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Publication Date

2014-10-01

DOI

10.1016/j.nbd.2014.05.028

Peer reviewed

HHS Public Access

Author manuscript

Neurobiol Dis. Author manuscript; available in PMC 2016 August 29.

Published in final edited form as:

Neurobiol Dis. 2014 October ; 70: 69–73. doi:10.1016/j.nbd.2014.05.028.

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.

Keywords

Seizures; Cerebral connectivity; MRI; MTLE; Sex difference; Generalized epilepsy

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 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.

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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 be that there is a gender-related lateralization in amygdala involvement in emotional memory (Cahill et al., 2001). Due to left lateralization of amygdala projections it might be that in females fear, which is mediated by the amygdala and its projections in the left hemisphere, is easier verbalized and encoded in the verbal memory networks.

An overall impression is that, although the investigations of possible gender differences in MTLE are still in an early phase, the initial reports about differences in seizure spread deserve further attention. They may influence the psychiatric comorbidity, reported in about 30% of patients with MTLE, where the underlying mechanisms remain unclear.

Possible implications of cerebral sex dimorphism for genetic generalized epilepsies

According to one meta-analysis (Kotsopoulos et al., 2002) females may have a slightly lower general susceptibility to epilepsy than males (46.2 vs. 50.7 per 100,000), which is probably because focal epilepsies occur more frequently in men (Christensen et al., 2005; McHugh and Delanty, 2008). Many of the well-described epilepsy syndromes have a genetic predominance (Table 1). The so-called genetic generalized epilepsies (GGE), which represent some 15–20% of all epilepsies, are, according to several surveys, more common among females. For example, childhood absence epilepsy (CAE) is reported to be 2–5 times more common in females, with some differences depending of 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.

Genetic generalized epilepsies are considered to be primarily Mendelian, monogenic or complex, and non-Mendelian (de Nijs et al., 2013; Gardiner, 2005; Pal et al., 2006). There is also a suggestion of maternal inheritance in GGE due to imprinting (Pal et al., 2006, see also Helbig and Lowenstein, 2013).

The GGE network has been defined by means of simultaneous EEG and functional magnetic resonance imaging (EEG-fMRI) (Bai et al., 2011; Gotman et al., 2005; Masterton et al., 2012). These studies have shown that during epileptogenic discharges there is a relative increase in the BOLD signal in the thalamus along with a decrease in the “default-mode

network" (Wang et al., 2012). GGE patients also show increased cortical excitability between the paroxysmal events (Badawy et al., 2007) and also mild ongoing cognitive impairments (Henkin et al., 2005; Pavone et al., 2001), which suggest that the activity and function of GGE brain networks may also be affected during the baseline state between the generalized spike and wave events. MRI studies of GGE patients have shown an atrophy of the thalamus, and depending on the syndrome, also changes in regional cerebral gray matter volumes and densities (Ciumas and Savic, 2006; Koepp et al., 2013; Wang et al., 2012). Whether these structural and functional changes are more common in women compared to men with GGE is presently uncertain. Most of the studies that have been described were limited by a low number of subjects, especially those carried out with brain imaging methodology. Furthermore, either they were based on gender-matched populations without specifically investigating possible gender difference, or the group differences in these studies were calculated using gender as a nuisance variable.

Theoretically, it is possible that sex differences in the architecture of various brain regions, as well as in the functional connections between these regions, could be involved in the genesis of the observed sex differences in the epidemiology of epilepsy. Possible differences in regional cyto-organization could influence the regional susceptibility to develop/generate seizures in males vs. females, whereas sex differences in functional and structural long distance connections could be important for the mode of seizure spread in the brain. In the following two paragraphs we will discuss whether and how gender may have an impact on the functional and structural correlates of JME and CAE — two forms of GGE which are more prevalent among females.

Childhood absence epilepsy—While epileptic seizures of CAE are considered to be "generalized," evidence suggests that in reality spike and wave discharges in CAE patients emerge from focal abnormal circuits in both hemispheres (Blumenfeld, 2005). In particular, there seems to be an engagement of the orbitofrontal circuits. Using EEG-fMRI Bai et al. (2011) compared between-hemisphere resting-state functional connectivity in 16 patients vs. 16 matched controls and found increased connectivity between the right and left orbitofrontal cortex in CAE patients, with no significant differences observed in the other 15 ROIs examined. In some MRI studies with voxel-based morphometry the left orbitofrontal gray matter volume was found to be smaller in CAE patients compared with age matched controls, thus, supporting the possibility of a more localized orbitofrontal abnormality (Caplan et al., 2009; Chan et al., 2006). Other structural changes reported are a decreased age related thinning of the left frontal lobe cortex, and increased thinning in the right posterior central and the paracentral gyrus (Tosun et al., 2011). In addition, thalamic atrophy has been found in CAE (Betting et al., 2006) as in several other forms of GGE (Helms et al., 2006; Koepp et al., 2013; Mory et al., 2003). None of the structural and functional abnormalities reported in CAE provides an obvious explanation to the female predominance in this condition.

Juvenile myoclonic epilepsy—Structural frontal lobe abnormalities also have been described in JME. They are characterized by an increase in the concentration of gray matter and thickness of the cortex (Betting et al., 2006; Vulliemoz et al., 2011), along with

reductions in N-acetyl aspartate (Savic et al., 2004) and increases in glutamate (de Araujo Filho et al., 2009; Simister et al., 2003). A recent study also reported a significant increase in cortical thickness in the precentral gyrus (Alhusaini et al., 2013). Like in other GGE syndromes a reduction in the thalamic volume has been detected (primarily in the dorsomedial nucleus), and also decreases in the concentration of NAA (Helms et al., 2006; Koepp et al., 2013). Congruent with the clinical observation that photic stimuli and cognitive efforts may trigger myoclonic jerks, it has been reported that, in patients with JME, the functional connections between the motor cortex and areas within the frontal and parietal lobes are increased, as are the FA values (reflecting axonal diameter, packing density and myelination) between the supplementary motor cortex and the occipital cortex (Vollmar et al., 2011; Vulliemoz et al., 2011). Some of the described findings have been detected already one year after seizure onset, and are unlikely to be a mere effect of seizures. They could reflect migrational changes including cortical dysplasia. In some JME families linkage has been detected to a susceptibility gene at the EJM1 locus of chromosome 6 (Pal et al., 2006). This gene has now been preliminarily identified as BRD2, a putative transcriptional regulator (Pal et al., 2003), and mutations of this gene are reported to lead to microdysgenesis.

Again, none of the aforementioned brain imaging studies paid special attention to gender aspects, and the mechanisms behind the reported female excess in JME are unknown. One interesting notion, however, is that the majority of regions described to be involved in JME constitute parts of the motor network. Recent studies suggest that this network differs between males and females, and is modified by X-chromosome genes, as well as by testosterone and estrogen (Lentini et al., 2013; Neufang et al., 2009; Savic, 2010; Savic and Arver, 2013). Considering the pubertal onset of JME, it is possible that expression of genes promoting susceptibility to myoclonic seizures could be up-regulated by sex-steroids at puberty, and perhaps more by estrogen than testosterone. An additional possibility is that sex hormone related shaping of axonal and dendritic connections in the seizure generating network could facilitate the onset of JME. Indeed, estrogen is reported to delay dendritic pruning, whereas testosterone promotes it (Savic, 2010). Low testosterone levels are associated with lower FA values (Rametti et al., 2012). Thus, the described frontal lobe increases in the gray matter volume, reductions in the thalamic volume, and connectivity changes in JME, are all compatible with known sex hormone effects (Neufang et al., 2009; Witte et al., 2010) and provide a context for female dominance in the liability to develop JME. It should, however, be emphasized that JME is a heterogeneous epilepsy syndrome, in which frontal lobe dysfunction seems present only in a subgroup of patients (Helms et al., 2006). One future project addressing the mechanisms behind the reported sex difference in the prevalence of JME would be to investigate whether this distribution varies among the different subtypes of JME, as it seems to do in CAE (Asadi-Pooya et al., 2012).

Conclusion

Like in other neuropsychiatric conditions, sex differences are found in epilepsies. These differences are not prominent, and exist in only some forms of epilepsy. In MTLE gender seems to matter primarily with regard to the primary projections from the epileptogenic region, and may reflect innate sex differences in networks supporting seizure propagation, as

well as in the manner in which these networks are reorganized due to seizures themselves. In CAE and JME, two conditions where the pathophysiology is less clear, and perhaps less homogenous, the higher prevalence in females might be related to the inherent sex differences in seizure generating motor circuits. Independently of the exact underlying mechanisms the observed differences deserve further attention as they might have clinical relevance and help understand the origin of some epilepsy conditions.

Acknowledgments

The Insurance Council for Working Life and Social Science (FAS), the Swedish Research Council, and VINNOVA are acknowledged for their financial support (IS). NIH grants P01 NS02808, R01 NS33310, U01 NS42372, and P20 NS 80181, the Epilepsy Therapy Project, CURE, the Epilepsy Foundation, and the Resnick Foundation (JE) are also acknowledged.

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Table 1

Some epilepsy syndromes with gender differences. Derived from Engel (2013) and Panayiotopoulos (2010).

Female predominance
Myoclonic encephalopathy in non-progressive disorders
Childhood absence epilepsy
Idiopathic photosensitive occipital lobe epilepsy
Photosensitive epilepsy
Male predominance
Myoclonic epilepsy of infancy
West syndrome
Dravet syndrome
Epileptic encephalopathy with continuous spike-and-wave during sleep
Landau–Kleffner syndrome
Epilepsy with myoclonic atonic seizures
Benign epilepsy with centrotemporal spikes
Epilepsy with myoclonic absences