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REVIEW ARTICLE

Cluster headache: insights from resting-state functional magnetic resonance imaging

Stefania Ferraro[1] · Anna Nigri[1] · Maria Grazia Bruzzone[1] · Greta Demichelis[1] · Chiara Pinardi[1] · Luca Brivio[1] · Luca Giani[2] · Alberto Proietti[2] · Massimo Leone[2] · Luisa Chiapparini[1]

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Abstract

The comprehension of cluster headache (CH) has greatly benefited from the tremendous progress of the neuroimaging techniques over the last 20 years. Since the pioneering study of May et al. (1998), the neuroimaging results have indeed revolutionized the conception of this disease, now considered as a dysfunction of the central nervous system. Clinical, neuroendocrinological, and neuroimaging studies strongly suggested the involvement of the hypothalamus as the generator of cluster headache attacks. However, the latency of the improvement and the inefficacy of the hypothalamic deep brain stimulation (DBS) in the acute phase suggested that the hypothalamus might play a modulating role, pointing to the presence of some dysfunctional brain networks, normalized or modulated by the DBS. Despite the great importance of possible dysfunctional hypothalamic networks in cluster headache pathophysiology, only quite recently the scientific community has begun to explore the functional connectivity of these circuits using resting-state functional magnetic resonance imaging. This is a neuroimaging technique extensively employed to investigate the functional connectivity among separated regions of the brain at rest in the low-frequency domain (< 0.1 Hz). Here, we present a review of the few resting-state functional magnetic resonance imaging studies investigating the hypothalamic network contributing to a deeper comprehension of this neurological disorder. These studies seem to demonstrate that both the hypothalamus and the diencephalic-mesencephalic junction regions might play an important role in the pathophysiology of CH. However, future studies are needed to confirm the results and to clarify if the observed dysfunctional networks are a specific neural fingerprint of the CH pathophysiology or an effect of the severe acute pain. It will be also crucial to clarify the neural pathways of the chronicization of this disorder.

Keywords Cluster headache · Resting-state functional magnetic resonance imaging · Hypothalamic network

Cluster headache (CH) is the most distinctive primary debilitating headache characterized by a prevalence of 0.1–0.4% and a clear male predominance. This condition is supported by the activation of the trigeminal nerve in mediating pain and of the parasympathetic component of the seventh cranial nerve in producing the local ipsilateral autonomic signs such as rhinorrhea, conjunctival injection, and lacrimation. The pain is among the most severe known to humans: it is strictly unilateral, mainly around the orbital and temporal regions, and it is typically characterized by a striking circannual and circadian pattern. The disorder is characterized by recurrent and intense unilateral attacks lasting 15 to 180 min. In episodic CH, the cluster periods have a duration that varies from weeks to months and they are separated by remission states that usually last for several months or years. In chronic CH, attacks can continue for years [1].

The pathophysiological mechanisms of CH are still to be clarified. Clinical, neuroendocrinological, and animal studies [2] together with the seminal neuroimaging study of May et al. [3] strongly suggested the involvement of the hypothalamus as the generator of CH attacks. These findings led our group to the pioneering successful treatment of the refractory chronic CH with hypothalamic deep brain stimulation (DBS) [4]. However, the latency of the improvement and the inefficacy of the hypothalamic DBS in the acute phase suggested that the

✉ Anna Nigri
anna.nigri@istituto-besta.it

[1] Department of Neuroradiology, IRCCS Fondazione Istituto Neurologico 'Carlo Besta', 20133 Milan, Italy

[2] Department of Neurology and Headache Centre, IRCCS Fondazione Istituto Neurologico 'Carlo Besta', Milan, Italy

hypothalamus might play a modulating role, pointing to the presence of some dysfunctional brain networks, normalized or modulated by DBS [2]. The hypothesis of dysfunctional brain networks is also supported by the evidence that DBS is also successful when directly stimulating the ventral tegmental area [5] or slightly modified hypothalamic targets [6].

In this framework, there is an increasing interest in the study of the cerebral functional connectivity, in order to try to clarify the presence and the role of possible abnormal functional networks in the transformed in CH condition.

Resting-state functional magnetic resonance imaging (RS-fMRI) is a neuroimaging technique extensively employed to investigate the functional connectivity among separated regions of the brain at rest in the low-frequency domain (< 0.1 Hz). Importantly, the studies of neurological disorders have greatly benefited from RS-fMRI: this technique offered new perspectives in various neurological and psychiatric diseases providing new diagnostic and prognostic tools. Various methods have been developed to investigate the functional connectivity of large-scale networks. Among these, one of the most frequently employed, is the seed-based analysis. Particularly important for the study of hypothalamic networks, the seed-based approach is a hypothesis-driven method based on the choice of one region of interest: the functional connectivity map will reflect the correlation of the signal between the seed and the other regions of the brain.

Despite the large employment of RS-fMRI, only quite recently, the scientific community has begun to explore the functional connectivity of the hypothalamic regions. In the seminal RS-fMRI study of Kullmann et al. [7], the lateral and medial hypothalamus were shown to present an overlapping functional connectivity within the striatum, the thalamus, the brainstem, and some cortical regions, such as the orbitofrontal cortex, the cingulum, and the temporal areas. However, the two investigated hypothalamic sub-nuclei also revealed distinct patterns of functional connectivity: in particular, the lateral hypothalamus was shown to map onto some areas of the salience network (frontoinsular cortex and anterior cingulate cortex) and of the executive control network (prefrontal cortex). Based on these results, the authors argued that the lateral hypothalamus modulates, in concert with other regions, the response to stimulus salience (opercular and anterior cingulate cortex) and goal-directed behaviors.

In regard to the investigations of the hypothalamic functional connectivity in CH pathophysiology, it is important to be aware that some studies used as hypothalamic region of interest the standard coordinates of the activation observed in the posterior hypothalamic region during a CH attack and reported in the seminal study of May et al. [3]. Importantly, reconsideration of the localization of these coordinates led to hypothesize that this region is located in the midbrain areas, possibly in the ventral tegmental area (from here, this region will be defined as diencephalic-mesencephalic junction).

In the first RS-fMRI study investigating episodic CH patients in out-of-bout condition, Rocca et al. [8] showed an increased functional connectivity, in comparison to control subjects, between the hypothalamus (seed in the diencephalic-mesencephalic junction) and the anterior cingulate cortex, the secondary somatosensory cortex and the occipital regions, indicating therefore possible stable alterations of this functional circuit.

Qiu et al. [9] in a larger study confirmed the presence of abnormality in the functional connectivity of the hypothalamus (seed in the diencephalic-mesencephalic junction) also in in-bout condition. In this study, episodic CH patients in-attack condition, compared to out-of-attack condition, presented increased functional connectivity between the hypothalamus ipsilateral to the cranial pain and several cortical and subcortical areas such as the anterior cingulate cortex, the posterior cingulate cortex, the superior, middle, and inferior frontal gyrus, and ventral medial prefrontal cortex, the superior temporal gyrus, the inferior parietal lobule, the parahippocampal gyrus, and the amygdala. Importantly, some of the identified areas belongs to the so-called default mode network (i.e., posterior cingulate cortex, inferior parietal lobule, ventral medial prefrontal cortex, and parahippocampal gyrus), a functional circuit integrating the sensory-visceromotor processing (occurring in the ventral medial prefrontal cortex), with the self-referential activity (occurring in the medial prefrontal cortex) and the recalling of the previous experience (occurring in the precuneus/parietal cortex and in the hippocampus).

Two observations are important in this regard: (1) the central processing of the parasympathetic activity occurs in the regions of the default mode network; therefore, the typical autonomic symptoms of the CH during the attack well explain the dysfunctional connectivity in regions belonging to the default mode network; (2) the observed abnormal functional connectivity of the hypothalamus with some default mode network regions occurs in areas involved in the recalling of the past experience, namely the posterior cingulate cortex/precuneus, the parietal cortex, and the hippocampus. The different dysfunctional connectivity observed in in-attack condition in comparison to out-of-attack condition suggests, therefore, that during the attack, the central processing of the parasympathetic activity and the pain processing might have a direct effect on the functional connectivity between the hypothalamus and the regions of the default mode network. It is tempting to speculate that the acute modulations observed in the functional connectivity between the hypothalamus and the regions of the default mode network might be the cause of the abnormalities observed in both in-bout and out-of-bout condition within the default mode network itself; importantly, this dysfunctional activity seems not to have a role in the shift from the in-bout to the out-of-bout condition or vice-versa.

Interestingly, the investigation of the anatomical hypothalamus provided, as expected, other very interesting results.

Yang et al. [10] reported that the hypothalamic functional connectivity (seed in anatomical hypothalamus) is different between the in-bout and out-of-bout conditions: remarkably, the in-bout condition revealed decreased functional connectivity with the regions of the default mode network (i.e., the precuneus) but also with the middle frontal gyrus and the cerebellar areas. In this case, this could suggest that the hypothalamus might play a role in shifting from the in-bout to the out-of-bout condition or vice-versa. The same study reported that episodic CH patients differ from healthy participants in hypothalamic functional connectivity in visual region (i.e., the cuneus) and in the middle frontal gyrus, confirming that the functional connectivity abnormalities are well beyond the pain matrix.

In addition, our group investigated the functional connectivity of the anatomical hypothalamus in a sample of chronic CH patients in out-of-attacks [11]. Trying to reconcile the hypothesis of the involvement of the hypothalamus (as indicated by clinical, neuroendocrinological, and animal studies) and the evidence emerged from DBS that calls in cause more diencephalic-mesencephalic junction areas, we focalized our analyses on interactions between the hypothalamus and these regions. Crucially, we evidenced an increased functional connectivity between the ipsilateral posterior hypothalamus and a number of diencephalic-mesencephalic structures, comprising the ventral tegmental area, the dorsal nuclei of raphe, and the bilateral substantia nigra, the sub-thalamic nucleus, and the red nucleus. We concluded that in chronic CH patients, there is a deranged functional connectivity between the posterior ipsilateral hypothalamus and diencephalic-mesencephalic regions that mainly involves structures that are part of (i.e., ventral tegmental area, substantia nigra) or modulate (dorsal nuclei of raphe, sub-thalamic nuclei) the midbrain dopaminergic systems. These results suggest that the midbrain dopaminergic systems could play a role in CH pathophysiology and in particular, in the chronicization process.

The studies of hypothalamic functional connectivity demonstrate that both the diencephalic-mesencephalic junction regions and the anatomical hypothalamus might play an important role in the pathophysiology of CH. Future studies are necessary to confirm these results and to clarify if the observed dysfunctional networks are specific neurophysiological patterns of CH pathophysiology or an effect to the severe acute pain. Moreover, it will be very important to define the role played by the hypothalamus and the diencephalic-mesencephalic junction regions in the chronification of CH.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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