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Neuroimaging and electroencephalographic (EEG) methods for investigating neural circuits in mental disorders

Métodos de neuroimagem e eletroencefalografia (EEG) para investigação de circuitos neurais em transtornos mentais

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ABSTRACT: It is increasingly recognised that dysfunction in neural circuits plays a key role in the neurobiological basis of mental disorders. The efficacy of pharmacological and behavioural treatments for mental disorders could therefore be improved by targeting dysfunctions in neurocircuits. However, to achieve this, a better understanding of the specific alterations in neural circuits involved in different mental disorders is required. Such understanding can be acquired by using advanced neuroscience methods to examine the pathways and function of neurocircuits in both typically developing individuals and in those with mental disorders. This article provides an overview of currently available neuroscience methods of investigating neural circuits, including advantages and limitations of different techniques, and highlights the importance of using multi-modal imaging in future research.

Keywords: Magnetic resonance imaging; Diffusion tensor imaging; Electroencephalography; Mental disorders; Multimodal imaging.

RESUMO: É cada vez mais reconhecido que a disfunção nos circuitos neurais desempenha um papel fundamental na base neurobiológica dos transtornos mentais. A eficácia dos tratamentos farmacológicos e comportamentais para os transtornos mentais pode, portanto, ser melhorada por direcionar as disfunções nos neurocircuitos. No entanto, para isso, é necessário um melhor entendimento das alterações específicas nos circuitos neurais envolvidos em diferentes transtornos mentais. Tal entendimento pode ser adquirido usando-se métodos avançados de neurociência para examinar as vias e a função dos neurocircuitos em indivíduos com desenvolvimento típico e naqueles com transtornos mentais. Este artigo fornece uma visão geral dos métodos da neurociência atualmente disponíveis na investigação de circuitos neurais, incluindo vantagens e limitações de diferentes técnicas, e destaca a importância do uso de imagens multimodais em pesquisas futuras.

Descritores: Imagem por ressonância magnética; Imagem de tensor de difusão; Eletroencefalografia; Transtornos mentais; Imagem multimodal.

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INTRODUCTION

It is increasingly recognised that dysfunction in neural circuits plays a key role in the neurobiological basis of mental disorders, including obsessive-compulsive disorder (OCD), depression, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and schizophrenia[1-9]. One approach to improving the efficacy of treatments for mental disorders is therefore to ensure that pharmacological and behavioural therapies are targeted at remedying dysfunctions within the neurocircuit(s) involved in the disorder. However, the exact neurocircuits and specific dysfunctions within those circuits involved in different mental disorders are not yet fully understood. To address this issue, advanced neuroscience methods should be used to understand the anatomical projections and function of neurocircuits in typically developing individuals, and then to identify alterations in those circuits in individuals with different mental disorders. A number of different neuroscience techniques are available to probe the integrity and function of neurocircuits, including magnetic resonance imaging (MRI), functional MRI (fMRI), electroencephalography (EEG), magnetoencephalography (MEG) and functional near infra-red spectroscopy (fNIRS). This article will provide an overview of three of these methods, diffusion tensor imaging (DTI), resting state fMRI (rs-fMRI) and EEG, illustrating how each method can be used to investigate neurocircuits. Advantages and limitations of each technique and future directions for investigating neurocircuit dysfunctions in mental disorders will be discussed.

DISCUSSION

DTI

DTI is a non-invasive type of magnetic resonance imaging that uses a bipolar magnetic field gradient pulse to encode molecular diffusion of water[10]. Using different measures of diffusion in multiple directions, it is possible to employ tensor decomposition and extract information that is related to the direction of water diffusion and amount of diffusion[11]. DTI measures the parallel and perpendicular diffusivities of a tensor in a fiber[11], from which it is possible to calculate the fractional anisotropy (FA) and the mean diffusivity (MD) of a white matter tract[12]. These measures can provide indexes of white matter fiber density and integrity, orientation, and myelination. Therefore, DTI yields a quantitative analysis of anatomical connectivity in the white matter fibers throughout the brain *in vivo*. Using a deterministic or probabilistic algorithm, it is also possible to extract the fiber tractography image[13] to determine intervoxel connectivity based on anisotropic diffusion of water and visualize white matter tracts in 3D[14]. Tractography can show the microstructure of white matter tracts, improving the analysis of the structure of white matter and allowing the investigation of neuroanatomical projections, i.e. tractography facilitates the investigation of structural connectivity (Figure 1).

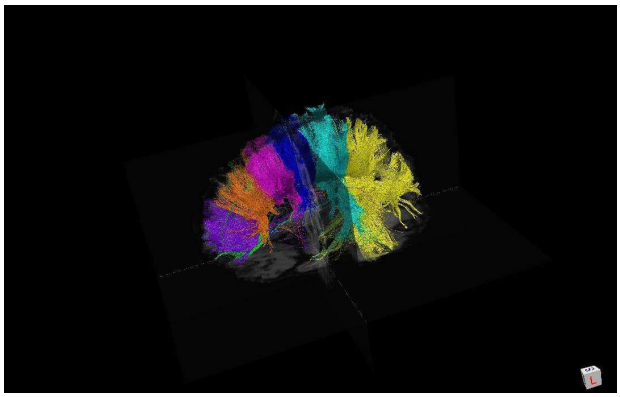

Figure 1: Example of tractography image of the corpus callosum. Tractography is a tool that allows the researcher and the clinician to visualize the connectivity and the white matter trajectory in vivo and noninvasively of patients. Image from Elizabeth Shephard (King's College London)

DTI has several potential applications for the understanding of structural brain connectivity in both typically developing individuals and in those with mental disorders. For example, in typically developing individuals, DTI revealed that the ventral part of the anterior limb of the internal capsule (ALIC) carries fibers of the ventral medial prefrontal and orbitofrontal cortices, whereas the dorsal components carry fibers of ventral lateral prefrontal cortex (ventrolateral ALIC), dorsal lateral prefrontal cortex (dorsolateral ALIC), dorsal anterior cingulate cortex (ventromedial ALIC), and medial prefrontal cortex (dorsomedial ALIC)[15]. Interestingly, Makris and colleagues have shown that these projections have a high inter-individual variability in their topography[16].

In psychiatric disorders, studies using DTI showed that frontal-temporal connectivity is disrupted in schizophrenia[17]. Specifically, the uncinate fasciculus (UF), a white matter tract connecting temporal and frontal brain regions that have a role in decision-making, episodic memory and emotions, was abnormal in patients with schizophrenia[18]. Further, other research has indicated that the cingulum bundle, a tract that is related to spatial orientation, memory, emotions, and attention, is also abnormal in patients with schizophrenia[19]. DTI has revealed structural connectivity alterations in other disorders as well. For instance, a recent meta-analysis

reported reduced organization of limbic connectivity and microstructural disorganization of the anterior limb of the internal capsule, temporal-parietal white matter and left posterior cingulum in patients with bipolar disorder (BD)[20]. These microstructures were related to altered emotional processing and dysfunctional limbic connectivity in BD[21]. Another cluster of dysfunctional tracts in BD is the integration of the inferior occipital fasciculus, the inferior longitudinal fasciculus, the superior longitudinal fasciculus and the posterior thalamic radiations that are related to the parahippocampal gyrus[22,23]. In addition, other studies have revealed lower FA in several brain regions, including the anterior cingulate gyrus, supramarginal gyrus, cingulate gyrus and lingual gyri, in OCD patients compared with controls[24,25].

DTI is also a technique that can help in the improvement or development of neuromodulatory targeted treatments[26] such as transcranial magnetic stimulation, transcranial direct current stimulation, deep brain stimulation, and ablative neurosurgeries because it can map specific brain circuits to be modulated by these procedures[16]. Riva-Posse et al.[27], for example, have used an individualized, patient-specific, deterministic tractography approach for individually targeting subcallosal cingulate deep brain stimulation surgery in patients with depression.

In sum, the major strength of diffusion techniques is the ability to indirectly measure anatomic structure *in vivo*, allowing the investigation of white matter integrity and the construction of structural connectivity maps. However, this method has limitations including its level of resolution and its inability to determine complex fiber organization, such as in regions that have crossing fibers, which has led to the failure to detect already known pathways[28]. Yet, DTI and tractography are powerful imaging techniques to assess microstructural white matter tracts in psychiatric disorders.

Rs-fMRI

Rs-fMRI is a tool to investigate brain regions that show correlated fluctuations in activity and is a suitable technique to uncover functional activation within the brain. Rs-fMRI provides information about functional connectivity[2,29-35], i.e. this technique measures temporal correlations in blood oxygen level dependent (BOLD) low-frequency fluctuations between distinct remote brain areas by assessing the coherence of spontaneous neural fluctuations over time. This concept is based on the observation that distant direct or indirect interconnected brain regions often show strong correlations in their activity levels (Figure 2).

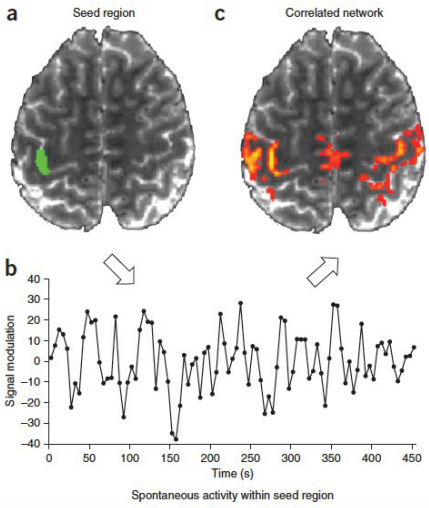

Figure 2: The basic strategy of intrinsic functional connectivity MRI (fcMRI). The basis of fcMRI is that spontaneous activity fluctuations measured at rest are correlated between regions. Inferences can be made about the organization of the brain by measuring correlations among brain regions. (a) An example seed region in the motor cortex (green). Activity in this region is measured indirectly through the blood oxygenation level–dependent MRI signal. (b) The time course of intrinsic activity fluctuations for the seed region for a period of 7 min. The general strategy of functional connectivity is to determine the network of brain regions that show correlated activity fluctuations over time with the seed region. (c) In this example, many cortical regions in the motor system are correlated with the seed region. Image from K. Van Dijk (Massachusetts General Hospital)

Thus, rs-fMRI is particularly useful for providing a sensitive measurement of functional connectivity in large-scale brain networks in humans. There are several different ways to assess resting state functional connectivity. Two of them are: 1) a seed-based approach that calculates the correlation between extracted regions of interest and 2) an ICA (Independent Component Analyses)-based approach that uses all brain voxels' activity to separate brain functional networks that are correlated with spontaneous component of BOLD signal[36]. Anatomical models have suggested that information in the brain is transferred along a ventral to dorsal gradient through striatum circuits that go from emotional/motivational (prediction error; feedback-related reinforcement; reward anticipation; incentive salience) brain regions to decision making/executive control (e.g. verbal and spatial working memory; response inhibition; task switching; reasoning; planning) regions and then to motor control regions[37]. As in anatomical models, Di Martino and colleagues performed a rs-fMRI study to map the functional connectivity of the striatum circuitry in typically developing individuals[38]. They subdivided striatal subregions by defining 6 seed regions in dorsal caudate (DC), superior ventral caudate (VCs), inferior ventral caudate/nucleus accumbens (VCi), dorsal

rostral putamen (DRP), dorsal caudal putamen (DCP), and ventral rostral putamen (VRP) and hypothesized that differential patterns of connectivity would be noted across these 6 striatal subregions. According to their hypotheses, among the caudate subregions, the inferior ventral striatal region (VSi) exhibited greater connectivity with limbic and medial orbitofrontal regions whereas the VSs seed predicted patterns of activity in more superior and lateral portions of the orbitofrontal cortex. Specifically, VSi predicted activation within regions implicated in emotional processing such as parahippocampal gyrus, and posterior cingulate cortex, whereas the VSs seed predicted activity in regions associated with executive function, decision-making, and motor planning such as dorsolateral prefrontal cortex, inferior frontal gyrus, and rostral anterior cingulate. On the other hand, dorsal caudate showed greater connectivity with the dorsolateral prefrontal and parietal cortices, areas that are involved in cognitive control. The caudal putamen seeds were significantly correlated with primary and supplementary motor cortices, whereas the rostral putamen seed revealed patterns of connectivity with frontal regions implicated in executive function control. Thus, these findings suggest dorsal/ventral distinction in striatum connectivity, which are consistent with structural anatomical models postulating an affective/ cognitive/ motor division between ventral and dorsal portions of the striatum[37].

Striatum functional connectivity has also been studied in several psychiatric conditions associated with emotional and executive/motivational deficits, including schizophrenia, substance use disorders, OCD, major depressive disorder, and ADHD. Some examples: in patients with schizophrenia, the functional connectivity between the salience network covering prefrontal-limbic cortices to mediodorsal thalamus and ventral parts of striatum was hypoconnected. Interestingly, this pattern of hypoconnectivity was correlated with impaired cognition[39]. Individuals with cocaine dependence demonstrated reduced functional connectivity between ventral portions of the ventral striatum with ventromedial prefrontal cortex (vmPFC) and increased dorsal-anterior ventral striatum functional connectivity with visual cortex compared to controls[40]. In a study performed in OCD, patients presented increased functional connectivity between ventral corticostriatal circuits compared to controls, implicating the orbitofrontal cortex[2]. Using an ICA approach, Leaver and colleagues have shown that patients with depression exhibited hyperconnectivity between ventral striatum (VS) and the ventral default-mode network (vDMN), while simultaneously demonstrating hypoconnectivity with the anterior DMN (aDMN)[41]. In ADHD patients, inattention and hyperactivity/impulsivity symptom were correlated with increases in functional connectivity in the networks of posterior putamen and ventral caudate whereas increased connectivity of posterior putamen with motor cortex and cerebellum was associated with decreased motor performance[42].

In sum, rs-fMRI is a tool that allows mapping functional brain organization in both typically developing individuals and in those with mental disorders. Nevertheless, it should be kept in mind that this technique does not provide direct information for anatomical connectivity and is subject to several types of technical artifacts that confound its interpretation, such as head motion and physiological artifacts related to cardiac and respiratory rhythms.

EEG

EEG measures electrophysiological (electrical) neural activity from electrodes placed on the scalp. The electrophysiological signal (Figure 3) is a summation of electrical fields generated by post-synaptic potentials in cortical neurons; these electrical field are conducted through the layers of brain tissue and the skull to the scalp, where they are detected as voltage changes in the electrical potential of the skin[43,44]. The electrophysiological signal must be generated by synchronously-firing post-synaptic potentials in large (10,000–50,000) populations of neurons to be detectable at the scalp; signals generated by smaller populations of neurons will diminish during the conduction process and will dissipate before reaching the scalp[43,45]. There are some brain regions from which it is impossible to measure electrophysiological activity with EEG, specifically the deep brain structures (amygdala, hippocampus, insula) and the inner surfaces of cortical fissures, because in these regions the electrical fields generated by neurons are too distant for the signals to reach the scalp or cancel each other out due to their opposing alignment[43-45]. Another important limitation of EEG is volume conduction: during the propagation of the electrophysiological signal from cortical neurons to the scalp, the signal becomes smeared outwards as well as upwards. Consequently, it is not possible to determine which specific brain regions generated a signal recorded on the scalp, and the spatial resolution of EEG is therefore limited. Still, EEG is a powerful tool for investigating brain function and, unlike fMRI, measures neuronal activity directly as opposed to blood flow to different brain regions. Furthermore, EEG has an exceptionally high temporal resolution and measures neural activity in the millisecond time-range, rather than in the second time-range of fMRI.

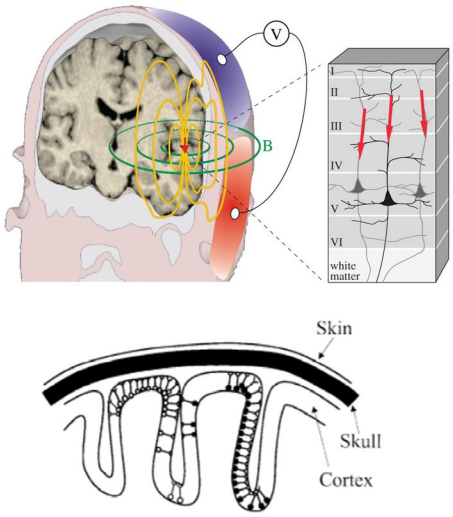

Figure 3: Top panels: The electrophysiological signal. Electrical fields (indicated in yellow) are generated by post-synaptic potentials (red arrows) and are conducted through the layers of brain tissue and skull to reach the scalp, where they are detected as voltage changes (blue/red areas) on the skin by electrodes. Bottom panel: To be detectable on the scalp, electrical fields must be generated by large (10,000 – 50,000) populations of geometrically aligned neurons, and not from neurons inside fissures (because their electrical fields will cancel each other out). Figure adapted from Hari and Parkkonen[45]

There are several methods of processing and analysing EEG data, which are informative about different aspects of brain function. The simplest and most widely used is referred to as *event-related potentials* (ERPs). An ERP is the averaged electrophysiological activity (averaged across experimental task trials) that occurs in response to a specific event (e.g. a stimulus or motor response). The ERP waveform consists of positive and negative deflections which are referred to as *ERP components*; these components are defined in terms of their amplitude (the magnitude of the positive or negative deflection measured in microvolts, μv), latency (the time in milliseconds, ms, for the deflection to reach its maximal positive or negative amplitude) and topography (the distribution of the electrical potential across the scalp) (Figure 4). Different ERP components reflect different neurocognitive processes (see Luck[46], Nelson and McLeery[47] for reviews of common ERP components)[46,47], which can be used to probe the function and dysfunction of different neural circuits in typical developing individuals and in those with mental disorders. For example, the N170 component (a negative component that peaks ~170ms post-stimulus) indexes neurocognitive processes specialised for face perception in right-hemisphere brain circuits[48]. The N170 changes in amplitude and latency across typical child development, indicating that neurocircuitry responsible for processing social stimuli such as faces matures slowly from infancy through to adolescence and early adulthood[49]. The N170 has been extensively studied in ASD and shows robust atypicalities in individuals with the disorder and in unaffected first-degree relatives, suggesting that impaired face processing is a key deficit in ASD and may act as an endophenotypic trait that indexes genetic risk for the disorder[50,51]. Interestingly, the N170 shows similar atypicalities in individuals with schizophrenia[52,53], which adds to the growing body of evidence that there is a high degree of overlap in the neurocircuits affected in ASD and schizophrenia[54]. Another ERP component that has been particularly valuable in understanding neurocircuit alterations in mental disorders is the error-related negativity (ERN) which indexes behavioural monitoring and reinforcement learning functions of the anterior cingulate cortex and is atypically increased in OCD[55] and atypically decreased in ADHD[56].

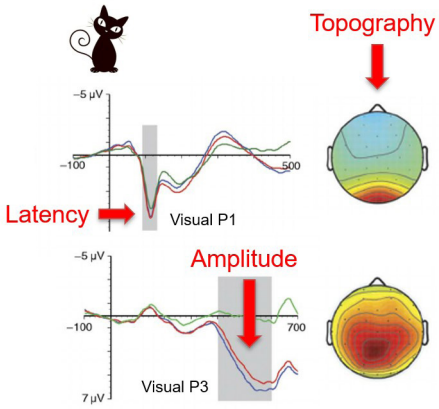

Figure 4: Event-related potentials (ERPs). An ERP is the average electrophysiological activity that occurs in response to an event (e.g. a cat stimulus). The ERP waveform consists of positive and negative peaks, termed ERP components. These components (e.g. P1, P3) are characterised by their amplitude (magnitude of positivity and negativity), latency (time to reach maximal amplitude) and topography (the distribution of the electrical potential on the scalp)

A second method of analysing EEG data is to decompose the time-domain electrophysiological signal into the frequency domain and examine oscillatory neuronal activity in different frequencies. Oscillatory activity is particularly important because it is believed to be the mechanism by which both local and large-scale populations of neurons communicate with one another and the basis for functional connectivity[57]. Oscillatory activity in different frequencies is associated with different neurocognitive functions. Low-frequency theta (4-8Hz) activity is associated with self-regulatory executive functions[58,59], mid-frequency alpha (8-12Hz) is associated

with attention and cortical inhibition[60], and high-frequency gamma (>30Hz) is associated with perceptual integration and learning[44,61]. Oscillatory activity can be quantified by its magnitude (power, amplitude^2) at different scalp regions and by its functional connectivity, i.e. the extent to which oscillatory signals are synchronised (have the same timing) across different scalp regions (Figure 5; for in-depth discussion of oscillatory activity measures see Cohen[62], Roach and Mathalon[63]). Both power and synchrony measures have revealed important insights into the neural mechanisms affected in mental disorders. For example, reduced oscillatory power and connectivity in the alpha frequency is a robust finding in children and adults with ASD and is present across resting and cognitive task[64-66]. Since alpha oscillations index cortical inhibition and are mediated by inhibitory GABA-ergic neurotransmission[60], the reduced alpha in ASD indicates that impaired or inefficient inhibitory neuronal circuitry is a key mechanism involved in this disorder; indeed, recent research indicates that GABA-modulating drugs may be effective in reducing ASD symptoms and restoring functional neural connectivity[39].

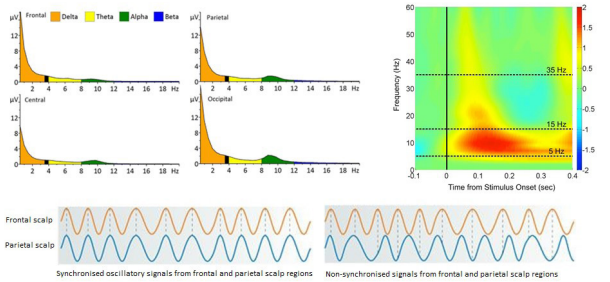

Figure 5: Oscillatory power measures. Power (amplitude^2) of oscillatory activity in different frequencies (delta, theta, alpha, beta, gamma) can be measured as the average across a certain time-period (top left) or as time-varying fluctuations following an event (top right) at different scalp regions. Oscillatory synchrony (bottom) reflects the extent to which oscillatory activity from different scalp regions occurs with the same timing

CONCLUSIONS

Dysfunctions in neurocircuits play an important role in the neurobiology of mental disorders and now we have better tools for exploring human brain connectivity in more detail. Herein, we have discussed three main techniques that allow the investigation and mapping of the in vivo human brain in a non-invasive way: DTI, rs-fMRI and EEG. As mentioned, all these methods measure different things and have their own strengths and weaknesses, but they are complementary to each other. Thus, we acknowledge the importance of using multi-modal imaging in future research in order to generate more precise and complex information about the structural and functional connectivity of the human brain both in typically developing individuals and in those with mental disorders.

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