


Is the migrainous female brain different?
Some new evidence

Migraine is a very widespread and debilitating disease and, according to the World Health Organization, one of the most common disorders of the nervous system. It is twice as common in females as in males (Le et al., 2011), and much more prevalent in females over the age of 12 years (Lipton et al., 2001). In fact, the picture of migraine differs by sex before and after puberty. Under the age of 12 years, boys have a slightly higher incidence of migraine. Thereafter, prevalence increases for both sexes, peaking between ages 35 and 45 years, with an increase in the female-to-male ratio from 2:1 at the age of 20 years to 3:3:1 at the age of 40 years (Lipton et al., 2001). This higher prevalence in females than males is common in many other chronic pain conditions, although the mechanisms underlying this difference are still poorly understood. Indeed, current knowledge of migraine pathogenesis is based primarily on experimental studies conducted in male animals, and lack of migraine research in female animals limits the clinical relevance given the sex bias in humans.

The disproportionate number of females of reproductive age with migraine suggests that hormonal factors may play a role, but the complex pathophysiology indicates that additional factors are likely to be involved.

It is now well recognized that: (i) at puberty females begin to demonstrate an increase in migraine prevalence compared to males; (ii) >55% of females have menstrual-related migraine; and (iii) the majority of females show improvement in migraine frequency and/or severity with pregnancy and at the menopause. More recently, migraine research has begun to help expand our understanding of the mechanisms underlying these differences, and how they can impact on treatment choices. Several hypotheses have been proposed to explain these differences in migraine and other pain conditions, including fluctuations in sex hormones and receptor binding, genetic factors and differences in exposure to environmental stressors as well as response to stress and pain perception.

A number of other sex differences in migraineurs may be relevant, including: sex-related responses to treatments such as triptans; higher incidence of cutaneous allodynia in female migraineurs (Bigal et al., 2008); reversal from chronic to episodic migraine in females by hormonal preventives; increased levels of depression and anxiety (Guidetti et al., 2009); and higher mean scores for psychic and somatic anxiety in female migraineurs. Awareness of these differences may stimulate further research and enhance therapeutic opportunities for headache patients.

Very little is known about the role of sex differences in brain structure in migraine; for this reason, the article by Maleki et al. (2012) published in this issue of Brain is innovative. In the published literature, studies have focused only on differences between people with headache and healthy controls. The results are interesting but sometimes contradictory. Some authors report differences in cortical thickness of migraine sufferers (Granziera et al., 2006). Granziera et al. (2006) examined the visual cortex of migraineurs and found that areas involved in motion processing are thickened in migraineurs with or without aura. Additionally, they found that one area of thickening corresponds to the region in which they had previously found the source of cortical spreading depression during migraine aura. The second group reported increased thickness in the somatosensory cortex of migraineurs, specifically in the area of head and face representation. Datta et al. (2011), like other previous authors, used 3 T MRI to show grey matter alterations in patients with migraine, particularly thinning of the cingulate gyrus and thickening of the somatosensory
cortex with visual motion processing areas (V3A/MT+). No differences in cortical thickness between patients with migraine and controls could be identified. Local morphological alterations of the brain have recently been detected in cluster headache and chronic tension-type headache, but not in migraine. Schmidt et al. (2008) investigated patients suffering from migraine and compared them with healthy controls with no headache history. Using MRI and voxel-based morphometry, they found a significant decrease of grey matter in areas linked to the transmission of pain (cingulate cortex), but not those specific for migraine, such as the brainstem. The authors suggest that the grey matter change in migraine patients is the consequence of frequent nociceptive input and should thus be reversible when migraine attacks cease.

Now, Maleki et al. (2012) report that brains are differentially affected by migraine in females compared with males, supporting the presence of a ‘sex phenotype’ in migraine. The subjects with migraine, although limited in number, had suffered from episodic headaches for at least 3 years or longer and had no migraine 72 h prior to the scan and no symptoms of migraine during or 24 h after the scans. They used high-field MRI in a sample consisting of male and female age-matched interictal migraineurs and matched healthy controls to determine alterations in brain structure. Female migraineurs had thicker posterior insula and precuneus cortices compared with male migraineurs and healthy controls of both sexes, while previous studies on cortical thickness in healthy subjects have not found sex differences in the posterior insula (Sowell et al., 2007). The present finding may indicate some specificity of altered function in this brain region of female migraineurs. It is likely that there is an insular involvement in interoception, emotional processing and pain perception. In particular, Maleki et al. (2012) only find a significant sex-related difference in healthy control subjects in the right rostral middle frontal gyrus ($P < 0.002$). The same comparison in the migraineurs revealed multiple areas with significant cortical thickness differences between male and female migraineurs including left superior frontal, right caudal middle frontal gyrus, right supramarginal gyrus, left and right precentral gyrus, left and right insula and left precuneus. In all of these areas, cortex was thicker in females. While there were no significant differences in cortical thickness between male migraineurs and male healthy control subjects, the comparison in female subjects revealed significant thickening in migraine patients in the precuneus, posterior insula, superior temporal and inferior temporal lobes. Additionally, the evaluation of functional responses to heat within the migraine groups indicated concurrent functional differences in male and female migraineurs and a sex-specific pattern of functional connectivity of posterior insula and the precuneus with the rest of the brain. Furthermore, the results also support the notion that sex differences involve both brain structure as well as functional circuits, in that emotional circuitry compared with sensory processing appears to be involved to a greater degree in female than male migraineurs. In support of this functional/structural change, the functional connectivity analysis indicates that female migraineurs display a significant negative connectivity between the (thick) posterior insula and the primary somatosensory area, posterior cingulate, precuneus and temporal pole, not present in male migraineurs. Similarly, Liu et al. (2011) have shown that female migraineurs may be more vulnerable to the disease in terms of network robustness, nodal centrality and functional connections. Previous functional MRI studies on sex differences in healthy subjects have found greater pain activation of the insular cortex in males (Straube et al., 2009). Others have shown sex-similar insula activation to pain. Sex differences are also observed in female migraineurs with significant thickening in the dorsal and ventral portion of the precuneus in comparison with male migraineurs and healthy controls. Brain imaging studies indicate higher perfusion in the precuneus in females (Liu et al., 2011). A compelling potential function of the precuneus may be that active inhibition of arousal systems by migraine in some cortical regions leads to cortical deactivation in other cortical areas (Danielson et al., 2011). Tomasi and Volkow (2012) found that while precuneus is the main resting state functional connectivity hub for healthy adults of both sexes, the degree of connectivity is 14% higher in females, while Liu et al. (2011) found significant alterations of cuneus resting state connectivity in female, but not male, migraineurs. In the study by Maleki et al. (2012), female migraineurs show greater activation in brain regions involved in emotional processing; and they report similar intensity but higher unpleasantness of their headache than males, a difference that may relate to the observed sex differences in brain regions involved in emotional processing: the amygdala, parahippocampus, basal ganglia and posterior cingulate cortex. Sex differences in migraineurs are also present in the parahippocampus, a region involved in numerous behaviours including stress and anxiety (Sauro and Becker, 2009) and the integration of complex information. Maleki et al. (2012) stress that the parahippocampal grey matter volume is smaller in male migraineurs, consistent with some studies on sex differences in healthy populations. Some authors have found differences in activation of the spinal trigeminal nucleus to be higher in females than males, and others relate to the differences in sensitivity of the trigeminal system in females versus males to hormonal or yet undefined processes (Bolay et al., 2011). The study by Maleki et al. does not consider the role of periaqueductal grey matter, a crucial modulator of somatic pain transmission, important for aspects of nociception and somatosensory processes (Mainiero et al., 2011). It would be extremely interesting to verify if these features also show sex-related differences. Also, despite 70% of female migraineurs being aware of a menstrual association with their headaches, females included in the article by Maleki et al. (2012) were studied without assessing their stage in the menstrual cycle. This we know can affect pain processing as shown by non-imaging and imaging studies (Pletzer et al., 2010).

Although based on a small number of patients, the study by Maleki et al. (2012) opens new horizons for future lines of research relating to specific responses of females that suffer from migraine. The increased recognition and attention to sex differences in both human and animal research will only help to strengthen and further our understanding of migraine and guide the direction of future headache research. The potential is there to...
advance therapeutic options available for the treatment of migraine and other headache disorders.

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