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Sex differences in neurodevelopmental and neurodegenerative disorders: Focus on microglial function and neuroinflammation during development

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Abstract

Several neurological conditions are associated with sex differences in prevalence or outcome. For example, autism predominantly affects boys, depression is more common in women, Parkinson's disease more common in men, and Multiple sclerosis in women. In the case of stroke, women have a less favorable outcome and suffer from a more precipitous drop in health status compared to men. As a result, treatment of such diseases is difficult and yields variable results. Despite this, sex is rarely considered when making treatment decisions. The mechanisms underlying sex differences in disease progression are not well understood, however a strong link exists between different inflammation states of men and women and their propensity to develop certain diseases. As neuroinflammation is an important component of pathophysiology in many neurological conditions, it can be speculated that any changes in the state of inflammation in the brain during normal development can potentially lead to an increase in susceptibility to neurological and neurodegenerative diseases. Microglia play a crucial role in onset and modulation of inflammation and thus sex differences in microglial function could explain, at least in part, differences observed in susceptibilities and outcomes of neurological disorders in men and women. Understanding the mechanisms behind sex differences could help develop more targeted therapy with higher success rate, especially in diseases where sex differences are most prominent.

Keywords

Microglia; Sex differences; neurodevelopment; neurodegeneration; neuroinflammation

1. Introduction

Neurological and neuropsychiatric diseases are a complex set of diseases affecting brain health and the general well-being of patients. According to the World Health Organization (WHO), neurological disorders affect up to 1 billion people, whereas 450 million people

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suffer from a mental or behavioral disorder worldwide. An estimated 6.8 million people die every year as a result of brain-related disorders. Not only is the economic cost for treatment very high, patients suffering from mental illnesses and neurological diseases are subject to stigma and social exclusion as well as acute loss of quality of life. Many neurological diseases follow a clear developmental pattern. For example autism is detected in children as early as 2 years of age, depression is generally first diagnosed in adolescents, schizophrenia in young adults, and Alzheimer's disease in aged individuals. One hypothesis is that perturbation of factors affecting normal neurodevelopment could be implicated in the occurrence of certain neurological disorders and their age of onset. Specifically, the immune system, both in the central nervous system (CNS) and in the periphery, is crucial in shaping and influencing normal brain functions, and any disruption of immune function could adversely impact the brain too. Immune signaling via microglial cells during CNS development is critical for maintaining homeostasis, neurogenesis, synaptic plasticity and circuit formation (Bilbo & Schwarz 2012, Garay & McAllister 2010). Notably, our laboratory has shown that activation of the immune system with diverse challenges during early development in rodents can have far-reaching consequences on neuroimmune function and behavior later in life (Bilbo & Schwarz 2009, Bolton et al 2014, Bolton et al 2012). Thus, perturbation of the fine balance between the immune system and developing brain may pre-dispose individuals to an array of neurodevelopmental disorders.

For several neurological disorders mentioned above, there is a stark sex difference in their incidence, severity, and/or progression. For example autism is more prevalent in male children whereas females suffer from depression and anxiety disorders on a much larger scale (Altemus 2006, Mandy et al 2012). Females have a lower incidence of stroke (which depends on age as well), however they display poorer outcomes and suffer a more precipitous decline in function following stroke compared to males (Roy-O'Reilly & McCullough 2014). Sex differences in occurrence and outcome of neurological disease pose complications for diagnosis and treatment of patients, thus further emphasizing the need to understand the molecular pathways underlying these differences.

In this review, we discuss in further detail functions of the immune system, in particular that of microglia, the resident immune cells of the CNS, and their likely contribution to sex differences in the incidence and/or outcomes of neurological and neuropsychiatric disorders.

2. Sex differences in disease prevalence

Sex differences in disease prevalence and resistance are well described. Females of many species including humans generally exhibit enhanced immune responses and increased resistance to disease and infection than males (Gaillard & Spinedi 1998, Klein 2000, McClelland & Smith 2011, McMillen 1979, Schuurs & Verheul 1990, Washburn et al 1965). The more robust nature of the female peripheral immune response may significantly increase the risk of developing autoimmune diseases when compared to males (Kivity & Ehrenfeld 2010, McCombe et al 2009). For example, more than 80% of the patients diagnosed with diseases such as Grave's disease, Addison's disease, and systemic lupus erythematosus (SLE) are female (Cooper & Stroehla 2003); similarly, between 65–70% of patients diagnosed with rheumatoid arthritis, multiple sclerosis, and myasthenia gravis are females

(Selmi 2008). While they have received less attention, there are also sex differences in the incidence and severity of neuropsychiatric and neurodegenerative conditions, including depression, Alzheimer's disease and Parkinson's disease (Alzheimer's 2014, Gillies et al 2014). These sex differences have been attributed, in large part, to the direct and indirect immuno-modulatory actions of sex steroid hormones (Bouman et al 2005, Gaillard & Spinedi 1998, Klein 2000, Olsen & Kovacs 1996). Given the robust sex difference in the prevalence of many diseases, research has been extensive in trying to understand the interactions of sex chromosomes and hormones and the underlying mechanisms of these devastating disorders, listed extensively in (Cooper & Stroehla 2003, Libert et al 2010, Selmi 2008). In general, exogenous estradiol has immuno-enhancing effects on humoral immunity (Cutolo et al 2004, d'Elia & Carlsten 2008, Seaman & Gindhart 1979, Song et al 2008), but may either enhance or suppress cell-mediated immunity depending on low or high doses, respectively (Kovacs et al 2002). Exogenous testosterone generally depresses both humoral and cell-mediated immunity, and increases susceptibility to bacterial and viral infections (Muller et al 2005, Roberts & Peters 2009, Roberts et al 2007, Viselli et al 1995). In contrast, very little research has been done to understand the effects of sex, sex chromosomes, or hormones on the CNS immune system, in particular microglia.

In Table 1, we summarize some of the known sex differences in the incidence and outcomes of other neurological disorders. While every disorder is unique and has different mechanisms and pathways governing its pathology, as well as sex differences, neuroinflammation may be a common thread. If true, then a consideration of immune factors in neurodevelopment may be a valuable and informative approach when considering the mechanisms by which sex differences in these diverse pathologies may develop.

3. Sex differences in brain disorders (human clinical studies)

As mentioned previously, robust sex differences in neurological disorders, many with origins in development, are increasingly being recognized. Here we consider and discuss in detail what is perhaps the best described sexually dimorphic neurodevelopmental disorder, autism, and the role that neuroinflammation, and microglial activation in particular, likely plays in its etiology. Thereafter, we consider the canonical neurodegenerative disorder, Alzheimer's disease, which also presents dimorphically between the sexes, and the now well-characterized role of neuroinflammatory mechanisms in its etiology.

3.1 Neurodevelopmental disorder: Autism

Autism spectrum disorders (ASD) are a group of disorders arising in early childhood characterized by deficits in social communication and social interaction, low emotional reciprocity, low verbal communication and repetitive behaviors.

Clinical studies and sex differences—ASD is well-documented for its proclivity to affect male children over female children with a diagnosis rate of 4:1 in males vs. females (Fombonne 2003). However, it was found that this is dependent on the functional status of the patients as well as diagnostic criteria. The ratio of males to females with ASD is higher in high-functioning patients (approximately 9:1), but with increasing intellectual instability, the ratio tends to be lower (2 males to 1 female) (Fombonne 1999, Wing 1981).

Additionally, male and female autistic patients show divergent symptoms – with males presenting increased aggressiveness and repetitive behavior, and females showing greater anxiety and depression (Hattier et al 2011, Mandy et al 2012). However, some age-matched and IQ-matched studies show little or no sex differences in behavior of ASD patients (Mesibov et al 1989, Tsai & Beisler 1983), thus contributing to the heterogeneous literature of ASD. This can be explained partially by the fact that there is a bias when diagnosing a male child with autism as opposed to a female child due to the differences in symptom presentation between the two (using male-centric behavior as the criteria), resulting in earlier diagnosis in males. In other words, the early signs of autism presented by females might be different from that of males, hence the diagnosis may vary even when controlling for certain variables such as IQ or age. This has been demonstrated in a study where early signs of autism before diagnosis were obtained from caregivers and compared between males and females who later went on to be diagnosed with autism (Hiller et al 2015). It was found that there are sex differences in several “core” autistic symptoms early on, in that females were more likely to engage in mimicking in social settings as well as displaying a stronger desire to interact with peers, which is in contrast to males who displayed social isolation. Regardless, there is a clear difference in the pathology of autism in males and females, thus pointing to differences in biological pathways underlying the development of autism in the sexes.

3.2 Neurodegenerative disorder: Alzheimer's disease

Neurodegenerative diseases are a large group of neurological conditions that are characterized by progressive loss of neurons or subsets of neurons either in the brain or the spinal cord. The effect of such neurodegenerative processes is well-known – rapid and often irreversible loss of crucial cognitive and motor functions. These diseases are closely associated with age, in that in most cases the incidence of being affected with the diseases increases with age.

Clinical studies and sex differences—Alzheimer's disease (AD) is characterized by acute memory loss, cognitive deficits and behavioral changes. About 5.4 million Americans have AD of which 5.1 million people are of the age 65 years or older. Of the 5.1 million above 65 years of age, 3.2 million are women and 1.9 million are men (Alzheimer's 2014). Several theories have been proposed to explain the sex difference in AD. The most simplistic theory is that women have greater longevity at a basal level, thus making it appear that there are more women living with AD than there are men (Hebert et al 2001). Of course, it would be important to account for other age-related disorders that patients might be suffering from such as diabetes or cardiovascular diseases that could further exacerbate the ongoing condition or contribute to the inflammatory state. Related to this concept, as stated above autoimmune disorders are highly prevalent in women compared to men, however the mechanism for this bias is not clearly understood (Lehrer & Rheinstein 2014). It can be speculated that the inflammatory state of women may lead to an increase in susceptibility to AD. Indeed, some studies characterize AD as an autoimmune disease not just for understanding the pathophysiology but also for treatment purposes (Lehrer & Rheinstein 2014).

3.3. Mechanisms underlying sex differences

Autism and Alzheimer's disease appear to be two distinct diseases on the outside - affecting patients in a quite disparate manner, both from the point of view of pathology as well as age of onset. Furthermore, sex differences associated with these diseases seem to follow opposite trajectories as discussed above. However, we believe that for both AD and ASD, a root cause may lie in brain development, for which microglia are especially critical.

Microglial origins and functions—Microglia are well characterized as the primary immune cells of the CNS. They are derived from primitive yolk sac myeloid progenitors, and start colonizing the brain during early stages of embryonic development (E9-10) (Ginhoux et al 2010), which makes them ontogenically distinct from macrophages which originate from bone-marrow derived monocytes (Parwaresch & Wacker 1984). They are often classified as existing in two *distinct* morphological states - 1) Ramified and 2) amoeboid; although microglia are also known to exist in several other states intermediate between amoeboid and ramified (Schwarz et al 2012). Traditionally, ramified microglia were considered to be functionally “resting” or “quiescent”, having long thin processes, and a small cell body, whereas amoeboid microglia were considered to be in “active” state with larger cell bodies and shorter and thicker processes, typically found after injury or inflammatory insult. However, amoeboid microglia are also observed in the normal brain during early stages of development (Boya et al 1979). For many years it was considered that the “activated” amoeboid form of microglia was the more important functional state of microglia – secreting cytokines and engulfing pathogens - and that ramified morphology indicated a somewhat “quiescent” or inactive state of microglia. However, recent studies have shown that “resting” microglia constantly survey their environment by actively retracting and extending their motile processes (Nimmerjahn et al 2005).

Another important function of microglia (in the absence of any external immune stimulus) is during critical stages of neuronal development when synaptic connections are being formed and refined. During this time, microglia aid in the elimination of synapses in an activity dependent manner (synaptic pruning) thereby modulating the maturation of neuronal synapses in a healthy developing brain (Schafer et al 2012, Tremblay et al 2010). Moreover, as the primary immune cells of the brain, microglia are exquisitely sensitive to perturbations, e.g., from environmental influences, and thus have the capacity to alter brain development trajectory. The impact that microglia make on the CNS during development is reason enough to investigate further how these cells might be involved in the occurrence of CNS disorders hitherto considered to be purely neuronal in nature. We speculate that perturbation of normal immune pathways (either due to environmental factors and/or genetic mutations) during brain development may set the stage for exacerbated inflammation and susceptibility to neurological disorders later in life. We have found that in rodents, sex differences exist during several time points in normal neurodevelopment and this could affect how glia and neurons dynamically interact with each other, setting the stage for either resistance or susceptibility to the development of the neurological disorders in a sex-specific manner. Thus, an appreciation of the sex differences in neurodevelopment especially from the point of view of microglia may aid understanding of the sex differences observed in the neuroimmune pathologies of these diseases.

3.3.1. Microglia and sex differences during development: Although several studies have looked at the role of inflammatory microglia in the pathogenesis of neurological disorders, few examine how these processes may differ in males and females. Microglia colonize the rodent brain during early stages of embryonic development, starting around embryonic day 9.5. Although no direct studies have been performed to specifically investigate whether there is a sex-dependent difference in the initiation of microglial colonization of the rodent brain, we have shown that at time points just prior to parturition (embryonic day 18 or E18) there are no differences in the number of microglia found in the fetal brain of male and female rats (Schwarz et al 2012). However, sex differences in both number and morphology (and gene expression) begin to manifest postnatally, which begin to organize the brain after birth in rodents. Specifically, males have significantly more microglia than females at postnatal day 4 (P4) within the parietal cortex, CA1, CA3 and dentate gyrus (DG) regions of the hippocampus (HP), and the amygdala (Schwarz et al 2012). Similarly, female rat pups have significantly fewer microglia than male pups at P2 in the pre-optic area (POA), as well as fewer amoeboid microglia characterized by large cell bodies (Lenz et al 2013). It is clear that a sex difference in microglial morphology and number exists in different areas of the brain during neonatal time points that are important for specific functions later in life.

The literature on baseline sex differences in *adult* microglia, however, is sparse. We have shown that at P30 (juvenile) and P60 (early adulthood), female rats have significantly more microglia with thick, long processes than males in sub-regions of the hippocampus as well as in the amygdala and parietal cortex (Schwarz et al 2012). It is especially interesting to note the switch from the increased number of microglia in males during early developmental time points (discussed above) to the increased number in females in adulthood.

The patterns of microglial number and morphology changes in males and females is rather interesting and point to specific susceptibility windows during which any perturbation may lead to divergent outcomes in the sexes. For example, during early developmental time points when males have more amoeboid microglia than females, an inflammatory insult may lead to altered microglial function (and eventually altered neuronal function) due to microglial over-activation. This may then manifest as a neurological disorder, especially if overlaid onto susceptible genetic mutations. As discussed above, in humans, males tend have higher incidence of neurological disorders that develop earlier in life, whereas females are more vulnerable to diseases that arise later on. These female-biased disorders include those that arise in adolescence such as depression and anxiety, a time during which females have more microglia than males. Thus, it might be detrimental (i.e. in the context of immune or inflammatory challenge) to have higher number of microglia during crucial stages of development and this may govern the time point at which certain disorders arise. As discussed above, in AD more women above the age of 65 years suffer from the disease than men. The causes for AD are yet not clear, however it is possible that perturbation of microglial function during crucial stages of development along with underlying genetic mutations may set the wheels in motion for emergence of neurodegenerative disorders later in life. Clearly, the mechanisms for sex differences in different diseases may be different and are likely multi-faceted. However, we would propose it is important to recognize the importance of immunological differences in males and females within the CNS at different

developmental time points, and their relevance as a key susceptibility factor for the development of neurological conditions later in life.

3.3.2. Other mechanisms

3.3.2.1. Genetics: It has been proposed that genetic mutations implicated in the development of ASD could partially explain the sexually dimorphic nature of the disease. One model proposes that females have a higher threshold for developing autism, as females with ASD may be carrying a higher number of mutations (mutational load) than affected males (Skuse 2000). But why do females have an apparent "inherent" protective mechanism built into their genes in the first place? An obvious explanation is that ASD (or at least some forms of it) is an X-linked disorder, in which females having deleterious mutations in one X-chromosome may be protected due to a normal copy of the gene in the second X-chromosome. There are some genes that fall into this category and are implicated in higher risk for development of autism such as FMR1. FMR1 protein has been shown to be important in key neuronal functions such as synaptic plasticity and is implicated in the development of fragile-X syndrome, a disease which is also highly male-biased. However, not much is known about the role of FMR1 protein (FMRP) in non-neuronal cell types, especially glia. Only a few studies have looked at the role of FMRP in astrocytes and microglia (Yuskaitis et al 2010) or in oligodendrocytes (Giampetruzzi et al 2013, Pacey et al 2013). It appears that in FMRP knockout mice, there is a high level of astrocyte activation, but primary microglia isolated from the mutant mice show normal immune responses to LPS challenge (Yuskaitis et al 2010). This observation, however, is not encompassing of all functions of microglia as these cells are also involved in several other important functions such as synaptic pruning, phagocytosis of cell debris, or providing essential trophic support to developing neurons and dendrites – roles that are crucial to normal development of the CNS and not investigated in the context of FMRP. Furthermore, the heterogeneous nature of the disease may be due to different mutations affecting different cell-types in the brain, thus giving rise to a complex disease phenotype. Thus, an important consideration when evaluating risk factors for ASD would be "where" rather than "what" of genetic mutations. Identifying cell-type-specific gene mutations is crucial to understand the molecular etiology of ASD, as was recently shown (Chang et al 2015, Stoner et al 2014) which could further elucidate on the sexual dimorphism associated with this group of diseases. Determining gene expression changes in neuronal as well as non-neuronal cells in post-mortem tissues of patients and normal humans will be of utmost importance.

Similar to ASD, AD too has a genetic component associated with its pathology, for both early-onset and late onset disease. In the case of early-onset Alzheimer's disease, which is the heritable form of AD, mutations in APP, PSEN1 and PSEN2 genes have been shown to be the cause (Guerreiro et al 2012). In late-onset AD, the most common form is the disease, having one form of the apoliportein A (APOE ε4) gene in chromosome 19 increases the risk of developing the disease (Spinney 2014). TREM2 is a newly discovered gene that is associated with an increased risk of AD (Guerreiro et al 2013, Jin et al 2014). TREM2 is a transmembrane protein that is expressed on microglia in the brain and can regulate microglial functions such as phagocytosis and inflammatory reactivity (Hsieh et al 2009, Rivest 2015). However, very little is known about the mechanisms by which TREM2

variants can increase the risk to develop AD. Even less is known about the role of genetic mutation in sex differences in AD pathology or incidence.

3.3.2.2. Hormone-environment interaction: Other factors that may play a crucial role in differential susceptibilities of the sexes are hormones and environment. In autism pathology, both these factors are closely related to each other and can further contribute to epigenetic changes in the genome that are then passed down generations. For instance, a prenatal androgenic environment in rats can lead to masculinized behavior of offspring later in life, regardless of their sex (Lenz et al 2013). This effect was dependent on microglia, as inhibition of microglial activity could inhibit the masculinizing behavior. Another study has shown that prenatal androgenic environment in maternal rats could predispose female offspring to develop autism-like characteristics such as lowered social interaction (Xu et al 2015) and that elevated fetal testosterone is a potential risk factor for ASD (Baron-Cohen et al 2011). Although the role of microglia was not investigated in this study, the divergence in the response of male and female offspring to the same prenatal stimulus leads to another question – is there a difference in "fetal programming" in males and females that makes one sex more vulnerable to maternal or fetal hormone levels over the other? Although the basic male/female phenotype is determined during embryonic development by the sex-determining region Y (SRY) gene on the Y chromosome, both maternal and fetal-derived sex hormones (especially testosterone and estrogen) play crucial role in sexual differentiation of neuroendocrine system and behavior in both sexes, thus affecting the fetal brain during gestation. Once testicular differentiation takes place in the male fetus, Leydig cells start producing testosterone which is converted to 17β-estradiol (a form of estrogen) by a process called aromatization in neurons which then exerts its masculinizing actions via estrogen receptors. Both the male and female fetal brain are exposed to high levels of estrogen produced by the placenta and mother. However, in females, alpha-fetoprotein, a plasma glycoprotein, binds estrogen and acts as a carrier, and thus protects the fetal brain from the masculinizing effects of estrogen by preventing entry into the cells (Karaismailoglu & Erdem 2013, Wilson & Davies 2007). Interestingly, it has been demonstrated that fetal and postnatal microglia are closely involved in this process by responding to the release of sex steroid hormones, particularly in the pre-optic area, consequently resulting in microglial activation affecting fetal brain programming in a sexually dimorphic manner (Lenz & McCarthy 2015). A full description of this process goes beyond the scope of this review, but we direct the readers to an elegant review on this topic by Lenz & McCarthy (Lenz & McCarthy 2015).

In terms of activation patterns, it has been shown that estrogen can regulate cytokine expression by microglia at basal level as well as in the presence of an inflammatory challenge (Mor et al 1999, Vegeto et al 2001), whereas testosterone is known to have an inhibitory effect on glial activation (Barreto et al 2007). The presence of sex-steroid receptors has been shown in adult microglia (Sierra et al 2008), yet the level of expression of these receptors prenatally on microglia still remains to be determined. An important question would be, what are the relative expression levels of these receptors in male and female microglia over different prenatal developmental time points? How these hormones specifically alter the activity of microglia resulting in sexual differentiation of the brain is

still not well understood. It is proposed that synaptic pruning abilities of microglia may be altered by specific sex steroid hormones although much remains to be known in that aspect. Simply put, any sex differences in the expression of hormone receptors in fetal microglia may be crucial to determine susceptibility to maternal or fetal sex-steroid hormone levels, and to the risk or resilience to the development of neurological disorders later in life.

4. CONCLUSION

Inflammation is an important component of several neurological disorders. Most studies look at the role of reactive microglia from the point of view of response to a pathological insult. Although this might be a reasonable approach, it should also be taken into account that basal differences in microglia do exist at different time points, in different areas of the brain and between males and females. It will be important to investigate and understand these differences. Interactions of the brain immune system with environment and genetics during development could very well set the stage for increased risk of specific disorders. Finally, microglial activation is only a part of a larger system that involves the dynamic interplay of several sub-systems including hormones, environment, genetics and other glia and neurons. It will thus be necessary to take an interdisciplinary approach to understand the molecular basis of this phenomenon.

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Highlights

1. There are sex differences in the incidence and outcome of many neurodevelopmental and neurodegenerative diseases
2. Sex differences in microglia number and morphology exist at crucial time points during development.
3. Perturbation of microglial function during development can impact behavior and cognition later in life in a sex-dependent manner.
4. Studying sex differences in microglial function could be crucial to the understanding of sex differences in the emergence of neurological conditions as well as their treatment.

Table 1

Sex differences in incidence and outcomes of neurological conditions commonly seen in humans

Neurological condition	Sex difference in incidence and prevalence (F : M)	Sex difference in severity or outcome	References
Attention deficit hyperactivity disorder	Higher prevalence in boys vs. girls (1:3)	Severe deficiency in motor skills and higher distractibility in boys	(Balint et al 2009, Catala-Lopez et al 2012, Cole et al 2008, Willcutt 2012)
Alzheimer's disease	Higher prevalence in women above age 65 years (1.6 -3 :1)	Greater cognitive deterioration in women	(Irvine et al 2012, Plassman et al 2011, Seshadri et al 1997)
Amyotrophic lateral sclerosis	Higher prevalence in men (1:1.6), earlier onset in men. Higher risk in post-menopausal women	Worse survival for women with ALS	(del Aguila et al 2003, McCombe & Henderson 2010)
Autism Spectrum Disorders	Higher incidence and prevalence in boys (1:4)	Ambiguous and heterogeneous findings. Meta-analysis shows that females have less severe stereotyped and repetitive behaviors	(Fombonne 2003, Hattier et al 2011, Hiller et al 2015, Mandy et al 2012, Van Wijngaarden-Cremers et al 2014)
Depression and Anxiety disorder	Higher prevalence in females (2:1)	Increased severity of symptoms, higher incidence of subclinical depression in women	(Altemus et al 2014, Kessler et al 1993, Nolen-Hoeksema & Girgus 1994)
Juvenile Batten's Disease	Data on incidence unclear, later onset in females	Females suffer from more severe symptoms, higher morbidity	(Cialone et al 2012)
Multiple sclerosis	More common in women (2–3 :1)	Faster progressing in men	(Confavreux et al 2003, Voskuhl & Gold 2012)
Parkinson's disease	Higher incidence in men (1:3.5)	Slower rate of decline in women	(Baldereschi et al 2000, Elbaz et al 2002)
Schizophrenia	Higher incidence in men, earlier onset too	Worse prognosis in men due to severe symptoms and poorer response to antipyschotic drugs	(Aleman et al 2003, Goldstein et al 2013, McGrath et al 2008)
Stroke	Later onset in women, higher incidence in men (1:2)	Women have less favorable outcomes after stroke and suffer from more severe physical disabilities following stroke	(Appelros et al 2009, Reeves et al 2008)