2

Functional Neuroimaging

Neuroimaging has experienced significant progress in the past few decades, especially since the advent of magnetic resonance imaging (MRI) in the 1970s and 1980s and functional MRI (fMRI) at the beginning of the 1990s [OGA 90].

There are two types of neuroimaging. The first type is structural imaging, which employs magnetic resonance. Images thus produced determine the brain's anatomy as well as the white matter tracts that connect the different regions of the brain (this method is known as "tractography"). The second type is functional imaging, which has the objective of identifying regions involved in a given cognitive task or in certain pathologies, as well as understanding the interactions between the different regions.

Several different methods are used to map the regions of the brain, each of which employs very different mechanisms. The activation of a given brain region produces a host of events, including electromagnetic fields and changes in blood flow, which provide signals gathered by the different mechanisms.

In this chapter, we will provide an introduction to the functional neuroimaging methods that can have implications for brain–computer interfaces and related fields. We will first study fMRI, then electroencephalography (EEG), magnetoencephalography (MEG) and finally simultaneous EEG-fMRI. EEG and MEG are establishing themselves as

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fully-fledged neuroimaging systems, since they now produce activation images on the cortical surface thanks to inverse problem methods. We will also outline the general principles guiding signal processing techniques that make it possible to detect brain activity.

2.1. Functional MRI

2.1.1. *Basic principles of MRI*

MRI provides a signal proportional to the number of a certain kind of atoms at each point in the brain. In the context of biology, hydrogen is commonly studied, since it is present in large quantities due to the presence of water in tissues.

Magnetic resonance is based on the fact that an atom placed in a strong B_0 magnetic field has a spin that aligns with the field [HOR 96]. We can represent this metaphorically by saying that each atom behaves like a spinning top, revolving on its own axis which in turn also revolves in the manner of a cone of precession (just like a spinning top that slows down). The rotation frequency depends on the magnetic field strength and on the nature of the atom, which is known as its Larmor frequency. When a magnetic wave at the Larmor frequency is sent to the atom, its magnetic moment changes dramatically and then returns to normal, while emitting a signal at the same frequency as that of the wave that excited it – this is magnetic resonance.

The key element of this technique is to slightly modify the magnetic field in space using gradient coils, which allows encoding space with frequency: at each point in the brain, the resonance frequency is different. Brain images are thus obtained using the inverse Fourier transform.

Each volume element is known as a "voxel". MRI has long used a B_0 field in the order of 1.5T, and now often uses 3T or even 7T, which makes it possible to obtain higher resolution and/or a higher signal to noise ratio.

2.1.2. *Principles of fMRI*

At the beginning of the 1990s, the Ogawa team demonstrated that MRI can detect the presence of deoxyhaemoglobin (dHb), which modifies the

magnetic field locally by causing a phase shift in oxygen atoms, thus diminishing the gathered signal at that point. This is known as the "blood oxygen level dependent" (BOLD) effect [OGA 90]. When a region of the brain is activated, oxygen is consumed and dHb is produced, giving way to a temporary drop in MRI signals. However, the vascular response quickly supplies blood to the activated region, diluting dHb and increasing the BOLD signal [HOG 99]. The hemodynamic signal takes about 5 seconds to reach it peak. By rapidly producing images (usually echo planar imaging) every 2 or 3 seconds, it is possible to obtain a series of functional images that allow tracking of the brain's activity at intervals of several minutes.

When no stimulation protocol is used, other than requesting the patient to remain calm and not to think about anything in particular, this is called resting state imaging, a topic that is currently of great interest to the neuroscience community [RAI 07]. In order to study the brain's response to a given type of stimulation, there are two strategies: either sending sets of same-kind stimuli to obtain a strong response in a given region (block-related design), or sending different kinds of interwoven stimuli (event-related design). Event-related design has several advantages in terms of data analysis [BUR 98].

2.1.3. *Statistical data analysis: the linear model*

fMRI detection of active regions is traditionally accomplished with a linear model (general linear model) [WOR 02]. The model predicts the BOLD response at each point in the brain (at each "voxel") through a linear regression. Regressors considered "of interest" represent the brain's response to stimulation. They are typically obtained using the convolution of pulses representing stimulation times with a model of the hemodynamic response. Regressors "of no interest" model other sources of fluctuation observed in the data, like the subject's movements and low frequencies.

For each combination of regressors of interest (for example the contrast between two conditions), it is possible to produce a statistical map that tests the significance of that regressor (Figure 2.1). Since the test is repeated on all of the brain's voxels (in the order of several million), one of the major difficulties is controlling for the multiple comparisons in order to decide which region is active or not.

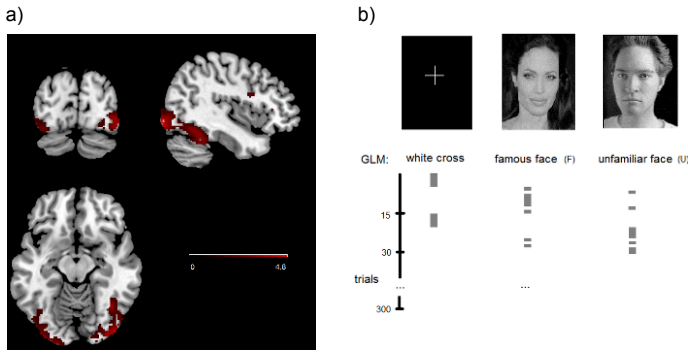

Figure 2.1. *Example of an fMRI statistical analysis in face recognition design (data: Jonathan Wirsich and Maxime Guye, CEMEREM-CRMBM, UMR 7339): a) statistical map contrasting faces with a white cross; b) occurrence time for events used in the linear model (white cross, famous face, unfamiliar face) (from [WIR 14]). For a color version of this figure, see www.iste.co.uk/clerc/interfaces1.zip*

A classical strategy is to control type I errors (false positives), that is to say the probability of exceeding the threshold in the null hypothesis (no activation; i.e. there is just noise at that voxel). Let us imagine that the threshold is set at 5% ($p < 0.05$), which is the norm in parametric statistics. If the test is repeated a large number of times (e.g. several million times), the number of false positives will increase: the probability of exceeding the threshold by chance increases with the number of tests. For a small number of tests, n, it is possible to use a Bonferroni correction, which assumes the tests to be independent and uses a threshold of $p = 0.05/n$. However, in imaging data, there is a strong correlation between neighboring points, and the large number of points would make the threshold far too conservative (it would lead to an overly large number of false negatives).

A large amount of research has been carried out in the field of fMRI statistics. Controlling for false positives can be achieved with Gaussian field theory, which uses the spatial correlation of noise. When this theory is applied to amplitude peaks, it produces relatively high thresholds. Indeed, it controls for the error rate known as the "family wise error rate" (FWER), which represents the probability that a single voxel exceeds the threshold [WOR 96], which is a very tight condition [NIC 03]. Another possibility is to apply it to the size of clusters i.e. the connected voxels exceeding an arbitrary threshold

(for example $p = 0.001$ without correction) [FRI 94]. Yet another possibility is the "false discovery rate" (FDR) threshold, which is less demanding since it tolerates a certain percentage of false positives [GEN 02].

One interesting option for determining thresholds is using non-parametric thresholds. For example, when there are two conditions, it is possible to randomly exchange the labels "condition 1" and "condition 2" through stimulation repetitions and to measure the maximum statistic value throughout the brain (thereby controlling the FWER). By repeating this label permutation a large number of times, it is possible to obtain a distribution of the maximum statistic in the null hypothesis (no significant difference between the conditions that have been randomly permuted) [NIC 02]. On this distribution, it is possible to calculate the threshold corresponding to a given critical value, for example $p < 0.05$.

2.1.4. *Independent component analysis*

Independent component analysis (ICA) is a multivariate method that makes it possible to blindly extract the structure present in the data [COM 94]. Each component has a spatial map, which represents the voxels whose activity evolves in a similar manner, and an associated temporal part; that is, the fluctuations in time of that component's amplitude. The observed data are the sum of all components. Since this linear decomposition is non-unique, it is necessary to apply a constraint, which in this case is the statistical independence of spatial maps [MCK 98]. The formula for ICA is the following: $U = W\,X$, where X represents fMRI data (time x voxels), W is an "unmixing" matrix (components $\times$ time) and U is the matrix of spatial components (components $\times$ voxels). ICA assumes the lines of U to be mutually independent (that is, according to the spatial dimension).

This type of analysis has produced excellent results in resting state imaging and has made it possible to extract several activity patterns that are reproducible across subjects [DAM 06]. Another reason this method is interesting is because it makes it possible to eliminate physiological noise from the data [PER 07].

2.1.5. *Connectivity measures*

The linear allows identification of active regions during a given protocol. Connectivity measures seek to define the interactions between those regions. In other words, they seek to determine "who talks to whom".

The simplest method is correlation (linear or nonlinear). For this measurement, it is important to take into account physiological fluctuations such as breathing and heartbeat, which produce correlations in the signals that are not directly related to brain activity.

Typically, correlation is computed between each pair of voxels or cerebral regions. It has been used in several contexts: cognitive tasks, at resting state or pathologies such as epilepsy [BET 11].

This type of bivariate measurement is very useful, but it is also sensitive to indirect correlations. For example, if region A is related to region B, and region B is related to region C, a correlation may be found between A and C that does not correspond to a physical link between those two regions. In order to eliminate indirect links, several methods have been proposed. They may be based on correlation such as partial correlation [MAR 06], or on a regression through multivariate linear models (combined with a Granger causality test). They may also employ *a priori* assumptions, like structural equation modeling, or dynamic causal modeling [PEN 04].

Granger causality is of great interest to the neuroimaging community. By definition, there is causality as defined by Granger in a signal X toward a signal Y if X's past state helps predict the present of Y better than the past state of Y alone [ROE 05]. It is important to note that the term "causality" is controversial, since in order to measure causality in a physical system, it is usually necessary to modify the system (which could, for example, be done by actively inhibiting a given region). Some researchers highlight the fact that Granger causality is strongly related to correlation [DAV 13], and that it is difficult to extract time information by using fMRI responses [SMI 11].

2.2. Electrophysiology: EEG and MEG

2.2.1. *Basic principles of signal generation*

The basic element generating a signal is a neuron. When it receives a postsynaptic potential, a movement of ions is produced throughout the membrane, which creates a current that propagates in the head [LOP 05]. The current generated by a single neuron (a small dipole with an elementary current) is undetectable. In order for there to be signals with an amplitude sufficiently large to be measured, a large number of neurons must be active at the same time, which can be represented with an equivalent dipole. A spatial organization producing a summation of currents is also necessary, which is the case in cortical pyramidal neurons, which are aligned in parallel (see Chapter 3). EEG is the measure of the electric potential difference between a point on the scalp and a reference electrode. This difference in potentials is created by currents that propagate in the head. A major factor in current propagation is the skull, which is less conductive than the brain and the scalp. The skull is a place where currents attenuate and diffuse, which produces a spatial smoothing of electric potentials [NUN 05].

MEG is a measure of the magnetic field on the surface of the head (though not necessarily in contact with it). The propagation of a magnetic field is much less influenced by the media through which it travels than that of an electric field. MEG is therefore relatively insensitive to the skull's presence, which produces good spatial properties. On the other hand, a so-called "radial" dipole – that is one pointing toward the surface – produces only a very weak magnetic field [HÄM 93].

2.2.2. *Event-related potentials and fields*

The simplest analysis of EEG and MEG is carried out at the level of each sensor. On continuous data, it is possible to characterize the frequency content using spectral analysis. For a stimulation or cognitive protocol, the average response to each condition (with a condition being a type of stimulation or a cognitive task) is separately calculated [COL 96].

This is referred to as event-related potentials for EEG and event-related fields for MEG. A statistical test is carried out in order to compare responses

at each point in time and at each sensor, and to detect the regions/temporal neighborhoods where a difference is induced by the protocol (see section 2.2.7).

In general, it is necessary to calculate averages over a large number of repetitions of the same stimulus or of the same task because a single response is too weak and too easily fades into noise. It is important to note that averaging may mask some variability at the level of individual events. For example, temporal variability (i.e. jitter) that may be more pronounced in one condition can result in a lower amplitude on average: a latency effect becomes an amplitude effect [HOL 06]. Noise reduction methods can be used to estimate responses at each individual event, and thus overcome the limitations inherent to averaging.

2.2.3. *Source localization*

MEG and EEG data are measured on the surface of the head. It is therefore useful to employ source localization techniques to estimate the location of that activity within the cerebral cortex [BAI 01]. The challenge is to calculate the electric and magnetic fields produced by an elementary dipole current. It requires a model of the head and of the different tissues' conductivity. The simplest model is a sphere, which is the first to have been used. More recently, finite element surface and volume models have been developed in order to have a more accurate representation of the tissues (brain, skull, scalp). The inverse problem uses the direct problem to infer the amplitude and location of sources within the brain that have produced the measurements. This problem is ill-defined, since it has an infinite number of possible solutions and is very sensitive to noise. It is therefore necessary to limit the problem by making mathematical assumptions. Several approaches have been proposed to solve the problem, which may differ in terms of the constraints they impose, but which often have strong connections to one another [BAI 01].

Most approaches are based on a linear model that describes observed fields as the superposition of the activity of one or several dipolar sources. When a small number of dipolar sources is used, the procedure is known as an equivalent dipole solution [SCH 85]. A large number of sources uniformly distributed in the volume or on the cortex is referred to as distributed sources. Since in that case there are many more unknowns than measurements, a

regularization method must be used, the most common one being the minimum energy constraint on the sources [HÄM 94].

For sources distributed along the cortex, an additional constraint is used, assuming that their dipoles are perpendicularly oriented toward the cortical surface, which is consistent with the hypothesis about the importance of pyramidal cells in signal generation. Another approach (known as "beamforming") uses spatial filters, which seek to estimate activity at a given point of the brain by limiting the influence of other regions [VAN 88].

All these methods make it possible to observe brain activity with high temporal resolution (in the order of milliseconds). Figure 2.2 illustrates a source localization result on MEG over an average of eight epileptic discharges considered at the discharge peak. The temporal progression is reconstructed in two symmetric regions in the occipital cortex and shows a fast propagation of activity from the right toward the left, as confirmed by an intracerebral EEG [GAV 14].

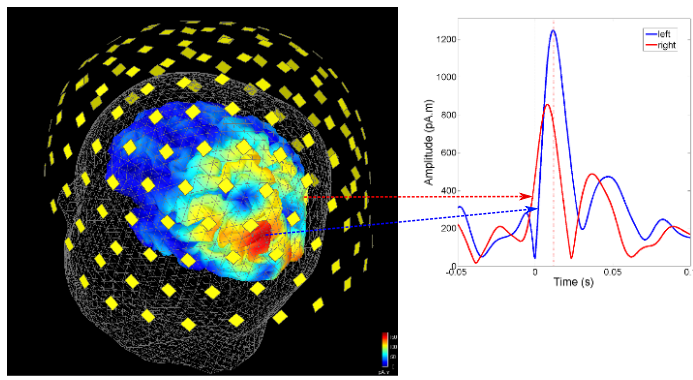

Figure 2.2. *Example of source localization through MEG on an average of eight epileptic discharges. The amplitude map is shown at the activity peak. On the right hand side, the time courses reconstructed on two homologous regions in the occipital regions show a rapid propagation from the right toward the left. For a color version of this figure, see www.iste.co.uk/clerc/interfaces1.zip*

2.2.4. *Independent component analysis*

As in fMRI, independent component analysis decomposes the signal (of dimension sensors $\times$ time) into a sum of component, each component with an associated spatial component (topography) and a time course. One of the reasons the linear model is interesting is because it makes it possible to separate activities that are mixed at the level of sensors. The difference with fMRI is that the independence constraint is defined across the temporal part of the components, and not the spatial part. This is mostly due to the fact that a large number of points is necessary in order to estimate the independence between two variables with a sufficient degree of soundness; in electrophysiology, the largest dimension is time (several thousand samples versus a few hundred sensors), whereas in fMRI space is the largest (several million voxels versus a few hundred samples).

ICA has been successfully used to remove elements like blinking, or to disentangle cognitive processes [JUN 01]. As with any method, it is important to respect mathematical assumptions. In the case of ICA, this means the separability of space and time, which assumes that the spatial part of each component does not vary in time. This assumption can be violated if there is local propagation of an activity throughout the cortex (a "wave" of activity), or if the subject's head moves with respect to the MEG sensors.

Other multivariate methods have been proposed for resolving the blind separation problem, like for example the SOBI method [BEL 97]. One of the advantages of multivariate methods is to be able to take all sensors into account at the same time, and therefore better account for noise and decrease data's dimensionality (which can help to reduce the problem of multiple comparisons).

2.2.5. *Time–frequency analysis*

One of the great advantages of electrophysiology, which comes with its temporal resolution, is the possibility of isolating oscillations that emerge at different frequencies. There is of course the classic alpha oscillations (around 10 Hz, see the first EEG observation in the 1920s), and theta oscillations (4–8 Hz), which are present in cognitive protocols. More recently, oscillations beyond 40 Hz have been shown in surface EEG, MEG and intracerebral EEG

[TAL 99]. These may be as high as 300–500 Hz for pathological oscillations in epilepsy [URR 07].

Time–frequency analysis allows characterizing such oscillations, both in terms of frequency and time duration. Several methods exist, which differ in the possibility of reconstructing data within a given window of time and frequency, as well as in their resolution in temporal and frequential dimensions. Short-term Fourier transforms are calculated with a sliding window. The greater the size of the window, the better the frequency resolution and the worse the temporal resolution will be. Another classic method is based on Morlet wavelets, which have a higher temporal resolution for higher frequencies (like in time-scale analysis). These wavelets enable a more visual representation of data, with oscillations producing characteristic time–frequency patterns [TAL 99]. On the other hand, they do not allow the reconstruction of filtered data, unlike orthogonal wavelets [LIN 14].

One of the advantages of these kinds of analyses is that, unlike simple filtering, they make it possible to study the structure of events in the time–frequency plane. In particular, it is possible to distinguish between activities that actually oscillate and transient activities that have energy at all frequencies [JMA 11].

One potential problem with these methods is that they may be sensitive to muscular activity. It has thus been shown that microsaccades that occur during the processing of a visual stimulus can produce spurious gamma activations [YUV 08].

2.2.6. *Connectivity*

Connectivity measurements seek to construct interaction graphs between different brain regions; they can be calculated on time intervals in the cortex after source reconstruction. In particular, electrophysiology measurements enable a good temporal resolution that makes it possible to measure delays between brain regions. They therefore seem to be particularly well suited for measuring oriented networks; that is, for obtaining graphs with arrows indicating the direction of information transfer from one region to another.

The simplest method is cross-correlation between two different temporal series, which measures the correlation for a series of time lapses and picks out the correlation peak. A coupling value and a time lapse are thus obtained.

Coherence is the equivalent of correlation in frequency. For each frequency, a normalized value between 0 and 1 measures the correlation level in both amplitude and phase. It is important to note that it is also possible to determine delays between the signals based on the phase slope in a given frequency band [GOT 83].

Other methods exist, like nonlinear correlation [WEN 09] or Granger causality [BRO 04]. Just like in fMRI, bivariate analyses can have limitations and it may be interesting to go on to multivariate analyses, like partial directed coherence or the directed transfer function [KU 04].

One difficulty in the application of connectivity methods comes from the existence of instantaneous correlations. At the level of sensors, these correlations come from volume conduction (one source is reflected on a large number of sensors in the same instant). At the level of sources, this is referred to as "source leakage", since one source is reconstructed with a large spatial extension. This extension comes from biophysical properties (close sources with similar orientation have very close contributions at the level of sensors) and from the resolution of the inverse problem (regularization smooths the reconstruction image). One solution for overcoming this correlation problem is to use the imaginary part of coherence [NOL 04], but this reduces the amount of information available.

2.2.7. *Statistical analysis*

In order to be able to identify the active regions in a cognitive protocol, it is necessary to calculate statistical maps in a manner similar to that used for fMRI. These maps can, for example, represent a *t*-test between two experimental conditions in each point in space for the time sample. One additional difficulty as compared to fMRI is the fact that the multiple comparison problem is even more pronounced. Indeed, tests are potentially replicated at each point in space (for example for each dipole on the cortical surface), at each point in time (typically several hundred samples) and even at each frequency.

Non-parametric methods make it possible to handle multiple comparisons (see section 2.1.3). Some have proposed using the maximum amplitude statistic among sources [PAN 03], or a "cluster" measurement that adds all statistics in t over contiguous time spans that exceed a certain threshold [MAR 07].

2.3. Simultaneous EEG-fMRI

2.3.1. *Basic principles*

As discussed in the fMRI section, the BOLD response has low temporal resolution; moreover, it is difficult to detect spontaneous events on the MRI. In order to overcome these difficulties, it can be interesting to record an EEG during an fMRI session, which may provide measurable temporal information from EEG during the MRI's data analysis [IVE 93].

Of course, this simultaneous recording is not without its technical difficulties. In particular, fMRI gradients produce large amplitude currents in EEG cables, as well as a slight movement of the head and a strong magnetic field. However, these difficulties have for the most part been resolved and it is now possible to find commercially available systems for recording simultaneous EEG-fMRI.

2.3.2. *Applications and data analysis*

One of the most important applications of EEG-fMRI is to use EEG detection of spontaneous epileptic discharges in order to analyze fMRI data. This information is useful in presurgical evaluation of patients. In this case, a linear model is constructed based on the time of observed discharges and a BOLD response model [BEN 02].

One other application on continuous data is to follow oscillation fluctuations in the frequency bands that are visible on the EEG. This makes it possible to characterize regions in the fMRI that are involved in brain rhythms, like the alpha rhythm [GOL 02].

For cognitive protocols, a strategy is based on constructing parametric regressors to bring out regions involved in different waves visible on the EEG.

In order to do this a single trial estimation of the wave amplitude (or latency) is carried out, and the amplitude of a new regressor reflects that of the parameter [BÉN 07].

In order to go further in data analysis, it is advantageous to combine the data in a joint analysis. Bayesian methods seem well suited for this task [DAU 07].

2.3.3. *Connections between EEG and fMRI*

One major question during the combination of EEG and fMRI data is the relationship between the two types of signals. In this regard, the study of neurovascular coupling is an active topic of research. Several studies have shown that the strongest connection seems to occur at the level of resting potentials and not of action potentials [LOG 01]. Moreover, this link has been observed to be more prominent in the frequency band of gamma oscillations (40–120 Hz) [NIE 05].

Numerous efforts have been carried out to represent this coupling through computational modeling [BLA 11]. Enhanced modeling techniques will eventually help to better understand the mechanisms that underlie these observations – for example negative BOLD signal fluctuations – as well as to improve data merging.

2.4. Discussion and outlook for the future

The different modalities of functional neuroimaging, EEG, MEG and fMRI, are often thought to compete with one another, but they are in fact complementary. EEG and MEG can trace back brain activity within the temporal scale of cerebral functions – that is at the millisecond level – even though they must solve an inverse problem to do so. fMRI makes it possible to directly reconstruct activity emanating from a voxel of approximately 1 cubic mm, although it is based on a relatively slow response (of about 1 s). Concerning fusion of EEG and MEG, several studies have shown that some activities are more visible in one than in the other. EEG is more sensitive to radial dipoles, whereas MEG is much less influenced by the skull and seems well suited to measure high frequencies.

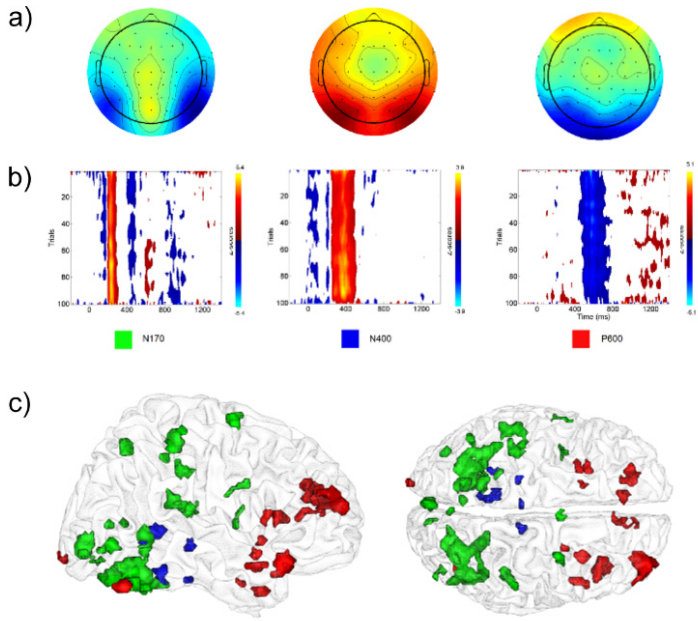

Figure 2.3. *Example of data analysis for simultaneous EEG-fMRI in a face recognition protocol (data: Jonathan Wirsich and Maxime Guye, CEMEREM-CRMBM, UMR 7339). Independent component analysis (carried out on the entire subject group) finds components corresponding to different waves observed on the EEG (N170, N400, P600). The amplitude values are then used in a parametric regression to determine the regions where the MRI signal correlates with the parameter of interest (according to [WIR 14]): a) component topography; b) visualization of tests for each component; c) results of the fMRI analysis; each color indicates the voxels for which a significant correlation with the corresponding parameter (amplitude from N170, N500 or P600) was found. For a color version of this figure, see www.iste.co.uk/clerc/interfaces1.zip*

Due to this complementarity, it seems particularly interesting to record the different imaging modalities at the same time, either EEG-MEG or EEG-fMRI. These simultaneous recordings have the great advantage of picking up the same brain activity from different angles, but they also present new technical challenges for the analysis of this complex data.

Among several avenues for future research, we can highlight the importance of confirming non-invasive measures with invasive measures

[DUB 14], and improving data interpretation with biophysical and computational modeling [VOG 12].

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