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Emerging neuroimaging technologies: Towards future personalized diagnostics, prognosis, targeted intervention and ethical challenges.

Urs Ribary[1,5,6,7,14], Alex L Mackay[8,9,13,14], Alex Rauscher[6,13,14,15], Christine M Tipper[7,15], Deborah E Giaschi[10,14,15], Todd S Woodward[7,15], Vesna Sossi[9,14], Sam M Doesburg[2,5], Lawrence M Ward[11,14], Anthony Herdman[5,12], Ghassan Hamarneh[3,4], Brian G Booth[3,4,16], and Alexander Moiseev[5].

[1]Departments of Psychology, [2]Biomedical Physiology and Kinesiology, [3]Computing Science, [4]Medical Image Analysis Lab (MIAL), [5]Behavioral and Cognitive Neuroscience Institute (BCNI), at Simon Fraser University (SFU), Vancouver, Canada; [6]Departments of Pediatrics, [7]Psychiatry, [8]Radiology, [9]Physics and Astronomy, [10]Ophthalmology and Visual Sciences, [11]Psychology, [12]Audiology, [13]UBC MRI Research Centre, [14]Brain Research Centre, at University of British Columbia (UBC) Vancouver, Canada; [15]Child & Family Research Imaging Facility (CFRIF) at BC Children's Hospital, Vancouver, Canada; [16]iMinds-Vision Lab, University of Antwerp, Belgium.

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Abstract

The human brain is a fine-tuned and balanced structural-, functional- and dynamic electro-chemical system. Any alterations, from slight slowing of partial brain networks to severe disruptions in structural, functional and dynamic connectivity across local and large-scale brain networks, will result in slight to severe changes in cognitive ability, awareness and consciousness as seen in the many cognitive disabilities and neuropsychiatric pathologies including traumatic brain injury (TBI). The common future goal is to relate typical or atypical resting-state, sensory-motor functions, cognition and consciousness to underlying typical or altered quantified brain structure, biochemistry, pathways, functional brain networks and connectivity using non-invasive brain imaging technologies in healthy subjects, cognitive disabilities, and neurological or psychiatric patients. Multimodal brain imaging technologies have come a long way; they are already and will continuously provide all the required tools necessary to analyze and visualize such many diverse and detailed alterations of the typical and atypical human brain with the highest spatial and temporal resolution and precision. This will pose enormous ethical challenges for the implementation of quantitative diagnostic and prognostic strategies into clinical practice in the future, according to best practice and the highest ethical standards, due to better and more accurate detection of even the slightest typical variations of the healthy human brain or the slightest sub-type specific abnormalities in cognitive disabilities or pathologies.

Introduction

In this chapter, we highlight a selection of advances, future challenges, and limitations of emerging multimodal neuroimaging technologies, data signal processing and visualization strategies. We bring these examples to the forefront as experts in the field who are also attentive to the ethical challenges they pose for personalized diagnostics, prognosis, and targeted intervention into clinical practice.

Advances in structural magnetic resonance imaging (MRI): Toward the quantification of tissue properties

The basis of structural MR imaging is the three conventional MR contrasts: proton density, T_1 weighting and T_2 weighting. While the detailed mechanisms of T_1 and T_2 in brain tissue are not well understood, these processes provide qualitative contrast weightings that yield superb *in vivo* visualization of central nervous system tissue and have proved invaluable as a diagnostic and patient management tool. These days, MR is evolving into a quantitative tool due to incorporation of improvements in both hardware and software that allow for much faster scanning, such as parallel imaging (Pruessmann et al. 1999) and simultaneous multislice imaging techniques (Barth et al. 2016). These approaches facilitate the introduction of otherwise time consuming MRI scans into clinical research and potentially into routine clinical practice. New MR imaging sequences have vastly expanded the types of information available by MRI and the latest developments blur the boundaries between structural and functional information. The new frontier in MRI is the quantification of changes in tissue due to development, aging, disease and therapy. In this very brief overview we highlight a few of the most exciting developments.

A variety of imaging techniques measure brain perfusion (MacDonald and Frayne 2015). For example, arterial spin labeling can yield estimates of cerebral blood flow rates without requiring injection of a contrast agent. While most MR images arise from water, by using magnetization transfer techniques, one can access protons resident on other molecules; chemical shift saturation transfer (CEST)(Ward, Aletras, and Balaban 2000) promises to be able to produce images of the distribution of

several biologically important molecules like glucose (Nasrallah et al. 2013) and amino acids residues in proteins. Inhomogeneous magnetization transfer produces images that are specific for membrane lipids in brain (Varma et al. 2015).

There is a large literature on measurement of water diffusion in brain (Jones 2016). Diffusion tensor imaging (DTI) enables tractography, which is the visualization of nerve tracts in brain. DTI provides mean diffusivity and fractional anisotropy, which are highly sensitive to subtle changes in microscopic brain structure. Despite limitations in terms of specificity (Jones, Knösche, and Turner 2013; Beaulieu 2002), DTI has been used widely in neuroimaging. Advanced diffusion techniques, e.g., diffusion based size imaging (Wang et al. 2011), enables more quantitative analyses including the proportion of axonal water and of inflammatory cells.

A specific measurement of myelin can be accomplished by myelin water imaging (MacKay et al. 1994; Prasloski et al. 2012). Assessment of myelin using this technique has been done in multiple sclerosis (Vavasour et al. 2009; Laule et al. 2008; Manogaran et al. 2015), schizophrenia (Lang et al. 2014), stroke (Borich et al. 2013), and mild traumatic brain injury (Wright et al. 2016).

Probing the central nervous tissue using the phase information of MRI scans has become an active field of research. Phase provides information on the magnetic properties of tissue at high spatial resolution (Rauscher et al. 2005; Duyn et al. 2007). Considerable research efforts have been going into turning the phase images into maps of underlying magnetic tissue properties (quantitative susceptibility mapping - QSM (Schweser et al. 2011; Schweser, Deistung, and Reichenbach 2016; Bilgic et al. 2011; Liu et al. 2015)). Applications of phase based contrast and QSM range from the investigation of the developing (Lodygensky et al. 2011) and aging brain (Li et al. 2014) to the assessment of changes in tissue structure and composition in neurodegenerative diseases (Wiggermann et al. 2013; X. Li et al. 2015; Guan et al. 2016).

Using MR spectroscopy (Oz et al. 2014), researchers can create images of the concentrations of important brain metabolites, for example, N-acetyl- asparate (measure of neuronal integrity), the

creatine/phosphocreatine pool (brain energetics) and glutamate (an important excitatory neurotransmitter).

Surgical procedures can become much less invasive and more effective when the surgeon has access to real time MR images of the subject. For example, abnormal brain tissue may be ablated using high intensity focused ultrasound while monitoring the health of adjacent organs of risk using MR images sensitive to temperature (Coluccia et al. 2014).

Imaging of nuclei other than hydrogen introduces novel new imaging contrasts: hyper-polarized MRI with carbon 13 nuclei enables detailed measurement of metabolic pathways (Ross et al. 2010) and sodium imaging (Shah, Worthoff, and Langen 2016) provides an indication of cellular and metabolic integrity.

Fueled by the imagination of MRI scientists, advancements in MRI hardware have been driving progress in MRI software (i.e., scans) and vice versa, transforming MRI from a tool for the visualization of structure into a science of quantitative mapping of central nervous system tissue properties.

Advances in functional magnetic resonance imaging (fMRI)

By measuring brain activity-related changes in blood oxygenation that are linked to specific sensory or cognitive events, fMRI provides a remarkable window into the mind, and has revealed a great deal about patterns of functional brain anatomy underlying attention, memory, perception, social understanding, and affective responses. The first fMRI studies used simple blocked designs and echo-planar imaging to measure changes in blood-oxygenation-level dependent (BOLD) contrast in response to robust visual (Kwong et al., 1992; Ogawa et al., 1992) or motor (Bandettini et al., 1992) stimulation. Advances in scanner technology, experimental design and data analysis techniques have led to improved spatial and temporal resolution, making it possible to image more complex aspects of perception and cognition. These advances have also paved the way for the use of fMRI as a tool to

establish the neural basis and determine the effects of treatment of neurodevelopmental disorders such as amblyopia, dyslexia, and autism spectrum disorder.

Typical event-related fMRI analyses rely on comparing brain activity engaged by experimental and control tasks, with the assumption that the only difference is the particular cognitive process of interest. While this approach has been fruitful in revealing brain activity associated with broad cognitive domains, such as attention and memory, advancing fMRI depends on developing nuanced techniques for quantifying complex interactions between concurrently engaged cognitive processes that support these broader cognitive domains (Decety and Cacioppo, 2010; Poldrack, 2010).

Embracing cognitive complexity

Significant advances in the past decade in the investigation of the brain basis of complex cognitive functions have opened up new domains of cognitive and clinical neuroscience research. There is growing momentum toward investigating the brain basis of complex, deeply human aspects of the mind that define experience in both health and illness, such as attitudes (McCall et al. 2011), morality (Kaplan et al. 2016), creativity (Beaty et al. 2015), and social understanding (Tipper et al. 2008; Immordino-Yang and Singh, 2013; Saggar, Vrticka and Reiss, 2016). A notable example is that of observing and understanding the actions of other people. Observing actions engages a distributed brain network of parietal, frontal, and temporal sensorimotor brain regions known as the action observation network (Buccino et al. 2001). An experimental design and analysis technique known as *repetition suppression/fMRI adaptation* (Grill-Spector, Henson and Martin, 2006) exploits the greater sensitivity of neural circuits to novel information than repeated information to reveal neural populations that decode distinct dimensions of a stimulus. During an action observation task, several dimensions of the action are processed concurrently (e.g., kinematics, goals, outcomes, intentions, expressive meaning). Using repetition suppression, brain processes that decode each of these dimensions have been localized to distinct, hierarchically organized functional modules nested within the larger action observation network (Grafton and Hamilton, 2007; Tipper, Signorini and Grafton,

2015). By identifying more precise functional granularity within functional brain networks, the precision of the measuring sticks we use to assess brain pathology across of broad range of clinical conditions is greatly increased.

Advances in fMRI study design are made possible in part by an increasing willingness to utilize ecologically valid, complex, dynamic stimuli and tasks that employ video displays, interactive tasks, physical manipulanda, virtual reality, and wide-field 3D immersion. As tasks and stimuli better match real-world conditions, the richness of available behavioral measures is opening a window onto the significance of individual variability. The result is a growing appreciation that clever new tools are needed to quantify this meaningful social, cognitive, and behavioral information to define nuanced *sociocognitive phenotypes*, and map them to distinct patterns of brain function. This new perspective is critical to developing new tools for improving diagnostics and individualized interventions for numerous neurodevelopmental, neurological, and neuropsychiatric conditions.

Clinical application: localizing neuropathology in amblyopia

Amblyopia is a common developmental visual disorder that is characterized by reduced visual acuity in one eye that cannot be immediately corrected with lenses. Based on animal models, amblyopia is classically attributed to changes in the primary visual cortex (V1), such as shrinkage of ocular dominance columns driven by the amblyopic eye and reduction in the number of binocular neurons (Crawford and Harwerth, 2004; Hubel, Wiesel and Levay, 1977). Very-high-resolution fMRI has been used to confirm the shrinkage of ocular dominance columns in humans with amblyopia (Goodyear, Nicolle and Menon, 2002). fMRI has also established the involvement of extra-striate visual areas outside of V1 in human amblyopia (Ho and Giaschi, 2009; Muckli et al., 2006; Lerner et al., 2006; Thompson et al., 2012). These studies extend our understanding of the neural basis of amblyopia beyond that available through animal models (Kiorpes and McKee, 1999), and confirm the need for a revised definition of amblyopia to include a broader range of behavioral deficits (Wong, 2012). For example, we used an event-related, *parametric* fMRI design to study the neural correlates of

a behavioral deficit in multiple-object tracking (the ability to use attention to track several randomly moving targets in a field of moving distractors; Ho et al., 2006), measurable through both amblyopic and non-amblyopic eyes. Area MT in lateral occipitotemporal cortex, the anterior intraparietal sulcus and the frontal eye fields, but not V1, were implicated in the visual deficit (Secen, Culham and Giaschi, 2011). Other studies used the subvoxel resolution provided by repetition suppression to confirm the involvement of V1 and extra-striate regions in amblyopia (Li et al., 2011a), and to demonstrate abnormal binocular interactions in these regions (Jurcoane et al., 2009).

fMRI is now being used to assess new treatment approaches to amblyopia aimed at augmenting visual cortex activity. A recent study reported an increase in BOLD response in visual cortex with amblyopic eye viewing after 30 days of perceptual learning treatment, but no structural change measurable with DTI (Zhai et al., 2013). In another study, anodal direct current stimulation was found to improve vision in the amblyopic eye in some adults with amblyopia; it also equalized the BOLD response of the visual cortex to inputs from each eye (Spiegel et al., 2013). In a more controversial study, oral administration of levodopa produced a small improvement in visual acuity in the amblyopic eye and a correspondingly small increase in V1 activation measured with fMRI (Yang et al., 2003).

From localization to organization

As novel imaging technologies, experimental paradigms, and analytical procedures enable the investigation of the finer granular sub-structure within functional brain networks, there is growing interest in not only mapping the *localization* of specific brain functions to specific brain anatomy, but also in quantifying patterns of functional *organization* of brain networks. For example, studies using *resting state* fMRI have reported disrupted spontaneous activity patterns and/or reduced *functional connectivity* between visual and visuo-motor areas in amblyopia (Ding et al., 2013; Lin et al., 2012; Wang et al., 2014b). One study used task-activated fMRI and found reduced *effective connectivity* involving thalamic, V1 and extra-striate visual areas for both feed-forward and feedback connections (Li et al., 2011b). Such analytical advancements in data analysis enable a more complete understanding

of the neural basis of amblyopia, which is essential to improving treatment interventions. More generally, examining how functional brain networks interact under changing task demands may provide new insights into neuropathology linked to neurodevelopmental, neurological, and neuropsychiatric conditions.

A range of functional connectivity analysis techniques is now available to quantify brain organization, each taking a slightly different approach. Multivariate techniques such as constrained principal component analysis for fMRI (fMRI-CPCA; Woodward et al. 2006) reveal distinct functional networks based on coherent patterns of task-related variation in whole-brain activity. Other task-based approaches include seed-voxel connectivity maps, which reveal functional brain networks based on correlations in activity under various task conditions, psychophysiological interaction maps, which reveal differences in inter-regional connectivity associated with the experimental manipulation, and Granger causality maps, which estimate the direction of information flow through various regions of a network (Rogers et al. 2007).

Another key advance in characterizing functional brain network organization is the emerging field of topological network analysis (Bullmore and Bassett, 2010). This approach relies upon parcellating a brain network into a set of nodes, computing the functional relationships between each node-pair (e.g., activity correlations, coherence, mutual information, transfer entropy; Wang et al. 2014a), and then quantifying the overall organizational structure, or architecture, of the network as a whole. A range of graph metrics is available to quantify properties of brain network organization, such as strength, efficiency, clustering, modularity, path length, centrality, and assortativity (Rubinov and Sporns, 2010). An important advantage of these metrics is their ability to reveal organizational features that are unobservable with traditional fMRI analyses. As fMRI is used to characterize brain pathology linked to heterogeneous symptom profiles that occur with neurodevelopmental and neurological disorders, topological network analysis provides a promising analytical tool (Kaiser, 2011).

Topological network metrics can be applied not only to functional brain organization, but also to anatomical brain organization based on tractography analyses of diffusion imaging data, which estimates probabilistic measures of white matter connectivity between brain regions (Basser et al., 2000). Functional and anatomical network metrics can then be compared to identify structure-function relationships related to task performance (Hermundstad et al., 2013) and individual variability in how underlying brain architecture is utilized to achieve particular cognitive states (Hermundstad et al., 2014). This approach is also being applied to move beyond identifying static patterns of functional organization to reveal dynamic brain changes that unfold over time (Bassett et al., 2011, Betzel et al., 2016). New techniques for characterizing interactions and transitions between identifiable coherent brain states are providing promising avenues for enabling distinctions between neurologically healthy and pathological brain function.

Task-based fMRI signal reliability and validity

Task-based fMRI data provides well-localized and compelling heat images depicting brain activity in response to a wide range of tasks. Typically, brain images depict the magnitude and reliability of differences of parameter estimates derived from individual conditions. However, task-based fMRI data provides richer information than brain activation (e.g., difference) images, such as task-based network information, and network-level hemodynamic response (HDR) shape estimates which may be informative in terms of understanding the cognitive operations driving their shape. The percentage of variance in raw BOLD signal that is predictable from task timing typically ranges from 5% to15%, but this percentage depends on the task design, task timing, and the nature of the task. Even if the percentage of task-related signal in the BOLD data is as low as 5%, as long as that signal can be accurately extracted, it can still be reliable and valid, a concept identical in principal to the case of true-score correlations between two tests and unattenuated correlations (Spearman, 1904).

In order to determine that reliable and valid task-related signal is being extracted from the BOLD signal, we suggest that task-based fMRI data should meet at least two and ideally three validity

checks, and one reliability check, before being interpreted; namely, spatial, temporal and possibly experimental validity, as well as reliability over subjects at the level of task-based networks. *Spatial validity* requires observation of network configurations that resemble those well known in the literature, first described as the task positive and negative networks (Fox et al., 2005). *Temporal validity* requires observation of a biologically plausible HDR shape for each network (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). *Experimental validity* requires observation of HDR shape and magnitude changes with important experimental manipulations and/or measured cognitive operations (Friston et al., 1998). Finally, *reliability in HDR shape over subjects* at the level of whole-brain networks should be observed (Lavigne et al., 2015b; Metzak et al., 2012; Woodward et al., 2015). fMRI-CPCA efficiently meets all of these requirements as part of its standard analysis procedure which involves two essential steps: (1) constraining variance in BOLD signal to that predictable from task timing using multivariate multiple regression; and (2) extracting multiple task-related functional brain networks using principal component analysis (PCA). The percentage of variance in BOLD signal that can be predicted from task timing is part of the fMRI-CPCA output, as is this value for each brain network extracted. Component loadings are displayed on the brain images, and component scores are combined with the design matrix to estimate network-, subject- and condition-specific hemodynamic response (HDR) shape estimates, averaged over trials. For each task-related functional brain network, observed HDR shapes can be submitted to repeated-measures analysis of variance (ANOVA) to test temporal validity (i.e., the HDR shape is not a random shape that changes between subject), experimental validity (i.e., differences in HDR shape between experimental conditions. This step can also be used to carry out-group fMRI-CPCA, for testing differences between clinical samples in the HDR shape (Woodward, Leong, Sanford, Tipper, & Lavigne, 2016; Woodward et al., 2015).

Experimental manipulation/spatial and temporal replication

If the task-related BOLD signal displays spatial, temporal and possibly experimental validity, as well as reliability in HDR shape over subjects at the level of task-based networks, a very powerful

methodology is available through manipulation of functional brain networks with a variety of different tasks (and/or task conditions), and comparison of the nature of the BOLD signal associated with different tasks and/or task conditions. We quantify these principles as *spatial* and *temporal replication*, and below we outline how these concepts can use harnessed to identify the cognitive function of brain networks.

In order to assess spatial and temporal replication of network configurations, and take advantage of spatial replication combined with temporal differences to interpret function of brain networks, two tasks (or task conditions) can be compared though simultaneous analysis of two datasets (Lavigne, Metzak, & Woodward, 2015a). When two (or more) experiment versions elicit the same underlying cognitive operation (for example, visual attention), *spatial and temporal replication* would be observed if HDR shapes for the network in question were not distinguishable between the two experiment versions, and this should be the case if the timing elicited by that cognitive operation does not differ between experiments. In contrast, *spatial but not temporal replication* would be observed if HDR shapes were reliably different between the two experiment versions, and this should be the case if the timing of the cognitive operation differs between experiments. This case (viz., spatial but not temporal replication) provides an important scientific opportunity to use differences between experiments to help test the theorized timing of cognitive functions of brain networks. That is to say, if a theorized cognitive function can be manipulated using (for example) variation in task timing between experiments, it can be determined whether or not the BOLD signal pattern supports the account of the cognitive operation performed by that functional brain network, at least for the task in question. This is tested using the ANOVA method mentioned above with experiment as a within- or between-subject factor. Finally, if a cognitive operation is elicited by only one version of the experiment but not the other, the version not eliciting this cognitive operation would show a flat HDR shape for that functional brain network, and therefore it could be concluded that *neither spatial nor temporal replication* has

been observed. This methodology has been used in past work to test theoretical accounts of the function of brain networks across closely matched experiments (Lavigne et al., 2015a).

Future directions

Moving forward, the combination of more nuanced experimental paradigms to assess complex cognitive functions and characterize individual sociocognitive phenotypes and more sophisticated analyses of functional and anatomical brain network organization open up a new frontier for clinical neuroscience research. The potential to improve diagnostic and assessment capabilities and enhance individualized care across a range of neurodevelopmental, neurological, and neuropsychiatric conditions is unpredecented.

Advances in functional and biochemical positron emission tomography (PET) imaging

Many brain diseases are known to start well before clinical symptoms become manifest. The ability to correctly diagnose disease early is expected to enhance the probability of successful intervention. In this context, the network degeneration hypothesis (Palop et al. 2006), which suggests that initiation and progression of disease-specific pathological changes occur within specific brain networks and are mediated by protein misfolding, inflammation and impaired cellular energetics coupled to abnormal neurotransmission, suggests that multi-parameter information may lead to significantly enhanced understanding of brain function and thus disease. This approach is encouraging development of novel PET imaging tracers that target abnormal protein aggregation, multimodality imaging, either sequential or simultaneous, such as that enabled by hybrid PET/MRI scanners, and application of analysis methods that are able to extract relevant features from multi-parametric information.

Aggregations of the ß-amyloid protein, considered a hallmark of Alzheimer's disease (AD), are fairly well studied with several established PET tracers (Villemagne 2016). Imaging of tau aggregation, implicated in AD, chronic traumatic encephalopathy, progressive supranuclear palsy, and corticobasal syndrome is more recent; three promising novel tracers are currently used in human

studies, ^{11}C-PPB3, ^{18}F-T807 or ^{18}F-AV-1451 and ^{18}F-THK5351 (Villemagne et al. 2015). The tau tracers are not equivalent in their ability to detect deposits of different tau isoforms which are selectively associated to different aspects of neurodegeneration: the precise relevance of each tracer to specific diseases is thus still under investigation. Development of PET tracers for other targets of interest such as a-synuclein, whose aggregations are implicated in the pathogenesis of Parkinson's disease (PD), is a very active research area, but no successful candidates have been developed as yet (Eberling et al. 2013, Kikuchi et al. 2010).

The ability to identify abnormal protein aggregation or alterations in metabolic pathways observable with ^{18}F-FDG, does not always by itself lead to accurate differential diagnosis or to improved understanding of pathogenic mechanisms. Informed combination of data obtained from different imaging modalities has been shown to yield superior information; for example a recent study performed on a hybrid PET/MRI demonstrated that the combination of regional metabolism, functional connectivity and gray matter volume, which were derived from disease characteristic networks, was able to achieve high classification accuracies for separating patients with different neurodegenerative syndromes of 77.5% for AD versus others, 82.5% for behavioral variant frontotemporal dementia versus others, 97.5% for semantic dementia versus others, and 87.5% for progressive nonfluent aphasia versus others – this multimodal classification was superior to unimodal approaches (Tahmasian et al. 2016). In addition to combing data from different modalities, novel image analysis approaches for PET images are also emerging and are proving complementary to the traditional ones based either on kinetic modeling or radioactivity concentration values. Such approaches include information about specific tracer distribution patterns within anatomically relevant regions of interest (Liu et al. 2016; Klyuzhin et al. 2015). Combinations of such patterns or features applied to the analysis of ^{18}F-FDG data coupled with MRI-derived information, resulting in the definition of multi-parameter based biomarkers, have been shown to be associated with different aspects of AD progression (Liu et al. 2016). Such

biomarkers will be of great relevance when stratifying patients and evaluating mechanisms of action and effectiveness of emerging treatments.

The hybrid PET/MRI provides access to novel measurements, such as direct investigation of the interactions between neurotransmitter activity and brain function either at rest or as stimulated by a pharmacological or behavioural intervention. This is a very exciting area of research relevant to many aspects of brain function that will see growth as the availability of the hybrid PET/MR scanners increases. For example, it will be possible to investigate correlations between responses to reward, pain or treatment in terms of dopamine release and activation of cognitive networks and how such correlations differ amongst different subject populations. Ideally, it will be possible to identify imaging-based biomarkers that identify subjects at risk and thus promote development of disease prevention strategies. Optimization of such approaches will drive development of joint PET/MRI image processing methods, either in the image reconstruction step or image analysis step (Kang et al. 2015; Sander et al. 2013). In summary, over the last decade PET imaging has been enhanced by development of novel tracers, technical improvements that allow simultaneous PET/MRI data acquisition and novel data processing methods, thus catalyzing and reflecting the increased recognition of the interactions between neurochemistry and distributed brain networks.

Advances in functional and dynamic magnetoencephalograpy (MEG) imaging

New horizons for mapping spontaneous neuromagnetic networks

Magnetoencephalography (MEG) offers a direct measure of neural activity, and enables mapping of neural activity with a combination of spatial and temporal resolution that is superior to any other non-invasive neuroimaging modality. This makes MEG ideal for mapping neural oscillations and their coordination among brain areas (Palva and Palva 2012), which has been proposed as a mechanism supporting dynamic functional interactions among neuronal populations to support cognition and perception (Fries, 2015). The theoretical perspective of understanding brain function through neural oscillations and their inter-regional synchrony, together with the technical advantages for mapping such

large-scale brain networks and dynamics provided by MEG, has opened new frontiers for understanding distributed human brain function, dysfunction and development.

Like most human functional brain imaging approaches, much initial research in MEG focused on how the brain responds under various types of sensory stimulation, or cognitive or motor demands. It has been increasingly appreciated that most brain activity is comprised of spontaneous background fluctuations rather than task and/or stimulation dependent activation, and that much can be gleaned by mapping intrinsic functional connectivity at rest (Raichle, 2015). It is also becoming increasingly clear that the dynamics of intrinsic connectivity are highly informative regarding the organization of brain function (Zalesky et al., 2014). This highlights the advantages of MEG, as the timing accuracy of MEG enables connectivity dynamics to be measured with millisecond precision and in fast physiological frequency ranges critically relevant for cognition, perception and behavior.

Mapping intrinsic neurophysiological amplitude network correlations and dynamics

Correlations in slow fluctuations in neuromagnetic amplitudes, particularly in beta and alpha frequency bands, have been shown to recapitulate many of the resting state networks previously observed using other imaging modalities such as fMRI (Brookes et al., 2011). These functional networks, expressed at rest, are also modulated by cognitive activity (Brookes et al., 2012). Graph analysis of resting MEG amplitude correlations also conform to major anatomical divisions of the brain, with global hubs for different frequency ranges concentrated in different brain loci (Hipp et al., 2012). Inter-regional amplitude correlations have been shown to increase with age throughout childhood and adolescent development, particularly in beta and alpha frequency ranges (Schäfer, et al., 2014). EEG studies suggest that such increasing spontaneous electrophysiological connectivity may be associated with the acceleration of the alpha peak (Miskovic et al., 2015), suggesting that acceleration of spontaneous oscillatory connectivity may lead to the predominant expression of intrinsic connectivity networks in the beta band in adulthood.

One important advantage MEG has over fMRI is temporal resolution. This allows mapping of the dynamics of intrinsic connectivity networks at faster time scales. For example, this approach has been useful for exploring the expression of connectivity in these networks in the time domain, and for elucidating sequential transitions between relative dominance of specific intrinsic connectivity networks (Baker et al., 2014). For example, it has been observed that it is much more likely for there to be a transition between a default mode network (DMN) dominant state and the predominance of another intrinsic connectivity network than it is to transition directly between two non-DMN resting state networks, and that these internetwork transitions primarily involve inter-regional amplitude correlations in the beta frequency range (de Pasquale, et al., 2012). This could be interpreted as indicating that the DMN serves to shift the pattern of inter-regional communication of the brain between different functional states. For example, beta amplitude correlations involving the DMN could mediate transitions between a motor focused state supported by the motor network and a spatial attention focused state supported by the dorsal attention network. Another advantage conferred by the millisecond timing accuracy of MEG network mapping is the ability to determine that certain networks, such as the motor network, may actually be comprised of a larger number of sub-networks which serially express periods of relative predominance (O'Neill et al., 2015). Notably, expression of local neuromagnetic spectral power has been shown to have clinical utility for detecting and characterizing conditions such as mild traumatic brain injury (mTBI; Huang et al., 2014). Recent observations that inter-regional amplitude correlations are altered in mTBI and associated with cognitive and affective symptoms in this group (Dunkley et al., 2015) buttresses the hope that this type of connectivity measure may also hold future clinical applicability.

In addition to mapping of amplitude correlations in spontaneous MEG, another dominant approach has been to measure inter-regional phase locking, which is typically investigated at faster time scales. It has been proposed that the slower amplitude correlations are more closely related to underlying structural brain connectivity, whereas phase-phase relations encode more transient cognitive

and/or computation specific information (Engel et al., 2013). Though much remains to be discovered regarding the relevant roles of amplitude and phase coherence, it is worth noting that spontaneous phase locking effects are often observed at faster gamma frequencies which are much more spatially refined (Jerbi et al., 2009) and have been proposed to play a more computational role relative to oscillations at lower frequencies (Fries, 2009). It should be noted, however, that phase and amplitude should not be viewed as independent in this context, as inter-regional correlations in cross-frequency phase amplitude coupling in spontaneous MEG has also been shown to correspond to resting-state networks evident in resting fMRI correlations (Florin and Baillet, 2015).

Spontaneous phase synchrony in neuromagnetic networks and its alteration in brain disorders

In addition to mapping of amplitude correlations in spontaneous MEG, another dominant approach has been to measure inter-regional phase locking, which is typically investigated at faster time scales. It has been proposed that the slower amplitude correlations are more closely related to underlying structural brain connectivity, whereas phase-phase relations encode more transient cognitive and/or computation specific information (Engel et al., 2013). Though much remains to be discovered regarding the relevant roles of amplitude and phase coherence, it is worth noting that spontaneous phase locking effects are often observed at high gamma frequencies which are much more spatially refined (Jerbi et al., 2009) and have been proposed to play a more computational role relative to oscillations at lower frequencies (Fries, 2009). Phase and amplitude should not be viewed as independent in this context, however, as inter-regional correlations in cross-frequency phase amplitude coupling in spontaneous MEG has also been shown to correspond to resting-state networks first identified using fMRI (Florin and Baillet, 2015).

Spontaneous neuromagnetic phase locking has been particularly successful for capturing atypical connectivity in neurological and neuropsychiatric populations, adding to the emerging network perspective on neurological disorders (Stam, 2014), and adding credence to the notion that brain oscillations and their coherence may constitute a type of neural syntax for information processing and

communication that is critical for understanding the brain basis for psychiatric disorders (Buzsáki and Watson, 2012). For example, it has been shown that resting-state MEG synchrony is altered in post-traumatic stress disorder (Dunkley et al., 2014). Source mapping of such atypical neural synchrony has demonstrated that such altered neural synchrony prominently involves areas such as amygdala and hippocampus, and is associated with symptom severity as well as associated cognitive and affective sequelae (Dunkley et al., 2014). An exhaustive review of atypical resting MEG phase synchrony is too long for the present chapter, but it appears to be relevant for a broad array of conditions including neurodegenerative diseases such as Alzheimer's disease (de Haan et al., 2012), movement disorders such as Parkinsons's disease (Berendse and Stam, 2007), and epilepsy (Elshahabi et al., 2015), suggesting that such measures are tapping a fundamental aspect of neuronal communication and its disruptions in brain disorders.

Electroencephalographic research using a large sample has demonstrated reorganization of spontaneous network phase synchrony during child development (Boersma et al., 2011). Clinical child populations have been shown to express characteristic alterations in spontaneous MEG synchrony. Children with dyslexia have been shown to exhibit atypical neural synchrony, which was also shown to be associated with language difficulties (Dimitriadis et al., 2013). Frequency- and network specific of resting neuromagnetic phase synchrony have been reported in adolescents with autism (Ye et al., 2014), and altered MEG synchrony has also been reported autistic children (Kikuchi et al., 2015). Such alterations of inter-regional MEG synchrony have been related to autistic symptomatology (Kitzbichler et al., 2015). Spontaneous MEG synchrony has been shown to be reduced in school-age children born very preterm across multiple physiologically-relevant frequency ranges (Ye et al., 2015), which may be related to well characterized alterations in white matter development in this group (Pannek et al., 2014).

Bright future through big data? Toward quantitative translational MEG

Increasing emphasis in neuroimaging is being placed on the importance of large sample sizes to improve the accuracy and reproducibility of findings. This will be aided by large open source

databases of resting state MEG recordings. For example, the Human Connectome Project will provide hundreds of such scans with accompanying high quality structural and functional MRI data (Larcon-Prior et al., 2013). Open source data repositories more explicitly focused on MEG such as "OMEGA" will also help to provide large samples of MEG data collected across multiple centers (Niso et al., 2016). Hope is increasing that big data in neuroimaging, combined with techniques such as machine learning, will provide new translational opportunities for diagnosis and predicting treatment response with sufficient sensitivity and specificity to enable translation (Deco and Kringelbach, 2014). Major future trends in resting MEG network mapping will likely include mapping normative networks, their development and relation to function, together with how such refined population data could be used for detection of neural network abnormalities and to guide treatment and rehabilitation for those suffering from disorders of the brain.

Advances in functional and dynamic electroencephalograpy (EEG) imaging

From identification of neural sources of electrical activity to fast neural network dynamics

Functional imaging involves describing how the brain implements sensory, perceptual, cognitive, motor, and emotional processes at several scales of space and time. fMRI is efficient at doing this at several spatial scales but only at time scales from several seconds to several minutes. MEG can do a great job at shorter time scales of tens of milliseconds (ms) to seconds, and at spatial scales comparable to those of fMRI, but it is expensive and not portable. Arguably the greatest promise for bedside functional imaging is provided by current and near-future EEG technologies. It is relatively inexpensive, portable, and operates at time scales of tens of ms. Its major drawback, spatial inaccuracy, is being addressed by new techniques of data analysis and recording technology. Here we describe recent advances and promise for this elderly technology that is being reborn.

EEG has been used in medicine for, e.g., diagnosis of epilepsy foci, for many years. These uses will continue, but EEG is now poised to contribute significantly to the growing knowledge of the fast dynamics of brain networks and their vicissitudes in challenged brains. First, new techniques of data

analysis allow increasingly accurate identification of the neural sources of electrical activity recorded at the scalp by EEG. Independent component analysis (ICA) coupled with single dipole fitting (Delorme, et al., 2012) has successfully recovered specific brain loci, associated with perceptual and cognitive processing, that have been previously identified by fMRI (e.g., Bedo et al, 2014). Similarly, beamformer analysis can perform this function well when applied to EEG data (e.g., Doesburg, et al., 2009; Green, et al., 2011). Moreover, some of the sources of inaccurate localization can be removed by using a wearable, dry, rigid electrode array rather than one that flexes and/or requires wet electrolytes (e.g., Mullen, et al., 2013). The latter paper also presents evidence that ICA can remove much of the movement-related artefact that plagues all neuroimaging techniques. Similarly, ICA also can be used to remove the artefacts generated by tiny shivers, etc. of the muscles around the eyes, head and neck (EMG; Fitzgibbon, et al., 2016). Thus, EEG is becoming a cleaner neuroimaging technique that can begin to approach the more expensive fMRI and MEG results, but more flexibly and at much less expense.

Second, the fast time scale at which EEG can be recorded allows the analysis of moment-to-moment dynamics in the neural networks that support cognition, emotion, and behavior. Two currently available techniques are especially useful in this regard. Various synchronization indices are available to measure phase synchronization of oscillatory neural activity. The first evidence of neural oscillations recorded by EEG was the alpha wave (around 10 Hz; Berger, 1929). Since then oscillatory activity in several frequency bands has been closely associated with perceptual and cognitive processes (e.g., Varela, et al., 2001; Ward, 2003). Phase synchronization between oscillations at the same or different frequencies is an indication of functional coupling between the brain areas generating the oscillations. Although the most direct evidence for such functional coupling comes from studies with implanted electrodes (e.g., Lewis, et al., 2016), EEG data treated with advanced analysis techniques can also detect transient functional connectivity between neural sources at fast time scales of tens of ms (e.g., Bedo, et al., 2014; Doesburg, et al., 2009; Figure 1. In addition, new techniques of measuring directed

information flow between oscillatory sources, such as transfer entropy (Schreiber, 2000; Vicente, et al., 2011; Wibral, et al., 2011) and phase transfer entropy (Lobier, et al., 2014), can actually allow us to make (weak, or Granger-type) causal inferences about interactions between brain areas, for example in reading (Bedo, et al., 2014). Finally, when there are competing network topologies or interaction models based on previous data, dynamic causal modeling can be applied to choose the most useful model (Friston, et al., 2003).

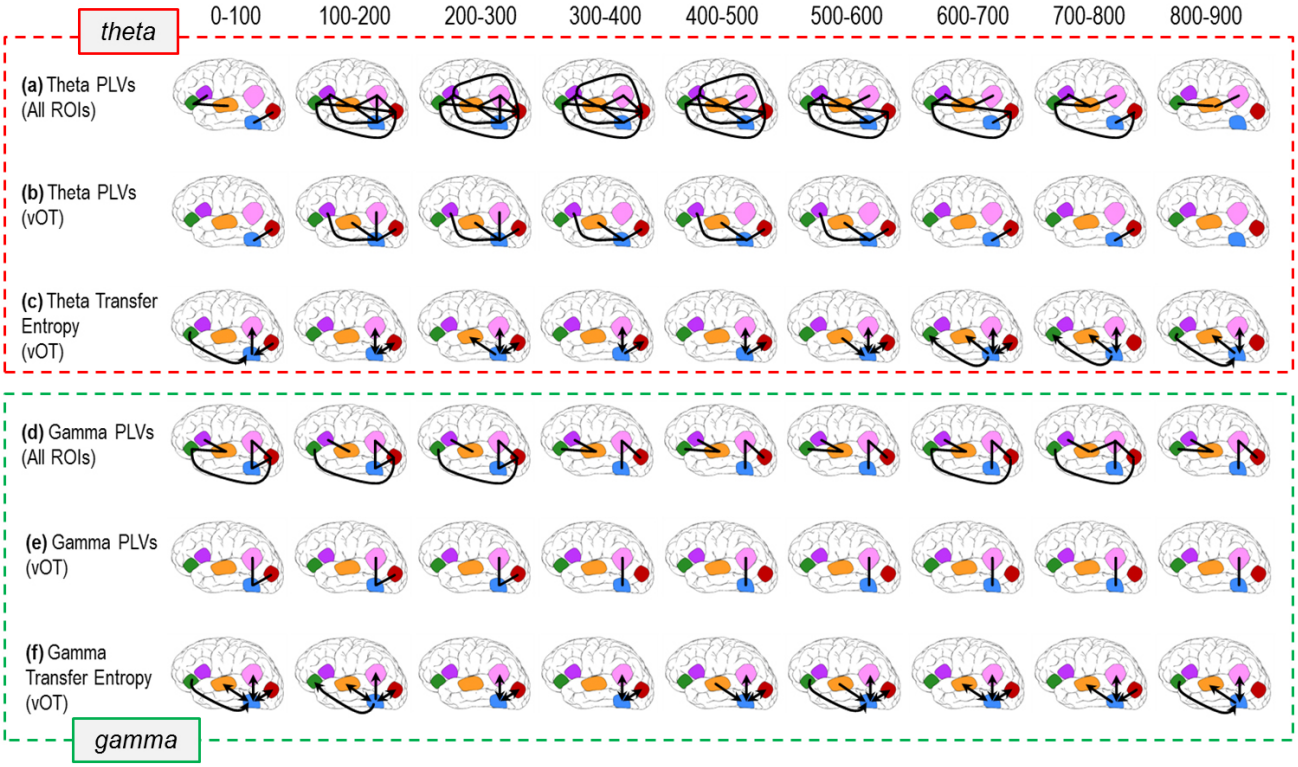

Figure 1: Example of dynamic EEG synchronization and transfer entropy results from a word reading task. Synchronization was measured with phase locking value (PLV), and narrow band transfer entropy was measured using an adaptation of the Kullback entropy (for vOT to/from other areas only). Theta band is 3-7 Hz and gamma band is 35-45 Hz. Black lines (arrows) indicate significant interaction (directed information flow) between the connected reading-related brain areas during the time period (ms after stimulus presentation) indicated at the top of the figure. vOT indicates ventral Occipital-Temporal brain region, the putative word-form area. Open access from Bedo, et al. (2014).

There are still significant limitations to be overcome, however. One of the most important is the inability of EEG to visualize subcortical areas. MEG also is not good at this, but fMRI does it well. Thus, it will be important to develop linkages between fMRI and EEG/MEG results to allow inferences of fast dynamics from fMRI when subcortical brain regions are heavily involved. This is especially important for the thalamus, which is implicated in nearly every brain operation and network (Ward, 2013). Another limitation is the relatively low signal to noise ratio enjoyed by EEG. Measures to increase this, such as ICA, have been successful, but still more is needed. Synchronization and transfer entropy analysis suffer particularly from this problem and new methods of filtering out the noise are needed. But even given what is now available it should be possible to use EEG both to characterize normal fast dynamics in neural networks, and to discover how aberrations in these networks can lead to dysfunction. Of course, it will then be necessary to decide what actions to take to ameliorate or rehabilitate these dysfunctions. The neuroimaging techniques will help point to the necessary treatment foci, and they can help assess whether the applied treatment has succeeded. But they will not answer the difficult ethical problems given rise to by the knowledge of the source or extent or cause of a brain dysfunction, especially if treatment is expensive, risky, or impossible. This is particularly true for EEG-facilitated discoveries of residual functions, and even indications of conscious processes, in severely compromised brains, such as those of patients with unresponsive wakefulness or minimal consciousness (e.g., Cruse et al., 2011).

Applications and challenges in clinical neuroimaging: localization and synchronization

As scientists, we are ethically responsible to conduct the necessary basic research to be able to take the next steps in conducting clinical research. With the growing interest in personalized health care, we need to provide tools that allow clinicians to make diagnosis and recommend management options at the individual patient level. Many neuroimaging tools exist (MRI, fMRI, PET, MEG, EEG, NIRS [Near Infrared Spectroscopy], etc.) and many are clinically used to screen, diagnose, and/or prognosticate many types of neurological diseases and disorders (e.g., epilepsy, schizophrenia,

dementia, dyslexia). Several of these neuroimaging methods have a long history of clinical use, while other methods have a more recent history. The literatures on these different neuroimaging methods are extensive and beyond the scope of this brief communication to be able to cover them in any great depth. Therefore, we very briefly highlight one neuroimaging method, the auditory event-related potential (ERP), that is used to assess sensorineural hearing loss and neurological disorders (e.g., vestibular schwannoma screening). We do this in order to stress the ethical responsibility of the scientific community to conduct basic and clinical research on neuroimaging tools that can be easily and effectively used clinically. We then go on to briefly discuss the importance of thoroughly investigating and validating neuroimaging methods prior to recommending their use clinically. We provide an example from our recent methodological work in beamformer source modeling and its role in functional connectivity imaging to emphasize this point.

Auditory ERPs directly reflect the electrical signal generated from neural responses in the auditory system and thus can be used as a neuroimaging tool. One example of an auditory ERP that is used clinically is the auditory brainstem response (ABR). ABR testing has been used for screening and diagnosing sensorineural hearing loss in infants for many years (Picton, 2011, p213-246, p449-492). This testing is based on decades of basic research that helped inform clinical researchers to investigate its utility in evaluating hearing function in humans across all ages. ABR is commonly used to assess hearing thresholds in infants because infants younger than eight months old are unable to provide reliable behavioral responses (i.e., raising a hand to a sound). The reason for using ABR to evaluate infant hearing thresholds is that research showed that detection of a hearing impairment in infants by 3 months of age and intervention by 6 months of age significantly improves the child's later language development (Yoshinaga-Itano et al., 1998; Yoshinaga-Itano et al., 2000). Beginning in the 1990s, another ERP method called the 80-Hz auditory steady-state response (ASSR) was suggested to improve hearing diagnostics because they could be a faster, more reliable, and more objective test of hearing thresholds in infants (Picton 2011, p285-334). However, this excitement diminished because basic

research helped inform the scientific community that ASSR testing of infant hearing was as reliable as the gold-standard ABR method but ASSR testing had a noteworthy caveat; artefactual responses could be elicited at high sound intensities. This would lead to falsely indicating that individuals with profound sensorineural hearing loss had residual hearing. In other words, ASSRs would show residual hearing in individuals who were known to have no residual hearing. Although ASSR testing is not recommended currently for diagnostic hearing threshold testing in infants, enough basic and clinical research was conducted to provide evidence for its use as a tertiary-stage hearing screening tool. In addition, research is continuing to identify other potential clinical uses of ASSR in evaluating hearing functions (Picton 2011, p320-325).

Neurological ABR testing is another auditory ERP method that is used clinically to screen for vestibular schwannomas (aka acoustic neuromas; Selters and Brackmann, 1977; see also Picton, 2011, p500-505). Although neurological ABR testing is not a spatial neuroimaging method for detecting tumors, it is a useful neuroimaging method for detecting delayed or disrupted neural communication along the auditory pathway (i.e., between the cochlear nerve and brainstem nuclei). There are clear guidelines and normative data collected in non-clinical and clinical populations (Campbell et al., 1981; Chiappa et al., 1979; Stockard et al., 1978). This evidence has informed researchers and clinicians about the validity of ABR to screen for tumors and brainstem lesions along the auditory pathway. Importantly, clinical research has clearly identified that the sensitivity and specificity for neurological ABR in detecting 1-2cm tumors are 90-100% and 60-75%, respectively (see Picton 2011, p503). Notably, this performance is based on large samples of patients. ABR's tumor-detection performance lead early researchers to recommend that it is a good screening tool for discriminating between individuals with and without retrocochlear pathologies (e.g., vestibular schwannomas). As MRI became a more prevalent neuroimaging tool and its diagnostic performance was to be superior to ABR, the MRI became the recommended tool for screening and diagnostics. However, the financial expense of MRI precluded much of its use as a screening tool (until recently) and when MRI is contraindicated

in certain populations (e.g., patients with cardiac pace-makers). Thus, neurological ABR is still routinely used as a screening tool before using more expensive MRI diagnostic methods or when MRI is contraindicated. When MRI testing is available, MRI screening is recommended over ABR screening because of the added benefits of better sensitivity and better ability to identify the etiology of auditory pathology (Fortnum et al., 2009). However, a current challenge for using MRI as a screening tool is that MRI testing facilities typically reside only in major urban areas, which add barriers and costs to providing health care in rural communities. Neurological ABR testing, on the other hand, is easily performed in any clinical setting with significantly less expensive equipment as compared to an MRI scanner. Thus, screening in rural communities using neurological ABR and then referring patients for MRI testing in urban areas can be more cost effective and easier for the patients and health-care system. The history of basic and clinical research for using ABR and MRI to diagnose retrochochlear pathologies highlights the importance of initial and continued validation of using neuroimaging tools for clinical purposes (see Fortnum et al., 2009). This evidence inevitably reduces the uncertainty that clinicians often face when making decisions about diagnoses, prognoses, and management.

The above brief historical accounts of using auditory ERPs showcase some of the basic principles that are needed for recommending clinical uses of specific neuroimaging tools. Some of the basic challenges to the tests are to determine: (1) specific validity and reliability relating to technical algorithms used; (2) diagnostic performances relating to the applications on pathological sub-populations (e.g., sensitivity, specificity, predictive value); and 3) cost-effectiveness and cost-utility (Medina et al. 2013, p3-18). The histories of using auditory ERPs to diagnose hearing loss and screen for tumors are interesting with respect to how neuroimaging can be used as tools for screening and diagnosing sensory and neurological impairments. These histories are also a reminder of the diligence required to sufficiently evaluate and validate neuroimaging tools in order to recommend their use in health care at single-patient and population-based levels.

Validating the neuroimaging tools from a methodological point of view is essential before recommending their use for clinical purposes. One major goal of methodological research in neuroimaging is to improve our ability to confidently identify local and global brain function. For example, we are investigating the reliability of specific neuroimaging analyses to localize the neural generators underlying EEG and MEG and to identifying the neural communication within the human brain. However, some recent caveats have come to light that we are currently investigating and attempting to overcome. Here we highlight one of the major challenges in neural communication analyses of EEG and MEG data (aka functional connectivity analyses). We briefly present this research here to illustrate the point that basic methodological research is highly important before using tools for clinical purposes. A major challenge in functional connectivity analyses is making sure that the brain regions (aka, sources) under investigation do not contain activity from other brain regions because of the inherent physics of the neuroimaging measure and/or the mathematics underlying its analyses. When using some neuroimaging tools and analyses, nearby (<20 mm) brain regions can contain a mixture of signals that are separately generated from different brain regions. This is known as source mixing and can lead to false conclusions regarding how these regions are functionally connected and how they communicate information among themselves (Sekihara and Nagarajan 2015)(Figure 2). Traditional beamforming and minimum-norm source modeling methods (Hamalainen and Ilmoniemi, 1994; Van Veen et al., 1997; Van Veen and Buckley, 1988; see also Sekihara and Nagarajan, 2015) cannot avoid source mixing where neighbouring sources will be modeled to contain contributions of each other's activity. Unfortunately, this source mixing can generate deceptively false oscillatory phase-coherence between sources; thereby causing misleadingly strong inter-source connectivities (i.e., Type I errors). To overcome this source-mixing challenge, different connectivity measures of phase-coherence (e.g., phase-lag index or imaginary-phase coherence; Ewald et al., 2012; Stam et al., 2007; Sekihara and Nagarajan, 2015) have been suggested and implemented with some success. However, these compensatory algorithms become increasingly blinded to identifying true connectivities as inter-

source phase differences approach zero (Type II errors). Another method to overcome the possible Type I errors of source mixing is to average across many participants. However, this often leads to Type II errors or spatial smearing of the connectivity maps because individual participant's inter-source connection pairs usually do not exactly line up spatially across participants brains. Moreover, providing personalized health care would require neuroimaging tools to provide reliable connectivity maps at the individual patient level, not at the population level. Overall, source mixing leads to traditional beamformers being less sensitive and less specific to detecting true functional connections in local networks. Thus, to be able to confidently evaluate functional connectivity among locally connected brain regions in individual patients, we need better tools that minimize or negate source mixing.

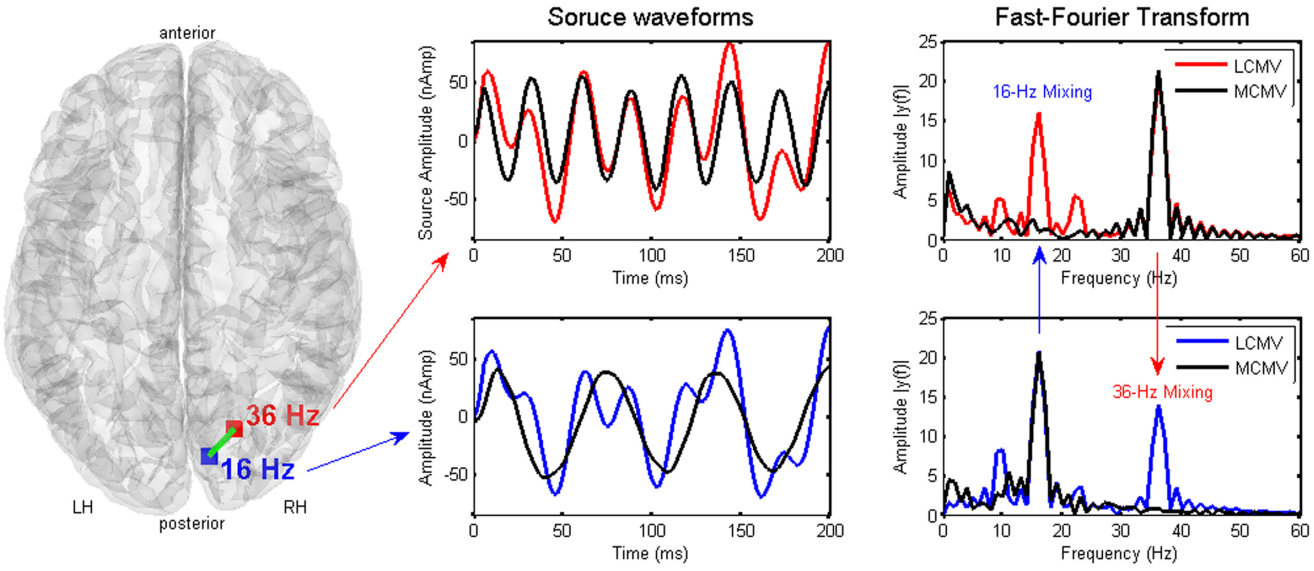

Figure 2: EEG localization and connectivity accuracy: Left panel shows a simulated source location (blue square) that had only a 16-Hz oscillation and a neighbouring (within 15 mm) source location (red square) that had only a 36-Hz oscillation. Source Mixing of 16- and 36-Hz oscillations were clearly visible in the traditional beamformer (LCMV) reconstructed source waveforms (blue and red lines; middle panel). Amplitude spectra (right panels) showed that both red and blue LCMV sources contained energies at 16 and 36 Hz (i.e., source mixing). Because of this source mixing, phase-coherence between the sources existed and functional connectivity was falsely revealed (green line; left panel). Our MCMV beamformer (black lines); however, prevented source mixing. MCMV sources only had 16-Hz (lower panels' black lines) or 36-Hz oscillations (upper panels' black lines). Obviously, false-connections were not found for the MCMV beamformer.

Multiple-Constrained Minimum-Variance (MCMV) beamforming (Moiseev et al., 2011) is one such neuroimaging method that overcomes source mixing. MCMV beamformer technology mathematically constrains the sources to be independent of each other; thereby, preventing source mixing (Figure 2; for mathematical proofs and methods see Moiseev et al., 2011 and Moiseev et al., 2013). Figure 3 demonstrates the ability of MCMV-connectivity analyses to accurately resolve network connectivity in real EEG data by overcoming source mixing among nearby brain regions. Phase-locking connectivity maps (Lachaux e al., 1999) using traditional LCMV beamformers revealed significantly strong alpha-band (9-10 Hz) synchronization (red lines) among nearby sources in the posterior left visual network (Figure 3, left brain map). However, when analyzed using a MCMV beamformer, the connectivity map for these nearby sources had significantly larger alpha-band desynchronizations (blue lines; Figure 3, right brain map). The MCVM results in Figure 3, are likely the more valid result because the EEG data analyzed were from a visual discrimination task and from a post-stimulus interval (380 ms) where event-related desynchronization in the scalp recordings occurred. In addition, this interval is well known to contain event-related desynchronizations over occipital scalp regions. Thus, it is highly unlikely that the local visual network would be synchronized within this interval as revealed by the traditional LCMV beamformer. Therefore, the LCMV connectivity map on the left is likely showing *false* synchronizations among nearby posterior visual sources due to source mixing. Given the advantage of MCMV beamforming not having source mixing, we can now be more confident that our results of local functional connections represent the true underlying functional connectivity. By combining MCMV beamforming with functional connectivity measures (such as phase-locking values; Lachaux et al., 1999), we can significantly enhance our ability to image local and global network connections. This will further improve the validity of our results obtained from network graph-theory analysis (Sporns 2003). Overall, thoroughly investigating and validating our methods will

enhance our ability to accurately represent the local and global network dynamics underlying the EEG and MEG recorded from individual patients.

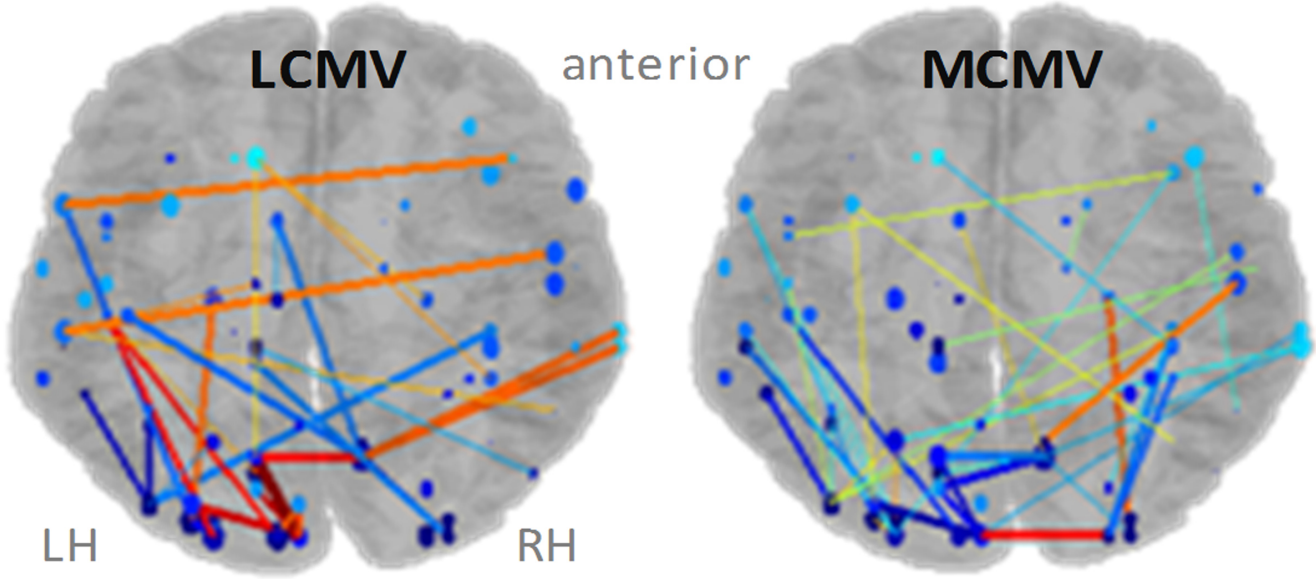

Figure 3: Challenge in EEG connectivity maps: Traditional LCMV-beamformer connectivity map (Left) for alpha-band (9-10 Hz) revealed highly synchronized (red lines) local couplings in visual cortices at 380 ms after letter onset. However, MCMV-beamformer connectivity map (right) revealed strongly desynchronized (blue lines) couplings. The MCMV-connectivity maps fits better with known event-related desynchronizations that occur after a visual stimulus onset for this band and latency. Thus, the MCMV map is likely the real map.

The above brief overview of ABR testing provided examples of how basic research has provided suitable evidence for using neuroimaging tools for clinical purposes. In addition, continued research in validating neuroimaging analyses (such as source modeling methods) is essential so that we can obtain the most confident and accurate depiction of brain function. It is imperative that basic and clinical researchers work together to provide clinicians with strong evidence that validates new neuroimaging tools in order to improve patient care.

Advances in brain imaging signal processing

In past years, the main focus of analysis of brain signals was on studying responses of individual brain areas, associated with certain functions, to external stimuli. More recently, however,

this focus shifted to investigating interactions between a large number of brain regions, often functionally connected with each other, in both task-related environments and in the case of resting state brain activity. As a consequence, modern processing methods are more oriented on analysing large sets of correlated and interacting brain sources, rather than on individual ones.

Such analyses in MEG/EEG brain imaging, which we broadly call *brain network* or *connectivity analyses*, typically involve the following steps. First, an inverse problem must be solved, which means reconstructing signals from specific locations within the brain, using data from physical MEG/EEG sensors, located outside the brain. Second, connectivity (or interaction) between different areas should be estimated. Third, this connectivity data should be statistically evaluated, to detect true connections and discard spurious ones. Let us briefly discuss each step in more detail.

Start with the source reconstruction. There are several methods to solve the inverse problem, which are popular in MEG/EEG community (Baillet et al., 2001). An important example that we'll consider here is called minimum variance beamformer solution (Van Veen et al.1997, Robinson and Vrba, 1999, Sekihara and Nagarajan, 2008), but similar considerations apply to other methods. Technically, the original beamformer solution was developed assuming that electromagnetic field registered by the sensor array is produced by a single brain source of interest, plus noise. This is called a single-source beamformer approach. Of course in reality even performing very simple tasks engages many brain areas, and consequently many sources are simultaneously activated. It turned out though that single-source beamformer, applied to each source individually, is still quite successful in locating and reconstructing multiple active sources, as long as they are not too close to each other and their correlations are negligible. However, if sources are close and/or they are strongly synchronized, localization accuracy and spatial resolution of the beamformer degrades. Besides, reconstructed signals become contaminated with artefactual contributions from other brain areas. This phenomenon is called *source leakage*. To overcome these problems, more advanced multi-source beamforming methods were developed (Dalal et al., 2006, Hui et al., 2010, Moiseev et al., 2011, Moiseev and Herdman, 2013). In

particular, these methods allow for strong interactions (correlations) between the sources, and they take care of signal leakage by rejecting any direct contributions from one reconstructed signal to another.

The next step is estimating connectivity between the brain signals. No matter which one of many known measures of synchronization between signals is applied (Lachaux et al., 1999, Palva and Palva, 2012, Vinck et al., 2011, Schoffelen and Gross, 2009), it is important to ensure that such synchronization is not artificial, occurring for example due to the common noise components in the signals, or due to the signal leakage. One possible way to achieve that is to use connectivity measures that are insensitive to correlations between signals, which have no time delay. Linear mixing due to leakage involves no time delay, therefore measures in question are immune to those artefacts. The flip side of this approach is that these measures are almost insensitive to connections with time lags which are small compared to the time period of the signal frequency. Consider an alpha frequency for example. Its period is around 100 ms, therefore in the alpha range connections with physiologically feasible propagation delays of several or even 10 – 20 ms may not be detected. An alternative way to exclude spurious connectivity due to linear mixing is to eliminate the leakage at the very beginning – that is, at source reconstruction step. In this case, a broader set of connectivity measures, including those sensitive to zero-delay connections, can be applied. This is where the multi-source beamformers become handy, because direct leakage from one source to another is rejected.

The third step in the analyses consists of recognizing distinct groups of interacting brain regions, or brain networks, based on the connectivity data. The difficulty here is that the number of possible pairwise connections between different regions is usually very large, while existence of each connection can only be established with certain probability (say, 95%) - in other words, involves statistical error. It follows then that some of the found connections will be not real, occurring simply because of random fluctuations. For example, suppose we consider locations corresponding to ~50 known Brodmann areas. The number of possible pairwise connections between those is around 1200. If our statistical error per connection is 5%, then around 5% of all detected connections – say, 50 or 60

ones – will be false, and there is no way to distinguish between the real and spurious connections. The situation we described is called a "multiple-comparisons problem" in statistics (Shafer, 1995).

There is no general way to overcome the multiple comparison problem. Depending on specific situation, different approaches can be used. Here we'll just mention a few popular ones.

The most straightforward approach is to try to reduce the number of statistical tests (comparisons) using prior knowledge. For example, if one can limit the number of brain areas to look at from 50 to 5 based on neurophysiological considerations, the number of pairwise connections will go down from ~1200 to 10. Then by limiting statistical error for each pair to 0.5%, one can guarantee with 95% certainty that all detected connections are the true ones. When such reduction of the number of connections is not possible, another useful approach is to apply statistical tests pertaining to (sub)networks as a whole rather than to individual connections. For example, one can look at subsets, or "clusters" of locations with mutual connectivity values above a certain threshold. Probability of such a cluster to occur by chance can be estimated (Zalesky et al., 2010), and if it is small enough, one can argue that the locations involved constitute a brain network. This way, interconnected brain areas can be identified in spite of the curse of multiple comparisons, even though it might be not possible to make conclusions about individual pairwise connections within the network. Another method is to consider a set of areas strongly connected to a single location (a seed point) to form a separate network (Brookes et al., 2012). Yet another set of approaches involves representing a signal from each location as a linear combination of a certain number of uncorrelated or statistically independent components (so called principal or independent component analysis). When any such component mostly consists of contributions from a well-defined, distinct subset of locations, one can argue that corresponding areas operate synchronously and constitute a single network (Luckhoo et al., 2012, Whitman et al., 2016).
In summary, we discussed how the focus on interactions and connectivity within the human brain affected MEG/EEG analyses of brain signals. We showed that new, more sophisticated signal processing techniques were developed to deal with the new challenges. However, this journey is far

from over, and we need more novel, even more advanced techniques to emerge in this field in coming years to further improve the quality of brain connectivity analysis.

Advances in brain imaging processing and visualization: Interpretation of diffusion MRI for the brain

As advances have been made in brain imaging techniques, the quantity and complexity of the outputted images has also increased, leading to data visualization and interpretation challenges, challenges most prominently seen in the area of diffusion MRI (dMRI) (Booth and Hamarneh 2015). In dMRI, image sequences are used to measure, non-invasively and *in vivo*, the rates of molecular diffusion in the brain. This diffusion is impeded by cell structure in such a way that fibrous tissue (e.g. white matter) shows a maximal rate of diffusion along the direction of the fibers (Le Bihan and Breton 1985, Stejskal and Tanner 1965). Uncovering these directions of maximal diffusion - and therefore the fiber directions - requires the use of diffusion-sensitizing gradient pulses to sample diffusion along tens, or even hundreds, of directions (as in High angular resolution diffusion imaging (HARDI), e.g. Q-Ball Imaging (QBI)) (Tuch 2004). The result is a high-dimensional 3D image with a (fibre) orientation distribution function (ODF) (Tournier et al. 2007) at each voxel - an image that is difficult to manually examine and interpret.

Initial attempts to visualize dMRI datasets revolved around reducing their dimensionality to a single scalar-valued image by computing statistics across the sampled diffusion directions. By computing the mean and variance in diffusion across the sample directions, we obtain the commonly used Mean Diffusivity (MD) and Fractional Anisotropy (FA) measures (Figure 4 (a,b)). MD is sensitive to the amount of cell structure present while FA is sensitive to how fibrous the tissue is. It is also common to see the FA image color-coded to show the directions of maximal diffusion, which approximate the fiber directions (Figure 4 (c)). Other scalar measures include: radial, axial, and relative diffusivity; linear, planar, and sphericity measures; mode, and volume ratio (Westin et al. 2002). Finally, it has also become customary to reduce the dimensionality of a dMRI dataset by fitting models,

at each voxel, to the sampled diffusion measurements. Through the use of tensors (i.e. Diffusion Tensor Imaging, DTI) and spherical harmonics (SPHARM) (Basser et al. 1994, Jian and Vemuri 2007), we can reduce the dimensionality of a dMRI dataset, from the number of diffusion samples to the much lower number of parameters of the model, thus facilitating visualization (Figure 4 (d)).

More recent work has looked at producing dMRI visualizations that highlight different geometric properties. For example, recent work has led to colour visualizations of dMRI datasets that match the perceptual differences in colour to the real differences in measured diffusion (Figure 4 (e)) (Hamarneh et al. 2011). Other works have looked at extracting regions of interest - usually axon bundles - from a dMRI scan through the use of specially-designed structure detectors (Figure 4 (f)) (Nand et al. 2011) or segmentation techniques (Figure 4 (g)) (Booth and Hamarneh 2013, Hamarneh and Hradsky 2006, Weldeselassie and Hamarneh 2007). Similarly, those regions of interest can also be detected through the use of image registration: By aligning two dMRI scans and examining the differences in the image data at the level of individual voxels, we can flag regions of interest where the scans differ (Figure 4 (h)) (Smith et al. 2006, Booth et al. 2016). In all of these techniques, the high-dimensional dMRI scan undergoes multiple processing steps in order to generate the visualization. As a result, various mathematical models have had to be extended to account for the dMRI's high dimensionality and to ensure that its measured diffusion values remain positive (Booth and Hamarneh 2011a). Further, these processing and analysis techniques benefit from pre-processing algorithms that remove imaging noise (Hamarneh and Hradsky 2007, Nand et al. 2012) and ones that capture relations between neighbouring voxels (Booth and Hamarneh 2011b).

The most appealing aspect of dMRI may be its unique ability to examine structural connectivity within the brain. As dMRI can identify the direction of tissue fibers, in a process called tractography (Booth and Hamarneh 2012, Mori and van Zijl 2002), we can trace out 3D curves called streamlines that estimate the location of white matter axonal pathways, thereby uncovering connections between different brain regions. Tractography techniques range from streamline-based techniques (Figure 4 (i))

to probabilistic techniques that capture the uncertainty in the fiber tract location (Figure 4 (j)) (Brown et al. 2013a, Brown et al. 2013b). Recently, groups have begun summarizing the structural connections tractography uncovers by building networks known as connectomes (Sporns et al. 2005). In a connectome, nodes are defined as functional regions in the brain (usually identified by registering a labeled atlas to the dMRI scan under evaluation) and weighted edges are placed between nodes based on how strongly connected the tractography results show the regions to be. Visualizing connectomes remains an area of open research, but two common approaches include the use of circular graphs (Figure 4 (k)) and spatially overlaying the network's properties onto a brain image (Figure 1(l)) (Brown et al. 2014).

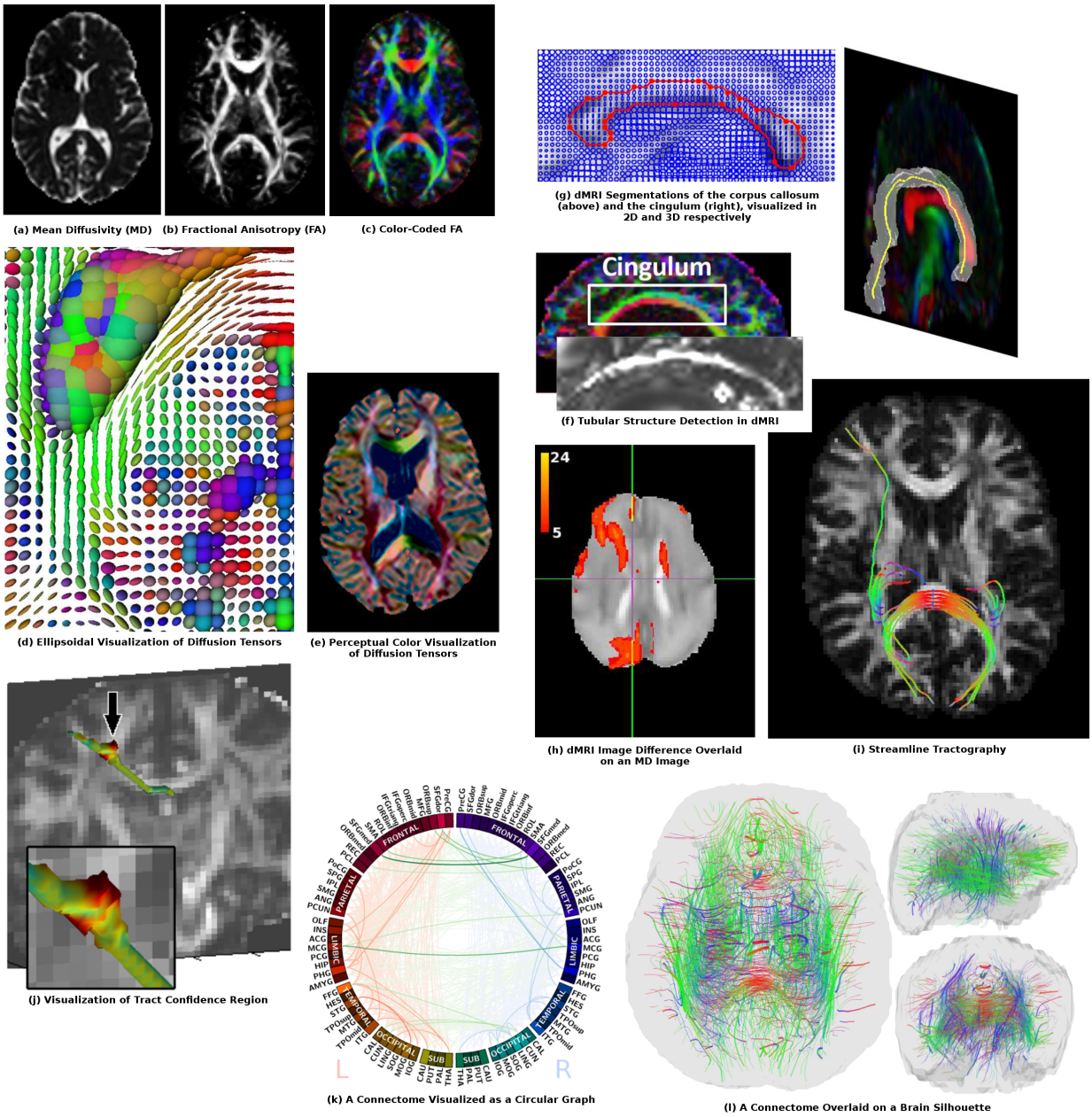

Figure 4: Examples of visualizations associated with diffusion MRI (dMRI) data. Some visualizations highlight the brain's diffusion properties (a-e), while others highlight its geometric properties (f-h), while still others highlight brain connectivity (i-l). See the text for a description of each visualization technique: (a) Mean Diffusivity (MD), (b) Fractional Anisotropy (FA), (c) Color-Coded FA, (d) Ellipsoidal Visualization of Diffusion Tensors, (e) Perceptual Color Visualization of Diffusion Tensors, (f) Tubular Structure Detection in dMRI, (g) dMRI Segmentation of corpus callosum (above) and the cingulum (right), visualized in 2D and 3D respectively, (h) dMRI Image difference Overlaid on MD Image, (i) Streamline Tractography, (j) Visualization of Tract Confidence Regions, (k) A Connectome Visualized as a Circular Graph, (l) A Connectome Overlaid on a Brain Silhouette.

While the visualization techniques presented here provide the ability for a human operator to examine and interpret a high-dimensional, complicated dMRI dataset, the value of these visualization techniques can be further strengthened by having complementary automated computational methods that identify which features or aspects would be most valuable to visualize. Recently, researchers have begun using machine learning algorithms (e.g. support vector machines, decision forests, or deep neural networks) to model relationships between the image data and clinical variables of interest. By coming up with a model for this relationship, we identify regions in the images, or edges in the connectomes, that are the most important to the model. We then visualize these image-based features using the above techniques. For example, Figure 4 (j) shows the presence of abnormal geometry in a fiber bundle, while Figure 4 (h) highlights voxels that are significantly different between a subject's scan and a healthy population, and Figure 4 (k) shows edges in a connectome most predictive of motor outcome in preterm infants (Brown et al. 2015). By using machine-learning techniques, not only are we able to automatically identify relevant visualizations, but also seek imaging biomarkers of neurological disorders (Booth et al. 2016, Brown et al. 2015).

Emerging neurophysiological frameworks for unified thalamo-cortical processing

Sensory, motor and cognitive functions are associated with oscillatory changes within task-relevant cortical brain regions, as well as alterations in functional and effective connectivity between those regions associated with neuronal synchronization (Llinás and Ribary 1993; Varela et al. 2001; Ward 2003; Uhlhaas et al. 2009; Wang 2010; Ribary et al. 2014). Recording methodologies with sufficient temporal resolution to measure fast above 1Hz neural oscillations, such as electroencephalography (EEG) and magnetoencephalography (MEG), have shown that brain dynamics within and between regions often differ markedly across frequencies, and that brain rhythms often interact across widely separated frequency ranges (Llinás et al. 1999; Sauseng et al. 2008; Doesburg et al. 2009, 2012; Holz et al. 2010; Palva et al. 2010; Palva and Palva 2012). It has further been reported

that cross-frequency interactions may play an important role in local processing within the thalamus and neocortex, as well as information transfer between them (FitzGerald et al. 2013). Strong commonalities in rhythmic network properties have been observed across recording techniques and task demands, but strong neuroscientific theories to situate such observations within a unified framework that has direct relevance to the explanation of neuropathologies remain scarce.

Our recent comprehensive review into the animal and human literature indicates a further thinking beyond synchrony and connectivity and the readiness for more hypothesis-driven research and modeling toward unified principles of thalamocortical processing (Doesburg et al. 2015). We further introduced such a possible emerging framework: "The alpha-theta-gamma (ATG) switch". We probed and introduced this neurophysiological framework to explain how coordinated cross-frequency and interregional oscillatory cortical dynamics may underlie typical and atypical brain activation, and the formation of distributed functional ensembles supporting cortical networks underpinning sensation and cognition (Doesburg et al. 2015). We also discussed evidence that alpha-theta-gamma dynamics emerging from thalamocortical and cortico-cortical interactions may be implicated in cognition across diverse contexts, and that the disruption of such processes is implicated in numerous neurological and neuropsychiatric conditions. Moreover, this emerging framework further challenges the dominant view in current neuroscience on the classical activation of the brain per se and rather suggests an inhibitory induced dis-inhibition of intrinsic cortical activity during sensory and cognitive processing, a novel plausible mechanism to integrating local and large-scale brain networks and its related alterations in clinical pathologies (Doesburg et al. 2015).

Such neuroscientific advances, emerging neurophyisiological frameworks and more future hypothesis-driven basic and clinical research and modeling will further pose future ethical challenges for the implementation of quantitative diagnostic and prognostic strategies into clinical practice according to best practice and the highest ethical standards.

Conclusions

This comprehensive chapter, highlighting advances in multimodal brain imaging, signal processing and visualization from related expert perspectives, points to the next necessary step in cognitive and clinical neuroscience brain imaging, namely to more basic and clinical research and the quantification of the *5D human brain (across 3D space, frequency and time)* in health and disease. In this chapter, we urge quantification of the biochemical, structural, functional and dynamic network connectivity and causality of the brain underlying typical/atypical sensory and cognitive processing, to establish objective diagnostic neuromarkers for the identification and better characterization of sub-types of neurological disabilities and pathologies. In addition, we believe that it is essential to indicate new innovative ways of how such sub-types can be selectively and optimally targeted with existing or additionally modified neuroscience-based interventional training programs that exploit brain plasticity with neuropharmacological or neurosurgical interventional strategies, and that thereby validate and monitor their effectiveness with the highest possible precision and accuracy across five dimensions. It is incumbent on us, as experts in neuroscience, and on experts in neuroethics and biomedicine, to proactively consider and advance the best possible diagnostic evaluation, utilization of criteria and prediction of interventional outcome to researchers, educators, clinicians and healthcare practitioners at large.

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The co-authors are listed in chronological order of their contributions: MacKay and Rauscher (MRI), Tipper, Giaschi and Woodward (fMRI), Sossi (PET), Doesburg (MEG), Ward (EEG-1), Herdmann (EEG-2), Moiseev (Signal Processing), Hamarneh and Booth (Processing and Visualization), Ribary, Doesburg and Ward (Emerging Neurophysiological Frameworks).

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