Global Approach to Brain Activity: from Cognition to Disease

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Recent advances in neuroimaging have revealed that the working brain operates in a highly coordinated way, with different regions working in synchrony at different spatio-temporal scales during normal functioning. Synchronization is a ubiquitous phenomenon in Nature, and has been profusely studied in the past decades using the methods of nonlinear science and complexity theory. These methods should help us determine the functional role of normal and aberrant synchronization mechanisms during cognitive processing or associated to brain diseases.

This chapter describes the research developed within a consortium of European laboratories from public universities and research centres in Finland, France,

Germany, Israel, Italy, and Spain, established in 2006. The consortium was funded by the European Commission's 6th Framework Programme, within the NEST-Pathfinder initiative "Tackling Complexity in Science", and consisted of an interdisciplinary group of basic neuroscientists, physicists, computational neuroscientists, and engineers, devoted to a joint effort that allowed us a better understanding of how local and long-range interactions scale-up to a global activity in the brain. The project, named GABA (an acronym that stands for "Global Approach to Brain Activity"), ran from the beginning of 2007 to the end of 2009.

The GABA project addressed the phenomenon of neuronal synchronization at a wide range of spatial scales as a major orchestrator of brain integration processes. To accomplish this goal, the GABA partners recollected and analyzed collective cerebral activity with methods such as multichannel electro-encephalograms (EEG), intracranial EEG, magneto-encephalographic (MEG) and local field potential recordings, under different normal and abnormal physiological conditions: from cognitive performance (sensory processing, attention, and memory in humans) to pathological mechanisms underlying Alzheimer's disease and epilepsy. The project made use of linear and nonlinear methods, as well as tools from stochastic analysis and from the theories of complex networks and delayed dynamical systems. Such approaches had been proven in the past to be very useful in the characterization of complex systems in generic models, and the goal of the GABA project was to apply them for a better understanding of how higher cerebral functions arise in the normal brain and how aberrant synchronization underlies neurological diseases. The project results are expected to contribute to the early diagnosis of Alzheimer's disease and the anticipation of epileptic seizures. Additionally, the project also addressed the generalizability of the results obtained to the collective dynamics of other complex networks, in fields such as sociology, systems biology, and photonics.

1. Complexity and the brain

Traditionally, clinical observations of brain activity are based on a pure visual description of raw EEG recordings. Signals are considered as pathologic when certain unexpected features (such as spikes, bursts, and irregular frequency oscillations) are detected by the naked eye. However, certain pathologies are revealed more clearly not in the independent dynamical behaviour of an EEG electrode, but on the correlation between pairs of electrodes located in different brain areas.

Interactions between different brain regions (and even, at a different scale, between pairs of neurons) are usually quantified by means of cross-correlation

and coherence measures, which provide a first understanding of the cerebral mechanisms involved in the generation and propagation of brain activities [1]. Other linear measures of information flow (causality) have also been used in the study of brain connectivity [2,3]. Although linear correlation and coherence are the most common measures describing the relationship between two time series, several limitations are associated with the use of these classical measures for brain recordings: (i) they require stationarity of the data; (ii) it is unclear to which extent the coherence between two signals is due to a common input from a third signal; and (iii) coherence is sensitive to both amplitude and phase dynamics. Furthermore, the cortical networks involved in the generation of the EEG are complex *nonlinear* systems; hence a nonlinear character of their interactions is expected. By way of example, in temporal lobe epilepsy linear relationships have been found to be very weak when compared with nonlinear ones [4,5]. To deal with these issues, more robust methods for the study of brain signals have to be developed.

In recent years the nonlinear dynamics of the brain has been a focus of increasing interest in complex systems theory [6]. It is well known that a global structure results from local interactions among constituents in several natural complex systems (such as cardiac pacemakers, ecosystems, laser dynamics, chemical reactions, etc). Within that context, changes in brain dynamics have been related to phenomena such as intermittency, bifurcations and phase transitions. In this sense, neural activity takes the form of a global coherent dynamics. These global effects will naturally depend on the topology of the network on which the neurons reside.

Recent years have witnessed a large interest in the study of *complex networks*, i.e. networks whose structure is irregular, complex and dynamically evolving in time [7]. The comparative analysis of networks from different fields has produced a series of unexpected results [8]. The first issue that has been faced is certainly structural. It was shown that the coupling architecture has important consequences on the network's functional robustness and response to external perturbations, such as random failures or targeted attacks [9].

Those structural studies have been lately followed by investigations of the dynamical behaviour of large assemblies of dynamical systems interacting via complex topologies [9]. The results obtained point to the crucial role played by the network topology in determining the emergence of collective dynamical behaviour, such as synchronization, or in governing the main features of propagation phenomena, such as the spreading of epidemics, information and rumours. Furthermore, due to adaptive and dynamical wirings, networks are themselves dynamical entities. This happens when the topology of edges is

allowed to evolve and adapt in time, driven by some external action, or by the action of the internal elements, or following specific predetermined evolving rules. Prototypical applications of these results are brain networks.

Neural assemblies (local networks of neurons transiently linked by selective interactions) are supposed to be largely distributed and linked to form a web-like structure of the brain [10]. The resulting complex networks, extremely sparse, are capable to coordinate and integrate distributed cerebral codes in a unified neural process. An important question in contemporary neuroscience is whether the structure and dynamical reorganization of the neural wiring is related to specific brain functions, and whether disruption of this brain organization underlies some neurological and psychiatric diseases. Within this framework, some methods related to synchronization theory have been used in order to detect nonlinear interdependencies in time series [11,12].

2. Scale integration in the brain

Both in experimental and theoretical scenarios, there is a gap in the characterization of brain activity between small and large spatial scales. It is well known that in the scale of micrometers, brain operation relies on the spiking activity of individual neurons, which can be experimentally measured with microelectrodes and theoretically reproduced with detailed neural models (Hodgkin-Huxley, FitzHugh-Nagumo, integrate-and-fire, etc.) with well-defined mathematical properties stemming from their excitable behaviour [13]. Coupling architectures have been proposed at this level of neural modelling that enhance synchronization (see for instance [14] for work within the GABA project on zero-lag synchronization between distant neuronal populations). On the other hand, brain oscillations are routinely monitored with macroscopic techniques that cover relatively large areas, ranging from LFPs in the millimetre range to EEGs in the centimetre range. The resulting LFP activity, for instance, is an average of the spiking behaviour of a large number of neurons, and it is natural to expect that synchronization at short scales plays a relevant role in the averaged properties of the monitored neuronal population.

In a further integration level, neuronal activity can be measured at spatial scales encompassing the whole brain via techniques such as functional magnetic resonance imaging (fMRI) and multichannel EEG. The relation between those measurements and single-cell spiking activity [15,16] involves issues such as effective connectivity and collective dynamics of distant brain areas, and their influence on long-range synchronization.

3. Synchronization disruption in normal and abnormal aging

Normal and pathological aging are among the most important challenges of social and health care systems in developed countries. In particular, dementia is a multidimensional disease with well-defined bio-psycho-social consequences, which have exerted a considerable impact on health policies in the last decade. Recent epidemiological reports by the World Health Organization have revealed that (i) 37 millions of people suffer dementia in countries of developing world, and (ii) about 5% of men and 6% of women older than 60 years have been diagnosed with Alzheimer's disease (AD). These numbers have major consequences on national health systems expenditure. Dementias consume between 3-6% of the total health system resources in developed countries. As prototypic example, annual costs of AD in United States amount to $90 billions [17]. European countries are not an exception, as revealed by the progressive aging of the population reported by the European Commission in 2005 [18].

The early detection of AD is extremely difficult, delaying diagnosis and early intervention. Early signs are commonly detected by caregivers a few years before referral to a specialist. At this stage, cognitive dysfunction is mild and often includes isolated deficits in different memory systems. Subjects who show failures in memory but don't fulfil conventional criteria for dementia convert to AD at an annual rate of approximately 10% per year [19]. Although important efforts at the level of genetics, neuroimaging and neuropsychology have been made to find the specific combination of biomarkers that anticipate conversion from mild cognitive impairment (MCI) to AD, there are no definitive results to date.

AD is characterized by a progressive loss of cholinergic neurons in the basal forebrain, which drastically affects cholinergic innervations reaching association cortical regions [20]. These cholinergic inputs to the cortex are involved in selective attention and memory processes, but also in the generation of cortical synchronization [21]. Therefore, the coordinated activity of the brain is compromised in AD.

4. Synchronization enhancement in epilepsy

Epilepsy is a common disorder resulting from seizures that temporarily impair brain function. These seizures can take many forms, from brief lapses of attention to severe and frequent convulsions. Ignorance about the disease and discrimination against sufferers are widespread. More than 75% of individuals with epilepsy remain untreated; in developing countries this figure rises to 80-98% [22]. Epilepsy can impair an individual's economic potential and overall

social well-being; indeed, negative social attitudes may cause more suffering than the seizures, affecting family and social relationships, schooling, and employment.

Despite the availability of many new anti-seizure medications, about one-third of epilepsy patients remain refractory to drug therapy. The best alternative for some of these patients is surgical resection of the epileptic foci, although substantial involved risks limit this approach to only the best candidates. Some types of drug-resistant epilepsies are harder to control than others, depending on both the frequency and severity of the seizures and associated disorders [23]. The unpredictability of seizures is a major threat for all patients suffering from uncontrolled epilepsy, because of the dangerous and life-threatening situations they pose. This factor is the most important cause of morbidity in patients diagnosed with epilepsy disorders [24]. Therefore, a system able to herald seizures far enough in advance to allow preventive action would reduce morbidity and mortality, and greatly improve the quality of life and safety of many epilepsy sufferers.

Statistical indices derived from EEG recordings, such as amplitude variations and frequency content of signals, have been used in the detection and characterization of paroxysmal activities [25]. Although some results have been reported in the past about changes in the spatial organization of these indices under pathological conditions (e.g. prior to epileptic seizures), such changes are not systematic and they are very dependent on the spatial position of electrodes [26]. Complex systems theory can be applied to characterize the underlying dynamics of epileptic seizures. Different studies, at different spatial scales, suggest that transitions towards seizures take the form of a dynamical bifurcation into a more ordered state. In general, these studies are based on the temporal evolution of a few parameters (or their spatial topography) such as the correlation dimension, Lyapunov exponents, etc. These parameters are estimated directly from time series recordings of cellular activities, local field potentials, or EEG signals. The main results of these approaches in clinical research are related to the seizure anticipation problem [27].

Several reports have provided evidence of complex dynamical interactions between brain signals in areas involved in epileptic seizures [28]. Epileptic processes have been considered as a dynamical re-organization of local interactions during all states of the illness. In this sense, brain structures involved in the primary discharge of the seizure are coupled by multi-directional couplings, whereas the other structures are unidirectionally coupled to this area. At a cellular level, a similar approach has also been used to detect causalities and interdependencies in the motor system [29].

5. Main results

5.1. Functional connectivity

Many networks in Nature have been found to exhibit small-world features. Small-world (SW) networks are characterized by having a small average distance between any two nodes, as random graphs, and high clustering, as regular lattices. A SW architecture is an attractive model for brain connectivity because it leads distributed neural assemblies to be integrated into a coherent process with an optimized wiring cost.

Another property observed in many networks is the existence of a modular organization in the wiring structure. Examples range from RNA structures, to biological organisms and social groups. A module can be defined as a subset of units within a network such that connections between them are denser than connections with the rest of the network. It is generally acknowledged that modularity increases robustness, flexibility and stability. The widespread character of modular architecture in real-world networks suggests that a network's function is strongly ruled by the organization of their structural subgroups.

Functional connectivity (patterns of statistical dependencies) can be computed between brain activities recorded by EEG, MEG, and fMRI techniques. In functional brain networks, two different nodes (representing two electrodes, voxels or source regions) are supposed to be linked if some defined statistical relation exceeds a threshold. Regardless of the modality of recording activity (EEG, MEG or fMRI), topological features of functional brain networks are currently defined over long periods of time, neglecting possible instantaneous time-varying properties of the topologies. Nevertheless, evidence suggests that the emergence of a unified neural process is mediated by the continuous formation and destruction of functional links over multiple time scales.

Empirical studies have lead to the hypothesis that transient synchronization between distant and specific neural populations underlies the integration of neural activities as unified and coherent brain functions. Brain regions would be partitioned into a collection of modules, representing functional units, separable from -but related to- other modules. Thus, specialized brain regions would be largely distributed and linked to form a dynamical web-like structure of the brain. Characterizing the dynamical modular structure of the brain may be crucial to understand its organization during different pathological or cognitive states. An important question is whether the modular structure has a functional role on brain processes such as the ongoing awareness of sensory stimuli or perception.

To find the brain areas involved in a given cognitive task, clustering is a classical approach that takes into account the properties of the neurophysiological time series. Previous studies on human brain networks have successfully used different methods to identify clusters of brain activities. Some classical approaches, such as those based on principal components analysis (PCA) and independent components analysis (ICA), make very strong statistical assumptions (orthogonality and statistical independence of the retrieved components, respectively) with no physiological justification.

Within the GABA project, we have developed an approach that allows characterizing the dynamic evolution of functional brain networks [30,31]. We illustrated this approach on connectivity patterns extracted from MEG data recorded during a visual stimulus paradigm. Results reveal that the brain connectivity patterns vary with time and frequency, while maintaining a small-world structure, as shown in Fig. 1 below. The results also reveal a non-random modular organization of brain networks with a functional significance of the retrieved modules. This modular configuration might play a key role in the integration of large-scale brain activity, facilitating the coordination of specialized brain systems during cognitive brain processes.

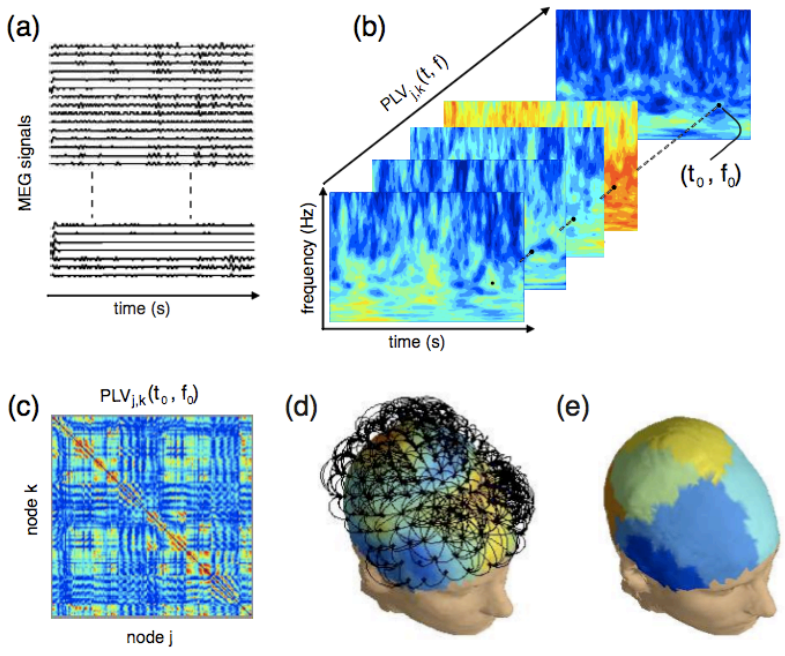

Figure 1: Extraction of a time-varying functional brain network

5.2. Abnormal synchronization

Studies on spontaneous brain oscillations have tested the functional

disconnection hypothesis in AD and MCI patients by estimating the loss of neural synchrony with linear measures such as coherence and nonlinear techniques based on phase relationships. Changes in cortico-cortical coupling have been observed to correlate with cognitive decline. A fundamental problem is that correlations between scalp EEG time-series are not only due to synaptic flows of activity between the underlying neural sources but can also be due to non-neural electromagnetic conduction effects.

Measuring phase synchronization between EEG sources of the alpha rhythm rather than between scalp EEG signals avoids the undesirable effects of volume conduction, allowing us to determine abnormalities in the functional connectivity patterns underlying alpha generation. Furthermore, evaluating different properties of phase synchrony between alpha EEG sources may reveal complementary neural codes required for the generation of this cerebral rhythm. For instance, studying time-varying phase differences between EEG-alpha sources informs us about the strength of the coupling between the interacting neuronal generators, whereas determining how the phase of one alpha source predicts the phase of another alpha source informs us about the level of functional dependence between neural sources involved in alpha generation.

Within the framework of the GABA project, we aimed at determining how normal aging and MCI status affects the functional coupling between EEG-alpha sources and the intrinsic complexity of each independent EEG-alpha source. To achieve these goals, a novel analytic methodology was applied to remove the effects of volume conduction from EEG recordings and to estimate the original source signals as well as their corresponding spatial patterns of scalp potentials [32]. Next, two different indices of phase synchronization were employed to understand how normal aging and pathological senescence differentially affect neural coupling strength and the level of phase dependence between EEG-alpha sources. We observe not only an abnormal synaptic transmission between alpha sources [33] but also a significant loss of neural complexity within specific alpha generators in MCI patients when compared to healthy elderly subjects [34].

5.3. Connectivity topology

The dynamics of most biological networks, including brain networks, involves the coordinated organization of modular tasks, performed by groups (or cliques) of nodes that form strongly connected sub-networks. The collective performance of such networks (also referred to as community networks) requires coordination and synchronization among the functions of the individual cliques.

These two processes (coordination of cliques and synchronization within them) are, indeed, the essential features that afford networks both the maximal

enhancement in the performance of specific tasks, and the necessary functional plasticity for an efficient parallel functioning. In turn, such global dynamics implies a delicate balance of two apparently opposite requirements: clique segregation and large-scale integration (or clique functional merging). On one side, the modular structure of community networks is common to various neuronal systems at different levels of organization (e.g. ganglia, strata, columns or maps), while on the other side, large-scale coordination among distributed neuronal centres lies at the basis of all motor as well as cognitive functions.

The inter-segmental coordination of multiple locomotor structures and the visual binding in different areas of the visual cortex are well-studied examples of nervous systems that demonstrate such a balance. One of the major mechanisms mediating integration among neuronal modules is that of the dynamical binding of their temporal activity by means of phase synchronization.

Interconnected modular organizations are also apparent in in-vitro networks of cultured neurons. In such networks, non-trivial structural and functional organizations are spontaneously formed from initially homogenous preparations of individual cultured neurons. This includes the formation of packed interconnected clusters and collective networks whose electrical activity is characterized by increasing inter-neuronal synchronization and a non-arbitrary, functionally complex, temporal ordering.

The cultured networks evolve from neurons and glial cells that are initially dissociated from their original connections and spread over suitable substrates. The cells regenerate neuronal processes (axons and dendrites) and consequently self-assemble into elaborate neuronal networks. The networks display a spontaneous development of modular organization, or cell clusters, that is concomitant with the emergence of synchronized bursting events (SBEs) and the formation of functional cliques, i.e. the segregation into sub-classes of SBEs.

Motivated by these experimental observations, we aimed to understand the associated structure-to-function organization in such networks (and to reveal the advantages of modular organization, while focusing on the clique's segregation/ integration interplay). In particular, the development of computer-simulated neuronal networks has shown that: (i) a series of newly devised measures are able to identify the arousal of specific dynamic motifs connected with synchronization distribution and functional centrality; and (ii) these motifs are formed at the edge of merging (i.e. when the competition between segregation and integration is balanced), implying that structural modularity, when regulated to operate in this specific connectivity regime, affords the network an elevated functional plasticity, thus allowing for efficient multiple-task performance. Motivated by this, we have performed an exhaustive analysis of the centralities

of nodes, and a direct comparison between the values of centrality that the nodes assume due to the structure of the network, and that is pertinent to their functional role.

5.4. Connectivity dynamics

As described in section 5.2 above, abnormal patterns of thalamocortical synchronization and complexity have been reported in MCI patients, suggesting that different neural mechanisms underlie the slowing of alpha rhythm present in normal aging and incipient neurodegeneration. Changes in the topological properties of functional brain networks have also been observed in AD patients.

Functional studies demand a theoretical framework in which the anatomical changes known to occur in normal and pathological aging can be related to the functional variations observed experimentally. We have developed such a framework on the basis of a mesoscopic description of the complete brain stemming from a neural mass model [35]. Neural mass models reproduce the average behaviour of large populations of neurons by representing their global transfer properties from spike trains to average post-synaptic potentials and *vice versa*. Using this approach and generalizing it to describe the dynamics of the whole brain, we studied in a systematic way the influence of different types of structural connectivity (long-range cortico-cortical connectivity, long-range thalamocortical connectivity, and short-range connectivity) on the neural phase synchronization in selected brain areas, as measured by the dominant frequency of signals obtained at different electrodes and the phase synchronization between electrode pairs. Our results allow us to establish a potential scenario of structural connectivity changes that leads to a pattern of functional connectivity variations in agreement with what is observed experimentally as the brain ages normally and pathologically.

5.5. Scale integration

Identification of visual scenes is a brain process in which integration of brain activity across multiple scales plays a crucial role. Shape information is distributed across populations of neurons in the ventral pathway of the visual cortex. The population code for shape has to accommodate the virtual infinity of possible objects as well as the variability of a given object’s retinal image. This complex representational problem can be solved by encoding shapes in terms of their component parts, and binding this information among the neurons representing these component parts.

We have used a behavioural paradigm for exploring short and long-range interactions in the visual system, based on a well-established contour integration paradigm that is often used in human psychophysics. The paradigm requires that

local information on the orientation of single Gabor elements is grouped and used to construct a continuous and smooth contour. This in turn requires an integration of information beyond the size of receptive fields in the visual area V1. To be able to use this paradigm in combination with spike recordings from neurons, we extended the well-established Gabor contour integration paradigm. Specifically, we developed a dynamic version of the standard static paradigm. We also changed the task from FIGURE and NO-FIGURE detection, to detection of whether the figure is OPEN or CLOSED to allow for smooth figures based on cubic splines that match the actual receptive field positions per recording session. We compared the paradigm with the standard static paradigm based on psychophysics with human subjects. Based on these improvements, we can conclude that the new paradigm is comparable to the standard Gabor contour integration paradigm, while at the same time is suited to studying the mechanism underlying contour integration with electrophysiological recordings of spiking activity.

6. Conclusion and outlook

The GABA project has been a Europe-wide collaborative effort among researchers of multiple disciplines, whose results help us increase our understanding of how global activity, and therefore high-level cognitive functions, emerge in the brain. The studies performed, and the techniques developed, should pave the way to the establishment of early diagnosis protocols that could be applied to illnesses such as Alzheimer’s disease, making use of complexity techniques that would detect in advance the synchronization loss characteristic of this neurological disorder. Similarly, understanding how enhanced synchronization is associated with diseases like epileptic disorders, should lead to new approaches to deal with these illnesses.

In the particular case of epilepsy, the results obtained on the spatio-temporal organization of epileptic activity should lead to a quantified description of the brain network's organization during different states of epileptic episodes. These results could be useful not only for a pre-surgical evaluation, but for a functional classification of epileptic seizures according to their spatio-temporal dynamics. The identification and characterization of epileptogenic networks should lead to consider some clinical perspectives. Indeed, a robust characterization of the spatio-temporal dynamics underlying the epileptic activities should allow (for certain types of epilepsies) the detection of early changes before the transition to seizures.

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