Sex Steroid Hormones and Brain Function Associated With Cognitive and Emotional Processing in Schizophrenia

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We have been flooded by the functional neuroimaging studies of psychiatric patients since the introduction of functional MRI (fMRI) to the field in the late 1990s, and subsequent popularization and increased availability of MR scanners in this century. PET and related methods (e.g., SPECT) have been around for longer, but the fact that they are more expensive and require injection of radioactive tracers has made their use less widespread (this despite some important advantages of PET over fMRI; for example, PET allows assessment of an absolute, rather than a relative baseline [in PET we simply compare no radioactivity with a count of radioactive tracer, while the fMRI typically requires comparison of a relative change in hemoglobin oxygenation in two different states], as well as possibility to visualize function of selected neurotransmitter systems).

After initial excitement about the application of functional neuroimaging techniques in psychiatry and promise of great discoveries and therapeutic breakthroughs, the enthusiasm has been somewhat tempered by the fact that up to date the fMRI or any other neuroimaging methods have not been very helpful in either the development of better treatment strategies or in the diagnosis of psychiatric disorders. Nevertheless, functional neuroimaging methods allowed us to validate certain neuropsychological and behavioral observations more directly (e.g., cognitive deficits observed in some schizophrenia patients are associated with the prefrontal cortex dysfunction);[1] and their use has sometimes helped patients to feel better about their psychiatric symptoms (e.g., it can be reassuring for the hallucinating patients to see that their psychosis stem from an atypical brain function). Moreover, selected neuroimaging literature reminds us of the brain's complexities, the brain–body and brain–environment interactions. These complexities and interactions contribute to great variability of results in the fMRI literature, especially those investigating heterogeneous clinical populations, such as schizophrenia (SZ), during performance of complex cognitive and emotional tasks.

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In addition to symptom heterogeneity and variations in the applied tasks, we and others have observed that sex and sex steroid hormones must be taken into consideration while evaluating the neural function of psychiatric patients (as well as healthy controls). For example, while our initial studies simply showed the existence of sex differences in the pattern of brain activation during various tasks, our more recent observations point to the fact that these sex differences appear to be at least partly accounted by the levels of circulating sex steroid hormones. Specifically, our initial studies involved simple re-analysis of already existing fMRI datasets collected in SZ patients during processing of negative emotions. We have found a very different pattern of cerebral activations between males and females,[2] but the absence of a healthy control group prevented us from drawing any definitive conclusions regarding the nature of this sexual dimorphism. This question had been explored further and subsequent studies generated some provocative results not only during processing of emotional material, but also during performance of a purely cognitive task of visuo-spatial processing. The task involved mental rotation of 3D figures and both the behavioral and the neuroimaging components of the study showed the reversal of normal sexual dimorphism. Thus, we observed a diagnosis-by-sex interaction with healthy men performing significantly better than healthy women (a relatively well-documented finding) and the opposite pattern in patients: women performing better than men.[3] The fMRI results revealed a similar pattern of extensive cerebral activations (in the parietal and lateral prefrontal cortex) and deactivations (in the medial prefrontal cortex) in healthy men and SZ women. In contrast, both healthy women and SZ men showed much more restricted activations and no significant deactivations.[4] Interestingly, our
subsequent study has shown that the selected cerebral activations during mental rotation were positively correlated with the level of testosterone in healthy males and in female patients, but not in healthy females or male patients. The brain activations during processing of emotional stimuli also revealed interesting relationship with sex steroid hormones, but in this case the most important were estradiol and progesterone.

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So, what does it all mean? First, it shows that the levels of circulating sex steroid hormones can affect brain function in neuroimaging studies, or at least it appears as this is the case; we have to remember that these are all correlational data and we really do not understand the relationship between hormonal levels in the peripheral and central nervous systems. Of course, we have known for decades about the important interplay between sex steroids and the brain, which starts very early in the neurodevelopment and then continues throughout our lives influencing our reproductive function, as well as cognitive and emotional processing. However, it took several years to remember about this important relationship in fMRI studies of psychiatric population, and now we need to figure out what is the nature of this relationship. But can we do it by sticking solely to the fMRI data? Most likely we cannot and we need to face the fact that the fMRI will never give us any 'final' etiological explanations. Functional neuroimaging studies provide correlational data that are mainly descriptive. As such, they cannot explain much, but they can help in generating new hypotheses. For example, we proposed that brain processing in male SZ patients may be feminized/demasculinized, while brain processing in female SZ patients may be masculinized/defeminized.

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The idea is not entirely novel in the field of psychiatry. For example, 'the extreme male brain' theory of autism proposes that the condition may be a result of exposure to elevated levels of testosterone during fetal neurodevelopment. SZ is also considered to be a neurodevelopmental disorder with origins during second and third trimester of the fetal development, which coincides with sexual differentiation of the brain. Interestingly, it has been suggested that autism and psychosis represent two extremes of a cognitive spectrum, with social cognition being underdeveloped (e.g., gaze-avoidance, 'literal-mindedness', and so on) in autistic-spectrum disorders and overdeveloped ('hyper-mentalizing', over-interpretation of mental states and intentions, and so on) in psychotic-spectrum disorders (the most severe being SZ). It has been further proposed that as autism involves traits representative of an 'extreme male brain', psychotic-spectrum disorders may be characterized by a 'female-typical' neuroanatomy, cognition and behaviors. However, while the 'extreme male brain' theory of autism works relatively well with males, it is harder to apply to females affected with the autism-spectrum disorders. Similarly, while it is likely that males affected with psychosis may be de-masculinized/feminized, the situation may be different for females, as our data in chronic SZ patients imply.

This hypothesis deserves further exploration, but the fMRI data can take us only so far. The 'neuroimagers' need to join forces with geneticists, molecular biologists, endocrinologists, epidemiologists, as well as clinicians if we want to progress in psychiatry.

References


