

On the role of vascularization in pathoconnectomics

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Abstract

In recent years, pathoconnectomics emerged as an interesting framework for the investigation and better comprehension of disorders affecting the brain. Research in this field has used so far structural, functional, metabolic and genetic data, but limited attention was addressed to the possible role of vascularization. In the present work the following aspects making it a valuable candidate to pathoconnectomics investigation are discussed: i) The vascular system is by its nature a network, endowed with directionality information on the basis of circulation; ii) The current imaging techniques allow in vivo detection of the vascular system to a good level of detail; iii) The information extracted from this kind of data could interact in a meaningful way with the functional profile of the brain, being the BOLD effect in turn based on blood flow; iv) Further evidence could be found in support of the trophic failure hypothesis; v) Data about vascularization could allow to bring in the pathoconnectomics framework cardiovascular and metabolic disorders. We suggest, therefore, that the evaluation of vascular connectivity (which we propose to name “vesselomics”) could enhance the pathoconnectomics paradigm, and provide new elements towards the understanding of brain pathology.

Keywords

vasculature; connectomics; pathoconnectomics; connectivity; brain

In a seminal paper of almost ten years ago, Darran Yates stated that while spreading through the brain, pathological alteration “follows disease-specific patterns that resemble the architecture of brain connectivity networks” (Yates, 2012). This vision was to become a tenet of the aborning field of pathoconnectomics (Seeley et al., 2009). Since then, convincing evidence was found in support of that groundbreaking intuition (Cauda et al., 2018a; Cauda et al., 2018b; Manuello et al., 2018; Raj et al., 2012; van den Heuvel and Fornito, 2014; Zhou et al., 2012). Based on findings, different non-mutually exclusive hypotheses have been postulated trying to explain the mechanisms behind this non-random spread, the most investigated being “transneuronal spread” (i.e. the pattern of brain alteration is due to the propagation of toxic agents along structural connections) (Clavaguera et al., 2014; Clavaguera et al., 2013; Goedert et al., 2010; Goedert et al., 2017; Jucker and Walker, 2013), “nodal stress” (i.e. the pattern of brain alteration is due to excitotoxic effects of intense functional activity) (Crossley et al., 2014; Olloquequi et al., 2018; Zhou et al., 2012), and “shared vulnerability” (i.e. the pattern of brain alteration is due to shared gene expressions) (French and Pavlidis, 2011; French et al., 2011). These hypotheses can be related with structural, functional, and genetic brain connectivity respectively (Cauda et al., 2018b). Considerable attention was given to maps of misfolded proteins deposition too (Bourdenx et al., 2017; Goedert, 2015). However, further modalities containing meaningful information to disentangle the principles of pathological networking could have being overlooked so far. In our opinion, this is likely the case of brain vascularization. While meaningful research was carried out in animal models (Ji et al., 2021; Miyawaki et al., 2020; Vazquez et al., 2014), the transition to human is still mostly missing. In the following paragraphs, several aspects in favor of the inclusion of vascularization in the framework of pathoconnectomics will be presented. Consistently with connectomics jargon, we propose to refer to this as “vascular connectivity”. This term is meant to account not only for the anatomical system of vessels but, more generally, for further information concerning circulation suitable to be represented as node’s and edge’s properties in a network (e.g. flow velocity, diameter of the vessel, smooth muscle functionality).

The network-like nature of the vascular system

Pathoconnectomics is nowadays strongly related, both technically and theoretically, with network analysis (Behrens and Sporns, 2012). After all, brain networks are the analytical foundation of its superordinate field, connectomics (Seung, 2013), and backed up by a sizable repertoire of evidence the network-like properties behind the organization of the brain are no longer called into question (Avena-Koenigsberger et al., 2014; Bullmore and Sporns, 2009; He et al., 2007). It follows from this that to fit whatever kind of data into the pathoconnectomics framework, the soundness of its network-oriented description is a desirable feature. Vascularization certainly meets this criterion, moreover allowing to maintain the distinction between structural and functional properties currently in use in connectomics. In this sense, structural vascular connectivity could be assessed analysing the branched-out system of vessels. The presence of hematic flow into the vessel would define functional vascular connectivity instead. Notably, the presence of the circulation allows to build a directed network, a purpose as desired as difficult to achieve for other types of connectivity (Havlicek et al., 2017; Smith et al., 2010; Ting et al., 2015). In other words, identifying that an occlusion in vessel A induces a reduced flow in vessel B would be much simpler than to infer the influence of activity in brain region A over brain region B. A further peculiarity of vascular connectivity is the possibility to measure both structural and functional properties starting from the same system. This is not strictly

the case of standard MRI-based connectivity. In fact, while white matter tracts, as measured by DTI, provide the gross pathways along which electric signals propagate, functional connectivity is then essentially based on blood flow. Although physiological mechanisms, as the action of nitric oxide interneurons, have been proposed to play a role in the coupling of neuronal activity with cerebral blood flow (Duchemin et al., 2012; Radhakrishnan et al., 2020), the analysis of a common biological substrate could ease the evaluation of the interplay between structural and functional vascular connectivity. Finally, the network of structural vascular connectivity exhibits relevant properties. First, given the organization into vessels of decreasing (from arteries to capillaries) or increasing (from capillaries to veins) diameter, structural vascular connectivity could be described by means of hierarchical graphs. Second, the presence of collateral circulation shapes a redundant topography, yet conferring considerable resistance to network damage (Betz et al., 2017; Ji et al., 2021). Lastly, the microvasculature follows an uneven distribution across the brain, even within a same region, as in the case of blobs in the visual cortex (Nakagawa and Tanaka, 2004). This peculiarity is associated with variation in metabolic activity, and it crucially influences the vulnerability to specific kind of traumatic events. Moreover, capillary geometric organization could influence local resistance to vessel rarefaction (known as percolation) (Hudetz, 1993). Based on these facts, we suggest that the analysis of structural and functional vascular connectivity could establish a new research branch named “vesselomics”. This network-based approach can be extended beyond the domain of brain disease, providing new insight into the organization of the healthy brain as well.

The availability of imaging techniques to visualize the vascular system

The building of each kind of connectome relies on the availability of a suitable technique to detect data of the underlying modality. The constant development of the imaging field has simplified the investigation of several aspects. PET exam allows to map deposition of misfolded proteins (Schöll et al., 2016). Functional MRI (fMRI) is an established option for the analysis of resting state networks and functional connectivity in general (Biswal, 2012). Diffusion Weighted Imaging (DWI) sequences, together with tractography algorithm, allow the estimation of structural connectivity (Glasser et al., 2013). However, none of these sequences return the direct visualization of a network, that is instead obtained by means of post hoc statistical analyses. On the contrary, angiography deterministically depicts the vascular system of the brain. Therefore, if labelling the offshoot of an arteriole from a small artery as node A, and the branching of a capillary from that arteriole as node B, the exact path between nodes A and B is directly traceable, and can be represented as an edge (Fig. 1). Different techniques to perform automatic vessel segmentation have been developed (Cetin et al., 2013; Hu et al., 2018). Moreover, advances in Arterial Spin Labelling (ASL) allow the in vivo identification of vascular territory to a considerable level of detail, and without the injection of contrast agents (Hernandez-Garcia et al., 2019). Therefore, nodes localized in the vascular territory of an impaired vessel could all be considered as vascularly co-altered. In addition to ASL, non-invasive measurements based on cerebral blood volume (CBV), as in the case of the vascular space occupancy (VASO) method (Huber et al., 2014), could provide meaningful information in this framework. Ji et al. (2021) recently analysed the whole-brain microvasculature in adult mice with sub-micrometer resolution, linking topographical features with metabolism, and proposing several network measurements. Although technically challenging, the future translation of this approach to the human brain would provide to pathoconnectomics meaningful data.

Relationship of the vascularization with other kind of connectivity

One of the ongoing debates in connectomics concerns the relationship between functional and structural connectivity (Díaz-Parra et al., 2017). This topic was recently extended to the framework of pathoconnectomics by Cauda et al. (2018b), additionally considering the role of genetics in influencing the development of grey matter patterns of pathological alteration. Vascular connectivity suggests, at least in theory, a possible tight relationship with functional connectivity, being BOLD effect dependent on blood flow. To the best of our knowledge, only one attempt to directly compare resting state connectivity measured through MRI angiography and fMRI has been reported so far (Park et al., 2015). However, vascular anatomy is likely to have an influence on resting state networks (Griffanti et al., 2017). As very recently showed by Sobczak et al. (2021), the analysis of vessel-specific resting-state fMRI signal can elucidate the relationship between localized brain states and global-signal fluctuations. Therefore, besides the presence of functional vascular connectivity, based on the identification of hematic flow, further signal features could be computed (e.g. flow velocity, blood volume) and operationalized as edges' properties, as in the case of ALFF, fALFF and ReHo for common functional connectivity. The addition of vascular connectivity to other existing modalities could hence improve the current comprehension of functional dynamic, both in the pathological and in the healthy brain. On the structural side, recent findings suggest the existence of a relationship between anisotropy of the mouse vascular system and directionality of white matter (Ji et al., 2021; Kirst et al., 2020). Finally, the analysis of genetics may further enrich this landscape, as in the case of evidence of vascular endothelial growth factor (VEGF) genes playing a role in neuroprotection but also in Alzheimer's disease (Mahoney et al., 2021). The concept of "neurovascular unit" (Iadecola, 2017), defined before the birth of pathoconnectomics, might be an early and unwilled signal of the value of vascular connectivity.

Further evidence in support of the trophic failure hypothesis

As mentioned before, several mechanisms have been proposed so far to interpret the spread of alteration across the brain, the most considered being transneuronal spread, nodal stress and shared vulnerability. A further, less examined, hypothesis named "trophic failure" considers the possible failure in the production of trophic factors, leading to pathological deterioration of neural wiring (Fornito et al., 2015). In this sense, one of the main roles of circulation is indeed the distribution of nutrients and oxygen to the tissues through the blood. A reduction in blood flow, as in the case of brain ischemia, can induce excitotoxicity and apoptosis (Radak et al., 2017; Sekerdag et al., 2018). In recent years, alteration of perfusion and several vascular factors were put into relationship with increased risk for dementia (de la Torre, 2017; Suri et al., 2021; Wolters et al., 2017), aside from vascular dementia and the relevant role of microbleeds. Evidence of neurovascular dysfunction was found in amyotrophic lateral sclerosis (Murphy et al., 2012; Winkler et al., 2013) and idiopathic Parkinson disease (Al-Bachari et al., 2014; Janelidze et al., 2015). Even ischemic brain stroke could be seen, in some way, as a sudden interruption of the supply of trophic factors, leading to neuronal death and brain atrophy.

Inclusion of cardiovascular disorders into the pathoconnectomics framework

The pathoconnectomics approach has been successfully applied to the investigation of both neurodegenerative (Manuello et al., 2018; Raj et al., 2012) and psychiatric (Shafiei et al., 2020) disorders. However, cerebrovascular complications escape both categories, and have not been taken

into consideration so far. The commonality of risk factors between stroke and dementia (Livingston et al., 2017), together with the evidence of altered functional connectivity in patients suffering for hypertension (Carnevale et al., 2020), might suggest the validity of the inclusion of this class of medical conditions into the pathoconnectomics paradigm, especially when questing for pathological processes generally accounting for brain alteration and degeneration. As mentioned before, in virtue of collateral circulation a vascular alteration must be of relevant extent to cause a detectable ischemia (Verdolotti et al., 2020). Therefore, the analysis of vascular connectivity could allow to evaluate in the framework of pathoconnectomics systemic alteration before the onset of clinical symptoms.

Conclusion

We proposed the introduction of a new framework named vesselomics, based on the analysis of structural and functional vascular connectivity. Several theoretical, technical, and clinical elements suggest that this approach could provide a valuable drive towards the understanding of pathological mechanisms responsible for brain disorders. Although further research is probably needed to develop ad hoc methodologies allowing to analyze new data modalities, vesselomics looks promising for a better comprehension of the interplay between vascularization and healthy brain functioning.

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Competing interests

The authors report no competing interests.

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