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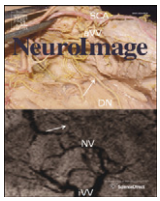

The emergence of abnormal hypersynchronization in the anatomical structural network of human brain

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ABSTRACT

Brain activity depends on transient interactions between segregated neuronal populations. While synchronization between distributed neuronal clusters reflects the dynamics of cooperative patterns, the emergence of abnormal cortical hypersynchronization is typically associated with spike-wave discharges, which are characterized by a sudden appearance of synchronous around 3 Hz large amplitude spike-wave discharges of the electroencephalogram. While most existing studies focus on the cellular and synaptic mechanisms, the aim of this article is to study the role of structural connectivity in the origin of the large-scale synchronization of the brain. Simulating oscillatory dynamics on a human brain network, we find the space–time structure of the coupling defined by the anatomical connectivity and the time delays can be the primary component contributing to the emergence of global synchronization. Our results suggest that abnormal white fiber connections may facilitate the generation of spike-wave discharges. Furthermore, while neural populations can exhibit oscillations in a wide range of frequency bands, we show that large-scale synchronization of the brain only occurs at low frequencies. This may provide a potential explanation for the low characteristic frequencies of spike-wave discharges. Finally, we find the global synchronization has a clear anterior origin involving discrete areas of the frontal lobe. These observations are in agreement with existing brain recordings and in favor of the hypothesis that initiation of spike-wave discharges originates from specific brain areas. Further graph theory analysis indicates that the original areas are highly ranked across measures of centrality. These results underline the crucial role of structural connectivity in the generation of spike-wave discharges.

Introduction

Normal brain function requires the dynamic interaction of functionally specialized but widely distributed cortical regions. Long-range synchronization of oscillatory signals has been suggested to mediate these interactions within large-scale cortical networks by dynamically establishing task-dependent networks of cortical regions (Varela et al., 2001). Disturbances of such synchronized networks have been implicated in several brain disorders, such as schizophrenia, autism, epilepsy, Alzheimer's disease, and Parkinson's disease (Uhlhaas and Singer, 2006). Especially, while synchronization between distributed neuronal clusters reflects the dynamics of cooperative patterns, the emergence of abnormal cortical hypersynchronization is typically associated with the occurrence of ~3 Hz spike-wave discharges (SWD) recorded on the electroencephalogram (EEG). The sudden appearance of SW patterns from a normal background leads to the traditional concept of sudden hypersynchronous and widespread activity during generalized seizures.

The mechanisms underlying spike-wave patterns are complex and may involve cerebral cortex and thalamus, intrinsic properties of neurons, and various types of synaptic receptors present in the circuit. There has been notable effort devoted to understanding seizure dynamics and various hypotheses have been proposed to explain the underlying mechanisms (Lytton, 2008; Yan and Li, 2011). Some studies (Destexhe, 1998; Destexhe et al., 1996, 1998; Giaretta et al., 1987; Pollen, 1964) demonstrate that synaptic receptors are especially important in the generation of epileptic seizures while others believe intrinsic properties of neurons play an important role (de Curtis et al., 1998; Dichter and Ayala, 1987; Halliwell, 1986; Schwindt et al., 1988; Timofeev and Steriade, 2004; Timofeev et al., 2004; Wong and Prince, 1978). While those studies shed light on the intrinsic and synaptic mechanisms of seizure generation, they do not take into consideration the structural connectivity, which may play an important role in the emergence of global synchronization.

Traditionally, the abnormality of structural connectivity is often explored in a localized pathologic brain region, which is typically the focus of partial seizures. For example, in (Dyhrfjeld-Johnsen et al., 2007; Santhakumar et al., 2005), the abnormal structural changes (mossy fiber sprouting, mossy cell death, etc) in dentate gyrus are studied to explore the genesis of temporal lobe epilepsy. Recently, the role of structural connectivity underlying generalized epilepsies has received more and more attention. From computational perspectives, in (Benjamin et al., 2012), a phenomenological model of seizure initiation is used to demonstrate that network structure (identified from EEG) in patients with idiopathic generalized epilepsies correlates with smaller

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escape times relative to network structures from controls, suggesting that network structure may play an important role in seizure initiation and seizure frequency. Using the same model, the study in (Terry et al., 2012) demonstrates that EEG discharge representing either generalized or focal seizure arises purely as a consequence of subtle changes in network structure, without the requirement for any localized pathological brain region. In (Goodfellow et al., 2011), the authors show that in an extended local area of cortex, spatial heterogeneities in a model parameter can lead to spontaneous reversible transitions from a desynchronized background to synchronous SWD due to intermittency.

While successfully demonstrating the potential role of network structure underlying generalized epilepsies, none of these studies has been done based on the time-space structure of biologically realistic connectivity of human brain. In fact, as explicit time delays are neglected, these studies are restricted to interacting local populations. To explain the emergence of synchronization at large spatial scales ranging up to almost 20 cm, we believe the network structure of the brain should be taken into consideration. The anatomical connections between areas of the brain form a structure network upon which various neural activities unfold. Brain areas are dynamically coupled to one another forming functional networks associated with perception, cognition, and action, as well as during spontaneous activity in the default or resting state. Existing computational studies demonstrate the important role of the characteristic "small-world" structure of the underlying connectivity matrix between different brain areas in the spontaneous emergence of spatio-temporally structured network activities (Cabral et al., 2011; Deco et al., 2009, 2011; Ghosh et al., 2008; Honey et al., 2007, 2009). Especially, recent studies (Cabral et al., 2011; Deco et al., 2009) have revealed that resting state activity (the temporally coherent activity in the absence of an explicit task) is closely related to the underlying anatomical connectivity. During rest, spontaneous blood oxygen level dependent (BOLD) signal is characterized by slow fluctuations (<0.1 Hz) and anti-correlated spatiotemporal patterns. By modeling each brain region as a neural oscillator and simulating in a biologically realistic brain network, the slow fluctuating and anti-correlated spatiotemporal patterns have been linked to fluctuations in the neural activity and synchrony in the gamma range. Especially, the most agreement of the simulated results with the empirically measured results has been found for a set of parameters (coupling, delay, noise, etc) where subsets of brain areas tend to synchronize in clusters while the network is not globally synchronized.

The aim of this article is to study the role of structural connectivity in the mechanistic origin of the large-scale synchronization of the brain, which may relate to the spread of SW epileptic seizure activity. While synchronization phenomenon in large populations of interacting elements has been widely studied in many areas of natural science, mathematics, and social science (Arenas et al., 2008), there has been little work done specifically considering the space–time structure of a biologically realistic cortical network. To reveal the role of brain structural connectivity in the emergence of such global synchronization, we perform a simulation study based on biologically realistic connectivity of brain areas. The structural connectivity was derived from a macroscopic cortico-cortical connectivity network derived from a diffusion-magnetic resonance imaging (MRI) data set using the method in (Zalesky and Fornito, 2009). The connectivity between all brain area pairs is quantified by a connectivity strength matrix and a fiber length matrix. Different from exiting works (Cabral et al., 2011; Deco et al., 2009, 2011; Ghosh et al., 2008; Honey et al., 2007, 2009), in which the neural dynamics at each brain area is modeled by a single neural oscillator (FitzHugh–Nagumo oscillator, Wilson–Cowan oscillator, etc), we use a system of coupled phase oscillators described by Kuramoto (1984) models to represent neural dynamics at each local brain area. Therefore, the proposed model is capable of representing not only the synchronization on a global level but also the local synchronization on different brain areas.

Specifically, to take into consideration the interplay of local and global processes at different time scales, we use local coupling strength, global coupling strength, time delay, and intrinsic frequency as independent parameters. An extensive exploration of the parameter space illustrates that the space–time structure of the coupling defined by the anatomical connectivity and the time delays can be the primary component contributing to the emergence of global synchronization. Our results will show that the global synchronization is highly dependent on the time delays and the intrinsic frequencies of the oscillators. To highlight the crucial role of interrelationship between local processes and the global activity, we further characterize the initialization of synchronization in both time and space. Our results will demonstrate that the initialization of global synchronization has a clear anterior origin involving discrete areas of the frontal lobe. While experimental observations of frontal epileptic focus do exist (Amor et al., 2009; Holmes et al., 2004; Pavone and Niedermeyer, 2000), there is a lack of understanding of the underlying mechanism. In this paper, by performing graph theory analysis of the structural connectivity, we will point out that the initialized areas of global synchronization ("hot spots") correspond to the nodes with highest degree of centrality ("structural hubs"). This once again underscores the crucial role of structural connectivity in the generation of SW epileptic seizures.

Methods

Structural connectivity

We use the structural connectivity between 80 cortical areas of the human brain. The areas are divided according to a functional subdivision of the cortex derived from the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). The structural data for brain connectivity is provided by Andrew Zalesky and Alex Fornito. The structural connectivity is obtained from a macroscopic cortico-cortical connectivity network derived from a diffusion-magnetic resonance imaging (MRI) data set using the algorithm proposed in (Zalesky and Fornito, 2009).

In (Zalesky and Fornito, 2009), a new DTI-derived measure of cortico-cortical connectivity is established based on the notion of information flow. The measure is intended to reflect the maximum rate at which information can be transmitted between a pair of cortical regions, which is quantified by the net capacity of all interconnecting fiber bundles. The set of all voxels comprising DTI space is first partitioned into two sets: white-matter $\mathcal{W}$, and grey-matter $\mathcal{G}$ using either manual tracing or any of a number of automated segmentation algorithms. The set $\mathcal{G}$ is then subdivided into N continuous cortical regions according to existing functional subdivision of interest to the researcher. Then, a 3-D lattice scaffolding for white-matter is constructed by drawing a link between each pair of voxels in a 26-voxel neighborhood for which their two respective principal eigenvectors form a sufficiently small angle. Let g_i be the set of voxels comprising cortical region $i=1,\ldots,N$. Let $E(i)\in\mathcal{W}$ denote the set of white-matter voxels comprising the interface cortical region g_i. A path between a pair of nodes u and v is said to be an (i,j)-*path* if $u\in E(i)$ and $v\in E(j)$. Let $f_{i,j}$ denote the maximum number of link-disjoint $(i,j)-$paths that can be established. Since the capacity of a fiber bundle is measured as the maximum number of link-disjoint paths that can be established between opposing ends of a fiber bundle, the net capacity provided by all fiber bundles interconnecting cortical region g_i and g_j, given by $f_{i,j}$, is used as a measure of connectivity strength.

The connectivity between all brain area pairs is quantified by two 80×80 matrices: a connectivity strength matrix $\mathbf{C}$ and a fiber length matrix $\mathbf{L}$. As described above, the connectivity strength is estimated based on the density of the white fiber tracts, which is given by the net capacity of fiber bundles $f_{i,j}$. The length of fiber connecting two brain areas is calculated as the average length across all the fibers connecting them. Both matrices are obtained by averaging over 31