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EEG functional connectivity, axon delays and white matter disease

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HIGHLIGHTS

- Many brain diseases are associated with white matter defects.
- Axon conduction speed is plastic, determined largely by myelination.
- EEG and high resolution EEG provide complementary measures of functional connectivity.

ABSTRACT

Objective: Both structural and functional brain connectivities are closely linked to white matter disease. We discuss several such links of potential interest to neurologists, neurosurgeons, radiologists, and non-clinical neuroscientists.
Methods: Treatment of brains as genuine complex systems suggests major emphasis on the multi-scale nature of brain connectivity and dynamic behavior. Cross-scale interactions of local, regional, and global networks are apparently responsible for much of EEG's oscillatory behaviors. Finite axon propagation speed, often assumed to be infinite in local network models, is central to our conceptual framework.
Results: Myelin controls axon speed, and the synchrony of impulse traffic between distant cortical regions appears to be critical for optimal mental performance and learning.
Results: Several experiments suggest that axon conduction speed is plastic, thereby altering the regional and global white matter connections that facilitate binding of remote local networks.
Conclusions: Combined EEG and high resolution EEG can provide distinct multi-scale estimates of functional connectivity in both healthy and diseased brains with measures like frequency and phase spectra, covariance, and coherence.
Significance: White matter disease may profoundly disrupt normal EEG coherence patterns, but currently these kinds of studies are rare in scientific labs and essentially missing from clinical environments.

1. Introduction

1.1. Multi-scale structural connectivity

Radiologists use several imaging technologies to diagnose and treat diseases or support basic science. Brain imaging can reveal both structure and function; however, so-called "structural" measures like computed tomography (CT) and magnetic resonance imaging (MRI) may also be viewed as dynamic imaging, that is, imaging on very long time scales–yearly scales in maturating brains and weeks or months in the case of growing tumors. By contrast, intermediate time-scale methods like functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) track brain changes over seconds or minutes. Electroencephalography (EEG) provides complementary information on much faster time scales (milliseconds). In this paper we outline several potential new relationships between large scale structural and functional imaging, the former focused on white matter and the latter employing EEG.

EEG functional connectivity at large scales is believed to be strongly influenced by white matter axons, especially the

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cortico-cortical axons, which outnumber thalamo-cortical and callosal axons by perhaps 50–1 in humans (Braitenberg, 1978; Katznelson, 1981; Nunez, 1995; Braitenberg and Schüz, 1991); our anatomical focus here is on these cortico-cortical axons. Axon connectivity may be estimated from the injection of tracers transported along cell projections in the living brains of animals (Braitenberg and Schüz, 1991; Kotter, 2007). In humans, structural connectivity is accessible by postmortem examination of dissected tissue (Krieg, 1963, 1973) or noninvasive brain imaging methods like diffusion tensor imaging (DTI). In DTI, MRI is used to measure the preferred direction of water diffusion in each brain voxel, thereby providing estimates of major white matter tracks at the 1 mm scale (Sporns, 2011). This approach is based on the idea that the direction of fastest diffusion indicates voxel fiber orientation, where here the label "fiber" suggests bundles of multiple parallel axons.

While DTI demonstrates impressive technology, it currently falls far short of the resolution required to view most individual axons. Diameter histograms of human white matter axons are peaked in the 1 μm range (Tomasch, 1954; Bishop and Smith, 1964; Blinkov and Glezer, 1968); that is, about 1000 times smaller than the 1 mm resolution of DTI. Human white matter actually contains about 10^{10} cortico-cortical axons, that is, one axon for each cortical pyramidal cell (Braitenberg, 1978), far more than the number of tracts revealed by DTI images. Thus comprehensive maps of axon connectivity at multiple mesoscopic and macroscopic scales may be "years away" as argued by Sporns (2011).

1.2. Multi-scale functional connectivity

Measures with much higher temporal resolution than fMRI and PET are obtained with EEG, which operates on millisecond time scales, providing dynamic images faster than the speed of thought. By "images," we mean multiple spatial–temporal dynamic scalp patterns, including frequency and phase spectra, topographic maps, traveling and standing waves, covariance, and coherence structure, all potentially important brain state-dependent measures of neocortical dynamics, including functional connectivity (Thatcher et al., 1987; Gevins et al., 1994, 1997; Nunez, 1995; Nunez et al., 1997, 1999; Srinivasan, 1999; Barry et al., 2004; Nunez and Srinivasan, 2006a,b; Murias et al., 2007; Jirsa and McIntosh, 2007).

The price paid for EEG's excellent temporal resolution is poor spatial resolution. While MRI and PET provide excellent mm scale spatial resolution, unprocessed scalp potentials (EEG) provide very coarse (e.g., 5–10 cm) spatial resolution. Thus, each scalp electrode records neural source activity averaged over tissue containing something like 100 million neurons. Despite this extreme space averaging, EEG has revealed many robust relationships to behavioral, cognitive, and clinical states in thousands of studies published since Hans Berger's original paper in 1929. Thus far, most of the clinically useful relationships have involved distinct EEG frequency spectra observed in different brain states, the delta, theta, alpha, beta, and gamma oscillations. Here we propose multi-scale coherence structure as a potentially viable new clinical measure.

The broad field of electrophysiology spans about five orders of magnitude of spatial scale as summarized in Table 1, indicating recording of local field potentials (LFP), electrocorticography (ECoG), low (spatial) resolution EEG, and *high resolution EEG* (HR-EEG) (Nunez et al., 1994; Srinivasan et al., 1998). Also included is magnetoencephalography (MEG), which provides spatial and temporal resolution similar to EEG, but is mainly sensitive to cortical dipole axes parallel to MEG coils, typically sources in cortical folds (Salmelin and Hari, 1994; Srinivasan et al., 2007). The theoretical and experimental bases for the estimated resolutions in Table 1 are reviewed in (Nunez, 1995; Nunez and Srinivasan, 2006a).

Table 1
Estimated spatial resolution of recorded potentials or magnetic fields generated by cortical sources.

Recording method	Typical spatial resolution (mm)
Microelectrode of radius ξ	$\geqslant\xi$
LFP	0.1–1
ECoG	2–5
Intra-skull recording	5–10
Untransformed EEG	50–70
Untransformed MEG	50–70
High resolution EEG	20–30
High resolution MEG	Unknown

HR-EEG methods employ computer algorithms (e.g., Laplacian or dura image) to provide estimates of brain or dura surface potentials at roughly the 2–3 cm scale by employing dense scalp electrode recordings (e.g., 64–256 electrodes) processed with estimated geometric and electrical properties of head tissue. Thus, the effective scale of HR-EEG is intermediate between ECoG and EEG. Since the classical inverse problem, i.e., locating brain sources based only on surface measurements, suffers from notorious (and often understated) non-uniqueness (Nunez and Srinivasan, 2006a), we avoid such methods here. By contrast, the inward continuation solutions of HR-EEG provide "unique" estimates of dura potential distributions, which are independent of assumptions about sources, although accuracy is limited by head model uncertainty, noise, and scalp electrode density.

Fundamental questions about relationships between anatomical and functional connectivity involve the spatial and temporal scales at which such measures are obtained. Here we promote the idea that brains are genuine complex systems; this view, if actually taken seriously, demands a strong emphasis on the multi-scale nature of brain tissue, which is believed responsible for much of its dynamic behavior: spatial–temporal patterns of synaptic action, action potential firing rates, cell assembly formation, dominant frequency bands, coherence structures and so forth, recorded at various spatial scales of electrophysiology summarized in Table 1. Our focus on multiscale neocortical dynamics motivates a close look at ECoG/EEG relationships as well as multiscale scalp measures of functional connectivity estimated with EEG and HR-EEG coherence. Freeman (2003) suggests a colorful metaphor for this complex multimodal, multiscale information transport: *the wave packet: an action potential for the 21st century*. Traveling wave packets in numerous scientific fields are generally composed of multiple components with a broad range of wavelengths and phase velocities, all contributing to information and/or energy transport.

2. White matter matters

Here we propose close relationships between EEG or HR-EEG functional connectivity measures like narrow band (e.g., 1 Hz) alpha and theta coherence to cortico-cortical axon propagation; such relations may have important implications for diagnosis and treatment of brain diseases. While scalp coherence patterns must be partly determined by the (mostly) myelinated cortico-cortical axons, this does not imply that pairs of cortical locations with high coherence need be directly connected. Rather, cortical coherence structure is part and parcel of the global dynamic system, and changes robustly with behavioral or cognitive tasks. While EEG coherence is not wholly determined by white matter myelination and connection structure, it is expected to be strongly constrained by such properties.

Myelin controls action potential speed, and the synchrony of impulse traffic between distant cortical regions may be critical for optimal mental performance and learning. A broad range of