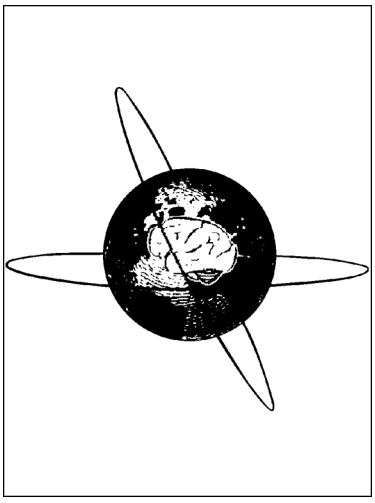

Review

Methods for analysis of brain connectivity: an IFCN-sponsored review

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Methods for analysis of brain connectivity: an IFCN-sponsored review

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Highlights

There are a variety of technologies valuable for exploring human brain connectivity.

The main aspects of anatomical, functional and effective connectivity are described.

A multimodality approach can be useful to evaluate the human brain connectome.

Abstract

The goal of this paper is to examine existing methods to study the "Human Brain Connectome" with a specific focus on the neurophysiological ones. In recent years, a new approach has been developed to evaluate the anatomical and functional organization of the human brain: the aim of this promising multimodality effort is to identify and classify neuronal networks with a number of neurobiologically meaningful and easily computable measures to create its *connectome*. By defining anatomical and functional connections of brain regions on the same map through an integrated approach, comprising both modern neurophysiological and neuroimaging (i.e. flow/metabolic) brain-mapping techniques, network analysis becomes a powerful tool for exploring structural–functional connectivity mechanisms and for revealing etiological relationships that link connectivity abnormalities to neuropsychiatric disorders. Following a recent IFCN-endorsed meeting, a panel of international experts was selected to produce this current state-of-art document, which covers the available knowledge on anatomical and functional connectivity, including the most commonly used structural and functional MRI, EEG, MEG and non-invasive brain stimulation techniques and measures of local and global brain connectivity.

Keywords

Brain connectivity; anatomical connectivity; functional connectivity; effective connectivity; human brain connectome; connectomics; fMRI; EEG; MEG; TMS-EEG; non-invasive brain stimulation.

Abbreviations list

BOLD Blood Oxygenation Level Dependent
CBI cerebellar inhibition
CLARITY Clear Lipid-exchanged Acrylamide-hybridized Rigid Imaging / immunostaining / in situ hybridization-compatible Tissue Hydrogel
CNS Central Nervous System
CRS-R Coma Recovery Scale-revised
CS Conditioning Stimulus
CST Cortico Spinal Tract
dMRI Diffusion Magnetic Resonance Imaging
DNA DeoxyriboNucleic Acid
DREADDs Designer Receptors Exclusively Activated by Designer Drugs
DSI Diffusion Spectrum Imaging
DTI Diffusion Tensor Imaging
DWI Diffusion Weighted Imaging
EEG Electroencephalography
eLORETA exact Low Resolution Electromagnetic Tomography
EMG Electromyography
ET Ensemble Tractography
ETC Ensemble Tractography Connectome
fMRI functional Magnetic Resonance Imaging
GABA Gamma-Aminobutyric Acid
GM Grey Matter
HARDI High Angular Resolution Diffusion Imaging
HCP Human Connectome Project
ICA Independent Component Analysis
ICF Intracortical Facilitation
ICMs Intrinsic Coupling Modes
IHF Interhemispheric Facilitation
ISI Interstimulus Interval
LCD Late Cortical Disinhibition
LICI Long Interval Intra Cortical Inhibition
LiFE Linear Fascicle Evaluation
LIHI Long Latency Interhemispheric Inhibition
M1 Primary motor cortex
MCS Minimally Conscious State
MEG Magnetoencephalography
MEP Motor Evoked Potential
MRI Magnetic Resonance Imaging
mTMS multilocus Transcranial Magnetic Stimulation
NIBS Non-Invasive Brain Stimulation

pcTMS paired coil Transcranial Magnetic Stimulation
PFC Prefrontal Cortex
PMd dorsal premotor cortex
PMv ventral premotor cortex
PPC Posterior Parietal Cortex
ppTMS paired pulse Transcranial Magnetic Stimulation
ROIs Regions Of Interest
SAI Short latency Afferent Inhibition
SICF Short Interval Intracortical Facilitation
SICI Short Interval Intracortical Inhibition
SIHI Short Latency Interhemispheric Inhibition
SMA Supplementary Motor Area
SPC Single Parameter Connectomes
spTMS single pulse Transcranial Magnetic Stimulation
STM Single Tractography Methods
tACS transcranial Alternating Current Stimulation
tDCS transcranial Direct Current Stimulation
TEPs TMS-evoked EEG Potentials
tES Transcranial Electrical Stimulation
TMS Transcranial Magnetic Stimulation
TS Test stimulus
UWS Unresponsive Wakefulness Syndrome
VS Vegetative Wakefulness Syndrome
WM White Matter

1. Introduction

The human brain contains about one hundred billion neurons, each establishing several thousand synaptic connections in an intricate matrix, which can be mathematically modeled in several ways. One approach models the brain as myriads of oscillators (i.e., cyclic firing of individual neurons and/or of spatially separated neuronal assemblies) organized in network structures at micro-meso-macro-scale levels, with nodes and links that dynamically cooperate with time-varying aggregations via transient locking/unlocking (i.e. orchestrated synchronization) of their cyclic firing (Singer, 1990; Jung et al., 2001; Makeig et al., 2002; Fuentemilla et al., 2006; Fries, 2015). Neural networks continuously re-shape via plastic mechanisms of synaptic Long Term Potentiation/Depression reflecting the flow and type of input from internal and external environments, including daily experiences, learning/training, and emotional and aging processes. Therefore, when evaluating the brain's anatomical and functional organization from the perspective of complex networks (Bassett and Bullmore, 2006; Bullmore and Sporns, 2009; Sporns, 2011), the neuronal system can be modelled by a set of nodes (anatomical/functional neuronal aggregates) and interconnecting edges (structural/functional connections) (**Fig. 1**). This kind of architecture is regarded as a key substrate for two fundamental, coexisting and dynamically interplaying brain properties: 1) the functional *segregation* of different regions and their involvement in cognition, sensorimotor integration, perception, and behavior (Tononi et al., 1994); 2) the functional *integration* ranging from the neuron (microscale) to inter-areal interactions (macroscale), to overall cognitive and behavioral output (Sporns and Zwi, 2004). In recent years, numerous studies approached human brain modeling using a new multidisciplinary method known as complex network analysis, with the aim of classifying neuronal networks with a small number of neurobiologically meaningful and easily computable measures (Rubinov and Sporns, 2010) and creating its ***connectome*** (Sporns, 2012). Modern brain mapping techniques — such as diffusion MRI, functional MRI, Non-Invasive Brain Stimulation (NIBS), EEG, and MEG— have produced and continue to produce increasingly larger datasets of anatomical or functional connection patterns. While neuroimaging techniques are able to faithfully reproduce the scaffold where the "quest" for brain function dynamics take place within a time frame during which inhibitory and facilitatory connections fluctuate simultaneously, such temporal dimensions—particularly the time epochs which selectively define connectivity patterns before, during, and following a given task—can be reliably discerned by different brain mapping techniques. By explicitly defining anatomical and functional connections on the same map of brain regions, network analysis is a powerful tool for exploring structural–functional connectivity relationships (Zhou et al., 2006; Honey et al., 2007, 2009;) and revealing the causative linkage between connectivity changes and task performance in the healthy or presence/severity of symptoms in neurologic neuropsychiatric disorders and aberrant connectivity (Stam et al., 2007; Bassett et al., 2008; Leistedt et al., 2009; Stam et al., 2009). The goal of this review is to examine existing and innovative methods for the human brain connectome exploration –particularly for the neurophysiological ones– providing measures of local and global connectivity from an IFCN-endorsed meeting of a panel of international experts. The present review complements another IFCN-endorsed guideline on topographic and frequency analysis of resting-state EEG rhythms (Babiloni et al 2018 in press).

2. Structural brain connectivity: experimental approaches and *in vivo* studies of the human brain

2.1. Chasing neuronal circuits: a never-ending story

Over the centuries, many paradigm shifts have occurred in the views on neuronal connections, their behavioral output and their alterations in diseases (Bentivoglio and Mazzarello, 2010). The "neuron doctrine", which extended cell theory to the nervous system, was enunciated in 1891 (Shepherd, 2015). A breakthrough in the visualization of neurons was provided by the "black reaction", the metallic impregnation introduced in 1873 by Camillo Golgi (1843-1926). Golgi staining revealed neurons, including their processes, in their entirety and with unprecedented detail. This allowed studies of neuronal circuits (Golgi, 1885), and still allows the investigations of the local neuronal circuitry of randomly impregnated neurons (**Fig. 2A**), also in tissue blocks of *post-mortem* human brain. The revelation power of the Golgi method is only matched after more than one century by genetic cell tagging with fluorescent proteins, or intracellular neuron filling (e.g., in surgically resected tissue blocks of the human brain) (**Fig. 2B and 2C**).

The champion of the "neuron doctrine" was Santiago Ramón y Cajal (1852–1934), who accomplished a monumental work, largely based on the Golgi stain, in which he provided a map of neuronal connectivity in the mammalian brain (Cajal, 1909, 1995). The debate between Cajal and Golgi—who had adhered to the reticular theory of nervous system organization—boosted neuroscience studies, focusing interest on the gray matter. White matter investigations were essentially descriptive, based on manual dissections and on the study of brain sections with the myelin stain introduced by Carl Weigert (1845–1904). Seminal contributions on the organization of fiber bundles in the human brain were provided by Carl Wernicke (1848–1900) and Joseph Jules Déjérine (1849–1917) (Schmahmann and Pandya, 2007).

The second half of the twentieth century witnessed a revolution in the experimental studies of neuronal connections, together with the explosion of neuroscience in the last decades of the century. As briefly discussed below, novel powerful techniques were introduced. The exploration of connectivity in the human brain remained, however, a challenging problem until the introduction of *in vivo* imaging.

2.2. Long-range neuronal connectivity

2.2.1 Anterograde and retrograde degeneration techniques

Pioneering early studies revealed that retrograde degeneration ("secondary atrophy") of neuronal cell bodies and anterograde degeneration of fibers can provide effective tools to trace neuronal connections (Bentivoglio and Mazzarello, 2010) (**Fig. 3A**). Towards the end of the nineteenth century, neuronal alterations consequent to retrograde damage could be assessed by the cell stain (with thionin or toluidine blue) introduced in 1884 by Franz Nissl (1860–1919). Especially influential was the observation of anterograde degeneration of nerve fibers after transection reported in 1851 by Auguste Volney Waller (1816–1870) and named after him "Wallerian degeneration" (**Fig. 3A**).

Besides its implications for the trophic dependence of the axon from the cell body, this finding paved the way to the introduction of anterograde tract tracing methods based on silver impregnation of degenerating fibers after experimental lesions (Nauta and Gygax, 1951; Fink and Heimer, 1967). Metal impregnation stains are capricious and laborious, and degeneration methods have limited sensitivity, but these techniques gave a great impulse to experimental neuroanatomical studies. Importantly, anterograde degeneration revealed by modifications of silver impregnation was also applied to *post-mortem* investigations on the human brain, especially after restricted lesions occurring a few weeks before death (Mesulam, 1979).

2.2.2. Classical experimental tract tracing techniques based on axonal transport

A turning point in the study of structural brain connectivity was the discovery of anterograde and retrograde axonal transport (Bentivoglio, 1999). Axonal transport requires live axons; the active transport of tracers obviously cannot be applied to the human brain. Findings obtained

with tract tracing based on axonal transport represent nowadays the "ground truth" for studies of the human brain based on *in vivo* imaging, and in particular on diffusion tractography.

Anterograde tract tracing based on the use of tritiated amino acids revealed by autoradiography was introduced in the early 1970s (Cowan et al., 1972). With this approach, trajectories and terminal fields of fibers originating from the tracer injection site could be delineated in detail. Anterograde tract tracing approaches have then been implemented (Gerfen and Sawchenko, 1984; Glover et al., 1986). In the same years, the discovery of retrograde axonal transport (Kristensson, 1970; Kristensson and Olsson, 1971) introduced as a tool the enzyme horseradish peroxidase (HRP), visualized by a histochemical reaction, which was soon applied to experimental retrograde tracing of the origin of projections to the tracer injection site (LaVail and LaVail, 1972).

The introduction of other retrograde tracers rapidly followed to increase sensitivity, combine tracers for multiple retrograde labeling for the study of branched connections, combine retrograde tracing with immunohistochemistry or in situ hybridization for the neurochemical characterization of pathways, and so forth. Fluorescent retrograde tracers turned out to be especially effective and versatile for these applications (e.g. Bentivoglio et al., 1980; Kuypers et al., 1980; Schmued and Fallon, 1986).

Conventional tract tracing has been implemented in recent years with genetic tracing for the study of the connectivity of specific neurons using cell-type-specific promoters (Oh et al., 2009). Most anterograde and retrograde tracers explore monosynaptic connections since they can cross synapses only in minute amounts, ineffective for transsynaptic tracing unless a bolus is injected, which is not feasible in the brain. Neurotropic viruses, which travel through axons and replicate in infected neurons, can instead provide tracing tools (Kristensson et al., 1974) applicable to trans-synaptic tract tracing (Kuypers and Ugolini, 1990) thanks to their propagation across synapses.

2.2.3. Novel approaches to experimental tract tracing: optogenetics and chemogenetics

These innovative techniques are increasingly used to investigate the relationship between neuronal activity, neuronal circuits, and behavior.

The term optogenetics was introduced in 2006 (Deisseroth et al., 2006) referring to the general optogenetic discovery (Boyden et al., 2005). By combining genetic and optical methods, optogenetics utilizes molecular light-sensors to switch on and off neuronal electrical activity. Optogenetics thus allow to investigate neurons and neuronal circuits underlying specific behaviors at the time scale of milliseconds. By this approach, functional effects of defined neuronal cell types can be controlled in living tissue and in freely moving animals (Deisseroth, 2015). Optogenetics has also been combined with functional MRI for the experimental study of cell-type-specific contributions to behavioral output together with a "whole brain read-out" at the millimeter scale (Lee et al., 2017). From the translational point of view, applications of optogenetics in humans for therapeutic purposes are currently envisaged. Clinical applications of the optogenetic system will require obvious implementation and cross-disciplinary know-how (Delbeke et al., 2017).

The term "chemogenetics" was used to describe experiments of site-specific functional group modifications for the analysis of DNA-protein interactions (Strobel, 1998). Currently, the term is used to indicate the processes by which "designer macromolecules" interact with previously unrecognized small molecules (Roth, 2016). Over the past two decades, chemogenetically engineered molecules (kinases, non-kinase enzymes, G protein-coupled receptors, ligand-gated ion channels) have been used experimentally for cell-specific targeting; these molecules modulate cell signaling, turning neuronal circuits on and off. Among chemogenetically engineered protein classes, the most commonly used are the so-called Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) (Roth, 2016).

2.3. Local neurocircuitry in the human brain

2.3.1 Diffusion of dyes

An attempt to trace connections in the human brain using in vitro diffusion of wheat germ agglutinin conjugated with HRP gave very limited results (Haber, 1988). More interesting findings were obtained using the diffusion of lipophilic dyes along cell membranes in fixed tissue blocks (**Fig. 2E**). The fluorescent dyes carbocyanines, and in particular DiI and DiO (Honig and Hume, 1989) proved useful for this application. However, dye diffusion can label axons only for a few millimeters, requiring a tracing time of several weeks. Other dyes have been introduced (Heilingoetter and Jensen, 2016), and in particular NeuroVue dyes, which can trace axons for slightly longer distances and at faster diffusion rates than carbocyanines (Fritzsch et al., 2005). The limitations of *ex vivo* tracing, however, hamper its application for extensive fiber tracking in the human brain.

2.3.2 Seeing through: tissue clarification

The natural 3D structure of cells – especially neurons and glial cells, which extend their ramifications in many directions – requires volumetric imaging. The heterogeneous chemical composition of biological tissues (mostly water, proteins, and lipids) generates substantial scattering of the transmitted light, especially at the interface between aqueous protoplasm and membrane lipids, thereby hindering microscopic observation of histological sections beyond a certain thickness. Replacing lipids with a medium characterized by the same refractive index as proteins can effectively render tissues transparent while preserving the native molecular profile and tissue structure, allowing the microscopic observation of the microcircuitry of labeled (e.g., by immunohistochemistry or fluorescent protein tagging) elements.

Aqueous-based clearing techniques are currently widely used and are based on the reduction of light scattering by immersion in a high-refractive-index molecule solution. A breakthrough has been provided by a brain-hydrogel hybrid formed by the so-called CLARITY (Clear Lipid-exchanged Acrylamide-hybridized Rigid Imaging / immunostaining / in situ hybridization-compatible Tissue Hydrogel) (Chung et al., 2013). The clarification of thick tissue blocks, such as those useful for the study of the human brain (**Fig. 2D**) remains, however, a challenge. A method to adapt CLARITY to human brain samples with a thickness up to 8 mm has been recently proposed (Morawski et al., 2018). Of note, bridging historical and modern approaches to microcircuits, the Golgi (Golgi-Cox) stain is currently optimized for the use with CLARITY approaches, and could be useful for the study of microcircuitry and the comparison with microstructure MRI data (Kassem et al., 2017).

2.4. Diffusion tractography

Diffusion-weighted imaging (DWI), a computational reconstruction method of diffusion-weighted MR images (tractography), allows quantitative estimates *in vivo* of the organization of fiber bundles (tractograms). The characteristic color coding of reconstructed fiber bundles results in images attractive also to the public at large, thus making this approach a very popular insight in the human brain. This method is extensively presented in another part of our review.

The diffusion coefficient measures the ease of the translational motion of water in tissues. Main DWI acquisition schemes are provided by diffusion tensor imaging (DTI) (**Fig. 3B**), diffusion spectrum imaging (DSI), and high angular resolution diffusion imaging (HARDI). DTI utilizes a tensor model (a matrix of measured diffusion in three orthogonal planes) to characterize the water diffusion properties through myelinated nerve fibers (Basser et al., 1994). Fiber orientation profiles derive from the statistical profile of the displacement of water molecules at a voxel scale and fiber trajectories are inferred from adjacent similar diffusion profiles (Thomas et al., 2014). DSI adds to DTI the capability of resolving multiple directions in each voxel (Wedeen et al., 2005), thus improving also the tracking of

intersecting fibers. HARDI improves the accuracy of tractography by using a large number of diffusion-encoding gradients with a reasonable scanning time.
After the first validation study in the macaque brain (Parker et al., 2002), a number of validation studies have been performed, with rather positive or more critical conclusions. For example, the comparison of DSI in the light of extensive autoradiographic tract tracing data on long association pathways in the monkey cerebral hemispheres was found to replicate main features of these fiber tracts (Schmahmann et al., 2007). This comparison proved useful and effective for major cortical fiber bundles (superior, middle and inferior longitudinal fasciculi, fronto-occipital fasciculus, uncinate and arcuate fasciculi, cingulum bundle) (Schmahmann et al., 2007). Another study, based on DWI approaches to the monkey brain, reached more critical conclusions on the potential for accurate fiber tracing (Thomas et al., 2014). The results of a recent "open international tractography challenge", tractograms produced by 20 research groups turned out to contain 90% of the ground truth bundles, but were also reported to "contain many more invalid than valid bundles" (Maier-Hein et al., 2017). These results encourage innovation.

2.5. Macroscale of Connections

An exhaustive description of the intra- and inter-hemispheric anatomical bundles connecting different cortical and subcortical areas and nuclei cannot be done within the frame of this review. However, a rapid overview of the main connecting fiber bundles is provided in the following (see **Fig. 4**).
There are a number of short and long association tracts that provide intra-hemispheric communication within the cerebral cortex. The cingulum is an example of a long association tract. Commissural fibers provide communication between homologous regions of the hemispheres, the largest one being represented by the corpus callosum. Other commissures include the anterior commissure, which connects homologous cortical frontal lobe areas and the fornix, which is the efferent projection from the hippocampus. The posterior fibers (called the post-commissural fornix) of each side continue through the hypothalamus to the mammillary bodies; then to the anterior nuclei of thalamus, which project to the cingulate cortex. The anterior fibers (pre-commissural fornix) end at the septal nuclei and nucleus accumbens of each half of the brain. The internal capsule is a projection tract that contains many fibers carrying information between cortical and subcortical regions and the spinal column. It descends lateral to the head of the caudate nucleus and medial to the lentiform nucleus and thalamus. The corona radiata is where the internal capsule fans out superiorly. It is divided into several parts: the anterior limb contains frontopontine and corticothalamic fibers; the genu contains corticobulbar fibers; the posterior limb contains corticospinal and parieto-occipito-temporo-pontine fibers; and the retrolentiform/sublentiform part includes the auditory and optic radiations. The internal capsule becomes the crus cerebri in the midbrain.
Cascades of short association fibers interconnect modality-specific primary with secondary sensory association areas and these latter with multimodal sensory areas located at the borders. They may remain within the gray matter of the cortex or pass through the superficial white matter between neighboring cortical areas as U fibers. Long association systems connect the modality-specific association cortex and the multimodal areas in the occipital, temporal and parietal lobes with the premotor and prefrontal cortex. Short association fibers interconnect the prefrontal cortex, the premotor area and the motor cortex with the primary somatosensory cortex. Connections from multimodal association cortices and prefrontal cortex (PFC) to limbic structures pass via the cingulum to the medial temporal lobe; other fibers originating from association cortices reach limbic structures via the insula. Most association connections are reciprocal.

3. Methods for connectomics

A long-term goal of neuroscience is to develop models that integrate brain structure and function to predict human perception, cognition and behavior (Goldstone et al., 2015; Pestilli, 2015), but they often lack characterization at the level of the *individual subject.* Neuroimaging research has only begun to address this knowledge gap, and substantial work needs to be carried out before we can reliably study individuality and variation of brain networks (Finn et al., 2015; Laumann et al., 2015; Smith et al., 2015). Recent proposals have been made for the development of innovative technologies that can enable the study of the computational architecture of brain connections in individuals. The brain connectome is comprised of both grey matter (GM) regions representing neuronal units of information processing (the *nodes*,**Fig. 5A**), and white-matter tracts (WM), serving as structural communication pathways (the *edges*,**fig. 5B**)(Bullmore and Sporns, 2009). To date, methods for precision measurement of brain networks have been developed, but not been fully optimized and agreed upon. To approach this issue, innovative technologies for the study of the computational architecture of brain connections in individuals and building precision models of brain connection patterns have been proposed.

DTI and fiber tractography allow investigators to measure the properties of the connectome in living human brains at the meso- and macro-scale (*mm* to *cm*), providing information about brain computational machinery that –because of experience and training– changes over minutes, hours, days, months and years (Sowell et al., 2003; Fields, 2008b; Westlye et al., 2009; Behrens and Sporns, 2012; Jbabdi et al., 2015). Recent technologies allow us to automatically identify major white matter tracts in living brains (see **Fig. 5A and B**) (Mori et al., 2005; Yeatman et al., 2012; Pestilli et al., 2014). These tracts are the most prominent edges in the connectome, information highways that implement communication about the senses, motor control, cognition and language. So far, we have learned that the biological properties of these tracts change transiently in response to experience, and can be steadily modified by learning, development and aging (Fields, 2008a, 2015; Risacher and Saykin, 2013). Even though much important work has been done to map the human connectome, to date the full set of connectome edges is still unknown, and we name only a few. Limitations to mapping the full human connectome have been due to two sources of variability in connectome estimates: **(1)** the dependency of connectomes on the tracking methods and **(2)** insufficient reliability of connectome estimates in individual brains or even in intra-individual brain when explored at different times. For example, **Fig. 6A** and **6B** show eleven major human WM tracts identified in the same brain, using a single diffusion imaging data set, but two different tracking methods. These remarkable algorithm-dependent differences within single brains have imposed limits to the application of tractography for studying individuality and variation. Which algorithm should we use?

To approach these two issues, several methods have been developed. For instance, methods such as Linear Fascicle Evaluation (LiFE), have recently been proposed exploiting tractography evaluation. LiFE takes as input the set of white-matter fascicles generated using any tractography method and returns as output the subset of fascicles that predict the DTI measurements with smallest error. LiFE predicts diffusion measurements in individual brains by representing connectomes as systems of linear equations. It models the diffusion signal using the prediction of the combined WM fascicles in a connectome. Each fascicle is associated to a weight. Weights represent the contribution of fascicles to predicting the measured diffusion.

Fascicle predictions are organized by LiFE as columns of a large matrix of linear equations (M). The diffusion signal (Y) is predicted by least-square optimization $||Y - Mw||_2^2$ (Eq. 1). M is a matrix where each column is a single fascicle prediction of diffusion and w are the set of weights assigned to each fascicle to predict the diffusion measurements in all brain voxels (Y). The root mean square error (r.m.s.) generated by the optimization (Eq. 1) can be used to

compare connectome models. **Fig. 6C** shows a comparison of r.m.s. error computed by LiFE for the two models in **fig. 6A** and**6B**. Errors were computed on a single brain from the Human Connectome Project (HCP) using LiFE and two different tractography methods: a *probabilistic* tractography method based on constrained-spherical deconvolution (**fig. 6A**), and a *deterministic* tractography method based on the tensor model (**fig. 6B**) using the HCP data (90 directions, b value = 2000 s/mm^2).

Comparing connectome errors can be used to select the connectome models that best represent the diffusion measurements in a single individual. Better connectomes have lower error. The fundamental insight here is to use the r.m.s. error produced by LiFE to establish the accuracy of a connectome in a single individual. This error is proposed below as the foundation for developing a precision connectome science, a connectomic of the individual. Additional advances in methods for mapping structural connectomes have more recently exploited similar statistical evaluation approaches. Ensemble Tractography (ET; Takemura et al., 2016a), for example, uses a large set of candidate connections generated with multiple tractography algorithms to 'learn' the best connections, given the data, that best predict brain measurements. **fig. 6C** shows that the probabilistic tractography model is better than the deterministic one in a majority of the voxels. Yet, the probabilistic model is not better in *all voxels*. In some voxels, the deterministic model does reasonably well. These are voxels where the r.m.s. error is below the diagonal. This indicates that the deterministic model is better in these few voxels. Thus, no single tracking method is always best – this insight motivated the development of a multiple tractography method, Ensemble tractography (ET). ET provides improvements over single-tractography methods (STM). It is a new way of tracking that exploits ensemble methods. ET (1) identifies more WM connections, (2) increases white matter volume coverage, (3) decreases error in predicting the diffusion signal and (4) improves the anatomical representation of the human WM. All enhancements are achieved at standard data resolution. First, a set of single parameter connectomes (**SPC**) is created, each generated using a different tractography method (e.g., deterministic and probabilistic) or parameter setting (e.g., fascicle curvature). All these SPCs are combined into a single group. LiFE is used to find fascicle weights and eliminate all fascicles with zero weight. The result is the Ensemble Tractography Connectome (**ETC**) (**Fig. 7**).

ETCs consistently outperform SPCs. For example, the number of non-zero weight fascicles is higher for ETCs than any tested SPC. The proportion of total WM volume covered by the ETC is higher. The ETC is more accurate (lower error) than any tested SPC. Maps of the diffusion signal show better signal prediction by the ETC. Finally, ETCs contain important anatomical features absent in SPCs (Takemura et al., 2016b).

LiFE and Ensemble Tractography –or other modern methods– can be used to build *customized* connectomes for individual brains. A crucial element necessary to apply the methods on many individual brains is the ability to run the methods routinely and efficiently. To tackle this challenge, preliminary results for a sparse-factorization method that drastically reduces the size of the LiFE model are briefly presented; this Sparse Factorized LiFE model (**LiFE$_{SF}$**) achieves accuracy quite close to the original LiFE, at a fraction of the computational cost. The factorization approach is an example of multivariate approaches that represent a new paradigm with the potential to open new avenues of investigation for computational neuroscience (McIntosh and Bratislav, 2013; Cichocki et al., 2015).

Pestilli and colleagues developed a sparse multiway factorization (Caiafa and Cichocki, 2013) to represent the LiFE matrix Mefficiently by combining a dictionary of precomputed diffusion prediction (D) and an array (Φ) of voxels, fibers and diffusion predictions in D (**fig. 8A**). The factorization approach compresses the model by eliminating redundancies and precomputing diffusion predictions. The approach can reduce the size of the LiFE model by factors of 30 or above; e.g., from 30GB to 1GB (**fig. 8B**). LiFE$_{SF}$ accurately approximates the original LiFE model (**fig. 8C**). Preliminary results show that LiFE$_{SF}$ (1) has r.m.s. error in

predicting diffusion identical to LiFE (**fig. 6C** scatter plot); (2) reproduces the LiFE matrix accurately (**fig. 6C** top inset); (3) supports identical connectome weights as the original LiFE (**fig. 8C** lower inset). The factorization method allows running the ET method routinely on many brains at scale, and create rich databases of candidate connections in individual brains that can be used to map variation in connections across large human populations.

Whereas previous approaches to brain connectivity (as described in the previous section) have focused on validating results using either animal models or synthetic data, a recent trend has been to use statistical approaches to evaluate results in individual brains, one brain at the time. These approaches focus on *in-vivo* brain measurements (for a review see Maier-Hein et al., 2017;Rokem et al., 2017; Wandell and Le, 2017). Recently, new approaches to evaluate and validate the results of tractography have been developed (Pestilli et al., 2014; Smith et al., 2014; Daducci et al., 2015; Takemura et al., 2016a; Caiafa and Pestilli, 2017). These approaches have the potential to advance discovery by providing mechanisms to evaluate and apply tractography to the study of individual brains, by leveraging statistical and computational methods (Pestilli, 2015; Wandell and Le, 2017).

4. Techniques of measurement of brain function [fMRI, EEG, MEG]

Perceptions and actions emerge from temporally coordinated local brain activities at multiple sites in distributed neuronal networks (Engel et al., 1991; Singer and Gray, 1995; Classen et al., 1998; Gerloff et al., 1998b; Singer, 1999a; Buzsaki and Draguhn, 2004; Engel et al., 2013; Bönstrup et al., 2014). This temporal coordination of brain activity can be measured at multiple scales and in distinct states of activation or rest with different metrics, each one with its own advantages and disadvantages. The interpretation of the measured signals is often challenging. In the human, EEG and MEG allow for non-invasive measurement of neuronal firing at high temporal resolution, i.e., in the range of milliseconds, however, with relatively low spatial resolution in the centimeter range. Excellent spatial resolution is in the domain of functional MRI (fMRI) which allows for the measurement of fluctuations of local blood flow and metabolism through detection of blood-oxygenation-level-dependent (BOLD) changes of the magnetic field with millimeter precision. Another advantage of fMRI is its capability to detect activity changes in the depth of the brain much more reliably than EEG or MEG. However, its temporal resolution is limited due to physical properties of hemoglobin relaxation that introduces a significant time delay between the synchronized and relatively sharp neuronal firing and changes of local blood flow producing the BOLD signal with a smoothing effect on the firing sharpness during rise/decay times of the neurovascular reaction; moreover –and probably more important– the BOLD signal is based on changes of energy consumption and therefore it does not reflect those mechanisms of communication among neuronal assemblies which do not modify energy consumption (i.e. synchronization/coherence, phase locking-unlocking without any change of firing frequency/intensity). The spatial resolution of EEG and MEG is poor due to the relatively small number of channels and the non-uniqueness of the solution of the inverse problem; moreover such techniques are little or no sensitive at all to activity in neuronal assemblies located far from the scalp surface (either in the depth of sulci, or in the fronto-orbital and temporo-mesial areas including the hippocampal formation and insula) and/or due to a neuronal architecture producing a closed field organization like in subcortical nuclei. In the following survey (which has a focus on electrophysiological methods), commonly used approaches and excerpts of their mathematical bases are described, some caveats are mentioned, and hints towards their interpretation are given.

4.1. Resting-State vs. task-related measurements

Historically, PET and fMRI allowed for describing some of the "scaffolds" of functional brain connectivity; they include the default mode, fronto-parietal, and dorsal attention networks. The brain's default mode network consists of discrete, bilateral and symmetrical cortical areas, in the medial and lateral parietal, medial prefrontal, and medial and lateral temporal cortices unexpectedly described in brain-imaging studies first performed with positron emission tomography in which various novel, attention-demanding, and non-self-referential tasks were compared with quiet response either with eyes closed or with simple visual fixation (for a review see Raichle, 2015); the fronto-parietal network is mainly involved in task monitoring and reporting (for review see Koch et al., 2016); finally, the dorsal frontoparietal network assumes a puzzling variety of functions, including motor planning and imagery, mental rotation, spatial attention, and working memory (Ptak et al., 2017). In distributed networks, such as the described ones, neuronal activity at rest shows distinct spatiotemporal patterns of oscillatory fluctuations (for review see Engel et al., 2013). These so-called intrinsic coupling modes (ICMs) are of high interest as they contain significant information, request little or no changes of energy consumptions and have a meaningful spatiotemporal structure. It is likely that in the healthy brain ICMs reflect previous learning and can bias the processing of upcoming stimuli. In addition, any perception or action will impose some sort of (local or distant) synchronization, thereby altering the temporal relationship between signals. As a consequence, directly or stimulus-related (evoked) responses or oscillatory responses triggered by and outlasting the stimulus (induced) can be measured. All of them, ICMs and evoked or induced responses, can be described with several mathematical approaches at the network level. This type of neuronal coupling can be described in the time or the frequency domain.

In their pioneering work, Gevins and colleagues have used time-averaged evoked potentials and their temporal covariation in order to describe simultaneous, connected EEG activity, so-called event-related covariances (Gevins et al., 1989). In more recent years, frequency-domain-based approaches have been more common in the analysis of human EEG and MEG data. The degrees of freedom of neuronal coding in the frequency domain are enhanced by the wide range of cyclic firing that can be generated by neuronal assemblies both in frequency (range between 0.025 and 600 Hz; Bressler et al., 1993; Curio et al., 1994; Kandel and Buzsaki, 1997; Penttonen et al., 1999; von Stein and Sarnthein, 2000) and in amplitude. Coding in and across different frequencies of oscillation is of particular interest for EEG and MEG analyses. The ICMs are, at the very end of the very slow frequency spectrum (delta and sub-delta), mirrored to some extent by fMRI resting-state signals, which are increasingly used to reconstruct human brain networks (Cordes et al., 2002; Fransson, 2005; Scholvinck et al., 2010).

4.2. Whole-brain approaches vs. hypothesis-driven analyses in subnets

Coherence (Coh)(Gerloff et al., 1998b), partial coherence (pCoh), Phase-Locking Value (PLV)(Lachaux et al., 1999), Mutual Information (MI) (Kraskov et al., 2004), and Directed Transfer Function (DTF) (Kaminski et al., 1995; Bönstrup et al., 2014) are commonly used mathematical techniques to address interregional connectivity in EEG or MEG data. With respect to network nodes and connections, they are primarily hypothesis-free and can be used as whole-brain approaches. This is an advantage because it allows for an unbiased global view on resting-state or task-related changes in brain connectivity. However, this also carries some risk of false-positive results, or, if strictly corrected for multiple comparisons, can lack statistical power to detect modulations of subnets which are pivotal to a given function. An alternative is Dynamic Causal Modeling (DCM, Friston et al., 2003) where the modulation of interactions in preselected networks is analyzed. While initially applied to fMRI, this concept has also been extended to EEG / MEG (Kiebel et al., 2009). Of course, it is also possible to

use the aforementioned methods like Coh, pCoh, PLV, or DTF hypothesis-driven on predefined networks with few nodes of interest. In contrast, DCM is not suited as an exploratory technique.

4.3. Acquisition and processing of fMRI and EEG/MEG data for connectivity analyses

4.3.1. Functional MRI (fMRI)

The use of functional MRI data relies on the blood-oxygenation dependent (BOLD) signal. The magnitude of the BOLD signal depends on multiple factors like, among others, the change in cerebral oxidative metabolic rate (CMRO2), the change in blood flow, volume, and oxygen extraction rate (Bandettini, 2014). Simultaneous measurements of BOLD signal and electrical neuronal activity indicate that the BOLD contrast reflects local field potentials (summed postsynaptic potentials) rather than spiking activity of neurons (Logothetis et al., 2001). MR scanners with 1.5 or 3 Tesla field strength are typically used to acquire the raw data. In order to co-register the BOLD signals with individual anatomy, high-resolution T1-weighted anatomical images of the brain are measured as well (e.g., so-called MPRAGE). For functional imaging, gradient EPI sequences are used. To measure the BOLD signal, a subvolume is defined and, for example, one scan is acquired every 1-2 seconds. The spatial resolution of fMRI is high. Typical voxel size is, for example, 4 x 4 x 4 mm but even smaller voxels are possible. The exact settings vary depending on the experimental paradigm and the scanner used. In addition to block designs (task on/off) and event-related designs (time series of BOLD signal locked to single behavioral events), resting-state fMRI (rs-fMRI, Biswal et al., 1995) has gained much attention recently, especially with respect to connectivity analysis. It has become evident that voxel-wise correlations of BOLD signal time series contain information about the functional organization of the brain. For rs-fMRI, spontaneous fluctuations of the BOLD signal during rest are measured and analyzed to reconstruct neural networks (for review see, e.g., Keilholz et al., 2017). In general, fMRI data can be analyzed with various tools, e.g., with the Statistical Parametric Mapping software (Welcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm), implemented in Matlab (The Mathworks Inc., Massachusetts, USA), or with BrainVoyager (Brain Innovation B. V., Maastricht, The Netherlands, https://brainvoyager.com). The strength of local activation in each voxel is typically calculated by means of multiple linear parametric modeling with general linear models (GLMs) of the measured BOLD signal, using a canonical synthetic hemodynamic response function (HRF).

4.3.2. EEG/MEG

EEG signals have been conventionally recorded from at least 19 scalp electrodes positioned according to the International 10-20 system, but the IFCN now suggests an extended array (see Seeck et al, 2017). The higher the number of simultaneously recording electrodes, the higher is the spatial resolution at least for sources on brain convexity (and the correspondence between the recording electrodes/sensors position and the functional relevance of the underlying cortical areas), but the higher the computational needs. The sampling rate of the EEG signal should be about four times the analog bandwidth; thus, it is sufficient to sample at 512 Hz when frequencies below about 130 Hz are investigated. If signals oscillating at 600 Hz are studied, a much wider bandwidth and higher sampling rate must be used (up to several KHz). The monitoring of eye movements can be obtained with two different EOG channels, vertical and horizontal; skin/electrode impedances of all channels (this is an important issue only for EEG, but not for MEG) should be kept in the $k\Omega$ range (preferably below $5k\Omega$) to minimize noise and external electromagnetic interference that may cause artifacts.

Before digitization (sampling) the EEG signals must be band-pass filtered so that the above-mentioned sampling-frequency rule is satisfied. Artifacts represent another important source of biased information. The digitized EEG data can be segmented to epochs (e.g., 2 seconds) for visually identifying and rejecting visible artifacts (i.e., eye movements, cardiac activity,

and scalp muscle contraction); further, independent component analysis (ICA, a method widely used also in fMRI analysis) is very effective for further artifact rejection (Vecchio et al., 2017), but only provided that the artifacts are independent of the brain signals we wish to study. Thus, stimulus-triggered artifacts and stimulus-evoked brain signals are not generally fully separated by ICA, because they are not independent. Data can be analyzed with a number of different Matlab (MathWorks, Natick, MA) toolboxes, such as EEGLAB (Swartz Center for Computational Neurosciences http://www.sccn.ucsd.edu/eeglab). ICA in EEGLAB can be performed using the Infomax ICA algorithm (Bell and Sejnowski, 1995).
While EEG is a powerful tool for measuring neuronal activity and connectivity, the lack of spatial resolution could be a drawback: as said before, in fact, EEG but also MEG are not sensitive to deep cortical activation. Inverse methods and approaches such as BEANFORM in MEG and LORETA in EEG data claim to detect deep sources but there is the possibility that a lot of information from deep structures in the higher frequency domains could be lost. Usually these methods allow to obtain good sources' reconstruction but it should be always taken considering their theoretical limitations.

4.4. Metrics of connectivity in EEG, MEG, and fMRI
4.4.1. Coherence
Coherence can be calculated for each frequency bin λ according to the equation:

$$\mathrm{Coh}_{xy}(\lambda) = |R_{xy}(\lambda)|^2 = \frac{|f_{xy}(\lambda)|^2}{f_{xx}(\lambda) f_{yy}(\lambda)}$$

which is an extension of Pearson's correlation coefficient (*R*) to complex number pairs. In this equation, f_{xx} and f_{yy} are the auto-spectra, and f_{xy} is the cross-spectrum of two signals *x* and *y* for a given frequency bin λ (Gerloff et al., 1998b; Bönstrup et al., 2018).Two nodes A and B (generating the signals *x* and *y*, respectively) can exhibit coherent activity because of emergent or stimulus/task/lesion-induced coupling of neuronal oscillatory activity but they can also be coherent because both nodes receive the same synchronizing input from a third node C (generating the signal *z*). This could, in practical terms, be a higher-order cognitive area or a lesioned brain section controlling two connected brain regions in a top-down organization. Such scenario can be probed by applying *partial coherence* analysis *which* provides a measure of the coupling between two nodes, after taking into account any linear interaction between two signals *x* and *y* and a third signal *z* which can be referred to as 'predictor'. Mathematically, the partial cross-spectra between *x* and *y*, with *z* as a predictor, are defined as:

$$f_{xy/z}(\lambda) = f_{xy}(\lambda) - \frac{f_{xz}(\lambda) f_{yz}(\lambda)}{f_{zz}(\lambda)}$$

where λ is the frequency bin under study and f denotes the spectral estimate of the EEG or MEG signals *x*, *y*, or *z* for a given frequency bin λ. The partial auto-spectra of *x,* with *z* being the predictor, are defined as:

$$f_{xx/z}(\lambda) = f_{xx}(\lambda) - \frac{|f_{xz}(\lambda)|^2}{f_{zz}(\lambda)}$$

The other partial auto-spectrum, $f_{yy/z}(\lambda)$, is defined likewise.

The actual partial coherence between the signals *z* and *y,* with *z* as a predictor, for the respective frequency bin λ, $pCoh_{xy}$ (λ), can then be estimated similarly to the ordinary coherence as:

$$\mathrm{pCoh}_{xy/z}(\lambda) = |R_{xy/z}(\lambda)|^2 = \frac{|f_{xy/z}(\lambda)|^2}{f_{xx/z}(\lambda) f_{yy/z}(\lambda)}$$

Coherence as well as partial coherence provides a measure of linear association, with values between 0 and 1. For example, if Coh_{xy} is high but $pCoh_{xy/z}$ (after removing the 'driving' influence of the third node C) is low, the interpretation would be that node C contributes substantially to the coupling between nodes A and B. If Coh_{xy} and $pCoh_{xy/z}$ are similar in magnitude, then a relevant influence of node C cannot be assumed. This is a relatively straightforward approach to get an impression about functional network interdependencies.

4.4.2. Mutual information

Mutual information (MI) is another metric of functional connectivity and similarly addresses the interdependence between two or more signals. However, in contrast to coherence, MI does not assume linearity of the interaction between the signals, i.e., it measures the linear and non-linear relationships (Kraskov et al., 2004). MI can be computed according to:

$$I(X,Y) = \sum_{y \in Y} \sum_{x \in X} p(x,y) \log \left(\frac{p(x,y)}{p(x)p(y)} \right)$$

where p(*x,y*) is the joint probability distribution function of the discrete variables X and Y, and p(*x*) and p(*y*) are the marginal probability distributions of these variables (Kumar et al., 2017). Of note, functional connectivity measures like Coh, pCoh, or MI cannot differentiate between direct and indirect connections. It is always possible that two regions of interest, showing high coherence, are not connected at all but influenced by a third region. This needs to be taken into account when interpreting the results.

4.4.3. Phase-locking value

Coherence cannot reliably separate amplitude and phase contributions. The phase relationship between two signals independent of the amplitudes of the respective signals can be quantified by phase-locking statistics. To compute the PLV, bandpass-filtered epochs are Hilbert-transformed, then the phase (φ) of the Hilbert-transformed data is extracted for all time bins (*t*), trials (*n=1,..., N*), and all electrodes (EEG), sensors (MEG), or sources (EEG, MEG) if the calculations are done in the source space (e.g., after beamforming and spatial filtering). The difference of the phases between two electrodes ($\Delta\varphi$) is then calculated at each time point *t*. The phase-locking value (PLV) is defined as the consistency of phase differences between two electrodes at a given time point *t*; it measures the inter-trial variability of the phase differences (Lachaux et al., 1999; Aydore et al., 2013), according to:

$$\mathrm{PLV}_t = \left| \frac{1}{N} \sum_{n=1}^{N} \mathrm{e}^{j\,\Delta\varphi\,(t)} \right|$$

where:

$$\Delta\varphi\,(t) = \varphi_{mk}(t) - \varphi_{nk}(t).$$

Here, *k* indexes the trial number and *m* and *n* index the first and second channels of interest, always for a given time point *t*. The PLV separates amplitude and phase, and is thus less

affected by amplitude variability of the power spectrum. PLV is less prone to be affected by volume conduction which represents one of the major confounding aspects for EEG (not for MEG) signal analysis.

4.4.4. Directed Transfer Function

From a physiological point of view, a matter of great interest is *directionality*, i.e., which node leads or lags in the interaction. One approach to address this is termed *Directed Transfer Function* (DTF) and requires multivariate autoregressive (MVAR) modeling of the epoched EEG (Kaminski et al., 1995) in the sense of Granger causality. In brief, every time point of each channel is predicted by the information that all the other channels' time series at previous time points offer. If knowledge of the past values of time series X significantly improves prediction of time series Y, one can assume that there is a causal relationship between them. However, it has to be borne in mind that even if X does not influence Y but Y influences X, the measured past values of X generally improve the prediction of Y, in particular if X is measured with a higher signal-to-noise ratio than Y. Importantly, this relationship is not reciprocal and thus allows assessing the direction of information flow (Bönstrup et al., 2014). The time lag is predefined as the model order. The MVAR model of order p can be described as:

$$\vec{Y}(t) = \sum_{k=1}^{p} A(k)\vec{Y}(t-k) + \overrightarrow{X(t)}$$

where $\vec{Y}(t)$is the observed EEG data at channel Y and time t, $\vec{X}(t)$ is the so-called innovation process, and $A(k)$ is the k^{th} autoregressive parameter, with p being the number of incorporated past time points. This gives a matrix of parameters $A_{x,y}(k)$ for each channel combination and time lag. This can be transformed from the time to the frequency domain in order to obtain derived measures in frequency space, which then can be described according to:

$$\mathrm{DTF}_{xy}(f) = \frac{|H_{xy}(f)|^2}{\sum_{y=1}^{n} |H_{xy}(f)|^2}$$

where H_{xy} is the transfer matrix of the system. It contains information about all relations between the signals of interest (including phase relations). The DTF_{xy} describes directional influences of channel x on channel y at frequency f. This directionality of information flow can then be interpreted as causal influence of the 'sending' brain area on the 'receiving' brain area. Multivariate autoregressive statistics can also be combined with the concept of partial coherence, which is then referred to as *partial directed coherence* (see, e.g.,Huang et al., 2016).

4.4.5. Dynamic causal modeling

The techniques and metrics described up to this point have predominantly been applied to electrophysiological signals, less so to the slower modulations of the BOLD signal for fMRI (Arfanakis et al., 2000; Xiong et al., 1999). Network analyses based on the BOLD signal have been developed using multiple methods such as ICA (Independent component analysis) related methods (for reviews see: Bressler and Menon, 2010; van den Heuvel and Hulshoff Pol, 2010; Avena-Koenigsberger et al., 2017) Among these methods are the hypothesis-driven computation of interactions in pre-defined networks derived from anatomical or functional *a priori* knowledge, such as structural equation or dynamic causal modeling (Buchel and Friston, 1997, Penny et al., 2004).

Dynamic causal modeling (DCM) allows for addressing causal interactions between distinct (predefined) brain regions by constructing and testing realistic models of interacting neuronal areas (Friston et al., 2003). That is, away from a whole-brain approach and hypothesis-independent testing of possible interactions, DCM needs always to build on an extended *a priori* knowledge. DCM aims at estimating the coupling between brain areas and how that coupling is influenced by changes of the experimental context. Starting from a neuronal model of interacting cortical regions, DCM adds a forward model of how neuronal or synaptic activity is transformed into a signal that can be measured by fMRI (BOLD) or EEG (or MEG). For fMRI, this includes a hemodynamic response model to explain how neuronal electric activity translates into BOLD changes. Besides its use on fMRI data (Friston et al., 2003, 2011, 2014), DCM can also be applied to EEG and MEG data (David et al., 2006, Kiebel et al., 2006). The multimodal use of DCM for fMRI and DCM for induced responses in EEG / MEG (DCM-IR) is challenging but –when the intrinsic differences of the methods are carefully taken into account– it can generate mutually confirmative results that might be more robust and give deeper insights into cortical physiology than separately (Bönstrup et al., 2016). Technically, in a Bayesian framework, DCM models the instantaneous change of a neuronal state vector z based on a neurodynamic forward model of how neuronal activity is transformed into the measured response. This can be described by:

$$\frac{dz}{dt} = \left(A + \sum_{j=1}^{m} u_j B^{(j)}\right) z + Cu$$

where t represents the continuous time and u the (j^{th}) experimental input. In DCM for fMRI, endogenous context-independent coupling among the different regions is described by the so-called A-matrix. Changes in coupling parameters that are caused by the experimental input (contextual modulators) are represented by the B-matrix. Finally, the C-matrix specifies which regions receive exogenous influences of inputs on neuronal activity. Parameters in the A, B and C-matrices are estimated during the model inversion process and describe the architecture and interactions among brain regions at the neuronal level.

For DCM, the choice of a proper experimental design is crucial because this approach was designed for explicitly testing specific hypotheses rather than for using it as an exploratory tool. For example, a straightforward experiment for DCM analysis would be a sensory stimulation that is applied in multiple perturbated ways in combination with another factor that changes systematically the context of the sensory-evoked responses. As Friston pointed out in his original paper, the former could be a variation of visually presented words and the latter could be either the cognitive set or simply time (i.e., change of context by learning / plasticity over time) (Friston et al., 2003). More recently, however, also a DCM for resting-state data has been proposed (Friston et al., 2014).

The model of DCM-IR (for MEG / EEG) assumes that the interactions between two brain regions in the frequency domain can be linear (within-frequency coupling) or non-linear (cross-frequency coupling) (Chen CC et al., 2008). In this model, the neuronal state vector z at region i is represented by spectral densities over k frequencies according to:

$$z_i(f,t) = \begin{bmatrix} z_i(f_1,t) \\ \dots \\ z_i(f_k,t) \end{bmatrix}$$

The event-related spectral signal changes are modeled as the response of distributed coupled electric sources to a spectral perturbation (Bönstrup et al., 2016).

In summary, DCM refers to 'effective' (causal) connectivity, addressing directional interactions between brain areas. It necessitates strict hypothesis-driven experimental designs and circumscribed, predefined neuronal network structures. In contrast, coherence, partial coherence, phase-locking value, mutual information analyses, or any other form of correlation analyses in the time or frequency domain relate to 'functional' connectivity, i.e., metrics of neuronal coupling that do not allow for conclusions on causal interactions or direct versus indirect pathways between nodes of interest. Functional connectivity measures can be supplemented by information on directionality if combined with DTF or other forms of MVAR-based computations (e.g., partial directed coherence).

4.5. Functional connectivity analysis with LORETA

EEG recordings can be used for estimating the neuronal electrical activity distribution (current density vector field) on the cortex. Time series of cortical electrical neuronal activity can be analyzed, for example, with the minimum-norm estimation method (MNE; Hämäläinen and Ilmoniemi, 1994) or LORETA, to estimate cortical connectivity, based on the following informal definition: "*Two places are functionally connected if their activity time series are similar*" (Worsley et al., 2005). However, from a formal point of view, there are many different ways to define *similarity* between signals. Here, the "exact low resolution electromagnetic tomography" or eLORETA method is introduced (Pascual-Marqui et al., 2011). The eLORETA algorithm is a linear inverse solution for EEG signals that has no localization error to point sources under ideal (noise-free; error-free volume-conductor modeling) conditions (Pascual-Marqui, 2002). The connectivity values are obtained by Lagged Linear Coherence algorithm as a measure of functional physiological connectivity. Based on the scalp-recorded electric potential distribution, eLORETA computes the cortical three-dimensional distribution of current density (Pascual-Marqui, 2007a, 2009). Several recent studies (Canuet et al., 2011; Barry et al., 2014; Aoki et al., 2015; Vecchio et al., 2014a, 2014b; Ikeda et al., 2015; Ramyead et al., 2015; Vecchio et al., 2015, 2016) supported the idea of an accurate source localization using eLORETA. However, the expected accuracy can be realized only if the assumptions (e.g., source being sufficiently point-like) of the sources are valid. Via an individual analysis, brain connectivity is computed by eLORETA in the regions of interest (ROIs) defined according to the available Brodmann areas (BA) for left and right hemispheres (Talairach and Tournoux, 1988). Intracortical Lagged Linear Coherence, extracted by "all nearest voxels" or those in a sphere of 19-mm radius, selected on the basis of the number of considered nodes (Pascual-Marqui, 2007b; Pascual-Marqui et al., 2011), is individually computed between all possible pairs of ROIs for each EEG frequency band (Kubicki et al., 1979; Niedermeyer and da Silva, 2005): delta, theta, alpha 1, alpha 2, beta 1, beta 2 and gamma. eLORETA current-density time series of each BA can be used to estimate functional connectivity; Lagged Linear Coherence (LagR) algorithm has been implemented in eLORETA as a measure of functional physiological connectivity not affected by volume conduction and low spatial resolution. For each EEG frequency, the mean connectivity matrix is computed between all frequency bins for each subject.

4.6. Describing network properties by graph-theoretical parameters

In order to describe properties of large, e.g., whole-brain networks the original empirical data can be represented in the form of a graph. Graph theory has been widely applied to MRI tractography (for a review see Crossley et al., 2016), but in this paragraph is mainly reviewed for applications in EEG/MEG analysis. This graph can be weighted or unweighted, and it can be directed or undirected. The first step is to decide what can be considered as a node, and what can be considered as a link (Stam, 2014; Miraglia et al., 2017).

Core measures of graph theory can be computed with http://www.brain-connectivity-toolbox.net and adapted by Matlab scripts (Vecchio et al., 2014b; Miraglia et al., 2015, 2016).

In such scripts, *segregation* refers to the degree to which network elements form separate clusters and correspond to clustering coefficient (*C*) (Rubinov and Sporns, 2010), while *integration* refers to the capacity of the network to become interconnected and exchange information (Sporns, 2013); it is defined by the characteristic path length (*L*) coefficient (Rubinov and Sporns, 2010). The mean clustering coefficient is computed for all nodes of the graph and then averaged. It is a measure for the tendency of network elements to form local clusters (de Haan W et al., 2009). Starting by the definition of *L*, the weighted characteristic path length L^wrepresents the shortest weighted path length between two nodes (Onnela et al., 2005; Rubinov and Sporns, 2010). Small-worldness (SW) parameter is defined as the ratio between normalized *C* and $L -C^w$ and $L^w -$ with respect to the frequency bands. For example, to obtain individual normalized measures, one can divide the values of the characteristic path length and of the clustering coefficient by the mean values obtained by the average values of each parameter in all EEG frequency bands of each subject. In this case, it should be stressed that a normalization of the data with respect to surrogate networks cannot be done due to the weighted values of the considered networks. The SW coefficient describes the balance between local connectedness and global integration of a network. SW organization is intermediate between that of random networks, the short overall path length which is associated with a low level of local clustering, and that of regular networks or lattices, and the high level of clustering which is accompanied by a long path length (Vecchio et al., 2014b). This means that nodes are linked through relatively few intermediate steps, and most nodes maintain few direct connections. Surrogate analysis plays a pivotal role for testing the significance of functional connections in both bivariate and multi-variate estimators; it also represents a significant methodological approach when applying a data-driven topological filtering scheme on statistically significant functional connections (Moharramipour et al., 2018).

Currently, network science is developing along a sophistication of network measures and models, introducing new concepts, such as cost-efficiency, hierarchical modularity, vulnerability to random or targeted attack, and the notion of rich clubs (as summarized in **Fig. 9**). An important challenge is to find simple yet meaningful ways to characterize brain networks while avoiding arbitrary choices and in addition to extract new diagnostic measures or biomarkers from network data (Stam, 2014).

Generally speaking, most of the studies on brain connectivity with various techniques are relatively weak because they do not report on inter- and/or intra-subject test-retest variability. In order to evaluate the within-subject test-retest variability (Vecchio et al., 2014a), statistical analysis was performed on normalized characteristic path length of EEG cortical sources for a 10 subjects group that accepted to come back for a second recording after about two weeks, introducing the factor Time (First and Second recording session). The statistical analyses showed no significant interaction including Time, highlighting the stability of the present methodology on “small world” analysis of EEG signal. More recently, findings from 3 recording sessions have been compared from 34 healthy subjects (mean age of 45 years) at one week distance one from the other. A between factors ANOVA was carried out: Frequency Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, and gamma) and Time (first, second and third recording) for the Small World parameter. The statistical analysis showed that the interaction including Time was not significant ($F(12, 396)=.48995$, $p=.92057$), highlighting the stability of the proposed parameters at least when carried out in clinically stable subjects. Recently, the importance of reliability studies based on repeat-scan sessions protocol of connectomics in any modality has been recognized with publication of a number of freely available papers and datasets (Zuo and Xing, 2014; Colclough et al., 2016; Dimitriadis et al., 2017, 2018).

4.7. The added value of multimodal connectivity analyses

Non-invasive connectivity measures derived from EEG, MEG, or fMRI, but also from various (i.e., paired-pulse non-invasive brain stimulation) NIBS paradigms, naturally address 'only' certain aspects of the actual neuronal network activity. EEG and MEG depict population signals that closely resemble local field potential activity. fMRI measures a very indirect signal, which is composed of oxygen consumption and blood-flow changes as a reflection of transient modifications of energy consumption following similar changes in local neuronal firing. TMS probes responses elicited by non-physiological activation of the stimulated neuronal populations. In all of these studies, anatomical constraints to network structures should be taken into account. There are multiple ways to get around spurious results and wrong conclusions, starting with basic precautions like sufficient sample sizes and well-controlled experimental variables. However, this cannot exclude that the method selected has an inherent bias. For example, interregional inhibitory interactions are readily detected by TMS techniques (Gerloff et al., 1998a; Wahl et al., 2007), can regularly be modeled by DCM for fMRI (Rehme et al., 2011), but are less easily seen in EEG metrics (Bönstrup et al., 2016). Any network dynamics of neuronal firing that occur at the millisecond time scale which are separate, but adjacent in time will entirely or partly escape blood-flow related measurements like fMRI (or positron emission tomography or near-infrared spectroscopy) due to the time delay between neuronal firing and BOLD signal production and it smoothed rising/decaying slope unless they cause a secondary, sustained net effect on neuronal activity over longer periods of time (seconds to minutes at least); because of this, the time-hierarchy of sources (nodes) connected in a network supporting a given brain activity cannot be easily discriminated by flow-metabolic techniques when the internode activation intervals are too short. Similarly, network dynamics which do not require changes in energy consumption (i.e. phase locking-unlocking with a stable firing frequency) do not produce a BOLD signal in fMRI. In fact, 'coding by synchrony' is possible in the absence of changes in energy consumption and of significant net changes of averaged neuronal population activity over time (Singer, 1999b). This implies that selecting *a priori* networks on the basis of significantly enhanced local activation may miss relevant network nodes. EEG and MEG (or invasive electrophysiological methods with millisecond resolution) better address this type of information coding in neuronal networks. On the other hand, neurophysiological techniques has a well-known limitation, that is the lack of information about locations of the brain sources: coupling between scalp EEG signals do not necessarily imply coupling between the underlying neural sources of EEG. In fact, scalp EEG recordings reveal not only averaged post-synaptic activity from localized cortical areas but also the overlapping activity of all coherent neural sources situated anywhere in the brain, together with the signal mixing owing to the volume conductance and reference electrode: this makes the interpretation of the sensor-space synchronization measures and evaluation pf large-scale connectivity difficult. Moreover, as repeatedly mentioned before, EEG and MEG are blind to most of the subcortical neuronal activity, including subcortical-cortical connections and those brain relays which are of paramount importance both in healthy and in diseased conditions like the hippocampal formation, the temporo-mesial region and the limbic areas. To minimize the bias inherent in each technique before drawing extensive conclusions on the physiology of neuronal networks, it may therefore be advisable to integrate two or more techniques –by carefully considering what they really reflect and do not reflect in brain function- and attempt to arrive at interpretations that hold true independent of the network-probing technique used. Mutually informative data have been derived from combinations of EEG and fMRI (Bönstrup et al., 2016), MEG and fMRI (Ahlfors et al., 1999), TMS and fMRI (Volz et al., 2014) but also from TMS and structural MRI metrics like DTI (Wahl et al., 2007, 2016) and many others (Nguyen et al., 2014; Klamer et al., 2015; Petro et al., 2017). With respect to modeling of neuronal networks, e.g., coupled oscillator models, informing functional connectivity matrices derived

from EEG recordings integrated by structural information from DTI appears to be suitable and improves the model quality (Finger et al., 2016).

5. Non-invasive brain stimulation (NIBS) methods for testing brain connectivity

5.1. MEP, I-waves

The motor evoked potential (MEP) is recorded from a target muscle by surface electromyography (EMG) and reflects the activation of corticospinal cells in primary motor cortex (M1) by single-pulse transcranial magnetic stimulation (spTMS) (Barker et al., 1985). Therefore, the MEP is a marker of the connectivity between motor cortex, the alpha spinal motoneurons and muscle. The MEP amplitude increases sigmoidally with stimulation intensity (Hess et al., 1987; Devanne et al., 1997). Voluntary target muscle activation shifts this input-output curve to the left (Hess et al., 1987; Devanne et al., 1997; Chen et al., 2008). It is important to note that spTMS typically results in multiple descending corticospinal volleys, an early D-wave (for direct activation) followed by I-waves (for indirect, i.e., synaptic activation) (Amassian et al., 1987). The neuronal mechanisms underlying the different I-waves are still unclear (Ziemann and Rothwell, 2000; Triesch et al., 2015). Several hypotheses are being discussed, ranging from oscillating properties of the corticospinal cells to distinct circuits of excitatory and inhibitory interneurons impacting on corticospinal target cells (Kernell and Chien-Ping, 1967; Sakai et al., 1997; Di Lazzaro et al., 1998a).

The multiple descending, stimulus-triggered volleys are spatially and temporally integrated at spinal alpha motoneurons. If the summed excitatory post-synaptic evoked potentials reach the firing threshold, an action potential is generated that leads to excitation of the corresponding motor unit. TMS at low intensity activates primarily small motor units that are also first recruited with voluntary activation according with Henneman's size principle (Rossini et al., 1995). In summary, MEP measurements assess connectivity between a pathway consisting of cortical interneurons, cortico-motoneuronal neurons originating from layer V of M1, and alpha motoneurons in spinal cord and muscle (Lemon, 2008). Excitation of cortical interneurons and cortico-motoneurons is controlled by inhibitory interneurons (Ilic et al., 2002; Kawaguchi and Kondo, 2002; Markram et al., 2004). Therefore, MEP amplitude is influenced by the balance of excitation and inhibition in M1, which can be highly abnormal in neurological diseases and affected by CNS-active drugs (Ziemann et al., 2015). Also, the instantaneous state of M1 excitability impacts MEP amplitude, as has been revealed by recent measurements that combined EEG recordings of endogenous brain oscillations and the underlying connectivity networks with spTMS, as reported in previous papers (Mäki and Ilmoniemi, 2010; Bergmann et al., 2012; Keil et al., 2014; Ferreri et al., 2014; Giambattistelli et al., 2014; Triesch et al., 2015; Zrenner et al., 2018), and summarized in **Fig. 10**(Ferreri et al., 2014); moreover this impact is age dependent (Ferreri et al., 2017a).

5.2. Paired-pulse TMS protocols

The paired-pulse TMS (ppTMS) protocols summarized here (**Fig. 11**) are defined by two pulses delivered through the same stimulating coil. These methods can be used to look at connectivity between neurons in a cortical column or in close neighboring brain areas. Stimulating over the motor cortex, if the first (conditioning) pulse is subthreshold for M1 excitation, the second (test) pulse suprathreshold, and if the interstimulus interval (ISI) is 1–5 ms, then the test MEP is inhibited, (short-interval intracortical inhibition; SICIKujirai et al., 1993). SICI can be elicited by first pulses of very low intensity, indicating that, according to a "cortical size principle", small inhibitory interneurons are activated and mediate this effect (Kujirai et al., 1993; Ziemann et al., 1996; Ilic et al., 2002). This is supported –at the 'micro' connectivity level– by pharmacological studies that reported increase of SICI by

benzodiazepines, i.e., positive allosteric modulators at $GABA_A$ receptors (Ziemann et al., 2015). However, zolpidem with selective affinity to the alpha-1-subunit-bearing subtype of the $GABA_A$ receptor, did not enhance SICI (Di Lazzaro et al., 2007), strongly suggesting that SICI is largely mediated by the alpha-2-subunit-bearing subtype of the $GABA_A$ receptor and, therefore, by Chandelier cells that make predominantly synaptic contacts with the pyramidal cells axonal hillock (Kawaguchi and Kondo, 2002).

Experiments with two coils on top of each other demonstrated that SICI is local, i.e., it rapidly declined when moving the stimulating coil delivering the first stimulus away from the motor hot spot (Ziemann et al., 1996). Furthermore, SICI was independent of the orientation of the coil delivering the first stimulus, suggesting that the activated inhibitory interneurons do not have specific excitability characteristics linked to a particular stimulus orientation (Ziemann et al., 1996). Altogether, a bulk of scientific findings support –including epidural recordings– the concept that SICI is a marker of effective connectivity between local inhibitory interneurons and cortico-motoneuronal cells, and/or the excitatory pyramidal cells projecting onto cortico-motoneuronal cells (Di Lazzaro et al., 1998b; Ilic et al., 2002).

A ppTMS protocol with longer ISIs of 7–15 ms typically results in MEP facilitation, referred to as intracortical facilitation (ICF) (Kujirai et al., 1993; Ziemann et al., 1996) which is supposed to be a marker of effective connectivity between excitatory interneurons and cortico-motoneuronal cells.

A ppTMS protocol that uses a suprathreshold first and a subthreshold second stimulus (Ziemann et al., 1998), or two threshold stimuli (Tokimura et al., 1996) at short ISIs of 0.5–4.5 ms results in MEP facilitation at discrete ISIs of 1.1–1.5 ms, 2.3–2.9 ms and 4.1–4.5 ms, with no significant facilitation in between (Ziemann et al., 1998). This is referred to as short-interval intracortical facilitation (SICF) with 3 peaks having an inter-peak interval of approximately 1.5 ms (equivalent to 660 Hz) reminiscent of the interval separating two successive I-waves (see above Ziemann and Rothwell, 2000, Ziemann et al., 1998).

A ppTMS protocol that uses two suprathreshold pulses at ISIs of 50–150 ms results in MEP inhibition and is referred to as long-interval intracortical inhibition (LICI) (Valls-Sole et al., 1992). LICI is enhanced by baclofen, a selective agonist at the $GABA_B$ receptor (McDonnell et al., 2006); moreover, LICI duration is compatible with $GABA_B$ receptor-mediated inhibitory post-synaptic potentials (Connors et al., 1988). Evidence strongly suggests that LICI is a marker of effective connectivity between inhibitory interneurons and cortico-motoneuronal cells and/or the excitatory pyramidal cells projecting onto cortico-motoneuronal cells, through the $GABA_B$ receptor (Di Lazzaro et al., 2002).

The same ppTMS protocol of two suprathreshold pulses at ISIs of around 200–250 ms results in MEP facilitation, termed late cortical disinhibition (LCD) (Cash et al., 2010, Cash et al., 2011). The mechanism underlying LCD is likely $GABA_B$ receptor mediated presynaptic autoinhibition of $GABA_A$ergic inhibitory interneurons, as has been demonstrated in paired-pulse depression experiments (Deisz, 1999). Importantly, it was also shown that the duration of $GABA_B$ receptor mediated inhibitory post-synaptic potentials is shorter than the pre-synaptic autoinhibition (Deisz, 1999). In summary, LCD likely is a marker of $GABA_B$ergic pre-synaptic autoinhibition of inhibitory interneurons in M1.

Finally, peripheral nerve electrical stimulation (e.g., of the median nerve at the wrist) followed by suprathreshold spTMS of contralateral M1 provokes a MEP inhibition at ISIs of the individual N20 wave latency of the median nerve somatosensory evoked potential plus 0–4 ms while MEP facilitation is observed with ISIs of N20 wave latency plus 6–10 ms (Mariorenzi et al., 1991; Tokimura et al., 2000). The MEP inhibition is referred to as short-latency afferent inhibition (SAI), and is associated with reduction of late I-waves but not the I1-wave in epidural spinal recordings (Tokimura et al., 2000).

5.3. Paired-coil TMS protocols

Paired-coil TMS (pcTMS) protocols deliver TMS pulses through separate coils to different sites of the brain and enable investigation of effective connectivity/mutual influence between separate brain areas; M1 and other, typically motor-related, areas of the brain, such as the contralateral M1, other frontal or parietal areas, and the cerebellum have been investigated by this technique (Hallett et al., 2017). In the pcTMS protocols, one stimulating coil is placed over the target M1 to elicit the test MEPs, and another one over a different area to test the effect of conditioning pulses on test MEP amplitude. Key parameters are timing and intensity of the conditioning stimulus (CS), in addition to placement of the conditioning TMS coil. Test stimulus (TS) intensity can also have an impact on the results.

A suprathreshold CS delivered to the M1 on one side given at ISI of 6–30 ms prior to TS of the contralateral M1 results in inhibition of the test MEP (Ferbert et al., 1992). Maximum inhibition occurs at an ISI of around 10 ms, later termed short-latency interhemispheric inhibition (SIHI), which is mediated by transcallosal fibers projecting onto inhibitory interneurons in the test M1(Ferbert et al., 1992; Daskalakis et al., 2002; Kukaswadia et al., 2005; Müller-Dahlhaus et al., 2008; Ni et al., 2009; Tsutsumi et al., 2012). In addition to SIHI, other interhemispheric interactions have been reported, in particular, long-latency interhemispheric inhibition (LIHI) and interhemispheric facilitation (IHF). Except for the ISI, which is typically around 40–50 ms (Gerloff et al., 1998a), LIHI can be tested in the same way as SIHI. LIHI is believed to be mediated by a different mechanism compared to SIHI. Although both seem to be associated with $GABA_B$ receptor mediated inhibition (Daskalakis et al., 2002; Kukaswadia et al., 2005), only LIHI is related to the ipsilateral silent period, another spTMS measure of interhemispheric inhibition (Chen et al., 2003). In summary, it is currently thought that SIHI, LIHI and IHF are mediated through glutamatergic excitatory transcallosal M1-M1 connections, and that interhemispheric inhibition occurs through activation of interposed inhibitory interneurons in the M1 of the test hemisphere (Daskalakis et al., 2002; Ni et al., 2009).

Conditioning stimulation of various other cortical areas such as dorsal premotor cortex (PMd), ventral premotor cortex (PMv), supplementary motor area (SMA; Oliveri et al., 2003), and posterior parietal cortex (PPC) can also affect MEP amplitudes elicited by TS of the test M1. Anatomical connectivity of these areas with M1 is reported in animal studies (Muakkassa et al., 1979; Ghosh et al., 1987; Ghosh and Porter, 1988; Luppino et al., 1993; Stepniewska et al., 1993; Tokuno et al., 2000; Dum and Strick, 2005; Dea et al., 2016; Quessy et al., 2016), providing the rationale for testing effective connectivity in humans using pcTMS protocols. Since the ipsilateral PMd is adjacent to M1, revealing ipsilateral PMd–M1 connectivity was not straightforward due to difficulties in placing two coils appropriately on the scalp (Civardi et al., 2001; Koch et al., 2007b; Bäumer et al., 2009). More recently, Groppa et al. (2012) introduced a specially designed small coil with decentralized coil windings to overcome this problem, reporting MEP facilitation if CS was given 2.4–2.8 ms or 4.4 ms after the TS. In contrast, there is cumulative evidence on inhibitory effective connectivity between the contralateral PMd and M1. Mochizuki et al. reported MEP inhibition if the CS was given 8 ms prior to the TS (Mochizuki et al., 2004), which was confirmed by subsequent studies (Koch et al., 2007b, Ni et al., 2009

The SMA is another important secondary motor area, with predominantly facilitatory projections to M1 (Tokuno et al., 2000). Congruent with this observation, two pcTMS studies reported MEP facilitation by SMA conditioning. Arai et al. (2012) used a highly focal small CS coil over SMA to avoid current spread to the M1, and reported that relatively strong CS (140% of active motor threshold) resulted in MEP facilitation at an ISI of 6 ms. This facilitation was coil-orientation specific and observed only if the induced current in the brain was directed from medial-to-lateral towards the stimulated SMA. Using a weaker CS, another study showed no effect on MEP amplitude but a facilitatory effect on SICF (Shirota et al.,

2012) providing evidence that conditioning stimulation of SMA interacts with the excitatory interneuron circuitry in M1 responsible for the generation of I-waves.
PPC is a part of the fronto-parietal network that is important for visuomotor planning. Koch et al. revealed MEP facilitation at an ISI of 4 ms, specifically at a CS intensity of 90% resting motor threshold, but not at lower or higher CS intensities (Koch et al., 2007a). A more recent study revealed both facilitatory and inhibitory effective connectivity, dependent on the exact PPC stimulation site (Karabanov et al., 2013), suggesting that different sub-divisions of the PPC play diverse roles in the fronto-parietal network.
For conditioning stimulation of the cerebellum, the main target is the cerebello-dentato-thalamo-motor cortical pathway. Within this network,Purkinje cells in the cerebellar cortex send inhibitory input to the dentate nucleus, which in turn has a di-synaptic excitatory connection with the contralateral M1 through the ventrolateral nucleus of the thalamus with a net inhibitory effect(Ito et al., 1970; Allen and Tsukahara, 1974). Ugawa et al. (1991, 1995) were the first to report cerebellar inhibition (CBI), probably activating this pathway. CBI is observed when the CS to the cerebellum precedes the TS of contralateral M1 by 5-7 ms, with a typical CS intensity of 90–95% of the active motor threshold to directly activate the pyramidal tract at the level of the pyramidal decussation using the double-cone coil. This hypothesis of net effect was approved by several cerebellar stimulation studies in patients with ataxia (Ugawa et al., 1994, 1997). A focal figure-of-eight coil would predominantly activate peripheral components of the cervico-brachial plexus near the coil rather than the cerebellum, resulting in another type of inhibition starting at slightly longer ISIs (7–8 ms) than the CBI, and potentially contaminating CBI at these longer ISIs (Werhahn et al., 1996). With enough caution about these factors, CBI can provide a unique opportunity to test effective connectivity from cerebellum to contralateral M1 through the cerebello-dentato-thalamo-motor cortical projection.
The recently developed *multilocus* TMS (mTMS; Koponen et al., 2018), which allows one to electronically adjust the location of the stimulated cortical location, will enable new kinds of pcTMS thanks to the possibility to stimulate also close-by cortical targets at programmable time intervals and intensities. Preliminary results show that (Nieminen et al., 2017) short-distance (0-30 mm) or lateral inhibition depends both on ISI and the distance between CS and TS targets.

5.4. Combined TMS approaches for testing cortico-cortical effective connectivity

Effective connectivity includes a definition of causality, which cannot be provided by techniques like high-density EEG and fMRI *per se*. Obtaining measures of effective connectivity with high-density EEG requires in fact complex causal models based on pre-existing data and the inferential power of such techniques on cortical effective connectivity relies on a priori assumptions about the involved network and the validity of the implemented model. In this perspective on the other hand, brain responses to TMS are intrinsically causal (Paus, 2005) even if not entirely “natural” and behavioral effects that follow the perturbation may be immediately detected/reported. Then, the online combination of EEG with TMS, due to the ability of EEG to detect changes of neuronal activities evoked by magnetic perturbation in a timescale of milliseconds, can return unprecedented hints on the functional properties of human cortical circuits in health and disease (Siebner et al., 2009; Ziemann, 2011).
Only when a TMS-compatible EEG amplifier is employed, electromagnetic artifacts caused by the TMS discharge are prevented (Virtanen et al., 1999; Ilmoniemi and Kičić, 2010). Besides the electromagnetic TMS-evoked artifacts, TEPs can reliably reflect genuine responses of cortical circuits to TMS provided that biological artifacts, such as somatosensory or auditory evoked potentials, are appropriately reduced or abolished (Gosseries et al., 2015) and state-of-the-art methodologies are applied to minimize confounding factors (Casarotto et al., 2010; Rogasch et al., 2014). Moreover, the TMS-evoked muscle artifacts constitute a

major challenge with TMS–EEG when areas below cranial muscles are stimulated (Mutanen et al., 2013) as well as secondary to reflex muscle responses due to cranial nerves excitation. A large number of studies have been published as to how these artifacts could be filtered from the signal. One attractive alternative is Independent Component Analysis (ICA; Korhonen et al., 2011), but it suffers in this context from the fact that TEPs and muscle artifacts are not independent. Fortunately, more effective methods have been developed to solve the problem (e.g., Mäki and Ilmoniemi, 2011; Ilmoniemi et al., 2015; Mutanen et al., 2018). Finally, in order to obtain reproducible and reliable TMS–EEG measurements, it is necessary to use a neuronavigation system that allows to precisely target desired cortical locations, to keep the stimulation parameters constant over different sessions (Casarotto et al., 2010; Hannula and Ilmoniemi, 2017). TEPs can be used to reliably keep track of cortical excitability and effective connectivity in both research and clinical settings (Ziemann, 2011; Rossini et al., 2015).

Once the appropriate equipment is employed and the correct experimental procedures are implemented TMS–EEG coregistration (Cracco et al., 1989; Ilmoniemi et al., 1997) contributes estimating fundamental indices of cortical functioning (Bonato et al., 2006; Ilmoniemi and Kicic, 2010; Rogasch and Fitzgerald, 2013) and discriminating causal interactions from mere temporal correlations.

TMS-evoked EEG potentials (TEPs) occurring in the first 20–40 ms after the TMS pulse most likely reflect the responses of cortical circuits excited underneath the stimulator (Mueller et al., 2014; Li et al., 2017). On the contrary, later TEPs result from the propagation of the initial response to TMS to remote cortical circuits (Massimini et al., 2005; Bonato et al., 2006; Ferreri at al., 2011). Thus, to keep track of cortical excitability, defined as the electrical reactivity of the cerebral cortex to a direct perturbation, one should measure the slope and amplitude of the very early TEPs. To capture more global features of cortical excitability, the analysis of TEPs could be carried out also in the frequency and time-frequency domains. More in detail, TMS–EEG studies showed that the human cerebral cortical areas react differently during non-REM slow wave sleep compared to wakefulness (Massimini et al., 2005, Bergmann et al., 2012), that cortico-thalamic modules generate electrical responses with a regionally specific natural frequency (Rosanova et al., 2009; Ferrarelli et al., 2012), that cortical excitability changes are ‘naturally’ present during the day (Huber et al., 2013; Ly et al., 2016), during cortical development (Määttä et al., 2017) and physiological aging (Ferreri et al., 2017b). Moreover, TEPs are affected by CNS-active drugs (Premoli et al., 2014; Darmani et al., 2016; Premoli et al., 2017; Casarotto et al., 2018), alcohol use (Kähkönen et al. 2001) and abuse (Kaarre et al., 2018), and by psychiatric and neurological disorders, such as schizophrenia (Ferrarelli et al., 2012), depression (Canali et al., 2015), Alzheimer’s disease (Casarotto et al., 2011; Ferreri et al., 2016), or epilepsy (Kimiskidis et al., 2017).

Since the beginning , TEPs were used to measure cortico-cortical connectivity, such as interhemispheric propagation time (Cracco et al., 1989). However, measuring effective connectivity within cortical circuits by means of TMS–EEG is challenging since the local and remote cortical responses to TMS arise from excitation of axons in both orthodromic and antidromic directions regardless of their physiological “directionality” (Ilmoniemi and Kicic, 2010). Most important, localization of scalp EEG potentials is strongly affected by electrode positioning for TEP recordings and volume conduction and may lead to computation of wrong connectivity patterns (van den Broek et al., 1998; Cohen, 2017). For this reason, a reliable assessment of cortical effective connectivity must be conducted at the level of cortical sources that generate TEPs (Schoffelen and Gross, 2009). For instance, in the first seminal TMS–EEG study (Ilmoniemi et al., 1997), TEPs after stimulation of the primary motor and visual cortical areas were analyzed at the scalp and cortical levels providing the first non-invasive measures of cortical excitability and effective connectivity in humans. Later on,

using a similar approach, Massimini and colleagues observed that cortical effective connectivity collapses in healthy subjects during non-REM slow wave sleep, when consciousness physiologically fades away, despite preserved cortical excitability (Massimini et al., 2005). The same research group has developed a semi-automatic procedure to analyze TMS-EEG data, which provides three indices as readouts: significant current density (SCD), phase-locking (PL), and significant current scattering (SCS) (Casali et al., 2010). They showed that cortical effective connectivity breaks down during unconscious states induced by deep sedation (Ferrarelli et al., 2010; Sarasso et al., 2015) or by severe brain lesions (Rosanova et al., 2012; Ragazzoni et al., 2013; Rosanova et al., 2018). Accordingly, indices of cortical effective connectivity based on TMS–EEG measurements recover when consciousness returns, but behavioral responses are still absent or inconsistent, such as during dreaming (Massimini et al., 2010), ketamine anesthesia (Sarasso et al., 2015), Minimally Conscious State (MCS), and emergence from MCS (**Fig. 12**; adapted from Rosanova et al., 2012).

Another metric derived from TMS–EEG measurements is able to detect the joint presence of cortical differentiation and cortical integration (Casali et al., 2013). The index, termed Perturbational Complexity Index (PCI) is computed in two steps: (i) a perturbation of the cortex with TMS to trigger causal and distributed interactions within brain circuits (ii) a compression of the cortical responses computed at the source level to measure their algorithmic complexity (Casarotto et al., 2016).

Assessment of cortical effective connectivity based on TMS–EEG recordings can also be applied to address cognitive neuroscience issues such as the mechanisms underlying attention shifts (Morishima et al., 2009), or the modulation of language circuits by other non-invasive brain stimulation techniques (Pisoni et al., 2018). On the same line, future studies should fully exploit the potential of TMS–EEG to extensively and automatically map cortical circuits (Harquel et al., 2016) in order to measure effective connectivity in dysfunctional brains (Ferrarelli et al., 2008, Adhikari et al., 2017). This approach can hopefully pave the way to novel rehabilitative treatments for brain disorders that will be aimed at promoting adaptive rather than maladaptive processes in response to neurological or psychiatric diseases (Fornito et al., 2015).

A major challenge with TMS–EEG is constituted by the huge muscle artifacts when areas below cranial muscles are stimulated (Mutanen et al., 2013) as well as secondary to reflex muscle responses due to cranial nerves excitation. A large number of studies have been published as to how these artifacts could be filtered from the signal. One attractive alternative is Independent Component Analysis (ICA; Korhonen et al., 2011), but it suffers in this context from the fact that TEPs and muscle artifacts are not independent. Fortunately, more effective methods have been developed to solve the problem (e.g., Mäki and Ilmoniemi, 2011; Ilmoniemi et al., 2015; Mutanen et al., 2018).

Another TMS approach is its combination with fMRI for the exploration of connectivity. As compared to EEG, relevant advantages of TMS-fMRI include better spatial resolution, and the option to explore also cortico-subcortical connectivity with enhanced reliability. The main shortcoming of TMS-fMRI is however its relatively poor temporal resolution, which limits opportunities to explore fast oscillation-based dynamic alterations of connectivity with this technique. This does however not exclude to obtain information about dynamic task-related alterations of connectivity in general, as shown for motor cortical networks (Bestmann et al., 2008), but also the interplay between large-scale network interactions relevant for cognitive and emotional processing (Chen et al., 2013). Thus both tools fulfill partially complimentary needs, regarding exploration of functional connectivity in the human brain, and combination of EEG with fMRI and brain stimulation might be a future direction worthwhile to explore.

Repetitive (rTMS) and patterned type TMS (i.e. theta-burst TMS) is now considered an advantageous probe to test brain networks underlying cognitive functions since the use of

TMS follows the rule of inference. If cortical area A is involved in cognitive process B and is not involved in process C, perturbation of the activity of area A will result in altered performance in B and not C. Thus, for deductive reasoning, area A plays a causal role in the performance of B. Moreover, TMS can be safely repeated in subjects on different occasions, eventually allowing an intra-lab or between-lab retest of a given experimental hypothesis. Finally, in some specific fields, as memory tasks requiring a two-stage cognitive process (i.e., encoding and later retrieval of items), TMS allows to tease apart the effects on one of these two tasks more easily than in the case of lesion studies (e.g., Rossi et al., 2001; 2004).

Because information processing of higher brain functions is integrated within several parallel distributed networks involving "nodes" in many cortical areas, a single pulse is often inadequate to interfere with the brain activity at a behaviorally relevant level, although a very first example of TMS use outside the motor cortex used single pulses to transiently suppress the visual perception, by stimulating the occipital cortex about 80-100 msec after the presentation of the visual stimulus (Amassian et al., 1989) or producing a transient "neglect" to a sensory hand stimulation (Oliveri et al., 1999, 2000). In this context TMS may be used as a tool to investigate and understand the role and timing of the involvement of a target area in a specific performance (Walsh and Cowey, 2000), the contribution of different sites to different aspects of a cognitive function (Terao et al., 2001; Robertson et al., 2003), the relative timing of the contribution of two or more areas to task performance and the function of intracortical and transcallosal connectivity (Jahanshahi and Rothwell, 2000). In short, what information is processed in a given brain network, and when does this processing occur. In general, the possibility of understanding the location, timing (i.e., cognitive chronometry) (Walsh et al., 2006) and functional relevance of a given node activity within a network underlying cortical functions makes rTMS an essential technique mainly in perception and cognitive research.

In general, it should be taken into account that at present the application of non-invasive brain stimulation approaches – including TMS, but also tDCS/tACS, which is introduced in the next section - to explore functional connectivity is still in its early days. Major approaches include exploration of spatio-temporal maps of brain activity alterations elicited by stimulation of a specific area, and refer to the whole brain, or specific interactions between a seed region of interest, and remaining structures. Network stimulation involving not only stimulation of a single hub, which indirectly alters network activity, but of a larger set of relevant areas, has rarely been conducted. Double coil approaches for TMS, and specific tACS protocols (see below) are exceptions, and might pave the way to more complex brain stimulation protocols in future to explore the dynamics and causality of functional connectivity in larger detail.

5.5. tDCS and tACS

Tonic or oscillatory stimulation with weak electrical currents, labelled transcranial direct and alternating current stimulation (tDCS, tACS), which are subsumed under the general term transcranial electrical stimulation (tES), induces alterations of cortical activity and excitability via subthreshold modulation of neuronal membrane potentials; prolonged stimulation can generate neuroplastic after-effects (Nitsche et al., 2008; Stagg and Nitsche, 2011). However, tES can be also valuable in inducing and probing connectivity of the human brain, including its relevance for psychological and behavioral processes. Hereby, (a) controlled modulation of regional cortical activity and excitability by tES in combination with neuroimaging or TMS can reveal specific functional connections of the targeted areas, (b) combination of stimulation with cognitive or motor processes and neuroimaging approaches can reveal the relevance of the targeted area for task-related functional connections, and (c) tES based on connectivity data obtained during task performance can be used to explore the causal relevance of respective connections for performance.

For revealing functional connections of a targeted cortical area tDCS studies have been conducted, mainly to explore motor network connectivity. Combination of tDCS with fMRI showed that activation of the primary motor cortex via tDCS enhanced functional connectivity of this target area with the premotor, and parietal cortex, but also with subcortical areas like the ipsilateral thalamus (Polania et al., 2011b; Polania et al., 2012b). Furthermore, combining tDCS with TMS demonstrated that tDCS over the premotor cortex can alter SICF and SICI presumably by altering premotor-M1 connectivity, while corticospinal excitability as tested by single-pulse TMS over M1, which most likely is elicited by stimulation of intrinsic pyramidal tract neurons, was not altered (Boros et al., 2008). Similar effects on M1 excitability, tested by alterations of parieto-motor effective connectivity by a double coil approach, were revealed for posterior parietal cortex tDCS (Rivera-Urbina et al., 2015). One advantage to use brain stimulation approaches such as tDCS to probe connectivity is their specificity, i.e., the restrictedness of stimulation to a pre-defined target area, as compared to task-related activation, which in most cases goes along with multi-modal brain area activation. This requires, however, specific intervention protocols, including computational model-based stimulation approaches, and use of small area electrodes (which, however, decreases the depth and amount of current reaching the underlying cortex). Unfortunately, most of the studies did not use a control condition exploring eventual effects of real stimulation of a non-target brain area in order to demonstrate a site-specific effect. Taking these caveats into account, relative specific effects of the stimulation, dependent on electrode position, can be expected, and help to define connectivity of the targeted brain network (Nitsche et al., 2007, Boros et al., 2008, Rivera-Urbina et al., 2015). Beyond these purely physiological measures, tDCS can also be used to explore the relevance of a targeted area for task-related connectivity. The concept here is to modulate activity and/or excitability of the target area, and then to explore effects on task-related functional connectivity by functional imaging approaches. Polania et al. (2011a) conducted an experiment, in which resting state EEG and task-related EEG during finger tapping were obtained before and after anodal tDCS over the primary motor cortex. They showed that tDCS alone had only minor effects on connectivity of the resting state EEG, but that task-related connectivity, specifically in the high gamma frequency band, between motor, premotor, and sensorimotor areas were enhanced after tDCS. For all other frequency bands, the tDCS effects on connectivity were less clear and not focused on areas involved in motor task performance. Thus, tDCS can be used as a probe to specifically enhance task-relevant functional connectivity.

Finally, tES can be used as a tool to specifically modulate physiological processes underlying functional connectivity, and thus probe the relevance of connectivity for psychological and behavioral processes. For functional connectivity, temporal association of oscillatory brain activity, so-called “binding” processes, are thought to play a crucial role. Thus, synchronizing the cycling firing of remote, but functionally connected areas should improve performance, whereas desynchronization of this distributed activity should have detrimental effects. For such a modulation of oscillatory brain activity, transcranial alternating current stimulation (tACS) is a versatile tool. For delayed letter discrimination, i.e., a working memory process, it has been suggested that left-hemispheric fronto-parietal interactions play a crucial role. Polania and co-workers (2012) tested the causal relevance of this connection for working memory performance using tACS. During task performance, activity of fronto-parietal areas in the theta frequency band was enhanced. Furthermore, about 200 ms after stimulus presentation, activity in this frequency range started to synchronize between fronto-parietal areas. Moreover, stronger synchronization was associated with better task performance. Thus, it was hypothesized that not only enhanced theta activity of left hemispheric prefrontal and parietal areas, but also their synchronization was causally related to task performance. This was directly tested by delivering tACS over the prefrontal and parietal target areas during task performance. Real or sham tACS with a frequency of 6 Hz was applied in phase or out of

phase, and thus in synchronized or desynchronized mode. In accordance with expectations, synchronized tACS enhanced, whereas desynchronized tACS reduced working memory performance relative to the sham stimulation condition. Moreover, these effects were specific for theta frequency stimulation, since a control experiment, in which gamma frequency tACS was applied, had no effect. This paradigmatic experiment demonstrated how tACS can be used to explore the relevance of functional (in this case frequency-specific) connectivity in a distributed neuronal network for task performance. Ideally, the stimulation experiment would have included also EEG recordings concurrent with tACS (Helfrich et al., 2014; Voss et al., 2014); the combination of tACS with EEG recordings will make it possible to explore physiological and cognitive stimulation effects in the same experiment, and will help to derive causality between connectivity and function more directly in future studies.

Taken together, the examples given here posit tES as a valuable tool for exploring connectivity in the human brain, including its behavioral relevance. tES can be used to induce/enhance connectivity originating from a specific area and, thus, to characterize connections independent from complex, often multi-modal, task-related activation. It furthermore can be useful to explore the contribution of a target area to a task-dependently activated network, and it can be applied to explore the causal relevance of functional connectivity for task performance, including specific features, such as frequency-dependency, and mode of synchronization. One important aspect of tES is its primary neuromodulatory effect. In contrast to TMS, it does not induce, but modifies spontaneous cerebral activity. Dependent on the context to be explored, this can be advantageous or disadvantageous. Thus, the non-disruptive online effects of tES might be crucial for its bi-directional effects on task performance, but, together with limitations regarding temporal and spatial resolution, might limit its suitability regarding physiological determination of connectivity. Future protocols, including closed-loop, and multi-electrode systems, might further enhance precision of these tools, and enable exploration of larger and more complex functionally connected networks **in vivo** in the human brain.

6. Conclusions

This review provides an extensive, multimodal and updated approach to the topic of methods for the exploration of brain connectivity, with a consideration of the strengths and weaknesses of each technology. A complex and multifaceted variety of aspects including those concerning structural, functional, effective, time-varying and dynamic brain connections cannot be approached and solved with a single method, but needs multiple and integrated methodologies for solving its individual facets. Within this line a multidisciplinary team of researchers are needed in order to select the optimal methods to track the scientific targets in the most appropriate way. Knowledge of the structural connections logically comes first; what parts of the brain are anatomically connected. As noted here, information about structure can build from microscopic to macroscopic scale. On that basis, it is possible to explore and understand the functional connectivity. Moreover, information flow will vary dynamically with brain state. Much information can be, and is being collected, in the resting state, but ultimately it will be crucial to know information flow related to different tasks and behaviors. As has been pointed out, since the brain operates in networks, it will be necessary to have descriptors of network operation to fully understand the neural processing. With this type of approach, future studies and an enriching "connection" within the research community will enable neuroscientists to disentangle the inner mechanisms regulating connectivity architecture of the major brain activities, including learning, memory, mood level, emotional expression, language, task-related skills and other domains, both in health and in neuropsychiatric diseases.

Looking at the functioning brain as a "society" of dynamically interconnected neuronal assemblies represents a change of paradigm not only in neuroscientific research, but also (or even mainly) in clinical neurosciences. In the near future it will be possible to disentangle "good" (i.e. by recognizing online the presence of optimal network architecture for learning, memory, task-related function) and "aberrant" networks (i.e. those sustaining a symptom like an epileptic spike, a dystonic movement, a behavioral/cognitive dysfunction) and to tailor therapeutic and rehabilitative approaches having a central "marker" to measure their efficacy and to better personalize the interventions of cure.

Disclosures

None of the authors have potential conflicts of interest to be disclosed.

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Figure Legends

Figure 1.

Construction of a brain network.

Figure 2.

Histological methods to study local neuronal connectivity and applicable to human brain samples. **A**. The Golgi silver impregnation entirely fills neuronal cell bodies and their processes, allowing detailed visualization and reconstructions; on the other hand, with the Golgi stain it is impossible to predict which cells will be impregnated in any given preparation. **B**. Filling neurons with fluorophores, as part of *in-vitro* electrophysiological experiments (for example in surgically resected brain tissue), allows correlating microscopic morphology with the functional properties of individual neurons. **C**. Immunocytochemistry targets specific cellular markers, and combining different labels allows the study, for example, of connectivity at the individual synapse level. **D**. Schematic representation of the clarification approach in which brain tissue blocks are rendered transparent and immunocytochemically labeled neurons can be visualized in 3D. **E**. Lipophilic dyes applied on *ex-vivo* samples of nervous tissue are taken up by cell membranes and diffuse to a certain distance, thereby tracing short-range connections, also in human preparations.

Figure 3.

Methods to study long-range connections in the human brain. **A**. Transections of nerves or CNS fiber bundles invariably cause anterograde (Wallerian) degeneration, i.e. destruction and elimination of the portions of axons and terminal ramifications distal to the lesion; depending on lesion location and size, degeneration can also

follow a retrograde path and involve neuronal cell bodies. **B**. Diffusion-weighted magnetic resonance imaging is used to identify *in vivo* the spatial orientation of fiber bundles in the brain, making it possible to reconstruct central pathways. An important limitation of the technique is that in areas where fibers intersect, the signal averages out and accurate directions cannot be established.

Figure 4.
Frontal section of the human brain (modified from © Pearson Education, 2013).

Figure 5.
A. Connectome nodes. Cortical terminations of the arcuate fasciculus. Yellow higher, red lower termination density. **B**. Connectome edges. Two major WM tracts, cortico-spinal tract (CST) & arcuate fasciculus.

Figure 6.
The problem of tractography for precision connectomics. Major human WM tracts generated using probabilistic (**A**) and deterministic (**B**) tractography algorithms differ for a single individual. **C**. Comparison of the r.m.s. errors of the connectomes in **A** and **B** in predicting the diffusion signal using the LiFE method. Probabilistic tractography (**A**) shows a smaller prediction error in a majority of voxels for this individual.

Figure 7.
Ensemble tractography (ET). Connectomes generated with multiple tracking algorithms are merged. LiFE is used to "learn" from the data. The ET connectomes contain all fascicles best contributing to predicting diffusion.

Figure 8.
Factorization method for the LiFE model, memory efficiency & model accuracy. **A**. LiFE$_{SF}$ model. The 2D matrix representation of LiFE (Pestilli et al. 2014) is replaced by a 3D indicator array (Φ) and dictionary of diffusion predictions (D; colors indicate precomputed prediction signals for different directions of diffusion). **B.** Factorization reduces LiFE model size from over 30GB of RAM per brain (old LiFE, low saturation symbols) to 1GB (saturated). **C.** Scatter plot**.** LiFE$_{SF}$ r.m.s. error in fitting the diffusion data is indistinguishable from the original LiFE. **Insets.** Errors in reconstructing fascicles`weights and LiFE model are extremely low.

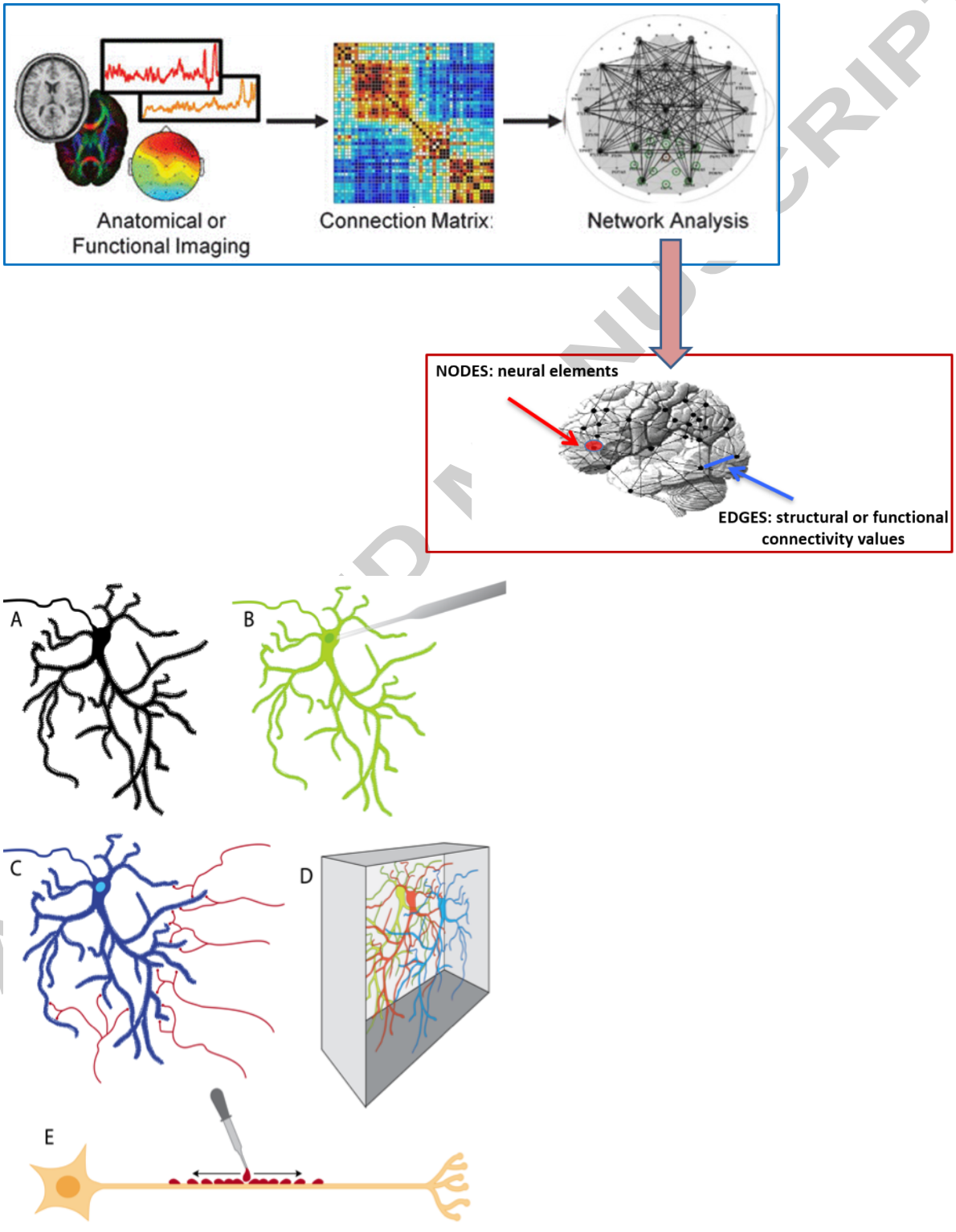
Figure 9.
Network science is developing along a network of measures and models, introducing new concepts, such as cost-efficiency, hierarchical modularity, vulnerability to random or targeted attack, and the notion of rich clubs (from Vecchio et al., 2018).

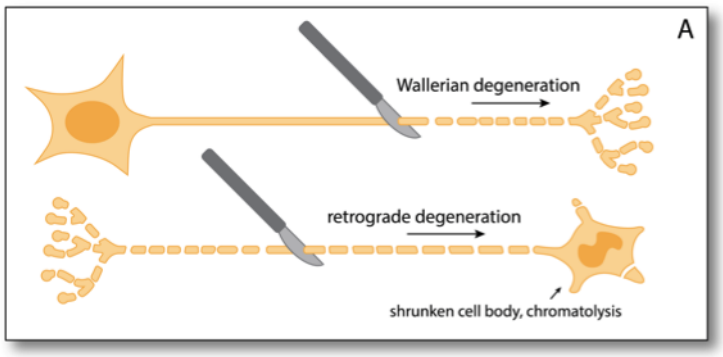
Figure 10.
Prestimulus electroencephalography (EEG) connectivity patterns from M1 for the "high" and "low" amplitude motor-evoked potentials (MEPs) in δ and β rhythms. The larger the MEPs, the larger is the functional coupling in δ (inhibition) between M1 and temporo-parietal nodes and β2 (facilitation) bands between M1 and frontal nodes (from Ferreri et al., 2014; Vecchio et al., 2018).

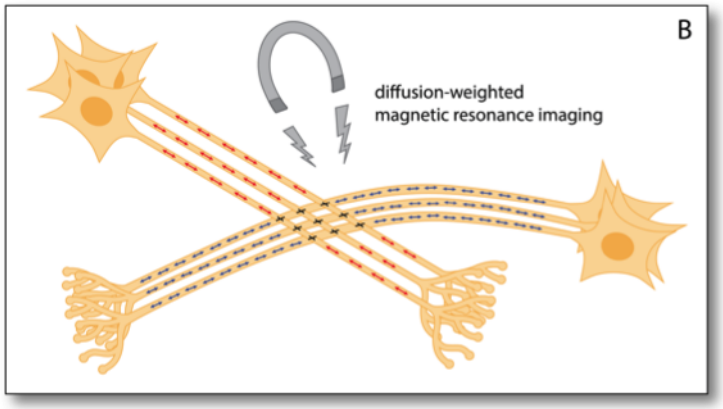
Figure 11.
Markers of effective connectivity assessed by paired-pulse TMS protocols. TP: test pulse; CP: conditioning pulse; *ES: electric stimulation; ISI: interstimulus interval; SAI: short-latency afferent inhibition; ICF: intracortical facilitation; SICF: short-interval intracortical facilitation; SICI: short-interval intracortical inhibition; LICI: long-interval intra-cortical inhibition; LCD: late cortical disinhibition.

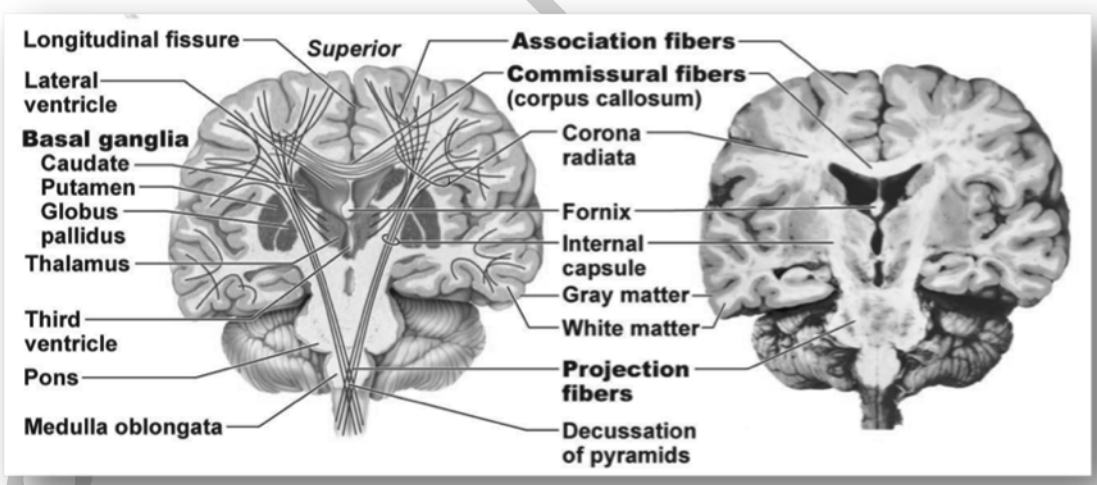
Figure 12.
Cortical responses to TMS across recovery in a patient evolving from vegetative/unresponsive wakefulness syndrome (VS/UWS, black arrow) to a minimally conscious state (MCS, blue arrow), then to emergence of MCS (EMCS, red arrow) as assessed by the Coma Recovery Scale-revised (CRS-R). The figure illustrates both the spreading over the cortical mantle and the time-courses of cortical currents after a TMS pulse when stimulating parietal (top) and frontal (bottom) cortical targets (white crosses). In VS/UWS, the response is local and simple,

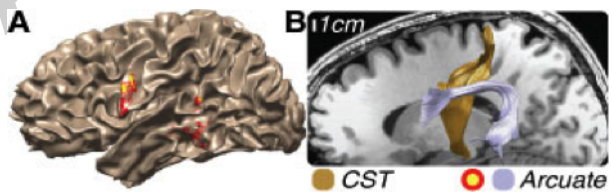
while involves different cortical sources at different times in MCS and EMCS. Figure adapted from Rosanova et al., 2012.

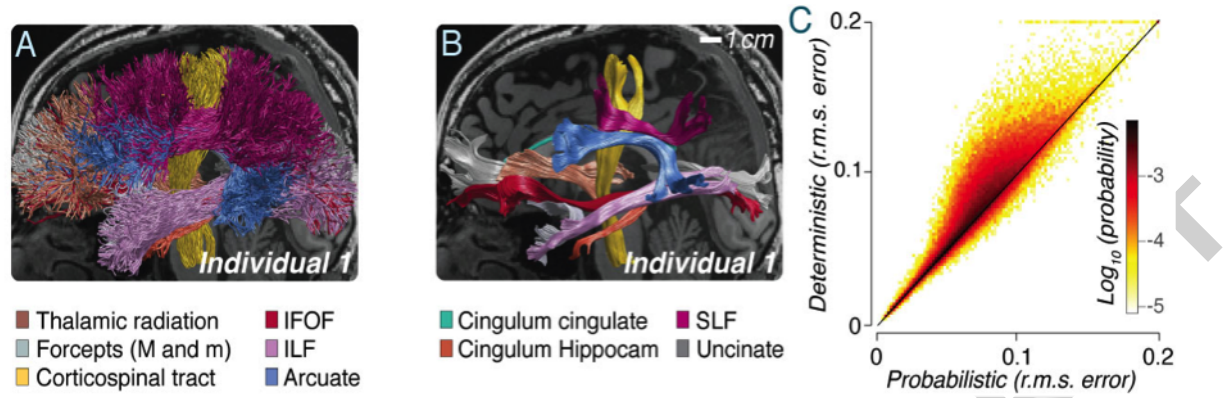


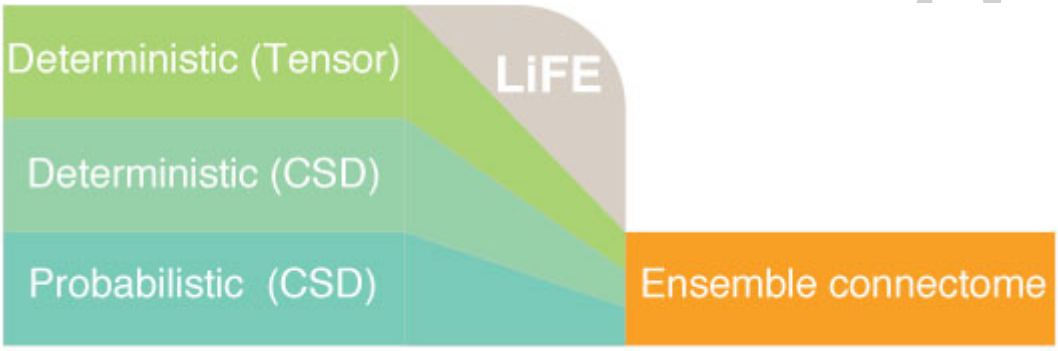


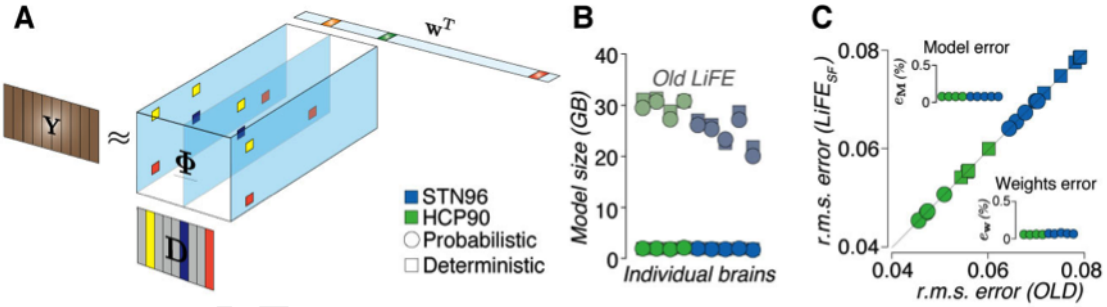


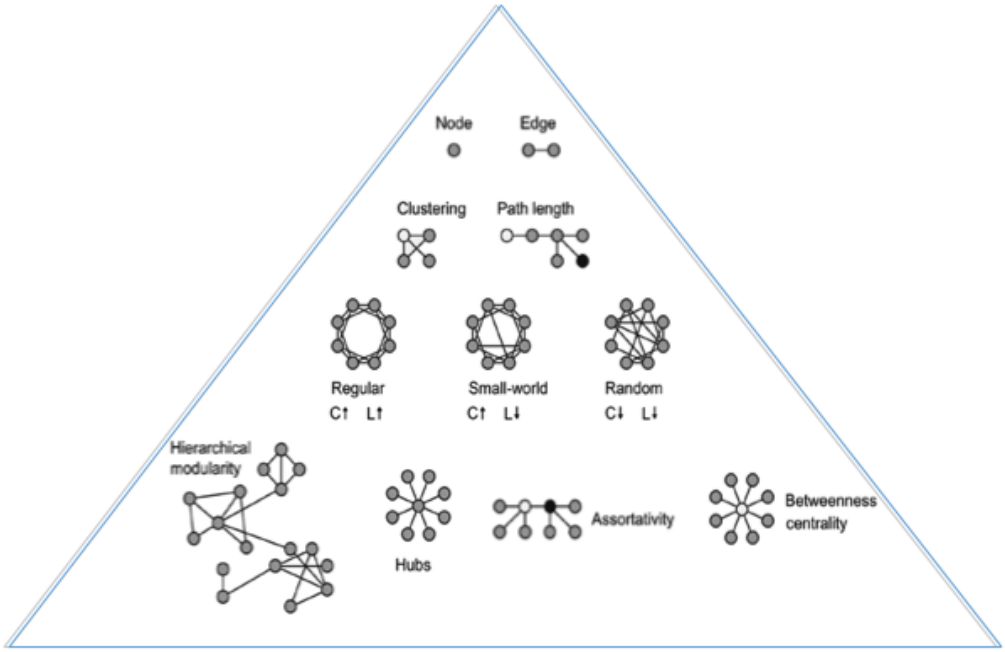


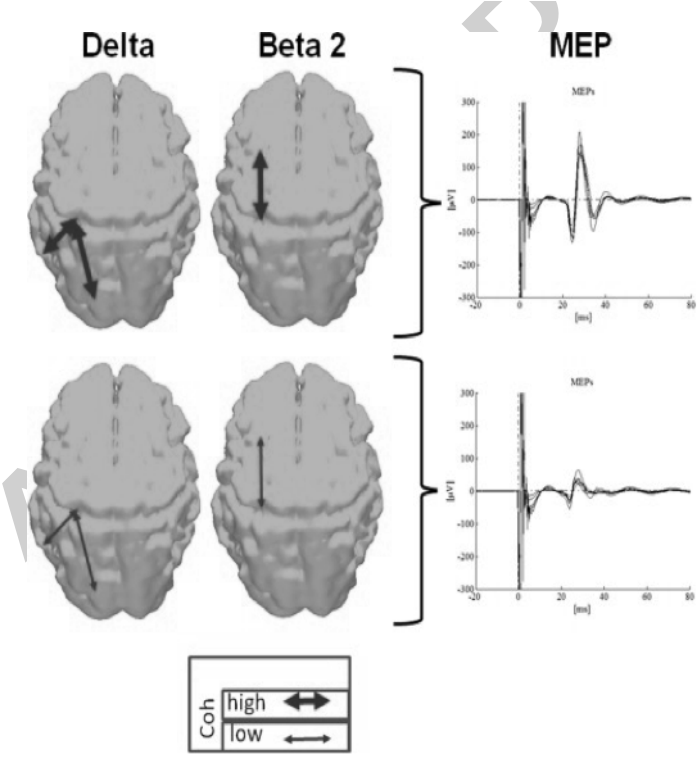



A
Individual 1
B
1 cm
Individual 1
C
Deterministic (r.m.s. error)
Probabilistic (r.m.s. error)
Log10 (probability)
Thalamic radiation
Forcepts (M and m)
Corticospinal tract
IFOF
ILF
Arcuate
Cingulum cingulate
Cingulum Hippocam
SLF
Uncinate


Deterministic (Tensor)
Deterministic (CSD)
Probabilistic (CSD)
LiFE
Ensemble connectome


A
Y
Φ
D
STN96
HCP90
Probabilistic
Deterministic
B
Old LiFE
Model size (GB)
Individual brains
C
Model error
Weights error
r.m.s. error (LiFE_SF)
r.m.s. error (OLD)


Node
Edge
Clustering
Path length
Regular
C↑ L↑
Small-world
C↑ L↓
Random
C↓ L↓
Hierarchical modularity
Hubs
Assortativity
Betweenness centrality


Delta
Beta 2
MEP
MEPs
MEPs
Coh
high
low