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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

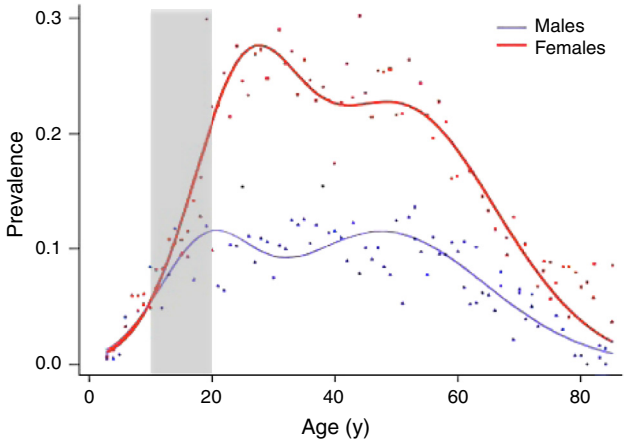

Fig. 1. Sex and age in migraine. Migraine prevalence (adapted from Fuente-Martin et al., 2013 with permission): Prevalence measured over a 1-year period of self-reported and physician-diagnosed migraines. The prevalence in boys and girls is similar until puberty (approx. 10–11 yrs. of age) after which 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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