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Review

Sex differences in human epilepsy

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ABSTRACT

In the majority of neuropsychiatric conditions, marked gender-based differences have been found in the epidemiology, clinical manifestations, and therapy of disease. Emerging data suggest that gender differences exist also in the epidemiology, and pathophysiology of epilepsy. The present review summarizes the current information regarding gender and epilepsy. These differences are regarded from the perspective of innate sex differences in cerebral morphology, structural and functional connections, and assuming that these differences may render men and women differently vulnerable to epileptogenicity.

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Introduction

Epileptic seizures are generated by specific cerebral networks. Depending on the networks involved the semiology of seizures, as well as the interictal behavioral, cognitive, and emotional changes may vary. Different regions in the brain seem to have a different propensity to generate and sustain seizure activity in humans (Engel, 2013). During the last decade there has been a rapid increase of reports on sex differences in cerebral structure and function (Giedd et al., 2006; Savic, 2010). These new data highlight the possibility that in epilepsy, similarly to other neuropsychiatric conditions, epidemiological and phenomenological sex may exist, and that some of these differences may be explained by inherent sex differences in cerebral structure, connectivity, and function. Such differences are important to identify, as they may potentially offer valuable information when trying to understand the mechanisms of epileptogenesis, and develop new treatment strategies.

The present review discusses possible sex differences in epilepsy in humans addressing four different issues. First of all, is the general sensitivity to develop epileptic seizures different in women compared to men? Secondly, is there a sex difference in the epidemiology of various epilepsy syndromes? Third, given the described sex differences in

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cerebral anatomy, is the location of the region of seizure onset differently distributed in male and female epilepsy patients, in other words, could there exist a sex difference in regional liability to generate seizures? Fourth, are there any sex differences in primary projections of the epileptogenic region, in the spread of epileptic seizures and their semiology? Finally, are there sex differences in interictal behaviors, cognitive deficits and psychiatric comorbidity?

Sex differences in the epidemiology of epilepsies in humans

According to a large epidemiological report (Hauser et al., 1993) and a subsequent meta-analysis (Kotsopoulos et al., 2002), the prevalence of epilepsy is slightly lower in females compared to males (46.2 vs. 50.7 per 100,000). This difference seems to be constituted by the higher preponderance in males to develop partial epilepsies (Christensen et al., 2005; McHugh and Delanty, 2008), and partial epilepsies most common among the various types of epilepsies. The male excess in prevalence of partial epilepsies is often explained by the higher prevalence of lesional epilepsy in men (i.e. epilepsy associated with detectable changes in cerebral morphology which are co-localized with the region generating epileptic seizure), (Christensen et al., 2005). Lesional epilepsy is more common in men either because lesions are more prevalent in men, or, because men are more prone to lesion-associated epileptogenesis. The first alternative is supported by an early theory launched by Taylor stating that the cerebral maturation is slower in boys, and therefore, the time frame for a potential seizure-producing insult (which is more likely to affect a brain still undergoing maturation), is longer in boys (Taylor, 1969). The second is supported by findings from some animal models of mesial temporal lobe epilepsy (MTLE), showing a higher vulnerability to develop epilepsy in male rats when the model is based on lesion and hyperthermia, or lesion and early life stress (Desgent et al., 2012). To the contrary, when the model is not associated with lesion, for example, when seizures are induced by amygdala kindling + stress, the vulnerability is found to be higher in females, (Salzberg et al., 2007). This latter observation is compatible with some epidemiological reports from humans, according to which cryptogenic temporal lobe epilepsy (defined by a lack of obvious etiological factors and lesions) is more common in females (62% vs. 38%, $p < 0.001$), (Christensen et al., 2005; McHugh and Delanty, 2008).

A significantly higher female prevalence has in several surveys been found also in idiopathic generalized epilepsies (IGE), which represent some 15–20% of all epilepsies. For example, childhood absence epilepsy (CAE) is reported to be 2–5 times more common in females, with some differences depending on whether early onset typical CAE is described (Asadi-Pooya et al., 2012; Waaler et al., 2000). Juvenile absence epilepsy (JAE) is three times more common among females, and juvenile myoclonic epilepsy (JME) about 1.5 times more common among females (Christensen et al., 2005; Kleveland and Engelsen, 1998). The mechanisms underlying this uneven gender distribution are unknown. Nevertheless, it needs to be pointed out that, although IGE is not associated with any lesions, the cerebral networks processing IGE show changes in both white and gray matter as well as areas of functional hyper and hypo-connectivities in the affected subjects. Whether these structural and functional changes differ between male and female IGE patients is presently uncertain. Most of the studies of cerebral anatomy and function in various forms of epilepsy have been carried out with brain imaging methodology and were often limited by low numbers of subjects. Furthermore, they were either based on gender-matched populations without specifically investigating possible gender difference, or, the group differences were calculated using gender as a nuisance variable. Of clear interest is, however, that the reported structural correlates to MTLE as well as IGE seem confined to networks in the brain that show structural differences among male and female healthy controls. This raises the general question as to whether sex differences in the architecture of various brain regions, and in the functional connections between these regions could be involved in the genesis of the observed sex differences in the epidemiology of epilepsy. Theoretically, the regional cyto-organization could influence the regional susceptibility to develop/generate seizures in males vs. females, whereas sex differences in functional and structural connections could be important for the modality of seizure spread in the brain. To provide background to this discussion, the major sex differences in the healthy human brain will be discussed in the next paragraph.

Cerebral sex differences in the healthy brain and the tentative mechanisms underlying these differences

There is increasing evidence for sexual differences in the human brain. They have been found in structural volumes, in regional gray (GM) and white matter (WM) volumes, in cortical thickness, as well as in the structural and functional connections. In general, the amygdala and thalamus volume is found to be larger in men, the hippocampus and caudate volume larger in women (Filipek et al., 1994; Giedd et al., 1997, 2006; Murphy et al., 1996; Neufang et al., 2009; Paus et al., 1996; Raz et al., 1995). The GM volumes are reported to be greater in men in the mesial temporal lobe, the cerebellum, and the lingual gyrus (Carne et al., 2006; Good et al., 2001; Lentini et al., 2013; Savic and Arver, 2011), and greater in women in the precentral gyrus, the orbitofrontal and anterior cingulate gyri, and the right inferior parietal lobe (Good et al., 2001; Lentini et al., 2013; Luders et al., 2005, 2009a,b; Nopoulos et al., 2000; Savic and Arver, 2011; Strange et al., 1999). Women seem also to have generally thicker cortex, (reflecting dendritic connections, neuronal size and packing) particularly in the motor strip, and the occipital and parietal lobes (Luders et al., 2006; Savic and Arver, 2013). In contrast, the white matter connections between cortical regions are found to be stronger in men, as shown in higher fractional anisotropy (FA) values (reflecting myelinization, the axonal size, and packing) in, for example, the corticospinal tract and the thalamic radiation, (Allen et al., 2011; Filippi et al., 2013; Gong et al., 2011; Hsu et al., 2008; Oh et al., 2007; Rametti et al., 2011; Wang et al., 2014; Westerhausen et al., 2011). These findings might suggest a higher local clustering in women, and more long-distance connections in men.

The described sex differences are believed to derive from specific processes that shape brain morphology during development. Recently, it has been suggested that the motor-networks could be affected by processes coded by genes expressed on the X-chromosome, whereas the mesial temporal and occipito-parietal networks could be influenced by testosterone and estrogen (Lentini et al., 2013; Savic and Arver, 2013). Sex differences detected in these networks may have implications for the prevalence and expression in several disorders of cerebral connections, including epilepsy. The observed sex differences in thalamo-cortical and cortico-spinal tracts as well as in the motor cortex, thus in the networks, which are fundamental in IGE, may influence the development and expression of both JME and CAE. The described sex dimorphism in the limbic networks, on the other hand, is of interest for temporal lobe epilepsy, and MTLE in particular. Of special relevance is the observation of a sex differentiated functional connectivity from the amygdala with greater *right* amygdala connectivity in *men*, and greater *left* amygdala connectivity in *women* (Kilpatrick et al., 2006; Savic and Lindstrom, 2008). Of further interest is that the brain regions showing stronger functional connectivity with the right amygdala in men (the sensorimotor cortex, striatum, and pulvinar) are different from those showing stronger functional connectivity with the left amygdala in women (the subgenual cortex and hypothalamus). As shown in the next paragraphs, these sex differences in functional connectivity may shape both ictal expression and the interictal behaviors.

Possible implications of cerebral sex dimorphism for genetic generalized epilepsies

Many of the well-described epilepsy syndromes in idiopathic generalized epilepsies have a genetic predominance (Table 1). The so-called