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Review

Sex/gender differences in the brain and cognition in schizophrenia

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ABSTRACT

The early conceptualizations of schizophrenia have noted some sex/gender differences in epidemiology and clinical expression of the disorder. Over the past few decades, the interest in differences between male and female patients has expanded to encompass brain morphology and neurocognitive function. Despite some variability and methodological shortcomings, a few patterns emerge from the available literature. Most studies of gross neuroanatomy show more enlarged ventricles and smaller frontal lobes in men than in women with schizophrenia; finding reflecting normal sexual dimorphism. In comparison, studies of brain asymmetry and specific corticolimbic structures, suggest a disturbance in normal sexual dimorphism. The neurocognitive findings are somewhat consistent with this picture. Studies of cognitive functions mediated by the lateral frontal network tend to show sex differences in patients which are in the same direction as those observed in the general population, whereas studies of processes mediated by the corticolimbic system more frequently reveal reversal of normal sexual dimorphisms. These trends are faint and future research would need to delineate neurocognitive differences between men and women with various subtypes of schizophrenia (e.g., early versus late onset), while taking into consideration hormonal status and gender of tested participants.

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1. Introduction

Significant sex/gender differences in schizophrenia have been noted already by Kraepelin (1919/1971) who wrote: "The male sex appears in general to suffer somewhat more frequently and to be affected more severely by the *dementia praecox*". In the scientific literature we often use terms 'sex' and 'gender' interchangeably, but over the past decade several researchers suggested to be more specific and refer to 'sex' as a biological variable defined principally by sex chromosomes and sex steroid hormones, while using the term 'gender' as a psychosocial construct determined mainly by family, society and culture (Holdcroft, 2007; Mendrek, 2015). Nevertheless, it is difficult to disentangle the influence of these two sets of variables, as they continually interact with each other, especially in humans. This is why we sometimes use 'sex/gender' throughout this paper, to indicate that in many discussed studies it is impossible to determine if the differences we are presented with were mainly due to a biological sex or a psychosocial gender, and most likely reflected a combination of both factors. In this review we concentrate on neuroanatomical, neurofunctional and cognitive studies of differences between men and women diagnosed with schizophrenia. Some of these studies have assessed sex steroid hormones, but gender identity and socialization was almost never taken into consideration. Before delving into this literature, a brief introduction to schizophrenia is in order.

2. Schizophrenia overview

Schizophrenia is one of the most complex and least understood psychiatric disorders. It is typically referred to as a 'chronic and debilitating' condition because it may lead to a progressive functional decline impacting cognitive, affective and social domains (Tandon et al., 2009). However, some individuals diagnosed with the disorder function relatively well, maintain their employment, and have families and friends. In addition to the varied course of the illness, the clinical presentation of schizophrenia is also quite heterogeneous with symptoms ranging from hallucinations and delusions, disorganized speech and behavior, to flat affect, lack of motivation, and cognitive deficits (Green, 2006; Rund and Borg, 1999). The symptoms are typically classified under three or four broad categories: (1) positive symptoms, such as delusional ideation and altered perceptual experiences; (2) negative symptoms, including social withdrawal, avolition and poverty of speech; (3) disorganization, which is sometimes included under the positive category and includes bizarre behavior and incoherent speech; (4) cognitive symptoms, such as poor concentration, disorientation in time and space, lack of judgment and insight, difficulties in abstract thinking, as well as prominent attention, executive function and memory deficits. It is cognitive deficits that have been associated most significantly with the functional outcome of schizophrenia (Green et al., 2004) and it is cognitive deficits, more specifically sex and gender differences in the neurocognitive deficits, that are the focus of the present review.

In contrast to the clinical presentation and course of the illness, the onset of schizophrenia is less varied and occurs typically in early adulthood with life-time prevalence around 0.7–1% across different cultures (Jablensky et al., 1992; Maibing et al., 2015). More recent studies suggest that the prevalence of the disorder is typically higher in developed than in developing countries (Tandon et al., 2008), and higher in migrant groups than in native-born populations (Saha et al., 2005). Regardless of the culture, people diagnosed with schizophrenia often suffer from a wide range of psychosocial difficulties and stigmatization that may be more detrimental than the psychiatric symptoms of the disease (Kadri and Sartorius, 2005; Burton, 2006; Makinen et al., 2008). Approximately 10–15% of people diagnosed with schizophrenia commit suicide (Lewis and Lieberman, 2000; Funahashi et al., 2000) and almost half of the patients attempt suicide during their lifetime (Bertelsen et al., 2007; Andreasen and Carpenter, 1993; Saha et al., 2007). Overall, mortality in schizophrenia population for all causes, has been shown to be two to threefold higher than in the general population (McGrath et al., 2008).

The in-depth discussion of etiology of schizophrenia is beyond the scope of the present article, but a few possible factors involved in the development of the disorder should be mentioned, as they may interact with sex and gender. Thus, over the past few decades, researchers have argued for the importance of heritability, obstetric complications, perinatal/prenatal viral infections, severe environmental stress, environmental toxins and hormonal perturbations (Weinberger, 1995; Sham et al., 1993). One of the most widely accepted theories is that schizophrenia stems from some neurodevelopmental anomaly (genetic, environmental and/or hormonal), occurring most likely around the first or second trimester of gestation. This anomaly produces faulty wiring of the brain, which may become behaviorally explicit during adolescence, especially if the adolescent is exposed to high levels of stress or drug abuse (Fatemi and Folsom, 2009; Keshavan and Hogarty, 1999; Keshavan, 1999; Walker and Diforio, 1997; Walker et al., 2010; Helle et al., 2014; Jonsson et al., 2014; Limosin, 2014). However, the nature of the initial anomaly or how it leads to atypical neural wiring, and ultimately to schizophrenic symptoms, remains unknown. There may be a wide range of early neurodevelopmental disruptors, including specific genes or viruses, and there may be a wide range of subsequent factors present during childhood or adolescents, including experience of trauma and hormonal perturbations, that could individually or in combination result in expression of schizophrenia. Thus, the prevalent view is that schizophrenia is a polygenic/multifactorial disease (Tandon et al., 2008; Lichtermann et al., 2000; Sun et al., 2010). Moreover, we cannot exclude the possibility of dealing with several separate disorders or at least of separate etiologies leading to a similar clinical presentation. This is important to remember while discussing sex/gender differences in schizophrenia, as the disorder might have slightly different combination of etiological factors in men and women.

3. Sex differences in the development and clinical expression of schizophrenia

3.1. Birth complications & premorbid function

Obstetric complications have been linked to an overall increased risk to develop schizophrenia, an earlier age of illness onset, a poorer course of the illness and a ventricular enlargement (Kelly et al., 2004; Allen et al., 2013). Several studies have examined sex differences in these effects and found that the risk of developing schizophrenia following obstetric complications was higher in males than in females (Dalman et al., 1999; Kirov et al., 1996; Lewis, 1992; Lewis and Murray, 1987; Susser et al., 1998; Stromgren,