From Modular to Centralized Organization of Synchronization in Functional Areas of the Cat Cerebral Cortex

Jesús Gómez-Gardeñes1,2, Gorka Zamora-López3, Yamir Moreno1,4, Alex Arenas1,5

1 Instituto de Biocomputación y Física de Sistemas Complejos (BIFI), Universidad de Zaragoza, Zaragoza, Spain, 2 Departamento de Matemática Aplicada, Universidad Rey Juan Carlos (ESCET), Móstoles (Madrid), Spain, 3 Interdisciplinary Center for Dynamics of Complex Systems, University of Potsdam, Potsdam, Germany, 4 Departamento de Física Teórica, Universidad de Zaragoza, Zaragoza, Spain, 5 Departament d’Enginyeria Informàtica y Matemàtiques, Universitat Rovira i Virgili, Tarragona, Spain

Abstract

Recent studies have pointed out the importance of transient synchronization between widely distributed neural assemblies to understand conscious perception. These neural assemblies form intricate networks of neurons and synapses whose detailed map for mammals is still unknown and far from our experimental capabilities. Only in a few cases, for example the C. elegans, we know the complete mapping of the neuronal tissue or its mesoscopic level of description provided by cortical areas. Here we study the process of transient and global synchronization using a simple model of phase-coupled oscillators assigned to cortical areas in the cerebral cat cortex. Our results highlight the impact of the topological connectivity in the developing of synchronization, revealing a transition in the synchronization organization that goes from a modular decentralized coherence to a centralized synchronized regime controlled by a few cortical areas forming a Rich-Club connectivity pattern.

Introduction

Processing of information within the nervous system follows different strategies and time-scales. Particular attributes of the sensory stimuli are transduced into electrical signals of different characteristics, e.g. regular or irregular spiking, the rate of firing, etc. Further aspects of the information are “encoded” by specialization of neurons, e.g. the color and orientation of a visual stimulus will activate only a set of neurons and leave others silent. For higher order processes such as feature binding and association, the synchronization between neural assemblies plays a crucial role [1–5]. For example, subliminal stimulation which is not consciously perceived, triggers a similar cascade of activation in the sensory system but fails to elicit a transient synchronization between distant cortical regions [6].

The neurons comprising the nervous system form a complex network of communications. To what extent this intricate architecture supports the richness and complexity of the ongoing dynamical activity in the brain is a fundamental question [7]. A detailed map of the neurons and their synapses in mammals is still unknown and far from our experimental capabilities. Only in a few cases, for example the nematode C. elegans, we know the complete mapping of the neuronal tissue. In the cases of macaque monkeys and cats a mesoscopic level of description is known, composed of cortical areas and the axonal projections between them. These areas are arranged into modules which closely follow functional subdivisions by modality [8–13]. Two cortical areas are more likely connected if both are involved in the processing of the same modal information (visual, auditory, etc.) Beyond this modular organization, some cortical areas are extensively connected (referred as hubs) with projections to areas in all modalities [14,15]. For the corticocortical network of cats, these hubs are found to be densely interconnected forming a hidden module [16], at the top of the cortical hierarchy which might be responsible for the integration of multisensory information. A core of cortical areas has also been detected in estimates of human corticocortical connectivity by Diffusion Spectrum Imaging [17]. Following the above discussion that synchronization plays a major role in the processing of high level information, it would be important to analyze the synchronization behavior of these networks in relation to their modular and hierarchical organization. To this end, we simulate the corticocortical network of the cat by non-identical phase oscillators and we follow the evolution of their synchronization from local to global.

The study of synchronization phenomena is a useful tool to analyze the substrate of complex networks. The dynamical patterns under different parameters unveil features of the underlying microscopic and mesoscopic organization [18]. In particular, recent studies highlight the impact that the topological properties such as the degree heterogeneity, the small-world effect

Downloaded from www.plosone.org on August 20, 2020
and the modular structure have on the path followed from local to global synchronization [18–21].

In this work we study the routes to synchronization in the corticocortical network of cats brain (see Figure 1) by modelling each cortical area as a phase oscillator with an independent internal frequency. This assumption considers that the ensemble of neurons contained within a cortical area behaves coherently having a well defined phase average whose dynamics is described by the internal frequency [22]. The coupling between areas is modelled using the Kuramoto nonlinear coupling and its relative strength can be conveniently tuned to allow for the observation of synchronization at different scales of organization. This seemingly crude approximation allows to obtain similar synchronization patterns as those observed with more refined models based on neuronal ensembles placed at each cortical area [23–25]. For instance, using the Kuramoto model one obtains that highly connected areas promote synchronization of neural activity just as revealed by the more stylized model used for the dentate gyrus [26].

Our results point out that complex structures of highly connected areas play a key role in the synchronization transition. In contrast to the usual partition of the brain cortex into four sets of modally-related areas, we find that this modular organization plays a secondary role in the emergence of synchronization patterns. On the contrary, we unveil that a new module made up of highly connected areas (not necessarily modally-related) drives the dynamical organization of the system. This new set is seen as the Rich-Club of the corticocortical network. Surprisingly, the new partition of the network including the Rich-Club as a module preserves the modular behavior of the system’s dynamics at low intercortical coupling strengths. This modular behavior transforms into a centralized one (driven by the Rich-Club) at the onset of global synchronization highlighting the plasticity of the network to perform specialized (modular) or integration (global) tasks depending on the coupling scale.

**Results**

As introduced above, we describe the dynamical behavior of the cortical network using the Kuramoto model [27], where the time evolution of the phase of each cortical area, $\theta_i(t)$, is given by

$$\dot{\theta}_i = \omega_i + \lambda \sum_{j=1}^{N} W_{ij} \sin(\theta_j - \theta_i),$$

where $\omega_i$ is the internal frequency associated to area $i$ and $W_{ij}$ is the weighted inter-cortical coupling matrix that takes a value 0 if area $j$ does not interact with the dynamics of area $i$ while $W_{ij} > 0$ otherwise. In this latter case $W_{ij}$ can take values 1, 2 or 3 depending on the axon density going from area $j$ to area $i$. Let us remark that the inter-cortical coupling matrix is not symmetric so that in general $W_{ij} \neq W_{ji}$. Besides, the inter-cortical dynamical coupling is modeled as the sine of the phase differences between two connected areas such that when $\theta_j > \theta_i$ the average phase of area $i$ accelerates while that of area $j$ slows down to approach each other. Finally, the parameter $\lambda$ accounts for the strength of the inter-cortical coupling.

In a system composed of all-to-all coupled oscillators, the Kuramoto model shows a transition from incoherent dynamics to a synchronized regime as $\lambda$ increases [28,29]. However, when the system has a nontrivial underlying structure this transition does not take place in an homogeneous manner. In complex topologies, and for moderate coupling values, certain parts of the system become synchronized rather fast whereas other regions still behave incoherently. Therefore, one can monitor the synchronization patterns that appear as the coupling $\lambda$ is increased and describe the path to synchronization accurately [18] by reconstructing the synchronized subgraph composed of those nodes and links that share the largest degree of synchronization (see Materials and Methods). The study of these synchronization clusters as the coupling $\lambda$ is increased allow to unveil the important set of nodes that drives these dynamical processes in the system.

We will analyze different scales of organization: i) the macroscopic scale referring to global synchronization of the network; ii) the microscopic scale of organization corresponding to the individual state of the oscillators; and finally iii) the intermediate mesoscopic scale of dynamical organization between the macroscopic and microscopic scales. Usually, it consists of groups of nodes classified

![Figure 1. The brain cortical network of the cat.](doi:10.1371/journal.pone.0012313.g001)
according to a certain additional information, for example that
provided by the anatomical-functional modules. Every scale of
organization requires a particular set of statistical descriptors. This is
especially important in the mesoscopic scale where changing the
groups, the characterization of the system is also changed.

Macroscopic analysis

We start by describing how global synchronization is attained as
the inter-cortical coupling \( \lambda \) is increased. Global synchronization
is characterized by the usual Kuramoto order parameter, \( r \), and the
fraction of links that are synchronized \( r_{link} \) \cite{20,21} (see Materials
and Methods). Both parameters take values in the region \([0,1]\),
being close to 0 when no dynamical coherence is observed and
close to 1 when the system approaches to full synchronization.

In Fig. 2 we show the evolution of \( r \) and \( r_{link} \) as a function of \( \lambda \).
The plot reveals a well defined transition from incoherent to
globally synchronized, the onset of synchronization occurring for
coupling strength \( 0.011 \leq \lambda \leq 0.021 \). When \( \lambda \approx 0.2 \), the system
reaches the fully synchronized state. In the following, we will explore
this transition in more detail and at lower scales of dynamical
organization.

Mesoscopic analysis as described by the four anatomical
modules

The measures \( r \) and \( r_{link} \) describe completely the dynamical state
of the system if one assumes that all the cortical areas behave
identically. However, it is possible to extract more information
about the local dynamical properties of the system. In particular, for
a given value of \( \lambda \) we can monitor the degree of synchronization
between two given areas \( i \) and \( j \), \( r_{ij} \in [0,1] \) (see Materials and
Methods).

The studies of the transition to synchronization in modular
architectures \cite{19,21} show that synchrony patterns appear first at
internal modules, \( i.e. \) synchrony shows up among the nodes that
belong to the same module due to a larger local density within the
module and similar pattern of inputs of the nodes. As the coupling
\( \lambda \) is increased, synchrony starts to affect the links connecting nodes
of different clusters and finally spreads to the entire system. Now,
we analyze whether the four anatomical-functional modules of the
cortical network of the cat act also as dynamical clusters in
the synchronization transition. To this end, we have analyzed the
evolution of the average synchronization within and between the
four anatomical modules taking into account solely the information
about the dynamical coherence \( r_{ij} \) between the network’s areas. We define the average synchronization between module \( \alpha \) and module \( \beta \) as:

\[
r_{\alpha \beta} = \frac{1}{L_{\alpha \beta}} \sum_{\alpha \neq \beta} r_{ij},
\]

where \( L_{\alpha \beta} \) is the number of possible pairs of areas from modules \( \alpha \)
and \( \beta \), \( i.e., \), \( L_{\alpha \beta} = N_{\alpha} N_{\beta} / 2 \) where \( N_{\alpha} \) and \( N_{\beta} \) are the number
of areas of modules \( \alpha \) and \( \beta \) respectively. If \( \alpha = \beta \) equation (2) denotes
the intramodule average synchronization.

The histograms in the left columns of Figure 3 and Figure 4
show the values of the set \( \{ r_{\alpha \beta} \} \) for several values of \( \lambda \)
corresponding to the region before (Fig. 3) and at (Fig. 4) the
onset of synchronization. From the histograms it is clear that the
degree of synchronization grows with \( \lambda \) as it occurs for the global
parameters \( r \) and \( r_{link} \) in the macroscopic description. Besides, the
histograms inform us about the importance of the anatomical
partition in the dynamical organization of the cat cortex. From
Figure 3 it becomes clear that the average dynamical correlation
within areas of the same anatomical module is higher than that
between areas belonging to different modules. Moreover, before
the onset of synchronization, for \( \lambda = 0.007 \) to \( \lambda = 0.11 \) all the
modules satisfy \( r_{xx} \geq r_{\alpha \beta} \) for \( x \neq \beta \). At the onset of synchronization
(left column of Figure 4) we observe that the initial intra-module
synchronization is progressively compensated by the increase of
inter-module dynamical coherence. In particular, the influence of
the Somatosensory-Motor on the remaining modules is remark-
ably relevant during the onset of synchronization and, for
\( \lambda > 0.021 \), this module shows the largest degree of synchronization
with the rest of the system.

Microscopic analysis: Unveiling the dynamical
organization

The mesoscopic analysis based on the partition of the cortex
into four modules has revealed a fingerprint of a hierarchical
organization of the synchronization based on the dominating role
of the Somatosensory-Motor module. Here we will analyze the
microscopic correlation between all the areas of the cortical
network to unveil whether there is a group of nodes that lead the
onset of synchronization in the system. To this purpose we study
the subgraphs formed by those pairs of areas sharing an average
synchronization value \( r_{ij} \) larger than a threshold \( T \). Certainly
when \( T = 1 \) the subgraph is the null (empty) graph and for \( T = 0 \)
the subgraph is the whole cortex.

In Figure 5 we show a ranking of the cortical areas at
coupling strengths \( \lambda = 0.015, 0.017, 0.019 \) and 0.021 corre-
sponding to the onset of synchronization. The rankings are
made by labeling the area \( i \) with the largest value of the
threshold at which the area is incorporated into the synchron-
ized subgraph as \( T \) is tuned from 1 to 0. Additionally, the
modular origin of the areas has been color coded to distinguish
the role of each module. From the rankings we find that there are
three areas 36, 35 and 36 from the Fronto-Limbic system,
that share the largest degree of synchrony. In all the cases,
several jumps in the threshold are observed that distinguishes
those groups of cortical areas that are more synchronized than

Figure 2. Synchronization diagrams. The figure shows the
evolution of the Kuramoto order parameter \( r \) and the fraction of
synchronized links \( r_{link} \) as the coupling strength is increased.
The transition from asynchronous dynamics to global dynamical coherence
as \( \lambda \) grows is clear from the two curves. The region in blue corresponds
to the onset of synchronization.

doi:10.1371/journal.pone.0012313.g002
the rest of the network. For instance, at $\lambda = 0.017$ we observe 14 areas spanning from the 36 area to the 2 (Somatosensory-Motor system) while for $\lambda = 0.021$ we find 16 areas ranging from the 36 to the area 4 (Somatosensory-Motor system). From these figures it is no clear that there is one module dominating the synchronization. Quite on the contrary both Somatosensory-Motor and Fronto-Limbic systems are well represented among the most synchronized areas.

A further analysis of the composition of these highly synchronized areas reveals that most of them take part in a higher-order topological structure of the cortical network: a Rich-Club (see Materials and Methods). The Rich-Club of a given network is made up of a set of nodes with high connectivity, which at the same time, form a tightly interconnected community [30,31]. Therefore, the Rich-Club of a network can be described as a highly cohesive set of hubs, that form a dominant community in the hierarchical organization. The
Rich-Club of the cat cortex is composed of 11 cortical areas of different modalities: 3 visual areas (20a, 7 and AES), 1 area from the Auditory system (EPp), 2 areas of the Somatosensory-Motor system (6m and 5AI) and 5 fronto-limbic areas (Ia, Ig, CGp, 35 and 36). In Figure 6 we show again the ranking of areas for the cases $\lambda = 0.015$, $0.017$, $0.019$ and $0.021$ but highlighting those areas belonging to the Rich-Club in black. From the plots it is clear that most of the Rich-Club areas are largely synchronized. In particular for $\lambda = 0.019$ and $0.021$ the 8 out of the 10 largest synchronized areas of the network belong to the Rich-Club, although originally they belong to the Fronto-Limbic, Somatosensory-Motor and the Visual systems in the partition into four modules.

**Mesoscopic analysis of synchronization including the Rich-Club**

Looking at the composition of the Rich-Club we observe that it is mainly composed of fronto-limbic areas. Taking into account that we previously observed how the Somatosensory-Motor system took the leading role within the description with 4 modules of the synchronization transition, this dominance of the Fronto-Limbic system in the Rich-Club may seem counterintuitive. To test the role of the Rich-Club in the synchronization transition we define a new partition of the cortical network into 5 clusters composed of the Rich-Club (as defined above) and the 4 original modules, but with the corresponding areas of the Rich-Club removed from them.

At the mesoscopic scale, we investigate the self-correlation of the new five clusters and their cross correlation according to Equation (2). In the right columns of Figure 3 and Figure 4 we present the histograms of the inter and intra correlations for different values of the coupling. In both figures the role of the Rich-Club orchestrating the process towards synchrony while increasing the coupling strength becomes clear. More importantly, the addition of the Rich-Club to the partition helps to elucidate the patterns of
synchrony: both the dynamical self-correlation of the four modally-related clusters and their correlation with the Rich-Club remain large. In particular, we observe in Figure 3 that, before the onset of synchronization, these new five modules keep a large self-correlation during this stage. On the other hand, at the onset of synchronization (Figure 4) the four modally-related clusters lose their large self-correlation in the following sequence: The “Fronto-Limbic” cluster remains autocorrelated until $\lambda \approx 0.013$, the “Visual” one until $\lambda \approx 0.017$, the “Auditory” system until 0.019 and the “Somatosensory-Motor” cluster until $\lambda \approx 0.021$. For larger couplings, all the clusters switch from autocorrelation to be synchronized with the Rich-Club, which acts as a physical mean-field of the system. Moreover, during the whole synchronization path the Rich-Club is always the cluster with the largest self-correlation. Thus, the distinction of Rich-Club in the partition preserves the autocorrelation of the four modal clusters before the onset of synchronization while, at the same time, rules the path to complete dynamical coherence during the onset of synchronization. This two-stage dynamics (modal cluster synchronization followed by a sequential synchronization with the Rich-Club) supports the idea that the modular organization with a centralized hierarchy described in [16] facilitates the segregation and integration of information in the cortex.

Characterization of the transition from modular to centralized synchronization

The results so far indicate a plausible transition from modular to centralized organization in the cortex, depending on the coupling strength. In particular, we have shown patterns of synchronization that change the behavior while increasing the coupling $\lambda$. Now we propose a characterization of this change in terms of statistical descriptors. To this end, we define two different measures: (i) the dynamical modularity (DM) and (ii) the dynamical centralization (DC). The dynamical modularity compares the degree of internal synchrony within the clusters with the average dynamical correlation across clusters. With this aim we define the DM as the fraction of the average self-correlation of clusters and the average intercluster cross-correlation. For a network composed of $m$ clusters we have:

$$DM = \frac{\sum_{\alpha} r_{\alpha \alpha} / m}{\sum_{\alpha, \beta} r_{\alpha \beta} / [m(m-1)]}.$$  

The DM will take values above 1 when the system contains true dynamical clusters while $DM < 1$ means that the entity of the partition is not consistent with a clustered behavior.
hand, the dynamical centralization of the network measures the relative difference in synchrony between the maximum among the \( m \) clusters of \( r_s = \sum_p r_{pj} / m \) and the average degree of synchrony over clusters, \( \langle r_s \rangle = \sum_a r_s / m \):

\[
DC = \frac{\max_a \{r_s\} - \langle r_s \rangle}{\langle r_s \rangle}.
\]

(4)

In the case of the DC we always obtain positive values. A large value of DC means that the system displays a highly centralized dynamical behavior around a leading cluster while we will obtain DC values approaching to 0 when the system behaves homogeneously, i.e. when there is no leading cluster that centralizes the dynamics.

We have measured both DM and DC for the original partition into \( m=4 \) modules and the new partition with \( m=5 \) incorporating the Rich-Club. In Figure 7 we show the evolution of the two quantities as a function of the coupling parameter. For the case of the DM we confirm that the partition with the Rich-Club keeps the modular behavior of the original partition along the whole synchronization path. The DM is remarkably high for low values of the coupling \( \lambda \) pointing out that before the synchronization onset the internal synchronization dominates over the cross-correlation between the clusters. Regarding the DC we find that in both partitions DC increases with \( \lambda \) reaching a maximum around the synchronization onset, signaling that at this point the synchronization is driven hierarchically and lead by one of the modules. However, the partition that incorporates the Rich-Club shows the remarkably larger values of DC along the whole path, specially around the synchronization onset. In particular, the dominant role of the Rich-Club is clearly highlighted by the maximum of the DC at \( \lambda = 0.015 \), just at the onset of synchronization. In order to verify that the Rich-Club is the cluster contributing to the term \( \max_a \{r_s\} \) in the dynamical centrality of the network we plot in Figure 7 the evolution of the DC considering each of the 5 modules as the central cluster by substituting \( \max_a \{r_s\} \) by the corresponding value of \( r_s \). From the plot it is clear that the Rich-Club is the central cluster orchestrating the dynamics of the system at the onset of synchronization.

The coupled evolution of DM and DC corroborates the two-mode operation of the cortical network when described with the Rich-Club and the remaining parts of the four original modules: At low values of the coupling, the modular structure of the network dominates the synchronization dynamics, pointing out the capacity to concentrate sensory stimuli within its corresponding module. When the coupling is increased the dynamical organization is driven by a leading subset of nodes, organized in a topological Rich-Club, that integrates information between different regions of the cortex.

Discussion

Previous simulations performed in the cat cortical network [23–25] have dealt with its synchronization properties. In these works, the transition towards synchronization is studied by using ensembles of neurons coupled through a small-world topology placed inside each cortical area whereas different neuronal populations are dynamically coupled accordingly to the topology of the cat cortical network. By means of this two-level dynamical model, numerical simulations allowed to find different clusters of synchrony as the coupling between the cortical areas is increased. It was found that only for weak coupling these clusters were closely related to the four modal clusters. In the light of these previous studies, and the recent report of a novel modular and hierarchical organization of the corticocortical connectivity [16], the issue regarding the relation between the mesoscopic structure of the cat cortex and its dynamical organization remains open.

Here, we have investigated the evolution of synchronization in a network representing the actual connectivity among cortical areas.
in the cat’s brain. We have confirmed, that the role of the different areas in the path towards synchrony is difficult to assess using the traditional partition into four groups of modally-related areas. On the contrary, we have shown that a subset of areas, forming a topological Rich-Club, orchestrates this process. The distinction of this subset permits the interpretation of a new mesoscale formed by the four modules, excluding some nodes that form the Rich-Club, which are considered here as the fifth module. This proposed structure allows us to reveal a transition in the path to synchronization as a function of the coupling strength, that seems to indicate a two-mode operation strategy. For low values of the coupling, a state of weak internal coherence within the five modules governs the coordination dynamics of the network. As the coupling strength is increased, the Rich-Club becomes the responsible of centralizing the network dynamics and leads the transition towards global synchronization.

Finally, the composition of the Rich-Club allows to make some additional biologically relevant observations. First, the Rich-Club comprises of cortical areas of the four different modalities, supporting the hypothesis of distributed coordination dynamics at the highest levels of cortical processing such as integration of multisensory information [32]. Second, the Rich-Club comprises of most of the frontal areas in the Fronto-Limbic module. Moreover, the areas of the Rich-Club collected from the original Somatosensory-Motor system contain the so-called supplementary motor area (SMA). The SMA is a controversial region of the motor cortex, since in contrast with the rest of somatosensory-motor areas it is in charge of the initiation of planned or programmed movements [33]. Furthermore, the area AES of the Rich-Club, originally assigned to the Visual module, is believed to integrate all visual and even auditory signals for their multimodal processing and transfer as coherent communication signals [34]. Summing up, the Rich-Club is basically made up of areas involved in higher cognitive tasks devoted to planning and integration. The prominent role of the aforementioned regions in the cortex activity is unveiled from our network perspective in terms of a Rich-Club leading the path to synchronization. Our proposal, after this observation, is to investigate the evolution of synchronization in the cat cortex by tracking the transient of five modules corresponding to the anatomico-functional areas (S-M, F-L, Aud, Vis) and the Rich-Club as a separate (but interrelated) functional entities.

Materials and Methods

Cortico-cortical network of cats’ brain

After an extensive collation of literature reporting anatomical tract-tracing experiments, Scannell and Young [8,9] published a dataset containing the corticocortical and cortico-thalamal projections between regions of one brain hemisphere in cats. The connections were weighted according to the axonal density of the projections. Connections originally reported as weak or sparse were classified with 1 and, the connections originally reported as strong or dense with 3. The connections reported as intermediate strength, as well as those connections for which no strength information was available, were classified with 2, see Figure 1(b). Here we make use of a version of the network [10] consisting of N = 53 cortical areas interconnected by L = 826 directed corticocortical projections.

Rich-Club areas

A key factor of the hierarchical organization of the corticocortical network of the cat is that the hub areas (those with the largest number of projections) are very densely connected between them [16]. The Rich-Club phenomenon [30,31] is characterised by the growth of the internal density of links between all nodes with degree larger than a given k’, referred as k-density, \( \phi(k') \):

\[
\phi(k') = \frac{L_k}{N_k(N_k - 1)},
\]

where \( N_k \) is the number of nodes with \( k(v) \geq k' \) and \( L_k \) is the number of links between them. As \( \phi(k) \) is an increasing function of k, a conclusive interpretation requires the comparison with random surrogate networks with the same degree distribution. The question is then whether \( \phi(k) \) of the real network grows faster or slower with k than the expected k-density of the surrogate networks. If \( \phi(k) \) grows slower, it means that the hubs are more independent of each other than expected.

In our case, the network is directed but the input degree \( k_{in}(v) \) and the output degree \( k_{out}(v) \) of the areas are highly correlated. Hence, we compute the k-density of the corticocortical network of the cat, \( \phi_{\text{all}}(k) \), considering the degree of every area as:

\[
k(v) = \frac{1}{2}(k_{in}(v) + k_{out}(v)).
\]

The result is presented in Figure 8 together with the ensemble average \( \phi_{\text{avg}}(k) \) of 100 surrogate networks. At low degrees \( \phi_{\text{all}}(k) \) follows very close the expectation, but for degrees \( k > 13 \), \( \phi_{\text{all}}(k) \) starts to grow faster. The largest difference occurs at \( k = 22 \), comprising of a set of eleven cortical hubs of the four modalities: visual areas 20a, 7 and AES; auditory area EPh; somatosensory-motor areas 6m and 5Al; and fronto-limbic areas Ia, Ig, CGp, CGa, 35 and 36.

Numerical simulation details

We integrate the Kuramoto equations, see equation (1), using a fourth order Runge-Kutta method with time step \( \delta t = 10^{-2} \). The system is set up by randomly assigning the initial conditions \( \theta_i(0) \) and the internal frequencies \( \omega_i \) randomly in the intervals \([0, \pi]\) and \([\pi/2, 1/2]\) respectively. The integration of the Kuramoto is performed for a total time \( T = 700 \). After a transient time of \( \tau = 300 \) we start the computation of the different dynamical measures such as the order parameters \( r \) and \( r\text{link} \).

Synchronization order parameters

The dynamical coherence of the population of N oscillators (areas) is measured by means of two different order parameters \( r \) and \( r\text{link} \). The first one is obtained from a complex number \( z(t) \)
defined as follows:

\[ z(t) = r(t) \exp[i \phi(t)] = \sum_{j=1}^{N} \exp[i \theta_j(t)]. \]  

(6)

The modulus of \( z(t) \), \( r(t) \), measures the phase coherence of the population while \( \phi(t) \) is the average phase of the population of oscillators. Averaging over time the value of \( r(t) \) we obtain the order parameter \( r = \langle r(t) \rangle \).

The second order parameter, \( r_{\text{link}} \), is measured looking at the local synchronization patterns, allowing for the exploration of how global synchronization is attained. We define \( r_{\text{link}} \) by measuring the degree of synchroly between two connected areas \( i \) and \( j \):

\[ C_{ij} = \lim_{\Delta t \to \infty} \frac{A_{ij}}{\Delta t} \int_{t}^{t+\Delta t} \exp\left[i \left( \phi_j(t) - \phi_i(t) \right) \right] dt. \]  

(7)

where \( A_{ij} \) is the adjacency matrix of the network, being \( A_{ij} = 1 \) when \( W_{ij} > 0 \) and \( A_{ij} = 0 \) otherwise. Each of the values \( \{ C_{ij} \} \) are bounded in the interval \([0,1]\), being \( C_{ij} = 1 \) when the connected areas \( i \) and \( j \) are fully synchronized and \( r_{ij} = 0 \) when these areas are dynamically uncorrelated. Note that for a correct computation of \( C_{ij} \) the averaging time \( \Delta t \) should be taken large enough (in our computations \( \Delta t = 400 \)) in order to obtain good measures of the degree of coherence between each pair of areas. Since \( C_{ij} = 0 \) for the areas that are not physically connected we construct the \( N \times N \) matrix \( C \) and define the global order parameter \( r_{\text{link}} \) as follows:

\[ r_{\text{link}} = \frac{1}{L} \sum_{ij} C_{ij}. \]  

(8)

Therefore, the parameter \( r_{\text{link}} \) measures the fraction of all possible links that are synchronized in the network.

In the more general case in which all possible pairs of areas are taken into account to compute the average synchronization between cortical areas, Eq.(7) and Eq.(8) can be rewritten as:

\[ C_{ij} = \lim_{\Delta t \to \infty} \frac{1}{\Delta t} \int_{t}^{t+\Delta t} \exp\left[i \left( \phi_j(t) - \phi_i(t) \right) \right] dt. \]  

(9)

and

\[ r_{\text{link}}^* = \frac{2}{N(N-1)} \sum_{ij} C_{ij}. \]  

(10)

respectively. Note that \( C_{ij} \) and \( r_{\text{link}}^* \) account for the degree of synchronization between areas \( i \) and \( j \) regardless of whether or not they are connected.

**Defining the average synchronization between areas**

To label two areas \( i \) and \( j \) as synchronized or not one has to analyze the matrix \( C^* \) and construct a filtered matrix \( F \) whose elements are either \( F_{ij} = 1 \) if \( i \) and \( j \) are considered as synchronized or \( F_{ij} = 0 \) otherwise. From the computation of \( r_{\text{link}}^* \), equation (10), one knows the fraction of all possible pairs of areas that are synchronized. Therefore, one would expect that \( N(N-1)r_{\text{link}}^*/2 \) elements of the matrix \( F \) have \( F_{ij} = 1 \), while the remaining elements are \( F_{ij} = 0 \). The former elements correspond to the \( N(N-1)r_{\text{link}}^*/2 \) pairs with the largest values of \( C_{ij} \).

In order to measure the average degree of synchronization between pairs of areas one have to average over different \( n \) realizations using different initial conditions \( \{ \theta(t) \} \) and different internal frequencies \( \{ \omega_l \} \) (typically we have used \( n = 5 \times 10^3 \) different realizations for each value of \( \lambda \) studied). To this purpose we average the set of filtered matrices \( \{ F^i \} \) \( i = 1, \ldots, n \) of the different realizations to obtain the average degree of synchronization between areas:

\[ r_{\text{avg}} = \frac{1}{n} \sum_{i=1}^{n} F^i_{ij}. \]  

(11)

In this way the value for \( r_{\text{avg}} \in [0, 1] \) accounts for the probability that areas \( i \) and \( j \) are considered as synchronized.

**Acknowledgments**

The authors are grateful to Jesús Gómez-Tolón for useful discussions and suggestions that helped to improve the manuscript.

**Author Contributions**

Conceived and designed the experiments: JGG GZL YM AA. Performed the experiments: JGG GZL YM AA. Analyzed the data: JGG GZL YM AA. Contributed reagents/materials/analysis tools: JGG GZL YM AA. Wrote the paper: JGG GZL YM AA.

**References**

1. Engel AK, Singer W (2001) Temporal binding and the neural correlates of sensory awareness. Trends Cogn Sci 5: 16–25.
2. Engel AK, Fries P, Singer W (2001) Rapid feature selective neuronal synchronization through correlated latency shifting. Nat Rev Neurosci 2: 704–716.
3. Fehley M (1993) Figure–Ground Discrimination from Temporal Information. Proc R Soc Lond B 254: 199–203.
4. Singer W, Gray CM (1995) Visual feature integration and the temporal correlation hypothesis. Ann Rev Neurosci 18: 355–386.
5. Ulhaas PJ, Pijl G, Lima B, Mellon L, Neunechvander S, et al. (2009) Neural synchrony in cortical networks: history, concept and current status. Frontiers Int Neurosci 3: 17.
6. Melloni L, Molina C, Pena M, Torres D, Singer W, et al. (2007) Synchronization of neural activity across cortical areas correlates with conscious perception. J Neurosci 27: 2858–2865.
7. Roccialetti S, Latora V, Moreno Y, eds. (2009) Handbook on Biological Networks. Singapore: World Scientific.
8. Scannell JW, Blakemore CW, Young MP (1995) Analysis of connectivity in the cat cerebral cortex. J Neurosci 15: 1463–1483.
9. Scannell JW, Burns G, Hilgetag CC, O’Neill MA, Young MP (1999) The neuronal organization of the cortico-thalamic system of the cat. Phil Trans R Soc Lond B 355: 91–110.
10. Hilgetag CC, Burns G, O’Neill MA, Scannell JW, Young MP (2000) Anatomical connectivity defines the organization of clusters of cortical areas in the macaque monkey and the cat. Phil Trans R Soc Lond B 355: 91–110.
11. Hilgetag CC, O’Neill MA, Young MP (2000) Hierarchical organization of macaque and cat cortical sensory systems explored with a novel network processor. Phil Trans R Soc Lond B 355: 71–89.
12. Sporns O, Chialvo DR, Kaiser M, Hilgetag CC (2004) Organization, development and function of complex brain networks. Trends Cogn Sci 8: 418–425.
13. Hilgetag CC, Kaiser M (2004) Clustered organization of cortical connectivity. Neuroinformatics 2: 333–360.
14. Zamora-Lopez G, Zhou CS, Kurths J (2009) Graphs analysis of cortical networks reveals complex anatomical communication substrate. Chaos 19: 015117.
15. Sporns O, Honey CJ, Kotter R (2007) Identification and classification of hubs in brain networks. PLoS ONE 10: e1049.
16. Zamora-Lopez G, Zhou CS, Kurths J (2010) Cortical hubs form a module for multisensory integration on top of the hierarchy of cortical networks. Frontiers Neuroinf, in press.
17. Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, et al. (2008) Mapping the Structural Core of Human Cerebral Cortex. PLoS Biol 6(7): e159.
18. Arenas A, Diaz-Guilera A, Kurths J, Moreno Y, Zhou CS (2008) Synchronization in complex networks. Phys Rep 469: 93–153.
19. Arenas A, Diaz-Guilera A, Perez-Vicente CJ (2006) Synchronization reveals topological scales in complex networks. Phys Rev Lett 96: 114102.
20. Gomez-Gardenes J, Moreno Y, Arenas A (2007) Paths to synchronization in complex networks. Phys Rev Lett 98: 054101.
21. Gomez-Gardenes J, Moreno Y, Arenas A (2007) Synchronizability determined by coupling strengths in complex networks. Phys Rev E 75: 066106.
22. Rulkov NF (2001) Regularization of synchronized chaotic burst. Phys Rev Lett 86: 103.
23. Zemanova L, Zhou CS, Kurths J (2006) Structural and functional clusters of complex brain networks. Physica D 224: 202–212.
24. Zhou CS, Zemanova L, Zamora G, Hilgetag CC, Kurths J (2006) Hierarchical organization unveiled by functional connectivity in complex brain networks. Phys Rev Lett 97: 298103.
25. Zhou CS, Zemanova L, Zamora G, Hilgetag CC, Kurths J (2007) Structure-function relationship in complex brain networks expressed by hierarchical synchronization. New J Phys 9: 178.
26. Morgan RJ, Soltesz I (2006) Nonrandom connectivity of the epileptic dentate gyrus predicts a major role for neuronal hubs in seizures. Proc Natl Acad Sci USA 105: 6179–6184.
27. Kuramoto Y (1984) Cooperative Dynamics of Oscillator Community. Prog Theor Phys 79: 223–240.
28. Strogatz SH (2000) From Kuramoto to Crawford: exploring the onset of synchronization in populations of coupled oscillators. Physica D 143: 1–20.
29. Acebron JA, Bonilla LL, Perez Vicente CJ, Ritort F, Spigler R (2005) The Kuramoto model: A simple paradigm for synchronization phenomena. Rev Mod Phys 77: 137–185.
30. Zhou S, Modrano RJ (2004) The rich-club phenomenon in the internet topology. IEEE Comm Lett 8(3): 80–182.
31. Colizza V, Flammini A, Serrano MA, Vespignani A (2006) Detecting Rich-Club ordering in complex networks. Nature Phys 2: 110–115.
32. Bressler SL, Kelso JAS (2001) Cortical coordination dynamics and cognition. Trends Cogn Sci 5: 26–36.
33. Nachev P, Kennard Ch, Husain M (2008) Functional role of the supplementary and pre-supplementary motor areas. Nature Rev Neuroscience 9: 856–869.
34. Stein BE, Stanford TR (2008) Multisensory integration: current issues from the perspective of the single neuron. Nature Rev Neuroscience 9: 253–266.