Human Brain Connectivity: Clinical Applications for *Clinical Neurophysiology*

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Highlights

The brain operates in networks and clinical neurophysiology can assess these networks

Methods include EEG, MEG, and functional MRI

Neurological and psychiatric disorders cause a breakdown in brain networks

Abstract

This manuscript is the second part of a two-part description of the current status of understanding of the network function of the brain in health and disease. We start with the concept that brain function can be understood only by understanding its networks, how and why information flows in the brain. The first manuscript dealt with methods for network analysis, and the current manuscript focuses on the use of these methods to understand a wide variety of neurological and psychiatric disorders. Disorders considered are neurodegenerative disorders, such as Alzheimer disease and amyotrophic lateral sclerosis, stroke, movement disorders, including essential tremor, Parkinson disease, dystonia and apraxia, epilepsy, psychiatric disorders such as schizophrenia, and phantom limb pain. This state-of-the-art review makes clear the value of networks and brain models for understanding symptoms and signs of disease and can serve as a foundation for further work.

Introduction:

The brain functions in networks. Information passes between regions, calculations are done, perceptions are created, and actions are carried out. The brain has many regions and many networks, and individual regions participate in more than one network. Activity is always ongoing, likely in many networks simultaneously, but only a few are prominent at any one time. The complexity is enormous, and it is astounding that ordinarily it can function so well. However, many disease processes cause these networks to malfunction giving rise to neurological and psychiatric symptoms. In order to understand these symptoms, it is possible to use the tools of clinical neurophysiology including functional neuroimaging to identify regions that are active or depressed and to measure flow of information among these regions. Then models can be made with this information to try to understand how the dysfunction leads to symptoms. Models can be made of parts of the brain, but the best ones in the long run will have to be whole-brain models.

Numerous investigations in human and animals using a large repertoire of non-invasive and invasive techniques have convincingly demonstrated that functional whole-brain activity depends both on effective connectivity and so-called *brain states*, reflecting system-properties such as anatomical organization, dynamic thalamocortical loops, and the function of ascending arousal systems. Evidently such evolving activity patterns are affected by diseases and may be eventually used to predict approaching “criticalities”, as the transition to disease is often preceded by robust, but gradual, reorganization of the complex system. Network neuroscience can significantly contribute to understand brain function and dysfunction (Bullmore and Sporns, 2009, Griffa et al., 2013), to assess the link between structural and functional changes and even to develop new therapeutic/rehabilitative strategies.

Network neuroscience is a recent venture aiming to explore the connection matrix built from the human brain called the human connectome. Network-based algorithms provide parameters that define global organization of the brain; when they are applied to electroencephalographic (EEG) signals network, configuration, and excitability can be monitored in millisecond time frames, as described in the first manuscript of the current pair (Rossini et al., 2019). These tools can also provide information on network instantaneous efficacy for a given task's performance before, during, and after the task (Vecchio et al., 2019). Studies of the connectome can also be done with transcranial magnetic stimulation, and this has been the subject in a previous manuscript (Hallett et al., 2017).

In this manuscript, a product of an International Federation of Clinical Neurophysiology (IFCN)-sponsored meeting held in Rome, we will look at a wide-range of neurological and

psychiatric disorders to illustrate how we can begin to understand their symptoms in terms of breakdown of normal networks. This depends, of course, on current models of how the brain normally functions. Importantly, study of disease will likely also improve the normal models.

From brain states to states of mind: theoretical considerations

With pathology, it would not be surprising that the nature of brain states would change. Given the lack of overt pathology in most psychiatric conditions, their understanding has been particularly difficult. As emphasized in this review, human brain activity emerges from the self-organization of large brain networks through complex interactions between interconnected neural populations. In order to gain a mechanistic understanding of brain function in health and disease, we need multimodal measurements of brain activity on various spatiotemporal scales, integrating neurophysiological and neuroimaging methods. Moreover, integrating this multimodal data with whole-brain models will allow for novel insights into the causal, generative mechanisms of brain function and ongoing neuronal dynamics. Below we show how this can be used to understand some of the mechanisms in schizophrenia. We also put forward novel hypotheses regarding how this can be conceptualized in terms of brain states and states of mind, which in turn can shed new light on one of the deepest questions in neuroscience, namely how brain functions arise from the underlying anatomical and neurodynamical skeleton. In particular, we show how such careful whole-brain modelling of multimodal neuroimaging data can lead to a better understanding of neuropsychiatric disease and potentially to novel treatments. For example, such an approach could guide us to directly alter brain state using electrical stimulation of specific brain regions in neuropsychiatric disorders by providing potential novel therapeutic targets rebalancing brain states in disease.

Whole-brain computational models aim to balance complexity and realism in order to describe the most important features of the brain in vivo. This balance is extremely difficult to achieve because of the astronomical number of neurons and the underspecified connectivity at the neural level. Thus, the most successful whole-brain computational models have taken their lead from statistical physics where it has been shown that macroscopic physical systems obey laws that are independent of their mesoscopic constituents. The emerging collective macroscopic behavior of brain models has been shown to depend only weakly on individual neuron behavior. Thus, these models typically use mesoscopic top-down approximations of brain complexity with dynamical networks of local brain area attractor networks. The simplest models use basic neural mass or mean-field models to capture changes in mean firing rate, while the most advanced models use a

dynamic mean field model derived from a proper reduction of a detailed spiking neuron model (Cabral et al., 2017, Deco and Kringelbach, 2014).

The link between anatomical structure and functional dynamics, introduced more than a decade ago (Jirsa et al., 2002), is at the heart of whole-brain network models. Structural connectivity data on the millimeter scale can be obtained in vivo by diffusion tensor imaging (DTI) combined with probabilistic tractography. The global dynamics of the whole-brain model results from the mutual interactions of local node dynamics coupled through the underlying empirical anatomical structural connectivity matrix. The structural matrix denotes the density of fibers between a pair of cortical areas ascertained from DTI-based tractography. Typically, the temporal dynamics of local brain areas in these models is taken to be either asynchronous (spiking models or their respective mean-field reduction) or oscillatory.(Deco and Kringelbach, 2014)

How topology can shape multiple dynamic content

More generally, whole-brain modelling can be understood in the words of the medieval philosopher Thomas Aquinas, who wrote that the container (or recipient) shapes the content. This foreshadowed the central problem of human mind complexity, namely how mind emerges from brain. In the context of cognitive science, one can interpret the container as the anatomy of the brain, while the content is a cognitive state that is computing a certain brain function (tasks such as perception, action and decision-making). These task-specific trajectory or structured flows over time are here called ‘states of mind’.

Aquinas presupposed that one simple container could give rise to only one content. Yet it has become clear that the complexity of human mind consists of multiple possible contents, where possible brain states could be analogous to the full palette of ‘colors’, corresponding to the complete repertoire of available brain dynamics in, say, resting wakefulness. From this complete palette of ‘colors’, task-driven ‘states of mind’ will emerge analogous to how a painter would use multiple combinations of ‘colors’ (but not the whole palette). This of course leaves open hard questions such as why it has to feel in a certain way to have a brain state; the qualia associated with consciousness. Still, it provides a useful operational definition where a brain state would correspond to wakefulness or sleep, while states of mind would encompass tasks (including perception and action) performed in a given brain state.

Within this framework, a key question is how best to characterize the task-driven states of mind (or combinations of colors) that can arise from just one special container, namely the human brain. It is clear that this container has evolved a particular topology that allows the generation of a

repertoire of different dynamics in a given brain state (e.g. resting wakefulness) and specifically the emergence from this repertoire of the states of mind (specific cognitive functions) that allow for survival and solve higher cognitive tasks. Thus, it is necessary to describe exactly this emergence of different states of mind (tasks) as a restricted combination of 'colors' arising from the full palette of the available dynamical repertoire in a given brain state (e.g. resting wakefulness) obtained from brain imaging data in human participants using many different modalities (fMRI (functional MRI), MEG, DTI). That is, by understanding the combination of different brain dynamics we can begin to understand how the brain might create mind (but not, of course, necessarily anything about qualia).

In this framework, a given state of the mind, i.e. the computation of a cognitive function, is distributed across the whole brain network, but that the underlying dynamics can be expressed in a much lower dimension than at the higher dimensionality composed of all neurons. As such, a task-driven state of mind can be described as a particular trajectory (i.e., a sequential combination of 'colors') consisting of a decomposition on the repertoire of the underlying brain state. This is similar to the idea of trajectories evolving on manifolds found in dynamical systems.(Huys et al., 2014)

Indeed, recent advances in whole-brain computational modeling allow us to estimate the neuronal time-series from multimodal neuroimaging data. Furthermore, this model allows to get both this estimate and a causal description of the underlying dynamical mechanisms such that one can explore how a given brain state (wakeful resting, sleep and anesthesia) can be described by a reduced repertoire of low-dimensional distributed dynamics (Deco et al., 2018, Deco et al., 2017c, Jobst et al., 2017, Stevner et al., 2019). In this framework, one can explore the hypothesis that task-driven states of mind can be fully described in terms of this reduced dynamical repertoire associated with a given brain state.

Characterizing brain states

To achieve this ambitious goal, difficult problems have to be solved. The first problem is to quantitatively characterize different brain states (the complete palette of 'colors', that is, the dynamical repertoire of, for example, wakefulness, sleep and anesthesia) in the absence of task and stimuli. This could appear to be a simple problem that could nevertheless provide a Rosetta stone to understand links from brain to mind. But the problem is in fact deceptively difficult, since, to paraphrase William James' famous quote about attention, although "everybody knows what a brain state is", it remains unclear at this point in time. To solve this conceptual problem, we propose a

practical framework using novel mixed whole-brain and data-driven methods to fully characterize a brain state.

We thus propose the hypothesis that a brain state can be fully described as the available dynamical repertoire (analogous to the complete palette of 'color') over time. Please note that the palette of available dynamical states (repertoire) in one brain state is not necessarily identical to the palette in another brain state. This equates to establishing the dimensionality, transients and life times of brain states. The dynamical repertoire corresponds to establishing a distributed 'cloud' of attractors where the dynamics can 'wander' over time and space with specific and precise stochastic properties (such as life times and transition matrix between different attractors).(Breakspear, 2017) This aim can be achieved using novel mixed whole-brain and data-driven methods from multimodal human neuroimaging of general brain states such as wakefulness, deep sleep and anesthesia. Two examples of data-driven methods include 1) estimation of spatiotemporal patterns in neuronal data using intrinsic ignition of brain regions, defined as their ability to propagate information to other brain regions,(Deco and Kringelbach, 2017) and 2) directly using non-linear dimensionality reduction (manifold learning) methodology.(Atasoy et al., 2018, Atasoy et al., 2016, Atasoy et al., 2017) Importantly, these methods can be applied on whole-brain models of the empirical data and are complementary but operate in different state spaces.

From brain states to states of mind

The second problem is to establish states of mind from task-driven neuroimaging and EEG/MEG data (e.g. in decision making and attention tasks). The same novel mixed methods as used above can used to identify specific states of mind used for a given task, as a particular structured flow through a restricted repertoire in the underlying brain state. In other words, the brain states identified above can be compared to 'mind-wandering' through the dynamical repertoire, while the states of mind are task-specific structured flow over time (trajectory), reflecting the necessary computational demands of a given task.

Hence, we propose the hypothesis that task-driven states of mind can be described as a particular structured flow through a restricted dynamical repertoire in brain states. This can be accomplished by establishing the specificity, variability and network distribution of states of mind found in task-driven data. By specificity, we mean the dynamics of a given structured flow, i.e. the probability of transition increases or decreases for the structured flow of a given state of mind. By variability, we mean a narrowing of the stability of the structured flow of a given state of mind across trials, in contrast to the high variability found in brain states where the dynamics are broader,

'wandering' through the space of the repertoire. By network distribution we mean the distributed nature of information processing, i.e., the broadness of communication and computation across a distributed system of brain regions.

Creating a model describing both brain states and states of mind

The third, and hardest, problem is to create a causal whole-brain neuronal model that can generate both the empirically obtained brain states, as well as the task-driven states of mind. We propose the hypothesis that a unifying whole-brain model can be constructed to generate the full repertoire of brain states as well as the corresponding collapse into a trajectory associated with task-driven states of mind. This can be accomplished by constructing causal whole-brain model constrained by neuroimaging and EEG/MEG data using both brain states and task-driven states of mind data. Typically, existing models use around parcellations from 100 to 1000 brain regions to successfully link anatomy and neuronal dynamics for resting state in wakefulness based on simple functional statistics.(Cabral et al., 2017, Deco et al., 2017a, Deco et al., 2017b, Glasser et al., 2016) However, it is possible to create a model which accounts for many brain states as well as task-driven states of mind, i.e. the collapsed trajectory within the dynamical repertoire. This is possible by constraining the model using novel proposed data-driven techniques in order to get new unifying insights into integrating states of mind with brain states. Furthermore, this model can be used to explore potential algorithmic, distributed brain solutions to compute specific tasks like decision making. The key idea is to use our mechanistic whole-brain model (constrained by multimodal task and resting state neuroimaging data) as computational reservoir machine,(Mante et al., 2013) but crucially constrained by the functional architecture of the human brain.

In order to give a flavor about how models could offer causal mechanistic interpretations associated for example with damage (stroke), Deco and colleagues (Adhikari et al., 2017) have shown that using whole-brain models it is possible to approximate at the level of individual patients the alterations of structural-functional disconnection measured with fMRI produced by a particular lesion. It is also possible to stimulate the model to estimate the variability of possible neural states, or entropy, both at the level of individual regions. This would not be possible clinically since patients cannot undergo many different experimental conditions. Notably, model parameters significantly correlate with behavioral deficits measured in the same patients suggesting that whole-brain models have the potential of estimating and causally explaining the clinical effect of disconnection. Furthermore, a very important application of the causal power of models is the

recent demonstration that stimulation of whole-brain models can force transitions between sleep and wakefulness patterns of activity (Deco et al., 2019).

Finally, further integration of information and modelling is undoubtedly important given the inadequacy of animal models and studies at the microscopic level to fully describe human neuropsychiatric disorders, which have contributed the paucity of effective clinical neuropharmacological interventions.

What is needed is a mechanistic understanding of the imbalances found in neuropsychiatric disorders, specifically at both local and global whole-brain levels, as demonstrated above in modelling the consequences of disconnection in schizophrenia and dementia.(Deco and Kringelbach, 2014) Furthermore, neuropsychiatric disorders are bound together by changes in a very specific network of the brain, namely in the reward network of the brain.(Berridge and Kringelbach, 2015) This is demonstrated by how anhedonia, i.e. lack of pleasure, is the cardinal symptom in neuropsychiatric disorders.(Romer Thomsen et al., 2015) Building whole-brain models could help open up for rational ways for effective brain interventions to rebalance the brain networks and help the identification of biomarkers stratifying a broad-illness phenotype into a finite number of treatment-relevant subgroups. Systematic studies of changes in local and global neuromodulatory activity, development, optimization and classification of models, and observations of drug effects on them, may greatly increase our understanding of pathological states and their potential treatment.

Whole-brain model in Neuropsychiatry: Example of schizophrenia

As an example of how multimodal neuroimaging and modelling can deepen our understanding of neuropsychiatric disorders, we here give an example of how schizophrenia can be modelled. Cabral and colleagues investigated the functional consequences of structural disconnection using two different computational models (using nodes with stable asynchronous state (Cabral et al., 2012a) and with self-sustained oscillations.(Cabral et al., 2012b) One of the advantages of using a whole-brain model is the potential for exploring the impact of the generative underlying parameters. In all models, the main point was to study the impact of a brain-wide decrease of the long-range synaptic efficacy, i.e. changing the model's dynamical working point, in the properties of simulated resting-state functional networks.

By way of analogy, Demirtas and colleagues (Demirtas et al., 2017) investigated the functional consequences of structural changes on the brain dynamics in patients with preclinical Alzheimer's disease (PAD), mild cognitive impairment due to AD (MCI) and mild dementia due to Alzheimer's

disease (AD). In the dementia case, the mean and standard deviation of the whole-brain synchronization reduced during the progression of AD. At the same time regional functional connectivity was found to show widespread decreases in AD group, whereas whole-brain computational modelling revealed that the left temporal lobe was at the core of these alterations. Interestingly, the amyloid-beta cerebrospinal fluid (CSF) biomarker primarily reflected the connectivity changes in patient groups compared to the healthy control group. Furthermore, total tau and phosphorylated tau CSF biomarkers showed distinct regional associations that are present also across clinical groups.

For the schizophrenia-relevant disconnection findings, fitting two different whole-computational models using either stable asynchronous state (Cabral et al., 2012a) or self-sustained oscillations.(Cabral et al., 2012b) changing the coupling strength in the whole-brain model reproduced healthy resting-state functional connectivity in fMRI with graph properties in the range of the ones reported experimentally. When the structural connectivity was decreased, either globally or locally, the simulated functional connectivity exhibited a network reorganization characterized by an increase in hierarchy, efficiency and robustness, a decrease in small-worldness and clustering and a narrower degree distribution, in the same way as reported for schizophrenia patients.(Lynall et al., 2010) Structural connectivity with DTI can also be combined with EEG. Using data from an odd ball task, patients showed larger structural path length and prestimulus density in the global and theta bands, and lower path length task-related modulation in the theta band.(Gomez-Pilar et al., 2018). Other EEG studies also show decreased connectivity during different cognitive tasks.(Jalili and Knyazeva, 2011, Naim-Feil et al., 2018, Olejarczyk and Jernajczyk, 2017).

Overall, structural connectivity is ensured by brain mechanisms involved in long-range signal transmission in the brain, including axonal connectivity (dependent on the number, density and coherence of axon fibers) and synaptic mechanisms (e.g. neurotransmission and plasticity). As demonstrated by the results, a disruption of these mechanisms, at either a global or a local level (such as occurring in certain brain pathologies), can have dramatic impacts on the resulting functional networks. Therefore, these and other results indicate that most disconnection-related neuropathologies are likely to induce pathology relevant qualitative changes in resting-state brain activity.

From a purely clinical point of view, studies have been done to identify schizophrenia brain patterns from normal. For example, Phang et al. (Phang et al., 2019) used a combination of various EEG connectivity features consisting of time and frequency-domain metrics of effective connectivity and complex network measures of network topology and achieved a 92% accuracy in classifying 45 patients and 39 healthy controls. Lei et al. (Lei et al., 2019) used a connectome

analysis of fMRI data from 295 patients and 452 healthy controls. They used a variety of measures, including functional connectivity matrix, with a support vector machine classifier and achieved 83% accuracy. Studies have also been done to identify possible connectome abnormalities in patients with first episodes of schizophrenia. Krukow et al. (Krukow et al., 2018) studied 42 patients with EEG as well as studies of processing speed in several tests. Loss of cortico-cortical synchronization was found in the patients and the abnormality correlated with slowing of processing speed. Cui et al. (Cui et al., 2019) studied 42 medication-free patients and 48 healthy controls with a combination of structural and functional MRI and found a significant abnormality of rich-club connection strength in the patients. They then replicated this finding in a second data set.

Connectivity information can potentially be used for therapy. In a recent resting state fMRI study of 44 patients, decrease in connectivity between cerebellum and dorsolateral prefrontal cortex was found to correlate with negative symptoms (Brady et al., 2019). In a second cohort of 11 patients, the cerebellar midline was treated with twice daily transcranial magnetic stimulation for five days. Improvement is connectivity correlated with improvement in symptoms.

Neurodegenerative Disorders

This section illustrates changes of brain connectivity in neurodegenerative diseases focusing on (1) normal and pathological aging, (2) Alzheimer dementia and (3) Amyotrophic Lateral Sclerosis. This question is of considerable theoretical and clinical interest as it is now increasingly accepted that functional brain changes precede structural ones in the development of neurodegeneration and may be helpful in early diagnosis as well as in monitoring and designing neuroprotective treatment and lifestyles (McMackin et al., 2019). Here, we provide an overview of state-of-the-art network analysis techniques, study outcomes, and new directions in this field.

Normal aging and Alzheimer disease

A brain graph-theory network is a mathematical representation of the functional and instantaneous brain architecture, consisting of a set of nodes (vertices) and their links (edges). Nodes usually represent brain regions, while links represent anatomical, functional, or effective connections. Network based algorithms provide parameters which define the global organization of the brain and its alterations. *Segregation* defined by the clustering coefficient C refers to the degree to which network elements form separate clusters while *integration* defined by the path length coefficient L refers to the capacity of the network to become *interconnected*. Small-worldness (SW)

is defined as the ratio between normalized C and *L* and describes the balance between local connectedness and global integration (Miraglia et al., 2015, 2016, Miraglia et al., 2017). Both measures of global integration and local segregation can discriminate cortical network features. On the basis of the "small-world" network model, this new approach aims to specify whether an optimal balance between local independence and global integration can be found as a favorable condition for information processing (Gaal et al., 2010).

Several studies have applied graph theory to EEG data for the investigation of brain network organization during brain maturation, adulthood, aging and, in particular, comparing normal aging (Nold), Mild Cognitive Impairment (MCI) and dementia (Vecchio et al., 2014a, Vecchio et al., 2014b) (Figure 1).

Resting-state eyes-closed EEG was evaluated in normal young children at 5 and 7 years of age (Boersma et al., 2011). Synchronization likelihood (SL) was used to weigh the graphs; an increase in C and L was found with age suggesting that a shift from random to more organized SW functional networks characterizes normal maturation of the brain. Micheloyannis et al. (Micheloyannis et al., 2009) studied SL in children (8–12 years) and young students (21–26 years) during mental rest and mathematical thinking. β and γ EEG rhythm C values in children were higher than in young students, and in β band SW was significantly higher in children. The higher synchronization of fast EEG frequencies observed in children during math was thought to reflect brain maturational processes. Connectivity and SW characteristics have been reported to change during life (Gaal et al., 2010).

Vecchio et al. (Vecchio et al., 2014a) analyzed the EEG from a sample of 113 healthy humans divided in three groups (young, adult and elderly) and found that in physiological aging the normalized L values follow a patterned sequence: Young >Adult>Elderly in the higher EEG frequency bands. The correlation between age and L showed that higher ages corresponded to higher L in delta and θ and lower in the α2 band; this pattern reflected the age-related modulation of higher (alpha) and decreased (delta) connectivity. Of note, a progressive deviation of the path length related to physiological aging might be responsible for an increase of processing time and an overall deterioration of the optimal and effective balance between local specialization and global integration observed in the elderly brain. The modulation of global but not of local network parameters during the aging process could be considered a loss in the balance of the most efficacious type of brain connectivity of the young-adult group. A possible interpretation of these results is that aging processes provoke progressive disconnection among neuronal assemblies.

Most EEG studies in dementia have been applied to Alzheimer disease (AD) patients despite the fact that EEG is not specifically sensitive to the different types of dementia. AD is considered to

initially (i.e., in a pre-symptomatic stage) affect synaptic transmission resulting in disconnection. The graph theory approach can describe the interaction between the spatial patterns of cortical atrophy, functional disruptions of synaptic viability and disease propagation along specific routes (Tijms et al., 2013).

Stam et al. (Stam et al., 2007) applied graph theoretical analysis to functional connectivity EEG in the β band in AD patients and control subjects. A loss of small-world network features was found to typify AD compared to frontotemporal dementia (FTD), suggesting a loss of complexity and a less optimal organization. De Haan et al. (de Haan et al., 2009) demonstrated reduction of both local clustering (C), especially in lower α and β EEG bands, and characteristic path length (L), especially in lower α and γ bands, in AD patients which points to less efficient information exchange and supports the disconnection hypothesis.

Vecchio et al. (Vecchio et al., 2014b) analyzed a dataset of 378 EEGs (174 AD, 154 mild cognitive impairment [MCI] and 50 normal old [Nold]). Normalized L showed a significant increase only in the θ band in AD compared to MCI and Nold. Normalized C showed a significant increment in θ band in AD compared to MCI and Nold and in α1 band in AD and MCI compared to Nold. The increase of both C and L in lower EEG frequency bands was considered as a sign of functional disconnection. Delta EEG activity in wakefulness is a "pathological" band and is correlated with brain disease when recorded during the resting state. An increase of global integration L in this band is a sign of synchronization of pathological activity that leads to a functional disconnection**.** The SW parameter revealed a significant interaction between AD and MCI groups showing a θ band increase in MCI. The α1 rhythm (8–10.5 Hz) is supposed to reflect the regulation of global cortical arousal, while the higher frequency α2 rhythms reflect the functional modes of thalamo-cortical and cortico-cortical loops that facilitate/inhibit impulse transmission and the retrieval of sensorimotor information processing. Since a decrease in L means a shift toward network randomness, it can be argued that an increase in high frequency C in both AD and MCI could reflect compensatory neuroplastic mechanisms based on recruitment of pre-existing but silent synapses/networks and of connections previously devoted to different functions, but now compensating for the declining ones. The fact that AD patients are more impaired than MCI subjects in the θ but not in the α band is in line with the hypothesis of an intermediate status of MCI between normal condition and overt dementia.

EEG reactivity during eyes open (EO) and closed (EC) conditions modulate cerebral integration and segregation in young and elderly subjects (Miraglia et al., 2016), and SW values reflecting such reactivity had different patterns in dementia with open/closed eyes EEG. Gaal et al. (Gaal et al., 2010) compared EEG resting state data in young (18–35 years) and elderly (60–75

years) subjects and found, in the elderly, C decreased after eyes opening in almost all frequency bands, L decreased in θ, α1, α2, β1 bands and SW parameter decreased for the β1 and β2 frequency bands. Tan et al. (Tan et al., 2013) found that the SW characteristics decreased in the θ band but slightly increased in the α band from EC to EO states. Reduction of SW characteristics in the θ band may be due to the external visual input in the EO condition which induces a decrease of resting state network activity. Age-related differences in EO resulting in a decrease of C and an increase of L were also described.

Miraglia et al. (Miraglia et al., 2016) studied 30 Nold subjects, 30 patients with amnestic mild cognitive impairment (aMCI) and 30 with AD, the SW parameter has been investigated which was sensitive to conversion of aMCI to AD (Toth et al., 2014). In the EC condition, aMCI displayed more SW compared to AD similarly to the Nold network topology, whereas in the EO condition aMCI showed less SW, resembling AD. Cognitive impairment of aMCI subjects correlated with SW architecture alteration, and the effect seen on the EO reactivity was considered to reflect such downgrading.

Correlation was studied between structural damage of corpus callosum as measured by fractional anisotropy (FA) in MRI-DTI and functional abnormalities as measured by L in resting state EEG source activity (Vecchio et al., 2015). The callosal FA reduction could be associated to a decrement of brain interconnection as reflected by an increase of delta and a reduction of path length in the α rhythm connectivity. The low frequency increase of L could be interpreted as a sign of functional disconnection. The correlation observed at low-frequency α rhythm (8-10.5 Hz) suggests a progressive (probably cholinergic) impairment of the attentional systems rather than inter-hemispherical coordination of the synchronization mechanisms.

Vecchio et al. (Vecchio et al., 2016) aimed to determine whether SW characteristics of the resting state brain networks correlate with memory measures in subjects with AD or MCI. Indeed, a significant correlation between the SW properties and short-term memory performance was found. Specifically, higher γ band SW characteristics during resting state EEG correlate with better performance in short term memory tasks. A functional connectome approach can represent an effective method for monitoring learning progress during training in both pathological and physiological aging (Vecchio et al., 2018b). A correlation analysis between hippocampal volume (MRI) and SW parameters in resting state EEG showed that α band SW was negatively correlated, while slow (delta) and fast-frequency (β, γ) bands positively correlated with hippocampal volume (Vecchio et al., 2017). Specifically, larger hippocampal volume was associated with lower α and higher delta, β, and γ SW characteristics. The authors speculated that SW connectivity pattern could be the functional counterpart of hippocampal atrophy. Recently, using the Alzheimer's Disease

Neuroimaging Initiative (ADNI)database, EEG metrics were evaluated in preclinical subjects identified by based on brain amyloid using 18F-florbetapir PET and neurodegeneration status using evidenced 18F-fluorodeoxyglucose PET (Gaubert et al., 2019). Findings included increased functional connectivity in the frontocentral region measured by weighted symbolic mutual information in theta band, and the authors concluded that EEG is indeed a useful biomarker for preclinical AD.

Musaeus et al. (Musaeus et al., 2019) using just the 19 electrodes of the 10-20 system with resting EEG and an analysis with coherence between each pair, including the imaginary part of coherence and weighted phase-lag index were able to classify with 95% accuracy 117 patients with AD, 117 patients with MCI, and 135 normal subjects. Changes in alpha coherence correlated with one of the memory tests. This result suggests that rather simple measures can do very well for diagnosis.

Another important group are those patients complaining of subjective cognitive decline but do not meet criteria for MCI. Some, but not all, will progress to dementia. In a meta-analysis of brain connectome studies of subjective cognitive decline, 16 studies using MEG and MRI measures found abnormalities in the patients, suggesting that this type of approach can be sensitive even in very early stages (Lazarou et al., 2019). Local properties such as degree and shortest path length show the early changes, while global properties such as small-world are normal.

New directions in Alzheimer's disease brain network analysis

In the past decade, the ability of brain network analysis to reflect progressive brain dysfunction and cognitive impairment in AD has become apparent (Pievani et al., 2011, Stam, 2014). These methods are a promising tool for non-invasive acquisition of novel neurophysiological markers for the pre-symptomatic diagnosis of AD and to predict MCI progression to dementia (Rossini et al., 2016). Judging from the majority of network-related studies that have been performed in AD, one could get the impression that network analysis is primarily about describing deviation from the theoretically optimal 'small-world' network configuration, using graph theory (Tijms et al., 2013). While the investigation of this global network efficiency feature has certainly been an important starting point for the application of network analysis concepts to the brain, it is just one example of a large and expanding array of techniques (Fornito et al., 2016). New markers enable a much more detailed analysis of structural and functional network damage, and many types of brain disease demonstrate network damage that correlates with disease severity. Particularly robust findings in AD emerging from this line of research are the disruption of modularity

(subnetwork presence), and an intriguing vulnerability of the highly connected network 'hub' regions, both structurally and functionally (Miraglia et al., 2017, Stam, 2014). These observations have led to new etiologic, diagnostic and therapeutic hypotheses and studies. The aim of this section is to briefly illustrate several upcoming approaches that may facilitate the evolution towards added clinical value, with a prominent role for neurophysiology. How broad is the scope of network analysis, and how could it help us to gain a better understanding, more accurate biomarkers or effective clinical interventions in AD?

Improved network comparison with 'minimum spanning tree' (MST) analysis

Since many graph theoretical measures are dependent on network size and density, comparing networks can be misleading, as it is unclear whether differences are really due to topological changes (Fornito et al., 2013). One solution is to attempt to extract from networks the most relevant 'backbone' of nodes, which means some information will be lost, but this enables comparison between networks with a focus strictly on topology. The minimum spanning tree (MST) analysis is an elegant graph theoretical way to do this, and it has been applied to AD and other forms of dementia, indicating that it can retain essential network information and produce meaningful differences (Tewarie et al., 2015). Frequency band-dependent differences in connectivity and network topology exist between AD and Lewy Body Dementia, while two different network damage types characterize AD and Frontotemporal Dementia (FTD) (van Dellen et al., 2015, Yu et al., 2016), in line with earlier studies. An alternative to MST analysis was proposed by De Vico Fallani et al. (De Vico Fallani et al., 2017), by showing an optimal way to choose a network threshold. These approaches enable more reliable network comparisons, although more methodological hurdles such as volume conduction and measure definition ambiguities must be taken into account as well (Colclough et al., 2016, Fornito et al., 2013, van Diessen et al., 2015).

Going deeper: source space analysis

Besides traditional cortical 'sensor space' analysis, various techniques enable investigation of subcortical brain activity in a non-invasive way. An increasingly popular method is the combination of magnetoencephalography (MEG) and beamformer techniques, which can map neuronal activity to an anatomical template, e.g., AAL (Automated Anatomical Labeling atlas)(Hillebrand et al., 2012). The high spatiotemporal resolution of MEG enables an unprecedented view on high-resolution deep brain activity in a non-invasive way. For AD this is relevant, since the hippocampus and entorhinal cortex play an important role. Lopez et al. (Lopez et al., 2017) explored source-space functional MEG networks of MCI patients, confirming network

disruption. A study using source-space EEG and graph theory to characterize age-related network differences, found a decrease in modularity and clustering and hub displacement in older subjects, mainly in the β band, confirming previous literature (Knyazev et al., 2015). By enabling subcortical region analysis, source localization combined with network analysis facilitates (multimodal) investigation of the relation between localized pathology, network status and cognitive dysfunction.

Incorporating system hierarchy: multilayer networks

For a long time, it has been known that the various frequencies in the oscillatory activity of the brain electromagnetic activity have different meanings for cognition, but also that they are interdependent. In many studies however, frequency bands are separately analyzed neglecting cross-frequency coupling and information flow. A novel approach to integrate the different frequency-based networks is multilayer or multiplex networks (Brookes et al., 2016, Muldoon and Bassett, 2016). Its application to AD showed that, indeed, the bands are not independent, and that for example hub vulnerability in the hippocampus, posterior default mode network and occipital regions is heterogeneously distributed between different bands, and can only be picked up by a multilayer approach (Guillon et al., 2017, Yu et al., 2016). Note that this method can also be used to study other types of hierarchical dependencies besides those in the frequency domain.

Dynamic processes in networks

While the first applied graph theoretical measures were mainly static, i.e., referring to rather constant properties of networks such as small-world topology, dynamic graph properties are now gaining a lot of interest (Sizemore and Bassett, 2018). These measures enable one to address questions relevant to the brain such as how network topology changes over time, how information traverses the network, or whether certain temporarily formed neuronal assemblies are related to certain cognitive tasks. Since cognition is a highly dynamic and distributed process, these are very relevant questions, and here, the role of neurophysiological techniques with their high temporal resolution is essential (O'Neill et al., 2018).

Directed connectivity: information flow in networks

Another highly desired ability is the determination of direction of impulse flow in network activity, in order to detect hierarchical relations between regions and within a network. Several approaches have been developed and applied to AD, confirming that global connectivity breaks down in AD and suggesting that the flow from precuneus and visual cortex towards frontal and subcortical regions was decreased, mainly in the β frequency band (Afshari and Jalili, 2017, Engels

et al., 2017). This disrupted posterior - anterior information flow was confirmed for AD in the β band, and for Lewy Body Dementia in the α band (Dauwan et al., 2016a). It appears that information flow is disrupted in a disease-specific manner in AD.

Network-based biomarkers in AD

An important clinical ambition is the development of potent biomarkers for AD. Although a range of distinct group-level effects have been found in network analysis based on EEG and MEG, both in resting-state and task scenarios, results have been inconsistent, and biased by different methodologies (Tijms et al., 2013). Recently, Lopez et al (Lopez et al., 2017) used a source-space resting-state MEG approach, showing that network markers (clustering and path length) did not discriminate as well as overall functional connectivity. Several electrophysiological markers in AD have been employed for classifying healthy controls, MCI patients that convert to AD, and AD patients (Dauwan et al., 2016b, Hojjati et al., 2017, Maestu et al., 2015, Vecchio et al., 2018b). Accuracy levels were around 80-90%, which is comparable to the more traditional spectral power-based markers. Network-related data may increase biomarker power, but this still has to be established. A review of EEG-based network biomarker studies from (van Straaten and Stam, 2013), pointed out that network measures may not correlate linearly with disease progression, and may have ceiling or floor effects. For progress, the author proposes that network-based measures should be incorporated as (secondary) outcome measures in clinical trials (see for example (de Waal et al., 2014, van Straaten et al., 2016).

S(t)imulating the brain: intervention modeling

Brain network damage can be studied both top-down using patient data, and bottom-up with computational network modeling. This enables the investigation of causality or temporal evolution as well. Moreover, simulating network changes is not limited to damage processes, but can also be used to test therapeutic strategies modifications mimicking medication or non-invasive brain stimulation (NIBS). A goal could be to aim for restoration of damaged functional networks, under the assumption that this will be beneficial for cognition (de Haan et al., 2017). Given the complexity of dynamic brain network data, this type of intervention modeling may not just be regarded as fancy sidestep, but as the only way to systematically predict realistic treatment options. In recent years, abnormal hippocampal and cortical hyperactivity, hyperexcitability and hyperconnectivity is found in early stage AD on various scales (Palop and Mucke, 2016). Therapeutic network-based effects are very limited at this point, but a recent project investigated

potential counter mechanisms to activity-dependent network damage in AD by introducing virtual network therapies (de Haan, 2017, de Haan et al., 2017).

While the techniques mentioned above illustrate various exciting new routes to travel in AD network analysis, it is certainly not a complete overview of the field. For example, combining EEG methods with genetic testing has been shown to be potentially valuable for predicting MCI progression (Vecchio et al., 2018a). However, for most of the new methods mentioned here, reliability and reproducibility still need to be explored in future studies.

Amyotrophic Lateral Sclerosis (ALS)

Available studies on brain connectivity in ALS have mainly focused on structural connectivity and aimed at early detection of upper motor neuron involvement, a requirement for the diagnosis (de Carvalho et al. 2008) which can be difficult to prove clinically. The co-occurrence of ALS with frontotemporal dementia and various other findings, however, have indicated that ALS is not purely motor. This induced an increasing number of studies of both structural and functional brain connectivity using predominantly imaging and only recently also clinical neurophysiological techniques.

Structural brain connectivity in ALS

Modern quantitative MRI techniques such as voxel based morphometry (Grosskreutz et al., 2006) or measurement of cortical thickness (Thorns et al., 2013) have shown atrophy in areas beyond the motor cortex raising the question how this may influence brain connectivity. Diffusion Tensor Imaging (DTI) has been intensively used in ALS for more than a decade to study the white matter connections of the motor cortex with other brain areas and the spinal cord. Early disintegration of transcallosal cortico-cortical fiber connections could be demonstrated in ALS as well as of the corticospinal tract proper (Douaud et al., 2011). Unfortunately, these changes rarely reach pathological significance on the individual level and are therefore not used diagnostically.

ALS is pathoanatomically characterized by protein aggregates with phosphorylated TDP43 (pTDP43) aggregates being the hallmark of ALS and associated frontotemporal dementia. The distribution of the pTDP43 pathology in the brain seems to follow fiber connections between separate brain areas and to gradually involve the motor cortex, premotor and frontal regions and finally the temporal lobe (Brettschneider et al., 2013). MRI studies using DTI confirmed that the propagation of the disease, i.e. of the pTDP43 pathology, follows a strongly interconnected brain

network which seems to serve as an anatomical infrastructure facilitating the spread of the protein aggregates to other brain areas. Finally, the most functionally and structurally affected connections overlap (Schmidt et al., 2016). Hypothetically this means that blocking axonal transport of pTDP43 in these brain networks could halt disease progression.

Functional connectivity studies using imaging techniques

A relatively new field in ALS research are studies of "functional connectivity" of remote brain regions using fMRI techniques. Since the analysis of motor actions can be difficult in a disease with motor deficits, resting state imaging has been widely used. One of the first studies of resting state brain networks in ALS (Mohammadi et al., 2009) focused on the default mode network (DMN), the sensorimotor network and the fronto-temporo-parietal network.

The DMN comprises a large frontal area, the posterior cingulate cortex, the inferior parietal cortex, and a temporal region involving the parahippocampal gyrus. There was generally reduced activity of the DMN in ALS patients as compared with healthy subjects. Agosta et al. (Agosta et al., 2013) described both a decreased connectivity (right orbitofrontal cortex) and an increased connectivity in the left precuneus of the DMN and enhancements as well as reductions in other networks. Other authors did not find changes of the DMN in ALS or even an increased activity in patients with greater disability (Chenji et al., 2016). These discrepancies may result to some extent from differences in the patient groups and may reflect the wide variability of the clinical phenotype. Further studies with more homogenous groups of patients with regard to the severity of the disease, site of onset, predominant upper or lower motor neuron involvement, signs of frontotemporal dementia and others appear necessary.

The sensorimotor network comprises the primary motor cortex, premotor cortex, anterior section of cingulate cortex, the somatosensory region and auditory cortex. In one study, ALS patients showed significantly lower activity than healthy controls in this network (Mohammadi et al., 2009). Another study described reduced activity only in patients with greater motor impairment (Chenji et al., 2016). Passamonti et al. (Passamonti et al., 2013) studied limbic networks in cognitively unimpaired ALS patients and found dysfunctions in early stage ALS including the amygdala and the primary motor cortex. Since there are no direct anatomical connections between these structures in humans, the authors considered indirect influences via involvement of the nucleus accumbens and the thalamus.

A particularly interesting field is the investigation of functional connectivity in asymptomatic gene carriers of ALS mutations. Menke et al. (Menke et al., 2016) reported increased functional connectivity in a network comprising the cerebellum and the cuneus in asymptomatic

gene carriers while the sensorimotor network appeared still normal, and there were no structural changes in DTI studies. They believe that these functional changes may be among the earliest detectable brain abnormalities in genetic ALS and may be a useful biomarker for monitoring future neuroprotective treatments.

Functional MRI may not be tolerable for ALS patients in later disease stages. An alternative may be provided by Near Infrared Spectroscopy (NIRS). The interhemispheric functional connectivity of non-motor areas in ALS patients using MRI DTI and NIRS showed resting state alterations by NIRS correlating well with corpus callosum degeneration in DTI (Kopitzki et al., 2016).

Functional connectivity studies using EEG

Most EEG studies in ALS /frontotemporal dementia focus on event related potentials in cognitive designs (Lange et al., 2016). However, the number of studies of functional connectivity in ALS using EEG techniques has been increasing in the last years. Many of these research activities have aimed at improvement of Brain Computer Interfaces (BCI) to allow for communication in the locked-in state of ALS (Chaudhary et al., 2017) or for the control of robot systems by motor imagery (Liu et al., 2017). While current BCIs utilize a limited number of electrodes, advances in functional connectivity may lead to some improvement.

Attempts to use connectivity studies diagnostically in ALS are still rare. Iyer et al. (Iyer et al., 2015) investigated functional connectivity using EEG frequency analysis and graph theory measures and found an increased connectivity in frontocentral regions and in areas corresponding to the default mode network. They discussed the role of these types of investigations as biomarkers for early detection of the disease. Other authors found that the EEG resting state functional network alterations correlate with the stage of the disease and may help to evaluate the clinical status (Dukic et al., 2019, Fraschini et al., 2016). Proudfoot et al (Proudfoot et al., 2018) reported increased resting state cerebral functional connectivity in a MEG study in ALS patients and in asymptomatic gene carriers. They attributed this result to the increased cortical excitability in ALS and discussed its possible role as an early biomarker reflecting a compensatory mechanism. Changes in EEG connectivity also correlate with degenerative changes in structural MRI (Nasseroleslami et al., 2019).

It is now generally accepted that ALS is not purely motor and can also cause cognitive deficits. This is an important aspect in the discussion of decision making by the patients in terminal stages of their disease. Fomina et al (Fomina et al., 2017) investigated self-referential processing associated with the default mode network in ALS patients. They found EEG correlates of self-

referential thinking in healthy subjects, but not in ALS patients. They concluded that the self-consciousness may be altered in ALS patients with consequences for self-conception, personal relations and decision making.

In summary, brain connectivity studies may have the potential to serve as biomarkers in very early diagnosis of ALS. Such biomarkers are urgently needed to enroll patients earlier than currently possible into clinical trials and to initiate effective treatment. This section makes clear, however, that the clinical relevance of functional brain connectivity studies for ALS needs further substantiation.

Conclusions

This review underlines the potential clinical utility of brain network analysis in studying neurodegenerative disease (Rossini et al., 2020). Network analysis has the potential to differentiate between normal aging, mild cognitive impairment and dementia, especially Alzheimer Dementia, early in the course or even in the preclinical stage of these disorders and in their follow-up. Premorbid studies can demonstrate early changes in brain connectivity in ALS as well. However, its main added value is to provide a better understanding of communication failure in the brain; it is not simply a loss of connections, but dysfunction strongly depends on the specific damage patterns and their influence on the entire network.

The brain network research field is expanding rapidly, and not a ‘small world’ anymore: new techniques such as multilayer analysis, network intervention modeling, and temporal network evolution capture essential system properties and bring the field gradually closer towards clinical purposes. Also, using these analytical tools it is becoming apparent that techniques based on neurophysiology produce obvious advantages over other functional techniques, considering their high temporal resolution. What is needed to ensure progress in this field is methodological consensus, inclusion of network-related biomarkers in clinical studies, and investigating the link between network prediction models and effective therapy.

Stroke

Stroke: A Network Disease

Stroke lesions are typically focal within a given vascular territory, confining their extent and localization. Hence, it seems reasonable to assume that stroke symptoms primarily arise from the loss or dysfunction of neural tissue in the affected vascular territory. Leaving this localizationist's view, however, we have started to understand that human behavior arises from the interaction of

distributed computational modules located in adjacent but also remote interconnected brain regions. Hence, focal brain lesions may have functional consequences beyond what could be expected when looking at the affected brain areas only. Also lesions to white matter may impact on cortical information transfer and thereby cause additional or even distinct symptoms. In his seminal paper 'Disconnexion syndromes in animals and man', Norman Geschwind described several specific patterns of functional impairment deriving from lesions of communication pathways between cortical areas (Geschwind, 1965a, 1965b). For example, a lesion affecting the arcuate fascicle, the neural fibers connecting Broca's and Wenicke's area, leads to conduction aphasia (Figure 2): The patient understands language, speaks fluently, but may use the wrong words and has difficulties or is unable to repeat spoken phrases. Thus, the loss of fibers connecting functional areas may lead to specific symptoms that are not observed after damage to the functional areas themselves.

More importantly, beyond such specific syndromes occurring after damage to specific white matter bundles, each focal lesion may have (additional) remote functional effects. Studying post-mortem brains, von Monakow noted as early as 1914 that symptoms observed in stroke patients do not entirely overlap with the functions ascribed to the neural tissue affected by the lesion (von Monakow, 1914). According to von Monakow's conceptual framework termed diaschisis, the functionality of interconnected regions (not directly affected by the lesion) may also be reduced contributing to the clinical impairment observed in a patient (Figure 2). A lack of facilitating influences from lesioned areas onto interconnected intact regions (passive inhibition) may cause additional functional impairment. In other words, the localization of symptoms is not equivalent with localization of function. According to this theory, early functional recovery partially arises from the alleviation of diaschisis, i.e., the reactivation of initially deafferented brain regions. In summary, diaschisis proposes a dynamical process of functional impairment and consecutive recovery thereof due to alterations of interactions between remote but interconnected areas that are part of the same functional network. In the last two decades, the concept of diaschisis has regained attention due the advance of non-invasive techniques that allow us to study the integrity and functional properties of cerebral neuronal networks. In particular, the human motor network has been intensely studied in-vivo by positron-emission tomography (PET), functional magnetic resonance imaging (fMRI), whole-head electroencephalography (EEG), magnetoencephalography (MEG), and non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). In particular, the analysis of connectivity, i.e., the estimation of neural interactions between remote but connected areas offers an appealing approach to study phenomena like diaschisis (for a review see, e.g., (Carrera and Tononi, 2014)) and pathophysiological mechanisms underlying functional impairment and recovery thereof after

stroke from a systems-level perspective. In the following, we will summarize, exemplify, and discuss how studying connectivity has (i) furthered our insights into cerebral reorganization underlying functional recovery after stroke and (ii) may serve as a biomarker in clinical practice in the future. We will primarily focus on research on motor network connectivity, as it is the most frequently studied functional system to date (Cassidy and Cramer, 2017).

Altered motor cortex activation and excitability after stroke

After pivotal studies on stroke-induced brain plasticity with PET (Chollet et al., 1991, Weiller et al., 1992), starting in the 1990's fMRI has been used to assess the activation of the stroke-lesioned brain while performing motor tasks, often simple hand movements. During movements of the paretic hand, altered neural activity has been observed in various motor-related areas, located in both the ipsilesional, i.e., affected, as well as the contralesional, i.e., "healthy," hemisphere (Chollet et al., 1991, Rossini et al., 2003, Ward et al., 2003, Weiller et al., 1992). Of note, such movement related activation is typically increased ("over-activated") compared to healthy controls, reflecting the additional recruitment of neural resources (for a review see e.g. (Grefkes and Fink, 2014)). In particular, the frequently observed bilateral co-activation of primary motor cortex (M1) seems surprising, given the strictly lateralized activation patterns in healthy subjects consisting of the almost exclusive activation of the M1 contralateral to the moving hand. However, the functional implications of such "over-activation" and hence the functional role of the contralesional hemisphere remains controversial (Buetefisch, 2015, Caleo, 2015). On the one hand, data from both animal models and humans support the vicariation model, hypothesizing a beneficial role of the contralesional hemisphere on motor function of the paretic hand (Di Pino et al., 2014, Rehme et al., 2011b). Similar changes have also been reported in other modalities capable of assessing brain activity more directly and with high temporal resolution, such as EEG or MEG. For example, EEG coherence analysis in well recovered chronic stroke patients with subcortical (capsular) lesions showed that after stroke cortico-cortical connections were reduced in the ipsilesional hemisphere but relatively increased in the contralesional hemisphere (Gerloff et al., 2006). From a theoretical perspective, an appealing line of argument arises from the fact that the clearly lateralized pattern of the healthy motor system activation observed during simple movements, shifts to a more bilateral pattern of activation during more complex motor task (Hummel et al., 2003, Verstynen et al., 2005). Hence, simple movements of the paretic limb may be processed like complex movements in healthy subjects, with the recruitment of bilateral neural resources converging in fine-tuned motor control (Di Pino et al., 2014, Rossini et al., 2003). However, fMRI and EEG studies performed in recovering (Bonstrup et al., 2015, Bonstrup et al., 2018) or chronic (Diekhoff-Krebs et al., 2017)

stroke patients revealed that increases of activity cannot simply be attributed to differences in task effort but rather represent true cortical reorganization.

Other studies have pointed towards a non-beneficial, i.e., maladaptive influence of the contralesional hemisphere, specifically for the contralesional M1 which may deteriorate motor function of the paretic hand (Grefkes et al., 2010, Takeuchi et al., 2012). For example, neural activity during a hand squeezing task in chronic stroke patients, increased activation of the contralesional M1 negatively correlated with motor performance of the paretic arm (Calautti et al., 2007). These competing interpretations have been attributed to different factors varying across different studies and their patient cohorts, such as the level of motor impairment, age or varying time points post-stroke, lesion characteristics or the task used in a given study (see (Grefkes and Ward, 2014) or (Di Pino et al., 2014) for detailed discussion). In summary, while it has become clear that a focal ischemic lesion induces complex alterations of motor cortex activation, excitability, and connectivity the question remains how the additionally recruited neural resources – i.e., areas that are not typically activated in healthy subjects – interact with the physiologically activated areas. Do the additionally activated areas support the lesioned motor system in accomplishing the goal of planning and performing a voluntary movement? Or are altered activation patterns rather alternative attempts to accomplish motor goals that are not integrated into the physiological activation pattern, i.e., lead to non-complementary, or even maladaptive neural processes after stroke? A way to more directly address the significance of regional changes in activation for the whole motor network lies in the assessment of the interactions, i.e., connectivity between involved regions.

A causal perspective: multimodal insight from effective connectivity and TMS

Using dynamic causal modelling (DCM) for fMRI data assessed for a simple fist clenching task, Grefkes and colleagues analyzed changes in effective motor network connectivity during movements of the paretic hand in subacute stroke patients on average 10 weeks after cerebral ischemia (Grefkes et al., 2008). During unilateral hand movements, healthy subjects typically feature various excitatory connections driving the M1 contralateral to the moving to activate the hand muscles, while interhemispheric inhibition from this “active” M1 (contralateral to the moving hand) onto the M1 ipsilateral to the moving hand is observed (cf. (Grefkes et al., 2008, Grefkes et al., 2010, Rehme et al., 2011b, Volz et al., 2015a, Volz et al., 2015b)). Of note, this interhemispheric inhibition between the M1 cortices is a very robust finding on paired-pulse TMS probing (Gerloff et al., 1998, Shimizu et al., 2002) and fMRI but not in EEG analyses (Bonstrup et al., 2016), and it is typically present at rest or during mild finger force execution but not during

maximal contraction (Hamzei et al., 2002). From a functional perspective, interhemispheric inhibition makes sense because it can prevent unwanted "mirror movements" of the other hand, thereby enhancing dexterity in higher primates (for a detailed discussion see (Volz et al., 2015a). However, "overflow" of M1 activation to its homologue M1 during power grip (Foltys et al., 2003) can stabilize posture or holding actions. During movements of the paretic hand, stroke patients show an abnormal inhibitory influence from contralesional (i.e., "healthy") M1 onto the ipsilesional M1 (Grefkes et al., 2008). Thus, while premotor areas are facilitating the contralesional M1, the contralesional M1 is concurrently exerting an inhibitory influence. The magnitude of this interhemispheric inhibition correlated with functional impairment of the paretic hand across patients (Grefkes et al., 2008). While the notion of a non-beneficial, i.e., maladaptive role of the contralesional hemisphere for motor recovery may be surprising at first glance, a similar narrative derives from electrophysiological data investigating interhemispheric inhibition (IHI) between bilateral M1 via TMS. When consecutively stimulating bilateral M1 at rest, the descending activation of the second TMS pulse ("test pulse") is reduced by the preceding first pulse ("conditioning pulse") applied over the contralateral M1. IHI is thought to arise almost exclusively from the activation of transcallosal inhibitory pathways by the conditioning stimulus (Ferbert et al., 1992), but there is also a smaller subcortical component (Gerloff et al., 1998). During the preparation and execution of unilateral hand movements in healthy individuals, IHI targeting M1 contralateral to the moving hand (exerted by ipsilateral M1) is reduced to enable the execution of a planned hand motor action (Hinder, 2012, Hinder et al., 2010). However, in chronic stroke patients, Murase and colleagues observed a lack of this movement-related disinhibition from the contralesional M1 onto the ipsilesional M1 for movements of the paretic hand (Murase et al., 2004). In other words, the typical IHI observed at rest from the contralesional onto the ipsilesional M1 is not completely alleviated during paretic hand movements. In summary, both effective connectivity estimated for fMRI data as well as IHI measured by TMS independently suggest that the physiological dynamics of inhibitory and dis-inhibitory modulation of the M1 ipsilateral to a moving hand, i.e., contralesional to an ischemic infarct if referring to the paretic hand, is altered after stroke. In essence, this seems to result in an inadequate inhibitory influence exerted by the contralesional over the ipsilesional hemisphere in patients with chronic motor deficits. Besides this change of interhemispheric inhibition targeting the contralesional M1, multimodal evidence also emphasizes pathophysiological alterations of the oppositely directed connection, i.e., from ipsilesional M1 onto contralesional M1, as predicted by the model of interhemispheric competition (Di Pino et al., 2014, Oliveri et al., 2000). In chronic stroke patients, a significant relationship has been reported between reduced cortical excitability of the ipsilesional M1 (assessed via TMS) and

reduced inhibition from ipsilesional M1 onto contralesional M1 (assessed via DCM). This observation suggests that the contralesional M1 is disinhibited (as shown by TMS excitability), potentially due to a lack of inhibitory inputs exerted by ipsilesional M1. Of note, strongest disinhibition of contralesional M1 and highest reductions in interhemispheric inhibitory connectivity were observed in patients suffering from severe motor deficits, which renders it possible that either altered interhemispheric communication hinders recovery (Volz et al., 2015b) or that the brain's attempt to mobilize maximal resources of the contralesional hemisphere is ineffective and, as an epiphenomenon, induces altered interhemispheric inhibition. Further studies are necessary to disentangle these different possibilities.

Beyond the interaction of primary motor areas, secondary motor areas and parietal integration areas seem to be relevant for effective reorganization of the cortical network after stroke. Using diffusion MRI and tractography, Schulz and colleagues demonstrated that white matter integrity of parietofrontal pathways connecting the ventral premotor cortex and the primary motor cortex and the anterior intraparietal sulcus and the ventral premotor cortex correlate with residual motor function after stroke (Schulz et al., 2015). This was supported by enhanced effective connectivity between frontal motor cortical areas and the intraparietal sulcus in well-recovered stroke patients in an DCM-fMRI study (Schulz et al., 2016). Bonstrup and colleagues (Bonstrup et al., 2018) applied EEG connectivity analyses and found, likewise, that parietofrontal coupling was significantly higher in chronic stroke patients than in age-matched healthy volunteers, and that this functional connectivity was correlated with residual impairment. Furthermore, a recent study showed that in well recovered stroke-patients, contralesional anterior parietal cortex features a difficulty-level dependent coupling with ipsilesional M1, implying a supportive role for increasing motor demands (Pool et al., 2018).

Using a longitudinal assessment of effective motor network connectivity after stroke, Rehme and colleagues found out that motor network interactions change alongside motor recovery (Rehme et al., 2011a). In the acute stage after stroke, a reduction of excitatory influences from premotor areas onto ipsilesional M1 was observed, while interhemispheric inhibition of the contralesional M1 was reduced (Rehme et al., 2011a) - as observed in chronic patients with persisting deficits (Volz et al., 2015b). Alongside early recovery, excitatory input onto the ipsilesional M1 reappeared, with ipsilesional M1 (potentially consequentially) also exerting stronger inhibition over contralesional M1. In line with earlier observations (Grefkes et al., 2008, Murase et al., 2004), patients featuring poor motor recovery of the paretic hand in the early chronic phase showed additional, pathophysiological inhibition of the ipsilesional M1 by the contralesional M1. These findings highlight the dynamic nature of motor network reorganization during motor recovery, with a special

emphasis on interhemispheric interactions, especially the influence of the contralesional upon the ipsilesional M1.

Causal regional contributions to motor recovery: disruptive "online" TMS interference

A more direct way to assess the functional role of a given brain region for a behavioral (motor) task lies in directly disturbing cortical activity with (typically repetitive) TMS. In contrast to "classical" applications of TMS like in motor mapping studies, which are usually performed at rest, repetitive TMS pulses are applied to the cortex of interest while the subject is performing the task under investigation. Such online TMS interference experiments ("jamming") rest on the assumption that a decline in task performance observed during stimulation of a given region reflects the functional contribution of the stimulated area as the transcranially applied electromagnetic pulses preclude physiological neuronal activity necessary for the task at hand. While several methodological aspects may complicate the designs of such experiments (e.g., timing, frequency, and duration of applied stimuli in relation to the task performed) and false negative findings may arise due to various reasons, online TMS interference allows to in principle investigate the causal functional role of a cortical region. In chronic stroke patients, interfering with neural activity of ipsilesional M1 (Werhahn et al., 2003) and ipsilesional dorsal premotor cortex (Fridman et al., 2004) slowed reaction times of the paretic hand, highlighting the role of both regions in functional recovery (Figure 3). Using online TMS interference, Johansen-Berg and colleagues showed that interference with the contralesional dorsal premotor cortex slowed down reaction times in chronic stroke patients, suggesting a supportive role of contralesional dorsal premotor cortex in movement initiation in stroke patients but not healthy subjects (Johansen-Berg et al., 2002). For more complex movements (finger sequence production), a supportive role of several motor regions of the contralesional hemisphere including contralesional M1 has been shown in chronic stroke (Lotze et al., 2006). Recently, Volz and colleagues investigated the role of the contralesional M1 in early cerebral reorganization after stroke with online TMS interference in a longitudinal design. The authors concluded that interfering with contralesional M1 during task performance improved finger tapping frequency, but not grip strength or reaction times in acute stroke patients (Volz et al., 2017). Importantly, no effects were observed in the chronic phase, suggesting that contralesional M1 may have a task- and time-specific negative influence on motor performance of the paretic hand in patients with mild to moderate motor deficits. Moreover, no effects were observed for a speeded reaction time task or maximum grip strength, highlighting the task-dependency of observations in stroke patients (Volz et al., 2017). Similar task- and time-dependent TMS interference effects were recently confirmed also for other contralesional regions such as dorsal premotor and posterior

parietal cortex (Tscherpel et al., 2020). These findings also somewhat explain the conflicting results between different (r)TMS interventions with some of them showing effects and others not which may in part derive from different outcome parameters (Grefkes and Fink, 2016).

In summary, our mechanistic understanding of cerebral motor reorganization at the network level has been significantly advanced using models of connectivity, electrophysiological measures such as cortical excitability or IHI, and testing functional roles of targeted areas via online TMS interference. This evidence pinpoints to a seminal role of dynamic changes in interhemispheric connectivity. While proof-of-principle studies give rise to hope that modulating pathophysiological changes in interhemispheric connectivity can beneficially impact motor recovery (for a review see, e.g., (Volz and Grefkes, 2016)), their detailed functional role remains a matter of ongoing debate. Opposing findings of different studies have been attributed to several experimental and patient specific factors such as severity of impairment, time since stroke, utilized tasks or lesion patterns. Future multimodal research is needed to further elucidate our mechanistic understanding of how network changes support recovery of motor function after stroke. At last, randomized, placebo-controlled, blinded clinical trials need to produce convincing evidence (Grefkes and Fink, 2016).

Biomarker in the making? Functional motor network connectivity

In recent years, the most popular way to study connectivity in stroke patients has been the acquisition and analysis of resting-state fMRI data. In contrast to task-based fMRI, subjects are not performing a structured task during resting-state fMRI, but are typically instructed to stay awake and let their thoughts wander. The absence of a structured task comes with several advantages in patient populations, most prominently that patients who are not able to perform a potentially demanding and complicated task due to their impairment can still participate in resting-state studies. Moreover, pathophysiological resting-state functional connectivity (rsFC) is not prone to the potential bias of the chicken-or-the-egg causality dilemma, frequently encountered with task-based fMRI data: For example, paretic hand movements performed by stroke patients are typically accompanied by pathophysiological activation patterns. Leading to the question which came first: are the observed neural alterations primarily caused by the stroke lesion or to what extent do cortical activation patterns also change due to the non-physiological nature of paretic hand movements? Finally, resting-state data is in principle comparable across different cohorts and does not require specialized in-scanner equipment. Thus, resting-state offers a highly suitable approach to study cerebral reorganization in stroke patients. On the other hand, experimental variables are better controlled in task-related paradigms, rendering the interpretation of the behavioral relevance of rsFC findings challenging.

Altered interhemispheric interaction within the sensorimotor network observed via TMS and effective connectivity can be reproduced in rsFC experiments. Evidence from animal and human studies suggest a characteristic time course of changes in motor network rsFC induced by stroke. Early after stroke, a decline in connectivity between the ipsilesional M1 and contralesional M1 is typically observed within the first 2–4 weeks. Using an animal stroke model, van Meer et al. (van Meer et al., 2010) reported this characteristic time-course of network changes post-stroke: interhemispheric rsFC between sensorimotor areas progressively decreases over the first 2 weeks, followed by a subsequent re-increase alongside recovery of sensorimotor functions. Highly similar findings were obtained in humans; e.g., Park and colleagues have found the lowest level of interhemispheric rsFC one month after stroke, followed by a subsequent re-increase in rsFC (Park et al., 2011). Volz and colleagues recently showed that stimulating ipsilesional M1 in early subacute stroke patients in combination with arm-related physiotherapy leads to a better motor recovery concurrent to higher interhemispheric resting-state connectivity of the stimulated motor cortex (Volz et al., 2016).

In summary, numerous studies have highlighted pathophysiological alterations of motor network rsFC in relation to motor functional impairment and recovery thereof (Guggisberg et al., 2019). Due to its clinical feasibility, interhemispheric changes in rsFC may hence serve as a biomarker for the individual potential of motor recovery and individualization of therapeutic approaches in the future. However, in order to yield valid estimates of network connectivity, also rsFC depends on some prerequisites like intact neurovascular coupling as well as some cooperation of the patients like not moving or talking or falling asleep during scanning. Hence, even this technique might not be applicable to all patients in clinical practice, calling for further methods or protocols to infer neural network properties at the level of individual patients such as advanced diffusion MRI for fiber tracking or EEG response profiles evoked by TMS (TMS-EEG).

Beyond the motor system: Functional connectivity and general recovery across domains

Several interesting aspects derive from a series of recent papers published by Corbetta and colleagues. This group found that behavioral impairment in 132 acute stroke patients measured across different behavioral domains (motor, attention, language, verbal memory) strongly correlated, which seems surprising when considering a “modular brain” perspective, where lesions differing in location and size across subjects should lead to the impairment of functionally distinct areas and hence result in heterogeneous clinical symptoms (Corbetta et al., 2018, Ramsey et al., 2017). Specifically, a decrease in inter-hemispheric functional connectivity within functional networks alongside increased intra-hemispheric connectivity between regions of distinct functional

networks was observed for different functional domains (Figure 4). From a theoretical perspective, the inter-correlation of deficits within and across domains may result from the fact that domain-specific behavior relies more on network level mechanisms of information integration rather than the modular function of distinct brain areas. Strikingly, disturbances in functional connectivity more accurately predicted impairment across multiple domains compared to lesion topography or size (Siegel et al., 2016). Hence, these findings suggest a "low dimensionality of behavioral deficits" across different functional domains that seems to be matched by a similarly "low dimensionality of correlated patterns" of abnormal rsFC which involve distributed networks of cortical areas rather than mapping onto specific functionally specialized regions (Corbetta et al., 2018). The authors speculate that alterations in rsFC after focal injuries may potentially "decrease the variability of neural states that the brain can explore both at rest and during tasks, hence the ability to process information effectively" (Corbetta et al., 2018).

In summary, besides elucidating pathophysiological mechanisms of domain specific stroke-induced impairment and recovery thereof, studies of connectivity may also help to further our insights into mechanisms underlying domain-general behavioral deficits induced by stroke lesions. Such domain general impairment may potentially be caused by a reduced capability of information integration across specialized networks or an impairment in the flexible allocation of multimodal cortical computational resources necessary for successful task performance in various domains.

Conclusion and outlook

The analysis of altered connectivity after ischemic infarcts has profoundly increased our understanding of recovery after stroke and helped to identify novel targets for therapeutic interventions, such as trying to normalize disturbed interhemispheric interactions rather than directly stimulating ipsilesional M1 with non-invasive brain stimulation (NIBS). While promising proof-of-principle results point towards a clinical potential of such approaches, large-scale prospective clinical trials are lacking and urgently needed to clarify the effectiveness of pathophysiology-driven NIBS treatments for clinical practice. While ongoing research continuously advances our mechanistic understanding of how the brain overcomes the sudden loss of neural tissue, new biomarkers of neural network properties need to be established at the level of single patients in order to assess the individual potential for functional recovery and responsiveness to neuromodulatory therapies.

Movement disorders:

Essential tremor

The thinking has been for a long time that the origin of tremor involves rhythmic activity in the cortical-pontine-cerebellar-thalamo-cortical loop with output to the spinal cord from the motor cortex. With posture, there is increased activity in the contralateral motor cortex and thalamus and bilateral cerebellum.(Bucher et al., 1997) Cellular bursts in the cerebellar receiving zone of the thalamus (ventral intermediate nucleus, VIM) correlate strongly with the tremor itself,(Hua and Lenz, 2005) and tremor frequency activity can be recorded with EEG over the motor cortex.(Muthuraman et al., 2012) A lesion in VIM will cause tremor to cease immediately. Studies of connectivity should confirm this hypothesis, but there is only partial confirmation raising new ideas of the pathophysiology.

The easiest connection to confirm should be the motor cortex to muscle, quantified by corticomuscular coherence. While corticomuscular coherence can be identified, the coherence is only intermittent.(Sharifi et al., 2017) One study varied the magnitude of tremor with ingestion of alcohol, but failed to find a correlation between tremor amplitude and coherence.(Pedrosa et al., 2017) In this same study, using Dynamic Imaging of Coherent Sources (DICS) beamformer, oscillatory activity could also be assessed in the cerebellum, and cerebellar-muscular coherence did correlate with amplitude of tremor. Another study looked at motor units in muscle rather than surface EMG.(Gallego et al., 2015) The first observation was that motor unit synchronization is higher in essential tremor than with a voluntary contraction in a healthy subject. Second, while coherence could be detected between motor units and the EEG, there was no correlation with tremor magnitude, and the net cortical contribution was not sufficient to explain the muscle activity. These studies, taken together, indicate that there is cortical drive at tremor frequency, but that it is only part of the input, and that another drive could be more important. It is possible that this second drive might come from the cerebellum via reticulospinal or rubrospinal pathways.

The connection from VIM to motor cortex was looked at directly by assessing EEG and local field potentials (LFPs) from VIM while also measuring tremor.(He et al., 2016) VIM LFPs were strongly correlated with tremor, while cortical correlation with tremor was weak, similar to what was described previously. Coherence (a linear measure) between VIM and motor cortex was weak, although a stronger linkage was found with a non-linear technique. The whole cortico-cerebellar-thalamo-cortical network was assessed with fMRI during varying magnitudes of tremor.(Buijink et al., 2015) A model was set up with cortical, cerebellar and thalamic nodes using dynamic causal modelling for effective connectivity. The model contained only unidirectional influences from cerebellum to thalamus and from cortex to cerebellum, both decisions consistent with standard

anatomical information. The main finding was increased cerebellar to thalamus connectivity, but there was no increased influence of thalamus to cortex. In a functional connectivity analysis, decreased connectivity was found between cerebellum and cortex. Tremor severity correlated with this decrease in connectivity as well as the increase in connectivity between cerebellum and thalamus. These studies suggest that the connection between thalamus and cortex, and even the influence of the cerebellum on the cortex is not strong during tremor and is not correlated with tremor magnitude. Moreover, further support is found for cerebellar influence on tremor.

Resting state fMRI studies have been done in essential tremor, but their interpretation is tricky because there is no tremor at rest, and studies in the VIM have shown that there is no abnormal oscillatory activity at tremor frequency at rest. One study, that used a seed in VIM, found decreased connectivity to the cerebellum and increased connection to the motor cortex.(Fang et al., 2016) A second study also found a specific increase in connectivity from VIM to sensorimotor regions and a general loss of connectivity to the cerebellum.(Mueller et al., 2017) These studies are surprising in view of the results during tremor, but possibly indicate an attempt at compensation. A third study analyzed the rsfMRI with a DCM, and one of the findings was an increased inhibition from VL (the region of VIM) to the dentate nucleus of the cerebellum.(Park et al., 2017) This result identifies the same connection, but in the opposite direction of the DCM finding during tremor noted above. The earlier model did not include a connection from thalamus to cerebellum, so it was not possible to find a similar result.

These connectivity studies reveal that the motor cortex appears to play only part in essential tremor and that another, perhaps more important drive, is identified in VIM and cerebellum. The VIM and cerebellum are indeed strongly connected, but the assumption would be only the direction of cerebellum to VIM. Problematically, current anatomical knowledge is that VIM does not to have any way of influencing motor output other than via the motor cortex. What appears to be missing anatomically is a back projection from thalamus to cerebellum, perhaps a thalamopontocerebellar pathway, and this would be worthwhile to search for. The last rsfMRI result noted above does show a possible influence in this direction.

Parkinson’s tremor

Parkinson’s resting tremor has been linked to the cerebello-thalamo-cortical circuit, the basal ganglia, and the interaction between these two circuits.(Helmich et al., 2012) Clinically, tremor behaves differently from the other cardinal motor symptoms of Parkinson’s disease: it often occurs early in the disease, its severity does not correlate with that of bradykinesia or rigidity, and tremor

does not always respond to dopaminergic medication. Furthermore, unlike rigidity and bradykinesia, tremor severity does not correlate with striatal dopamine depletion (measured using nuclear imaging). This suggests that non-dopaminergic mechanisms, likely outside the basal ganglia, play an additional role. Some of the earliest evidence for a role of the cerebello-thalamo-cortical circuit comes from deep brain recordings. These studies have shown that there are cells firing at tremor frequency ("tremor cells") in the ventral intermediate nucleus (VIM) of the thalamus,(Lenz et al., 1988) which receives input from the cerebellum. Activity in the VIM is coherent with the ongoing tremor, and deep brain stimulation of the VIM has a strong anti-tremor effect. Studies using magnetocencephalography (MEG) have indeed shown tremor-related oscillatory activity in the motor cortex, cerebellum, and a diencephalic area that is presumably the thalamus.(Timmermann et al., 2003) Furthermore, using concurrent EMG and fMRI recordings, it has been shown that activity in the cerebello-thalamo-cortical circuit is correlated with fluctuations in tremor power (Figure 5A,B).(Helmich et al., 2011) In addition to the cerebello-thalamo-cortical circuit, the basal ganglia must play an additional role. There are also tremor cells in the subthalamic nucleus (STN) and the internal globus pallidus (GPi).(Magnin et al., 2000) Furthermore, coherence between the STN and the motor cortex specifically increases during tremor episodes.(Hirschmann et al., 2013) Finally, deep brain stimulation in both the GPi and the STN suppresses tremor.(Odekerken et al., 2013) Taken together, these data suggest that both the basal ganglia and the cerebello-thalamo-cortical circuit are involved in Parkinson's tremor.

Connectivity studies have shown that the coupling between the basal ganglia and the cerebello-thalamo-cortical circuit is altered in Parkinson patients with tremor. For example, combined EMG and fMRI studies have found increased functional connectivity between the GPi and the motor node of the cerebello-thalamo-cortical circuit in tremor-dominant PD patients, as compared to non-tremor PD patients and to healthy controls.(Helmich et al., 2011) Furthermore, a dynamic causal modelling study has shown that the GPi drives tremor-related activity in the cerebello-thalamo-cortical circuit through effective connectivity with the motor cortex.(Dirkx et al., 2016) Other resting state fMRI studies have reported similar findings. For example, functional connectivity between the cerebellum and supplementary motor area (SMA) has been associated with Parkinson's resting tremor.(Ng et al., 2017) Furthermore, in tremor-dominant PD patients, the VIM had enhanced functional connectivity with several brain areas, including the motor cortex, cerebellum, and globus pallidus, as compared to non-tremor PD patients.(Zhang et al., 2016) These findings all suggest that increased connectivity between the basal ganglia and the cerebello-thalamo-cortical circuit is related to Parkinson's tremor. Other studies have tested for differences in structural connectivity between Parkinson patients with and without tremor (using diffusion tensor imaging,

DTI). The findings suggest that tremor-dominant patients have relatively spared structural connectivity between the substantia nigra and the basal ganglia, including the GPi.(Barbagallo et al., 2017) These results fit with an fMRI study showing that tremor-dominant patients have relatively normal cerebral activity during voluntary actions in several brain areas, including the GPi, when compared to non-tremor patients.(Prodoehl et al., 2013) This hints at a paradox: the GPi is involved in the generation of tremor, but tremor-dominant patients have a relatively intact GPi. This raises the question whether tremor may arise as a compensatory phenomenon in PD, possibly to reduce pathological beta oscillations within the motor system (Qasim et al., 2016). Dopaminergic medication has specific effects on the cerebello-thalamo-cortical circuit. Using dynamic causal modelling (DCM), Dirkx and colleagues have shown that dopamine influences the tremor circuit by inhibiting the thalamic VIM nucleus (Dirkx et al., 2017). A follow-up study showed differences between PD patients with dopamine-resistant versus dopamine-responsive tremor (Dirkx et al., 2019). Specifically, patients with dopamine-resistant tremor showed more activity in the deep cerebellar nuclei (interposed nucleus; Fig 5 C), while patients with dopamine-responsive tremor showed more activity in the thalamus (VIM) and somatosensory cortex (OP4), as well as increased connectivity between these two regions (Fig 5 D). This suggests that dopamine-resistant tremor in PD may be explained by increased cerebellar and reduced somatosensory influences onto the cerebellar thalamus, making this region less susceptible to the inhibitory effects of dopamine.

An important question has been where the tremor oscillator is located. Previous studies have put forward the “thalamic pacemaker” and “basal ganglia pacemaker” hypotheses.(Helmich et al., 2012) The data reviewed above suggest that both these hypotheses are incomplete, given the causal role of both circuits in Parkinson’s tremor. This has sparked the idea that the tremor rhythm emerges from a distributed network, rather than a single oscillator. Support for this idea comes from intervention studies, where rhythmic stimulation at tremor frequency at different sites within the tremor circuit (motor cortex, cerebellum, VIM, and STN) was able to entrain the ongoing tremor (meaning that the tremor adopted the phase of the stimulation).(Brittain et al., 2015, Brittain et al., 2013, Cagnan et al., 2014) These findings suggest that several nodes within the distributed basal ganglia and cerebello-thalamo-cortical network contribute to the tremor pacemaker. Within this distributed network, some regions may have a role in triggering tremor (the GPi), while other areas are involved in maintaining (or amplifying) the tremor rhythm (cerebello-thalamo-cortical circuit).(Dirkx et al., 2016) To further test the hypothesis that abnormal interactions between the basal ganglia and the cerebello-thalamo-cortical circuit contribute to Parkinson’s tremor, concurrent electrophysiological recordings across multiple nodes of the tremor circuit would be useful – but these studies are missing.

Studies assessing tremor-related connectivity may have clinical relevance. For example, unlike the STN or GPi, the VIM cannot be detected using even high-field MRI. Some groups now use DTI to localize the VIM, based on the location of pyramidal and somatosensory tracts.(Sammartino et al., 2016) Furthermore, several DBS studies have shown that the strength of structural connectivity between the stimulated tissue in the STN or VIM and the primary motor cortex is positively correlated with the tremor reduction.(Akram et al., 2017, Klein et al., 2012) This suggests that structural (or functional) connectivity studies may be used to localize the optimal DBS target for tremor relief.

Bradykinesia and Non-motor symptoms in Parkinson Disease

Bradykinesia

Bradykinesia is the most important reason for motor difficulties in PD, affecting almost all activities in daily life. However, the pathophysiology underlying bradykinesia remains unclear. Extensive neuroimaging studies have investigated network changes in PD patients and have provided important information in understanding bradykinesia. A characteristic fMRI network modulation in PD patients while performing self-initiated movements is the weakened functional connectivity between the striatum and cortical motor areas, specifically, primary motor cortex (M1), premotor cortex (PMC), and supplementary motor area (SMA), compared to healthy controls.(Taniwaki et al., 2013, Wu et al., 2011) In addition, simultaneous MEG and direct recordings from the subthalamic nucleus (STN) during functional neurosurgery showed that the connectivity between the STN-SMA paradoxically diminishes with the initiation of movements.(Litvak et al., 2012) As the SMA plays an important role in the planning, decision and preparation of self-initiated movements, the disconnection of the basal ganglia-SMA pathway secondary to dysfunction of the nigrostriatal dopamine system is likely an important reason for bradykinesia in PD patients. Simultaneous recordings of STN activity and EEG during walking showed a precipitous decline in 4 to 13 Hz activity that correlated with freezing of gait (FOG) (Pozzi et al., 2019).

Meanwhile, there are some increased functional connections in PD patients. EEG/MEG studies have demonstrated enhanced cortico-cortical coherence, e.g., the connectivity between the SMA and M1 (Pollok et al., 2013, Silberstein et al., 2005) and increased interhemispheric synchronization (Miron-Shahar et al., 2019). fMRI studies have found increased cortico-cerebellar connectivity.(Wu et al., 2011) The nature of these strengthened connections remains unclear. Although they have

been commonly explained as compensatory for basal ganglia dysfunction, pathological effects may also contribute to these phenomena.

Another common feature in PD patients is the loss of ability of motor automaticity, which has been proposed as another factor underlying bradykinesia.(Wu et al., 2015a) Motor automaticity is the ability to perform movements without attention directed toward the details of the movement. Motor automaticity dysfunction is apparent even in the early stages of PD, while most bradykinesia-related motor problems can be associated with loss of motor automaticity, such as akinesia, reduced arm swing, freezing of gait, and micrographia. In healthy people, the process of motor automaticity is accompanied by more efficiency of neural networks and less requirement for the attentional network.(Lehericy et al., 2005, Wu et al., 2004) In PD patients fMRI studies show that the connectivity of striatocortical motor pathways is weakened, the activity in the sensorimotor striatum is not enhanced, and the attentional networks remain active during automatic processing.(Wu and Hallett, 2005, Wu et al., 2015b) These findings indicate that the neural mechanisms of impaired motor automaticity include less efficient neural coding of movement, failure to shift automated motor skills to the sensorimotor striatum, instability of the automatic mode within the striatum, and use of attentional control efforts to execute movements usually performed automatically. As a consequence, PD patients lose previously acquired automatic skills and have difficulty in acquiring new automatic skills or restoring lost motor skills, which results in bradykinesia.

The sequence effect is a progressive reduction in speed and amplitude of repetitive action, which is a common feature in bradykinesia.(Iansek et al., 2006) The pathophysiological mechanism underlying sequence effect is not clear. A recent fMRI study revealed that the sequence effect is related to the dysfunction of basal ganglia motor circuit together with disconnections between the rostral SMA, rostral cingulate motor area and cerebellum.(Wu et al., 2016) Levodopa administration restored the function of the basal ganglia motor circuit, but did not repair other disconnected networks, which is a possible reason why levodopa has no significant influence on the sequence effect.

Non-motor symptoms

Network connectivity modulations in non-motor parkinsonian symptoms, such as cognitive, emotional, or olfactory impairments, have also been increasingly investigated. PD patients with cognitive dysfunction have a selective disruption of fMRI corticostriatal connectivity.(Seibert et al., 2012) Moreover, the connectivity of the so called "default mode network" (DMN) is disrupted.(Gorges et al., 2015) The DMN is a network showing consistent task-related deactivations, including the medial prefrontal cortex, anterior cingulate cortex, posterior cingulate

cortex, precuneus, and inferior parietal lobe. As the DMN is thought to facilitate cognitive performance by allocating neural resources to critical brain regions, the dysfunction of the DMN might be critical in cognitive deficits in PD.

Parkinson dementia was studied with EEG using phase lag index as a measure of functional connectivity together with graph theory analysis. Parkinson patients with dementia compared to patients with normal cognitive function showed decreased local integration in the alpha-1 frequency band (8-10 Hz).(Utianski et al., 2016) Another study used EEG and phase lag index to study MCI in PD (Chaturvedi et al., 2019). Abnormalities were found particularly in the theta band that correlated with memory loss. An MEG study used phase transfer entropy to analyze net information flow to and from each region.(Boon et al., 2017) Normally information flows posterior to anterior. In patients, beta band information outflow was significantly higher for the basal ganglia and frontotemporal cortical regions, and significantly lower for parieto-occipital regions in PD patients; and low information outflow from occipital regions correlated with poor global cognitive performance.

In PD patients with depression, disrupted fMRI connectivity of the limbic-cortical circuits has been detected, which may indicate impaired high-order cortical control or uncontrol of negative mood, and contributes to the depression in PD (Luo et al. 2014). PD patients with apathy have reduced functional connectivity mainly involving limbic striatal and frontal territories.(Baggio et al., 2015) Patients with olfactory impairment compared to those patients without olfactory impairment show decreased connections between the posterior cingulate cortex and bilateral primary sensory areas, right frontal areas, and right parietal areas, but higher striatocortical connections in the bilateral occipital areas and right frontal areas.(Sunwoo et al., 2015)

In summary, the basal ganglia have connections with much of the cortex and these become weakened in Parkinson disease correlating with a variety of abnormalities. Cortico-cortical connections as well as cortico-cerebellar connections also become disrupted, some decreasing and some increasing. Some of the latter might be compensatory, but this is not yet proven.

Dystonia

Dystonia has long been considered as basal ganglia disorder caused by an imbalance in the striato-pallido-thalamo-cortical loops. Recently, dystonia is rather seen as a network disorder implicating multiple loops and nodes, involving the cerebellar, striatal and cortico-cortical connections (Jinnah et al., 2017, Lehericy et al., 2013). The improvement of neuroimaging and clinical neurophysiology including non-invasive brain stimulation methods over the last twenty

years has permitted to deepen our knowledge of network connectivity underlying the pathophysiology of dystonia.

The cerebellum appears to be a critical node in the pathway associated with the expression of dystonia. Diffusion tensor imaging and voxel-based morphometry showed reduced fractional anisotropy (a marker of axonal integrity) and decreased gray matter volume in the cerebellum in different groups of dystonic patients, from generalized to focal (Ramdhani et al., 2014). Structural and functional integrity of the cerebellum and its connection to the thalamus was found altered in patients with inherited forms of generalized dystonia (Carbon et al., 2011). Probabilistic tractography helped to isolate genotype-specific fiber tract differences between manifesting and non-manifesting DYT1 and DYT6 gene carriers, with reduced integrity of the cerebello-thalamic tracts, suggesting an abnormal cerebellar outflow to the cortical motor areas through the thalamus. In patients with focal hand dystonia, the influence of the cerebellum on the primary motor cortex (M1) was explored using transcranial magnetic stimulation (TMS) with a twin coil approach of double-pulses (Brighina et al., 2009) or with repetitive TMS (Hubsch et al., 2013) and showed that the modulation of M1 hand area by the cerebellum was reduced. In cervical dystonia patients, cerebellar modulation of M1 is altered by neck proprioceptive feedback (Popa et al., 2018). In addition, the cerebellum communicates with the striatum without any cortical relay via a distinct intralaminar thalamic relay, and the striatum communicates with the cerebellum via subthalamic and pontine relays (Bostan and Strick, 2018). The cerebellum and basal ganglia can thus transmit abnormal activity to one another, possibly creating a vicious circle. For instance, aberrant cerebellar activity can cause dystonia by dynamically forcing dysfunction of thalamo-striatal pathway (Calderon et al., 2011).

Cerebellar and striatal loops that tune the motor cortical activity play a primary role during motor learning, which is abnormal in dystonia. The majority of motor learning studies in dystonia have investigated motor sequence learning, i.e., the ability to coordinate individual movements with greater accuracy and speed resulting from motor practice, which results in the acquisition of a sensorimotor representation in the posterior striatum (Lehericy et al., 2005). Motor practice-related activity in the posterior striatum is abnormal in focal hand dystonia patients, but patients reached the same performance as controls by over-recruiting the lateral premotor cortex (Gallea et al., 2015). Similarly, DYT1 carriers, who are asymptomatic, over-recruited the premotor cortex and the lateral cerebellum to reach performance level comparable to healthy controls (Carbon et al., 2011). In parallel with the over-recruitment of associative circuits during motor sequence learning, striato-cerebellar connectivity was disengaged in dystonic patients during complex finger tasks (Gallea et al., 2015). As observed in motor sequence learning, behavioral performance during reward-based

learning is intact in dystonic patient, while the dorsal anterior cingulate cortex connected to the dopaminergic cortical-basal ganglia-thalamic circuit was over-recruited (Zeuner et al., 2016). Recent findings suggest that the cerebellum also participates in the reward system with its connections with the basal ganglia (Carta et al., 2019). Cerebellar impairments in dystonia could contribute to network dysfunction in reinforcement-based motor learning.

Cortico-cortical interactions in the motor system are crucial in the execution of fine movements, motor planning and preparation, processes that seem impaired in dystonia. Coherent oscillations in large-scale systems in the beta band are important to control fine movements, and these are disrupted in dystonia (Jin et al., 2011a, Jin et al., 2011b). Cortico-cortical interactions are abnormal even before movement execution. Increased activity in the lateral premotor cortex was observed when imagining performing writing in patients with writer's cramp (Delnooz et al., 2013). A lack of premotor-motor inhibition, impaired surround inhibition, and abnormal cortical hyperexcitability affected the early steps of movement preparation in focal hand dystonia (Beck et al., 2008, Houdayer et al., 2012), suggesting that this network is crucial to the selection of voluntary movement representation and the inhibition of unwanted movements. Along similar lines, motor cortex excitability of unintended movement representation is abnormally high in dystonic patients and correlates with disease severity (Kishore et al., 2018). This impaired surround inhibition in sensorimotor areas partly originates in the loss of integrity of the GABAergic inhibitory interneurons measured with PET (Gallea et al., 2018). Furthermore, the loss of GABA-A receptor integrity in the sensorimotor system including the cerebellum could explain several factors at play in dystonia, namely maladaptive plasticity and abnormal sensory feedback processing. Indeed, the integrity of the GABAergic system influences plasticity mechanisms such as long term potentiation (LTP) of synaptic efficacy. Patients with focal hand dystonia have enhanced LTP-like plasticity and a loss of spatial segregation of plasticity effect (Quartarone and Hallett, 2013), thus increasing the excitability of the efferent projections to the impaired hand. In addition, the abnormal processing of somatosensory afferents with enlarged and overlapping finger representations must be closely linked to abnormalities of GABA-A receptors in the sensorimotor cortex (Conte et al., 2019).

Dystonia is a heterogeneous movement disorder in which all subtypes show common brain features, each subtype having also a specific brain signature. Motor control of well-trained abilities is facilitated by motor programs that are specifically and focally represented in specific brain networks. In task specific dystonia, symptoms are expressed only when a task requiring fine sensorimotor integration (writing, playing a musical instrument, speaking) is executed with a specific limb (hand, mouth) that has a large cortical representation, suggesting an abnormal interaction between the brain areas involved in recalling the motor program and the ones controlling

the limb. Abnormalities are localized discretely in specialized brain regions containing the cortical representation of the affected limb, each at the origin of descending motor tracts that show structural alterations (Delmaire et al., 2009, Simonyan et al., 2008). Abnormalities are also present in largely distributed systems. For instance, interactions between parietal and premotor areas containing the representation of specific motor skills are altered in different types of task specific dystonia during motor execution and resting state (Bianchi et al., 2019, Gallea et al., 2016), suggesting they share common features. When considering the complexity of the network architecture on the whole brain functional connectome, common features in different forms of dystonia are a breakdown of basal ganglia-cerebellar connections and loss of information processing in hubs like sensorimotor cortices (Battistella et al., 2016, Fuertinger and Simonyan, 2017). In contrast, the topography of large-scale cortico-cortical interactions seem more specific to each subtype of dystonia (Battistella and Simonyan, 2019, Simonyan, 2018)(Figure 6).

The functional integrity of striatal, cerebellar and cortical interconnected loops depends on a fragile balance sustained by plasticity mechanisms, structural pathway integrity and efficient neurotransmission that have a strong functional significance and clinical relevance in our understanding of dystonia pathophysiology. Future major challenges will be to investigate deeper the interconnection of these loops, i.e., how dysfunction of one node affects the others. Probing the interconnections between these networks can be done using simultaneous stimulation/recording systems with TMS-EEG to study causal cortico-cortical interactions or to modify information transfer across brain structures or testing the long-lasting effects of rTMS on the brain connectivity using fMRI (Hallett et al., 2017). Using long lasting effects of repetitive TMS on focal regions and investigating the subsequent changes of effective cortico-cortical connectivity will help identifying the functional weight of connections or the interactions of networks at play in dystonia.

Apraxia

Apraxia is one of the paradigmatic disorders resulting from disconnections in the brain. On the basis of lesion studies, Liepmann proposed that praxis depends on a left hemisphere parietal-premotor pathway.(Hallett, 2015) Although the hypothesis was denounced by the British school of neurology, Geschwind rejuvenated the concept in his masterful two-part paper in *Brain* on the Disconnexion Syndromes.(Geschwind, 1965a, 1965b) The general concept arose because lesions in either of the two areas produced the clinical syndrome. Such studies of lesions have continued, mainly with MRI, and have produced a more detailed picture. In a meta-analysis of lesions causing pantomime deficits, 50% percent of studies had lesions in the inferior parietal lobe, 14% in the

inferior frontal gyrus and 22% in the posterior temporal region.(Niessen et al., 2014) A large study of acute stroke patients confirmed these locations and noted that imitation relied more on dorsal regions, while pantomime needed also ventral regions, suggesting two relevant pathways.(Hoeren et al., 2014) Another large study looked at pantomime of tool use and imitation of meaningless gestures, and analyzed postural and kinematic aspects of the task.(Buxbaum et al., 2014) The left posterior temporal gyrus was significantly associated with the posture component for tool-related gesture tasks, while lesions in left inferior parietal and frontal regions led to poor performance on the kinematic component of all tasks.

fMRI studies of normal subjects performing praxis tasks confirm activations of these same regions.(Bohlhalter et al., 2009, Fridman et al., 2006, Niessen et al., 2014) In a study of actual tool use, the pattern of activations suggested 3 pathways, a ventral stream for processing semantic information and object properties, a dorso-dorsal pathway (i.e., superior occipital gyrus, superior parietal lobule, and dorsal premotor area) for monitoring the online control of objects, and a ventro-dorsal pathway (i.e., middle occipital gyrus, inferior parietal lobule, and ventral premotor area) for processing known object manipulations.(Brandi et al., 2014) Another study of imitation and pantomime of tool use, again suggested that a dorsal pathway was needed for both and that a ventral pathway was particularly needed for conceptual and semantic operations.(Vry et al., 2015) These pathways were then identified with DTI.

Connectivity studies confirm the hypotheses that the identified regions are actually connected during praxis tasks. For example, using functional connectivity measures with fMRI, a praxis network was identified during a precision drawing task.(Philip and Frey, 2016) Connectivity was seen in the left intraparietal sulcus, the ventral premotor cortex and bilateral mid-frontal gyrus for both left and right hand drawing. The left inferior frontal gyrus, premotor cortex, inferior parietal lobule, and superior parietal lobule showed fMRI correlation during planning for tool use pantomime.(Maki-Marttunen et al., 2014) During hand writing with the dominant hand, there was a specific connection identified between the left inferior parietal cortex and ventral premotor area (that was weakened in patients with writer's cramp).(Gallea et al., 2016) In patients with Parkinson disease, who show limb kinetic apraxia in a coin rotation task, there is a reduced connectivity between the left inferior parietal lobule and the dorsolateral prefrontal cortex (right middle frontal gyrus).(Kubel et al., 2017)

Praxis has also been studied with EEG which has the advantage of better time resolution than fMRI. With pantomime of tool use or meaningless gestures, ERD most distinct in the beta band began during planning about 3 seconds before movement.(Wheaton et al., 2005b) At movement onset, maximal amplitude was present over central and bilateral sensorimotor areas. Direct

comparison of complex movements and simple movements showed clearly that the complex movement began in the parietal region, while the simple movement began more centrally.(Wheaton et al., 2005c) Coherence studies showed left parietal-premotor coherence and premotor-motor coherence that began during preparation and increased more during movement execution (Fig. 7).(Wheaton et al., 2005a) There was no coherence between parietal and motor cortices. A similar EEG study of praxis movements was done with explicit stimuli for prepare and execute, which were 3 seconds apart.(Ewen et al., 2015) Parietal-motor coherence was similar bilaterally with only a trend for larger magnitude on the left. Additionally, there was a large coherence between left and right parietal areas. Effective connectivity was studied with Short-time direct Directed Transfer Function (SdDTF). The left parietal region was a net source for all connections during preparation, while the left frontal region was a net sink, suggesting a net information flow from parietal to frontal. Left parietal-motor coherence was studied at various phases of learning a motor sequence. Coherence increased during the motor practice and gradually reduced as the movement became better learned.(Karabanov et al., 2012)

Children with autism were studied in a complex movement task, and despite their having some apraxia, their parietal-motor coherence was larger than in normal children.(Pillai et al., 2018) This might be due to having to attend more to the task. Two patients with left hemisphere strokes and apraxia were trained on some praxis tasks until they could perform them close to normally.(Wheaton et al., 2008) During their planning and moving, there was no increase in left parietal-motor coherence, but there was an increase in right parietal-motor coherence, suggesting that switching motor control to the right hemisphere was responsible for compensation.

Connectivity studies directly confirm the original ideas of Liepmann and can give insights for the pathophysiology of disorders of complex movement in various conditions. As MRI has good spatial resolution and EEG has good temporal resolution, the studies complement each other.

Epilepsy

This viewpoint is based on a review of the recent literature dealing with resting-state functional connectivity (FC) changes in temporal lobe epilepsy (TLE). TLE is one of the most prevalent focal epilepsies. Epilepsy is considered to be a network disease; therefore, FC provides a useful tool for epilepsy research. Resting-state FC (rsFC) provides important information for understanding the network behavior of the brain in both healthy and pathological neuronal populations.

Functional connectivity

Not surprisingly, functional connectivity (FC) alterations in patients with generalized epilepsies affect extensive areas in the brain (Wang et al., 2011). It seems that even in focal epilepsies, FC alterations, assessed with either EEG or fMRI, are widespread and include connections that are remote from the epileptogenic zone (Terry et al., 2012). In this section, we review FC impairment in temporal lobe epilepsy (TLE) for which there are the most data.

The TLE network is formed by the mesiotemporal structures, the adjacent cortex including the entorhinal cortex, the lateral temporal cortex, and extratemporal structures including the thalamus and orbitofrontal cortex (Spencer, 2002). Despite the diversity of methods that have been used to evaluate FC in TLE, the results congruently show alterations in parts of this epileptogenic network, in other cortical areas within the same hemisphere, and even in the contralesional hemisphere. FC changes can also be seen in cortico-subcortical connections in fMRI (Vytvarova et al., 2017) and EEG (Chiosa et al., 2017) studies. These results all support the concept of TLE as a network disease; the study of FC may contribute to the understanding of the pathophysiology (Figure 8).

Neuropathological findings have shown neuronal damage in focal epilepsies in parts of the brain involved in seizures (Wong and Guo, 2013). It is not surprising that the part of the brain with epileptic activity and its surroundings show decreased FC. This was proven in studies using fMRI (Weaver et al., 2013) and EEG (Ortega et al., 2011). But it is not only the brain region with epileptic activity that shows altered FC. Pittau et al. (Pittau et al., 2012) found decreased rs-fMRI-FC in patients with TLE between the ipsilateral and contralateral mesiotemporal structures, between the mesiotemporal structures and parts of the default mode network (DMN) and the ventromesial limbic prefrontal regions. The same result, of decreased rs-fMRI-FC within the DMN, was also found in other studies (Burianova et al., 2017). Interestingly, even in the absence of interictal spikes, there is decreased FC in connections from posterior parts of the DMN (Coito et al., 2016).

Increased FC was also observed in TLE (and in other focal epilepsies) in other studies. Bettus et al. (Bettus et al., 2011), combining intracerebral EEG (iEEG) and fMRI, reported that FC measured from the BOLD signal was more decreased in epileptogenic areas than in non-epileptic regions. In contrast, FC measured from the iEEG signal was increased in affected areas.

This seemingly contradictory observation demonstrates that FC is a complex phenomenon that may display various patterns when seen from the perspective of whole brain hemodynamic changes via fMRI, and from the perspective based on focal recordings of bioelectric activity via EEG. Increased FC within the epileptic zone was reported in other iEEG studies (Bartolomei et al., 2008, Bettus et al., 2008) and in resting-state fMRI studies (Bettus et al., 2010). Increased FC in remote

areas outside of the epileptogenic zone have been described in several studies. Coito et al. (Coito et al., 2015) found increased FC in the connection of the ipsilateral temporal lobe to the ipsilateral frontal lobe in left TLE, and from the ipsilateral temporal to the contralateral temporal and bilateral frontal regions in right TLE. Maccota et al. (Maccotta et al., 2013) studied both intrahemispheric and contrahemispheric connections using rs-fMRI and showed increased intrahemispheric FC between several parts (hippocampus, insula, temporal gyri) of the hemisphere ipsilateral to the seizure focus, though weak effects were also seen in the contralateral hemisphere.

Findings concerning the impact of the epileptogenic hippocampus on the contralesional hippocampus in rs-fMRI-FC alterations are inconsistent. Bettus et al. (Bettus et al., 2009) showed that in two studies with TLE patients, there was increased connectivity within the non-epileptogenic temporal lobe. In contrast, Pereira et al. (Pereira et al., 2010) found reduced rs-fMRI-FC within the non-epileptogenic temporal lobe for left TLE patients.

These differences in FC changes could be caused by several variables. One important variable is the age of the patient at disease onset. TLE patients with early seizure onset are more inclined to functional reorganization in extratemporal regions than patients with late seizure onset. In patients with hippocampal sclerosis with early onset, the most altered FC is in the areas where seizures are generated; in patients with late onset, the whole-brain rs-fMRI-FC is the most altered (Doucet et al., 2015).

The impact of disease duration on FC seems to be more complicated. In the early stages of the disease, static FC is decreased in the ipsilateral and contralateral temporal network. The increasing duration of TLE brings decreasingly static FC in the ipsilateral temporal lobe network, but it also brings increasingly dynamic FC between the midline cingulate network and ipsilateral temporal network. This implies that as the disease progresses in the temporal lobe, it becomes more synchronous with the network of regions responsible for the secondary generalization of seizures, a process that may facilitate the spread of seizures across the brain (Morgan et al., 2015).

Over 10 years, interhemispheric rs-fMRI-FC of the hippocampi increases linearly with the disease duration. This proves that the early stages of the disease disrupt the interhemispheric hippocampal network, whereas over the long term these connections are rebuilt. These changes reflect the ability of the brain to use an aberrant network and to participate in various cognitive and behavioral activities by recruiting the healthy hemisphere to make up for the impaired hippocampus (Morgan et al., 2011).

It is evident from these findings that the laterality of the epileptogenic zone in TLE has a great impact on FC. The asymmetry in FC patterns of TLE is a well-known phenomenon. Several studies show that in left TLE, the network impairment is more excessive than in right TLE (Bettus et al.,

2011, Pereira et al., 2010, Rektor et al., 2013). The differences in FC between left and right TLE could explain clinical differences, such as differences in the cognitive domain between left and right TLE. The same lateralization effect is evident in focal epilepsy with the epileptogenic zone in neighboring regions, including the insula (Yin et al., 2019). Some results, such as the more pervasive FC abnormalities and potential maladaptive functional reorganization, suggest that left TLE is a more severe form of the disease (Doucet et al., 2013). The differences in FC alterations between left and right TLE are quite sensitive and specific, suggesting that FC could be a helpful indicator of the lateralization of TLE in presurgical evaluations. The presented studies show that rs-fMRI-FC can be decreased bilaterally in TLE, but as Bettus et al. (Bettus et al., 2010) showed, the decrease in rs-fMRI-FC is predominantly on the epileptic side. Another procedure in identifying the side of the epileptogenic temporal lobe was described by Lam et al. (Lam et al., 2016), who used scalp EEG coherence and identified mesial temporal lobe seizures in 40% of patients with no visible ictal correlate on scalp EEG.

The correlation between rsFC alterations and cognitive deficits may be clinically important. FC changes might explain cognitive deficits resulting from brain impairment distant from the epileptic focus and showing no neuronal substrate damage. Indeed, it has recently been shown that interictal discharges can produce spindles in distant parts of the brain, not involved in the epileptic network (Dahal et al., 2019). Decreased FC is generally considered to be a result of the disruption of neuronal connections within a functional network, and it is commonly considered to reflect cognitive impairments in brain disorders (Greicius, 2008). Increased connectivity is considered to be a compensatory mechanism that maintains cognitive function in epilepsy (Voets et al., 2009). Bettus et al. (Bettus et al., 2009) described increased rs-fMRI-FC in mesiotemporal lobe epilepsy (MTLE) between the posterior and anterior parts of the nonpathological hippocampus that positively correlated with working memory performance. The authors suggested that this change in the healthy hemisphere could be a cognitive compensation that functionally limits the effects of brain injury inside the temporal lobe involved in MTLE. Zhang et al. (Zhang et al., 2010) found increased rs-fMRI-FC within the posterior cingulate cortex in right MTLE but not in left MTLE patients, and hypothesized that compensatory mechanisms are more potent in right TLE than in left TLE.

A cognitive compensatory mechanism in right TLE was demonstrated by a positive correlation between delayed recall scores in a nonverbal memory task and rs-fMRI-FC between the left (nonpathological) mesiotemporal structures and the medial frontal cortex (Doucet et al., 2013). A negative correlation – probably a maladaptive change – was found between verbal memory

performance and rs-fMRI-FC between the left pathological mesiotemporal structures and the posterior cingulate cortex in left TLE.

Surgical outcome prediction could be one of the most important applications of FC measurements. FC analyzed with iEEG can predict seizure freedom after a temporal lobectomy (Antony et al., 2013). The FC analysis may be also important factor in epilepsy surgery timing, and FC changes should be an argument for not delaying surgical intervention. A successful operation does not restore FC alterations caused by long-lasting disease, as some FC changes are irreversible (Maccotta et al., 2017). We presume that these irreversible changes could have negative impact on brain functions (cognitive) even in seizure-free patients. Rs-fMRI-FC predicted a postsurgical cognitive decline in a study by McCormick et al. (McCormick et al., 2013), where stronger FC between the epileptogenic hippocampus and posterior cingulate was associated with greater postsurgical episodic memory decline. Stronger FC between the contralateral hippocampus and posterior cingulate was associated with lesser episodic memory decline in term of graph theory analysis and global network measurement.

Another clinically relevant application of FC analysis could be studying of antiepileptic drug effects on brain networks, as, for example, levetiracetam reduces abnormal network activations in TLE (Wandschneider et al., 2014).

The interpretation of the observed FC changes in TLE is rather hypothetical. One reason is that FC changes show temporal instability. FC instability was found in TLE in several areas, including the supplementary motor area, the pre- and postcentral gyri, the precuneus, middle occipital gyrus, and the superior frontal gyrus, regardless of the lateralization of the epileptogenic hippocampus, in a study by Laufs et al. (Laufs et al., 2014). They hypothesized that the interictal epileptiform activity in the hippocampus leads to increased FC. Temporal changes of FC are not restricted to specific areas, as shown in the scalp EEG study by Vega-Zelaya et al. (Vega-Zelaya et al., 2015), who described increasing global synchronization in the whole brain during the transition from the preictal to the ictal stage. How the temporal instability is related to clinical aspects of TLE (such as cognitive decline and seizures frequency) is a question that has not yet been answered.

Conclusion

All the FC alterations described in TLE or more generally in focal epilepsies reflect the high complexity of this disease. There is decreasing connectivity in particular parts of the brain and increasing connectivity in others, depending on variable aspects (laterality, seizure onset, interictal activity presence, etc.). All these results support the image of epilepsy as a network disease, and its network is very dynamic (Table 1).

FC is relatively rarely used in presurgical evaluation. Some of the most challenging work for the future will be to find better and more precise correlations between connectivity alterations and the clinical aspects of epilepsy. Better knowledge of these correlations will enable better understanding of epilepsy comorbidities, better presurgical evaluations, and better outcomes. EEG or rs-FMRI-FC should be helpful as an integral part of presurgical epilepsy evaluation, thus enabling better estimations of the surgical outcome in both seizure freedom and postsurgical cognitive defects.

Brain networks in epilepsy display dynamic properties. Decreased and increased FC could be demonstrated depending on variable aspects. Both EEG and rs-FMRI-FC might be used for clinical practice in the future. It could affect clinical practice in at least three domains. First, FC might indicate the hemispheric lateralization of the epileptogenic zone. Second, it might explain the cognitive impairment involving regions remote from the epileptic focus. Third, it might predict the impact of resective surgery in MTLE on postsurgical cognitive impairment. However, further studies are needed before its introduction in routine practice. More studies of the FC in MTLE are also needed to explain certain discrepancies (for example, between iEEG and fMRI studies) and contradictory results (for example, in the hemisphere contralateral to the epileptogenic zone). The introduction of new methods of signal processing, such as graph theory analysis, might be helpful.

Phantom Limb Pain

After an amputation, 90% of the patients experience sensations that the lost body part is still present and kinesthetically perceived; these phenomena are called "*phantom awareness*" and "*phantom sensations*". In addition, up to 80% of amputees feel a painful dysesthesic perception in the lost limb, a disorder known as *Phantom Limb Pain* (PLP). The underlying mechanisms of PLP are incompletely known, but it appears that the deafferented primary sensory area becomes progressively responsive to inputs from the parts of the body near to the missing area. Many studies have demonstrated this shifting of the cortical body map with an extension of the face and mouth regions into the expected hand territory in human amputees by the use of magnetic source imaging using MEG (during pneumatic stimulation of the mouth) and fMRI (during execution of lip movement), reflecting re-organization of sensory map following amputation (Karl et al., 2001).The cortical reorganization can be considered as an example of aberrant cortical 'plastic' reorganization (Flor et al., 2006).

Studies on brain connectivity in amputees have been carried out with the underlying assumption that, given that phantom pain experiences are decoupled from other sensorimotor experiences, the lack of co-activation of the cortical phantom area and other body parts (such as the intact hand)

could result in diminished interactions between different body part representations (i.e. between the phantom cortex and its contralateral counterpart). Pawela and colleagues (Pawela et al., 2010) provided the first demonstration of this hypothesis in a preclinical study, in which changes in functional connectivity were evaluated in adult rats following transection of the four major nerves of the brachial plexus. Functional connectivity MRI analysis, indeed, showed that intrahemispheric connectivity in the sensorimotor forelimb representations in both hemispheres were largely unaffected by deafferentation, whereas substantial disruption of interhemispheric sensorimotor cortical connectivity occurred. These differences were noted only in regions responsible for processing sensorimotor information, since no changes in connectivity were found in the primary visual cortex (studied as a control) upon forelimb deafferentation, Similar results were found in humans by Makin et al. (Makin et al., 2013); amputees suffering from chronic phantom pain showed maintained function and structure in the missing hand cortex while inter-hemispheric functional connectivity between the two hand areas was significantly reduced, as measured using resting-state fMRI, with a reduction of transcallosal white matter (Simoes et al., 2012). Furthermore, the higher phantom pain the greater was the reduction in inter-hemispheric functional connectivity, suggesting that persistent phantom pain representation might contribute to functional isolation of the phantom cortex from the sensorimotor system, as reflected by reduced connectivity between the hand areas. These lines of research have been largely focused on the evaluation of plasticity and connectivity in the primary sensorimotor cortex of the both “phantom” and hemisphere contralateral to the amputation.

Since the primary sensorimotor areas are interconnected with higher-order sensorimotor areas, as well as with association cortex, it has been hypothesized that the local massive remapping of the missing hand area could produce a cascade of changes in connectivity both within and beyond the sensorimotor system. With this idea in mind, resting-state fMRI was used to identify large-scale reorganization and global network-level changes in functional connectivity in arm amputees, compared with two-handed controls (Makin et al., 2015), by investigating changes in functional connectivity between the cortical territory of the missing hand in the primary sensorimotor cortex (‘missing hand cortex’) and two networks of interest: the sensorimotor network, typically strongly associated with the hand cortex, and the default mode network (DMN), normally dissociated from it. Lower levels of functional coupling between the missing hand cortex and the sensorimotor network were also associated with emerged coupling of this cortex with the DMN. It seems therefore likely that sensory deprivation, adaptive plasticity and increased aberrant input all contribute to the observed reduction in coupling between the missing hand cortex and the sensorimotor network. Since phantom sensations are manifested in an incorporeal body-part and

can be regarded as internal modes of sensation, the coupling with the DMN might not merely be a passive consequence of decoupling from the sensorimotor network. An alternative explanation of selective coupling of the missing hand cortex with the DMN could depend on the resting state set-up used in this study (i.e. participants not engaged with external stimuli, but asked to keep awake), a context which may particularly activate the DMN, as participants engage in internal modes of cognition (Buckner et al., 2008). More recently, other researchers investigated changes in functional connectivity in the sensorimotor network of long-term lower-limb amputees using tactile residual limb stimulation and fMRI (Bramati et al., 2019). These authors found a reduction of inter-hemispheric functional connectivity between homologous sensorimotor cortical regions in amputees, including the primary and secondary somatosensory areas, and primary (M1) and secondary (M2) motor areas, and an intra-hemispheric increased functional connectivity between primary and secondary somatosensory regions, and between the primary and premotor areas, contralateral to amputation. Altogether, plasticity following arm amputation is not restricted to local remapping occurring within the sensorimotor homunculus of the missing hand but rather produces a cascade of cortical reorganization at a network-level scale, which seems to persist over time even after years from the amputation.

Lyu and colleagues (Lyu et al., 2016) used EEG for a higher temporal resolution measure to delineate the dynamic network of the brain. They used phase synchronization index (PSI) to construct functional connectivity networks from resting-state EEG in alpha and beta bands and graph theory analysis to compare both global and local network parameters between twenty-two right-hand amputees and twenty-four healthy controls. In the aspect of global connectivity, amputees showed increased clustering coefficient (C), decreased characteristic path length (L) and increased small worldness (S) in alpha band, and an increase of L in beta band. The increased clustering coefficient, suggesting a stronger synchronization and functional inter-connections between nodes, might be related to the weakened inter-hemispheric inhibition after amputation, which would result in unmasking of ordinarily silent connections or strengthening of previously subthreshold connections. The strengthened connectivity after amputation would also result in the decrease of characteristic path length, with the manifestation of the reduced shortest path. The increased clustering coefficient and decreased characteristic path length consequently resulted in the increase of small worldness in amputees. Furthermore, amputees showed smaller nodal degree (k) in the sensorimotor area but higher k in the parietal area in the right hemisphere contralateral to the intact hand. The decrease of nodal degree observed only in the intact sensorimotor cortex could be due to a decreased inter-hemispheric inhibition and to an increase in connections between the affected sensorimotor cortex and other parts of the brain. Conversely, the higher nodal degree

observed in right parietal area might be related to the phantom phenomena after amputation, given the prominent part of parietal lobule in body image representation. A decreased inter-hemispheric inhibition seems to play a crucial role in network alterations following amputation reported in this work, thus compatible with the previous observations (Makin et al., 2013, Pawela et al., 2010).

Taken together, such connectivity changes described until now provide a new framework to understand phantom limb phenomenon and address future targets for rehabilitation therapies. For example, Scibilia et al. (Scibilia et al., 2018) described a case of a 69-year old patient with a severe pain with a phantom right lower limb. The authors assessed brain connectivity with resting-state functional MRI before and after the rTMS treatment. This kind of approach allowed pain relief after 1 month. Post-treatment fMRI showed increased connectivity, mainly in the sensorimotor network and the unaffected hemisphere. This report thus represents a proof-of-concept that promoting brain connectivity with a non-invasive method such as rTMS may be a functional strategy to reduce pain in PLP patients, also providing further evidence that an impaired connectivity could play a crucial role in generating phantom sensations. These results strengthen the hypothesis that plasticity following amputation is not limited to local remapping occurring within the sensorimotor cortex but rather produces a cascade of cortical reorganization at a network-level hierarchy.

Further insights have come from studies regarding the use of innovative nerve-interfaced hand prosthesis in amputees (Petrini et al., 2019, Raspopovic et al., 2014). After the implant of cybernetic hand and 4 weeks of training, Rossini and co-workers observed: 1) a clear restriction of the cortical excitable area of representation of muscles adjacent to the stump by means of TMS mapping, in parallel with decrement of PLS symptoms (Rossini et al., 2010); 2) a normalization of background rhythms for movement preparation (α/β band desynchronization) in the sensorimotor area contralateral to the missing limb and a restoration of the α band synchronization of Rolandic area with frontal and parietal ipsilateral regions (Tombini et al., 2012); 3) a normalization of functional balance of the directly-connected control areas within the bi-hemispheric system necessary for motor control (Di Pino et al., 2012); 4) a recovery of a partial disruption of the N46 wave's dipole, probably representing M1 functionality, in the phantom motor area by a TMS-EEG study (Ferreri et al., 2012). These findings provide further evidence that aberrant changes induced by the amputation are not restricted to the "phantom" sensorimotor cortex but involve the whole brain: the innovative system described in these studies appears capable of promoting a global brain re-organization and probably brain connectivity in the amputees, thereby controlling and alleviating PLP.

Resting-state connectivity analysis can be considered as a potential neuroimaging biomarker to evaluate cortical changes following amputation and also to evaluate the impact of therapeutic

intervention in the phantom limb syndrome. Further research with this kind of approach, better if performed with a multimodal analysis and in a larger cohort of patients, is necessary for an improved understanding of the complex phenomena of phantom limb syndrome.

Conclusion

The examples in this manuscript give strong evidence that neurological and psychiatric symptoms and signs can be best understood with a consideration of the information processing networks of the brain more than a single region analysis. Our models for brain function are still relatively simple, and as more information is gathered the models will be improved. There is room also for improvements in our capability to analyze the electrophysiological and neuroimaging data. The next step is to improve disorders by modulating the networks. This is now already happening with deep brain stimulation and to a lesser extent with non-invasive brain stimulation with TMS and tDCS. Much of the stimulation work is just empirical; we do it because it works. We will certainly do better as we understand more about how the networks function.

Conflicts of Interest (Full disclosures)

M.H. may accrue revenue on US Patent for an Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders and for a Coil for Magnetic Stimulation and methods for using the same (H-coil); in relation to the latter, he has received license fee payments from the NIH (from Brainsway). He is on the Medical Advisory Boards of CALA Health, Brainsway, and Cadent. He is on the Editorial Board of approximately 15 journals and receives royalties and/or honoraria from publishing from Cambridge University Press, Oxford University Press, Springer, and Elsevier. Grant research funds have come from Merz for treatment studies of focal hand dystonia, Allergan for studies of methods to inject botulinum toxins, Medtronic, Inc. for a study of DBS for dystonia, and CALA Health for studies of a device to suppress tremor.

R.De. is on the Executive Board of the German Society for Muscle Disorders, on the Editorial Boards of five scientific journals and receives honoraria from publishing from Thieme Verlag, Germany.

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R.H. is on the Medical Advisory Boards of Cadent Therapeutics. He has received honoraria from AbbVie and TouchIME. He receives research support from the Netherlands Organization for Scientific Research, the Netherlands Organization for Health Research and Development, and the Michael J. Fox Foundation.

P.M.R. is president of a university spin-off company (Neuroconnect) for diagnostic/therapeutic applications of neurophysiological technologies with pending patents.

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Table 1: Brain regions with altered resting state fMRI functional connectivity in TLE summarizing the quoted studies. Number of + signs for strength of evidence (+, ++, +++), "no" means no evidence.

Brain region	Decreases in FC	Increases in FC	Comment
Temporal lobe, ipsilesional	+++ within epileptogenic lesion ++ in connection with contralateral mesiotemporal structures	+++ within epileptogenic lesion	Alterations in connections of temporal lobes with other brain regions are mentioned below
Temporal lobe, contralesional	++ within mesiotemporal structures	++ within mesiotemporal structures	
Insula, ipsilesional	+ in connection with mesiotemporal structures	+ in connection with ipsilateral mesiotemporal structures	
Insula, contralesional	+ in connection with mesiotemporal structures	+ in connection with ipsilateral mesiotemporal structures	
Frontal lobe, ipsilesional	+++ in connection with mesiotemporal structures ++ in connection with other parts of DMN		Mostly affected, superior frontal gyrus, parts of DMN (ventromesial prefrontal structures, anterior cingulum)
Frontal lobe, contralesional	+++ in connection with mesiotemporal structures ++ in connection with other parts of DMN	++ in connection with mesiotemporal structures.	Mostly affected superior frontal gyrus, parts of DMN
Parietal lobe, ipsilesional	++ in connection with mesiotemporal structures ++in connection with other parts of DMN	+ in connection with temporal poles	Mostly affected postcentral gyrus and parts of DMN (posterior cingulum, angular gyrus and precuneus)
Parietal lobe, contralesional	++ in connection with mesiotemporal structures	+ in connection with temporal poles	Mostly affected postcentral gyrus

	++in connection with other parts of DMN		and parts of DMN
Occipital lobe, contralesional	no	no	
Occipital lobe, ipsilesional	no	no	

FC = functional connectivity; TLE = temporal lobe epilepsy; DMN = default mode network

Figure Legends

Figure 1 Graph theory analysis of dementia using EEG. Left panel: eLORETA connectivity maps for delta, alpha1 bands, in the moderate AD, mild AD, MCI and Nold groups. Each red tract among the 84 ROIs reports only the connectivity value higher than the cut-off threshold. Right panel: Correlations between callosal FA and Characteristic Path length in delta and alpha 1 band. AD = Alzheimer disease; MCI = mild cognitive impairment; Nold = normal old; FA = fractional anisotrophy. Source: (Vecchio et al., 2015)

Figure 2 **Dys-connection after stroke.** Stroke lesions to white matter bundles can result in specific symptoms, referred to as "disconnexion syndromes" (Geschwind et al. 1965). For example, a lesion to the arcuate fascicle can result in conduction aphasia *(left)*: the patient understands language, speaks fluently, but may use the wrong words and has difficulties to repeat spoken phrases. In addition, a focal lesion can have remote effects as summarized by the concept of diaschisis *(right*, von Monakow, 1914). A lesion to region A *(green)* may interrupt facilitating influences exerted from region A onto region B *(blue)* leading to "passive inhibition" and thus functional impairment of region B.

FIGURE 3 **Online TMS after stroke.** Interfering with the neural activity of a cortical region during task performance via TMS allows elucidating the functional role of the stimulated region for the given task. In chronic stroke patients, application of online TMS interference over the ipsilesional or contralesional primary motor cortex (M1), dorsal premotor cortex (PMd), or contralesional posterior parietal cortex has been shown to deteriorate motor hand function for different tasks (Johansen-Berg et al. 2002; Lotze et al. 2006)(Fridman et al., 2004, Werhahn et al., 2003). These findings indicate a supportive role of these regions for motor function in chronic stroke. Conversely, in acute stroke patients, online TMS applied to contralesional M1 improved finger-tapping performance (within the first 14d after stroke), pointing to a maladaptive influence of the contralesional M1 on finger-tapping performance of the paretic hand early after stroke (Volz et al. 2017).

FIGURE 4 **Beyond the motor system.** (A) Correlations among behavioral deficits across patients (correlation coefficients are superimposed on arrows), as computed for the behavioral scores obtained from 132 stroke patients tested for motor function, attention, spatial memory, verbal memory and language performance two weeks after stroke. (B) Behavioral deficits across domains correlate with patterns of altered resting-state functional connectivity: pronounced deficits are

observed in patients featuring decreased interhemispheric connectivity *(left)* and increased connectivity between intrahemispheric networks *(right)* which are typically not strongly interconnected in healthy subjects (here the dorsal attention network *(blue)* and the default network *(red)*). (adapted from Corbetta et al 2018, with permission of publisher)

Figure 5: The cerebral circuit of Parkinson's tremor. Panels A-B show brain regions where activity correlated with tremor power (measured with EMG)(Helmich et al., 2011). Panel C shows brain regions where tremor-related activity differed between Parkinson disease (PD) patients with dopamine-resistant versus dopamine-responsive tremor (Dirkx et al., 2019). Panel D summarizes the tremor circuitry involved in PD tremor, based on dynamic causal modelling (Dirkx et al., 2016). Circuit dynamics are driven by activity in the GPi (black arrow). Filled orange regions are more involved in dopamine-responsive tremor; filled gray regions are more involved in dopamine-resistant tremor. MC = motor cortex; VIM = ventral intermediate nucleus; GPe = external globus pallidus; GPi = internal globus pallidus; STN = subthalamic nucleus; INT = interposed nucleus; CBLM = cerebellar cortex; OP4 = parietal operculum; DA = dopamine.

Figure 6. Specific and common features of network deficiencies in dystonia. In the upper part, the lateral view of the brain displays the cortico-cortical interactions that are specific features of different forms of dystonia. The precentral gyrus (dark grey area) contains the lateral premotor areas (dorsal: PMd, ventral: PMv) and the primary motor cortex (M1) in the anterior bank of the central sulcus. The postcentral gyrus (light grey area) contains the primary somatosensory cortex, and posterior to it is the posterior parietal cortex (PPC). In the middle part, two planes are shown. First, the coronal plane (a) of the brain displays the striato-pallido-thalamo-cortical loop including the caudate (Caud) and putamen (Put) forming the striatum, the GPe and GPi (the external and internal parts of the globus pallidum), the thalamus (Thal) with its different nuclei (the ventro-lateral nucleus (VL) is the relay between the pallidum and the cerebral cortex, the ventral-intermediate (VIM) is the relay between the cerebellar dentate nucleus (Dent) and the cerebral cortex, the centro-medial nucleus (CM) is the relay between the dentate nucleus and the striatum). The subthalamic nucleus (STN) and the pontine nuclei (PN) are relays between the striatum and the cerebellum. Second, an axial plane of the cerebellum (b) displays the cerebello-dentate-thalamo-cortical loop. Note that the connection between the cerebral cortex and the cerebellum is not displayed in the figure. In the lower part, a lateral view of the cerebellum and the pons shows the slice localization of the axial cerebellar plane. Both the striato-pallido-thalamo-cortical loop and the cerebello-dentate-thalamo-cortical loop are common features of network deficiencies in dystonia.

The cerebello-striatal loop is displayed in dash lines, its involvement in dystonia being not clearly demonstrated in human pathology yet.

Figure 7. EEG coherence from left parietal area during praxis movements. Topological maps show the coherence in the beta band from P1 (electrode name of a left parietal site) to the rest of the brain at various times with respect to the beginning of movement, which is at time 0.0. A. Coherence with intransitive movements, B. Coherence with transitive movements. From (Wheaton et al., 2005a) with permission.

Figure 8. Resting state data from functional magnetic resonance imaging, left sided temporal lobe epilepsy versus healthy controls. Correlation matrix on the right – warm colors represent decreased connectivity, cold colors represent increased connectivity between areas. Graph theoretical approach on the left showing resting state network activated in left sided temporal lobe epilepsy (Výtvarová, unpublished)

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Figure 1

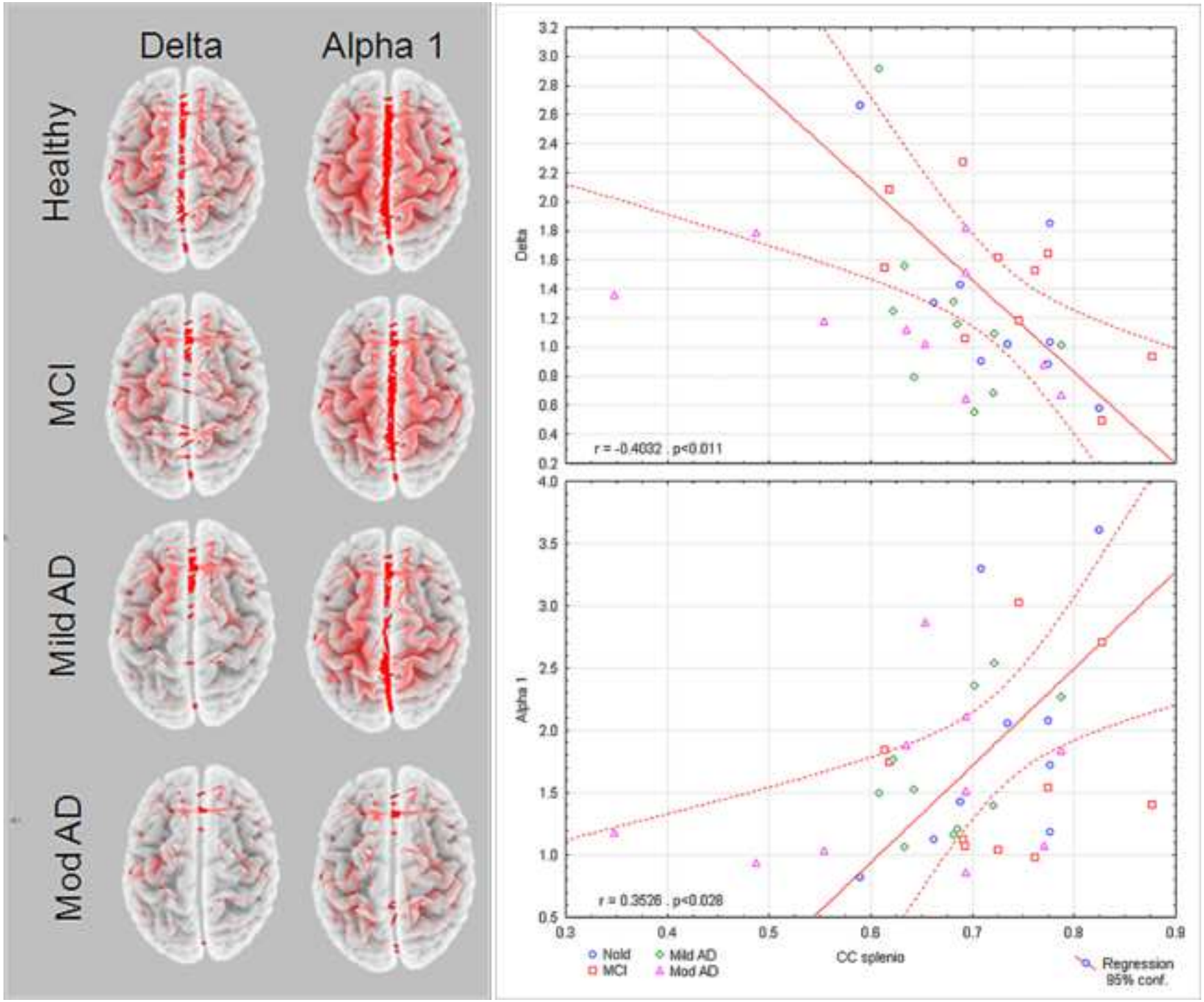
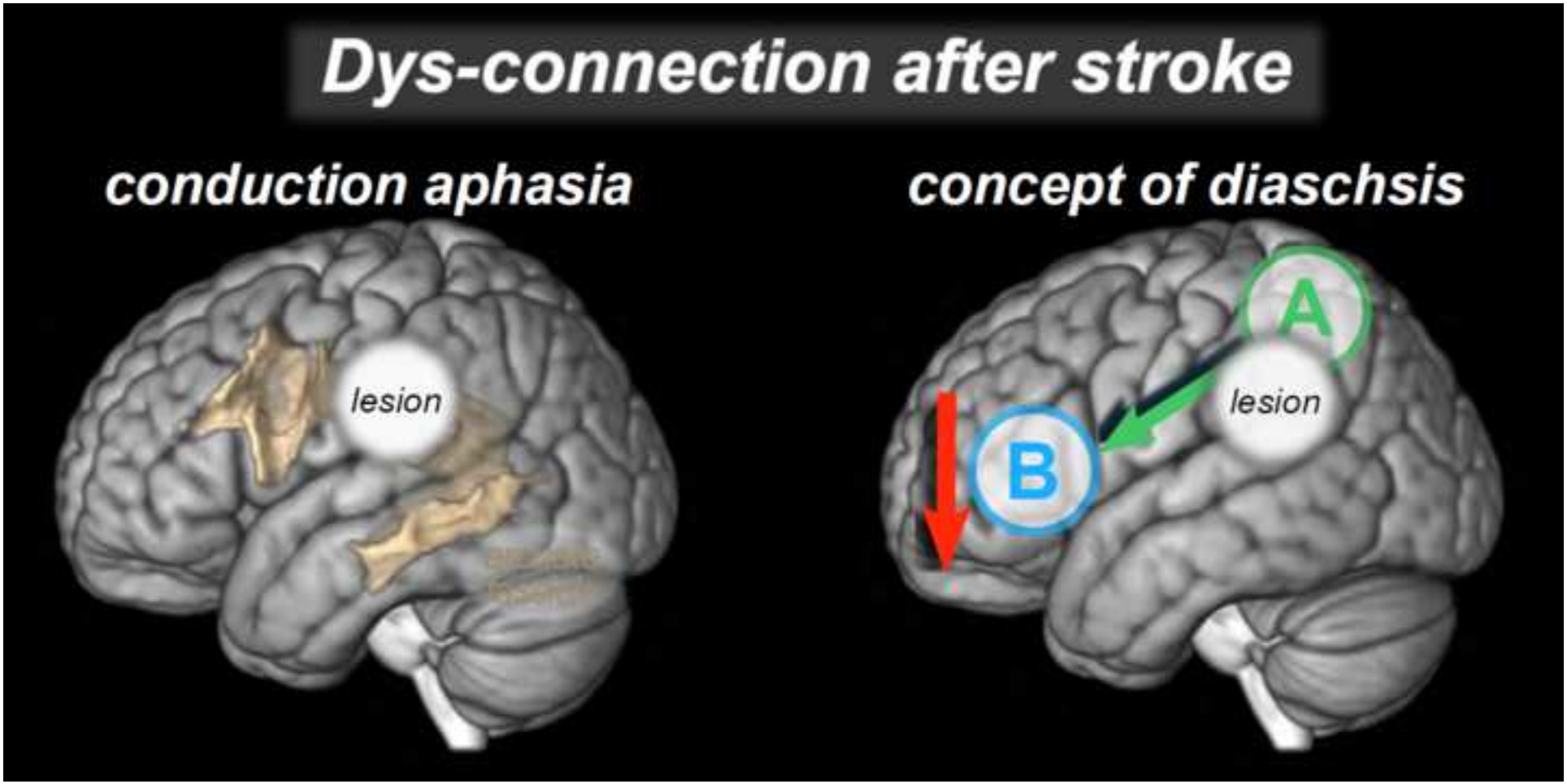


Figure 2



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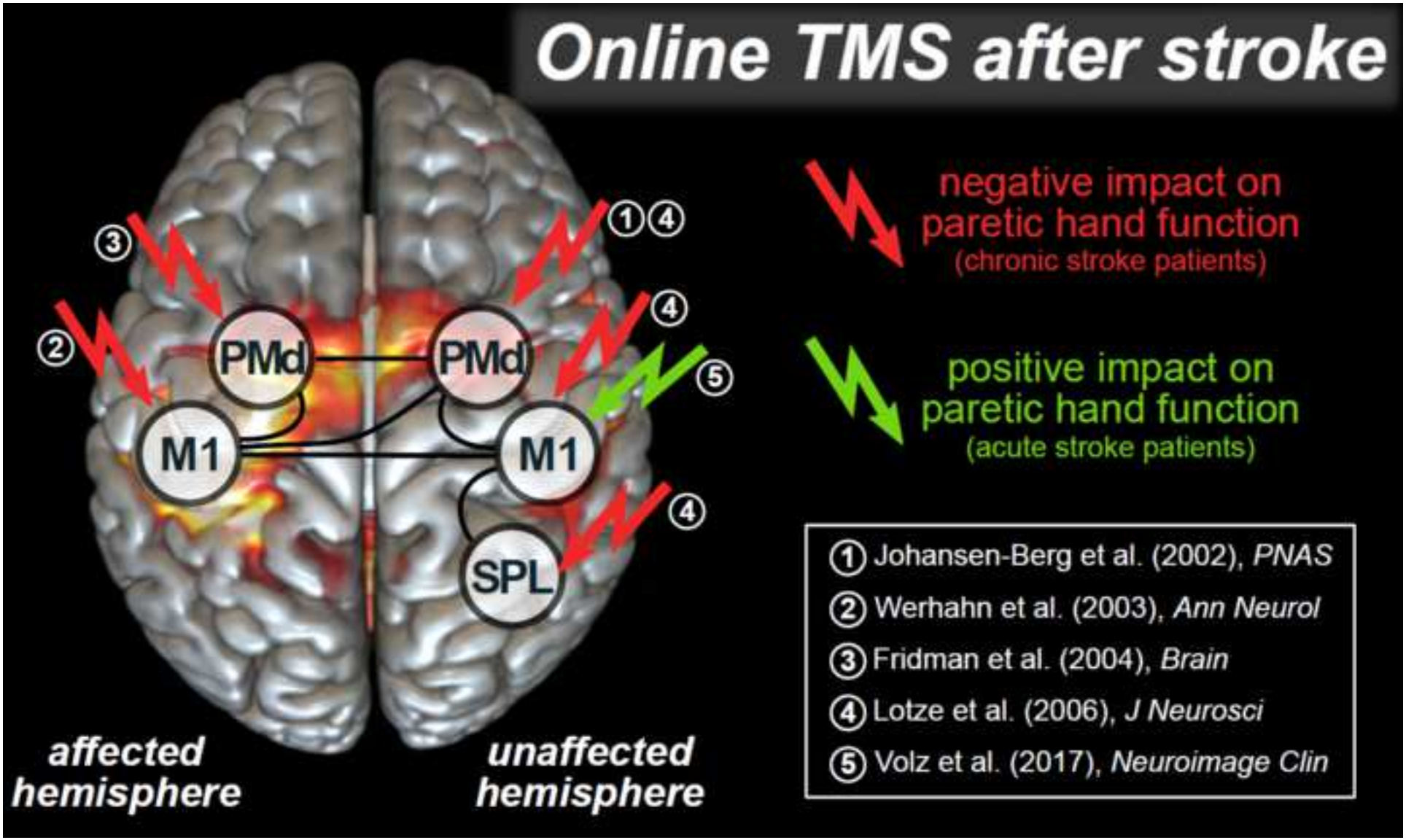

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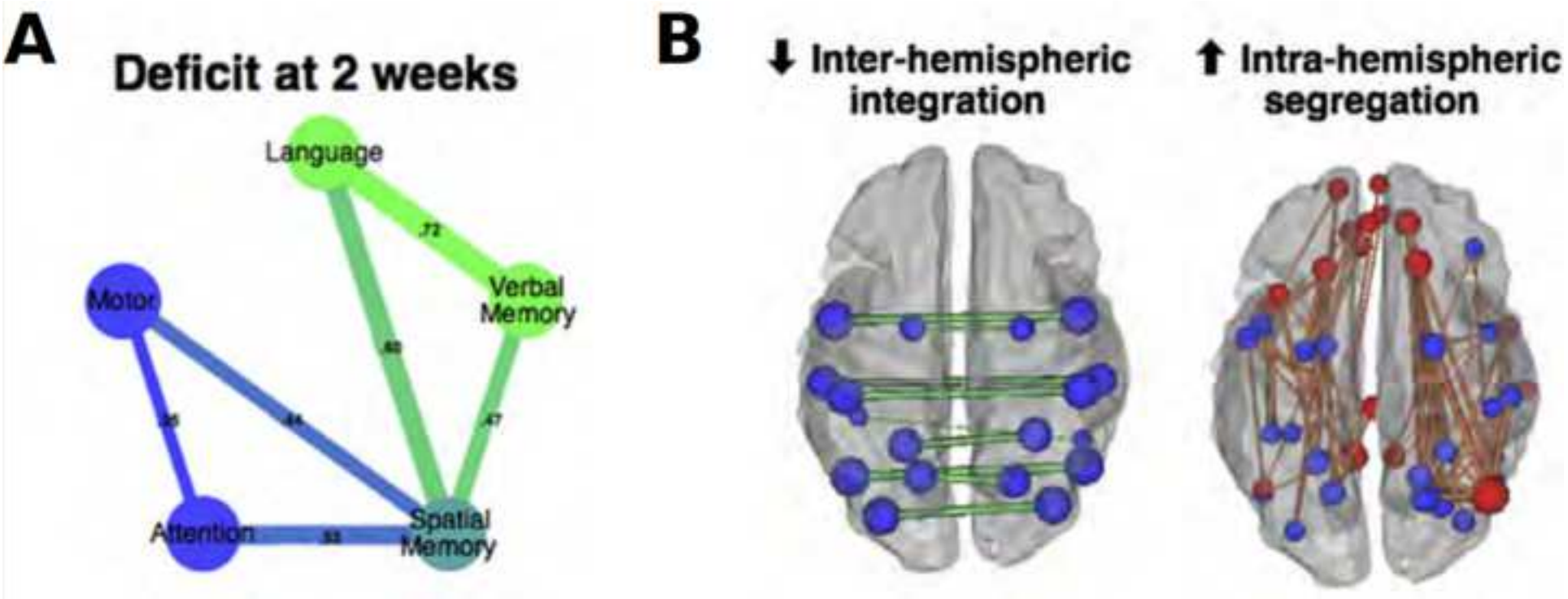

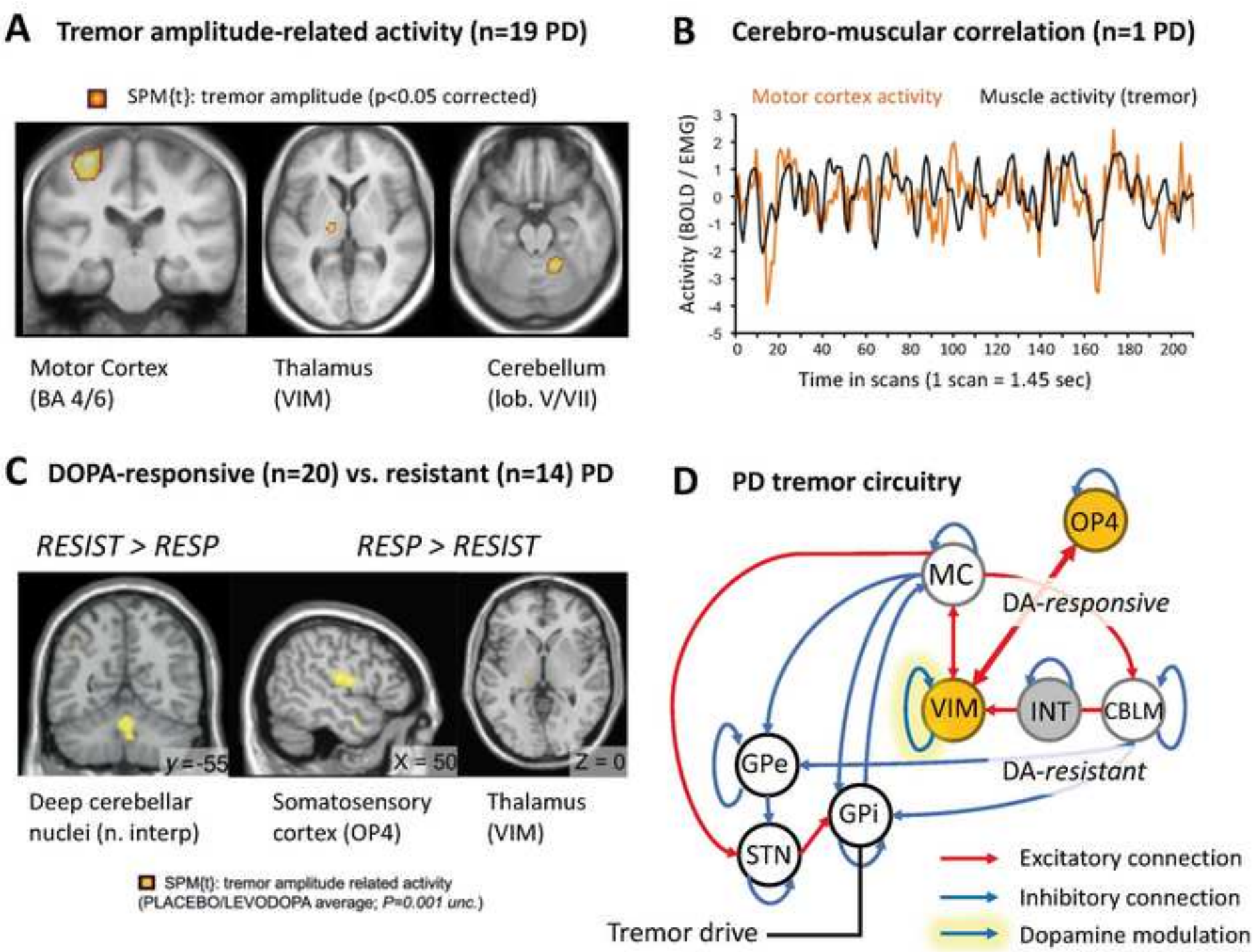

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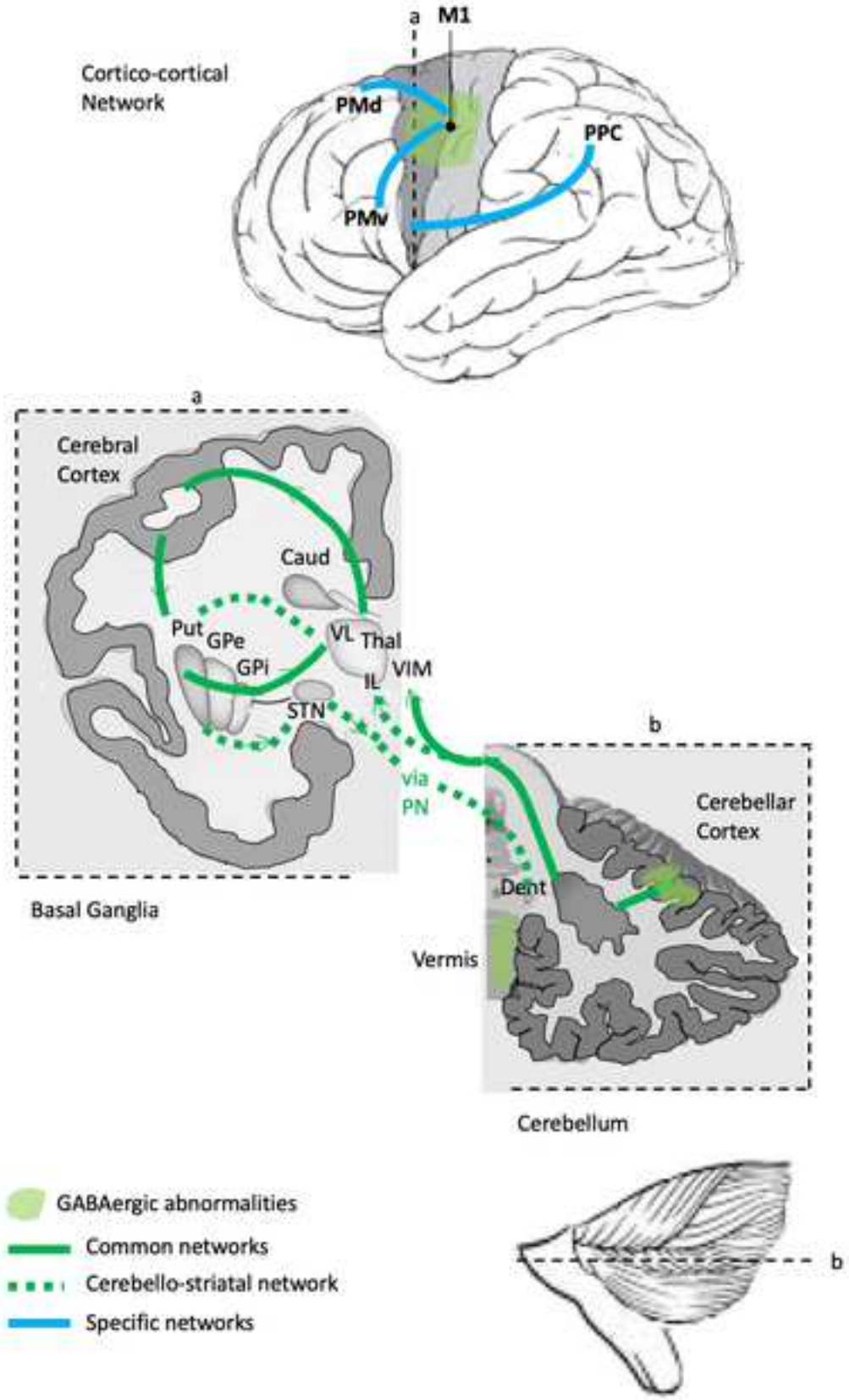

Figure 7

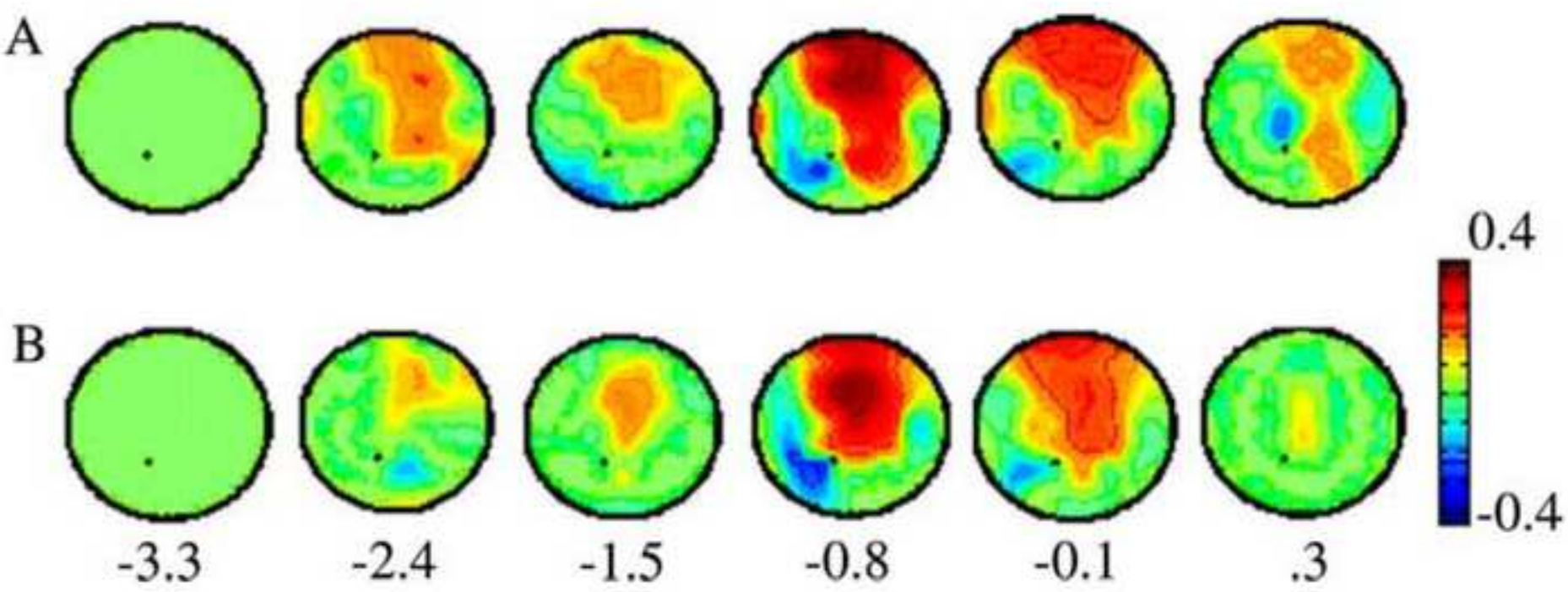

Figure 8