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Intracranial EEG and human brain mapping

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Abstract

This review is an attempt to highlight the value of human intracranial recordings (intracranial electro-encephalography, iEEG) for human brain mapping, based on their technical characteristics and based on the corpus of results they have already yielded. The advantages and limitations of iEEG recordings are introduced in detail, with an estimation of their spatial and temporal resolution for both monopolar and bipolar recordings. The contribution of iEEG studies to the general field of human brain mapping is discussed through a review of the effects observed in the iEEG while patients perform cognitive tasks. Those effects range from the generation of well-localized evoked potentials to the formation of large-scale interactions between distributed brain structures, via long-range synchrony in particular. A framework is introduced to organize those iEEG studies according to the level of complexity of the spatio-temporal patterns of neural activity found to correlate with cognition. This review emphasizes the value of iEEG for the study of large-scale interactions, and describes in detail the few studies that have already addressed this point.
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1. Introduction

The general purpose of this paper is to review how intracranial electro-encephalography (iEEG) can help us to understand the neural basis of human cognition.

In contrast with standard scalp EEG, iEEG is recorded by electrodes implanted directly inside the brain of some exceptional patients. Human Intracranial recordings usually measure local field potentials and occasionally spikes (we review both under the name iEEG in this paper), they were introduced in the late 1940s for diagnosis and therapeutic purposes [47] (see [9] for a review) and are still commonly used. Such recordings are mostly obtained from patients suffering from medically intractable epilepsy, but they are also recorded from Parkinsonian patients and some patients with brain tumors. In epileptic patients, electrodes can be left into place for up to a couple of weeks, while the patients are waiting for spontaneous seizures to occur, in which case iEEG provide invaluable clues about the anatomical origin of their seizures onset. During those weeks, patients spend most of their time in their hospital room and they may agree to use some of this long spare time to perform cognitive tasks while their iEEG is continuously recorded.

Needless to say, the selection of the electrode sites, as well as the duration of the implantations, are made solely on clinical grounds and without any reference to the cognitive protocols. However, they provide a unique window to the human brain for those interested in the neural basis of human cognition. And in addition to its value for research, the participation of patients in cognitive protocols can directly benefit them since such protocols help defining specific functional brain subregions close to the focus for which resection must be avoided because of their critical functional role. Such investigations could also help us to understand how for a given patient, his/her cognitive processes may interact with his/her brain activities involved in seizure induction, in an effort to develop with him/her cognitive strategies that could reduce the occurrence of seizures.

Because, fortunately, the population requiring such treatment is small and because those recordings require a complex combination of skills, there are relatively few

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reports of iEEG during cognitive studies (in the process of writing this review, we tried to establish an exhaustive list of such studies in the last 30 years and came to a total just above 170 published papers). Yet, if these constitute quantitatively a very minor stream of research within the more general field of human brain mapping, the spatio-temporal resolution of human intracranial studies make them very unique quality-wise, because they approach or go beyond the 'gold standard' of human brain imaging, the 'millimeter–millisecond' resolution.

This review is an attempt to highlight the value of iEEG for human brain mapping, based on its technical characteristics and based on the corpus of results it has already yielded.

In the coming section, we will introduce iEEG in further detail, putting an emphasis of its spatial and temporal resolution, and reviewing its main advantages and limits. In the subsequent section, we will review some of the main results obtained with iEEG, and sort them out along some of the main axis that structure the human brain mapping project.

2. What does iEEG measure?

2.1. Spatio-temporal resolution of iEEG

2.1.1. Temporal resolution

In theory, the temporal resolution of iEEG is that of the electrophysiological phenomena it measures, that is, submillisecond. In practical, it is only limited by the sampling frequency of the acquisition boards. It is common to record local field potentials (LFP) with a sampling rate of 512 Hz or more, a rate that can for instance provide good descriptions of oscillatory signals at frequencies up to 150 Hz. When using micro-electrodes (see next paragraph), the sampling rate can easily climb up to 30 kHz, which allows to sort spikes out and identify individual neurons within multi-unit activity.

2.1.2. Spatial resolution

The spatial resolution of human intracranial recordings ranges between two extremes. At one extreme, it is possible to record single and multi-unit activity from extracellular micro-electrodes. This is a rare situation that occurs typically for mapping purpose during a surgery. For instance, during palidotomy or thalamotomy procedures, in Parkisonian patients, the neurosurgeon moves an electrode downwards the basal ganglia in a search for the structure to be lesioned or to be chronically stimulated. Along this path, the firing patterns of the neurons constitute the most reliable signature of the structures that the electrode tip encounters. A handful of studies have used such micro-electrodes to describe specific changes of multi-units firing rates in relation to cognition (e.g. [10,22,33,45,55]). Needless to say, such 'micro-scale' recordings, usually performed in the operating room, are technically extremely challenging and impose severe constraints on the timing and design of the cognitive protocols. And, by far, the vast majority of human intracranial recordings do not have this cellular spatial resolution and measure instead meso-scale recordings, the LFPs, from surface strips or grids of electrodes or stereotactically placed depth electrodes in chronically implanted epileptic patients. We will focus on the resolution of those meso-scale recordings in the rest of this section.

Just as for scalp EEG, it is not straightforward to assess the spatial resolution of meso-scale iEEG. Each point of electrical contact between an electrode and the surrounding brain tissue records a weighted sum of activities: the sources of electric field present in the entire brain volume. But the weight of each source decreases with (is inversely proportional to) the square of the distance separating the source from the contact point [41].

This implies that parts of the brain far away from the electrode can theoretically have a significant influence in the signal it records, but this can only happen if those remote neural sources generate very strong electric fields relative to those created close to the electrode. Nevertheless, converging observations seem to indicate that the field created by neurons more than a centimeter away from a recording site contribute only for a negligible portion of the signal. For instance, we observed, on a 6×5 grid covering the temporo-occipital junction of an epileptic patient (with a 1 cm spacing between recording sites), that one of the site recorded strong interictal spikes while sites more than 1 cm away were silent. Practically, the spatial resolution of iEEG depends both on the impedance and on the size of the electrical contacts along the electrodes; it also depends on the volume conduction properties in the piece of brain tissue around the electrode. Therefore, the resolution should be estimated for each patient when possible.

This requires a systematic way to estimate, at least roughly, iEEG's spatial resolution from the recordings. We suggest the following approach: form all the possible pairs of recording sites, and compute for each pair an estimate of the correlation between their signals (using coherence for instance), computed over a long period of time (minutes to hours) then plot this correlation as a function of the distance separating the two sites of a pair. Fig. 1 shows an illustration of this procedure, as applied to the signals recorded by eight recording sites, consecutive along a single depth electrode, with an interelectrode separation of 3.5 mm. This procedure should allow one to define a background correlation level, and to determine the maximal distance for which the correlation stands above this level. Although tran-

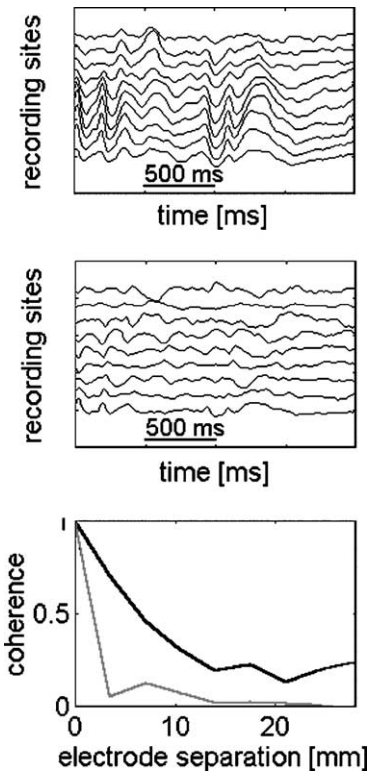

Fig. 1. Coherence measures can provide an estimate of the spatial resolution of iEEG recordings. In this epileptic patient, 10 signals were recorded during two minutes of normal rest on the same depth electrode from 10 contact sites regularly spaced by 3.5 mm (top graph). Nine bipoles were formed by considering the nine pairs of neighbor sites, and the signals are shown in (middle graph). Coherence was measured at 30 Hz between the deepest site (respectively, bipole) and the other nine sites (respectively, eight bipoles). The coherence value is shown in black (respectively, gray) as a function of electrode (respectively, bipole) separation (bottom graph).

sient, high, degrees of correlation can occur within any distance range because of functional coupling [36], the average level of correlation over long periods of time, various frequency ranges, and various experimental conditions is likely to depend solely on the volume conduction properties of the brain tissue that extends between the two electrodes.

Menon et al. [40] have measured the decay of coherence with intersite separation in a cortical grid of 64 stainless steel electrodes (each contact site extended over 5 mm in diameter and the interelectrode distance was 10 mm, center-to-center). They found that the distribution of coherence values differed from background level at intersite distances of 1 and 1.4 cm but not 2 cm. That, again, supports the view that iEEG measures the LFP generated within a centimeter radius.

2.1.3. Source reconstruction from iEEG

Sometimes, it is possible to localize the neural sources of iEEG (the patches of neuronal tissue whose coherent neural activity induces the measured electric field) with a high degree of confidence from the specific spatial distribution of the electric potential they create. For instance, when the polarity of the iEEG signal inverts when moving from one contact site to its neighbor, then the source of that activity is likely to be in a plane orthogonal to the line joining the two contact sites. Also, if this source can be modeled as a dipole, or a dipole sheet, then the orientation of those dipoles is roughly parallel to that line. More generally, if the voltage displays a large local gradient in a structure, but not in the surrounding structures, then one is recording from a local source [23].

Moreover, source modeling could be used to reconstruct locally the neural sources of the measured intracranial voltage [8], in a way similar to the reconstruction of the neural sources of scalp EEG (the so-called ''inverse problem'', [6]). But several critical questions need to get answers first, among them: (a) how many intracranial recording sites are needed to provide a precise (and unique) reconstruction? (b) What model shall be used for the sources (dipoles? Quadripoles?). (c) What are the volume conduction properties of the brain tissue around the sources (isotropic? Non-isotropic? Homogeneous? With what conductivities?).

For this last question, our knowledge may greatly improve from a systematic analysis of the iEEG recorded during sessions of electric stimulations (series of brief, low amplitude, electrical pulses delivered to each electrode in succession for mapping purposes or for seizure generation in epileptic patients). The stimulation of a site mimics a pulse of neural activity that propagates instantaneously towards all the other recording sites according to the volume conduction properties of the brain tissues. One expects therefore that those properties can be recovered from the relative amplitude of the signals recorded at the time of the stimulation.

2.1.4. Reference issue

One should bear in mind that the previous estimates of the iEEG spatial resolution assume a neutral reference. As any electrical potential, the signal measured by a site is the deviation from another potential recorded by a reference electrode. The reference electrode is also sensitive to the fluctuations of the electric field generated in its vicinity. So, those should always be an order of magnitude lower in amplitude than the fields close to the iEEG electrodes (this should be true for all frequency ranges). It seems sensible to chose an electrode with the same impedance as the other contact sites, and located in a region with no or little source of electrical field. For instance the reference could be one of the contact sites in the white matter, if there are, since in theory the white matter does not contain significant sources of electric signal.

The choice of the reference electrode is always a sensitive issue [60]. Many intracranial studies have used

external reference electrodes (tip of the nose, linked ears), which makes sense, since such potentials are attenuated by the skull compared to intracranial recordings. However, they may be contaminated by eye-movements artifacts (even minor ones) or electromyographic activity from subtle muscle contractions.

One way to make sure that the signal recorded has a local origin is to use for each recording site a reference that is specific to it, in its immediate vicinity. That is the idea of bipolar recordings, a very popular choice among clinicians monitoring the iEEG of their patients. With bipolar recordings, the potential that is measured is the difference between the signals recorded by two electrodes nearby, so that the influence of the external reference is cancelled (for a recent application, see [53]). In fact, the bipolar signal is the spatial derivative, along an imposed direction, of the iEEG originally recorded with a common reference. As such, bipolar recordings receive less contribution from remote sources, since the weight of those sources now decreases with the inverse of the distance to the contact pair to the power of three. Physiologically, a bipolar recording corresponds to the fluctuations of the very local electrical activity relative to its immediate surrounding. One obvious limitation is that this signal is blind to fluctuations that affect equally the two sites of the bipole. Also, phenomena such as travelling waves, that reach neighboring electrodes in succession, appear as a succession of two peaks of opposite polarity, which may complicate interpretations.

To eliminate this effect, other choices of local references can be thought of, such as the average signal of several contact sites instead of just the closest one. A performance charts of those various reference possibilities has yet to be establish (but see [60]).

2.1.5. Precise localization of the electrodes

Finally, the spatial precision of the iEEG depends in a trivial way on how precisely the localization of the electrodes is known, in relation to brain anatomy. It makes little sense to claim a millimeter precision for the recordings if the location of the recording sites themselves are not known with that precision. This resolution is rarely mentioned in reports, although most of them describe careful procedures to achieve a good localization. Ideally, what is needed is a precise MRI of the patients showing the exact coordinates of the sites. But there is no easy way to achieve this, as it is not good enough, for instance, to record the MRI of the patient with its electrodes in, because electrodes produce image artefacts. A better alternative is to perform the localization in three steps: (a) perform the MRI of the patient before the electrodes are in, with a special localization device mounted over the skull that appears clearly on the image; (b) perform a CT scan of the patient with the electrodes in, and with the same localization device (electrodes do not produce scanner artefacts); (c) using the device's image, match with extreme precision the non-artefacted MRI and the scan. Note that, even with such careful procedure, the exact precision of that mapping still depends on how much tissue deformation is induced by the electrode implantation.

2.2. Constraints of iEEG

Provided that all the requirements are met, so that iEEG can record the LFP coming a volume of brain tissue approximating a cubic centimeter, then its spatial resolution approaches that of fMRI or PET, as illustrated in Fig. 2. Since its temporal resolution equals that of EEG and MEG, iEEG comes close to the mm/ms ''holy grail' of human brain imaging. Given state-of-the-art imaging techniques, this resolution could only be matched by a combination of fMRI/MEG/EEG supported by source reconstruction algorithms that everybody would agree on, a perspective still out of reach for the time being.

In addition to this precision, iEEG has the other advantage of being somewhat immune to muscle and eye movements artifacts (see Fig. 3 for a comparison between signals recorded from scalp and depth electrodes during jaw contraction and eye blinks). This opens many possibilities inaccessible to the less robust EEG/MEG. Let us name a few: (a) it allows one to study the neural mechanisms of occulomotor control with high temporal precision; (b) it facilitates the extraction of neural high-frequency activities, such as gamma-band rhythms, the spectral profile of which overlaps with that of muscle-related artifacts; (c) it enables the study of patients performing motor tasks that prevent them from standing still.

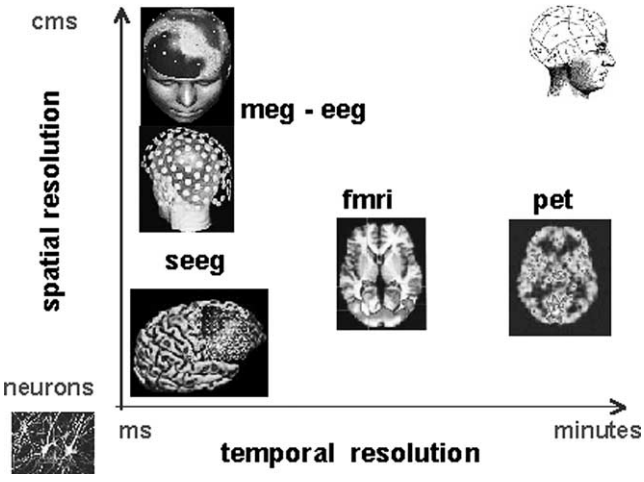

Fig. 2. Spatio-temporal resolution of the major brain imaging techniques. IEEG combines the temporal resolution of MEG and EEG with a spatial resolution close to that of fMRI and PET.

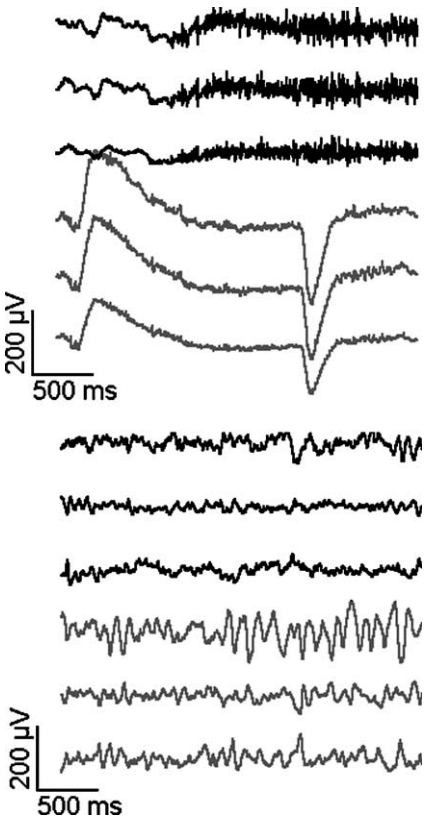

Fig. 3. IEEG is less vulnerable to muscle and eye-movements artifacts than scalp EEG. (Top graph) Signals from three scalp electrodes (F_z, C_z and P_z) during chewing (top three traces, black) and eye-movements (bottom three traces, gray) and (bottom graph) signals from three bipoles deep in the temporal lobe during chewing (top three traces, black) and eye-movements (bottom three traces, gray).

All those advantages come with a double-cost: (a) the obligation to record only from patients, whose cognition is only a model of the cognition of normal subjects; (b) the fact that implantations give only a very restricted window to the brain, since most of it remains uncovered by a set of contact sites that rarely extends beyond 100. Let us discuss these two points.

2.2.1. Relation to pathology

Since intracranial recordings come mostly from patients with severe epilepsy, this raises the concern that the tissue that is recorded from is not organized in the same way as normal tissue and therefore that the recordings could lead to a bad model of normal human neural computation and functional organization. This is always a possibility although our experience is that many patients perform behaviorally as well as normal subjects. Still, there could be some significant reorganization caused by the pathology or alterations due to the medication. One careful precaution (as suggested in [23]) is to focus solely on observations that appear to be constant across patients with different pathologies and anticonvulsant medication. This is a desirable goal, but somewhat difficult to achieve since it requires that large populations of patients with similar implantations perform the same cognitive tasks, a project that can take years. A simpler, yet not as powerful, precaution is to record the patient as early as possible after the surgery, (but at least three days after electrodes implantation to avoid the effects of anesthesia and the acute effects of electrodes implantation) when s/he is still under anticonvulsant drugs, and to consider only recordings that are made away from seizure activities (before and after).

Another concern, with epileptic patients, is that some abnormal activities (such as interictal spikes or high-amplitude slow waves) constitute a source of signal artefacts. This contamination must be minimized by selecting for analysis periods of time and recording sites that are virtually free from epileptiform activity. Sometimes, this means throwing away half of the data. For this reason, it is desirable to double the length of the experiments (in ERP paradigms, to double the number of trials) compared to their duration with normal subjects.

Still, identifying epileptiform activity is not always an easy task: some low amplitude spike discharges can easily be mistaken for normal oscillations, for instance. But in most cases one may assume that pathological activity does not carry specific links with the task at hand, and use this assumption to distinguish between normal and pathological patterns: for instance, in protocols that repeat the same sensory stimulation many times, patterns of neural activity occurring always at the same latency relative to the stimulus are likely to be of cognitive origin. Whether this assumption is always true is still a point of debate: in fact, we have shown that the distribution of epileptic ictal spikes can in some instances be modulated by sensory events (e.g. [38]).

2.2.2. Limited coverage

A further problem is that all implantations leave most of the brain volume unexplored. Halgren et al. [25] have calculated that in order to sample the whole brain volume with a spatial resolution of 3.5 mms, the inter-electrode spacing used in most studies, about 10 000 recording sites would be necessary. Fortunately for the patients, this number rarely goes above 100. This estimate should be qualified by the fact that the access to part of the volume, the white matter, is not primordial, (but many implantations, using depth electrodes for instance, pick up both white and gray matter), and by the fact that electrodes can be positioned to target specific functional systems, so that the spatial sampling precision is much higher within such systems. Note that this sampling problem is not unknown in EEG/MEG recordings since those are blind to certain source configurations because of the particular shape of the electric and magnetic fields. Yet the sampling problem is

certainly more critical with iEEG (see [28b] for further discussions on this topic).

This problem of limited coverage can be somewhat overcome by recording the patients during cognitive tasks that involve preferentially their implanted brain structures (and the functional systems that may have been targeted). This solution requires functional atlases that allow a precise mapping between structure and function. Such atlases are starting to appear based on fMRI and PET studies, and intracranial stimulation studies but it is not clear yet whether metabolic activations are good predictors of electric activations. A recent study seems to support this claim: in recordings from the visual cortex of monkeys viewing rotating checkerboards, Logothetis et al. [39] have shown a strong correlation between the LFP and the bold-fMRI signal. To investigate further the relationship between electric and metabolic signals in other parts of the brain, we have started comparing fMRI and iEEG recordings obtained in the same patients doing the same tasks (recordings are under way). This point is developed further in the conclusion.

Still, a functional atlas that would help optimize the protocol selection would not solve all the problems. Some structures are almost never recorded from (such as many subcortical structures) and tasks that involve heavily those areas are difficult to investigate with iEEG. Also, iEEG alone is not well suited to study interactions between very distant brain areas (for instance between occipital, parietal and frontal regions during visuo-motor coordination), since implantations tend to be anatomically focused for therapeutical reasons.

2.3. What does iEEG record, again?

iEEG record the local field potentials created by vast populations of neurons. This can seem a long way from single neurons, the basic unit of neural computation. And since most electrophysiology studies try to understand what makes neurons spike, and what that means when they spike [49], one can wonder what is the significance of iEEG for our understanding of the neural mechanisms underlying cognition. Two related issues need to be clarified: (a) the value of LFPs compared to spike recordings and (b) the value of the average activity of populations of neurons, compared to single-neurons activity.

2.3.1. From spikes to LFPs

First of all, LFP and Spike-density measures are strongly related. While spikes are the *output* of the neurons, LFP are believed to be the summation of dendro-somatic components of the input signals (that is Post-synaptic potentials) and thus represent the *input* of a neural population. It is not surprising, then, that some sort of relationship links input and output, especially since in neural populations of the size that is recorded by iEEG, 50% of the neurons receive their inputs from neurons in the same population [52]. Freeman [18] has estimated the transfer function between LFP and spike-density (''wave-to-pulse conversion for populations'') as a monotonous curve reaching a saturation plateau. This predicts that away from the saturation regime, LFP and spike-density measures should correlate well, and indeed such high-correlation has been repeatedly observed in many studies (e.g. [39]). In fact, due to their origin, LFPs should correlate better with the membrane potentials of the neurons, as they can be recorded with intracellular electrodes, since this potential is directly controlled by the postsynaptic potentials. This, also, has been reported [58].

2.3.2. From single units to neural populations

Second, one may rightly wonder whether the populations recorded by iEEG constitute relevant 'units' for our understanding of cognition. After all, those ''units'' are defined by the location and precision of the iEEG measure, and are, as such, arbitrary: neurons recorded by a LFP have no other a priori relationship with each other than to lie next to each other (and possibly, to belong to the same class of cells, pyramidal cells, since most of the iEEG is due to those cells). How can we define relevant units for the study of a system? Let us consider a brief metaphor: when 22 people play soccer, it makes sense to consider them as two teams, and to define for each team properties that are appropriate for that level, such as strategy, confidence, cohesiveness, that help us understand the game at the team level. Teams are relevant units for the study of a soccer game. In contrast, it would make no sense to define arbitrarily two random groups of 11 players and to describe the game from that group level. It only makes sense to study a group of neurons, if it is possible to define meaningful response properties for this group. If, for instance, all the neurons in the group share some common response properties, then the group will also have those properties. In many structures, the functional architecture is implemented into a systematic topographical organization, the brain maps where neighbor neurons tend to have the same general response properties (such as responding well to certain positions in the visual field in V1, or to visual shapes in IT, or the so-called motor and somatosensory homunculi, etc.). Yet, when considering *groups* of neurons, some of this specificity will blur, because neurons with different selectivity are averaged together. When averaging the response of all the neurons in MT for instance, one would find that the global activity is sensitive to motion, but not to direction. One big task for electrophysiology is to determine what properties are lost when going up to the group level. Maybe some properties would emerge, that are not present at the neuron level? What we can learn from

iEEG depends on what properties remain at the level of a population on a 1 cm radius.

Maybe the main limitation of LFP population recordings is that they do not quantify mechanisms of inhibition or excitation in a direct way, as opposed to single-unit recordings. While these mechanisms directly translate into negative or positive variations of the membrane potentials of individual neurons, their influence on the post-synaptic potentials cancel out in the local field potential of iEEG. In fact, changes in the amplitude of the LFP can be due to changes in the excitation state of the neural population, but also to changes in the synchronization within those neurons, even if the activity of those doesn't change. Also, variations of dipolar potential measured with the same sign on a given electrode can be elicited by excitatory as well as inhibitory processes if the synaptic sources of modulation are at different positions in relation to the soma of the neuron source. That limits the value of iEEG data for our understanding of neural computation, since this understanding depends largely on precise descriptions of the balance between inhibitory and excitatory influences between cell populations.

Yet, this does not mean that population recordings can not be used to quantify some measure of influence of one brain structure on the regions that are connected to it, (that is, to quantify the ''potential of influence'' of one brain region on its ''connected domain''), and several attempts have already succeeded to demonstrate functional links between distant brain areas (see [56] for a review, see also [31,53]). Such successful attempts using iEEG will be reviewed in the next section.

3. iEEG and human brain mapping

Human brain mapping is now at a turning point: until now, its focus has been primarily on identifying the individual components of the large-scale neural networks underlying cognition; it reaches now a second stage in which this focus is shifting to address the dynamic interactions and influences that allow those components to function together. In this section, we try to describe formally some axis that structure this research field in order to understand this evolution, and in order to better understand how iEEG contributes to it and how it is providing new directions for research.

3.1. Human brain mapping: a search for discriminant functions

Human brain mapping studies follow almost invariably the same steps: (a) assuming a certain behavior from a human subject that proves an ability of his cognitive system to perform a function (from pressing a button when a light flashes to answering a detailed questionnaire after viewing an emotional picture), a model is proposed that breaks down this global procedure into simpler cognitive procedures, following the classic methodology of cognitive psychology (we will use the term 'elementary' procedure, for sake of simplicity; that does not mean that they can not themselves be broken down further). Then (b) the research goes on to find the neural substrates of those elementary procedures and to describe their interactions. This is done by engaging subjects into series of behavioral tasks that manipulate, independently if possible, each elementary procedure, and by addressing five major questions: (1) *what* are the elementary mental processes needed to perform that procedure? (2) *where* do they take place, in which neural structures? (3) *when* are those processes performed? (4) *How* do those neural structures perform those processes, (how could we recreate neural networks models performing the elementary procedure in the same way?). (5) Based on the brain functional architecture, *how* does the global behaviour emerge from the interaction between all the elementary procedures? This approach is well illustrated for instance by the research on visual attention [35].

This implies that two conditions must be fulfilled for this human brain mapping project to be possible: (a) the global cognitive procedure must arise from the coordination of a fixed set of more elementary processes that repeat themselves in a relatively invariant way across multiple repetitions of the same global procedure, (b) given brain imaging techniques (such as iEEG), that provide a set of measurements of the brain activity during this global cognitive procedure (a 4-D description: 3-D anatomy $\times$ time); there must exist a mathematical function F of that descriptive 4-D space, (1) that keeps the same value each time the same specific elementary procedure is performed, and (2) that changes its value in a systematic way when a variation is introduced in the global procedure, that affects selectively that elementary procedure. In other words, it is possible to infer what that local procedure is doing from the value of F. F is a discriminant function, in the statistical sense.

Note that, the 4-D ''brain space'' is defined into an architecture including topological and functional relations between local brain activities and the search for discriminant functions should be guided by an understanding of the functional architecture that constrain the dynamics of the neural networks it observes.

According to this framework, it is theoretically possible, given the set of such functions F for each elementary procedure, and the model linking those procedures into the global cognitive procedure, to build a global discriminant function G for this global procedure.

This research effort parallels the very active search for a 'neural code' from animal electrophysiology studies, a quest that has sparked an intense debate in vision

research, among other fields [51]. It is the search for discriminant functions that can help us make sense of neural activity in terms of cognitive processes. Both human and animal brain mapping are evolving towards the search for discriminant functions of increasing complexity. In a first approximation, three levels of complexity can be distinguished (this typology has been the subject of much developments, and we use it here to "organize" the diversity of iEEG studies). Fig. 4 introduces in a cartoon-like manner the general distinction between those three levels of complexity.

3.2. Orders of complexity

First-order discriminant functions are only functions of the total activity (quantified by a spike density, or the amplitude of an LFP) present in a particular region of the 4-D anatomy-time space, that is, in one brain structure or one neuron, in a given time window.

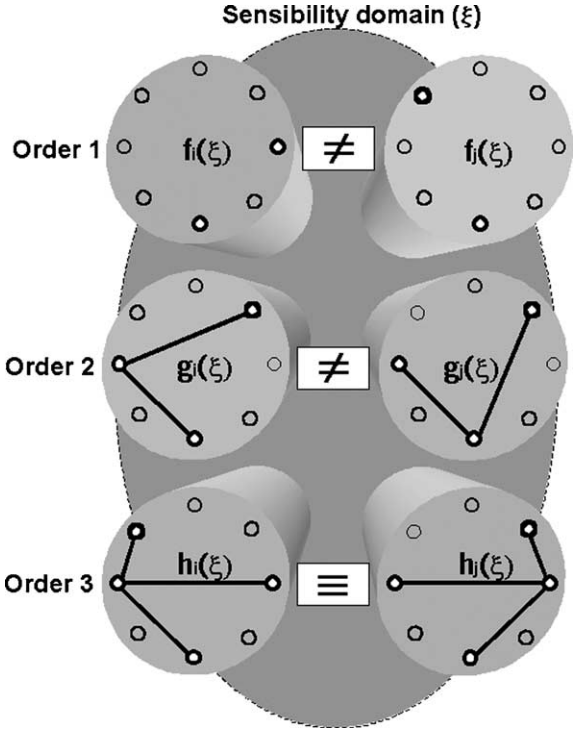

Fig. 4. Typology of analysis functions in the brain 4D space. ξ corresponds to the sensibility domain of the measured neural activities to an external or internal domain of variation (like a stimuli database for instance). Transfer "mapping" functions (f, g or h) relate ξ to a pattern projected in the 4D space, represented by several sources s (small circles on a bigger circle). (Order 1) The functions f_i and f_j correspond to local measure of activities in the source space without any quantification of the interactions between sources. If f_i and f_j are different the mappings are considered to be functionally different. (Order 2) The functions g_i and g_j correspond to quantification of interactions between sources. If g_i and g_j involve different sources or different interactions between the sources the mappings are considered to be functionally different. (Order 3) The functions h_i and h_j correspond to quantification of interactions between sources with a topological and/or dynamical criteria of invariance defining an equivalence class of functions. Under this assumption the mappings may be considered as functionally equivalent even if h_i and h_j are different.

At the neuron level, this order corresponds to the famous, and extreme, 'grand mother cell' example [7], in which single-neurons function as feature detector: each time the subject detects the presence of a yellow Volkswagen, the firing rate of this neuron increases. The micro-cognitive operation 'detection of a yellow Volkswagen' can be reproduced by a threshold function applied to a minimal portion of the 4-D brain space: the firing rate of this neuron during the presentation of the visual stimulus. At the meso-scale level of LFPs, one example of first-order discriminant function is the selective response of portions of the fusiform gyrus 200 ms after the presentation of a face. The amplitude of this N200 potential may serve by itself as an indication of whether the subject has seen a face among other possible visual stimuli [4]. Such belief that a localized brain structures may be associated with a specific cognitive function is often based on case studies of patients having specific lesions affecting specific 'stages' of the processing (such as the inability to recognize familiar faces in prosopagnosia) [4].

Second-order discriminant functions are not solely functions of the energy in one specific region of the 4-D brain space, but correspond to specific, but relatively invariant, distributions of this energy along the spatial axis (a), along the temporal axis (b), or along both spatial and temporal axis (c) in the form of possibly complex spatio-temporal patterns.

At the micro-scale level, the spatial second order corresponds to 'population codes', in which it is the relative firing rate of several neurons during a certain time-window that 'codes' for a specific cognitive procedure. The direction of arm movements in M1 can be reconstructed from neural populations in M1 using that principle [21]. A discriminant function of the *temporal* or *spatio-temporal* second order would have to be sensitive also to the temporal organization of neural activity within the window of observation. Such function is commonly referred to as a 'time-code'. For instance, it has been proposed that spike synchronization in specific oscillatory modes within populations of neurons in the mammal visual system could mediate feature integration (see [51] for a review). An extension of this synchronization mechanism at the meso-scale level, between distant cell populations, has been proposed to account for large-scale integration, it is now the inspiration of a very active field of research (see [56] for a review).

We can then imagine a third-order, much more difficult to capture, in which the neuronal realization of cognitive operation does not correspond to specific spatio-temporal patterns, but to classes of patterns. The brain being a dynamic spatially extended non-linear system, it may be useful, to guide our intuition, to

consider such a system (although of much lower complexity) and its response to an external stimulus: a group of fishes attacked by a predator. In a first approximation, the state space of the fish group is defined by the possible 3-D positions of each fish at each instant. The global response to repeated unfortunate attacks is always the same (no fish is hurt), yet the precise spatio-temporal pattern describing the reaction of the group to each individual attack is always different (even if the attacks always follow the same trajectory), because it depends on the initial state of the group before the attack. This implies that a discriminant function able to differentiate between two behaviors of the network (avoiding the predator or not) would have to generalize and discriminate between *classes* of spatio-temporal patterns: '' for this particular attack, this class of spatio-temporal patterns (the formation of a 'hole' around the predator) constitute a successful response of the group (although it never involves the same fishes)''. Whether, it is always feasible to create meaningful pattern classes for complex neural networks is an open question. From this answer depends our ability to find 'neural codes'.

4. Orders of complexity in iEEG studies

All the studies that have used iEEG during cognitive tasks contribute to the general human brain mapping project and have searched, implicitly or explicitly, for discriminant functions of some order. iEEG has been used for decades and it is virtually impossible to review the contribution of this technique extensively, however, this contribution can be divided into two streams, (a) a 'classic stream' that inherits from the traditions of scalp ERP and classic animal electrophysiology and that addresses the question of mapping at the first order, and (b) a more recent stream of research, that builds on those essential results to address the question of higher-order mapping, mostly through a description of synchronous cell assemblies. This section explores representative examples of iEEG that illustrate its value and give hints about its future developments. The illustrations are organized along two axis, addressing: (a) cognitive functions of increasing complexity and (b) analysis methods designed to capture invariant neural patterns of increasing order.

4.1. ERPs and PSTHs

The 'cognitive-iEEG' literature revolves around the calculation of mean evoked responses, Evoked potentials from LFP recordings, and post-stimulus time histograms (PSTH) from spike recordings. In an effort to review this literature exhaustively, we found roughly 170 studies describing intracranial recordings in humans (LFP (~140) or micro-electrode recordings (~30)) obtained during cognitive protocols. Out of the 140 LFP studies, a little more than 100 focused solely on evoked potentials. Micro-electrodes studies calculated PSTH, that is, the equivalent of evoked potentials for spike recordings (the average number of spikes recorded in response to repeated presentations of a stimulus at each latency relative to that stimulus).

The ERP is a descriptive of the first-order. It is the mean neural activity following (respectively, preceding) repeated presentations of the same sensory stimulus (respectively, repeated executions of the same action). Their interpretation relies on the assumption that in all the presentations, a systematic neural activity repeats itself at the same anatomical location and in the same time interval, embedded in some background activity not correlated to the processing of the stimulus (and therefore treated as noise). Neural responses to successive presentations are averaged to extract this component from the noise; a procedure that is robust even if the neural component does not happen always at the same latency relative to the stimulus, provided that this jitter is negligible compared to the duration of the component. This definition helps us to remind some limitations of that method: (a) short components, rising and falling within 20 ms for instance, can not be detected by this procedure, unless they are very precisely time-locked to the stimulus (with a ms precision), this makes invisible virtually any activity above 30 Hz in the frequency spectrum; (b) variations of the level of background activity are not considered. If, for instance, the standard deviation of this background activity drops when the stimulus appears, the ERP will not detect it, as illustrated in Fig. 5, because it is a measure of the signal mean and not of its standard deviation. Examples of such drops abound and they constitute potentially important cases where stimulations induce a reduction of activity in an area (a possible trace of population inhibition).

The iERP literature is remarkably homogeneous. It is dominated by a few paradigms that have been widely explored in a vast array of brain structures. For instance, out of the 100 studies of intracranial evoked potentials, 20 have studied the response to passive stimulations of the median nerve, or of the limbs, in a general effort to map the organization of somatosensory evoked potentials. (e.g. [2]). Another 20 papers tried to localize the sources of the scalp N2/P3 potential in oddball protocols (see for instance [25]). Roughly 20 papers again studied the sources of the motor potentials preceding movement onset during self-paced or externally cued movement (e.g. [34]).

In general, protocols are simple and involve simple sensory stimulations. And for the most part, the cognitive load and the complexity of the cognitive procedures required from the subject is minimal. There are notable exceptions, though: here are a couple of representative

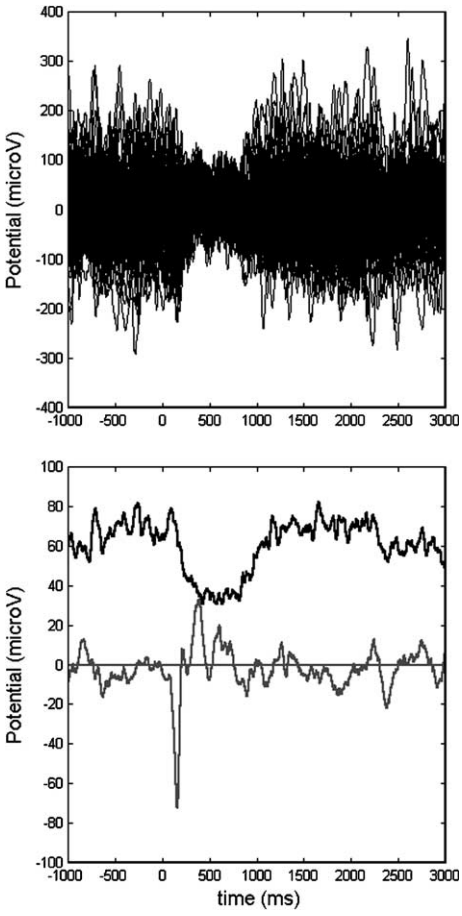

Fig. 5. Intracranial event related potentials. Top graph shows 100 signals recorded from the same site in the fusiform gyrus of an epileptic patient presented with 100 pictures of faces (at 0 ms). The stimulation clearly induced a decrease of the background activity. Bottom graph shows the mean (bottom gray plot) and standard deviation (top black plot) of those 100 signals. The mean displays the potential evoked at 200 ms by the face stimuli, but it does not show the reduction of background activity.

studies involving cognitive functions of growing complexity.

Median nerve stimulation studies give a good insight into the capacity of iEEG in terms of spatial and temporal resolution. For instance, in two companion papers, Allison et al. [2,3] reported, among others results, the responses of the sensorimotor cortex (hand representation area) to contralateral stimulations of the median nerve, obtained from 54 epileptic patients. Based on the polarity of the responses, they were able to distinguish between two series of components of alternate polarities peaking at 20, 30, 45, 80 and 180 ms latencies, recorded from area 3b, and in area 1 a series of peaks at 25, 35, 50, 90 and 190 ms. Such studies are especially helpful to map out which part of the sensorimotor cortex is active at which moment when stimulated peripherally, and to build a precise spatio-temporal representation of that response.

Similar high-resolution mapping has been performed for the visual (e.g. [24,61]), auditory (e.g. [62]) and olfactive [27] modalities. Interestingly, for visual and auditory stimuli, several studies have been able to differentiate the responses to specific subcategories of stimuli according to their anatomical origins and latencies (e.g. [24,43]). For instance, in an impressive study of 98 patients, Allison et al. [1] reported and localized ERPs specific to faces. Following a procedure comparable to the receptive field mapping of inferotemporal neurons in animals, they presented patients with pictures of faces, scrambled faces, letter-strings, number-strings, and animate vs. inanimate objects. They found three types of face-specific ERP components: (a) a surface negative potential picking around 200 ms (N200) and recorded from the ventral occipito-temporal cortex, (b) a lateral surface N200 recorded from the middle temporal gyrus, (c) a late positive potential P350 recorded from posterior the ventral occipito-temporal, posterior temporal lateral and anterior ventral temporal cortex.

This very detailed study is very representative of the majority of the ERP studies done with iEEG, except for the number of subjects that is exceptionally large. By pooling results obtained from 98 patients, they were able to build a detailed but extensive structure-based functional description of the extrastriate cortex. Assuming certain invariability in the anatomo-functional organization across the patients, at least for the parts of their brain that show little sign of epileptiform activity, this approach produced a mapping that covered much more of the brain that what could be accessed in single subjects.

Studies like this one have led to identify brain regions that produce evoked potentials selective to words, faces and other classes of visual stimuli [24,43]. Such category-specific mapping has also been done at the unit level, and in other modalities. For instance, Creutzfeldt et al. [12] were able to record units in conscious patients listening to various sounds, words and sentences during their brain surgery. Among other effects, they found neurons in the superior temporal gyrus that responded well to various aspects of spoken language but not or little to non-linguistic noises and tones.

In the studies just described, the difference between potentials evoked by different types of stimuli could always be attributed to physical differences between the stimuli. A number of studies have tried to map the sources of endogeneous potentials, that do not depend so much on the stimulus attributes than on the context and the kind of processing that they undergo. In the classic, evoked potential nomenclature, successive EP components are related to different stages of information processing [25], from the strictly sensory to other 'higher' integrative levels, termed 'endogeneous'. Interpreting endogeneous potentials is obviously a much

more difficult task, since it is hard to induce specific and precisely-controlled variations along complex cognitive dimensions, but they can provide tremendous help to assess the level of processing at which cognitive process take place.

A great deal of effort has been devoted to finding the sources of the N2/P300 complex (a negative wave at 200 ms followed by a long positivity 100 ms later) a component that can be recorded from scalp EEG in response to infrequent events [23].

Halgren et al. [25] recorded epileptic patients performing a series of visual and auditory oddball tasks, that consisted in detecting rare targets embedded in a series of frequent and rare non-target stimuli. They described a mosaic of iEEG evoked responses to the rare non-target stimuli, simultaneous to the scalp P300 and potentially contributing to it. Those were found in nine structures, respectively the superior temporal plane, the supramarginal gyrus, the dorsalateral prefrontal cortex, the cingulate gyrus, the rectus gyrus, the hippocampus, the superior temporal sulcus, the posterior parietal lobe and the ventrolateral prefrontal cortex. Each of those responses were components of the same scalp N2/P3 complex but are believed to serve different cognitive functions. For instance, the dorsolateral prefrontal, the inferior parietal and the cingulate components would participate in the orientation of attention to information potentially relevant for the system.

Such studies reveal the richness of iEEG data, compared to scalp EEG, to describe the complexity of the neural networks brought about by even simple cognitive tasks. More complex tasks have been studied from the point of view of endogeneous potentials, and language and memory have been the most popular themes (e.g. [16,19]). Other functions have been addressed in a much more marginal way, such as attention [42,46], mental imagery [33] or emotion [29]. From the point of view of iEEG, higher-order cognitive functions constitute an open and still uncharted territory.

Yet, some remarkable observations have been reported: Kreiman et al. [33] were able to find in the medial temporal lobe neurons selectively active during mental imagery. Out of 276 neurons, collected from nine patients in structures including the amygdala, the enthorinal cortex, the hippocampus and the parahippocampal gyrus, 23 neurons would increase their firing rate when the subjects imagined a picture previously seen. Moreover, 14 of those had the same stimulus specificity for visual imagery and vision, (that is, they would respond to an animal, seen or imagined, but not to another type of stimulus).

Such a mapping that resolves the mapping 3-D space–time at the scale of the individual neuron for complex functions, is not an isolated case. Vision, language and verbal memory have been probed that way in roughly 20 studies [32,44]. More recently correlates of emotion perception were also found in single-units activity [29]. Such studies are particularly impressive, since they not only match the precision of state-of-the-art animal electrophysiology studies, but also allow us to address directly in humans levels of cognition that would be extremely hard or impossible to test with animals.

In summary, the previous iEEG studies present two extreme but complementary views: on the one hand, they reveal that complex cognitive functions such as visual imagery or emotion perception, translate into specific variations of the firing rate of single neurons; on the other hand, they demonstrate that cognitive tasks as simple as target detection involve widely distributed cortical networks. One may wonder about the optimal level of description of neural activity for human brain mapping: the single neuron or vast and distributed cell populations. Both levels of description seem relevant and complementary, and the magic of iEEG is to provide a bridge between them in humans, and further to provide a link between single-neuron animal electrophysiology and human non-invasive imaging.

Yet, ERP and PSTH studies will not tell the whole story. The results mentioned above leave a lot of questions unanswered. For instance, Halgren et al. [25] mentioned in their N2/P3 study that discrimination tasks such as the ones they used can be performed by animals with no neocortex, while they observed the participation of numerous and distributed brain areas. That led them to postulate that the performance of a task activates most brain areas, and much more than strictly necessary.

In this perspective, it becomes crucial to extend the first-order approach of the ERPs to a second-order that aims at understanding how those distributed brain areas interact, and how to perform a mapping at the network level [56].

What characterizes all the previous studies is that space and time are considered as independent dimensions. Virtually all ERP studies describe a collection of ERPs independently of each other. Few studies have tried to go beyond the traditional ERP approach, to relate distributed ERP components into spatio-temporal patterns determined by interaction mechanisms. We will give an overview of those efforts now.

4.2. Second-order—beyond the classic ERP analysis

Fernandez et al. [17] for instance, tested whether the latencies of the potentials evoked by words along the ventral visual stream in the inferotemporal cortex were due to a propagation of activity from the most posterior parts to the anterior IT regions. They used a continuous visual word paradigm in which nouns were presented sequentially, and patients were asked to indicate for each word whether it was shown for the first time or not.

Using recordings from several points along the inferotemporal axis, they showed that the mean peak latency of the evoked potentials in the 200–400 ms window decreased linearly with the distance between their recording sites and the orthogonal projection of the temporal tip onto the IT plane, as if the potentials proceeded anteriorly along the inferotemporal cortex at a speed of 15 cm/s.

This study is different from most others ERP studies in that space and time were no longer considered completely independently of each other, the authors tried to combine them into a meaningful spatio-temporal pattern. Such studies, that constitute a transition from the first-order analysis to a second-order analysis, are rare. Indeed, of the 170 papers that have carefully analyzed iEEG recorded during cognitive tasks, only 40 of those have not focused solely on ERPs in the traditional way.

A vast majority of those second-order studies have shifted their focus to the oscillations produced by the brain during cognitive protocols. The main reason is that oscillatory activities are ubiquitous in iEEG recordings and that they are sensitive to major variations in the cognitive states of the subjects in a way that depends on their frequency (e.g. [26]).

ERP analysis is not well suited for the study of task-related oscillatory activity, because transient oscillations that are not precisely phase-locked to the stimulus disappear in the averaging procedure. Novel analysis techniques have been developed to analyze those phenomena and have yielded a new literature, complementary, but somewhat distinct from the ERP field.

Oscillations in the iEEG emerge from synchronization mechanisms that bring together distributed neural populations into oscillatory neural ensembles. A growing corpus of research seem to support the notion that such ensembles may mediate some form of integration within and between motor, sensory and association areas to produce a unified behaviour (for a review see [56]). The detection of oscillatory neural ensembles and their correlation with cognitive functions constitute the most vivid stream of research of higher-order correlates of cognition (see for instance [51]). In addition, this stream of research is drawing a renewed interest for the high-frequency components of the EEG, that were invisible in the evoked potentials, but that may constitute a very significant part of the neural response. In fact, most of the studies that have used ERPs as a marker of neural activity to test specific hypothesis about the functional organization of specific cognitive processes could in principle be replicated with a focus on the high-frequency components of the EEG.

The field is fairly new and requires millisecond temporal resolution imaging to probe interactions between the fine temporal structures of precisely localized activations. The first and major results have come primarily from animal recordings (e.g. [63]), but it is crucial to develop such studies in humans, with the resolution of iEEG, to test the role of such synchronous ensembles in high-order cognition.

At the iEEG level, one can distinguish between two types of studies. Most have described the formation of local ensembles, that produce an oscillatory trace in the signal of the electrode nearby (e.g. [13,37]). More recently, global ensembles have been found, that extend over several centimeters and can be detected from phase-locking effects between the oscillatory signals measured by distant electrodes [53].

The formation of local ensembles have been reported in a variety of frequency ranges and in very different cognitive situations. We have shown their formation in the gamma range (30–80 Hz) in response to simple geometric stimuli (Kanisza triangles) on the occipital side of a subdural grid covering the parieto-temporo-occipital junction in a patient performing a visual discrimination task [37]. They would form at latencies ranging from 200 to 400 ms depending on the location on the grid.

The formation of local ensembles in the gamma range have been observed in various paradigms in iEEG (e.g. (a) during visuo-motor tasks in the sensorimotor cortex [5], (b) in response to faces in the fusiform gyrus [30] and (c) in response to phonemes in the left superior temporal gyrus [13]). Those results echoed and further extended a peak of interest and results during the last decade for gamma oscillations and their putative role in neural integration [50,51,54,56]. Fig. 6 shows the formation of gamma ensembles specific to face perception in the posterior parietal lobe, an effect that we observed very recently.

Very recently, oscillations in the theta range (4–7 Hz) have also received a lot of interest. While epileptic patients performed a verbal short-term memory Sternberg task, Raghavachari et al. [48] have found that their brain produced very strong and sustained oscillations in the theta range. Those oscillations would stop as soon as the patient gave his response. Strikingly, this gating effect was observed in very distributed regions (mostly in the left hemisphere but in all lobes). This study was a follow-up of another one showing a similar theta enhancement during spatial navigation [28].

Such results immediately bring the question, not answered yet, of whether such local oscillatory networks are coordinated into a more global network or function independently of each other. Since oscillators interacting with each other at similar frequency have a tendency to phase-lock [14], interactions are likely to translate into phase-locking effects between distant brain regions, or large-scale synchrony because of the systematic reciprocal connections between brain regions (e.g. [11]).

This next step, to test whether such local resonant assemblies are able to synchronize with others in other parts of the brain to create large-scale assemblies

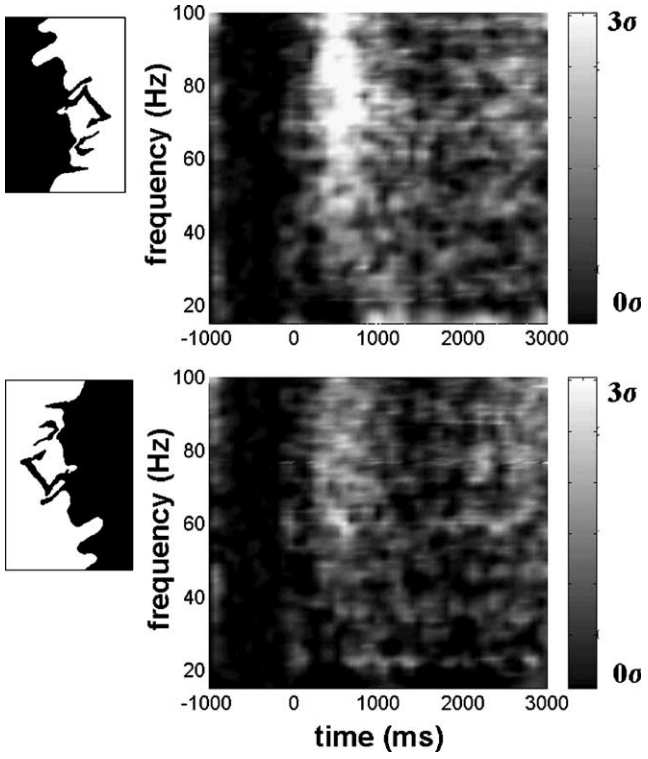

Fig. 6. Gamma band correlates of face-perception. An epileptic patient was presented with 200 Mooney faces presented upside-up (top graph) or upside-down (bottom graph). The patient usually (80% of the trials) recognized the faces in the upside-up figures but rarely (20%) in upside-down figures. This figure compares the variations of spectral energy in several frequency bands ranging from 15 to 100 Hz for the perception (top) and non-perception (down) conditions for one recording site in the posterior parietal lobe. To quantify the variations, wigner time-frequency transforms were computed for each signal, normalized (demean + divide by standard deviation) for each frequency with respect to a baseline (the 400 ms preceding the figure onset at 0 ms), then averaged across each trial of a condition. Face perception occurred with an increase of activity in the gamma range (40–100 Hz), that was virtually absent when the face was not perceived.

mediating large scale-integration, is really a step forward in the field of human brain mapping in that it provides the first real spatio-temporal second-order mapping.

Four studies went recently into that direction.

In a very representative study, Tallon-Baudry et al. [53] found episodes of synchrony during the retention phase of a short-term visual memory task, between limited regions of the extrastriate cortex separated by several centimeters. Two patients were presented briefly with an arbitrary shape, followed up to 2 s later by a second arbitrary shape, identical or very similar to the first one. Patients had to tell whether the two shapes matched. For both patients, synchrony was found in the beta range (15–25 Hz) during the retention phase, and absent in a control condition during which patients didn't have to remember the shape. In one patient, synchrony was found between the right fusiform gyrus and the right lateral occipital sulcus, in another patient, synchrony was between the right parieto-occipital sulcus and the right inferotemporal gyrus. The phase remained constant around a non-zero value.

Fell et al. [15] measured the synchrony between the rhinal cortex and the hippocampus of epileptic patients. The patients were presented sequentially with nouns that they were instructed to memorize. The authors compared the level of synchrony between the rhinal cortex and hippocampus in the gamma band (36–40 Hz) immediately after word presentation, and found that synchrony was higher for words that could successfully be retrieved by the patients.

Also, Klopp et al. [31] presented patients with series of words or faces, and had them signal the items that were shown for the first time. They observed a face-selective coherence increase 200 ms after stimulus presentation between the fusiform gyrus and multiple areas in the right temporal, parietal, rolandic and frontal regions. This coherence increase was not frequency-specific and extended over a broad 5–45 Hz range. The authors measured that the phase-lag between each structure and the fusiform gyrus was directly related to its distance with this fusiform gyrus. The authors suggested that after hitting the fusiform gyrus the signal propagated widely to other cortical sites to encode other dimensions of the stimulus.

Finally, Aoki et al. [5] recorded from 14 sites including sites in the forearm sensorimotor cortex during a tracking task (in which patients used a joystick to keep a cursor on a target moving on a computer screen) and other visuo-motor tasks. They found an increase of power in the gamma band during the performance of the task, and an increase in phase-locking between motor sites and sensory sites that was specific to the tracking task.

These studies constitute first, but significant steps towards a more complete human brain mapping, that does not only describe the components of the large-scale networks underlying cognition, but also the dynamic links that allow their formation.

It is striking to realize how little research has been devoted to understand those links. There are several obvious reasons for this: the systematic exploration of the statistical relationships between all pairs of channels in a recording set requires a computer power that was not available until recently. Also, many of the mathematical tools required to study interactions were developed only recently. In addition, we are caught in a vicious circle: to detect a functional link, one needs to know what kind of linking mechanism one is looking for (synchronization, for instance), in order to develop an analysis tool that will detect such a link. But there is no way to guess that a certain type of linking mechanism exists in the brain unless we detect an instance of it. In a sense, synchrony is a very simple form of statistical relationship because it can be readily detected by very

simple analysis techniques such as cross-correlation, which is maybe the simplest statistical test one may use to test for interactions between two signals. That may explain while it was the first type of link to be discovered. Much more complex relationships certainly exist, among an indefinite universe of possibilities. The current approach is to test for relationships of increasing complexity (see the paper from Le Van Quyen in this issue), that make sense from a biological point of view, such as generalized synchrony between signals evolving at different frequencies, using bicoherence for instance [57]. This will be a long but exciting process. The first studies described above suggest that the search for functional links requires a description of the temporal organization of neural activity with a millisecond precision, this makes iEEG data particularly well suited for this project.

5. Perspectives and conclusion: iEEG in combination with other imaging techniques

In this final section, we will focus on three possible developments, that all require promising combinations of iEEG and other techniques: (1) the combined use of iEEG with MEG to get a more extended view of the brain state-space; (2) the fusion fMRI/iEEG to better adapt the protocols to localization of the electrodes and (3) the analysis of iEEG during electrical stimulations to improve our understanding of functional connectivity patterns.

5.1. iEEG and MEG

Right now, the main limitation of iEEG as a brain imaging technique is that it does only give a very limited view of brain activity. To remedy this problem, increasing the number of electrodes without clinical justifications is obviously not a solution, but promising prospects may come from the combination with MEG.

iEEG can potentially be recorded simultaneously with MEG. The band that covers the patient's head is thin enough to allow its positioning into a whole-head 144 SQUIDS MEG helmet. This enables a dual recording of selected deep structures with the intracranial electrodes and superficial structures with MEG. However, the fusion of those two sets of data, measuring an electrical potential on one side, and a magnetic field on the other side is technically challenging. The technical solution is to use the iEEG as a constraint for the inverse problem that aims at reconstructing the neural activity generating the MEG signal. MEG alone does not provide unique solutions to that problem but iEEG could help us to decide between several solutions, by favoring the one, or the few ones, that are compatible with the iEEG recorded simultaneously. fMRI data have already been used as constraints for the inverse problem, with the assumption that the sources of the MEG signal create BOLD signals, an issue not everyone agrees on. This problem does not occur with iEEG/MEG fusion since both signals have the same physical origin. This approach seems more feasible that the fusion of iEEG and scalp EEG (although they are frequently co-recorded), because iEEG electrodes leave little space to position EEG electrodes on the scalp, and many scalp regions are left unrecorded, which is problematic for source modeling algorithms.

Having a more complete mapping of the brain state could allow to investigate a wider range of tasks than now, involving very distant brain areas usually not by intracranial electrodes in a single patient, such as for instance visuo-motor control that requires an interaction between motor areas and visual areas.

5.2. iEEG and fMRI

Another promising fusion is to combine fMRI and iEEG recordings in the same patient performing the same task. It is not possible to record both simultaneously and it could even potentially be hazardous for the patient. Yet, it is possible to record the patient in a task in the MRI magnet just before the implantation and then, a couple of days later with intracranial electrodes outside the magnet. This combination is especially meaningful for two reasons: (A) considering recent results from Logothetis et al. [39], there seems, as mentioned above, to be a strong correlation between the LFP and the bold signal, at least in the primary visual cortex of monkeys during basic visual tasks. The frequent combination of fMRI and iEEG recordings could allow us to test and maybe extend this conclusion to the whole brain and different tasks. If the result holds, then the whole corpus of fMRI studies could be used to design experimental optimally for a given implantation, which minimizes the disadvantages of having only a small window to the brain with iEEG. (B) Also, as functional interactions mapping develops with fMRI data analysis [20], it should be possible to use tasks that involve functional interactions between the bold signals recorded in the vicinity of electrodes, and to probe those interactions with the better temporal resolution of iEEG in order to describe their precise dynamic and nature, and to test how the coupling between brain areas translates into a statistical relationship between the fine temporal structures of the iEEG signals.

5.3. iEEG and electric stimulations

Finally, the recording of the iERP induced by stimulation can be used as a measure of connectivity, indicating the strength and delay of conduction. This technique has been used to map functional connections

within the limbic system [59]. Stimulation-induced Evoked Potentials can be fed back into a model indicating for instance which part of the signal from one electrode should affect the others, and with what delay. This procedure, if applied in a systematic way to very diverse electrode localizations, would allow to define a natural propagation model that could be compared to measures of coupling obtained from iEEG recordings during a protocol. This could be used to compare active connectivity vs. passive connectivity; the active connectivity being the connectivity during a task and related to that task, the passive connectivity being the one estimated from passive electric stimulations. A subsequent project is to test how passive conductivity could be modified by tasks, by measuring it before and after a task.

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