Exploring cerebral networks in cluster headache: Insights and perspectives

Massimo Leone¹, Anna Nigri², Luisa Chiapparini² and Stefania Ferraro²

In the last several years, neuroimaging studies have greatly increased our knowledge of cluster headache (CH) pathophysiology (1). The main neuroimaging techniques used to investigate functional and structural changes in CH include positron-emission tomography (PET) (2,3), functional magnetic resonance imaging (fMRI) (4–6), structural magnetic resonance imaging (sMRI) (7–9) and diffusion tensor imaging (DTI) (9–11).

PET and fMRI indirectly measure the neural activity that assesses, respectively, regional glucose uptake and blood oxygen level-dependent (BOLD) signal during the execution of a task or in a resting state condition (12). Advances in fMRI data processing, such as the use of independent component analyses and correlation analyses among signals detected in defined brain regions, have allowed researchers to assess the temporal dependency of neural activation patterns of spatially separated brain regions and therefore to investigate functional connectivity. While fMRI can assess functional connectivity, structural connectivity can be assessed with DTI (13). This imaging technique measures local fractional anisotropy (direction of water molecules diffusion) and enables mapping of white matter tracts. The imaging technique sMRI investigates structural brain abnormalities by assessing macroscopic volumetric changes of gray matter tissue, using methods such as voxel-based morphometry (VBM) (14) and the measure of cortical thickness (15).

Seminal PET studies initially suggested that the ipsilateral posterior hypothalamic area played a key role as the cluster headache generator (generator of pain attacks) (2,3). This result was supported by an sMRI study that showed volumetric abnormality of this structure (8). However, long-term results on the efficacy of deep brain stimulation (DBS) in CH (16) indicated that the hypothalamus is not the trigger of CH attacks but might play a role in the dynamic interactions between not-yet known cortical and subcortical areas and the hypothalamo-trigeminal pathway (17).

Other brain regions in the so-called pain matrix could play a role in CH pathophysiology (18). Indeed, during CH attacks, a PET study showed the involvement of brain regions related to pain processing, such as the anterior and posterior cingulate cortices and the insular and orbitofrontal cortices (2). More recently, a DTI study has shown microstructural changes in similar brain areas belonging to the pain network (10). Accordingly, resting state fMRI studies reported abnormal functional connectivity between the hypothalamus and pain-related regions during CH attacks (4). Interestingly, diffuse abnormal functional connectivity was also reported in areas beyond the pain matrix network during (4) and outside (5) the attack period.

To understand anatomic pathways employed by DBS to improve CH and facilitate a more precise patient-specific targeting of DBS, Clelland and colleagues used probabilistic DTI to map the common connectivity of DBS-targeted regions (19).

They showed that DBS targets project to the ipsilateral hypothalamus, the ipsilateral reticular formation, and the ipsilateral cerebellum, therefore indicating that anatomical regions corresponding to successful DBS are connected to some areas involved in antinociceptive processing.

The limitations of the study, well discussed by the authors, suggest caution in the interpretation and the generalization of the results to the chronic cluster headache population. This study considered a small number of healthy participants. A lack of statistical power due to small sample size is likely the root cause of some variability in the network target of the DBS. Indeed, some participants also showed projections to...
the orbitofrontal regions and temporal lobe. More important, the involvement of healthy participants does not allow for strong inferences about the anatomical connectivity in the chronic cluster headache population. The compelling evidence that several functional connectivity networks are altered in CH (2,3) suggests that the underlying anatomical connectivity is also abnormal. This is in agreement with several studies suggesting that chronic pain causes functional and anatomical network reorganization (20).

It is also important to consider that the DTI study of hypothalamic and midbrain regions presents several methodological issues. Regions around the hypothalamus and midbrain can give rise to distortions due to susceptibility for both diffusion and functional scans (21). Moreover, the results strictly depend on the seed/region of interest (ROI) selected. In particular, a variability in the results was observed due to the number of voxels and the spatial resolution of the seed mask used. In addition, the estimated orientation of the fibers in brain areas with complex white matter structure, such as hypothalamic and midbrain regions, may be ambiguous or misleading (i.e. crossing fiber problem) and cannot be completely addressed with conventional DTI imaging, although several different techniques have tried to overcome this issue (22).

Notwithstanding these limitations, DTI studies as shown by Clelland et al. (19) and other authors (10,11) lead the way for future researchers to gain insights into the pathophysiology of CH. The way to better understand this puzzling and complex picture is to study anatomical and functional connectivity in CH patients (both episodic and chronic) at the whole-brain level, but also at hypothalamic and midbrain regions as well. In addition, important new insights could arise from the simultaneous study of structural and functional brain connectivity in these patients, in order to explore spatially distributed and functionally linked brain regions sharing continuous information.

Conflict of interest
None declared.

References