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).