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Review

Sex and the migraine brain

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ABSTRACT

The brain responds differently to environmental and internal signals that relate to the stage of development of neural systems. While genetic and epigenetic factors contribute to a premorbid state, hormonal fluctuations in women may alter the set point of migraine. The cyclic surges of gonadal hormones may directly alter neuronal, glial and astrocyte function throughout the brain. Estrogen is mainly excitatory and progesterone inhibitory on brain neuronal systems. These changes contribute to the allostatic load of the migraine condition that most notably starts at puberty in girls.

Contents

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Introduction

Brain plasticity, influenced by genetic, epigenetic and environmental factors, refers to the ability of the brain to adapt to altering levels of neural signals, inflammatory molecules, drugs and hormones. Hypothalamic hormones, affecting neural network functioning and 'stability', have significant effects on migraine. We attempt to integrate brain systems neuroscience with endocrine regulation through the hypothalamus that drives hormonal, sex and gender differentiation of migraine by focusing on the following topics: (1) Phenotypic expression by physiological modulators in the developing migraine brain where we summarize the evolution of migraine from children to adults, with an emphasis on puberty in girls; (2) Sex hormones and brain function where we review the widespread expression of estrogen and estrogen receptors across the brain providing a target for estrogen mediated changes on brain function and behavior; (3) Sex and brain-related changes in migraine where we summarize morphometric and functional changes in women vs. men; (4) Hypothalamic role in hormonal regulation of brain dysmetria in migraine where we highlight the role of the hypothalamus as a center for the control of gonadotropin release and autonomic function that are critical in migraine related changes in patients; (5) Hormonal systems modulate the "set point" for migraine attacks where we cover the multiple processes (e.g., cortical spreading depression, sleep, etc.) that are affected by hormones that may alter the threshold for migraine attacks; (6) Hormonal allostatic load in migraine where we discuss the idea that repeated migraines contribute to a feed-forward maladaptive allostatic cascade on brain function; and (7) Future directions where we provide suggestions for future research studies needed to investigate hormonal effects on migraine.

Phenotypic expression by physiological modulators in the developing migraine brain

With age, brain networks extend the scope of their anatomical interactions and functional integration (Fair et al., 2009; Wu et al., 2012). This developmental change in functional connectivity, reflected by underlying structural gray and white matter changes (Fair et al., 2009; Power et al., 2010), are thought to involve segregation of local regions and integration of distant regions into disparate sub-networks (Vogel et al., 2010). These changes are functionally important as the nervous system may respond differently to external stimuli and/or disease (e.g., migraine), depending on brain maturation. The phenotypical expression of migraine in young children is different from pre- and post-pubertal children and adults. The prevalence of migraine changes with age (Merikangas, 2013; Stewart et al., 1994), with significant increases at puberty in girls and decreases in post-menopausal women (Fig. 1).

In infants, when networks that define resting state are still developing (Fransson et al., 2007; Smyser et al., 2011), migraine could be associated with infantile colic, facial pallor, irritability, sleep disturbance or mood changes (Romanello et al., 2013). Since anti-migraine treatment may improve infantile colic (Katerji and Painter, 1994), it is often referred to as 'abdominal migraine' and as such may be considered as behavioral representation of the level of brain development (i.e., a correlation of networks that may define the behavioral phenotype). Along this line, functional connectivity in the cortex of infants showed thalamocortical connections that may underlie the unusual presentation of what is believed to be migraine in very young children (Fransson et al., 2011, 2013; Hagmann et al., 2012; Hartley and Slater, 2013; Omidvarnia et al., 2013; Sakatani et al., 1999).

In prepubertal children, migraine occurs in 3–10% (Barnes, 2011) with no difference between boys and girls (Goldstein and Chen, 1982; Waters and O'Connor, 1971). In this age group, periodic symptoms such as benign paroxysmal torticollis, benign paroxysmal vertigo, abdominal migraine, and cyclic vomiting syndrome become more frequent (Arruda et al., 2010; Cuvellier and Lepine, 2010; Winner, 2013), potentially due to more mature brainstem effectors. In contrast, in post-pubertal children, the hypothalamus is thought to reset its hormonal (e.g., gonadotropin releasing hormone) and neural (e.g., autonomic) systems (Fig. 2), which in turn may make females more susceptible to migraine (Alstadhaug, 2009; Facchinetti et al., 2000). Puberty-related changes in brain function are not restricted to the hypothalamus (Blakemore et al., 2010). Puberty, which begins between the ages of 8–14 years in girls and 9–15 years in boys, is associated with pulsatile release of gonadotropin releasing hormone (GnRH) from the hypothalamus, and peak cortical gray matter (Giedd

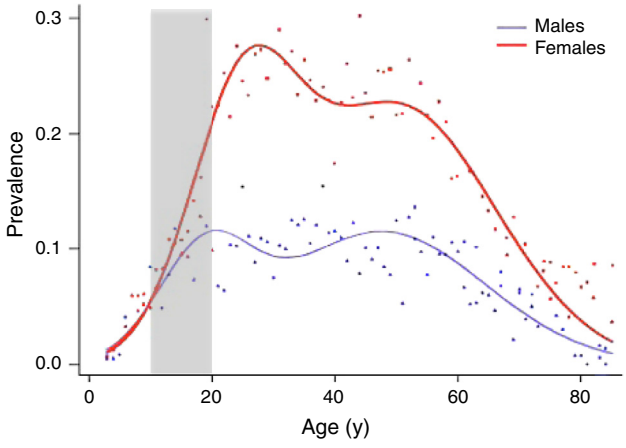

Fig. 1. Sex and age in migraine. Migraine prevalence (adapted from Fuente-Martin et al., 2013 with permission): Prevalence measured over a 1-year period of self-reported and physician-diagnosed migraines. The prevalence in boys and girls is similar until puberty (approx. 10–11 yrs. of age) after which it diverges between the sexes with age. The prevalence is ~6% in men and 15–17% in women (Stewart et al., 1994). Note that the rate of increased prevalence shoots up in the teenage years and appears to decrease some years after menopause. The prevalence is in line with other reported data in children and adults (Bigal et al., 2007; Peterlin et al., 2010). A comprehensive report on the prevalence in children has been reported (Bigal et al., 2007) with one group of children aged 3–11 yrs. reported (Verrotti et al., 2012).

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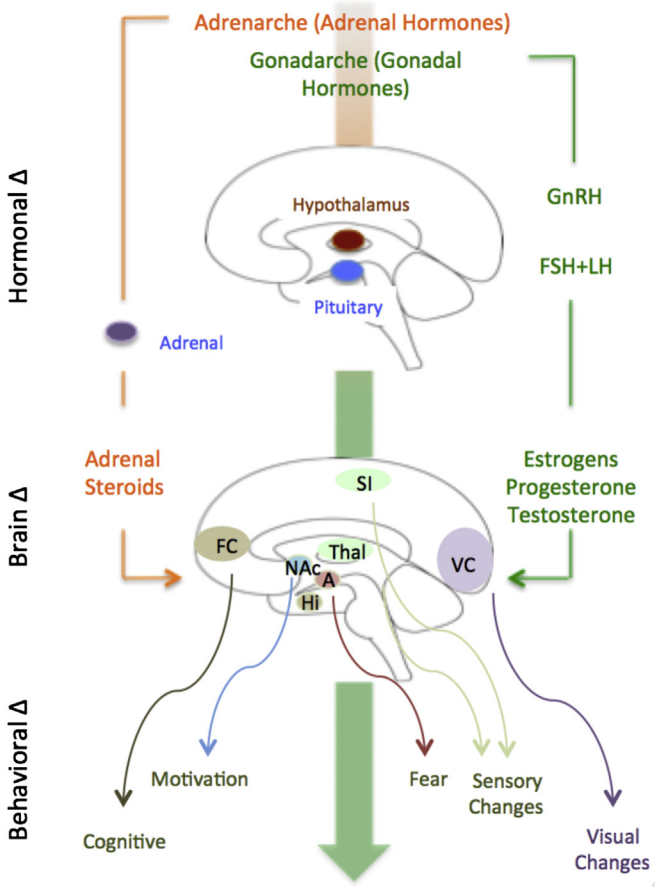

Fig. 2. Hormonal changes with puberty drives alterations in brain networks (see (Blakemore et al., 2010)). The two main hormonal systems that become active at puberty: (1) Gonadotrophic-hypothalamic-pituitary-gonadal axis: (shown on the right) that is initiated by pulsatile release of gonadotropin-releasing hormone (GnRH) in the hypothalamus and release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the pituitary. Subsequent release of gonadal (testes or ovaries) sex steroid hormones (estrogen, progesterone, or testosterone) has direct effects on neurons and consequently neuronal networks. (2) Hypothalamic-pituitary-adrenal axis: (shown on the left). This axis is the primary circuit that initiates, regulates, and terminates a stress response.

et al., 1999) and white matter (Barnea-Goraly et al., 2005) volume. In the context of migraine, there are ample examples of sex differences in brain structure (Herting et al., 2012; Ladouceur et al., 2012; Peper et al., 2011) and brain function, such as default mode brain connectivity, language, and visual systems (Sprenger and Borsook, 2012; Wu et al., 2013) (see Figs. 3A–D).

In the adult brain, women are more affected by migraine than men, and neuroendocrine drivers are thought to act as major modulators (Nappi and Nappi, 2012). In the 2011 National Health Interview Survey, 16.6% of adults >18 years reported having migraine or other severe headaches in the last 3 months, and the prevalence was shown to be highest in females 18–44 years and lowest in males >75 years (Smitherman et al., 2013). Fig. 4 illustrates the relationship to migraine frequency/prevalence, hormonal changes (hypothalamic, pituitary and gonadal) and brain changes across the menstrual cycle. Brain imaging studies have shown significant differences in gray and white matter, resting state functional connectivity, task-related neural activity, and brain chemistry between females and males (Allen et al., 2011; Liu et al., 2003; Peper et al., 2011; Sacher et al., 2013; Zuo et al., 2010). Intriguingly, there is also evidence of brain alterations across the menstrual cycle in females. For example, gray matter volume peaks were found during ovulation compared to follicular and luteal cycle phases (Hagemann et al., 2011). Other findings suggest gray matter and white matter fluctuations in brain regions related to emotion and cognition (De Bondt et al., 2013a,2013b; Ossewaarde et al., 2013) across the menstrual cycle phase. Additional evidence for the influence of sex steroid hormones on brain structure emerges from studies that have shown that women using a hormonal birth control method have greater gray matter volumes in prefrontal cortices, pre- and post-central gyri, parahippocampal/fusiform gyri, and temporal regions as compared to naturally cycling women (Pletzer et al., 2010).

Box 1: Gender and sex definitions

When discussing differences between men and women, terminology is important. Here, we use the term "sex" in reference to the biologically based differences, whereas the term "gender" refers to socially based phenomena. Biological sex exerts a major influence on one's gender identity, but the terms are not interchangeable. As discussed more extensively by Greenspan et al. (2007): *"… in any statistical analysis of human subjects, the dichotomous variable sex (male vs. female) is confounded with the social construct of gender. That is, in human studies in which the dependent measure is pain report, group differences are likely to be attributable to both sex and gender. Therefore, both constructs should be examined when possible in order to understand their relative contribution to differences in pain between men and women."*

Furthermore, there is evidence in healthy female volunteers that pain intensity, pain unpleasantness, and functional brain activity in response to noxious stimuli fluctuate over the course of the menstrual cycle (Choi et al., 2006; de Leeuw et al., 2006; Veldhuijzen et al., 2013), which likely contributes to the allostatic load (Borsook et al., 2012) and thus the increased susceptibility to migraine attacks may be related to migraine prevalence changes observed in women (Borsook and Burstein, 2012; MacGregor and Hackshaw, 2004; Stewart et al., 2000). With increasing age, changes in the neuroendocrine axis resulting from a loss of ovarian function leads to initial cycle deregulation, and, eventually, to the post-menopause state (Hall, 2007). Migraine usually improves in post-menopausal women (Neri et al., 1993), which is potentially due to low estrogen and high follicle-stimulating hormone (FSH) levels (Wang et al., 2003).

Sex hormones and brain function

Sex hormones (estrogen, progesterone or testosterone) alter brain function. Estrogens can modulate neuronal activity electrophysiologically and morphologically, potentially through estrogen receptors that are widely distributed throughout the brain, with high concentrations in the hypothalamus (Laflamme et al., 1998) (see Fig. 4). Examples of alterations in morphology include changes of hippocampal spines (Kato et al., 2013; Mukai et al., 2007; Ooishi et al., 2012) and their related circuits (Cyr et al., 2002). Estradiol biosynthesis takes place in neurons throughout the brain (viz., hypothalamus, basal forebrain, cerebral cortex, hippocampus, thalamus, cerebellum, and brainstem) and is catalyzed by the enzyme aromatase, which is also implicated in estrogen synthesis (Biegon et al., 2010). Importantly, many of the brain areas associated with estradiol biosynthesis are involved in migraine (Burstein et al., 2010; Maleki et al., 2012a, 2013; Moulton et al., 2008). Positron emission tomography (PET) approaches have been used to measure estrogen (via the aromatase inhibitor [11C]vorozole) in human subjects (Lidstrom et al., 1998). Of note, vorozole binding levels are high in (Wu et al., 2012) the pulvinar thalamus, a region implicated in increased sensory sensitivity to stimuli in migraine (Burstein et al., 2010), (Fair et al., 2009) the nucleus accumbens, an area involved in reward and aversion (Carlezon and Thomas, 2009; Volman et al., 2013), and (Power et al., 2010) the amygdala, a region involved in fear and anxiety (Talarovicova et al., 2007). Thus, estrogen may

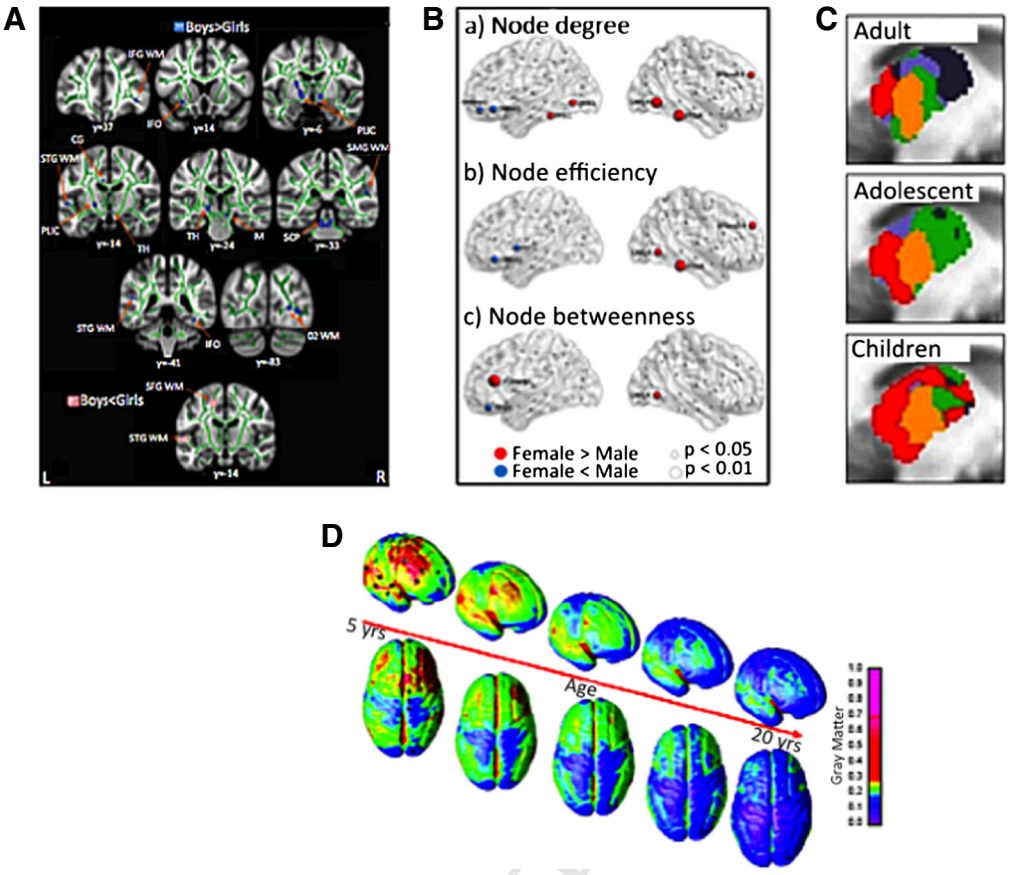

Fig. 3. Examples of sex and age differences in brain organization in children vs. adults. A: Sex differences in white matter changes: (from Herting et al., 2012 with permission). The figure shows differences in fractional anisotropy (FA) and MD controlling for age in girls and boys. Blue = FA b > g in a number of areas including PLIC — posterior limb of the internal capsule; SCP — superior cerebellar peduncle; IFO — inferior fronto-occipital fasciculus; and Pink = MD b < g in the SFG — superior frontal gyrus; STG — superior temporal gyrus; Green = mean FA skeleton. B: Effect of sex on nodal connectivity: The sex-related differences were seen predominantly in regions involved in the default mode network, language, and visual systems (from Wu et al., 2013 with permission). C: Thalamic functional organization with age: The figure shows thalamic functional organization differences in children, adolescents, and adults. For example, in children and adolescents, thalamo-temporal interactions involve a greater proportion of the anterior and middle thalamus (red) with frontal interactions involving less of the anterior thalamus. In contrast, thalamo-frontal interactions (blue) become more connected later in life. Somatosensory functional organization is shown in orange and remains relatively stable (from McEwen, 2000 with permission). D: Gray matter changes in children and young adults: LTP-like and LTD-like plasticity were large in young subjects but substantially smaller in elderly subjects (McEwen, 2002), suggesting that younger brains are more susceptible to migraine (from Calhoun and Ford, 2008 with permission).

modulate these brain areas, potentially contributing to migraine related behaviors of allodynia, mood changes, and dietary cravings. Intriguingly, some of these brain structures (e.g., the amygdala) show changes across the menstrual cycle, specifically, an increase in gray matter volume in the dorsal part of the left amygdala during the premenstrual phase compared with the late follicular phase (Ossewaarde et al., 2013). In

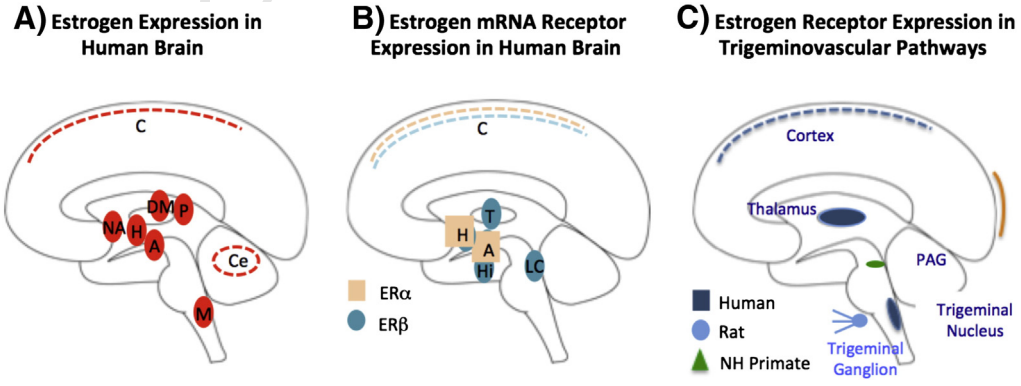

Fig. 4. Estrogen, estrogen receptors in the brain and in the trigemino-vascular system. A: Estrogen expression in the human brain: Areas noted in solid red are those expressing high levels of aromatase (the precursor for estrogen) based on in-vivo PET imaging using an estrogen specific ligand [N-methyl-11C] voroxole (Biegon et al., 2010). Key: A = amygdala; C = cortex; Ce = cerebellum; H = hypothalamus; DM = dorsomedial nucleus of the thalamus; NA = nucleus accumbens; P = pulvinar. B: Estrogen mRNA expression in the human brain: (Cseh et al., 2013). Some brain areas have high expression of the alpha (ERα) subunit (H = hypothalamus and A = amygdala), others have high expression of the beta (ERβ) subunit (T = thalamus, Hi = hippocampus, and LC = locus ceruleus), while areas such as the cortex have a lower expression of both subunits. C: Estrogen receptor expression in sensory pain pathways: The trigeminal nucleus and thalamus contain high estrogen receptor levels in humans (Cseh et al., 2013), in the trigeminal ganglion in rats (Guzel et al., 2013) and in the periaqueductal gray (PAG) in non-human primates (Oikari et al., 2013). It is postulated that estrogen and estrogen receptors in the sensory pathways may alter sensitivity to nociception in these neurons (Greco et al., 2013).

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addition, increases in the hippocampal volume and decreases in the dorsal basal ganglia volume have been observed in the post-menstrual phase (Protopopescu et al., 2008). Taken together, gonadal hormonal feedback to the hypothalamus and other brain regions (Gillies and McArthur, 2010; McEwen et al., 2012) has significant impact on behaviors or neurological adaptations through specific neurotransmitters (Fink et al., 1996; Scharfman and MacLusky, 2008). One such system is the serotoninergic system (Hamel, 2007). Serotonin-producing neurons are found in the mid- and hindbrain regions, and project to forebrain, limbic, diencephalic (rostral 5-HT nuclei), and the spinal cord (caudal 5-HT nuclei) (Bethea et al., 2002), all of which contain both estrogen and progesterone receptors. Thus, aside from changes that may influence migraine circuits per se, estrogen–5-HT interactions may influence behaviors including mood (Amin et al., 2005; Rubinow et al., 1998).

However, the influence of sex hormones on brain function is not limited to estrogen. Progesterone also has "*multiple non-reproductive functions in the central nervous system to regulate cognition, mood, inflammation, mitochondrial function, neurogenesis and regeneration, myelination, and recovery from traumatic brain injury*" (Brinton et al., 2008). Similarly to estrogen, progesterone has effects on diverse brain systems beyond the hypothalamus and research data supports that estrogen and progesterone have opposite effects on neuronal excitability (Finocchi and Ferrari, 2011). For example, neuronal activity during seizures is amplified by estrogen, whereas progesterone and its metabolites have anticonvulsant effects (Beyenburg et al., 2001). Thus, sex steroids may contribute to functional processing (including state of excitability) in the brain by acting through steroid receptors, which are dispersed throughout the brain (Joels, 1997).

Clinical observations suggest that testosterone may also play a role in migraine. First, it has been demonstrated that testosterone and its synthetic derivatives may improve migraine in both men and women (Calton and Burnett, 1984; Lichten et al., 1991). Second, it has been shown that males treated with gonadotropins for infertility experienced a marked improvement in migraine and migraine with aura attacks (Arango et al., 1996). Mechanistically, this finding may be related to the suppression of cortical spreading depression (CSD) by androgens in mice (Eikermann-Haerter et al., 2009).

Sex and brain-related changes in migraine

Brain alterations in migraineurs compared to healthy individuals have repeatedly been reported (Liu et al., 2013; Maleki et al., 2012a, 2013; Palm-Meinders et al., 2012; Valfre et al., 2008; Xue et al., 2013). Our group has previously shown prominent differences in brain structure and function of migraineurs compared to healthy controls, including the provocative finding that female migraineurs exhibit alterations in the precuneus and insula compared to male migraineurs (Guidetti et al., 2012; Maleki et al., 2012b) (see Fig. 5). With the knowledge that gonadal hormones are capable of altering brain circuits that regulate emotions in humans (van Wingen et al., 2011), we found that responses to noxious heat stimuli are distinctly segregated in men and women migraineurs and, therefore, proposed that this segregation is due to enhanced activation of the so-called 'emotional circuits' in women (Maleki et al., 2012b). This study suggests that the female brain is differentially affected by the disease state, with sex steroids as the prominent modulators (see Fig. 6).

Hypothalamic role in hormonal regulation of brain dysmetria in migraine

As noted by Facchinetti and colleagues, there is "*Hypothalamic resetting at puberty and the sexual dimorphism of migraine*" (Facchinetti et al., 2000). Prior to puberty there are no sex differences in the occurrence of migraine (Mavromichalis et al., 1999). After the onset of the menarche, however, the prevalence of migraine is higher in girls than in boys and appears to be associated with the menstrual cycle in nearly 50% of attacks (Brandes, 2006; Karli et al., 2012). Aside from clear-cut menstrual migraine, fluctuations in estrogen and other hypothalamic hormones may contribute to a lowered threshold for migraine susceptibility through the menstrual cycle; a concept supported by the observation that mean plasma estrogen and progesterone levels are significantly higher in migraine patients for most of the menstrual cycle compared to controls, with the biggest differences found in the late luteal phase (Epstein et al., 1975). Mechanistically, the increased prevalence of migraine at puberty may be driven by resetting of hypothalamic neuroendocrine circuits that determine sexual dimorphism (Facchinetti et al., 2000). In the context of migraine, resetting of hypothalamic hormones can also alter the trigeminovascular system; the main neural pathway involved in migraine (Pietrobon and Moskowitz, 2013). Possible mechanisms include enhanced excitability and sensitization of neurons through estrogen-driven mismatch in homeostatic gene regulation and the resultant mitogen-activated membrane hyperexcitability (Welch et al., 2006). A meta-analysis of estrogen polymorphism studies indicates that two variants, ESR-1 594G>A and 325C>G, increase the risk for migraine 40–60% (Schurks et al., 2010). Challenging that study, however, recent evidence indicates that aromatase polymorphisms (CYP19A1 rs10046 and CYP19A1 rs4646) also confer a risk for migraine and its protective effect, respectively, and may be more significant than estrogen polymorphisms (Ghosh et al., 2012). The latter hypothesis is supported by a twin study indicating that environmental and genetic factors have comparable contributions to migraine (Gervil et al., 1999).

Hypothalamus, gender, and migraine

A large number of studies suggest that altered sex hormones cause structural instability and hypothalamic dysfunction (Baroncini et al., 2010) that appear as abnormal activation during migraine (Alstadhaug, 2009; Denuelle et al., 2007; Geraud and Donnet, 2013). Such dysfunction may explain the link between migraine and hypothalamic-regulated circadian rhythms, such as time-keeping, gonadal hormones, and cortisol secretion. Furthermore, homosexual men have a higher incidence of migraine (7.2 vs. 15.5%) (Cochran and Mays, 2007), lower testosterone levels (Loraine et al., 1970), increased suprachiasmatic nucleus volume (Swaab and Hofman, 1990), and decreased interstitial nucleus volume of the anterior hypothalamus number 3 (INAH3) compared to heterosexual men, but volumetric similarities (in the different hypothalamic nuclei) with women (LeVay, 1991).

Gonadotropin releasing hormone

GnRH is secreted in a pulsatile fashion from the hypothalamus (Smith, 2013), initiating a cascade of events that may affect brain function (Fig. 7). The pattern of GnRH release changes markedly at puberty, with significant physiologic changes in brain and body in girls and boys. Prior to puberty, secretion of leptin and kisspeptin evokes the release of GnRH in limited amounts. During mid-puberty, GnRH is available in low/minimal amounts during the day and higher levels at night, and continues to increase in late puberty, prior to the classic levels observed at the end of puberty (post-menarche). In the latter, the baseline shows a large pulse at the time of ovulation after which the range of release remains larger during the luteal phase compared to the follicular phase (Marshall and Eagleson, 1999). Estrogen negatively regulates tonic GnRH synthesis except at the time of the preovulatory surge in GnRH through receptors on GnRH cells. In accordance with previous evidence linking estrogen to migraines (MacGregor et al., 2006), these changes in estrogen could be related to the increase in migraine prevalence in relation with puberty and ovulation.

GnRH controls the release of hormonal waves (estradiol peaks in the late follicular phase; progesterone peaks in the mid-luteal phase) through increases in luteinizing hormone (LH) and FSH in the mid-

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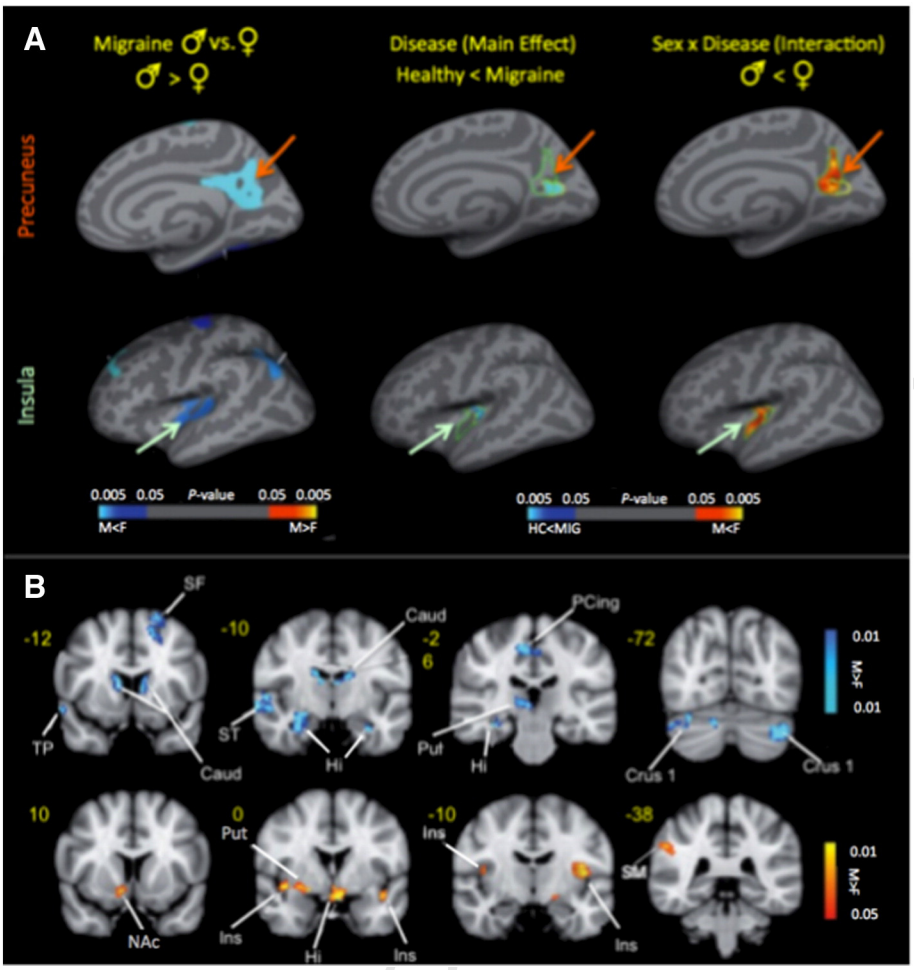

Fig. 5. Alterations in brain sex and migraine. A: Cortical thickness changes: (Right) Significant clusters from vertex-wise cortical thickness comparisons conducted on female versus male healthy subjects (*left* column) and female versus male migraine patients (*right* column). Blue–light blue colors represent areas with thicker cortex in female versus male and red–yellow colors represent areas with thicker cortex in male versus male in each of the cohorts. (Middle and left) Significant clusters from vertex-wise cortical thickness comparisons conducted on all of the subjects (migraine male and female and healthy control male and female) to determine the main effect (disease) effect and interaction effect (sex × disease). The disease effect (blue–light blue color map) and sex × disease interaction (red–yellow color map) are shown for (A) insula and (B) precuneus. B: Effect of pain across sex: Contrast analysis of the male versus female migraine group in response to the pain threshold +1 °C stimuli. Women had significantly ($P < 0.05$, corrected) greater activation in regions associated with emotional processing compared to men. Key: Caud = caudate; F = female; Hipp = hippocampus; Hypoth = hypothalamus; Ins = insula; L = left; M = male; NAc = nucleus accumbens; PCing = posterior cingulate; Pulv = pulvinar; Put = putamen; R = right; SF = superior frontal; SM = somatosensory cortex; ST = superior temporal (adapted from Maleki et al., 2012b with permission).

cycle (around day 14) (see Fig. 7). Sex hormones (estradiol and progesterone) and their releasing factors (FSH, LH) decrease to basal levels around day 28 with baseline (flat) levels for estrogen and progesterone observed in the first 7 days for estrogen and 14 days for progesterone that all contribute to a hormonal 'dysequilibrium'. Thus, the undulating changes in gonadal hormones in the mid-luteal phase may contribute to neuronal excitability around days 14 and 28 of the cycle. Specifically, there is an increase in excitability after the pre-ovulatory estrogen surge and during the mid-luteal rise in estrogen levels, coincidentally when migraine risk appears to increase (Scharfman and MacLusky, 2008).

Female sex hormones and the trigemino-vascular system

Sex steroid hormones such as estrogen are known to alter the responsiveness of the system at the level of the dura (Boes and Levy, 2012; Gupta et al., 2007), peripheral nerve (Rowan et al., 2010), trigeminal ganglion (Liverman et al., 2009; Yu et al., 2011), trigeminal nucleus (Amandusson and Blomqvist, 2010; Martin et al., 2007; Puri et al., 2011), thalamus (Reed et al., 2009), cortical systems (Eikermann-Haerter et al., 2007), and descending modulatory systems (Blurton-Jones et al., 1999). Estrogen receptors are located in the trigeminal nucleus in humans (Fenzi and Rizzzuto, 2011) and in the periaqueductal gray (a region involved in pain modulation) in rhesus monkeys, thus highlighting the importance of species-specific research in terms of understanding estrogen function in humans (Vanderhorst et al., 2009). Preclinical data also suggest that estrogens may be important in regulating sensitization of trigeminal neurons through modulation of mediators such as calcitonin gene-related peptide (Gupta et al., 2011) (see Fig. 4).

The complexity of the interaction of gonadal hormones and pain processing (Denuelle et al., 2007) is illustrated by studies that show that oscillations in hormonal levels during the 5 phases of the menstrual cycle (menstrual, follicular, ovulatory, luteal, and premenstrual) influence experimental sensitivity to thermal pain (Barbosa Mde et al., 2013) in healthy women (see Fig. 6) and to experimental muscle pain in women with dysmenorrhea (Iacovides et al., 2013). Other studies that show that changes in pressure, electrical, and cold pain thresholds, which occur over the menstrual cycle with higher thresholds to pressure and electrical pain stimuli on day 22 and to cold on day 14, are not correlated with changes in gonadal hormones (Teepker et al., 2010).

Positron emission tomography (PET) studies indicate that sex influences brain expression of dopamine (Laakso et al., 2002; Pohjalainen et al., 1998), serotonin (Parsey et al., 2002), neurokinin 1 (Engman

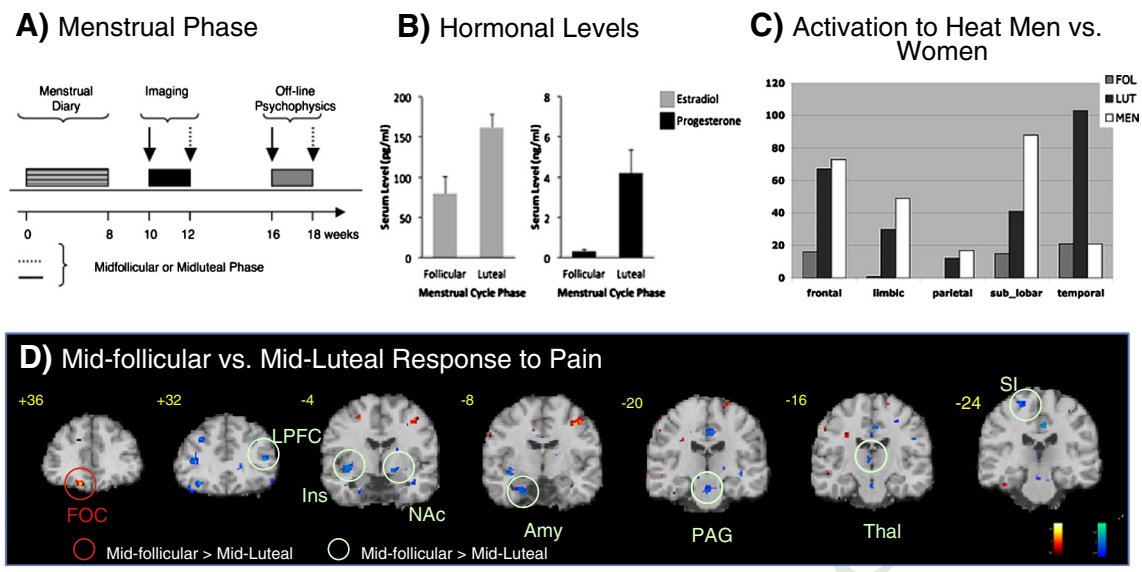

Fig. 6. Differential responses to heat pain across menstrual phase. A: Data collection: Ten men and 10 women were enrolled into the study. Using diaries, women provided a 3-month history of their menstrual cycle. Five women were scanned in the mid follicular phase first and 5 in their mid-luteal phase first. B: Hormonal levels: Serum levels were obtained form estradiol and progesterone during both phases of their cycles (i.e., follicular and luteal) at the time of scanning. C: Differences in regions in men and women: The histograms show volume of activation for women (mid-follicular — gray; mid-luteal — black;) and men (white). Note that activation volumes (in response to a 46 °C stimulus to the arm) were similar for men and mid-luteal women in all areas except the temporal. D: Differences between mid-luteal and mid-follicular women: Significant activations are noted in the statistical maps overlaid on coronal images. In the mid-follicular phase (shown in red), women had greater activations in the Gob compared to the mid-luteal phase. In the mid-luteal phase (shown in green), women had greater activations in the LPF, Ins, NAc, Amy, PAG, Thal, and S1 compared to the mid-follicular phase (from P.A.I.N. Group, unpublished observations). Key: FOC = frontal orbital cortex; LPF = lateral prefrontal cortex; Ins = insula; NAc = nucleus accumbens; Amy = amygdala; PAG = periaqueductal gray; Thal = thalamus; S1 = primary somatosensory cortex; PAG = periaqueductal gray; Thal = thalamus; S1 = primary somatosensory cortex.

et al., 2012; Nyman et al., 2007), and opioids (Zubieta et al., 1999). Autoradiography studies in rodents further indicate sex differences in AMPA, kainate, and NMDA (Palomero-Gallagher et al., 2003) as well as noradrenergic transmission (Johnson et al., 1988). Moreover, these systems interact with the estradiol cycle, providing a neurochemical milieu that women may be more susceptible to migraine attacks. Furthermore, female rats are reportedly more sensitive to orofacial pain compared to male rats (but not in non-facial regions) (Dominguez et al., 2009). Accordingly, these findings highlight the importance of sexual dimorphisms in brain neuropeptides and innervation that may be relevant for migraine pain.

Hormonal systems modulate the "set point" for migraine attacks

A set point is defined as the point at which a variable physiological state (e.g., body temperature or weight) tends to stabilize. As migraine depends on a number of conditions, including environmental (e.g., barometric changes), genetic, and physiological factors, the susceptibility of an actual migraine attack may be determined by the relative functional status of each system. We have previously suggested that initiation of migraine is determined by elements such as CSD, oscillatory susceptibility, and insufficient modulation of nociceptive inputs by the periaqueductal gray, and/or vascular drives (Borsook et al., 2012; Maleki et al., 2012c). Specifically, we propose that, in the susceptible subject, the onset of migraine must coincide with a point in the cyclic rhythmicity of brainstem activity that is intended to maintain homeostasis. In the context of this article, we propose that the hypothalamus may also be involved in defining a 'migraine set point' through its ability to modulate spontaneous and evoked activities in trigeminal nucleus neurons (Robert et al., 2013) (see Fig. 8). Dynamic changes of hypothalamic, pituitary, and gonadal hormones may alter brain function at a cellular (e.g., receptor), anatomical (e.g., dendritic spine growth and/or hydration status (Streitburger et al., 2012)), and functional (e.g., neural circuit) level (see Fig. 8). Table 1 summarizes set point perturbators thought to contribute to altered stability of biological systems (allostasis) and derange networks in migraine-susceptible brains.

Estrogen

The correlation between migraine onset and falling estrogen levels during the menstrual cycle is seen in estrogen withdrawal (Somerville, 1975). In menstrual migraine falling levels of estrogen seem to correlate with migraine onset. Estrogen acts predominantly as excitatory on neuronal circuits and it seems therefore counterintuitive that estrogen withdrawal induces migraine. While the underlying mechanisms remain unknown it is possible that estrogen alters neuronal excitability (Kelly and Ronnekleiv, 2009) in brain regions implicated in migraine pathophysiology such as the hypothalamus (Lee et al., 2008) and hippocampus (Zadran et al., 2009). Estrogens are also present in brain modulatory systems such as the periaqueductal gray (Loyd and Murphy, 2008) and excitatory effects of estrogens are likely to act on GABAergic neurons that enhance PAG outputs. Accordingly, low estrogen levels may reduce activity in pathways that inhibit pain processing. Nevertheless, the relationship between estrogen withdrawal and migraine is clearly more complex since estrogen supplements do not always prevent menstrual migraine (Macgregor and Hackshaw, 2002).

Cortical spreading depression

CSD, a well defined process in migraine pathophysiology, is a slowly propagated wave of depolarization followed by suppression of brain activity (Charles and Baca, 2013). Two well-studied hormones that may influence CSD include testosterone (Eikermann-Haerter et al., 2009) and estrogen (Nagel-Leiby et al., 1990). Regarding testosterone, the susceptibility to CSD in a mouse model of familial hemiplegic migraine has been shown to be reversed by orchiectomy (Eikermann-Haerter et al., 2009). Regarding estrogen, it is interesting to note that menstrual migraines, coinciding with low levels of estrogen, are usually not preceded by aura (MacGregor, 2000), the clinical manifestation of CSD. This observation is supported by findings that show no difference

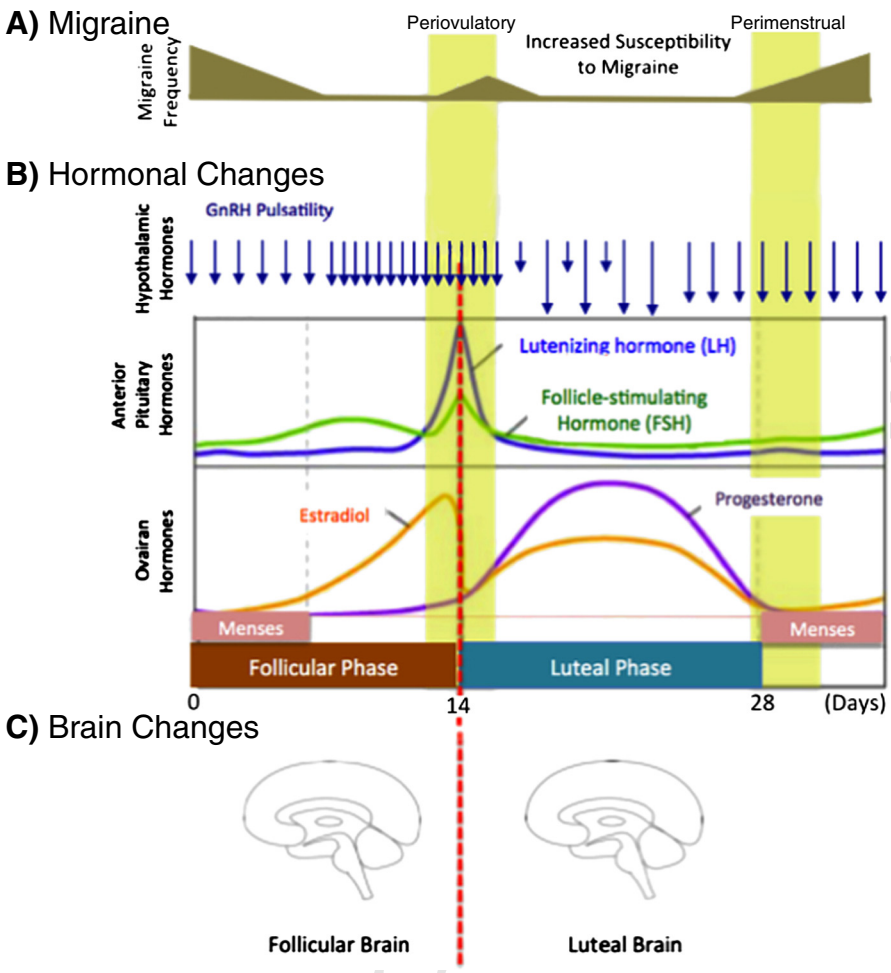

Fig. 7. Migraine Frequency, Hormones, and Brain Changes and Across the Menstrual Cycle. A: Incidence of Migraine across the Menstrual Cycle: More than 1/5 female migraineur aged 30–34 years have migraine in ≥50% of menstruations (Rumberg et al., 2010). Data suggest that migraine is most prevalent in the first few days at the onset of menses and the first few days at the beginning of the cycle (MacGregor et al., 2006). Falling levels of estrogen seem to contribute to migraine attacks and rising levels (perhaps associated with progesterone) protect from migraine attacks. Estrogen withdrawal is associated with increased migraine attacks (Mareckova et al., 2012). In addition, levels of estrogen and progesterone may be higher in migraine patients compared with controls (Epstein et al., 1975). Increased excitability of neurons (Scharfman and MacLusky, 2008) and migraine risk may occur during the menstrual cycle as a result of neuromodulation by factors such as BDNF (brain derived neurotropic factor) that is induced by estrogen. Progesterone is thought to decrease BDNF excitability. Note that the model correlates with migraine prevalence across the cycle. B: Hormonal changes across the cycle: GnRH pulsatility changes across the menstrual cycle. Estradiol and Progesterone variation is dependent on menstrual phase (Sisk and Zehr, 2005). C: Brain changes across the cycle: Behavioral changes across the menstrual cycle (reviewed in (Sisk and Foster, 2004)) are supported by imaging studies (191). Dramatic functional (192, 193) and morphological (e.g., increased amygdala volume in the luteal phase vs. follicular phase (Ossewaarde et al., 2013) or increased hippocampal and decreased in basal ganglia volume in the follicular phase (Protopopescu et al., 2008)) changes are observed across the menstrual phase.

Q3 Q2

in estradiol level in migraine patients with aura compared to migraine patients without aura (Nagel-Leiby et al., 1990).

Immunological/cytokine and other modulators of neuronal function

Given that the susceptibility to migraine is cyclical, one must take into consideration cyclical changes in both hormonal level and immune cell functions, such as, mast cells, cytokines, and microglia.

Mast cells

Meningeal mast cells (Metcalfe et al., 1997), which are rich in molecules that facilitate inflammation and activate pain fibers in the dura (e.g., histamine, serotonin, heparin) (Theoharides et al., 2005) (Levy et al., 2007), are stimulated by neuropeptides such as calcitonin gene-related peptide (CGRP), neurotensin (NT), pituitary adenylate cyclase activating peptide (PACAP), and substance P (SP). Once secreted, mast cell products can enter the central nervous system via transgranulation (Wilhelm et al., 2005) and affect brain areas such as the hippocampus (Nautiyal et al., 2012), a region first described by our group to be implicated in the migraine process (Maleki et al., 2013). Mast cells are also present in the thalamus and hypothalamus (Pang et al., 1996), providing access from the perivascular space into multiple brain regions. Mast cells also synthesize GnRH (Pang et al., 1996), a neuroendocrine hypothalamic hormone that regulates gonadotropin release in the pituitary and modulates neuronal activity in the central nervous system (Check, 2013; Gopinath et al., 2004).

Cytokines

Several lines of evidence support cytokines role in migraine: (a) migraine patients have higher serum IL-1beta and IL-6 levels, and lower IL-10 levels than healthy subjects (Uzar et al., 2011); (b) the trigeminal ganglia of a transgenic mouse model of familial hemiplegic migraine contains high levels of TNF-α, IL-1β, IL-6, and IL-10 (Franceschini et al., 2013); (c) menstruation is an inflammatory process (Evans and Salamonsen, 2012); and (d) increased levels of peripheral and central cytokines can alter neuronal activity in the central nervous system (Guyon et al., 2008) (Murray and Lynch, 1998; Nguyen et al., 1998).

Microglia

Brain microglia are involved in a number of functions including communication with astrocytes, neurons, endothelium, and leukocyte

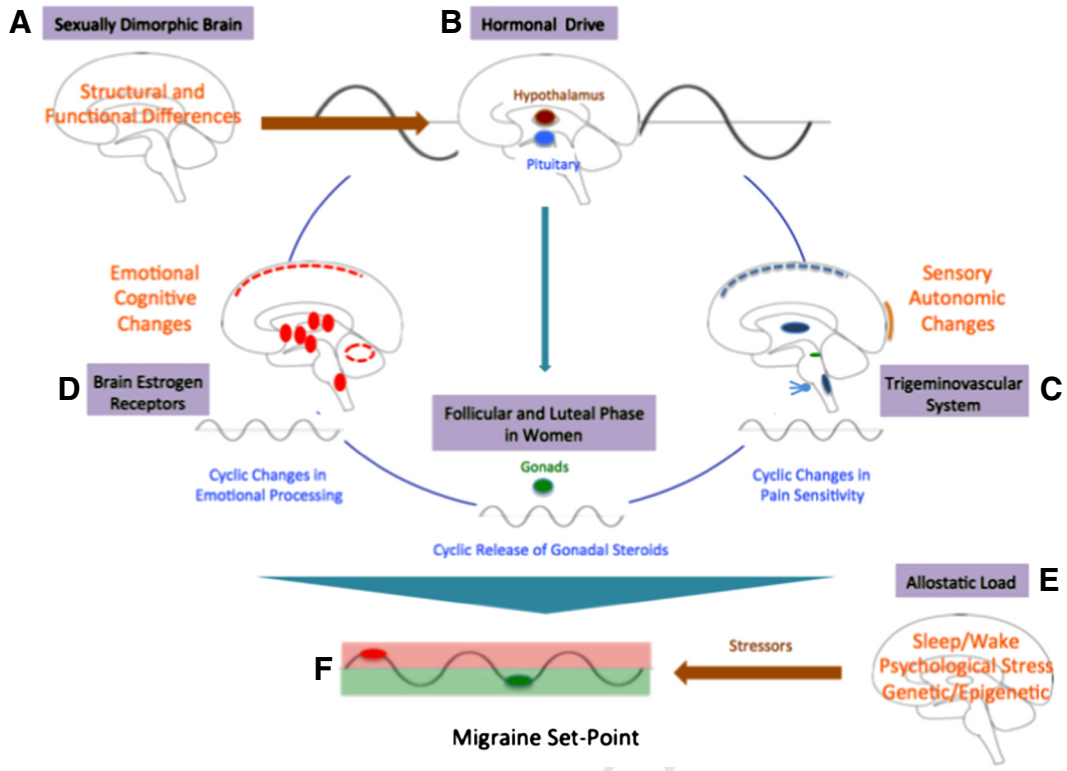

Fig. 8. Brain tone and migraine threshold: A model for hormonal stressors and migraine activation base on alterations in migraine "set point". A: Sexually dimorphic brain: Significant sex differences in brain structure have been reviewed elsewhere (194). Women have larger volumes in the frontal and paralimbic cortices; men in the hypothalamus and amygdala. B: Hormonal drive: In healthy women and men hormonal control is primarily through hypothalamic release of GnRH that drives the menstrual cycle through FSH and LH to release estrogen and progesterone in women. The cyclicity alters stability of neural systems (primarily sensory, emotional and cognitive — see below). C: Alterations in sensory and autonomic systems by estrogen: Pain thresholds alter over the menstrual cycle. Autonomic testing over the menstrual cycle has been reported to show differences across the menstrual cycle (195, 196). Sympathetic nervous activities are predominant in the luteal phase (197). Thus, cyclicity of physiological processes is also altered over the menstrual cycle. D: Alterations in emotional and cognitive systems by estrogen: Women have a higher prevalence of anxiety and depression that may relate to alterations or the integration of cognitive and emotional processes (191). E: Allostatic load: Allostatic load, internal and external (environmental) challenges or perturbations that result in an organism to respond to these challenges in order to maintain stability (allostasis). The burden of stress may lead to alterations in the brain and body and exacerbation of the disease state (198). Such changes (e.g., genetic constitution, sleep wake, diet, medications, psychological stressors) have also been considered to be important in the migraine state (Veldhuijzen et al., 2013). F: Migraine set point: In migraineurs, the state of brainstem tone may be unstable or less robust than in healthy individuals by prophylactic and may thus be susceptible to activation of the cascade of networks that trigger the migraine attack by normal afferent nociceptive signals (red dot), which would be inhibited in healthy individuals. Genetic, physiological, pharmacological, social, and other interactions define migraineurs' susceptibility. When processes are in synchrony (i.e., a harmonic or repetitive frequency), the model suggests that the migraine potential is sub-threshold (red circle); however, when these are altered either in magnitude, phase or duration, the system becomes unstable and the migraine threshold is exceeded (Borsook et al., 2012).

(Hanisch, 2002). In the context of migraine, brain microglia exhibit estrogen receptors (Mor et al., 1999), become activated during CSD, and release cytokines, which in turn can activate peripheral and central neurons (Grinberg et al., 2011).

Hormonally-mediated alterations in physiological parameters

Estrogens affect a number of physiological processes including the sleep–wake cycle, body temperature, and food intake.

Sleep–wake cycle

Insomnia is the most common sleep disorder in headache patients (Rains, 2008). Paradoxically, sleep frequently may stop migraine (Higashiyama et al., 1990). It has been suggested that sleep alterations are part of the migraine attack itself (Niederberger et al., 1998). In support of this hypothesis, under conditions that control for sleep/wake, light/dark, activity, position, and nutritional cues, there is no circadian rhythm of LH, FSH, or FAS in women during the early follicular phase (Klingman et al., 2011). However, recently, a gene mutation in casein kinase iδ has been linked to sleep (advanced sleep phase) and familial migraine disorders (Brennan et al., 2013), suggesting a potential link between sleep and hypothalamus that may lead to secondary effects of altered hormonal regulation.

Body temperature

A less noted correlation may exist between the body temperature cyclicity and the cyclicity of migraine. Given that the hypothalamus regulates the biological rhythm of core body temperature, sleep and energy expenditure (Alstadhaug, 2009), it is also likely to coordinate between them, potentially through neurons that contain orexin, melanin concentrating hormone, and histamine (Spinazzi et al., 2006). Accordingly, it may be reasonable to speculate that migraine may be associated not only with disturbed sleep or fasting but also with body temperature alterations (Ordas et al., 2013). This concept may provide novel explanation to the low occurrence of migraine onset at bedtime and high occurrence of migraines between 4 and 6 AM, when the body temperature begins to rise.

Obesity

Estrogen contributes to the regulation of the metabolism (Rettberg et al., 2013) and may influence body weight (Brown et al., 2010), usually exerting protective functions, perhaps by acting as a leptin-mimetic (Fuente-Martin et al., 2013). Migraine is associated with obesity in adults and children (Bigal et al., 2007; Peterlin et al., 2010; Verrotti et al., 2012) and low leptin levels (Rettberg et al., 2013).

Dynamic changes in hypothalamic, pituitary, and gonadal hormones may alter brain function at a cellular (e.g., receptor), anatomical

Table 1
Perturbators of set point as contributors to altered stability of biological systems (allostasis) in migraine patients.

A: Age-related mega-cyclic perturbators of homeostatic set point
Transition to puberty
Initiation and maintenance of cyclicity (174, 199)
Inhibition of cyclicity with Rx (200)
Transition through pregnancy
Inhibition of cyclicity through pregnancy (201)
Transition to menopause
Inhibition of cyclicity through loss of ovary response (202)
B: Endogenous cyclic perturbators of the homeostatic set point
Hormonal alterations (hypothalamic-pituitary-gonadal fluctuations)
– Fluctuations in hypothalamic hormone pulsatility (Pang et al., 1996, 203)
– Fluctuations in sex steroid levels (see text)
Non-hormonal physiological alterations
– Time sense rungs faster during luteal phases (Pang et al., 1996, 203)
– Sleep–wake alterations (204, 205)
– Exercise performance (206)
Emotional alterations
– Anxiety (207) induced through progesterone levels (208).
C: Migraine attacks as perturbators of the homeostatic set point
Preictal/prodrome
– Sensory/motor changes (visual aura; sensory, motor, or verbal disturbance; neck stiffness) (209–211)
– Autonomic changes (appetitive changes; dizziness; yawning) (212)
– Emotional changes (irritability or other mood changes; confusion; fatigue; sleep disturbances; difficulty concentrating) (213)
Ictal/attack
– Sensory/motor changes (head pain — lateralized or bilateral; visual changes including blurry and double vision; hypersensitivity to sensory stimulation (photophobia, phonophobia, osmophobia, allodynia; neck pain and muscle tenderness)) (214, 215)
— Autonomic changes (nausea and vomiting; teary eyes, stuffy nose and congestion, yawning, frequent urination; Transient amnesia, expressive aphasia, motor clumsiness, depression) (216, 217)
Post-ictal changes/postdrome
– Other changes (tiredness) (218)
Inter-ictal changes
– Mood changes (anxiety/depression) (219)
– Sensory changes (hypersensitivity to all sensory modalities) (220)

(e.g., dendritic spine growth and/or hydration status (Streitburger et al., 2012)), and functional (e.g., neural circuit) level (see Fig. 8 and Table 1).

Hormones and allostatic load in migraine

The pulsatile release of hypothalamic hormones leads to the stimulation of gonadal steroids that alter migraine susceptible brains, particularly estrogens in women. In susceptible individuals, the hormonal rhythm produces either increased or decreased sensitivity to the phase at which a migraine may be triggered (Borsook and Burstein, 2012). Repeated migraine attacks, precipitated by an altered brain state or hormonal stress may lead to allostatic load (i.e., increased effects on brain systems as a result of repeated stressors). The concept of allostatic load as it applies to migraine has been reviewed elsewhere (Borsook et al., 2012). Fig. 9 summarizes the McEwen concept of how alterations of homeostasis lead to allostatic load (McEwen, 2000), how hormonal load contributes to allostatic load (McEwen, 2002), and how the two lead to alterations in brain functions (McEwen, 2002). An example of the effect of allostatic load changing migraine frequency is the resolution of menstrual migraine that leads to a reversal of chronic migraine to episodic migraine (Calhoun and Ford, 2008).

Future directions

Migraine processing is not limited to ictal attacks but a prolonged process that may involve pre-ictal (e.g., prodrome), ictal (headache, nausea), and post-ictal (e.g., fatigue) phenomena. Inflammation has been a consistent theme in migraine in humans (Cseh et al., 2013; Guzel et al., 2013; Oikari et al., 2013) and animal models (Franceschini et al., 2013). We suggest that there are a number of important routes of research that may help us better understand how hormones affect the migraine brain. For example, it is important for future research to analyze the relationship between brain function and hormonal changes in migraine. Additionally, there is a need for basic science in translational medicine, as translating findings from animal models to the human condition has been a challenge. In the migraine field, there are a number of "animal models", however, most use male animals (e.g., (Boes and Levy, 2012; Greco et al., 2013)), which confounds sex differences in migraine. Another approach to study the influence of hormones is to investigate short term and long term effects of contraceptive use on migraine, as there is compelling evidence that oral contraceptives alter brain function (Mareckova et al., 2012; Rumberg et al., 2010) and structure in regions such as the prefrontal cortex, pre- and post-central gyri, parahippocampal and fusiform gyri, and temporal regions (Pletzer et al., 2010). However, the impact of oral contraceptives on brain function and structure in migraine susceptible individuals remains unknown. Finally, brain alterations that occur during puberty and headache point to the potential value of studying the relationship among age, hormones, genomic expression, and brain structure and function as it may improve our understanding of how puberty in girls exacerbates migraine and how these early changes may persist later into life.

Conclusions

Hormonal fluctuations are prominent during puberty and are known to alter behavior, and, particularly affective dimensions (Ladouceur et al., 2012). These changes produce dramatic phenotypic alterations in brain structure and function (Sisk and Zehr, 2005). Steroidal hormones alter neural circuits during adolescence, a time of ongoing neural development (Sisk and Foster, 2004). When pathological alterations in brain systems exist as a result of genetic, epigenetic or other reasons, the surge essentially acts to enhance the expression of the condition. Migraine is a preeminent example.

Disruptions of homeostasis normally require allostatic processes to normalize the biological process. In healthy pubertal girls and women, there is an ongoing oscillation of changes throughout their reproductive lives. The lack of hormonal stability, afforded to healthy men, is a process that may include hyperexcitability in neurons and networks throughout the brain. Allostasis is a normal physiological adaptation to a stressor. When stressors become pathological and lead to a feed-forward cascade, allostasis is no longer preserved (i.e., allostatic load). Migraine can therefore be considered a model disease of allostatic load and overload in women (Borsook et al., 2012), in which vulnerability to the hormonal cyclicity enhances the predisposition to migraine.

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