Relevance of cortical thickness in migraine sufferers

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"What do cortical thickness increases mean and what are the potential implications?"

Migraine is a very widespread and debilitating disease and according to the WHO, one of the most common disorders of the nervous system. Prevalence studies estimate that migraine affects 15–25% of women and 6–8% of men [1–4], and over 2.5 million people in North America have migraine at least one day per week. Migraine has a huge economic impact [5,6], amounting to several billion dollars annually due to increased healthcare utilization and costs associated with absenteeism and reduced efficiency. Despite the public health significance of this problem, the pathophysiology of migraine is not yet fully understood, and the available treatments to prevent and to cure attacks are not optimal.

Migraine attacks are characterized by unilateral and pulsating headache, lasting 4–72 h, often accompanied by nausea, phonophobia and photophobia [7]. In 30% of migraine sufferers, the headache is preceded by transient (<60 min) neurological symptoms known as 'aura'. Auras include visual symptoms in 94% of cases [8], but symptoms may involve sensory and speech deficits and can be very subtle [9]. According to its phenotype, migraine is classified as either migraine without aura, or migraine with aura.

Recently, our group has published two articles reporting cortical thickness differences in migraine sufferers [10,11]. In the first paper [10], we examined the visual cortex of migraineurs and found that areas involved in motion processing were thickened in migraineurs with or without aura. Additionally, we found that one area of thickening corresponded to the region where we had previously found the source of cortical spreading depression (CSD) during migraine aura [12]. The second article reported increased thickness in the somatosensory cortex of migraineurs, specifically in the area of head and face representation.

What do these cortical thickness increases mean and what are the potential implications?

We are at this point, facing a chicken and egg dilemma, not knowing whether our observations are the cause or the consequence of migraine. Our findings could indeed be explained in several ways, which are discussed below.

The first possible explanation is that migraineurs have brain structural differences compared with healthy people, due to their genetic background [13–15]. Anatomical changes underlying increases in cortical thickness may include an increased number and/or density of neuronal and/or glial cells in certain parts of the cortex. These focal dysplasias may render the cortex more excitable; one of the leading hypotheses in migraine pathophysiology is indeed that the brains of migraineurs are hyperexcitable [16–18]. Focal dysplasias in the visual and somatosensory cortices would explain why CSD seems to most often start in these specific brain areas [12]. Hyperexcitability in motion-sensitive regions of the visual cortex would also explain why children who are future migraineurs experience motion sickness and why a lot of visual stimuli such as stripes are usually unpleasant for migraineurs. A lower threshold of cerebral excitability could also be at the basis of sensitivity of migraineurs to specific foods, drinks and hormonal changes, stimuli that do not provoke headache in healthy subjects. Finally, the hypothesis

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of a hyperexcitable brain in migraine is supported by the fact that preventive treatment using drugs likely to reduce cortical excitability are beneficial in migraine with and without aura.

Conversely, if the observed increase in cortical thickness is a consequence of migraine, it could result from a plastic reaction to repetitive pain processing. In an elegant study published in 2004, Draganski *et al.* showed that learning to juggle induced changes in areas of the brain involved in juggling and that these changes were reversible when no more training was performed [19]. In the case of increased somatosensory cortex thickness in migraine, we could hypothesize that the brain, instead of being trained to become skilled in juggling, has been trained to process pain and that those areas representing sensation of the head and face, have grown as a consequence of these repetitive stimulations. Allodynia, the abnormal sensation of pain evoked by touch, which is experienced by some migraineurs [20], could be the consequence of such a plastic reaction.

Cortical thickness changes could also be a consequence of the reactive gliosis that often follows brain pathologies [21]. In the animal model, repetitive CSD provokes astrocyte hypertrophy and an increase in astrocyte-specific glial fibrillary acidic protein [22]. Ischemia also provokes astrocyte hypertrophy [23], and cerebral blood flow reduction has been demonstrated during a migraine attack [24–28]. Glial proliferation in humans has recently been demonstrated in the cerebellum of patients with familial hemiplegic migraine type 1 [29].

Finally, recent data also show that induced CSD stimulates persistent neurogenesis in the subventricular zone in rats and produces ectopic new neuron-like cells in the caudate, putamen and cortex [30]. Whether a similar phenomenon happens in migraine, however, needs to be examined.

How can we sort out these different scenarios? We need to underline the fact that they are not mutually exclusive, and an initial hyperexcitability could very well be accompanied by plastic changes and/or reactive gliosis. Future research needs to be conducted:

- With larger numbers of subjects, to ensure enough statistical power to look for correlations between cortical thickness and clinical data such as migraine duration and frequency;
- Follow-up studies on cohort of patients will inform us on the longitudinal evolution of cortical thickness changes. Of particular interest would be to observe a reversibility of changes after efficient migraine preventive treatment;
- Being able to measure cortical thickness in potential migraineurs (i.e., in children of parents who have migraine history), may shed some light on the underlying physiopathological events;
- Finally, the gold standard will be the histological examination of the somatosensory and visual cortices in autopsy brains, and the study of histological correlates of migraine history.

> "Understanding the pathophysiology of migraine is an essential step in the design of drugs aiming at preventing and treating migraine effectively."

Independent from the etiological nature of the cortical thickness increase in migraineurs, it is worth noting that the anatomical modifications that we described were present both in migraine with and without aura, supporting the hypothesis of a common pathophysiological substrate for these two clinical entities [31].

Sorting all these issues will demand time, effort and commitment, but eventually may lead to a better comprehension of this very common, yet poorly understood disorder. Different kinds of drugs are currently used to prevent and treat migraine symptoms, but none are optimal. Understanding the pathophysiology of migraine is an essential step in the design of drugs aiming at preventing and treating migraine effectively [32].

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