Neuroscience and Biobehavioral Reviews 83 (2017) 21–31

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Abnormal cortical asymmetry as a target for neuromodulation in neuropsychiatric disorders: A narrative review and concept proposal

Randy W. Beck[a], Jonathan Laugharne[b], Richard Laugharne[c], Wessel Woldman[d,i,j], Brendan McLean[e], Chiara Mastropasqua[f,k], Ricardo Jorge[g], Rohit Shankar[h,*]

[a] Institute of Functional Neuroscience, Perth, Australia
[b] School of Psychiatry and Clinical Neurosciences, University of Western Australia, Perth, Australia
[c] Cornwall Partnership NHS Foundation Trust and Hon, University of Exeter Medical School, Exeter, United Kingdom
[d] Living Systems Institute, University of Exeter, Exeter EX4 4QD, United Kingdom
[e] The Royal Cornwall Hospitals NHS Trust, Treliske, Truro, Cornwall, United Kingdom
[f] Institute of Functional Neuroscience, Sydney, Australia
[g] Institute of Functional Neuroscience, Perth, Australia
[h] Cornwall Partnership NHS Foundation Trust, University of Exeter Medical School, Exeter, United Kingdom
[i] Wellcome Trust Centre for Biomedical Modelling and Analysis, University of Exeter, Exeter EX4 4QD, United Kingdom
[j] EPSRC Centre for Predictive Modelling in Healthcare, University of Exeter, Exeter EX4 4QD, United Kingdom
[k] Neuroimaging Laboratory, IRCCS Santa Lucia Foundation, Via Ardeatina 306, 00179 Rome, Italy

ARTICLE INFO

Keywords:
Neuroplasticity
Brain mapping
Non-invasive brain stimulation
Cortical asymmetry

ABSTRACT

Recent advances in knowledge relating to the organization of neural circuitry in the human brain have increased understanding of disorders involving brain circuit asymmetry. These asymmetries, which can be measured and identified utilizing EEG and LORETA analysis techniques, may be a factor in mental disorders.

New treatments involving non-invasive brain stimulation (NIBS), including *trans*-cranial magnetic stimulation, direct current stimulation and vagal nerve stimulation, have emerged in recent years. We propose that EEG identification of circuit asymmetry geometries can direct non-invasive brain stimulation more specifically for treatments of mental disorders. We describe as a narrative review new NIBS therapies that have been developed and delivered, and suggest that they are proving effective in certain patient groups. A brief narrative of influence of classical and operant conditioning of neurofeedback on EEG coherence, phase, abnormalities and Loreta's significance is provided. We also discuss the role of Heart rate variability and biofeedback in influencing EEG co-relates. Clinical evidence is at an early stage, but the basic science evidence and early case studies suggest that this may be a promising new modality for treating mental disorders and merits further research.

1. Introduction

In 2010 the National Institute of Mental Health launched its Research Domain Criteria (RDoC) in response to the recognition that clinical diagnostic categories in psychiatry fail to align with findings in neuroscience and thus slow the development of new treatments targeted to underlying pathophysiological mechanisms (Insel, 2010). The RDoC approach conceptualizes psychiatric disorders as due to faulty brain circuits which can be identified via the tools of neuroscience, yielding biosignatures to guide clinical management.

This current paper aims to deliver a narrative review to help contribute to this innovative, neuroscience-based approach to improving outcomes in psychiatric disorders by reviewing key lines of current evidence regarding neuronal connectivity and cortical asymmetry to develop the clinical approach we described as EEG guided neuroplastic restructuring into a conceptual proposal of direct relevance to clinical treatment.

Evidence from animal studies suggests that some cortical systems can undergo plastic reorganization. Modulation of afferent input to the cortical areas represents at least one factor that determines the type of reorganization observed (Merzenich et al., 1984; Merzenich and deCharms, 1996). The human brain is a complex network. It consists of spatially distributed, but functionally linked regions that continuously share information with each other (vanden Heuvel and Sporns, 2011). It is generally accepted that to better understand the functioning of a network, one must know its elements and their interconnections (Sporns, 2014a). Thus the characterization of brain connectivity is necessary to increase the understanding of how functional brain states

* Corresponding author at: Chy Govenck, Threemilestone Industrial Estate, Highertown, Truro, Cornwall TR4 9LD, United Kingdom.
E-mail address: Rohit.shankar@nhs.net (R. Shankar).

http://dx.doi.org/10.1016/j.neubiorev.2017.09.025
Received 3 December 2016; Received in revised form 17 September 2017; Accepted 25 September 2017
Available online 25 September 2017
0149-7634/

emerge from their underlying structural substrate and how neurons and neural networks process information. Moreover, this approach can provide new mechanistic insights to understand the correspondence between structural disruption and the consequent changes in brain functioning (Sporns et al., 2005).

Normal brain function depends on the optimal performance of the integrated components of both long and short-term connectivity of neurons through out the brain (Catani et al., 2013; Park and Friston, 2013). The requirement for the brain to process both immediate and segregated short-term information (millisecond time frame) while also integrating this information into a coherent global model over a lifetime presents a complex problem for neuroplastic systems (Buzsaki, 2006).

Brain connectivity refers to a pattern of anatomical links ("anatomical connectivity"), of statistical dependencies ("functional connectivity") or of causal interactions ("effective connectivity") between distinct units within a nervous system. The units correspond to individual neurons, neuronal populations, or anatomically segregated brain regions. The connectivity pattern is formed by structural links such as synapses or fibre pathways, or it represents statistical or causal relationships measured as cross-correlations, coherence, or information flow. Neural activity, and by extension neural codes, are constrained by connectivity. Brain connectivity is thus crucial to elucidating how neurons and neural networks process information (Sporns, 2007). The dynamics of brain connectivity involve the development of complex network connection systems that can both maintain an appropriate level of integrity of synaptic connection and at the same time express neuroplastic properties in response to the constant change of environmental stimulus (Beck, 2013a,b; Bowyer, 2016). These network connection systems are categorized as Structural, Functional and Effective Connectivity (Friston et al., 1993; Greenblatt et al., 2012; Sakkalis, 2011) and are summarized in Table 1.

The discovery of neural organizational features such as functional MRI resting-state (RS-fMRI) networks (Damoiseaux et al., 2006) and functional hubs (Zalesky et al., 2011) has been instrumental in deepening our understanding of both normal and abnormal brain function including the concept of asymmetric cortical activity (Beck, 2013a). These asymmetries, which can also be measured and identified utilizing EEG and LORETA analysis techniques, may be a factor in mental disorders. EEG identification of circuit asymmetry geometries can be utilized to direct non-invasive brain stimulation more specifically for treatments of mental disorders.

1.1. Resting state networks

It was noted more than a decade ago that spontaneous Blood-oxygen-level dependent (BOLD) contrast imaging signal fluctuations are temporally correlated (or coherent) between brain regions of similar functionality (Biswal et al., 1995; Fox and Raichle, 2006). RS-fMRI allows the measurement of functional brain connectivity as expressed by synchronization of neural activity across different brain regions (Biswal et al., 1995; Friston et al., 1993). A mounting number of studies (Biswal et al., 1995; Damoiseaux et al., 2006) investigating spontaneous neural activity within resting brains identified synchronous fluctuations within anatomically separated regions. The view that coherencies in resting fluctuations represent functional resting-state networks linked to underlying neuronal modulations is consistent with the appearance of these coherencies within cortical gray matter areas of known functional relevance (Damoiseaux et al., 2006).

Moreover, support for a possible neuronal basis of resting-state fMRI signals comes from the observation that most of the resting-state patterns tend to occur between brain regions that overlap in both function and neuroanatomy (Biswal et al., 1995; Damoiseaux et al., 2006; van den Heuvel et al., 2008). Taken together, more and more studies are in support of a neuronal basis of the resting-state fMRI signal. The resting state can be used to determine several components of cortical asymmetry such as coherence analysis, and several metric ratios that are useful clinically.

1.2. Network analysis

Recently, new advances in resting state (RS) analysis techniques have shown the possibility of examining the overall structure of the brain network with high levels of spatial detail, using graph analytical methods, thus providing new valuable insights in how the human brain operates. Graph theory provides a theoretical framework in which the topology of complex networks can be examined, and can reveal important information about both the local and global organization of functional brain networks (Bullmore and Sporns, 2009). The graph model of the brain is an abstract structure used to represent pair-wise relations between interregional ensembles of neuronal elements, referred to as nodes (or hubs). These pair-wise relations, or links, can be either of functional origin and represent coherent physiological activity between neuronal ensembles, or they can be of a structural origin and represent anatomical connections formed by white-matter fibre tracts (Zalesky et al., 2011).

Occasionally, neuroplastic activity and the resultant changes in connectivity lead to asymmetric functional levels in cortical projection networks. This lowers the threshold for asymmetrical dysfunction, a critical level of imbalance of activity or arousal levels between one cortical hemisphere and the other, which can then result in a type of functional disconnect syndrome (Leisman and Ashkenazi, 1980; Stroka et al., 1973). The critical level at which this functional disconnect first becomes symptomatic from a clinical perspective seems to be individually specific. The symptomatic presentation of functional disconnection syndrome often manifests as a reflection of the area where the disconnection occurs but the symptom presentation may be complicated when diaschisis produces symptoms which may cause confusion as to the actual source of the disconnect. Diaschisis is a neurological term indicating a sharp modulation (inhibition/excitation) in activity at a site that is distant from a site of injury but is anatomically connected with it through fiber tracts. For example, prefrontal injury has been shown to lead to abrupt decreases in blood flow to the contralateral cerebellum and vice versa. Diaschisis can extend beyond focal lesions and include the possibility that disrupted molecular signaling pathways can interrupt long-distance guidance of neural circuit refinement.

Functional disconnection has been demonstrated in a range of

Table 1
Modes of Connectivity in the human brain.

Structural Connectivity (Fiber pathways)	Structural connectivity is based on detection of the fiber tracts that physically connect the regions of the brain. These are the anatomical network maps that indicate possible pathways that the signals can travel on in the brain (Le Bihan et al., 2001; Wedeena et al., 2008).
Functional Connectivity (Statistical Correlations)	Functional connectivity identifies activity in brain regions that have similar frequency, phase and/or amplitude of correlated activity. These areas may be involved in the resting state (i.e. task independent) or higher order information processing (i.e. task dependent) that is required for sensory responses, motor responses and intellectual or emotional processing (Towle et al., 2007).
Effective Connectivity (Information Flow)	Effective connectivity uses the functional connectivity information and then determines the direct or indirect influence that one neural system may have over another, more specifically the direction of the dynamic information flow in the brain (Bowyer, 2016; Cabral et al., 2014; Horwitz, 2003).

Table 2
Key differences between the disconnection and hyperconnection syndromes.

Disconnection Syndrome	Hyper-connection Syndrome
Hypo-connection or disconnection results in a slow inefficient transfer of information, which results in incomplete or slow thought formation diminishing the relevance of the systems' output to the environmental input received.	Hyper-connection causes the same neuronal pathways to be excited or inhibited over and over again which reduces the ability of the system to respond flexibly to altered states of activity. This results in a functional projection system that becomes functionally deficient, inflexible, debilitated, and incapable of reacting to environmental stimuli effectively.

psychiatric conditions including attention deficit disorder and attention deficit hyperactivity disorder (Melillo and Leisman, 2004), autism (Leisman and Melillo, 2009), and depression (Henriques and Davidson, 1991). It could also present as asymmetric control of the autonomic nervous system, immune system dysfunction, and asymmetric modulation of sensory perception while impacting on cognitive, learning, and emotional processes (Davidson and Hugdahl, 1995). The disconnection can be hypo-functional or hyper-functional in nature (Table 2).

There is some evidence that many of the most common psychiatric conditions may involve some form of identifiable brain network and/or processing dysfunction, including schizophrenia, autism spectrum disorders, depression and obsessive compulsive disorder (OCD) (Insel, 2010; Zalesky et al., 2011; Cocchi et al., 2012; Fornito et al., 2012).

The availability of non-invasive techniques has prompted neuroscientists to characterize the wiring diagram of the human brain (Sporns, 2005). These efforts have led to a number of multi-centric projects aiming at depicting the "human connectome". The main one is the Human Connectome Project (HCP) (http://www.humanconnectomeproject.org/), led by Washington University, University of Minnesota, and Oxford University (the WU- Minn HCP consortium). The aim of this and other similar projects is to comprehensively map the human brain circuitry in a target number of 1200 healthy adults using resting-state fMRI, diffusion imaging, task-related fMRI, magnetoencephalography and electroencephalography (MEG/EEG). In addition, behavioral data will be related to brain circuits to characterize individual differences in cognition, perception, and personality. Studies of the human connectome have provided a means to delineate subtypes of psychiatric disorders based upon neurobiology, to characterize the neural basis of specific symptoms, and to monitor the brain's response to treatment, as well as defining neural markers of illness (Filippi et al., 2013; Fornito et al., 2015; Scale et al., 2015).

The size and the attention received by these initiatives result from the realization that examining the brain as an integrative network of anatomically and functionally interacting brain regions can provide new insights about large-scale neuronal communication. It provides a platform to examine how cerebral connectivity and information integration relates to human behavior and how this organization may be altered in several diseases (Bullmore and Sporns, 2009) (Fig. 1).

Indeed, it is becoming increasingly recognized that many behavioral manifestations of neurological and psychiatric diseases are not solely the result of abnormality in one isolated region but represent alterations in brain networks and connectivity (Beck, 2007; Fox et al., 2013). Thus, the improved characterization of brain networks can have an enormous relevance in discovering the basis of common disorders of the brain, response to recovery from brain injury, individual differences, heritability, normal development and aging.

While relying primarily on DTI and fMRI, a broad range of neuroimaging network analysis approaches to study brain connectivity have been proposed. In the last few years, novel techniques and analysis methods have enabled the examination of whole brain connectivity patterns, enabling the in-vivo examination of functional and anatomical connectivity on a whole-brain scale.

The six main anatomical modules included: the posterior cingulate, the bilateral precuneus, the bilateral paracentral lobule, the unilateral cuneus, the bilateral isthmus of the cingulate gyrus, the bilateral superior temporal sulcus (Modified from Hagmann et al. (2008).

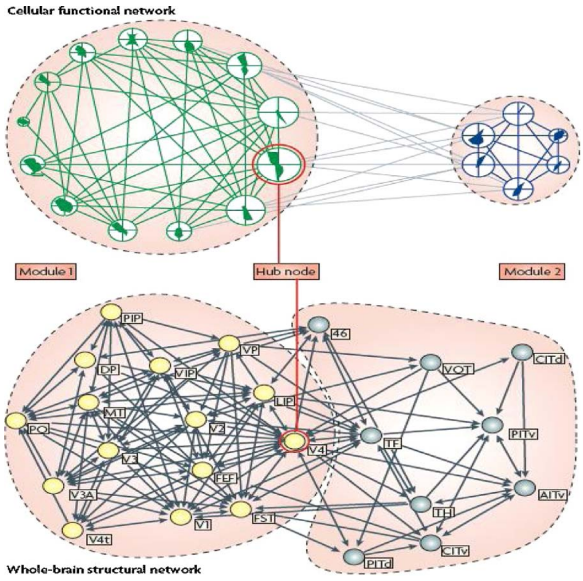

Fig. 1. Hagmann functional modules developed from Graph theory analysis. The six main anatomical modules included: the posterior cingulate, the bilateral precuneus, the bilateral paracentral lobule, the unilateral cuneus, the bilateral isthmus of the cingulate gyrus, the bilateral superior temporal sulcus (Modified from Hagmann et al. (2008)).

2. An overview of cortical asymmetry

The fact that the human brain functions in an asymmetric manner has been well established in the literature (Geschwind and Levitsky, 1968; LeMay and Culebras, 1972; Galaburda et al., 1978; Falk et al., 1991; Steinmetz et al., 1991). However, the exact relationship between this asymmetric design and the functional control exerted by each hemisphere remains controversial. A wide variety of systems may be influenced by aberrant cortical asymmetry (Table 3).

3. Development of cortical imbalances through asymmetry

Afferent stimulation is gated through the brainstem and thalamus, both of which are asymmetric structures, and indirectly modulated by their respective ipsilateral cortices (Savic et al., 1994). Imbalances may develop between the activation of one hemisphere and the other with a number of different etiological pathways including aberrant patterns of activation or arousal (Obrut, 1994), acute or chronic ablative lesions (Kreisel et al., 2006; Murase et al., 2004; Leipert et al., 2000), asymmetric afferentation excesses or deficits (Merzenich et al., 1983), inter or intra hemispheric transmission imbalances (Brown et al., 1994; Bastings et al., 2002), circulation deficits, diffuse axonal injury (concussion), asymmetric neurotransmitter concentrations (Xu et al., 2005; Hachinski et al., 1992) or asymmetric metabolic dysfunction. Neuroplastic changes may be maladaptive in cases of asymmetric cortical stimulation or inhibition resulting in a chronic state of disequilibrium in lateralized cortical systems. For example in stroke survivors ablative

Table 3
Functional Effects of Cortical Asymmetry.

Cortical Asymmetry and Cardiac Function	Functional hemispheric asymmetries have also been shown to exist with respect to cortical control of cardiovascular function. The research suggests that asymmetries in brain function can influence the heart through ipsilateral pathways. It is quite clear from the literature in this area that stimulation or inhibition at various levels on the right side of the neuraxis results in greater changes in heart rate, while increased sympathetic tone on the left side of the neuraxis results in a lowered ventricular fibrillation threshold. This occurs because parasympathetic mechanisms are dominant in the atria, while sympathetic mechanisms are dominant in the ventricles.	Lane and Jennings (1995), Lane et al. (1992)
Neurotransmitter Asymmetry	Neurotransmitter asymmetries in the cortex have been discovered. Quite consistent results have been reported in a number of studies that have suggested that noradrenergic innervation, the biological substrate of arousal shows a clear right hemispheric asymmetry.	Harrison (2015), Pearlson and Robinson (1981), Neveu et al. (1991), Hachinski et al. (1992)
	Several studies have also shown strong indications that the neurotransmitter serotonin shows a right hemispheric dominance which may occur from birth as an inborn feature of cortical function.	Tekes et al. (1988), Demeter et al. (1989), Arato et al. (1991), Frecska et al. (1990)
	The role of gating signals, such as acetylcholine, in the enhancement of cortical plasticity (may also play a role in the development of asymmetric activation).	Bakin and Weinberger (1996), Cruikshank and Weinberger (1996)
Hormonal Regulation and Cortical Asymmetry	Cortical asymmetries have been documented with respect to hormonal regulation.	Herrero et al. (2010), Wittling and Roschmann (1993)
	Cortisol secretion has been associated with the right hemisphere with predominance of control demonstrated in this hemisphere during emotionally-related situations.	Wittling and Schweiger (1993)
	Various studies have shown that right hemispheric chemical dominance was associated with up-regulation of the hypothalamic-mediated isoprenoid pathway and was more prevalent among individuals with various metabolic and immune disorders including a high body mass index, various lung diseases including asthma and chronic bronchitis, increased levels of lipid peroxidation products, decreased free radical scavenging enzymes, inflammatory bowel disease, systemic lupus erythematosus (SLE), osteoarthritis, and spondylosis. Left hemispheric chemical dominance was associated with a down-regulated isoprenoid pathway and was more prevalent among individuals with low body mass index, osteoporosis, and bulimia.	Wittling and Roschmann (1993)
Emotional Regulation and Cortical Asymmetry	A number of functional MRI studies have indicated that cortical asymmetries may exist when different emotional states are activated. The left frontal cortex appears to be activated during the expression or experience of positive emotional states, whereas the right frontal cortex seems to be activated during the expression or experience of negative emotional states.	Grimshaw and Carmel (2014), Davidson (1988), Davidson and Tomarken (1989), Leventhal and Tomarken (1986)
	The severity of symptoms in depression has been linked to the activation levels in the left frontal cortex. Those patients with left frontal cortex lesions with sparing of the right frontal cortex showed the most severe depressive symptoms.	Silberman and Weingartner (1986), Robinson et al. (1984)
Immune regulation and Cortical Asymmetry	Cortical asymmetry has also been shown to be important in immune regulatory functions. Natural killer cell activity was significantly increased in human females with extreme left frontal cortical activation when compared to females with extreme right cortical frontal activation. The level of hemispheric activation in these women was determined by electroencephalographic (EEG) determinants of regional alpha power density. This measurement has been shown to be inversely related to emotional or cognitive brain activation.	Sumner et al. (2011), Kang et al. (1991), Davidson (1988)
	A variety of animal studies have also provided direct evidence of the relationship between cerebral asymmetry and immune system function. Partial ablation of the left frontoparietal cortex in mice, which results functionally in relative right cortical activation, resulted in decreased immune responses and partial right cortical ablation, which would result functionally in a left cortical activation showed no change or a reduced immune response.	Barneoud et al. (1987), Neveu (1988), Renoux et al. (1983), Neveu et al. (1986)
	Other studies have shown that the development of the lymphoid organs including the spleen and thymus occurs with left cortical lesions, whereas increased development of the spleen and thymus occurs with right cortical lesions and activation of T cells is significantly diminished in lesions involving the left cortex and elevated with lesions of the right cortex.	Renoux et al. (1983), Renoux and Biziere (1986), Barneoud et al. (1988)
	These findings indicate that T-cell-mediated immunity is modulated asymmetrically by both hemispheres with each hemisphere acting in opposition to the other. Increased activity of the left cortex seems to enhance the responsiveness of a variety of T-cell-dependent immune parameters, whereas increased right cortical activity seems to be immunosuppressive.	
	On the other hand, B-cell activity was found not to be affected by cortical activation asymmetry.	LaHoste et al. (1989), Neveu et al. (1988)
	Summarizing, it appears from the findings of the above studies that changes in hemispheric activation because of either ablation of cortical areas or modulation in physiological activation levels result in changes in immunological response activity. Both hemispheres seem to be active in the modulation of immune response, with the left hemisphere enhancing cellular immune responses and the right inhibiting those responses. In addition, some evidence does suggest that the involvement of the right hemisphere may not act directly on immune components but may modulate the activity of the left hemisphere which does act directly to regulate immune function.	Renoux et al. (1983)

injury to areas of cortex may result not only in disruption of functional activities related to the site of the injury but also in a lack of inhibitory projections to the contra-lateral hemisphere (Bozzali et al., 2012). This sets into motion the chronic state of over excitation in the contra-lateral hemisphere (Liepert et al, 2000; Murase et al., 2004). The chronic disinhibition of the contra-lesional cortical area may result in a vicious cycle in which the lesioned area experiences a chronic increased inhibition due to the over excitation of the contra-lesional site which in turn inhibits the lesioned site to even greater degree.

4. Measuring cortical function

The human brain contains a vast network of connected pathways that communicate through synchronized electric brain activity along fibre tracts of variable lengths and speed. Synchronized activity within these neuronal networks can be detected by magnoencephalography (MEG) and electroencephalography (EEG) (Pfurtschellera and Lopes da Silva, 1999) then imaged using a variety of formats including topographic and network connectivity analysis (Zalesky et al., 2011). Connectivity analyses of the brain are performed to map out the communication networks needed for the brain to function (Bowyer, 2016).

To measure the complex patterns of brain activity tools are needed with the appropriate temporal and spatial resolution. This task is not as simple as it sounds because “appropriate resolution” varies with different types of analysis and utility expectation of the information. The measurement tool must measure the particular activity we are interested in without interfering with it to any great extent.

Neurons function through the production of two fundamentally different activities involving analogue (local field potentials) and digital (action potentials) components (Buzsaki, 2006). Both of these activities are continuously changing over time and involve multiple frequencies and amplitudes. Therefore the perfect measurement tool would be able to provide a time-frequency analysis algorithm that would provide a perfect picture of all changes in all frequencies continuously over time in whatever spatial dimension we choose to explore. All of the current methods of measuring brain function involve a compromise between the desired temporal and spatial resolution necessary for complete analysis. The desired temporal resolution is in the order of the operation speed of the neuron system is in the millisecond time frame. The desired spatial resolution varies between molecular interactions to global brain activity depending on the processes being investigated. No current method exists that can continually and instantaneously monitor between global activity and molecular spatial scales (Buzsaki, 2006). Obviously, the methods available at this time differ in their spatial and temporal resolution, and none of them achieve the highest resolution in both domains. For example what fMRI gains in spatial resolution it loses in temporal resolution and visa versa for EEG. Quantitative electroencephalography (qEEG) has been shown to be a valid instrument in the evaluation of a variety of components of cognitive function (Thatcher et al., 2003, 2005). Computer-assisted EEG analysis and interpretation offers multiple advantages over visual inspection of raw EEG tracings, including the ability to derive measures, perform data transforms, and identify subtle shifts in the types and patterns of EEG activity. Commonly used EEG metrics are summarized in Table 4.

Utilization of the EEG as a tool to measure brain function must take into account that the scalp-measured frequency of the electrical energy generated by groups of cortical neurons varies with:

i) The number of cortical neurons (i.e., as neurons are lost, the amplitude and therefore power of electrical energy recorded at the scalp diminishes);
ii) The integrity of the thalamocortical circuits in which they participate (i.e., injury to and/or dysfunction of those circuits results in a shift to slower frequencies recorded at scalp electrodes);
iii) The influence of ‘bottom-up’ activation from the reticular system (i.e., with increases in reticular activating system activity, shifts toward higher frequencies are observed, whereas decreases in the activity of this system shifts cortical activity towards lower frequencies).

Another way to measure cortical function is represented by MRI. Mapping functional connectivity across the whole brain has revealed several large-scale neural networks whose activity is relatively confined when participants are in a resting state (i.e., not engaged in an active task) (Bullmore and Sporns, 2009; Yeo et al., 2011). A growing body of literature suggests that the topology of functional networks identified with resting state fMRI (RS-fMRI) is correlated with patterns of neural activity observed during the execution of various tasks (Biswal et al., 1995; Greicius et al., 2003; Fox et al., 2006), suggesting that large-scale neural networks isolated in a state of rest may represent a fundamental property of brain organization (Fornito and Bullmore, 2010). In this context, the use of graph theory has facilitated the characterization of complex structures and dynamics supporting the optimal integration of activity across widespread neural populations (Scale et al., 2015). In essence, a graph is a mathematical representation of pair-wise relations between distinct objects. Graphs encompass nodes, or vertices, and lines defined as edges that connect them (Sporns et al., 2007; van den Heuvel and Sporns, 2011). Combined with neuroimaging data, models of the brain as a graph, or network, and the application of algorithms assessing different properties of such a network, are emerging as a powerful tool for understanding the modus operandi of the brain (Rubinov and Sporns, 2010; Sporns, 2014a,b).

5. Balancing the brain: conceptual understanding

In recent years it has become clear that various forms of non-invasive brain stimulation (NIBS), such as *trans*-cranial magnetic stimulation (TMS), *trans*-cranial electrical stimulation (tES), and peripheral sensory stimulation can modify ongoing brain activity (Scale et al., 2015). This has led to a dramatic increase in both research and clinical applications of various forms of non-invasive brain stimulation, with the goal of improving asymmetry and hence abnormal brain function in various conditions (Koch et al., 2011; Hummel et al., 2005; Hummel and Cohen, 2006; Passard et al., 2007; Floel, 2014; Liew et al., 2014). The rationale for the use of NIBS has been that if behavioral changes arising from a clinical condition occur due to altered activity within a given brain network, normalizing this activity with NIBS should lead to improved brain function and behavioral response (Scale et al., 2015). Such a rationale has motivated studies utilizing NIBS across a range of clinical conditions, including, but not limited to, stroke (Grefkes and Fink, 2014), schizophrenia (Frantseva et al., 2014), depression (Fitzgerald et al., 2010; Fox et al., 2013), and obsessive-compulsive disorder (Fitzgerald et al., 2010).

Our understanding of how local changes in brain activity can influence distant, but functionally related, brain regions has improved in parallel with advances in various forms of brain imaging and brain stimulation methods. For example, stroke patients with local brain lesions often have cognitive impairments that cannot be directly related to the site of damage (Verdon et al., 2010). Further, many of the most common psychiatric and neurological conditions, including depression, obsessive-compulsive disorder and schizophrenia, are associated with impaired integration of functionally-related neural networks (Insel, 2010; Menon, 2011; Filippi et al., 2013; Fornito et al., 2015).

The development and maintenance of functional projection systems of the neuraxis is dependent on the central integrative state of the neurons supporting the projection fibres of the system. The central integrative state of a neuron is the total integrated input received by the neuron at any given moment and the probability that the neuron will produce an action potential based on the state of polarization and the firing requirements of the neuron to produce an action potential at one or more of its axons. This is dependent to a large degree on the afferent input and efferent output transmitted by the system. Changes in cortical

Table 4
Common EEG Metrics.

Spectral Analysis	A measure of the frequency composition of the EEG over a given period
Absolute amplitude	A measure of μV2/cycle/second within a frequency range or at each electrode
Coherence	A frequency-specific quantitative measure for the similarity of two different signals i.e. between scalp electrodes. Applied to electroencephalographic (EEG) measures, coherence can be interpreted as a quantitative measure of the degree of functional connectivity between distinct brain regions (French and Beaumont, 1984; Yuvaraj et al., 2015). Previous studies have applied coherence to the examination of functional changes associated with the performance of a perceptual or cognitive task, and a coherence measure obtained from spectral EEG analysis is thought to be a useful technique in the assessment of cognitive function and an indicator of neural network connectivity and dynamics (Thatcher et al., 2005; Busk and Galbraith, 1975; Shaw et al., 1977; Gasser et al., 1987)
Phase	relationships in the timing of activity between two channels and symmetry between homologous pairs of electrodes
Low resolution brain electromagnetic tomography (LORETA)	LORETA is another functional imaging method based on electrophysiological and neuroanatomical constraints. LORETA and its variants have been employed by many studies seeking to analyse spectral components of EEG activation (Pascual-Marqui et al., 2002). LORETA also promises to be a useful method for the localization of neural generators in the study of long-distance neural synchronization and in identifying asymmetries in cortical function (Pascual-Marqui et al., 1999).

activation can result from changes or attenuation of afferent information arriving in the cortex from peripheral or subcortical structures. The changes resulting from attenuation of the afferent input that are manifested both morphologically and functionally in the cortex seem to also occur at all levels within the projection system involved (Merzenich et al., 1984). For instance changes in cortical somatotopic maps in cats also show acute and chronic changes at the level of the spinal cord, dorsal columns and the thalamus following nerve *trans*-section (Dostrovsky and Millar, 1976; Millar et al., 1976). Similar findings have also been found in monkeys (Merzenich et al., 1981; Merzenich et al., 1983, 1984).

There is extensive evidence that alterations in motor activities which involve both afferent and efferent projection systems can induce structural and functional plasticity within the cortex, basal ganglia, cerebellum and spinal cord in humans (Classen et al., 1998; De Zeeuw and Yeo, 2005; Graybiel, 2005; Kelley et al., 2003). It has been demonstrated that novel movement performance induces changes in cortical synaptic number, strength, and topography of cortical maps in the projection systems and neural assemblies involved in the performance of the movements (Montfils et al., 2005). Another study highlights the possibility of using peripheral sensory stimulation to induce long lasting modulation of cortical activation and cortical motor output (Ridding et al., 2001). Cortical representation of cranial nerves has also been shown to modulate with alterations in afferent input. Hamdy et al. (1998) reported an increase in excitation levels in the pharynx cortical representation maps following short term (10 min) stimulation of the pharynx. These changes lasted 30 min following the cessation of the initial stimulus. In a similar study, Ridding et al. (2000) showed that repetitive mixed nerve stimulation of the ulnar nerve increased the excitability of the cortical projections to the hand muscles of the same hand lasting at least 15 min longer than the stimulus. The rapid development of these plastic changes suggests that the mechanism involves unmasking or disinhibition of pre-existing weak (horizontal) projections (Boroojerdi et al., 2001).

6. Balancing the brain: EEG targeted neuroplastic restructuring

In recent years, brain connectivity research has shifted the focus of neurology and psychiatry from the study of local neural dysfunction to the study of altered activity of widespread neural networks (Bassett and Bullmore, 2009; Fornito and Bullmore, 2010; Bullmore and Sporns, 2012; Fornito et al., 2015). Such a paradigm shift calls for the development of new treatment methods that focus on specific pathologies associated with particular changes in the function of brain networks. EEG guided neuroplastic restructuring enables the development and clinical application of targeted system-level interventions, as opposed to approaches that lack functional specificity and which are often accompanied by significant side-effects, such as some of the presently available pharmacological interventions (Lambert and Castle, 2003). Although conventional pharmacological interventions are in many cases very effective at reducing symptoms of the disorder, some patients do not gain the expected benefit from this approach. NIBS offers a novel approach for reducing symptoms and restoring related brain activity. Indeed it is reasonable to assume that the interaction between NIBS and pharmacological interventions may reduce the effective dosage of the latter. Future clinical investigations should focus on evaluating the efficacy of pharmacological versus NIBS, and whether these treatments can be complementary in nature (Scale et al., 2015).

The generalized application of non-invasive stimulation, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), has demonstrated some evidence of efficacy in the treatment of epilepsy (Terra et al., 2013; DeGiorgio and Krahl, 2013) stroke (DiLazzaro et al., 2013), attention deficit hyperactivity disorder (Helfrich et al., 2012), tinnitus (Vanneste et al., 2013), headache (Jurgens and Leone, 2013), aphasia (Shah et al., 2013), traumatic brain injury (Bonnì et al., 2013), schizophrenia (Hasan et al., 2013), Huntington's disease (Berardelli and Suppa, 2013), pain (Andrade et al., 2013), major depressive disorder, Tourette's syndrome, dystonia, post-traumatic stress disorder(PTSD) and obsessive-compulsive disorder (Lozano and Lipsman, 2013).

The current status of the evidence into non-invasive brain stimulation from a clinical perspective has been reviewed (Tracy and David, 2015). The strongest evidence base is for repetitive TMS in depression although findings in randomised controlled trials are not consistent. A systematic review and meta-analysis of rTMS in treatment resistant depression (TRD) concluded that the treatment provides significant benefits in short-term treatment studies. However, the relatively low response and remission rates, the short durations of treatment, and the relative lack of systematic follow-up studies suggest that further studies are needed before rTMS can be considered as a first-line monotherapy treatment for TRD (Lam et al., 2008). TMS is still not recommended in the UK by the National Institute for Health and Clinical Excellence, but has been recommended by the FDA in the US since 2008 and is also used widely in Europe.

A recent meta-analysis has found that transcranial direct current stimulation (tDCS) was an effective treatment for acute depressive episodes compared to sham treatment and as effective as antidepressant medication in primary care and also as effective as TMS. However the effectiveness was negatively related to the level of treatment resistance in depression (Brunoni et al., 2016).

At present most other NIBS interventions are at the stage of innovations with theoretical evidence in basic science research and some case series evidence in open trials. There is a need for rigorous research assessment, although the research methodology is challenging because of the difficulty in blinding the treatment procedures and the establishment of a representative control population. Neuromodulation therapies have also tended to be used for patients resistant to other conventional treatments and not as a first line treatment strategy. Nevertheless, the recent review by Tracy and David (2015) suggests that there is potential for the development of significant new treatments

Table 5
Common Modalities Utilised in Neuroplastic Restructuring.

Modality	Application	Neuroplastic Effects
Unilateral Interferential Current (IF)	Electrical stimulation of wrist extensor and flexor muscles	Produce an activation pattern in the contralateral primary motor cortex, primary somatosensory cortex and pre motor cortex, ipsilateral cerebellum, bilateral secondary somatosensory cortex, the supplementary motor area and anterior cingulate cortex.
Novel cerebellar/vestibular stimulation in the form of Skilled Movement Performance	motor training utilizing discrete movements across different joints (i.e., hand, finger, legs) (Donoghue and Wise, 1982; Keller, 1993; Schieber, 2001). The coordinated activation of these assemblies then encodes complex, multi-joint movements such as reaching (Graziano, 2006).	Induction of structural, biochemical and functional adaptation ("plasticity") within several motor areas, including basal ganglia (Conner et al., 2003; Graybiel, 2005; Kelley et al., 2003), cerebellum (De Zeeuw and Yeo, 2005; Kliem and Wichmann, 2004; Martino Cinnera et al., 2016), and red nucleus (Hermer-Vazquez et al., 2004). Increases in protein synthesis, synaptogenesis, and map reorganization within motor cortex represent a set of coordinated neuronal changes that drive the acquisition and performance of skilled movement.
Focused breathing	We use breathing techniques in this study to increase blood oxygenation and stimulation in various areas of the brain.	Brain activation during volitional control of breathing occurs in the frontal, cortex in Brodmann areas 4 and 6 and in the parietal lobe bilaterally in gyrus post-centralis and in the temporal lobe mainly in Brodmann area 22 (Smejkal et al., 2000).
Unilateral superficial vibration	Conscious awareness of tactile stimulation (vibration) applied to the body surface	The left posterior parietal cortex processes information from contralateral space while the right posterior parietal cortex processes information from both spatial hemi-fields (Mesulam, 1981; Nobre and Plunkett 1997).
Listening therapy	Mozart strings and piano compositions in a specific ear to stimulate brain activity. (Schellenberg and Hallam, 2005).	Both The left and right hemispheres engaged in melodic perception (pitch contour) and timbre. However, some specific abilities, within these broad functions, in melodic perception, appear to have reverse hemispheric dominance (Peretz and Morais, 1980; Peretz et al., 1994) Broca's and insular areas in the left hemisphere, Poline and Mazoyer, 1994) Primary auditory areas (Liegeois-Chauvel et al., 1991), via the superior temporal gyrus, which is an auditory association area (Poline and Mazoyer, 1994; Zatorre et al., 1992)
Trans-Cranial Direct Current (tDCS) Application	Electrode application to the scalp and targeted positions based on the 10/20 electrode placement system.	A wide variety of cortical and deep brain areas can be effected. Depending on the stimulation parameters, cortical excitability can be reduced (inhibited) or enhanced (facilitated) (Nitsche and Paulus 2000, 2001).

involving neuromodulation techniques. There is also potential to evaluate the interaction between NIBS, psychological therapies and pharmacotherapy.

In addition to its clinical utility, emerging evidence suggests that peripheral afferent stimulation can also be used to optimize human performance in healthy individuals (Meinzer et al., 2014; Ferreri and Rossini, 2013), potentially by altering cortical plasticity (Ferreri and Rossini, 2013). Interventions that are known to result in targeted cortical neuroplastic change and which we suggest may therefore have clinical utility across a range of disorders are summarized in Table 5.

7. Neurofeedback and learning theories

Brain activity assessed by electroencephalography (EEG) has been demonstrated to respond to conditioning techniques.

Classical conditioning of learning procedure is when a biologically potent stimulus is paired with a previously neutral stimulus (Pavlov, 1927).

The first studies of the influence of classical conditioning on the brain using EEGs was in 1963 by Clemente and colleagues (Clemente et al., 1963) who demonstrated in cats that the EEG synchronization and behavioral manifestations of sleep could be conditioned with a tone (conditioned stimulus) and basal forebrain stimulation (unconditioned stimulus), where the conditioned stimulus eventually resulted in sleep preparatory behavior (Sherlin et al., 2011). This was further studied (Milstein, 1965) to demonstrate that the EEG is subject to learning principles. There are still unresolved questions as to whether the EEG results seen should be considered classical conditioning or simply reflect sensitization.

However classical conditioning does not explain all changes of behavior or the emergence of new behaviors. To address this gap the "law of effect" of Thorndike was put out which stated, responses that produce a satisfying effect in a particular situation become more likely to occur again in that situation and responses that produce a discomforting effect become less likely to occur again in that situation. This was further improved on by Skinner to deliver the rules of Operant conditioning.

Operant conditioning is a procedure that influences the response frequency by providing specific stimuli immediately after a spontaneous response by animals including humans (Reynolds, 1975) and has been recognized to be a core mechanism (Sakurai, 2014) in biofeedback (Schwartz and Andrasik, 2016). Recent research models inspecting the extension of the biofeedback mechanism to neural feedback have shown research models of neural operant conditioning in animal experiments and demonstrated that it is possible to change the firing frequency and synchronous firing of local neuronal populations in a short time period (Sakurai and Song, 2016). There has been demonstration that the neuronal populations activity changes dramatically in response to rewards within a short time period. However these are dependent on multiple issues such as neuron's firing rate, inter neuron synchrony and chosen reward method. A further limitation is changes generated are only in the conditioned local neuronal population. Further there is no evidence on the duration the change is retained for. Sustainability of new learning remains a challenge (Sakurai and Takahashi, 2013).

8. Heart rate variability biofeedback and cortical asymmetry

Heart rate variability (HRV) bio feedback has been shown as useful tool to manage stress in various populations. HRV is regulated by neural input from both the parasympathetic and sympathetic divisions of the autonomic nervous system.

Emotional regulation and processing are considered to be influenced by asymmetries between homologous frontal sites in the alpha

band (Davidson, 1998, 2004). Negative emotions are associated with greater right frontal alpha asymmetry while the opposite is true for greater left frontal asymmetries (Davidson, 1998, 2004). The parietal cortex asymmetries, with relatively greater right alpha band activity, are often thought to be stable over time and predictive for depression, but inconsistent findings with parietal area suggest that such a factor as arousal should be also taken into account in producing asymmetry in this region (Kentgen et al., 2000). A recent study looking at the effect of HRV biofeedback on EEG alpha symmetry as identified above has established a good association of demonstrating a reduction of frontal EEG asymmetry (F7/F8) and a shift towards greater alpha activity in left parietal– occipital region (O1/O2; P3/P4) linked to decreased clinical symptoms after biofeedback training (Dziembowska et al., 2016) This thus raises some interesting areas to further explore.

EEG and LORETA analysis together with detailed neurological examination and clinical history can be used to determine locations of dysfunction in the brain. Applying non-invasive techniques to correct cortical dysfunction centers on the understanding of neuroanatomy, neurophysiology, the application of the concepts of central integrative state and neuroplasticity. We propose the potential clinical utility of a number of non-invasive techniques that can be focused on identified areas of dysfunction to stimulate or inhibit specific afferent projection systems such as unique motor activities, specific application of sound and visual stimuli, proprioceptive stimulation, vestibular stimulation and a technique that directly modifies synaptic activity, *trans*-cranial direct current (tDCs) as innovative and effective approaches to the re-establishment of normal functional activity in these areas of dysfunction. We have several international multi-clinic projects in progress applying these techniques in a clinical setting and we expect to be following up this concept paper with the clinical results of these clinical trials in the near future.

9. Conclusion

Our aim was to describe and discuss the how neuromodulation can help in cortical asymmetry from a theoretical and contextual point of view. We are looking to propose a novel clinical approach with a clear understanding of the background evidence available to critically appraise it using the methodology of a narrative review.

There is significant evidence that the brain often works in an asymmetric fashion in order to produce accurate and efficient processing and integration of information. It also appears clear that if these asymmetric processes become unbalanced they can result in unwanted thoughts, actions and behaviors. The recognition and correction of these aberrant cortical asymmetries in clinical practice offers the great hope of improving the treatment of the neurological and psychiatric disorders that arise as a result of these dysfunctional states.

We have proposed an innovative neuroplastic restructuring approach to the treatment of these disorders utilizing EEG imaging which targets dysfunctional cortical areas utilizing a variety of different peripheral stimulation techniques. This is a conceptually novel approach that does not hinge on traditional diagnostic categories but rather focuses on identifying aberrant cortical activity for targeting treatment. The treatment techniques proposed include unilateral interferential current, unilateral joint mobilisation, unilateral superficial vibration, novel cerebellar/vestibular stimulation, focused breathing, and listening therapy.

The treatment of most psychiatric and neurological conditions is complex, expensive and frequently requires multimodal interventional strategies. Furthermore, a large proportion of patients fail to respond to current treatments. We present a novel clinical approach for the treatment of psychiatric and neurological disorders that is consistent with current neuroscientific evidence, non-invasive, testable and therefore represents an important potential contribution to the understanding and treatment of mental disorders. Several international multi-clinic projects are in progress applying these techniques in a clinical setting and the clinical results of these clinical trials will be published in the near future.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of conflict of interests

All authors declare no conflict of interest.

References

Andrade, D.C., Borges, I., Bravo, G.L., Bolognini, N., Fregni, F., 2013. Therapeutic time window of noninvasive brain stimulation for pain treatment: inhibition of maladaptive plasticity with early intervention. Expert Rev. Med. Devices 10, 339–352.
Arato, M., Frecska, E., Tekes, K., MacCrimmon, D.J., 1991. Serotonergic interhemispheric asymmetry: gender difference in the orbital cortex. Acta Psychiatr. Scand. 84, 110–111.
Bakin, J.S., Weinberger, N.M., 1996. Induction of a physiological memory in the cerebral cortex by stimulation of the nucleus basalis. Proc. Natl. Acad. Sci. U. S. A. 93, 11219–11224.
Barneoud, P., Neveu, P.J., Vitiello, S., et al., 1987. Functional heterogeneity of the right and left cerebral neocortex in the modulation of the immune system. Physiol. Behav. 41, 525–530.
Barneoud, P., Neveu, P.J., Vitiello, S., et al., 1988. Early effects of right or left cerebral cortex ablation on mitogen-induced speen lymphocyte DNA synthesis. Neurosci. Lett. 90, 302–307.
Bassett, D.S., Bullmore, E.T., 2009. Human brain networks in health and disease. Curr. Opin. Neurol. 22, 340–347.
Bastings, E.P., Greenberg, J.P., Good, D.C., 2002. Hand motor recovery after stroke: a transcranial magnetic stimulation mapping study of motor output areas and their relation to functional status. Neurorehabil. Neural Rep. 16, 275–282.
Beck, R.W., 2007. Functional Neurology for Practitioners of Manual Therapy. Elsevier.
Beck, R.W., 2013a. Identifying and treating cortical asymmetry with EEG and LORETA imaging. J. Funct. Neurol. Rehabil. 1 (1).
Beck, R.W., 2013b. Direct current stimulation guided by EEG and LORETTA imaging and post-scar epilepsy. Adv. Funct. Med. 1 (1).
Berardelli, A., Suppa, A., 2013. Noninvasive brain stimulation in Huntington's disease. Handb. Clin. Neurol. 116, 555–560.
Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. 34, 537–541.
Bonnì, S., Mastropasqua, C., Bozzali, M., Caltagirone, C., Koch, G., 2013. Theta burst stimulation improves visuo-spatial attention in a patient with traumatic brain injury. Neurol. Sci. 34, 2053–2056.
Boroojerdi, B., Ziemann, U., Chen, R., Butefisch, C., Cohen, L., 2001. Mechanisms underlying human motor plasticity. Muscle Nerve 24, 602–613.
Bowyer, S.M., 2016. Coherence a measure of the brain networks: past and present. Neuropsychiatr. Electrophysiol. 2 (1), 1. http://dx.doi.org/10.1186/s40810-015-0015-7.
Bozzali, M., Mastropasqua, C., Cercignani, M., Giulietti, G., Bonnì, S., Caltagirone, C., Koch, G., 2012. Microstructural damage of the posterior corpus callosum contributes to the clinical severity of neglect. PLoS One 7 (10), e48079 pmid:23110177.
Brown, W.S., Larson, E.B., Jeeves, M.A., 1994. Directional asymmetries in interhemispheric transmission time: evidence from visual evoked potentials. Neuropsychologia 32, 439–448.
Brunoni, A.R., Moffa, A.H., Fregni, F., Palm, U., Padberg, F., Blumberger, D.M., Daskalakis, Z.J., Bennabi, D., 2016. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br. J. Psychiatry 208, 522–531.
Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10, 186–198.
Bullmore, E., Sporns, O., 2012. The economy of brain network organization. Nat. Rev. Neurosci. 13, 336–349.
Busk, J., Galbraith, G.C., 1975. EEG correlates of visual-motor practice in man. Electroencephalogr. Clin. Neurophysiol. 38, 415–422.
Buzsaki, G., 2006. Rhythms of the Brain. Oxford University Press, New York.
Cabral, J., Kringelbach, M.L., Deco, G., 2014. Exploring the network dynamics underlying brain activity during rest. Prog. Neurobiol. 114, 102–131.
Catani, M., Dell'acqua, F., Thiebaut de Schotten, M., 2013. A revised limbic system model for memory, emotion and behaviour. Neurosci. Biobehav. Rev. 37, 1724–1737.
Classen, J., Knorr, U., Werhahn, K., Schlaug, G., Kunesch, E., Cohen, L., Seitz, R., Benecke, R., 1998. Multimodal mapping of human central motor representation on different spatial scales. J. Physiol. 512, 163–179.
Clemente, C.D., Sterman, M.B., Wyrwicka, W., 1963. Forebrain inhibitory mechanisms: conditioning of basal forebrain induced EEG synchronization and sleep. Exp. Neurol. 7, 404–417.
Cocchi, L., Harrison, B.J., Pujol, J., Harding, I.H., Fornito, A., Pantelis, C., et al., 2012. Functional alterations of large-scale brain networks related to cognitive control in

obsessive- compulsive disorder. Hum. Brain Mapp. 33, 1089–1106.
Conner, J.M., Culberson, A., Packowski, C., Chiba, A.A., Tuszynski, M.H., 2003. Lesions of the Basal forebrain cholinergic system impair task acquisition and abolish cortical plasticity associated with motor skill learning. Neuron 38, 819–829. http://dx.doi.org/10.1016/S0896-6273(03)00288-5.
Damoiseaux, J.S.1, Rombouts, S.A., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Beckmann, C.F., 2006. Consistent resting-state networks across healthy subjects. Proc. Natl. Acad. Sci. U. S. A. 103, 13848–13853. http://dx.doi.org/10.1073/pnas.0601417103.
Davidson, R.J., Hugdahl, K., 1995. Brain Asymmetry. MIT Press, Cambridge, MA/London.
Davidson, R.J., Tomarken, A.J., 1989. Laterality and emotion: and electrophysiological approach. In: Boller, F., Grafman, J. (Eds.), Handbook of Neuropsychology. Elsevier Science, New York, pp. 419–441.
Davidson, R.J., 1988. EEG measures of cerebral asymmetry: conceptual and methodological issues. Int. J. Neurosci. 39, 71–89.
Davidson, R.J., 1998. Anterior electrophysiological asymmetries, emotion, and depression: conceptual and methodological conundrums. Psychophysiology 35, 607–614.
Davidson, R.J., 2004. What does the prefrontal cortex do in affect: perspectives on frontal EEG asymmetry research. Biol. Psychol. 67, 219–233.
De Zeeuw, C., Yeo, C., 2005. Time and tide in cerebellar memory formation. Curr. Opin. Neurobiol. 15, 667–674.
DeGiorgio, C.M., Krahl, S.E., 2013. Neurostimulation for drug-resistant epilepsy. Contin.: Lifelong Learn. Neurol. 19, 743–755.
Demeter, E., Tekes, K., Majorossy, K., Palkovitis, M., Soos, M., Magyar, K., Somogyi, E., 1989. The asymmetry of H-imipramine binding may predict psychiatric illness. Life Sci. 44, 1403–1410.
DiLazzaro, V., et al., 2013. Inhibitory theta burst stimulation of affected hemisphere in chronic stroke: a proof of principle, sham-controlled study. Neurosci. Lett. 553, 148–152.
Dostrovsky, J., Millar, J., Wall, P., 1976. The immediate shift of drive of dorsal column nucleus cells following deafferentation: a comparison of acute and chronic deafferentation in gracile nucleus and spinal cord. Exp. Neurol. 52, 480–495.
Dziembowska, I., Izdebski, P., Rasmus, A., Brudny, J., Grzelczak, M., Cysewski, P., 2016. Effects of heart rate variability biofeedback on EEG alpha asymmetry and anxiety symptoms in male athletes: a pilot study. Appl. Psychophysiol. Biofeedback 41, 141–150.
Falk, D., Hildebolt, C., Cheverud, J., et al., 1991. Human cortical asymmetries determined with 3D-MR technology. J. Neurosci. Methods 39 (2), 185–191.
Ferreri, F., Rossini, P.M., 2013. TMS and TMS-EEG techniques in the study of the excitability, connectivity, and plasticity of the human motor cortex. Rev. Neurosci. 24, 431–442.
Filippi, M., van den Heuvel, M.P., Fornito, A., He, Y., Hulshoff Pol, H.E., Agosta, F., et al., 2013. Assessment of system dysfunction in the brain through MRI-based connectomics. Lancet Neurol. 12, 1189–1199.
Fitzgerald, K.D., Stern, E.R., Angstadt, M., Nicholson-Muth, K.C., Maynor, M.R., Welsh, R.C., et al., 2010. Altered function and connectivity of the medial frontal cortex in pediatric obsessive- compulsive disorder. Biol. Psychiatry 68, 1039–1047.
Floel, A., 2014. tDCS-enhanced motor and cognitive function in neurological diseases. Neuroimage 85 (Pt. 3), 934–947.
Fornito, A., Bullmore, E.T., 2010. What can spontaneous fluctuations of the blood oxygenation- lelvel-dependent signal tell us about psychiatric disorders. Curr. Opin. Psychiatry 23, 239–249.
Fornito, A., Zalesky, A., Pantelis, C., Bullmore, E.T., 2012. Schizophrenia, neuroimaging and connectomics. Neuroimage 62, 2296–2314.
Fornito, A., Zalesky, A., Breakspear, M., 2015. The connectomics of brain disorders. Nat. Rev. Neurosci. 16, 159–172.
Fox, M.D., Snyder, A.Z., Zacks, J.M., Raichle, M.E., 2006. Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. Nat. Neurosci. 9, 23–25.
Fox, M.D., Liu, H., Pascual-Leone, A., 2013. Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity. Neuroimage 66, 151–160.
Frantseva, M., Cui, J., Farzan, F., Chinta, L.V., Perez Velazquez, J.L., Daskalakis, Z.J., 2014. Disrupted cortical conductivity in schizophrenia: TMS-EEG study. Cereb. Cortex 24, 211–221.
Frecska, E., Arato, M., Tekes, K., Powchik, P., 1990. Lateralization of H-IMI binding in human frontal cortex. Biol. Psychiatry 27 (9a), 72.
French, C.C., Beaumont, J.C., 1984. A critical review of EEG coherence studies of hemisphere function. Int. J. Psychophysiol. 1, 241–254.
Friston, K.J., Frith, C.D., Liddle, P.F., Frackowiak, R.S., 1993. Functional connectivity: the principal-component analysis of large (PET) data sets. J. Cereb. Blood Flow Metab. 13, 5–14.
Galaburda, A.M., LeMay, M., Geschwind, N., 1978. Right-left asymmetries in the brain. Science 199, 852–856.
Gasser, T., Jennen-Steinmetz, C., Verleger, R., 1987. EEG coherence at rest and during a visual task in two groups of children. Electroencephalogr. Clin. Neurophysiol. 67, 151–158.
Geschwind, N., Levitsky, W., 1968. Human brain: left-right asymmetries in temporal speech regions. Science 161, 186–187.
Graybiel, A., 2005. The basal ganglia: learning new tricks and loving it. Curr. Opin. Neurobiol. 15, 638–644.
Greenblatt, R.E., Pflieger, M.E., Ossadtchi, A.E., 2012. Connectivity measures applied to human brain electrophysiological data. J. Neurosci. Methods 207 (1), 1–16.
Grefkes, C., Fink, G.R., 2014. Connectivity-based approaches in stroke and recovery of function. Lancet Neurol. 13, 206–216.
Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc. Natl. Acad. Sci. U. S. A. 100, 253–258.
Grimshaw, G.M., Carmel, D., 2014. An asymmetric inhibition model of hemispheric differences in emotional processing. Front. Psychol. 5, 489.
Hachinski, V.C., Oppenheimer, S.M., Wilson, J.X., Guiraudon, C., Cechetto, D.F., 1992. Asymmetry of sympathetic consequences of experimental stroke. Arch. Neurol. 49, 697–702.
Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., Wedeen, V.J., Sporns, O., 2008. Mapping the structural core of human cerebral cortex. PLoS Biol. 6, e159.
Hamdy, S., Rothwell, J.C., Aziz, Q., Singh, K.D., Thompson, D.G., 1998. Long-term reorganization of human motor cortex driven by short-term sensory stimulation. Nat. Neurosci. 1, 64–68.
Harrison, D.W., 2015. Brain Asymmetry and Neural Systems: Foundations in Clinical Neuroscience and Neuropsychology. Springer.
Hasan, A., Falkai, P., Wobrock, T., 2013. Transcranial brain stimulation in schizophrenia: targeting cortical excitability, connectivity and plasticity. Curr. Med. Chem. 20, 405–413.
Helfrich, C., et al., 2012. Monitoring cortical excitability during repetitive transcranial magnetic stimulation in children with ADHD: a single-blind, sham-controlled TMS-EEG study. PLoS One 7, e50073.
Henriques, J.B., Davidson, R.J., 1991. Left frontal hypoactivation in depression. J. Abnorm. Psychol. 100, 535–545.
Herrero, N., Gadea, M., Rodriguez-Alarcón, G., Espert, R., Salvador, A., 2010. What happens when we get angry? Hormonal, cardiovascular and asymmetrical brain responses. Horm. Behav. 57 (3), 276–283.
Hermer-Vazquez, L., Hermer-Vazquez, R., Moxon, K.A., Kuo, K.H., Viau, V., Zhan, Y., Chapin, J.K., 2004. Distinct temporal activity patterns in the rat M1 and red nucleus during skilled versus unskilled limb movement. Behav. Brain Res. 150, 93–107.
Horwitz, B., 2003. The elusive concept of brain connectivity. Neuroimage 19, 466–470.
Hummel, F.C., Cohen, L.G., 2006. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke. Lancet Neurol. 5, 708–712.
Hummel, F., Celnik, P., Giraux, P., Floel, A., Wu, W.H., Gerloff, C., et al., 2005. Effects of non- invasive cortical stimulation on skilled motor function in chronic stroke. Brain 128, 490–499.
Insel, T.R., 2010. Faulty circuits. Sci. Am. 302, 44–51.
Jurgens, T.P., Leone, M., 2013. Pearls and pitfalls: neurostimulation in headache. Cephalalgia 33, 512–525.
Kang, D.H., Davidson, R.J., Coe, C.L., et al., 1991. Frontal brain asymmetry and immune function. Behav. Neurosci. 105 (6), 860–869.
Kelley, A., Andrzejewski, M., Baldwin, A., Hernandez, P., Pratt, W.E., 2003. Glutamate mediated plasticity in cortico-striatal networks: role in adaptive motor learning. Ann. N. Y. Acad. Sci. 1003, 155–168.
Keller, A., 1993. Intrinsic synaptic organization of the motor cortex. Cereb. Cortex 3, 430–441. http://dx.doi.org/10.1093/cercor/3.5.430.
Kentgen, L., Tenke, C., Pine, D., Fong, R., Klein, R., Bruder, G., 2000. Electroencephalographic asymmetries in adolescents with major depression: influence of comorbidity with anxiety disorders. J. Abnorm. Psychol. 109, 797–802.
Kliem, M.A., Wichmann, T., 2004. A method to record changes in local neuronal discharge in response to infusion of small drug quantities in awake monkeys. J. Neurosci. Methods. 138, 45–49.
Koch, G., Cercignani, M., Bonnì, S., Giacobbe, V., Bucchi, G., Versace, V., Caltagirone, C., Bozzali, M., 2011. Asymmetry of parietal interhemispheric connections in humans. J. Neurosci. 31 (June (24)), 8967–8975.
Kreisel, S.H., Bazner, H., Hennerici, M.G., 2006. Pathophysiology of stroke rehabilitation: temporal aspects of neurofunctional recovery. Cerebrovasc. Dis. 21, 6–17.
LaHoste, G.J., Neveu, P.J., Mormede, P., et al., 1989. Hemispheric asymmetry in the effects of cerebral cortical ablations on mitogen-induced lymphoproliferation and plasma prolactin levels in female rats. Brain Res. 483, 123–129.
Lam, R.W., Chan, P., Wilkins-Ho, M., Yatham, L.N., 2008. Repetitive transcranial magnetic stimulation for treatment resistant depression: systematic review and meta-analysis. Can. J. Psychiatry 53, 621–631.
Lambert, T.J., Castle, D.J., 2003. Pharmacological approaches to the management of schizophrenia. Med. J. Aust. 178, S57–61.
Lane, R.D., Jennings, J.R., 1995. Hemispheric asymmetry, autonomic asymmetry, and the problem of sudden cardiac death. In: Davidson, R.J., Hugdahl, K. (Eds.), Brain Asymmetry. MIT Press, Cambridge, MA.
Lane, R.D., Wallace, J.D., Petrosky, P., et al., 1992. Supraventricular tachycardia in patients with right hemisphere strokes. Stroke 23, 362–366.
Le Bihan, D., Mangin, J.F., et al., 2001. Diffusion tensor imaging: concepts and applications. J. Magn. Reson. Imaging 13 (4), 534–546.
LeMay, M., Culebras, A., 1972. Human brain morphological differences in the hemispheres demonstrable by carotid arteriography. N. Engl. J. Med. 287, 168–170.
Leipert, J., Hamzei, F., Weiller, C., 2000. Motor cortex disinhibition of the unaffected hemisphere after acute stroke. Muscle Nerve 23, 1761–1763.
Leisman, G., Ashkenazi, M., 1980. Aetiological factors in dyslexia; IV. Cerebral hemispheres are functionally equivalent. Int. J. Neurosci. 11, 157–164.
Leisman, G., Melillo, R., 2009. EEG coherence measures functional disconnectivities in autism. Acta Paediatr. 98, 14–15.
Leventhal, H., Tomarken, A.J., 1986. Emotion: today's problems. Annu. Rev. Psychol. 37, 565–610.
Liepert, J., Bauder, H., Wolfgang, H.R., Miltner, W.H., Taub, E., Weiller, C., 2000. Treatment-induced cortical reorganization after stroke in humans. Stroke 31, 1210–1216. http://dx.doi.org/10.1161/01.STR.31.6.1210.
Liew, S.L., Santarnecchi, E., Buch, E.R., Cohen, L.G., 2014. Non-invasive brain stimulation in neurorehabilitation: local and distant effects for motor recovery. Front. Hum. Neurosci. 8, 378.

Liegeois-Chauvel, C., Musolino, A., Chauvel, P., 1991. Localization of the primary auditory area in man. Brain 114, 139–151.
Lozano, A.M., Lipsman, N., 2013. Probing and regulating dysfunctional circuits using deep brain stimulation. Neuron 77, 406–424.
Martino Cinnera, A., Bonnì, S., Iosa, M., Ponzo, V., Fusco, A., Caltagirone, C., Koch, G., 2016. Clinical effects of non-invasive cerebellar magnetic stimulation treatment combined with neuromotor rehabilitation in traumatic brain injury. A single case study. Funct. Neurol. 31 (2), 117–120.
Meinzer, M., et al., 2014. Transcranial direct current stimulation over multiple days improves learning and maintenance of a novel vocabulary. Cortex 50, 137–147.
Melillo, R., Leisman, G., 2004. Neurobehavioral Disorders of Childhood: An Evolutionary Approach. Kluwer, New York.
Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn. Sci. 15, 483–506.
Merzenich, M.M., Sur, M., Nelson, R.J., Kaus J.H., (1981). The organization of the Si cortex. Multiple representations of the body in primate. Cortical Sensory Organization, In: C.N. Woolsey (Ed.). 1: Multiple Somatic Areas. (Listed in the bibliography for Abstract 11:965): 303.
Merzenich, M., Kaas, J., Wall, J., Sur, R., Fellemena, D., 1983. Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation. Neuroscience 8, 33–55.
Merzenich, M., Nelson, R., Stryker, M., Schoppmann, A., Zook, J., 1984. Somatosensory map changes following digit amputation in adult monkeys. J. Comp. Neurol. 224, 591–605.
Merzenich, M.M., deCharms, C., 1996. Neural representations, experience, and change. In: Llinas, R., Curchland, P.S. (Eds.), The Mind Brain Continuum. Cambridge: MIT Press, pp. 61–81.
Mesulam, M.M., 1981. A cortical network for directed attention and unilateral neglect. Ann. Neurol. 10, 309–325.
Millar, J., Basbaum, A., Wall, P., 1976. Restructuring of the somatotopic map and appearance of abnormal neurological activity in the gracile nucleus after partial deafferentation. Exp. Neurol. 50, 658–672.
Milstein, V., 1965. Contingent alpha blocking: conditioning or sensitization? Electroencephalogr. Clin. Neurophysiol. 18, 272–277.
Montfils, M., Plautz, E., Kleim, J., 2005. In search of the motor engram: motor map plasticity as a mechanism for encoding motor experience. Neuroscientist 11, 471–483.
Murase, N., Duque, J., Mazzocchio, R., Cohen, L.G., 2004. Influence of interhemispheric interactions on motor function in chroic stroke. Ann. Neurol. 55 (3), 400–409.
Neveu, P.J., Taghzouti, K., Dantzer, R., et al., 1986. Modulation of mitogen-induced lymphoproliferation by cerebral neocortex. Life Sci. 38, 1907–1913.
Neveu, P.J., Barneoud, P., Vitiello, S., et al., 1988. Brain modulation of the immune system: association between lymphocyte responsiveness and paw preference in mice. Brain Res. 457, 392–394.
Neveu, P.J., Betancur, C., Barneoud, P., Vitiello, S., Le Moal, M., 1991. Functional brain asymmetry and lymphocyte proliferation in female mice: effects of left and right cortical ablation. Brain Res. 550, 125–128.
Nobre, A.C., Plunkett, K., 1997. The neural system of language: structure and development. Curr. Opin. Neurobiol. 7, 262–268.
Neveu, P.J., 1988. Minireview: cerebral neocortex modulation of immune functions. Life Sci. 42, 1917–1923.
Obrut, J.E., 1994. The geschwind-Behan-Galaburda theory of cerebral lateralization: thesis, anti-thesis and synthesis? Brain Cogn. 26 (2), 267–274.
Park, H.J., Friston, K., 2013. Structural and functional brain networks: from connections to cognition. Science 342, 1238411.
Pascual-Marqui, R.D., Esslen, M., Kochi, K., Lehmann, D., 2002. Functional imaging with low-resolution brain electromagnetic tomography (LORETA): a review. Methods Findings Exp. Clin. Pharmacol. 24 (Suppl C), 91–95.
Pascual-Marqui, R.D., Lehmann, D., Koenig, T., Kochi, K., Merlo, M.C., Hell, D., Koukkou, M., 1999. Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. Psychiatry Res. 90, 169–179. http://dx.doi.org/10.1016/S0925-4927(99)00013-X.
Passard, A., Attal, N., Benadhira, R., Brasseur, L., Saba, G., Sichere, P., et al., 2007. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. Brain 130, 2661–2670.
Pavlov, I.P., 1927. In: Anrep, G.V. (Ed.), Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex. Oxford University Press, London, UK (Trans.).
Pearlson, G.D., Robinson, R.G., 1981. Suction lesions of the frontal cortex in the rat induce asymmetrical behavioral and catecholaminergic responses. Brain Res. 218, 233–242.
Peretz, I., Kolinsky, R., Tramo, M., Labrecque, L., Hublet, C., Demeurisse, G., et al., 1994. Functional dissociations following bilateral lesions of auditory cortex. Brain 117, 1283–1301.
Poline, J.-B., Mazoyer, B.M., 1994. Enhanced detection in activation maps using a multifiltering approach. J. Cereb. Blood Flow Metab. 14, 690–699.
Renoux, G., Biziere, K., 1986. Brain neocortex lateralized control of immune recognition. Integr. Psychiatry 4, 32–40.
Renoux, G., Biziere, K., Renoux, M., et al., 1983. A balanced brain asymmetry modulates T cell-mediated events. J. Neuroimmunol. 5, 227–238.
Reynolds, G.S., 1975. A Primer of Operant Conditioning, 2nd revised ed. Scott Foresman, Glenview, IL, USA.
Ridding, M.C., Brouwer, B., Miles, T.C., Pitcher, J.B., Thompson, P.D., 2000. Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects. Exp. Brain Res. 131, 135–143.
Ridding, M.C., McKay, D.R., Thompson, P.D., Miles, T.S., 2001. Changes in corticomotor representations induced by prolonged peripheral nerve stimulation in humans. Clin. Neurophysiol. 112, 1461–1469.
Robinson, R.G., Kubos, K.L., Starr, L.B., et al., 1984. Mood disorders in stroke patients: importance of location of lesion. Brain 107, 81–93.
Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52, 1059–1069.
Sakkalis, V., 2011. Review of advanced techniques for the estimation of brain connectivity measured with EEG/MEG. Comput. Biol. Med. 41, 1110–1117.
Sakurai, Y., Song, K., 2016. Neural operant conditioning as a core mechanism of brain-machine interface control. Technologies 4 (3), 26.
Sakurai, Y., Takahashi, S., 2013. Conditioned enhancement of firing rates and synchrony of hippocampal neurons and firing rates of motor cortical neurons in rats. Eur. J. Neurosci. 37, 623–639.
Sakurai, Y., 2014. Brain-machine interfaces can accelerate clarification of the principal mysteries and real plasticity of the brain. Front. Syst. Neurosci. 8, e104.
Savic, I., Pauli, S., Thorell, J.O., et al., 1994. In vivo demonstration of altered benzodiazepine receptor density in patients with generalized epilepsy. J. Neurol. Neurosurg. Psychiatry 57, 784–797.
Scale, M.V., Mattingley, J.B., Zalesky, A., Cocchi, L., 2015. Imaging human brain networks to improve the clinical efficacy of non- invasive brain stimulation. Neurosci. Biobehav. Rev. 57, 187–198.
Schieber, M.H., 2001. Constraints on somatotopic organization in the primary motor cortex. J. Neurophysiol. 86 (5), 2125–2143.
Schwartz, M.S., Andrasik, F., 2016. Biofeedback: A Practitioner's Guide, 4th ed. Guilford Press, New York, NY, USA.
Shah, P.P., Szaflarski, J.P., Allendorfer, J., Hamilton, R.H., 2013. Induction of neuroplasticity and recovery in post-stroke aphasia by non-invasive brain stimulation. Front. Hum. Neurosci. 7, 888. http://dx.doi.org/10.3389/fnhum.2013.00888.
Shaw, J.C., O'Connor, P., Ongley, C., 1977. The EEG as a measure of cerebral functional organization. Br. J. Psychiatry 130, 260–264.
Sherlin, L.H., Arns, M., Lubar, J., Heinrich, H., Kerson, C., Strehl, U., et al., 2011. Neurofeedback and basic learninig theory: implications for research and practice. J. Neurother. 15, 292–304.
Smejkal, V., Druga, R., Tintera, J., 2000. Brain activation during volitional control of breathing. Physiol. Res. 49, 659–663.
Sporns, O., Tononi, G., Kötter, R., 2005. The Human Connectome: A Structural Description of the Human Brain. PLoS Computat. Biol. 1 (4), e42. http://dx.doi.org/10.1371/journal.pcbi.0010042.
Sporns, O., Honey, C.J., Kotter, R., 2007. Identification and classification of hubs in brain networks. PLoS One 2, e1049.
Sporns, O., 2007. Brain connectivity. Scholarpedia 2 (10), 4695.
Sporns, O., 2014a. Contributions and challenges for network models in cognitive neuroscience. Nat. Neurosci. 17, 652–660.
Sporns, O., 2014b. Towards network substrates of brain disorders. Brain 137, 2117–2118.
Steinmetz, H., Volkmann, J., Jancke, L., et al., 1991. Anatomical left-right asymmetry of language-related temporal cortex is different in left-handers and right handers. Ann. Neurol. 29 (3), 315–319.
Stroka, H., Solsi, P., Bornstein, B., 1973. Alexia without agraphia with complete recovery: functional disconnection syndrome. Confin. Neurol. 35 (3), 167–176.
Sumner, R.C., Parton, A., Nowicky, A.V., Kishore, U., Gidron, Y., 2011. Hemispheric lateralisation and immune function: a systematic review of human research. J. Neuroimmunol. 240–241, 1–12.
Tekes, K., Tothfalusi, L., Arato, M., Palkovits, M., Demeter, E., Magyar, K., 1988. Is there a correlation between serotonin metabolism and H-imipramine binding in the human brain? Hemispheric lateralization of imipramine binding sites. Pharmacol. Res. Commun. 20 (Suppl. 1), 41–42.
Terra, V.C., et al., 2013. Vagus nerve stimulator in patients with epilepsy: indications and recommendations for use. Assoc. Arq. Neuro-Psiquiatr. http://dx.doi.org/10.1590/0004-282X20130116.
Thatcher, R., Biver, C., North, D., 2003. Quantitative EEG and the Frye and Daubert standards of admissibility. Clin. Electroencephal. 34 (2), 39–53.
Thatcher, R., North, D., Biver, C., 2005. EEG and intelligence: univariate and multivariate comparisons between EEG coherence, EEG phase delay and power. Clin. Neurophysiol. 116 (9), 2129–2141.
Towle, V.L., Hunter, J.D., Edgar, J.C., Chkhenkeli, S.A., Castelle, M.C., Frim, D.M., et al., 2007. Frequency domain analysis of human subdural recordings. J. Clin. Neurophysiol. 24 (2), 205–213.
Tracy, D.K., David, A.S., 2015. Clinical neuromodulation in psychiatry: the state of the art or an art in a state? BJPsych Adv. 26, 396–404.
van den Heuvel, M., Mandl, R., Hulshoff Pol, H., 2008. Normalized cut group clustering of resting-state fMRI data. PLoS One 3 (4), e2001.
van den Heuvel, M.P., Sporns, O., 2011. Rich-club organization of the human connectome. J. Neurosci. 31, 15775–15786.
Vanneste, S., Fregni, F., De Ridder, D., 2013. Head-to-head comparison of transcranial random noise stimulation, transcranial AC stimulation, and transcranial DC stimulation for tinnitus. Front. Psychiatry 4, 158.
Verdon, V., Schwartz, S., Lovblad, K.O., Hauert, C.A., Vuilleumier, P., 2010. Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion- symptom mapping. Brain 133, 880–894.
Wedeena, V.J., Wanga, R.P., Schmahmannb, J.D., Bennera, T., Tsengc, W.Y.I., Daia, G., et al., 2008. Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. Neuroimage 41 (4), 1267–1277.
Wittling, W., Roschmann, R., 1993. Emotion related hemisphere asymmetry: subjective emotional responses to laterally presented films. Cortex 29, 431–448.
Wittling, W., Schweiger, E., 1993. Neuroendrocrine brain asymmetry and physical complaint. Neuropsychologia 31, 591–608.

Xu, Z.C., Ling, G., Sahr, R.N., Neal-Beliveau, B.S., 2005. Asymmetrical changes of dopamine receptors in the striatum after unilateral dopamine depletion. Brain Res. 1038 (2), 163–170.

Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., et al., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. 106, 1125–1165.

Yuvaraj, R., Murugappan, M., Norlinah, M., Sundaraj, K., Omar, M., Mohamad, K., Palaniappan, R., Satiyan, M., 2015. Inter-hemispheric EEG coherence analysis in Parkinson's disease: assessing brain activity during emotion processing. J. Neural Transm. 122, 237–252.

Zalesky, A., Fornito, A., Seal, M.L., Cocchi, L., Westin, C.F., Bullmore, E.T., et al., 2011. Disrupted axonal fiber connectivity in schizophrenia. Biol. Psychiatry 69, 80–89.

Zatorre, R.J., Evans, A.C., Meyer, E., Gjedde, A., 1992. Lateralization of phonetic and pitch discrimination in speech processing. Science 256, 846–849. http://dx.doi.org/10.1126/science.1589767.