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A divergent pattern in functional connectivity: a transdiagnostic perspective

Lu Zhang, Lorenzo Pini*

Functional magnetic resonance imaging (fMRI) is a popular tool used to investigate not only how the brain responds to specific stimuli during sensorimotor or cognitive tasks, but also brain activity at rest. The physics beyond this approach is based on the analysis of the blood oxygenation level-dependent signal. When performing a task, regions activated by a specific goal exhibit changes in the blood oxygenation level-dependent signal compared to the resting phase. Looking at the difference between the task-evoked signal and the spontaneous fluctuations allows identifying which brain regions are activated by specific tasks. However, spontaneous fluctuations are no more considered as a mere epiphenomenon as they allow unravelling how the brain "works" during resting state conditions. This approach is referred to as resting-state fMRI (rs-fMRI). Starting from this signal it is possible to quantify the functional connectivity (FC), a metric used to identify which brain regions show signal synchronization, and therefore are considered functionally connected within specific resting-state networks. Each resting-state network is characterized by specific spatiotemporal patterns, linked with sensory and high-cognitive order functions (e.g., memory, attention, and language), as highlighted by a study by Yeo et al. (2011). Being vascular in nature, rs-fMRI represents an indirect measure of neural connectivity. Despite this limitation, the study of rs-fMRI signals deeply increased our knowledge about brain mechanisms underlying cognitive and sensory abilities.

Among several kinds of information that can be retrieved from rs-fMRI, divergent brain network connectivity represents an interesting topic, but is still relatively unexplored. This pattern physiologically emerges mainly in circuits involved in high-order functions. In a pivotal study, Menon and Uddin (2010) reported that the salience network, a circuit usually activated by behaviorally relevant stimuli, acts as a gate shifting between recruitments of different circuits, namely the default mode network (DMN) and the frontoparietal network (FPN). According to this model, the DMN is deactivated when an individual engages in external tasks, which require activation of the FPN. This pattern suggests a continuous competitive request for resources among these networks involved in different aspects of cognitive functioning. Their interactions are considered a crucial aspect of functional brain dynamics as they allow the brain to reallocate resources from self-referential thought to task-related processing. Similarly, two main attentional networks (dorsal attention [DAN] and ventral attention [VAN]) showed competitive characteristics during different tasks (Corbetta and Shulman, 2002). Thus, there is a complex and not univocal interplay between cognitive performance and resting-state networks, as brain states can be characterized by anticorrelated patterns. Specifically, imbalances within and between networks can better predict clinical and cognitive impairment, rather than focusing solely on connectivity breakdown within a single dimension (e.g., hypoconnectivity of a specific network).

Notably, FC alterations in several brain disorders involve modifications in the balance between networks, highlighting divergent brain patterns. These findings reinforce the assumption that the brain is not a uniform "machine" in which reduced connectivity in a specific network is accompanied by changes following a similar direction (i.e., reduction) in other networks. Rather, FC alterations seem to be multifaceted (i.e., following divergent patterns) when linked with cognitive impairments and clinical symptoms. Alterations in physiological divergent connectivity patterns or the emergence of pathological anticorrelated relationships between networks are reported in several pathological conditions. Thus, divergent patterns hold the potential to represent a common trait between heterogeneous brain disorders, spanning from proteinopathies to brain lesions.

In Alzheimer's disease (AD), the most common neurodegenerative disease worldwide, the accumulation of misfolded proteins (amyloid-β and tau) represents the molecular hallmark. The protein accumulation exhibits a specific spatiotemporal pattern, starting from a localized area and gradually spreading throughout the brain. Interestingly, changes in the FC pattern match the protein diffusion pattern. Warren et al. (2013) proposed a link between the two through the molecular "nexhopaties" model, suggesting a close link between molecular pathology and FC. Recent studies complemented this theory, highlighting that the distribution of FC does not follow a linear trend, contrary to the neurodegenerative patterns. That is, brain volume linearly decreases as a function of disease severity, whereas network connectivity follows a different trajectory, characterized by both aberrantly increased and decreased FC strength. In line with this view, Shultz et al. (2017) conceptualized the molecular-network coupling distribution in AD as a "two-stages" model, in which each stage shows a differential effect on FC. The early amyloid-β accumulation of the first stage is associated with a significantly increased FC, which in turn is hypothesized to accelerate the spread of tau due to activity-dependent modulation of its release. The resulting tau accumulation marks the second stage in which FC undergoes a progressive decline. This assumption is in line with previous findings showing an anti-correlated pattern between DMN and salience network. Hypo-connectivity in the former is accompanied by hyper-connectivity in the latter in AD patients (Zhou et al., 2010). Interestingly, a reversed pattern is observed in patients with frontotemporal dementia (FTD): reduced salience network connectivity is accompanied by aberrant higher FC in the DMN (Zhou et al., 2010). Significantly, hyperconnectivity consistently manifested as a physiological trait in both dementia groups during the prodromal stage, affecting brain regions associated with the distinctive pathological processes of FTD (frontal) and AD (posterior); however, it waned in the later stages of AD and FTD. Overall, these findings indicated both within-disease (temporal; stage-dependent) and between-disease (spatial) divergent patterns, which are linked with the cognitive and clinical symptoms of these pathologies.

Notably, spatial and temporal divergent patterns have been observed on different α-synucleinopathies, which comprehend neurodegenerative diseases (Parkinson's disease [PD], dementia with Lewy bodies, and multiple system atrophy) characterized by the presence and accumulation of α-synuclein aggregates, eventually forming Lewy bodies, which lead neurons to death. Recent findings suggest increased connectivity between the subcortical network and the sensorimotor network - a unimodal circuit involved in sensory-motor functions. Interestingly, reduced connectivity between the latter and a specific subcortical nucleus, the putamen, was also reported, suggesting that hypo- and hyper-connectivity patterns can be simultaneously present within the same cortical-subcortical axis. Additionally, the cerebellum displays abnormally high inter-regional signal synchronization, supported by observations concerning its increased metabolic activity, but lower connectivity with basal ganglia and FPN. This pattern is in line with the observed deficits in initiation, maintenance, and direction of movements, and correlates with symptom severity. Concerning cognition- and attention-related networks, a general reduction of FC was reported, specifically within polymodal networks (e.g., DMN, VAN, FPN, and subcortical network). This could be related to the attentional deficits usually observed in PD. Interestingly, even emotional dysfunctions in α-synucleinopathies can be linked with a divergent connectivity pattern between both top-down emotional regulation networks (increased inter-network FC between FPN and DMN) and bottom-up emotional processing (decreased inter-network FC between VAN and parahippocampus, and temporal cortex with VAN). These results suggest that changes in emotional cognition are not characterized by a 1:1 relationship between altered connectivity in a specific network and impaired emotional abilities, but rather the emotional deficits are distributed and linked with alteration in the balance between several brain networks. In addition to these spatial divergent findings, recently Filippi and colleagues demonstrated longitudinal changes in FC in different disease stages of PD. It is particularly noteworthy that, akin to observations in AD, hypoconnectivity tends to be more pronounced in patients at advanced disease stages, while mild cases tend to exhibit a prevailing hyperconnectivity pattern. Both hypo- and hyperconnectivity have been shown to be closely associated with clinical deficits in PD at different disease stages (Filippi et al., 2021), supporting the hypothesis that alterations in network balance play a pivotal role in the cognitive and sensory impairments observed in neurodegenerative populations.

While the other addressed neurodegenerative diseases have both sporadic and genetically complex origins, the primary hallmark of Huntington's disease (HD) has been thoroughly established. This hallmark involves the expansion of CAG trinucleotide repeats within the coding sequence of the huntingtin gene. Thus, it is possible to study the patients' characteristics even before the disease manifestation, when they are in the pre-symptomatic phase. Neurodegeneration starts from a localized brain area, the striatum, and progressively spreads towards the whole central nervous system. The protein diffusion pattern is accompanied by stage-dependent FC alterations. The motor cortico-cerebellar network shows a decreased FC in the pre-symptomatic disease phase, while after symptom onset aberrant higher connectivity is observed. The temporal divergent shift represents the more robust phenotype observed in HD (as highlighted in Pini et al., 2020), in apparent contrast with the temporal characterization of AD, PD, and FTD. Notably, spatial divergent patterns have been observed in the clinical HD stage, involving a shift between the anterior (hyper-) and posterior (hypo-) connectivity hubs, suggesting a widespread unbalance in terms of connectivity in these patients (Pini et al., 2020).

The characterization of divergent FC patterns in neurodegenerative diseases may not be surprising, given a common biological substrate (i.e., spreading of misfolded proteins associated with neuronal death). The most compelling aspect is that alterations of divergent FC patterns are reported also in stroke patients, characterized by focal lesions. This brain disease is not linked with aberrant proteins traveling through synapses. Nevertheless, stroke induces a well-defined divergent pattern in terms of FC. Increased synchronization between intra-hemispheric hubs of the DAN and the DMN is observed. These networks are usually segregated in healthy controls (negative patterns), while in stroke patients this pattern approximates to zero, losing

the observed physiological anticorrelation. On the contrary, decreased FC between homotopic regions is observed. These abnormalities are linked with the clinical phenotype of stroke, suggesting that divergent network physiological abnormalities following a stroke influence the behavioral performance of these patients (Corbetta et al., 2018). Contrary to neurodegenerative disorders, stroke tends to exhibit a longitudinal normalization of inter-hemispheric hyper-connectivity and intra-hemispheric hypo-connectivity patterns. This restoration is associated with improvements in deficits. In this framework, stroke could potentially serve as a valuable disease model for studying divergent connectivity patterns in neurodegenerative patients, particularly in the context of brain stimulation aimed at normalizing brain connections in neurological patients.

The intimate meaning of this divergent pattern remains a subject of ongoing debate. In the context of neurological disease, the emergence of reduced connectivity in patients when compared to controls has mainly been attributed to pathophysiological processes (e.g., atrophy or diaschisis). However, the interpretation of hyper-connectivity patterns is more challenging. Recent theories suggest that increased connectivity acts as a compensatory mechanism aimed at balancing the incipient brain damage to maintain neuronal homeostasis. In contrast with the compensatory explanation, another point of view highlights the detrimental effects of the hyper FC. This assumption is corroborated by the observations that hyper-connectivity could be linked with balance alterations between excitatory and inhibitory neurons caused by progressive cell death, as recently discussed in FTD (Lee et al., 2019).

We believe that a deeper understanding of the biological meaning of divergent patterns in neurological diseases must require a multi-scale perspective, integrating micro- and macro-scale analysis, by means of meso-scale. This perspective would unravel cellular and molecular events linked with divergent FC. Within this perspective, different molecular mechanisms should be carefully considered, such as neuroinflammatory processes. We have highlighted a close match between connectivity and inflammation in AD and PD (Pini et al., 2023), although the association with divergent connectivity has never been assessed systematically. Recently, Passamonti et al. (2019) suggested a link between aberrant divergent FC and microglia activation, a signature of the neuroinflammation process. Within the DMN both positive and negative associations were reported with microglia distribution. Further studies should investigate whether similar molecular/cellular mechanisms provide the basis for the observed divergent connectivity alterations.

In conclusion, the shared hyper- and hypo-FC among such clinically heterogeneous pathologic conditions as neurodegenerative diseases and focal lesions (see **Figure 1** for a summary), highlights the potential of the observed divergent pattern to represent a common denominator. Since abnormalities in FC are linked with behavioral deficits, characterizing the pattern of altered FC in diverse pathologic conditions would be useful for the development of common future treatments.

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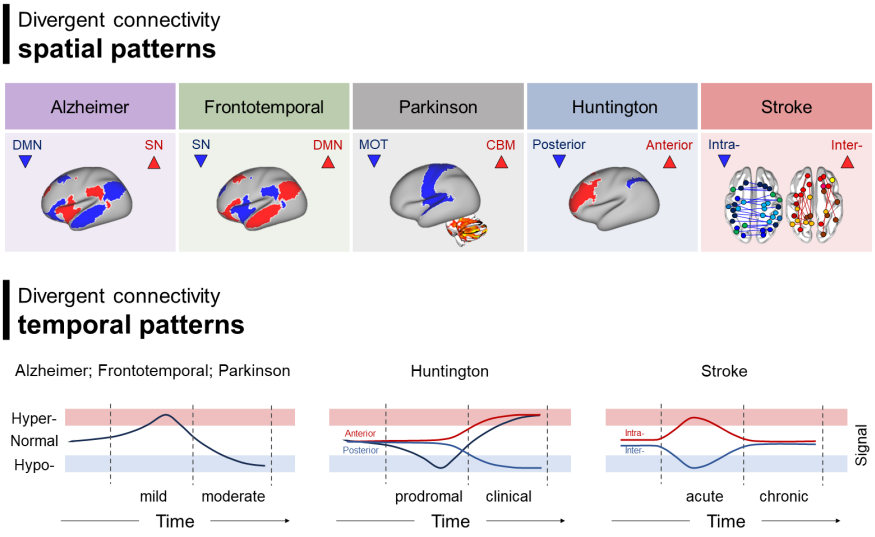

Figure 1 | **Divergent brain connectivity across neurological disorders.**
Panel A: main spatial divergent patterns in patients with neurological disorders observed at the onset of clinical symptoms. Blue marks networks/regions showing hypoconnectivity patterns compared to age-matched controls; red marks hyperconnectivity findings. In Alzheimer's disease (AD) reduced connectivity in the default mode network (DMN) along with increased connectivity within the salience network (SN) is reported. The opposite (i.e., higher connectivity in the DMN and reduced in the SN) is observed in frontotemporal dementia (FTD). Spatial divergent patterns are observed in motor diseases such as Parkinson's disease (PD): hyperconnectivity within the cerebellum network (CBM) is accompanied by motor network (MOT) hypoconnectivity. For Huntington's disease (HD), in the clinical stage, a divergent pattern is observed between the posterior (hypoconnectivity) and anterior (hyperconnectivity) regions of the control network. Similarly, stroke displays a spatial divergent pattern characterized by inter-hemispheric hypoconnectivity and intra-hemispheric hyperconnectivity. Network templates were obtained from Yeo et al. (2011) and superimposed onto an inflated surface template. Panel B: temporal divergent pattern shifts occur from the preclinical/mild to the clinical/moderate stage in neurodegenerative diseases and from the acute to the chronic stage in stroke. In AD, FTD, and PD, connectivity transitions from hyperconnectivity to hypoconnectivity patterns over time. In HD, a reversed pattern is reported for the motor network, alongside a divergent posterior-anterior gradient in the clinical stage (indicated by red and blue lines). In stroke, both inter- and intra-hemispheric hyperconnectivity and hypoconnectivity show a tendency to normalize in the chronic stage. Created using the open-source GNU Image Manipulation Program (GIMP) software (https://www.gimp.org/).

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