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Letter to the Editor

Unravelling the Parkinson's disease network: Taking the connectome beyond the brain

Neurological diseases are increasingly viewed in terms of the functioning of the brain as a network, arising from the interplay between both structural and functional connections. In this context, a disease is regarded as a deviation from the 'healthy network', either due to increased or decreased connectivity (van den Heuvel and Sporns, 2019). The human connectome is usually derived from measurable entities, such as electrophysiological signals captured with electroencephalography (EEG) or magnetoencephalography (MEG). Connectivity-derived matrices reflecting the strength of interactions between anatomically and physiologically separate brain regions may result in the computation of an individual global network (Geraedts et al., 2018), sometimes considered to consist of several distinct subnetworks within the brain. Alterations in network integrity and pattern are considered to be linked to the disease pathophysiology, whereas alterations in subnetworks may be linked to different symptoms of the disease. In this context, integration of the influence of molecular or genetic interactions on these brain networks may identify disease mechanisms in a way that transcends singular measurement instruments.

Parkinson's Disease (PD) is the fastest growing neurodegenerative disease worldwide, and has a relatively obscure etiology. A growing number of environmental and genetic risk- and protective factors has been identified, and many others will likely be studied in the near future. It has been the particular interaction between either hazardous or protective environmental factors and genetic risk factors that was described to be required for elucidation of pathogenic mechanisms (Kalia and Lang, 2015).

PD was until recently characterized as purely a brain disease, with Lewy bodies consisting of alpha-synuclein depositions rising from the vagal nuclei and the olfactory bulb towards the basal ganglia and cortex. Growing evidence now indicates alpha-synuclein aggregation beyond the central nervous system, with large stockpiles of alpha-synuclein in the intestinal nervous system (Breen et al., 2019). In an effort to identify early biomarkers and explore the poorly understood etiology of the disease, research on the involvement of a gut-brain-axis in PD has expanded exponentially (Breen et al., 2019). Vagotomy has been associated with modest protective effects for development or progression of the disease, by interfering with transmission of alpha-synuclein via the vagal nerve. Appendectomy has been associated with the development of PD, albeit in both a protective and hazardous way depending on the study. Clearance of alpha-synuclein from the appendix-reservoir was associated with a decreased risk of developing PD, whereas misfolding of alpha-synuclein via the appendicitis-mediated inflammation was suggested to induce PD in other studies (Breen et al., 2019). Alterations in gut-microbiome are considered a risk-factor for faster PD progression (Chapelet et al., 2019). Regardless of the level of evidence and the unelucidated direction of the correlation between the intestinal nervous system and brain pathology, an association between brain-networks and alterations in peripheral structures appears undeniable.

These results indicate a need for challenging the current concepts with regard to (brain) networks in PD. In terms commonly used to describe network properties, the appendix may have pathological hub-like properties, i.e. a central role within the global network reflecting disease pathology. The vagal nerve may represent a so-called highly weighted edge, i.e. a significant connection between subnetworks that may be pivotal in the spreading of alpha-synuclein throughout the global network.

Consequentially, brain regions with hub-like properties within a constrained electrophysiology-network may not necessarily be equally important within a global disease-network. Likewise, regions with low weighted connectivity may have highly weighted edges with regions outside of the brain and play a pivotal role in the upward spread of alpha-synuclein from sources external to the brain. Considering interactions beyond the brain, the amount of possible connections in the entire involved nervous system is vastly larger than what can be visualized after analyses with currently used measurement instruments. Equally, typical PD symptoms with no demonstrated association with brain-networks may actually correlate to more extensive networks, considering the interrelation of brain connectivity with peripheral subnetworks (Geraedts et al., 2018). For example, the contribution of the vagal nerve within the constrained network of the intestinal nervous system or the brain network may be limited, whereas it may serve as a crucial connection between these two subnetworks when both are considered to exist synergistically within a universal pathophysiological network. Such crucial connections may only be visualized from a global perspective.

The complex pathological framework of PD calls for a network approach transcending mono-dimensional measurement-instruments, by placing greater emphasis on the connections between structurally and functionally distinct subnetworks to achieve a more global overview of the exact disease mechanism. Such a matrix of separate instruments combined with weighted thresholds for connection strength would result in a compound 'tree' of distinct subnetworks (branches) connected through a variety of common pathways, i.e. alpha-synuclein aggregation (see Fig. 1). The interpretability of these connections is of course not straightforward, as the connectivity strengths within both the distinct subnetworks and within the global network are dimensionless and often considered on a relative rather than an absolute scale. However, the crucial connections between subnetworks will most

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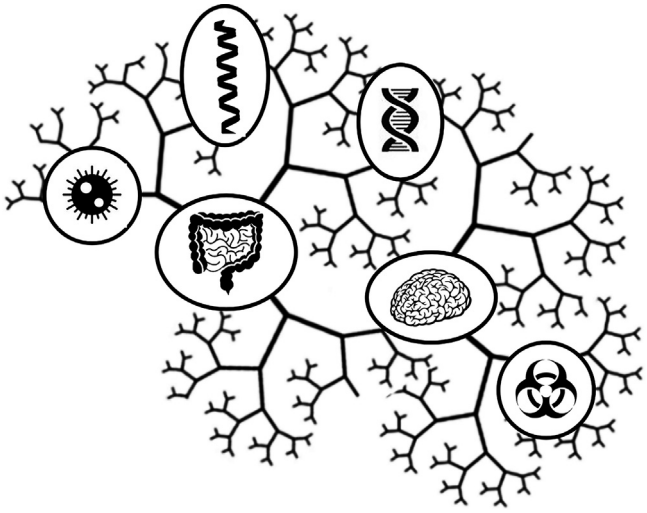

Fig. 1. Stylized fractal tree of integration of subnetworks. Combining monodimensional measurement instruments into a multidimensional matrix may result in a compound 'tree' reflecting the PD pathophysiology network. A combination of these various subnetworks may provide a better overview of the entire disease mechanism, visualize important connecting structure, and explain the variability of PD symptoms. From left-to-right, top-row: alpha-synuclein aggregation, genetic factors; middle: microbiome, intestinal nervous system, brain-involvement, bottom-row: hazardous environmental factors.

likely be highly weighted within the global network and therefore stand out clearly in the tree.

Whereas characterization of brain networks is limited by the resolution of the available measurement instruments, a network-compound of different scales may have greater likelihood of approaching the disease-specific pathophysiology. Similar to epidemiological multivariate analyses in which shared variance is being accounted for and interaction terms decrease the random error within models, joining distinct networks from different measurement instruments into a brain-transcending matrix of factors may better explain the commonly observed variability of PD symptoms between patients. The process of finding the one true pathophysiological network will continuously remain an ongoing process, as no model will be able to explain all variance and new risk-factors or associated features will continuously be discovered and therefore added to the network. Although a theoretical framework that combines genetic, molecular, structural and electrophysiological networks is still a future perspective, the key to brighten the obscurity around the pathophysiology of PD might lay in a more extensive and multidimensional approach towards connectivity in PD than constrained networks.

Author roles

VJG: conception of the study and responsible for scientific integrity, writing the manuscript. JJvH: critical revision of the manuscript. MFC: critical revision of the manuscript. MRT: conception of the study and responsible for the scientific integrity, critical revision of the manuscript.

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Declaration of Competing Interest

None relevant to this study.

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