models, the location of the generators that gave rise to the scalp potential map can be estimated with high reliability and reasonable precision (Michel et al., 2004b). In what follows, some basic topographic analysis methods are briefly explained before illustrating their use in the analysis of spontaneous and stimulus-related activity.

Topographic analysis the scalp potential field

The voltage potential field on the scalp is characterized by its topography ("landscape") and its strength ("hilliness"). The field topography is directly related to the location and orientation of the underlying sources, while the field strength is related to the amount of simultaneously (and synchronously) active sources. From an analytical standpoint, these parameters can be examined independently.

Global Field Power

The strength of the potential field can be quantified by a single measure termed Global Field Power (GFP; (Lehmann and Skrandies, 1980)). GFP is equal to the standard deviation across electrodes at a given instant in time. Because it is a global measure of response strength, GFP provides no information regarding modulations in source configuration or which electrodes are stronger/weaker. Statistical analysis of GFP between conditions can give information on differences of the global amount of synchronized activity at any given moment in time. The GFP measure can also be used to identify "events" that are consistent across trials in terms of the map topography (Koenig and Melie-Garcia, 2010; Tzovara et al., 2012). This approach, labeled topographic consistency test, relies on the observation that GFP of an averaged response is impacted by the spatial topographies of the single measurements contributing to the average. Only if the topographies were similar across trials will the GFP of the average map be elevated compared to an empirical distribution identified using a randomization test that shuffled the data at each electrode from each measurement contributing to the average. Significant GFP increases and thus the existence of a component that is above noise can be determined. The topographic consistency test can thus provide information about the quality of ERP recordings in terms of signal-to-noise ratio, the variability within experimental conditions, and most importantly about time-periods within an epoch where the topographies at a given latency are consistent across observations (i.e. subjects or trials).

Global map dissimilarity

Different map topographies directly indicate different generator configurations in the brain. Given this physical fact, one aim of the topographic analysis is to test for topographic differences between conditions, because it directly permits the conclusion that the underlying generators changed. Topographic differences independent of strength can be quantified using the so-called global dissimilarity index (Lehmann and Skrandies, 1980). It is defined as the root mean square of the difference between two normalized maps (i.e. divided by the GFP). It is a one-number measure of the dissimilarity between two electric fields and can range from 0 to 2, where 0 indicates topographic homogeneity and 2 topographic inversion. This measure can be used to assess statistically significant topographic differences between conditions or groups through non-parametric randomization tests using uni- or multi-factorial designs (Murray et al., 2008; Koenig et al., 2011).

An alternative approach is to measure the spatial correlation between maps, i.e. to test whether two maps are similar. It has to be noted, however, that similar maps do not directly indicate that the underlying generators were the same. The correlation coefficient is

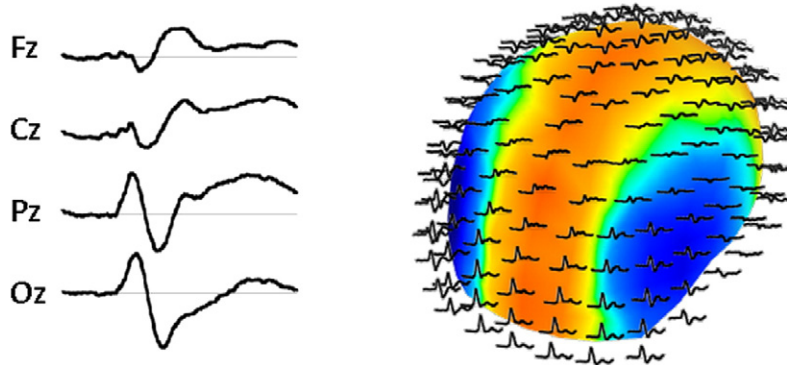
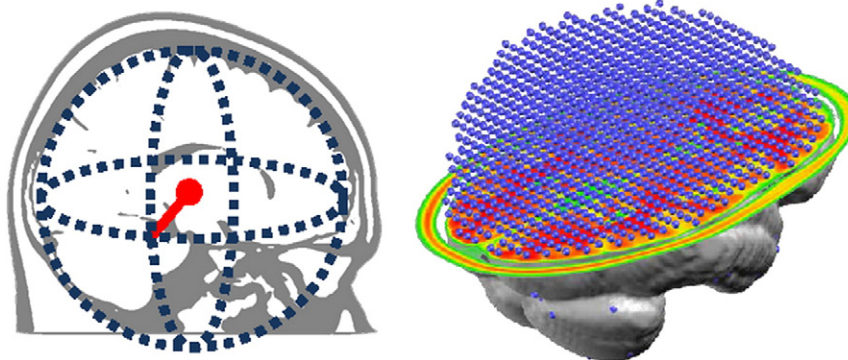
A. From low-density to high-density montages**B. From voltage waveforms to topographic representations****C. From equivalent current dipole to distributed source models**

Fig. 1. Progression of EEG data acquisition and analyses. (A) Electrode montages, including those suitable for pediatric and clinical populations, now cover the head with <2 cm inter-electrode spacing and including >100 channels. (B) With increasing numbers of channels, the visualization of the data has progressed from waveform representations (and analyses) to spatial/map representations (and analyses). (C) Source estimation methods have similarly progressed from a limited number of equivalent current dipoles within a spherical head model to distributed source estimations within realistic head models.

directly related to the spatial dissimilarity measure (i.e. it equals $(2-DISS^2)/2$) (Brandeis et al., 1992).

Topographic map classification

Different groups have proposed to separate different distinct topographies in a time series of multichannel EEG data using classification algorithms. Pascual-Marqui et al. (1995) proposed to use a cluster analysis to determine the predominant map topographies in a given dataset. Cross-validation and other criteria were proposed to determine the optimal number of cluster maps (Brunet et al., 2011). Popular alternatives to the cluster analysis, including principal component analysis (Skrandies, 1989; Spencer et al., 2001; Pourtois et al., 2008) and independent component analysis (Makeig et al., 1997) have been proposed to determine the most dominant spatial components in EEG or ERP time series. Independent of the classification algorithm used and the advantages and limitations inherent to each of them, all these approaches aim to describe the multichannel

EEG as a set of potential maps with different time courses (De Lucia et al., 2010). Subsequent analysis steps then allow determining when each map is dominantly present and which of them differs between experimental conditions or between groups. Results of such analysis can directly be interpreted as being due to different generator configurations in the brain.

EEG source imaging

Once the EEG is recognized as a metric of the brain's electric fields quantifiable at the scalp via high-density montages, it is easily seen how EEG can in turn provide information regarding its underlying generators. However, this version of the inverse problem has no unique solution. Infinite number and configurations of neuronal sources can lead to same scalp potential map. This is referred to as the non-uniqueness of the inverse problem in EEG/MEG. Due to this non-uniqueness, a priori assumptions that are based on physiological

and biophysical knowledge about source generation and propagation have to be incorporated to reduce the number of unknowns and to make the problem solvable. The correctness of these assumptions determines the correctness of the results. Over the last years EEG source localization algorithms have been evolved from single dipole iterative searching methods (Fig. 1) (Scherg, 1990) to comprehensive 3-dimensional distributed source estimations (Pascual-Marqui et al., 2009). Sophisticated realistic head models based on anatomical information derived from MRI scans have further advanced the precision of source localization. It is beyond the scope of this review to detail the different source localization methods. Several comprehensive reviews on this topic exist (Baillet et al., 2001; He and Lian, 2005; Michel and He, 2011; Michel et al., 2004b; Pascual-Marqui et al., 2009; Sekihara and Nagarajan, 2004). It is without any doubt that the precision and the spatial resolution of source localization with high-density EEG and head models with realistic geometry are very high and allow to directly image the neuronal activity in the brain in real time non-invasively. Many experimental and clinical studies have utilized these methods and have validated the correctness of the localization by other imaging methods or by direct intracranial recordings. Selected examples will be shown below in the application sections.

A long-lasting discussion concerning source localization with MEG and EEG concerns the localization precision of EEG as compared to MEG. Because of the distortion of the electric field by the different extra-cerebral tissues, it is still often claimed that MEG has advantages over EEG in source identification (e.g. Hari, 2011). However, there is no direct evidence for this claim. On the contrary, EEG has much higher sensitivity than MEG. EEG detects all source orientations equally well, while MEG is insensitive to radially-oriented sources, and EEG can detect deep sources, while MEG can detect only superficial sources (Ahlfors et al., 2010; Malmivuo, 2012). However, sufficient number of sensors, realistic head models and correct conductivity values are needed to properly exploit the localization capabilities of EEG (Brodbeck et al., 2011; Malmivuo, 2012; Ryyanen et al., 2006).

Connectivity analysis

The question of how brain regions in large-scale networks communicate with each other is of increasing interest in neuroimaging research. Methods to estimate connectivity in networks have been developed and are increasingly applied to fMRI as well as EEG and MEG data (Stephan and Friston, 2011; Kiebel et al., 2009). Because of the high temporal resolution of the electrophysiological measures and the fact that they directly measure synchronized neuronal activity across a wide range of frequencies, functional connectivity measures are of particular interest for the EEG and MEG communities.

A series of methods exist to determine the relationship between time series measured at two different nodes of a network. Calculation of cross-correlation or phase synchronization between two signals is most common. More recently, effective connectivity measures that allow capturing causal relationships and directionality within brain circuits have been introduced (Kaminski and Blinowska, 1991). Most of these latter methods are based on the Granger theory of causality (Granger, 1969). Multivariate methods such as structural equation modeling, partial directed coherence, and directed transfer function are among the most popular methods (Astolfi et al., 2007). All these analysis procedures are based on frequency transformation of the signals. It is important to note here that such connectivity analysis is problematic when applied to the signals measured on the scalp electrode, because of the spreading of the electromagnetic signals from the neuronal sources in the brain to the sensors on the surface, and because of the influence of the reference on phase measures. Coherence or phase synchrony analysis between two electrodes on the scalp gives ambiguous information and cannot be interpreted as

connectivity between areas underlying the two electrodes (Fein et al., 1988; Guevara et al., 2005; Hu et al., 2010; Schiff, 2005). As Steven Schiff put it, “There is far too much literature within the past decade that calculated phase synchronization from common-referenced EEG.” (Schiff, 2005, page 315).

The ambiguity of coherence and phase analysis of the potentials between scalp electrodes can best be solved by assessing functional connectivity between time series extracted from EEG inverse solutions, i.e. by applying the connectivity algorithms to signals in the source space instead of the signal space. Obviously, only full 3-dimensional distributed inverse solution should be used for this purpose. Several studies have shown that functional connectivity patterns of cortical activity in large-scale networks can be effectively determined when combining EEG source imaging with frequency-domain multivariate connectivity measures (Astolfi et al., 2005; He et al., 2011). Recently, such connectivity measures have also been used to study functional interactions between the brains of different subjects called “hyperscanning” (Astolfi et al., 2010; Dumas et al., 2010; Lindenberger et al., 2009).

Spatial analysis of the EEG at rest

In recent years the term “Resting State” has been established and has received considerable attention in the brain imaging literature (Fox and Raichle, 2007). It mainly refers to the coherent fluctuations of blood oxygen level dependent (BOLD) responses in different brain regions measured with fMRI, while the subject is at rest without any particular stimulus or task. Using independent component analysis, distinct patterns of coherent activity in large-scale networks have been identified, called resting state networks (Damoiseaux et al., 2006; Mantini et al., 2009). Besides the default mode network, networks involving predominantly visual areas, auditory areas, sensorimotor areas, areas known to be involved in attentional processes, and others have been described and have been shown to be reproducible across large subject populations (Biswal et al., 2010).

While these studies are fascinating and lead to a new avenue of studies on large-scale brain networks, they have severe limitations when it comes to the understanding of the neurophysiologic mechanisms leading to these correlated BOLD responses and the functional significance of them with respect to ongoing mental activities at rest (Boly et al., 2008). In fact, the BOLD correlations are found in very low frequency ranges of <0.1 Hz. This is much too slow to be relevant for ongoing cognitive activities that change much more rapidly and lead to different spatial patterns of coordinated networks within fractions of seconds (Bressler, 1995; Bressler and Tognoli, 2006; Dehaene et al., 1998).

The EEG with its very fast temporal resolution is much better suited to study the temporal dynamics of ongoing brain activity during rest. In fact, EEG studies on spontaneous activity fluctuations have been performed over the past several decades and have been related to different brain states in the continuum between alert wakefulness and deep sleep.

Multichannel analysis of the resting EEG in the frequency domain

It is widely believed that neuronal oscillations are the basic parameter that defines functioning and interaction within and between the modules of large-scale functional networks, and thus the basic mechanism of cognitive processing (Buzsaki, 2006; Buzsaki and Draguhn, 2004; Singer, 1999). Consequently, the commonly used method to analyze resting state activity with EEG is the frequency transformation, thereby describing neuronal activity as variation of power of brain rhythms in specific frequency bands or as uni- or multi-variate cross-correlation and phase synchronization. This type of analysis of the spontaneous EEG has provided many important findings in the understanding of brain functioning and variations of

these functions during sleep, drug intake, neuropathologies, psychiatric diseases or maturation (Buzsaki, 2006; Michel and Brandeis, 2010).

As already discussed above the interpretation of the results derived from frequency analysis of the EEG waveforms at the scalp electrode is ambiguous, because the results are strongly influenced by the choice of the reference. Absolute power as well as absolute phase of a scalp EEG signal in a given frequency depends on the activity at the reference electrode (Lehmann et al., 1986; Koenig and Pascual-Marqui, 2009; Lehmann and Michel, 1990). The observed power as well as phase changes when the recording reference is changed. However, analyses in the frequency domain of EEG data that are based on the *relationship* of phase and amplitude between channels and not on *absolute* phase and amplitude are reference independent. This can be easily visualized when displaying multichannel EEG data in the complex plane in the form of sine–cosine diagrams with each electrode representing an entry point in this diagram (Lehmann and Michel, 1990). Inspecting such diagrams for different frequencies shows that there is generally a phase that is predominating across all electrodes. This result indicates that the simultaneously active sources in the brain operate in an approximately phase-locked, zero-delay mode, i.e. that they are synchronized (Koenig and Pascual-Marqui, 2009). The amount of synchronization in a given frequency can directly be quantified by calculating the eigenvalue of the two first principal components based on the two-dimensional positions of the electrode-entries in the sine–cosine diagram. The more the eigenvalue of the first component dominates the higher the common phase across electrodes. This measure has been termed Global Field Synchronization (GFS, (Koenig et al., 2001a; Koenig et al., 2005a)).

In order to keep the excellent time resolution of the EEG also in the frequency domain, time–frequency analysis based on wavelets has been used. By combining spatial cluster analysis methods described above with time–frequency analysis, a topographic time–frequency representation of human multichannel EEG can be achieved (Koenig et al., 2001b). This method results in a small number of potential maps that vary in intensity as a function of time and frequency. Such methods allow decomposing the EEG into a succession of a limited number of separate events, where each such event is defined by a topography, by a time course, and by an oscillation with narrowly defined frequency and phase (Studer et al., 2006).

The conventional frequency analysis of multichannel EEG in terms of absolute power at each electrode (often labeled “quantitative EEG” (John and Pritchep, 2006)) is not only reference-dependent, but also does not allow to estimate the sources of a given frequency in the brain because phase information and thus polarity is discarded. In order to perform source localization in the frequency domain, phase information must be considered. This means that distributed inverse solutions have to be applied to the complex three-dimensional vectors. Consequently, frequency-domain inverse solutions are initially complex (Frei et al., 2001). A special case is the fit of a single dipole in the frequency domain. A single dipole cannot account for phase differences between electrodes. Therefore, before fitting a single dipole in the frequency domain, a single phase for all electrodes has to be estimated. Such a method has been proposed by Lehmann and Michel (1990) using the first principal component in the complex plane (the so-called FFT dipole Approximation).

Multichannel analysis of the resting EEG in the time domain

The EEG does not only consist of a summation of rhythmic activity of different frequencies. It has been repeatedly shown that a large (if not even the major) part of the EEG signal is arrhythmic (Bullock et al., 2003; He et al., 2010) and it has been proposed that this arrhythmic activity could also be involved in communication between neurons (Thivierge and Cisek, 2008). It is therefore inadequate to

consider the EEG only as a sort of oscilloscope measurement of brain activity.

An alternative to the conventional analysis of the EEG in the frequency domain is the spatial analysis in terms of time-series of the scalp potential maps and the variations of their spatial properties across time (Lehmann, 1971). When inspecting such time-series of scalp potential maps of the spontaneous EEG it becomes obvious that the topography of the map does not randomly and continuously change over time. Rather, the map topography remains stable for some tens of milliseconds and then very quickly configures into a new topography in which it remains stable again. Lehmann labeled these periods of stable map configurations the functional microstates of the brain (Lehmann et al., 1987). Thus the EEG map series can be described 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. Critically, at any given moment, only one microstate dominates. It has been shown with different classification approaches that only 4 microstate classes largely dominate the spontaneous EEG in awake, healthy adults (Strik and Lehmann, 1993; Britz et al., 2010; Wackerman et al., 1993). These four microstate classes have archetypical topographies that are highly similar across subjects (Lehmann et al., 2009; Lehmann et al., 1998) and are stable across the lifespan. One study with 496 subjects between 6 and 80 years showed that the mean durations for each of these four microstates are around 80–150 ms (Koenig et al., 2002). It is interesting to note that this is in the same time range as the duration of the transient coherent activation within large-scale networks that have been repeatedly proposed in the global workspace model of consciousness (Baars, 2002a; Dehaene and Changeux, 2004; Dehaene and Naccache, 2001), and the duration of the “perceptual frame” needed for conscious perception in backward masking studies (Efron, 1970; Sergent and Dehaene, 2004). 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” (Lehmann et al., 1998). The functional microstates could therefore represent 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 (Baars, 2002b; Changeux and Michel, 2004).

Several different studies have examined the EEG microstates under healthy and pathological conditions. In summary, these studies revealed the following characteristics of the microstates: First, EEG microstates are independent of the frequency of the EEG. The different microstates do not dominate in specific frequency bands (Wackerman et al., 1993), and the time course of the microstates do not correlate with the time course of the power in certain frequency bands (Britz et al., 2010). Second, while only a few microstate topographies dominate the healthy resting EEG, the temporal structure of these microstates allows for a rich syntax. 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” (Koenig et al., 2005b, page 1019). Third, in a combined EEG–fMRI study, the time-course of the EEG resting states was convolved with the time-course of the fMRI BOLD signals and the resulting GLM maps were correlated with the fMRI resting state maps derived from independent component analysis (Fig. 2) (Britz et al., 2010). This study showed that each of the microstates correlated with one of the well known resting state networks (visual network, auditory network, attention network, self-referential network). Thus, EEG resting states are representing the well-known resting state networks. Given the high temporal resolution of the EEG, this correlation now allows studying the temporal dynamics of these resting state networks. Fourth, the reason why the

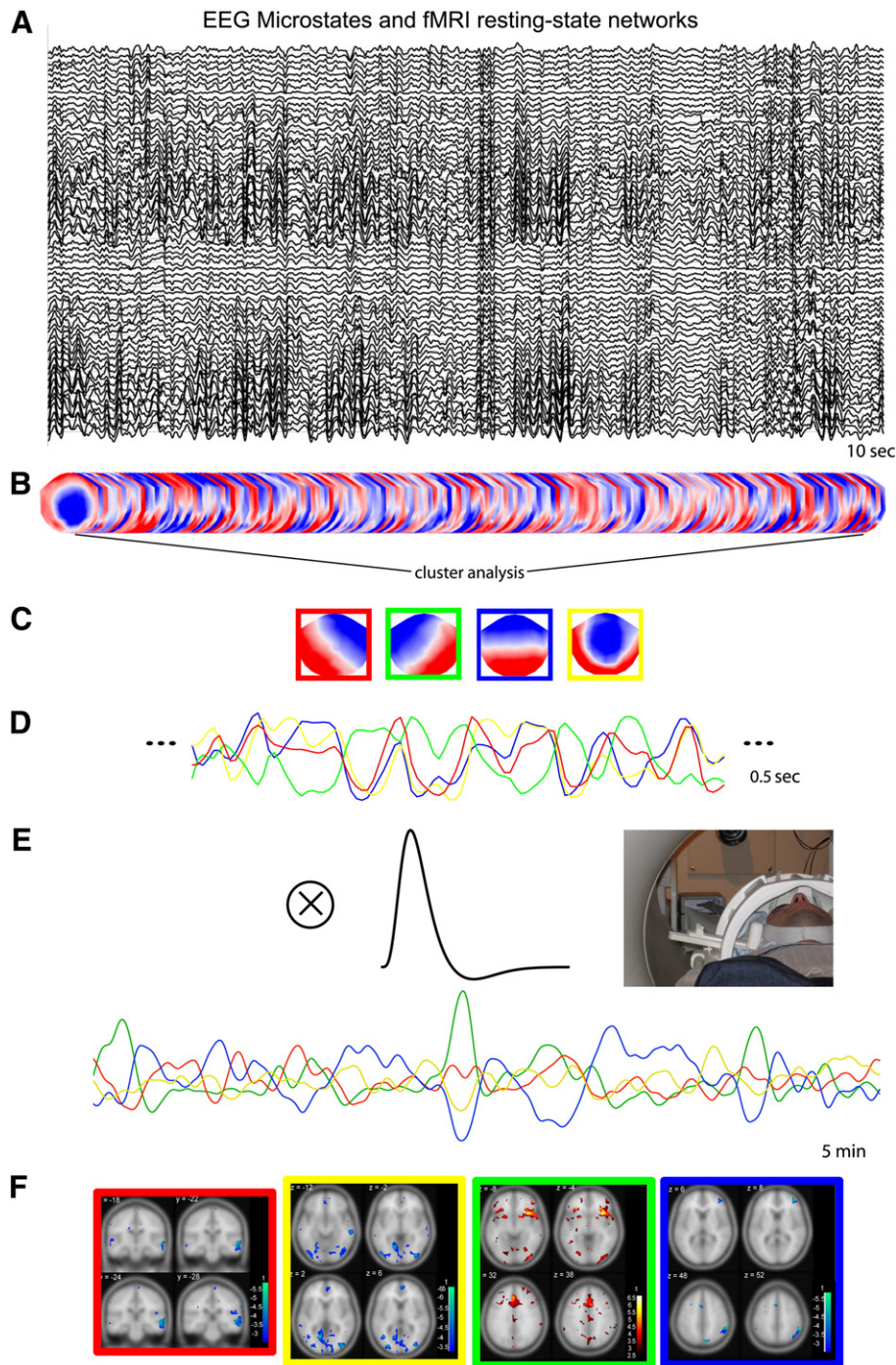


Fig. 2. Correlation between EEG microstates and fMRI resting state networks: (A) Ten seconds of 64-channel spontaneous EEG with eyes closed. (B) EEG is depicted as a series of scalp potential maps (seen from top). (C) Four dominant topographies can be identified at rest by means of clusters analysis. (D) Time course of the correlation of the four maps with the EEG, showing that often only one topography is dominant at a given instant and remains stable for a certain time period of approx. 100 ms. (E) Convolution of the time course of EEG microstates with the hemodynamic response function: the time courses of the EEG microstates remain similar after this low pass filter, indicating scale-free dynamics of microstates (Van de Ville et al., 2010). (F) Large-scale resting-state networks identified with microstate-informed GLM analysis: each microstate correlates with one of the well-known resting-state networks.

From Britz et al. (2010).

EEG microstate time-series correlate with fMRI BOLD signals even after the dramatic low-pass filtering is that the temporal structure of the microstate is scale-free, i.e. self-similar on different temporal scale (van de Ville et al., 2010). Such self-similarity, also called criticality or fractality, appears to be a general key feature of the brain resting-state network, allowing fast adaptations to the quickly changing environment (Sporns et al., 2004). It is interesting to note that such scale-free or fractal dynamics is also the main characteristic of

the arrhythmic brain activity (He et al., 2010), though the relation between the EEG microstates dynamics and the arrhythmic activity remains to be established.

Spatial analysis of multichannel stimulus-related activity

Aside from the analysis of spontaneous EEG, there is also a considerable body of research that focuses on stimulus-related brain activity

with a particular interest in how and when the brain processes specific types of information and/or generates decisions or actions in response to external stimuli in conjunction with mental operations. This line of enquiry into mental chronometry stems in large part from the pioneering efforts of Donders and later Sternberg (reviewed in Vaughan, 1990). Their overarching objective was to determine “the speed of mental processes” (Donders, 1868) by measuring reaction times, with the assumption that stages of processing were serial and independent. While more recent conceptualizations incorporate parallel and interactive architecture into models of brain function, the quintessential notion remains that a dynamic series of events unfolds in response to stimuli so as to generate a decision/response. When this notion was combined with the advent of EEG in the 1920s/1930s, with observations of electrical activity fluctuations in response to external stimuli when recording from the exposed cortex of animals and human patients, and with the introduction of computers capable of signal averaging, the field of sensory evoked potentials readily emerged. The benefit of signal averaging (at the time and even today) is that activity associated with the experimental parameter of interest can be augmented while background activity is diminished, facilitating quantification. Still, it should not be overlooked that rhythmic activity was certainly apparent and noted in the spontaneous EEG. Nonetheless, the confluence of technological advancement alongside increased investigation in animal models of neurophysiologic mechanisms of perception (e.g. the characterization of neuronal receptive fields during the 1960s by Hubel and Wiesel) provided the backdrop against which the event-related potential (ERP) (Vaughan, 1969) emerged as a method that provided a more objective and quantitative means of accessing Berger’s “window into the brain”.

However, a general division in how ERPs were and continue to be utilized is also worth noting. On the one hand, some saw/see ERPs as a correlate of mental operations that may be more precise than behavioral metrics, but nonetheless only serve to validate models of human perception/performance. Under this framework, the ERP can be considered as a sophisticated psychophysiological measure, whose underlying neurophysiology is only of peripheral interest because such is immaterial to addressing the research question focused on whether there exists a brain correlate of a given process. On the other hand, some saw/see the method as a way of narrowing the gap between hypotheses generated from models based on cognitive and experimental psychology (among other disciplines) and mechanistic

information gleaned from more invasive studies in animals/humans. For this purpose, it is insufficient to have only a marker of a process. Rather, one must instead garner details of how the ERP itself was generated and what produced its modulations.

This division can, in our view, be most readily noted when considering the term “ERP component” (Fig. 3). When ERP recordings were performed with one recording and one reference electrode, the definition of ERP components was uncomplicated because it was relatively protected from experimenter bias. There was a single time series with peaks and troughs that could be identified (assuming adequate signal quality) and labeled (Walter et al., 1964; Sutton et al., 1965). With increasing numbers of recording amplifiers (electrodes) and greater variability in the locus of the recording reference, there was a parallel propensity for experimenter bias in ERP component identification and statistical quantification. As intimated above, some steadfastly clung to waveform features and defined components accordingly, whereas others recognized the biophysical underpinnings of EEG/ERPs and thus the fact that components were forcibly spatial features of the electric field at the scalp: topography, strength, and latency. As already detailed above for spontaneous EEG, quantification and analyses that capitalize upon spatial features of ERPs can provide reference-free, unambiguous, and neurophysiologically interpretable results while also facilitating the restriction of data for submission to EEG source imaging.

Multichannel analysis of average stimulus-related activity

In this section we briefly overview some examples where conceptualizations of brain functional organization have been radically impacted by the consideration and analysis of spatial features of the ERP (as well as complementary findings from other imaging modalities and recordings in animal models, though these later sources of data are beyond the scope of the present review). We do not provide here a treatment of how EEG spatial analysis has contributed to better understanding induced brain activity (see e.g. recent works by Yuval-Greenberg, Deouell, and colleagues on the importance of spatial information in the detection of ocular-related induced gamma-band activity; (Yuval-Greenberg and Deouell, 2009, 2010; Yuval-Greenberg et al., 2008)).

One striking example is the mismatch negativity (MMN) (comprehensively reviewed by Deouell, 2007; Naatanen et al., 2007).

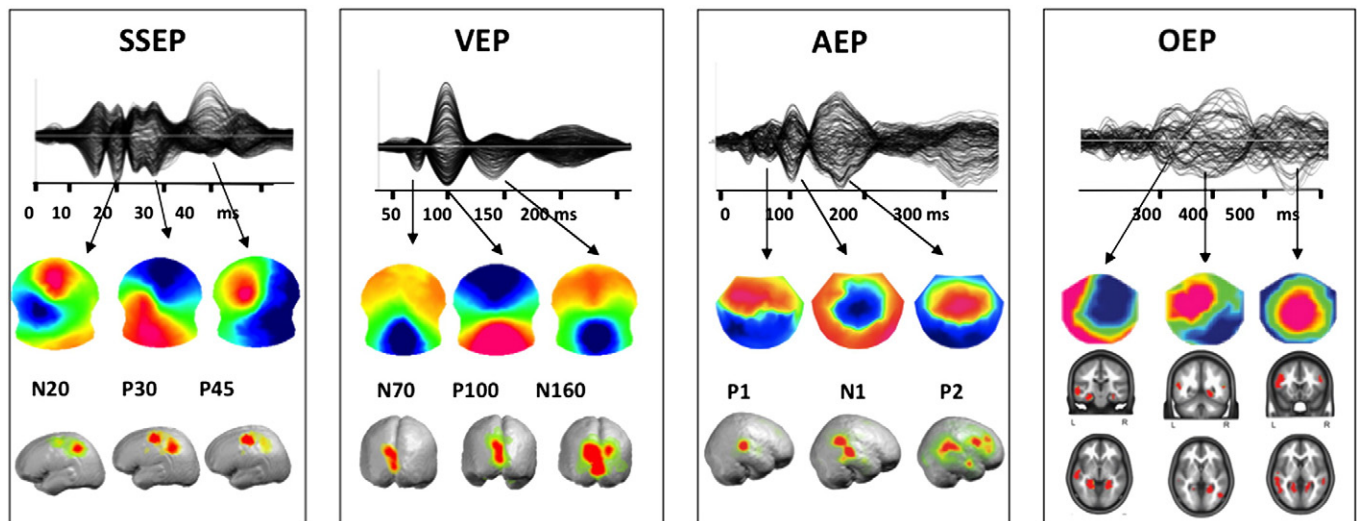


Fig. 3. Examples of EEG source imaging of event-related potentials (ERPs). Top row: butterfly plot of the overlapped averaged ERP waveforms. Middle row: scalp potential maps at the peak of the different components. Bottom row: Source estimation using a distributed linear inverse solution for each of the component maps. 1st column: 256-channel somatosensory evoked potential (SSEP) after right median nerve stimulation. 2nd column: 256-channel visual evoked potential (VEP) after full-field checkerboard reversal. 3rd column: 192-channel auditory evoked potential (AEP) after short tones. 4th column: 64-channel olfactory evoked potential after unilateral nostril stimulation with hydrogen sulfide. Adapted from Lascano et al. (2009, 2010).

Originally, the MMN was thought to originate within auditory cortices of the temporal lobe (Naatanen et al., 1978). This view quickly changed to incorporate the (likely) possibility of an additional frontal generator (Naatanen and Michie, 1979) or a set of generators (Deouell et al., 1998; Giard et al., 1990). At first, this conjecture was based on the use of extremely clever paradigmatic manipulations to differentially modulate and therefore dissociate ERP components (defined at the voltage waveform level mainly because at best only a few scalp electrodes were used). Later, this was augmented by higher-density montages and visualization of ERP topographic maps, including current source density derivations (Giard et al., 1990; Novak et al., 1990). These latter studies (and others) were confronted with an intriguing situation. Simple examination of the MMN topography revealed a clear frontal current sink that was dissociable from current source/sink distributions likely attributable to temporal sources. Yet, source estimations at the time, which were predominantly based on equivalent current dipole models, could achieve rates of explained variance over 95% by seeding a pair of sources within superior temporal regions. No frontal sources were deemed necessary, but the explained variance of dipole models nonetheless increased with the addition of a frontal source (Giard et al., 1991; Schonwiesner et al., 2007) and distributed source models likewise support there being frontal sources (e.g. Lavoie et al., 2008; Marco-Pallares et al., 2005; see also Tse and Penney, 2008 for combined ERP and optical imaging results). Nonetheless, MEG studies, including simultaneous EEG-MEG (Rinne et al., 2000) routinely failed to support there being a frontal MMN generator (perhaps due to MEG's reduced sensitivity to radially-oriented generators; Ahlfors et al., 2010). Hemodynamic imaging likewise provided conflicting evidence for frontal contributions to the MMN (reviewed in Deouell, 2007). Despite these controversial findings, the evidence from the ERP topography clearly points to frontal (aside from temporal) generators contributing to the MMN; a conclusion recently supported by dynamic causal modeling of ERPs (Boly et al., 2011; Garrido et al., 2008).

A second example where spatial analysis of ERPs has proven instrumental is in the delineation of the functional organization of auditory processing pathways. In the late 1990s a dual-pathway model for the primate auditory system was introduced (akin to that described for vision; Mishkin et al., 1983), with one pathway principally involved in processing stimulus identity and the other in processing spatial information (reviewed in Hackett, 2010; Rauschecker and Scott, 2009). Despite multiple lines of support for this general "what/where" model in humans (as well as non-human primates), controversy surrounded the question of the functional specificity of each pathway as well as the spatio-temporal dynamics of the particular functional sensitivity of a given region within each pathway. First, it was unresolved from microelectrode recordings in monkeys (Tian et al., 2001) and hemodynamic imaging in humans (Alain et al., 2001; Maeder et al., 2001; Warren et al., 2010; Weeks et al., 1999; Zatorre et al., 1999) whether or not functional subdivisions were to be considered relative or absolute. Source estimation results from EEG and MEG were similarly equivocal, with some reporting more lateral equivalent current dipole positions for spatial vs. semantic processing (Herrmann et al., 2002) and others the reverse pattern (Anourova et al., 2001). Second, because the time course of differential processing along putative "what/where" pathways was not investigated/reported (e.g. Tian et al., 2001), effects within a given circumscribed brain region could not be interpreted as deriving from either feedforward, feedback, or lateral activity. This was exacerbated by EEG and MEG studies that reported widely divergent latencies of differential activity, though admittedly also using widely divergent paradigms (Ahveninen et al., 2006; Alain et al., 2001; Anourova et al., 2001; Herrmann et al., 2002). Spatial analysis of ERPs in response to acoustically-identical sounds passively presented either in the context of changing pitch or changing location revealed there to be topographic differences beginning ~100 ms post-stimulus

onset (Fig. 4; De Santis et al., 2007; see also replication by Leavitt et al., 2011 using naturalistic stimuli and an active paradigm). One stable microstate over the 100–160 ms post-stimulus period accounted for responses during changes in pitch, whereas another microstate accounted for responses during changes in location. Such effects support there being pre-attentive, if not automatic, and intrinsic engagement of distinct brain networks for processing spatial and semantic information contained within acoustic signals. Plus, because effects manifested topographically but not in terms of response strength argues in favor of (partially) segregated functional "what/where" pathways and against a common network that simply modulates its gain as a function of the relevant stimulus attribute. Finally, distributed source estimations and statistical analyses thereof suggest that the initial differentiation between "what/where" processing pathways may not reside within primary or near-primary cortices but instead within relatively higher-order parietal regions (De Santis et al., 2007). These findings served as a springboard for investigating the spatio-temporal functional organization and plasticity of the human auditory system and more specifically the processing of spatial, temporal and semantic information conveyed by sounds (reviewed in Murray and Spierer, 2009).

Towards single-trial decoding

While the signal averaging of multiple EEG epochs that is required for ERP calculation improves the signal-to-noise ratio (SNR) and reduces the influence of several varieties of physiologic and instrumental noise sources, it preserves only the subset of brain activity that is time- and phase-locked to stimulus onset. As already mentioned throughout this review, it is clear that the EEG contains functionally important signals that are not time-/phase-locked to stimulus onset and can only be studied at the single-trial level (e.g. Davis, 1939; Knuth et al., 2006; Makeig, 2002; Shah et al., 2004). The detection of stimulus-related activity at the single-trial level can be used for studying the bases and significance of inter-individual variability as well as in improving metrics of treatment/training efficacy as well as diagnostic/prognostic specificity. Single-trial analysis methods can likely also enhance the benefit of simultaneous EEG-fMRI recordings where the number of trials is often limited.

Whereas decoding approaches are well established in fMRI research (reviewed in Haynes and Rees, 2006), in the EEG domain they are mainly used in Brain-Computer Interface (BCI) applications (e.g. Bianchi et al., 2010; Rivet et al., 2011; Sannelli et al., 2010; Vidaurre and Blankertz, 2009) where the research objectives are often focused on obtaining a differential metric of brain activity (e.g. a metric discriminating intention to move left vs. right) rather than forcibly metrics that reveal the underlying neurophysiologic process (e.g. a metric reliably describing how the brain represents the intention to move left vs. right). Moreover, the vast majority of BCI methods involving EEG/ERPs focus on the analysis of individual voltage waveforms (presumably for practical reasons linked to the objective of ease-of-use for patients), which as mentioned throughout this review have extremely limited neurophysiologic interpretability and statistical reliability due to their dependence on the choice of the reference channel(s).

More recently a decoding approach based on topographic information has been proposed (De Lucia et al., 2007a, 2007b; De Lucia et al., 2010; Tzovara et al., 2012). The single-trial decoding method is based on multivariate statistics and consists in modeling the statistical distribution of voltage topographies (defined as an N-dimensional vector, where N equals the number of scalp electrodes) by means of a Mixture of Gaussians (GMM) and then exploiting this model for defining typical voltage configurations appearing in each experimental condition/population (i.e. 'template maps' corresponding to the mean of each of the Gaussians in the mixture). Based on the statistical model it is also possible to assign posterior probabilities

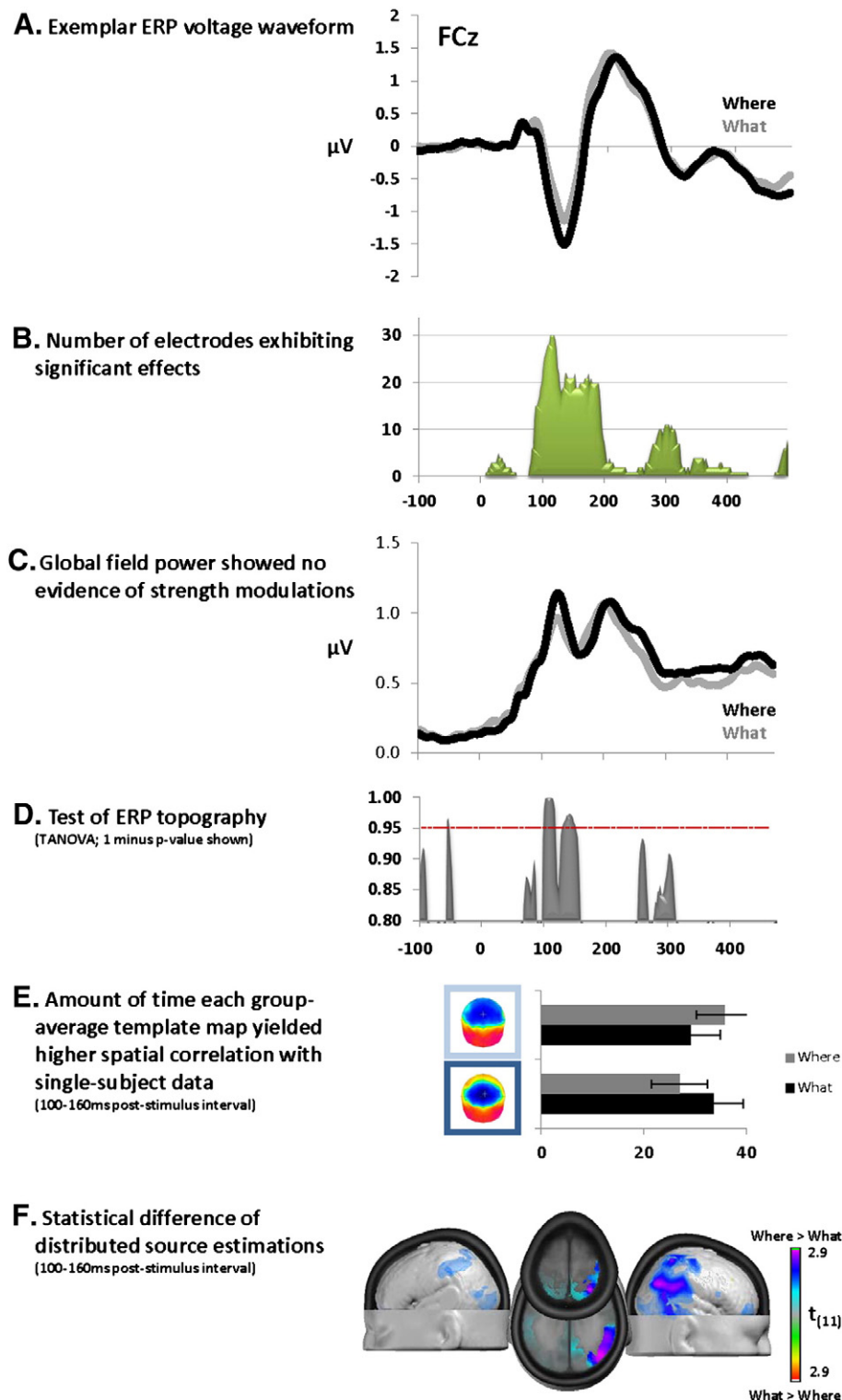


Fig. 4. Example of the application of EEG spatial analyses and source imaging to the question of auditory processing pathways. (A) Exemplar voltage auditory evoked potential (AEP) waveform at a fronto-central midline scalp site. (B) The number of electrodes from among the 128-channel montage exhibiting a significant modulation between experimental conditions. Statistical analyses entailed paired t-tests at each electrode as a function of time. An effect was considered reliable in time if it persisted for at least 20 consecutive milliseconds. (C) Mean global field power waveforms were analyzed but failed to provide evidence for significant modulations in response strength. (D) Global dissimilarity between conditions was statistically tested via a permutation test (detailed in Murray et al., 2008). Significant topographic differences were observed over the ~100–160 ms period. (E) The results of a topographic cluster analysis identified one map predominating the group-averaged AEPs from each condition. These template maps were then compared based on spatial correlation with each time sample of the single-subject AEPs to yield a metric of the amount of time over the 100–160 ms period that each template accounted for each condition (significant interaction between condition and template map; $F_{(1,11)} = 6.85$; $p < 0.03$). (F) The time period identified from the cluster analysis in turn guided the time period submitted to source estimations. Statistical differences identified regions with stronger activity in response to the “where” than “what” condition. Adapted from De Santis et al. (2007).

to each of these voltage topographies, time-frame by time-frame and for each trial in each dataset. The mean posterior probabilities can be compared statistically across conditions/populations in order to evaluate in a data-driven manner the time-window where conditions/populations are the most discriminative. This time period (and the corresponding template maps) can be used for classifying new test data at the single-trial level and also for testing whether the identified time-period is actually informative of the difference between experimental conditions/populations. Importantly, the classifier will in general determine more than one consecutive time-periods that are best discriminative. It is of course of interest to test the relevance of each of these latencies and the corresponding EEG activity in decoding. This test can help in clarifying their functional significance and in relation to the behavioral output, treatment efficacy, etc. This method has already been successfully applied to reliably classify single-trial responses in situations ranging from visual retinotopy (Tzovara et al., 2011), where the anatomo-functional organization of visual cortex would a priori result in distinct ERP topographies, to more subtle experimental settings such as perceptual decision-making with environmental sounds (Murray and Spierer, 2009), and prediction of subjective perceptions (Bernasconi et al., 2011). Similar methods based on a Hidden Markov Model have been applied to the classification of intracranial EEG in humans performing a sequence learning task and importantly take into account the distributed pattern of neural activity so as to identify those regions contributing most to classification accuracy (De Lucia et al., 2011). Such methods, and others like it (e.g. Blankertz et al.; De Martino et al., 2010; Schaefer et al., 2010), are likely harbingers of the continued development of signal analysis methods for ERPs.

Clinical applications of spatial EEG analysis

The spatial analysis methods of multichannel EEG described in this review have been applied to a wide range of clinical populations, and we review only a selected sampling here.

Spatial EEG analysis in epilepsy

The most obvious and thus most intensively studied application of spatial EEG analysis is in epilepsy, where the EEG still is the method of choice to determine the epileptic syndrome. An increasing number of studies demonstrated that EEG source imaging is a powerful tool to non-invasively localize the epileptic focus. The obvious major advantage of the EEG in epileptic focus localization compared to other methods such as fMRI or PET is the high temporal resolution that allows for separating initiation from rapid propagation of the epileptic activity. Sperli et al. (2006) analyzed the standard clinical EEG of 30 operated and seizure-free children with EEG source imaging. They reported correct localization on a lobar level in 90% of the cases. Using high-density electrode montages (128 electrodes), Michel et al. (2004a) showed 79% localization precision on a sublobar level. Brodbeck et al. (2010) analyzed 10 operated patients with normal MRI and showed correct localization within the resected margins in 8 of them. Zumsteg et al. (2005) performed EEG source imaging analysis in 15 mesial temporal lobe epilepsy patients and compared them with simultaneously recorded data from foramen ovale electrodes. They showed that 14 of the 19 different local field patterns seen by the foramen ovale electrodes could be correctly identified with EEG source imaging. These results indicate that even mesial temporal sources can be recorded by scalp EEG and properly localized by ESI; a result that has also been demonstrated by Lantz et al. (2001) in simultaneous EEG and intracranial EEG recordings. EEG source localization does not seem to be affected by brain lesions that potentially change conductivity values: Brodbeck et al. (2009) correctly localized spike activity

within the resected zone in 12 of 14 patients, despite large cerebral lesions. Given these promising studies, Plummer et al. (2008) concluded in their comprehensive review that EEG source imaging deserves a place in the routine work-up of patients with localization-related epilepsy, but that a prospective validation study conducted on larger clinical groups is still required. A recent prospective study on 152 operated patients filled this gap (Brodbeck et al., 2011). They showed that EEG source imaging has a sensitivity of 84% and a specificity of 88% if the EEG was recorded with a large number of electrodes (128–256 channels) and the individual MRI was used as head model. These values were comparable to those of structural MRI, PET and ictal/interictal SPECT. The sensitivity and specificity of EEG source imaging decreased significantly with use of a low number of electrodes (<32 channels) and a template head model. This large prospective study allowed the conclusion that EEG source imaging should be used as a standard tool in presurgical epilepsy evaluation, given its low cost and high flexibility compared to other imaging methods.

EEG source imaging has also been proven to be useful in epileptic focus localization in combination with fMRI. In a series of studies, the spike-related analysis has been informed by the EEG source imaging of the spikes recorded in the scanner. These studies revealed that the temporal resolution of EEG source imaging helps to identify those spike-related BOLD responses that correspond to the initiation of the epileptic discharge (Fig. 5) (Vulliemoz et al., 2009; Vulliemoz et al., 2010a, 2010b; Groening et al., 2009; Siniatchkin et al., 2010). The topographic analysis also helps to analyze fMRI data of epileptic patients that had no spike in the scanner or no spike-related BOLD responses (Grouiller et al., 2011); this study used the average spike-map of the EEG recorded during the long-term monitoring outside the scanner, fitted this map to the EEG recorded in the scanner in terms of spatial correlation (see above) and convolved this correlation time-course with the BOLD response. Using this approach, 78% of the otherwise inconclusive fMRI studies could nonetheless be interpreted.

Spatial EEG analysis of psychiatric and neurological disorders

Concerning the ongoing spontaneous EEG, spatial analysis in the time- as well as in the frequency-domains has been used to characterize different pathological states, particularly related to psychiatric disorders. Frequency-domain source localization allows identifying brain regions that show altered rhythms in patients with psychiatric disorders (Saletu et al., 2005). EEG microstate analysis showed that the spatial characteristics of the microstates are a sensitive measure for different mental diseases. For example, schizophrenic patients have a reduced number, a decreased duration, and an altered syntax of some microstate classes (Kinoshita et al., 1995; Koenig et al., 1999; Lehmann et al., 2005; Strelets et al., 2003), that reversed with medication (Kikuchi et al., 2007). Shortening of specific EEG microstates is observed during auditory verbal hallucinations (Kindler et al., 2011). Microstate duration was also decreased in depression and some microstates were repeated more frequently (Strik et al., 1995). Patients with Alzheimer's disease also showed decreased duration and an increased number of microstates (Dierks et al., 1997; Strik et al., 1997). Antipsychotic and anxiolytic drugs as well as meditation and hypnosis can also alter microstate characteristics (Katayama et al., 2007; Kinoshita et al., 1994).

In addition to spontaneous EEG, spatial analyses have been applied to ERPs recorded from clinical populations. In the case of patients with schizophrenia, convergent results are supporting there being low-level sensory processing deficits (Foxe et al., 2005; Knebel et al., 2011) that may provide biomarkers of disease state or endophenotypes, as well as metrics of neuropharmacological treatment efficacy that emerge prior to changes in clinical evaluation (Lavoie et al., 2008). In the case of patients with multiple sclerosis,

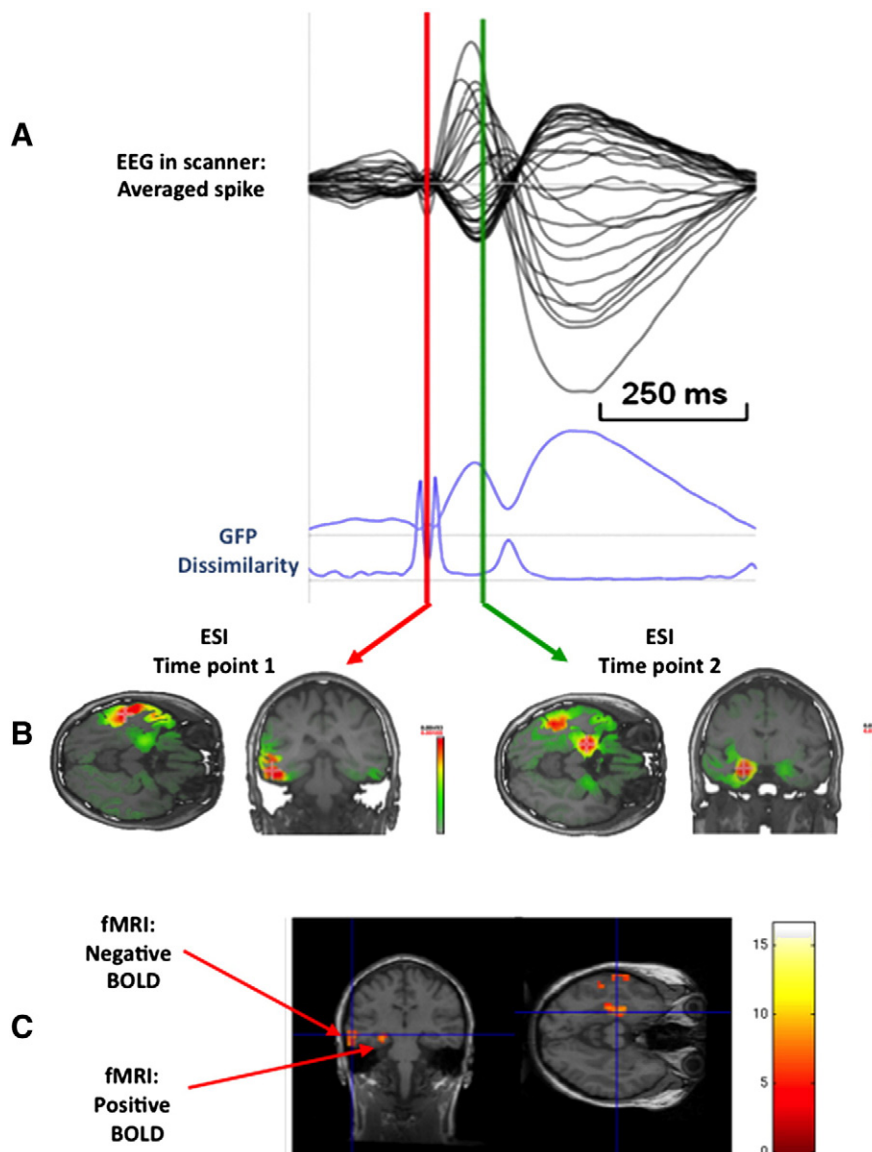


Fig. 5. (A) Combined EEG source imaging and fMRI for the localization of epileptic discharges. Top: averaged spike recorded from 32-channel EEG inside the scanner. Global Field Power and Dissimilarity curves are plotted in blue. (B) Source localization with a linear distributed inverse solution in the patient's MRI at two different time points of GFP peaks. Maximal activity is seen in the lateral temporal lobe at the first time point and in the mesial temporal lobe at the second time point. (C) Spike-related fMRI reveals negative BOLD correlates in the lateral temporal lobe, and positive BOLD correlates in the mesial temporal lobe. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Adapted from Vulliemoz et al. (2009).

spatial analyses of ERPs have been directly compared in their sensitivity and specificity to values obtained from canonical analyses of individual ERP waveforms (Lascano et al., 2009). It was shown that spatial analyses, particularly in the case of visual evoked potentials, outperformed canonical analyses. Spatial analyses have likewise been applied to study patients with amnesia and provide evidence for wholly different mechanisms of memory formation and retrieval, despite intact early stages of visual processing (Barcellona-Lehmann et al., 2010). Similar studies have been successfully conducted in patients with aphasia (Laganaro et al., 2011). Finally, spatial analyses of ERPs have been applied to characterize brain function difficulties in children with ADHD (McLoughlin et al., 2009; Valko et al., 2010), to predict reading skills in children (Bach et al., 2011), and to evaluate treatment efficacy and predict changes in use of grammar in children with specific language impairment (Yoder et al., 2012). It is important to emphasize the particular usefulness of EEG in this pediatric patient population, where other functional imaging methods are rather difficult or impossible to use.

Conclusions and outlook

The aim of this review was to illustrate the paradigm change that took place with respect to the EEG analysis in the last decade or so. EEG analysis moved away from the traditional analysis of graphoelements at certain electrodes to a comprehensive analysis of the brain's electric field at the scalp. This movement was certainly largely inspired by MEG work, which from the onset rather analyzed the spatial than the temporal patterns. We tried to show here that spatial EEG analysis is not solely synonymous with source localization. Many different studies revealed new insights in brain functioning by just analyzing the spatial changes of the scalp potential map over time or between conditions/populations. The added value of such spatial analysis is obvious in view of the fact that analysis of EEG waveforms, be it in terms of frequency of the spontaneous activity or amplitude of the evoked responses, is ambiguous. Volume conduction and reference-dependency make it impossible to reliably draw conclusions about the robustness of statistical effects, the neurophysiologic bases of observed

differences, or the sources in the brain that generated the signals at a given electrode. Spatial analyses of the EEG are unambiguous and allow determining the sources of the scalp signals. Given the high temporal resolution, the flexibility, the cost-effectiveness and the ease-of-use of EEG and the fact that high-density EEG recordings can now be performed very quickly, makes EEG mapping a powerful brain imaging device. We are convinced that EEG is not only a brain imaging tool for the poor, but that it actually is the ultimate brain imaging tool for those who are interested in the temporal dynamics of large-scale brain networks in real-life situations. EEG is currently experiencing a renaissance, particularly because it can easily be combined with other imaging techniques. However, more analysis tools and more engineering are still needed and deserve to be invested in this technique.

Acknowledgments

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