Chapter 8
Gender Differences in Imaging Studies in Migraine

Nasim Maleki

Migraine is a common neurological disorder that is characterized by recurrent intermittent headaches (1–14 headache days per month in episodic migraine and >14 headache days in chronic migraine) that last 4–72 h. Migraine is considered by the World Health Organization (WHO) to be in the top 20 causes of disability worldwide [1] and affects patients during the most formative and productive periods of their lives. In the United States, migraine affects 30 million adults, and some 17% of American children have headaches including migraine [2] (Fig. 8.1).

Migraine also has a significant sex disparity in prevalence in adults with a higher prevalence in women [5] with an incidence rate that is about twice as high in women compared to men [6–8]. In children, however, this difference in prevalence does not exist during the prepubertal years with the incidence of migraine being similar in boys and girls during prepubertal phase [9]. A considerable number of boys become migraine-free once they reach puberty, while on the other hand, the migraine becomes more frequent or more intense in girls during that same period [10]. Moreover, there is a higher likelihood for girls to experience the onset of migraine in the same year that their menstrual periods start than any other time [11]. The mechanisms underlying the disease onset and evolution specifically the sex-specific shift in the pattern of disease incidence in puberty are unknown [12].

Evidence from various basic science, epidemiological, and clinical studies strongly suggests that ovarian steroids (that change substantially during puberty) have an important influence on the phenotypic expression of migraine [13–19]. In women especially, the ovarian steroid cycling has an impact on the biological mechanisms of migraine. Changes in estrogen levels are thought to have an important influence on the phenotypic expression of migraine [11, 20, 21] in females: migraine can be triggered by the decline in estrogen that could occur naturally during the fall

N. Maleki (✉)
Psychiatric Neuroimaging Division, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
e-mail: nmaleki@mgh.harvard.edu

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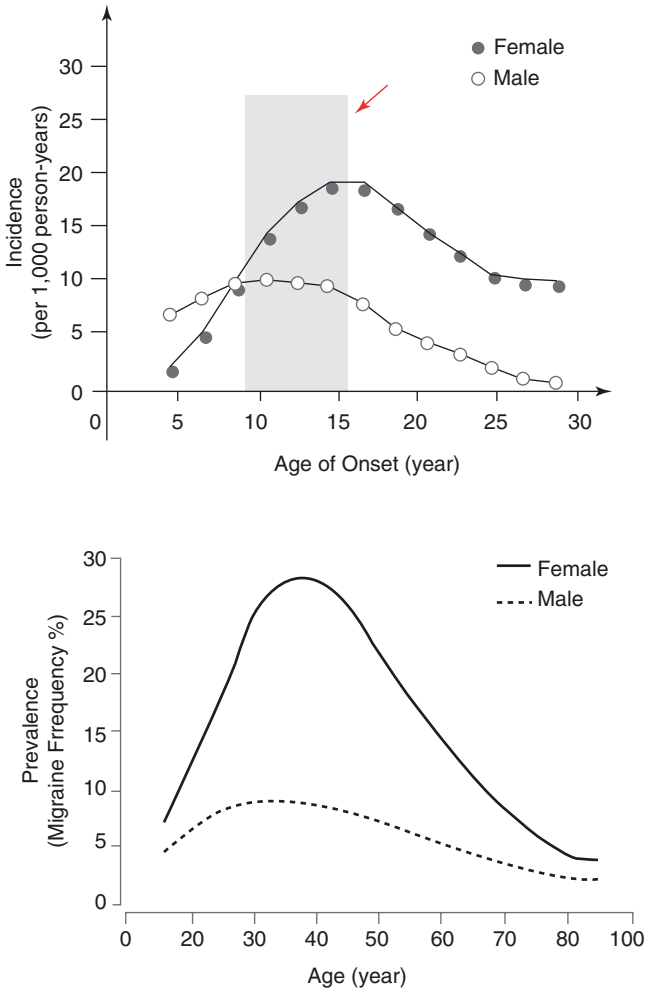

Fig. 8.1 Adjusted age-specific incidence (top) and prevalence (bottom) patterns of migraine by sex. Migraine is 2–3 times more prevalent in women. Sex-related differences in the incidence pattern start around puberty with a significantly higher incidence in girls compared to boys. Lipton and Bigal. Headache 2005. 45 Suppl 1: S3–S13. [3, 4]

in the estrogen immediately before menstruation and during the pill-free week in women who are on contraceptives or in women with bilateral oophorectomy [22].

There are changes in migraine patterns associated with menstrual periods, pregnancy, and menopause. Some women experience menstrual migraine or changes in the intensity or frequency of their migraine attacks during pregnancy. Migraine may improve during pregnancy, when estrogen levels rise gradually, but can reoccur immediately postpartum, when estrogen levels fall [11]. The hypothalamus

secretes GnRH that signals the pituitary to secrete the reproductive hormones that influence menstruation. Sex steroids (such as estrogen) promote secondary sex characteristics in peripheral tissues and regulate GnRH neurons via negative neuroendocrine feedback. These neurons originate in the nose and migrate into the brain, where they are scattered throughout the medial septum and hypothalamus [23].

The majority of women with migraine during the reproductive years become migraine-free after menopause. Moreover, it has been shown that in women, chronic migraine can be reversed to episodic migraine (in nearly 60% of individuals) by hormonal preventives [24]. Roughly 60% of women with migraine experience an attack pattern consistent with menstrually related migraine [13, 25]. Girls often experience the onset of migraine in the same year that their menstrual periods start [11] or their migraine becomes more frequent or more intense during that same period [10].

While the mechanisms of the migraine disease are still poorly understood, the sex-related epidemiological and clinical patterns described above have encouraged growing interest in examining sex differences in the brains of migraineurs as a way to better understand the pathophysiology of the disease. As advances in neuroimaging techniques have significantly improved our ability to assess the functional, morphometric, and chemical changes in the brain noninvasively, a growing number of neuroimaging studies have investigated the differences between the healthy brain and the migraine brain and have reported significant differences in multiple domains including the functional activity and connectivity, structural morphometry (thinning, thickening, volume increase or decrease), structural connectivity, and neurotransmitter or metabolite levels in the brain of migraine patients [26–33]. However, the sex specificity of such abnormalities and their links to the sex-related epidemiological and clinical patterns have been less studied and examined only in a limited number of studies.

In a study on sex-related differences in the structure and function of the brain of episodic migraine patients [34], two groups of opposite sex, age-matched migraine patients along with age- and sex-matched healthy control subjects, were recruited ($N = 11$ in each group). The patients in this study had all suffered from migraine for 3 years or longer and were matched for a number of attributes related to their migraine such as age of onset, medication type, and the average number of migraine attacks they experienced per month. The participants underwent high-resolution structural imaging as well as functional magnetic resonance imaging of the brain. High-resolution images of the brain were used to assess the thickness of the gray matter of the brain at a submillimeter level. Functional images of the brain were collected during evoked response to painful heat applied to the back of the hand. This study revealed:

1. Increased gray matter thickness in two areas of the brain that were specific only to women with migraine. These areas included the insula, which is an area in the brain involved in processing pain, interoception [35], autonomic function [36, 37], sensation [38, 39], and affective processing, and the precuneus that is less known to do with pain processing but more with self-awareness.

2. Reduction of the volume of the parahippocampal gyrus in male migraineurs. The parahippocampal gyrus surrounds the hippocampus and is involved in numerous behaviors including stress and anxiety.
3. More pronounced brain response to pain in women with migraine in brain regions involved in emotional processing such as the amygdala which was consistent with increased measures of pain unpleasantness for these women too (Fig. 8.2).

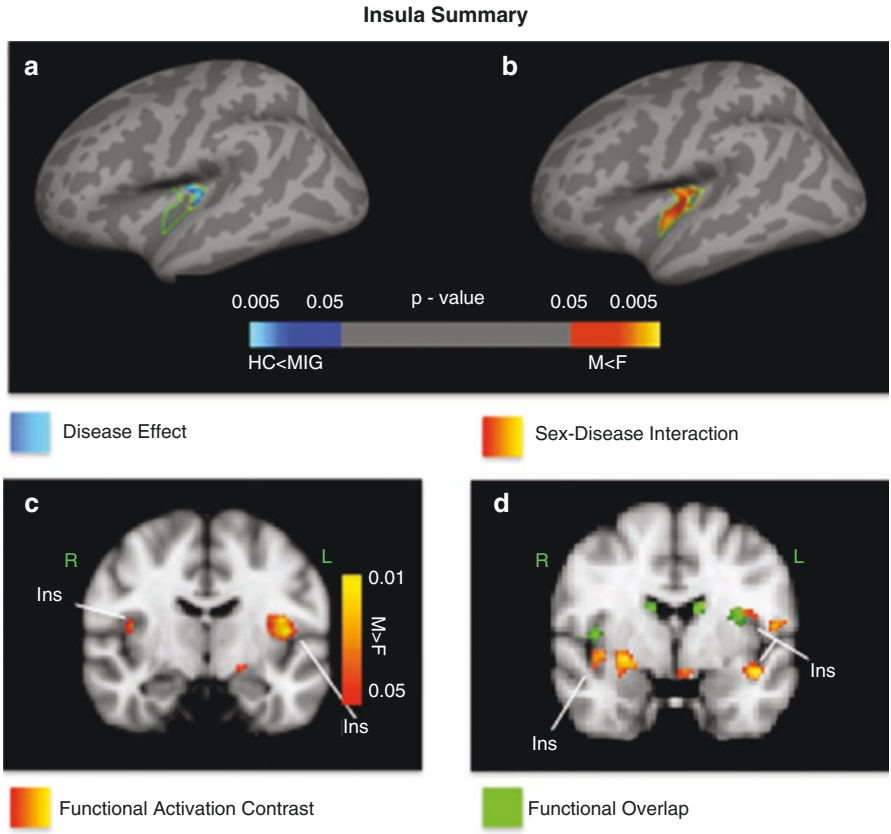

Fig. 8.2 Sex-related structural and functional insular abnormalities. Results of the comparisons conducted on female (F) vs. male (M) migraine patients versus healthy control subjects are shown. First row: (**a**) the disease effects on cortical thickness (blue-light blue) and (**b**) sex-disease interaction (red-yellow) are shown for the insula that is thicker in female migraineurs relative to healthy female subjects and also relative to both healthy and migraineur male subjects. Bottom row: (**c**) functional activation contrast map (male < female) in response to painful heat stimulation shows significant difference in insular activity in male versus female migraineurs and (**d**) overlap of disease-related functional differences between female migraineurs vs. female healthy control subjects (in green) and sex-related differences in female vs. male migraineurs in response to painful stimulation overlap in insula. Adapted from Maleki et al. [34]

A follow-up study evaluated changes in the cortical thickness by age in 92 female subjects (46 patients with migraine and 46 healthy controls) using high-field magnetic resonance imaging [40]. An abnormal pattern of bilateral lack of thinning of gray matter in the insula of adult female migraineurs was observed. While this was a cross-sectional study, the observed pattern was in contrast to the patterns of insular thinning reported in cross-sectional studies of healthy subjects where the relative gray matter loss rate of the insular cortex is reported approximately double of that seen in other cortical areas during aging [41]. Insular abnormalities in association with migraine are also reported in a number of other neuroimaging studies [32, 42–45].

A number of neuroimaging studies have assessed sex-related differences in the brain's intrinsic functional connectivity. In this approach, functional networks are derived from estimating correlations between time courses of brain activity in different regions which allows determining networks of functionally connected structures in the absence of an active task or an experimental manipulation. In one study, resting-state brain functional networks were compared in 38 migraine patients (20 females) and 38 healthy subjects (20 females). Using graph theory analysis, network properties such as small-worldness, network resilience, nodal centrality, and interregional connections were compared between these groups. The study revealed that there were more alterations of topological properties present in the brain functional networks of female migraineurs with more regions in the female migraineurs showing decreased nodal centrality (index for evaluating the importance of nodes within functional networks) and worse resilience which may reflect faulty communication within and between brain regions in female migraineurs. One of the main resting-state brain functional networks is the default mode network (DMN) [46] that is a neural network that is the most active at rest but deactivated when the brain is actively involved in external attention demanding goal-directed tasks. Default mode network includes precuneus, posterior cingulate, medial prefrontal, medial temporal lobe, and angular gyrus [47]. While the influence of hormonal fluctuations on the dysfunctional organization of RSNs in women with migraine needs to yet be studied, other studies in healthy women have shown that the resting-state functional intrinsic connectivity between the DMN and the executive control network (ECN) is modulated by the phase of the menstrual cycle (i.e., follicular vs. luteal) and also by the usage of oral contraceptive pills especially in the anterior cingulate cortex [48].

A more recent neuroimaging study [49] also using graph theory and a precise parcellation atlas of the brain (Brainnetome atlas [50]) to examine the topological organization of the functional networks of resting-state brain functional networks in 29 female migraineurs without aura and 29 female age-matched healthy controls has further revealed widespread disrupted functional connectivity in female migraineurs. In particular, the posterior insula exhibited decreased nodal centrality, smaller volume, and disrupted connectivity with many other brain areas in female migraineurs compared to healthy women. The study showed that the disrupted connections primarily involved subregions of the brain involved in the discrimination of

sensory features of pain, pain modulation or processing, and sensory integration processing (Fig. 8.3).

These studies suggest that functional networks of the female brain may be more vulnerable to dysfunctional organization [51]. This notion is further supported by another recent analysis of resting-state connectivity in 29 women with chronic migraine compared to 19 age- and sex-matched controls [52]. The findings revealed significant decrease in the resting functional connectivity of three major intrinsic brain networks in women with chronic migraine. These networks include the default mode network, salience network, and central executive network. Reduced connectivity in salience and executive networks was also associated with higher frequency of migraine attacks in these patients.

There are also sex-related differences in the incidence of brain white matter abnormalities in migraine patients. These abnormalities, which appear as small regions of high intensity on MRI images, are more prevalent in migraineurs than the general population [53]. Among women, deep white matter hyperintensity volume as well as the incidence of progression is greater in migraineurs than their matched healthy controls [53] which may reflect potential differences in the inflammatory markers in female vs. male migraineurs or, alternatively, sex differences in the sensitivity or the brain region-specific expression of the inflammatory marker receptors in the brain of female migraineurs or the modulatory effect of hormones on the inflammatory markers.

Finally, most recent advances in the field of migraine research have provided strong evidence for a link between the hypothalamus and migraine [54]. Research has suggested a main central role for the hypothalamus and its ascending and descending connections to pain-processing structures in the brain in the pathophysiology of migraine [42, 55] and the premonitory symptoms of a migraine attack that are mainly of hypothalamic origin. Recent positron emission tomography (PET)

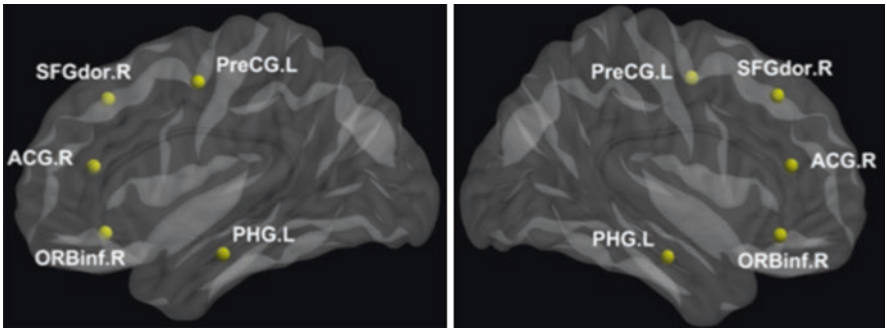

Fig. 8.3 Significant sex-related resting network differences. Comparing the brain's resting functional networks between migraineurs and healthy subjects revealed prominent nodal centrality differences in the precentral gyrus (PreCG), dorsolateral superior frontal gyrus (SFGdor), orbital inferior frontal gyrus (ORBinf), anterior cingulate gyrus (ACG), and parahippocampal gyrus (PHG) that showed interaction between sex (male vs. female) and disease state (patients vs. controls). Adapted from Liu et al. [51]

studies on patients during a migraine attack have further emphasized a pivotal role for hypothalamus in migraine onset and pathology [42, 55]. The hypothalamus is involved in the maintenance of the homeostasis in the body that is mediated by autonomic system signaling and through endocrine signals to the hypothalamus–pituitary–gonadal (HPG) and the hypothalamus–pituitary–adrenal axis. Given that the hypothalamus is part of the HPG axis, which is a central control and regulatory system that connects the central nervous system (CNS) with the reproductive hormonal system, and the important role that the ovarian steroid cycling has on the biological mechanisms of migraine, it is likely that some sex-related differences in migraine may have hypothalamic origin. Although this link has to be yet determined through more studies, there may be sex-related differences in hormonal abnormalities or in their modulatory effects on brain activity. For instance, a recent study of 119 migraine patients [56] showed that male migraineurs have lower progesterone levels compared to healthy males, whereas female migraineurs have lower follicular phase testosterone levels and lower luteal phase estrogen and testosterone levels compared to healthy females. Higher prevalence of depression and anxiety [57, 58] in female migraineurs may further implicate a role for hypothalamus in mediating sex-related differences in migraine.

There are multiple unmet needs in neuroimaging study of sex-related differences in migraine. To date, all of the studies on sex-related differences in migraine been have been done interictally and have focused on abnormalities in the brain outside of an attack; studies during the ictal phase with a naturally occurring or an invoked attack are still lacking. Moreover, all studies to date have relied on blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) to study the functional activity and connectivity of the migraine brain. BOLD-fMRI is a hemodynamic-based approach that, because of the coupling between the neuronal activity and the changes in the blood flow, can serve as a proxy for functional activity. However, functional activity in the brain is associated with electromagnetic and metabolic changes, in addition to hemodynamic changes. Therefore, while BOLD-fMRI is a strong technique, it lacks the excellent temporal resolution of the methods that rely on changes in the electrical potentials and magnetic field in the brain such as electroencephalography (EEG) and magnetoencephalography (MEG). Incorporating EEG and MEG in assessing sex-related differences may reveal additional insights into the pathophysiology of the disease. There are other unexplored neuroimaging areas in studying the sex-related differences in migraine such as magnetic resonance spectroscopy or positron emission tomography that are sensitive to metabolic changes with the latter also allowing tracking of various distinctively labeled cell types or receptors. For instance, using magnetic resonance spectroscopy on a high-power scanner (7 T), a recent study [59] has revealed higher glutamate levels in the visual cortex of migraine patients without aura providing more evidence for a pathophysiological link between glutamate and migraine via its neuroexcitatory effects, or its role in energy metabolism, or both.

Finally, it should be noted that one major limitation in neuroimaging studies in migraine is that female patients have dominated the majority of studies and there is a need for more studies in men. This is particularly important because basic science

studies mostly solely include male animals. Overall, in order to allow a better translation between basic science research and studies in human, particularly neuroimaging studies in humans, paying attention to sex-related differences in both the design and interpretation of the findings is a must. Indeed, neuroimaging studies on sex-related differences in migraine seem to confirm differences in the brains of men and women who suffer from migraine. The differences seem to involve both the structure of the brain and the functional activity and connectivity of the brain.

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