

Introduction to the ACNR Headache Series



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Headache is the most common neurological disorder seen in neurology outpatient clinics and in an emergency setting. Headache is associated with low mortality but high morbidity, largely affecting the working population. Yet medical attention and with it resources are instinctively driven towards the few with fatal outcome. In 2013, *ACNR* published the first part of this Headache series addressing these very issues – Secondary Headache (Bahra) and at the other end of the spectrum, Chronic Daily Headache (Katsarava and Obermann), where the burden of economic disability lies.

In 2014 the series will move on to look at the less common headache disorders, such as the Trigeminal Autonomic Cephalalgias, the prevalent but under-diagnosed Migraine with Vestibular aura, management of Headache in Pregnancy and Current Advances in Treatment options. Key to insightful management is a progressive understanding of central nervous system mechanisms in generating headache disorders. In the current issue Phil Holland and Shazia Afridi explain the complexities of an inherently dysfunctional pain network as demonstrated from both pre-clinical and clinical studies.

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Migraine Pathophysiology

Summary

- Migraine is a disabling neurovascular disorder
- Key diencephalic and brainstem nuclei play critical roles in the pathophysiology of migraine
- Functional imaging has revealed the dorsal pons is activated during migraine and the hypothalamus in the premonitory phase

Migraine is among the most common neurological disorders affecting humans, which is ranked 7th most disabling by the WHO. The underlying pathophysiology will be discussed herein; however the readers are also directed towards recent reviews exploring novel genetic susceptibility loci and therapeutic targets.^{1,2} It is now widely accepted that migraine is a disease of the brain with the pain component reliant on activation and disrupted modulation of the trigeminovascular system (Figure 1).³

The anatomy of the trigeminovascular system

The trigeminovascular system originates in the dense plexus of nociceptors which innervate the cranial vasculature and dura matter, the central projections of which travel via the trigeminal ganglion (TG) and synapse on second order neurons in the dorsal horn giving rise to the trigeminal cervical complex (TCC). Activation of these sensory afferents results in the release of a number

of neuropeptides, in both humans and animals, which have actions on the cerebrovasculature and spinal cord. The TCC has direct ascending connections with areas of the brainstem (locus coeruleus (LC) and periaqueductal grey (PAG)), thalamus and hypothalamus via the trigeminothalamic and trigeminohypothalamic tracts en route to cortical structures. In addition to the ascending projections there is also a reflex connection from the TCC to the parasympathetic system via the superior salivatory nucleus (SuS) and sphenopalantine ganglion (SPG). This connection results in cranial autonomic features, which are seen in approximately 30-40% of migraineurs, are diagnostic for cluster headache and, currently a target of neurostimulation and proposed action of oxygen,⁴ and efferent connections from the facial and cervical dermatomes (via cervical ganglia, CG).

Migraine is a disorder of dysfunctional central sensory processing

A combination of seminal preclinical and brain imaging studies have highlighted the importance of key pontine, brainstem and diencephalic structures involved in the pain neuroaxis in migraine.

Thalamus

The trigeminothalamic tract terminates in multiple thalamic nuclei, which are activated in migraine, SUNCT and cluster headache, and are involved in the parallel processing of nociceptive information, en route to cortical areas.⁴ Trigeminothalamic activation in experimental models activates specific nuclei which have been shown to be possible sites of action for anti-

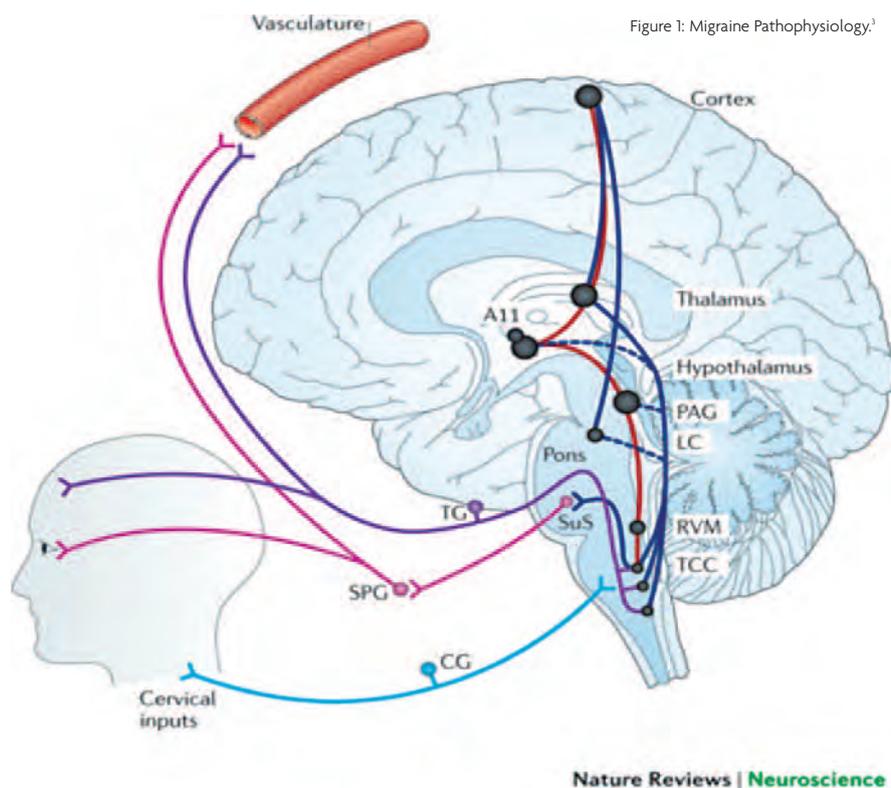


Figure 1: Migraine Pathophysiology.³

migraine therapeutics including the triptans. Moreover, sensitisation of thalamic neurons has been implicated in the spread of cutaneous allodynia and where convergent inputs from light sensitive ganglion cells exist, photophobia.⁵

Trigeminovascular modulation

It is now widely accepted that disruption of normal pain modulatory tone plays a critical role in primary headaches (Figure 1). The hypothalamus has a critical role in the pain neuroaxis and a multitude of functions, which may underlie certain migraine premonitory symptoms. The hypothalamus (and the associated A11 nuclei) has clear projections to the TCC and is activated during headache disorders⁶ and trigeminovascular stimulation. Recently the hypothalamic orexinergic⁷ and dopaminergic⁸ pathways have gained attention for their role in trigeminovascular modulation and associated symptoms, with a dual orexin receptor antagonist currently undergoing phase 2 clinical trials.

Activation of the trigeminovascular system results in neuronal activation in numerous pontine and brainstem regions including the LC and PAG.^{9,13} Stimulation of these nuclei can result in altered cerebral blood flow and inhibition of trigeminal neuronal activity, while pharmacological modulation can result in inhibition or facilitation of trigeminovascular nociceptive processing.¹⁴ Interestingly the brainstem has been implicated in the generation of central sensitisation, with a likely role in disease chronification.

While we have not discussed the role of cortical spreading depression (CSD) here, we refer the reader to an excellent recent review¹⁵ and imaging data below regarding the occurrence of CSD like events in humans, thought to underlie the aura of migraine.

Imaging Insights into the pathophysiology of migraine

migraine is considered to be a neurovascular disorder. It is thought that any vascular changes are a consequence rather than a cause. MRA

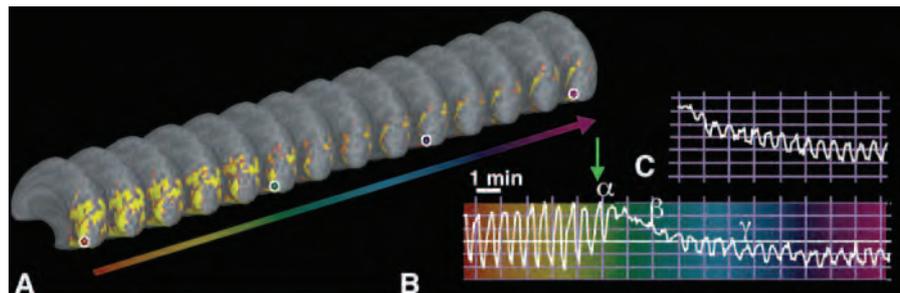


Figure 2: (A) A series of anatomical images, including BOLD activity on "inflated" cortical hemispheres. Time-dependent BOLD activity changes from a single region of interest in VI, acquired before and during episodes of either or induced (B) or spontaneous (C) visual aura.

has revealed an absence of extracranial artery dilatation during spontaneous migraine attacks in 19 subjects with unilateral headache.¹⁶ There was slight intracranial dilatation (10%) on the pain side but this was not altered by sumatriptan administration.

Premonitory phase

Many migraineurs experience premonitory symptoms such as yawning, thirst, neck stiffness or polyuria up to three days prior to the headache.¹⁷ A PET study of eight subjects used glyceryl trinitrate (GTN), a known migraine trigger¹⁸, to study the premonitory phase.¹² Hypothalamic activation was found in the early premonitory phase. The authors postulate that hypothalamic and ventral tegmental involvement would explain yawning related to dopaminergic mechanisms; frequent urination and thirst may relate to reduced vasopressin and mood changes through hypothalamic connections with the limbic system. Hypothalamic activation has been noted in only one previous study during migraine (within four hours of onset) although this study did not look at the premonitory phase specifically⁶.

Imaging aura

In a BOLD fMRI study signal intensities increased in the red nucleus, substantia nigra and occipital cortex when aura was triggered using a checker-board stimulus.¹⁰ The onset of headache or visual change was preceded by suppression of initial activation. No clear evidence of ischaemia was noted in this study.

In a more detailed study involving five attacks of migraine with aura, two induced by exercise and three spontaneous, an initial focal increase in BOLD signal (thought to reflect vasodilatation) developed within the extrastriate visual cortex.¹⁹ This signal then propagated contiguously at a rate of 3.5 ± 1.1 mm/min over the occipital cortex, congruent with the retinotopy of the visual percept (Figure 2). The BOLD signal then diminished, possibly reflecting vasoconstriction. The spreading phenomenon did not cross prominent sulci and were restricted to the hemisphere corresponding to the aura.

Headache

The first PET study detailing regional activation during migraine without aura involved nine subjects scanned within six hours of onset of migraine. Brainstem activation was revealed during the migraine and persisted after sumatriptan administration had relieved the pain.¹³ The resolution of the PET camera used was not high enough to identify specific nuclei, but the dorsal midbrain, which contains the dorsal raphe nucleus and PAG, was thought to be involved.

Brainstem activation was also demonstrated in a study of five subjects with spontaneous migraine.²⁰ Two had typical migraine aura prior to the onset of the headache. Activation was seen in the dorsal pons and

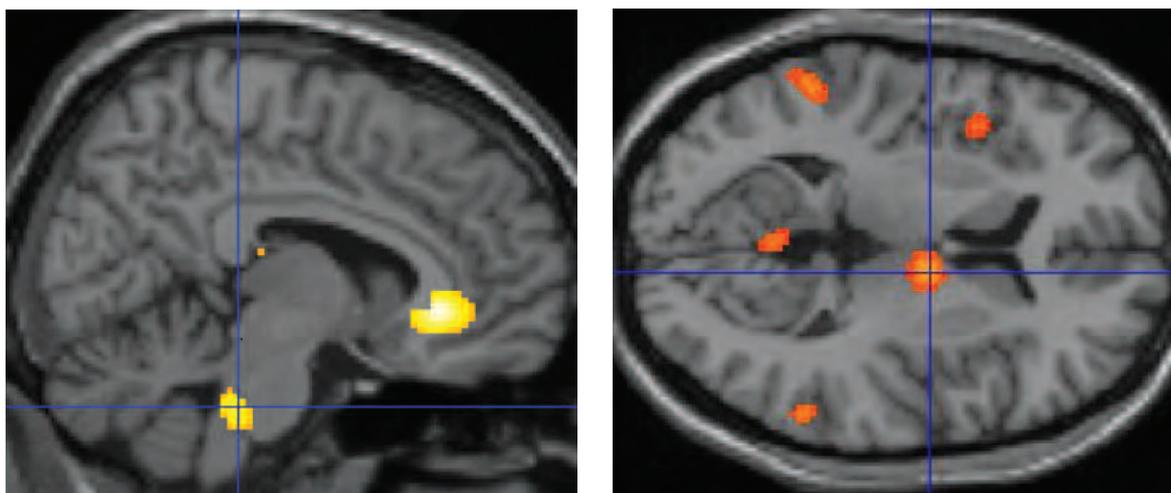


Figure 3: Activation in brainstem (a-left) and thalamus (b-right) during migraine.^{32b}

thalamus (Figure 3) but also in areas which form part of the pain matrix: right anterior cingulate, posterior cingulate, cerebellum, insula, prefrontal cortex and temporal lobes.

The largest PET study, to date, involved 24 migraineurs (with and without aura) and eight healthy controls⁹ and investigated laterality. The migraineurs were divided into three groups according to the site of their headache: right, left or bilateral. Migraine was induced using a GTN infusion. Brainstem

activation was seen in the dorsal pons during the migraine state versus the pain-free state when comparing migraineurs to controls. When each group was analysed separately to investigate laterality it was found that the dorsal pontine activation was ipsilateral in the right-sided and left-sided groups and bilateral in the bilateral headache group with a left-sided preponderance.

The demonstration of key brainstem and diencephalic involvement in migraine and

its experimental models, which form integral parts of the descending pain modulatory networks (Figure 1), highlights their critical role in primary headache disorders. They are ideally located to modulate the trigemino-vascular system, cerebrovasculature, cortical activity, and the integration of external stimuli. Thus it is likely that dysregulation of these central nervous system networks underlie not just the migraine attack, but also the array of associated symptoms. ♦

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