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Review

Functional brain networks and abnormal connectivity in the movement disorders

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ABSTRACT

Clinical manifestations of movement disorders, such as Parkinson's disease (PD) and dystonia, arise from neurophysiological changes within the cortico-striato-pallidothalamocortical (CSPTC) and cerebello-thalamo-cortical (CbTC) circuits. Neuroimaging techniques that probe connectivity within these circuits can be used to understand how these disorders develop as well as identify potential targets for medical and surgical therapies. Indeed, network analysis of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has identified abnormal metabolic networks associated with the cardinal motor symptoms of PD, such as akinesia and tremor, as well as PD-related cognitive dysfunction. More recent task-based and resting state functional magnetic resonance imaging studies have reproduced several of the altered connectivity patterns identified in these abnormal PD-related networks. A similar network analysis approach in dystonia revealed abnormal disease related metabolic patterns in both manifesting and non-manifesting carriers of dystonia mutations. Other multimodal imaging approaches using magnetic resonance diffusion tensor imaging in patients with primary genetic dystonia suggest abnormal connectivity within the CbTC circuits mediate the clinical manifestations of this inherited neurodevelopmental disorder. Ongoing developments in functional imaging and future studies in early patients are likely to enhance our understanding of these movement disorders and guide novel targets for future therapies.

Contents

Introduction

The basal ganglia-thalamocortical circuits were first proposed by Alexander et al. in 1986 (Fig. 1) as part of a 'parallel circuit' hypothesis identifying discrete pathways subserving skeletomotor, oculomotor, associative, and limbic functions (Alexander et al., 1986). Over the past two decades these cortico-striato-pallidothalamocortical (CSPTC) loops have undergone further refinement. In particular, it is now accepted that the motor loops are comprised of several subcircuits spanning the different precentral cortical fields (see e.g., Bergman et al., 1998; Middleton and Strick, 2000; Turner et al., 1998). Experimental investigations in animal models and neuropathological correlative studies in humans have further shown that alterations in the motor associated CSPTC loops offer an anatomical explanation for the common

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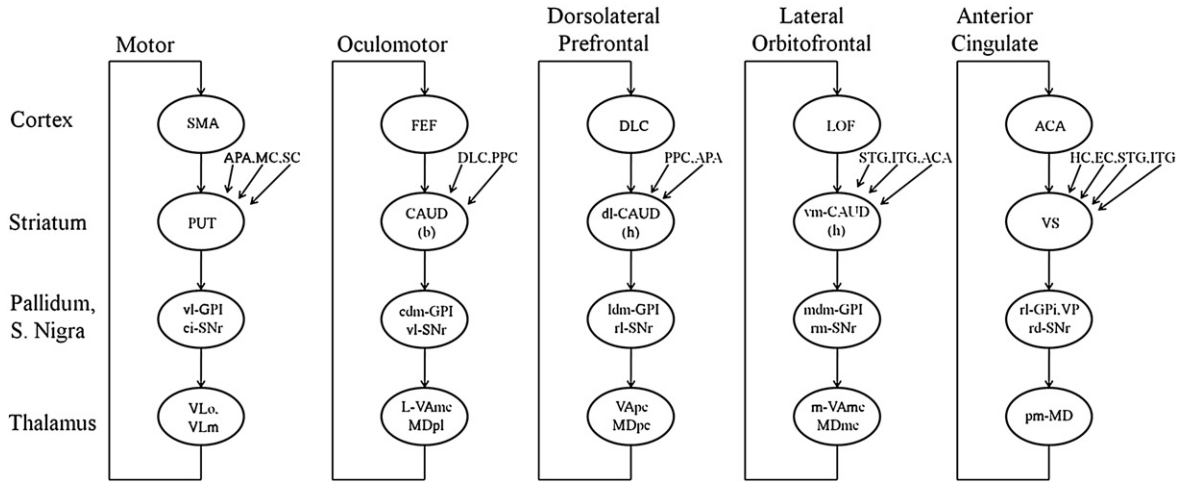

Fig. 1. Basal ganglia-thalamocortical circuits as proposed by Alexander et al. in 1986.Abbreviations: ACA, anterior cingulate area; APA, arcuate premotor area; CAUD, caudate nucleus (b) body (h) head; DLC, dorsolateral prefrontal cortex; EC, entorhinal cortex; FEF, frontal eye fields; GPi, internal segment of globus pallidus; HC, hippocampal cortex; ITG, inferior temporal gyrus; LOF, lateral orbitofrontal cortex; MC; motor cortex; MDpl, medialis dorsalis pars paralamellaris; MDmc, medialis dorsalis pars magnocellularis; MDpc, medialis dorsalis pars parvocellularisl PPC, posterior parietal cortex; PUT, putamen; SC, somatosensory cortex; SMA, supplementary motor area; SNr, substantia nigra pars reticulata; STG, superior temporal gyrus; VAmc, ventralis anterior pars magnocellularis; VApc, ventralis anterior pars parvocellularis; VLm, ventralis lateralis pars medialis; VLo, ventralis lateralis pars oralis; VP, ventral pallidum; VS, ventral striatum; cl-, caudolateral; cdm-, cudal dorsomedial; dl-, dorsolateral; l-, lateral; ldm-, lateral dorsomedial; m-, medial; mdm-, medial dorsomedial; pm, posteromedial; rd-, rostrodorsal; rl-, rostrolateral; rm-, rostromedial; vm-, ventromedial; vl-, ventrolateral.
Modified from Alexander et al. (1986).

movement disorders (DeLong and Wichmann, 2007; e.g., Vitek and Giroux, 2000). In recent years, functional brain imaging techniques have provided further insights into the organization and activity of CSPTC circuitry in health and disease. Indeed, the ability to probe the integrity of the different circuits and examine the discrete changes in functional connectivity associated with specific disease manifestations has broadened knowledge of the pathophysiology of the movement disorders. Moreover, network modeling tools have opened new pathways for the development of quantitative biomarkers of disease progression and the response to therapy. In this review, we will focus on recent advances in the characterization and use of large-scale rest-state networks in the study of Parkinson's disease (PD) and dystonia, two of the most common movement disorders.

Parkinson's disease

Network correlates of motor signs and symptoms in Parkinson's disease

For decades rest-state functional imaging studies of cerebral blood flow and glucose metabolism have been performed to localize and quantify regional abnormalities associated with neurodegenerative disease. Regional approaches such as group comparisons based upon prespecified volumes-of-interest (VOIs) or data-driven mass univariate methods have proven helpful in delineating characteristic local abnormalities in certain of these disorders (see e.g., Eckert et al., 2005). However, given renewed interest in the quantification of regional glucose utilization as an index of local synaptic activity (Attwell and Iadecola, 2002; Heeger and Ress, 2002; Vaishnavi et al., 2010), rest-state metabolic imaging techniques such as ^{18}F-fluoro-deoxyglucose (FDG) positron emission tomography (PET) have been found to be of value in the identification of specific spatial covariance patterns associated with brain disease (see e.g., Alexander and Moeller, 1994; Eidelberg, 2009; Habeck and Stern, 2010). This network mapping technique is based on the Scaled Subprofile Model (SSM), a double centered principal components analysis (PCA) of data that incorporates eigenvalue-based multivariate methods to identify significant spatial covariance patterns in combined samples of patient and control scans (Spetsieris and Eidelberg, 2011). The algorithm itself is used to isolate linearly independent (orthogonal) sources of variability in the data. Principal component patterns that discriminate between the two groups (i.e. patient and control) are referred to as being "disease-related" (see Spetsieris and Eidelberg, 2011 for the criteria used for pattern selection). Moreover, once a disease-related pattern has been identified, quantitative measures of pattern expression in individual subjects (i.e., scalars, or "subject scores") can be computed on an individual scan basis. Over the past two decades this approach to network analysis has been applied extensively to resting state imaging data from patients with a variety of brain disorders and has revealed characteristic metabolic topographies in Parkinson's disease (Eidelberg, 2009; Ma et al., 2007), atypical parkinsonian syndromes (Eckert et al., 2008), Huntington's disease (Eidelberg and Surmeier, 2011; Feigin et al., 2007b), primary torsion dystonia (Asanuma et al., 2005; Carbon and Eidelberg, 2009; Trost et al., 2002), Tourette syndrome (Pourfar et al., 2011), and Alzheimer's disease (Habeck and Stern, 2010; Habeck et al., 2008).

PD is the second most common neurodegenerative disorder in the aging population and is characterized by progressive motor features, such as bradykinesia, rigidity, and resting tremor, as well as non-motor features, such as executive cognitive decline, anxiety, and depression. Neuronal degeneration within the nigrostriatal pathway leads to the primary PD motor symptoms; however, the pathologic findings at autopsy are more extensive and widely distributed throughout the brainstem, basal ganglia, and frontal and parietal cortexes. Functional imaging is used to probe these whole brain changes in vivo and it has long been appreciated that PD patients exhibit altered subcortical and cortical metabolic activity, often at the earliest clinical stages of the disease (Eidelberg et al., 1994, 1995b; Huang et al., 2007b; Tang et al., 2010). Further application of network analysis has identified several distinct PD-related spatial covariance patterns relating to the major clinical manifestations of the illness (Eidelberg, 2009; Poston and Eidelberg, 2009). For each pattern prospectively computed individual subject scores are found to be elevated in PD patients relative to healthy control subjects (Ma et al., 2007), however the various metabolic networks exhibit specific relationships with the underlying clinical symptomatology. For instance, the PD-related spatial covariance pattern (PDRP) has been consistently associated with the major akinetic-rigid motor signs of the disease. This pattern is characterized by increases in pallido-thalamic and pontine metabolic activity and relative reductions in premotor cortex, supplementary motor area (SMA), and in parietal association regions (Fig. 2). Indeed,