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Review

Reprint of "Structural and functional correlates of epileptogenesis — Does gender matter?"☆

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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. One possible reason is that sex differences in cerebral morphology, structural and functional connections, render men and women differentially vulnerable to various disease processes. The present review addresses this issue with respect to the functional and structural correlates to some forms of epilepsy.

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Introduction

Epilepsy is a disorder of cerebral connections (Kramer and Cash, 2012) and is associated with both structural and functional changes. The specific location, extension, and prevalence of these changes vary with the type and duration of epilepsy (Engel, 2013). Recent brain imaging studies show that healthy men and women differ (at a group level) in the functional and structural organization of several cerebral networks that are known to process seizures. Some of these sex differences exist from birth to senescence (Giedd et al., 2006; Luders et al., 2005), and it is plausible that they may influence the expression

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and development of at least certain epilepsy syndromes in humans. The present review discusses gender differences in epilepsy based on information from current brain imaging, and pathological data, specifically addressing gender and epileptogenesis.

Cerebral regions showing sex differences in the healthy brain and possible implications of these differences for human epilepsy

There is increasing evidence for sexual dimorphism of 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 mainly due to the larger parahippocampal gray matter volume, 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, 2009b; 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, with potential implications for the prevalence and expression in several disorders of cerebral connections, including epilepsy. The observed sex differences in healthy controls are believed to derive from specific processes that shape brain morphology during development. Perhaps most interesting with respect to epilepsy 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).

In sum, sex differences are described primarily in the limbic and motor networks. They might, therefore, be relevant primarily for the temporal lobe epilepsy and some genetic generalized epilepsies (GGE).

Possible implications of cerebral sexual dimorphism for temporal lobe epilepsy

The hippocampus, amygdala, and the temporal neocortex are pivotal for processing of temporal lobe seizures. The development of these regions and their functional and structural connections is shaped by testosterone and estrogen, and shows known pubertal perturbations (Neufang et al., 2009; Nguyen et al., 2013), with interesting sex differences characterized by a generally earlier maturation in girls, specially with respect to the white matter tracts (Giedd et al., 2006). If relevant for epilepsy, these sex hormone related maturational differences would imply that also the age seizure onset during puberty could be earlier in girls, something that would be interesting to investigate. Testosterone and estrogen both modulate the susceptibility to temporal lobe seizures. Testosterone is believed to have primarily protective effect on seizures. Estrogen, on the other hand, is often stated to be proconvulsive, although this is questioned by some studies. For example, hormonal replacement therapy initiated as estrogen monotherapy in a postmenopausal woman, was shown to be associated with a decrease in seizure incidence (Peebles et al., 2000), and improvement in seizures has been observed following estrogen treatment in patients with absence and tonic–clonic seizures, and also around the ovulation, suggesting that estrogen also may have anticonvulsant effects (Jacono and Robertson, 1987). These apparent disparities are, possible, because estrogen may have dose dependent effects on seizures, as indicated in some experimental data on kainic-acid induced seizures (for a more detailed information, please see the review by Veliskova and Desantis (2013)). Of note is also that seizures can lead to changes in sex hormone levels, for example, it has been reported that temporal lobe seizures, may lead to reduced testosterone levels (Mejias-Aponte et al., 2002; Morris and Vanderkolk, 2005; Verrotti et al., 2012). Together, all these factors provide a rather complicated and intricate context for epileptogenesis, and call for further investigations, particularly in humans.

Reports of gender comparisons in tissue pathology within the area of seizure onset have hitherto been limited to patients with mesial temporal lobe epilepsy (MTLE). These reports do not suggest any sex differences neither in the distribution and extent of hippocampal sclerosis (Briellmann et al., 2000) nor in the degree of amygdala atrophy (Bower et al., 2003; Silva et al., 2010). This absence of sex differences in hippocampal sclerosis is of interest considering some reports from animal studies indicating immunoreactive changes in the dentate gyrus in male but not female rats (Lemmens et al., 2005). Interestingly, and at variance to this gender similarity with respect to the seizure generating region in MTLE, differences between genders have been reported in the areas of seizure spread, the areas of epileptogenic dysfunction and the regional atrophy outside the zone of seizure onset.

Using FDG-PET we detected "extramesiotemporal" (primarily the frontal lobe) decreases in glucose metabolism in men, but not in women with MTLE (Savic and Engel, 1998). This gender difference reflected a difference in the spread pattern of seizures. In a different study of a similar population, it was observed that women with MTLE had temporal hypometabolism contralateral to the zone of ictal onset, while ipsilateral frontal hypometabolism was seen in men (Nickel et al., 2003). Together, these findings might explain the observation that hippocampal seizures are more prone to generalize in men compared to women (Janszky et al., 2004). The findings are supported by a recent, and rather extensive MRI investigation (comprising 120 patients with MTLE) and showing that the extratemporal tissue loss was more pronounced in male patients, particularly in the frontal cortex, whereas the contralateral temporal cortex was more affected in females (Santana et al., 2014). The observed sex differences in the pattern of extratemporal changes may well be an effect of the observed differences in the pattern of seizure spread. Whether the higher tendency for generalization in men can be ascribed to gender differences in interhemispheric connections via corpus callosum (CC) is currently uncertain. Even if several studies suggest that CC is larger in men (especially in the genu CC) (Westerhausen et al., 2011), others are arguing in the opposite direction and recent report from Luders et al. (2014) suggests that individual differences in brain size account for apparent sex differences in the anatomy of the corpus callosum rather than the biological sex.

The possibility of gender dissimilarity in seizure spread deserves special attention, also because the consequences of spread patterns may, potentially, explain some ictal semiology, as well as the interictal behavioral and emotional problems in patients with MTLE. It has, for example, been reported that emotional responses obtained during electrical stimulation of patients with drug resistant epilepsy undergoing presurgical intracranial EEG recordings occur more often in women than in men (Meletti et al., 2006). Using a review of charts and video–EEG documentation of seizures of 2530 epilepsy patients, Chiesa et al. (2007) observed that prevalence of ictal fear was higher in female patients despite matched locations of seizure onset (which in about 70% of subjects was in the temporal lobe). A potential explanation might