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Editorial

EDITORIAL

Advanced network neuroimaging as an approach to unravel the pathophysiology of restless legs syndrome

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The idiopathic restless legs syndrome (RLS) or Willis–Ekbom syndrome is a highly prevalent sleep-related sensorimotor disorder that is defined by diagnostic criteria which address its clinical presentation [1]. Despite its prevalence and high impact on the affected patients´ quality of life, there is still very limited knowledge about the pathophysiology of RLS. Several mechanisms are proposed to be involved, including brain iron deficiency and dysregulation of the neurotransmission via dopamine (as the currently most important target for therapeutic action), glutamate, and adenosine [1]. However, the pathoanatomical correlates of RLS in the central nervous system still remain to be defined. To this end, advanced neuroimaging using magnetic resonance imaging (MRI) has proven its potential to identify alterations in brain structure and function in healthy and diseased conditions in vivo [2], beyond anatomical MRI. The (dynamic) functional connections are usually regarded as an effect of the underlying structural connectivity, but vice versa, functional communication may also affect the structural connections between any set of brain regions and finally, sets of structural and/or functional network characteristics may be combined to classify patient groups and the translation of network analysis findings may guide in understanding neurological and psychiatric diseases and ultimately improve clinical practice [3]. In RLS, neuroimaging findings have provided evidence of involvement of specific brain networks, although there were some discordances probably related to clinical differences in the studied samples and to different methodological approaches and technical parameters used [4]. More specifically, MRI analyses targeting structural connectivity by use of diffusion tensor imaging (DTI) have demonstrated tract-related alterations in sensorimotor areas, thalamic radiation, and limbic/nociceptive networks, but with considerably heterogeneous results between studies [5, 6]. The results of an advanced multiparametric MRI study in RLS identified alterations of key somatosensory circuits with significant decreases of fractional anisotropy in the anterior limb of the internal capsule and white matter volume decline adjacent to increases of gray matter volume of the primary sensory and motor cortices [7]. A meta-analysis of functional connectivity changes associated with RLS demonstrated decreased functional connectivity within the dopaminergic network (including the nigrostriatal, mesolimbic, and mesocortical pathways) as a correlate of sensorimotor dysfunction, while increased functional connectivity was observed in the thalamus as an adaptation to somatosensory dysfunction [8]. In addition, functional imaging is able to map treatment effects: lower cerebelloparietal connectivity in untreated RLS patients contrasted with intact cerebelloparietal communication and increased thalamic connectivity to the prefrontal regions in RLS patients on dopaminergic medication, suggesting treatment effects on the thalamus and normalization of the altered processing of sensory information [9].

The current graph theory-based DTI study by Park and colleagues [10] substantially adds to this constantly growing road map of RLS-associated cerebral network alterations: decreased segregation in the global brain network of the RLS patients was observed in correlation with RLS severity, together with changes in local structural connectivity in regions involved in sensorimotor function, including the middle frontal gyrus, superior frontal gyrus, orbital frontal gyrus, postcentral gyrus, supplementary motor area, and thalamic substructures (pulvinar and anterior thalamic nucleus). The results provide further evidence that an altered sensorimotor network may play a pivotal role in the pathophysiology of RLS.

These data demonstrate how advanced neuroimaging applications to RLS can provide information useful to improve the understanding of its pathophysiology, although additional and especially large-scale (e.g., multicenter) structural and functional MRI studies are still warranted to interrogate the impact of the cerebral alterations identified in this study on the characteristics of sensory and motor symptoms in RLS patients, perhaps in multimodal combination with radioligand imaging [4]. RLS, thus, might be considered as one disease that represents brain disorders not originating from malfunctioning of one or two specific brain centers, but mainly from deterioration of connections between multiple network centers [3]. As a consequence, the in vivo approach of neuroimaging will be most promising to unravel the pathological central nervous system dysfunction in RLS. It should be noted well in that context, however, that the central nervous system also includes the spinal cord which is considered to be substantially involved in RLS pathoanatomy according to many disease models [1, 11], so that the currently scarce neuroimaging approaches addressing the structure and function of the spinal cord in RLS need to be expanded.

The constantly evolving statistical postprocessing models will help to disentangle the multiple levels of structural and functional integration in different networks and their alterations in complex disorders like RLS. Further advances in automation and standardization of processing methods, including machine learning approaches, will increase the reproducibility and reliability of these tools [12]. Longitudinal study designs with multiple timepoints to investigate both natural history (in the few diagnosed but untreated patients) and especially effects of pharmacotherapy or other interventions will guide in the dynamic mapping of the pathophysiology over time, at least at group level. This approach might, as a possible future perspective, help to establish network neuroimaging as a potential biological marker for RLS.

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