Sex, hormones and affective arousal circuitry dysfunction in schizophrenia

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Abstract

Women with schizophrenia express affective disturbances disproportionately more than men. Brain regions implicated in the affective arousal circuitry also regulate the hypothalamic-pituitary-adrenal and -gonadal systems, which are dysfunctional in schizophrenia. This review will argue that understanding the etiology of affective arousal deficits in schizophrenia is intimately connected with characterizing the role of neuroendocrine dysfunction and sex effects in schizophrenia. Further, the etiology of these neuroendocrine deficits begins during fetal development, during a period of time that coincides with the sexual differentiation of the brain and the vulnerability for schizophrenia. Studying the links between deficits in neuroendocrine systems and the affective arousal system in schizophrenia will provide clues to understanding the development of sex differences in schizophrenia and thereby its etiology.

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Schizophrenia has long been thought of as a disorder of disturbed affective arousal. In fact, Bleuler, when he coined the term schizophrenia, listed affective dysregulation as one of its four key attributes (Bleuler, 1911/1950). However, understanding the anatomical basis of affective disturbances in schizophrenia has not had a long history of research as compared with research on the affective arousal circuitry in psychiatric disorders such as depression and anxiety disorders. Further, women in general express higher rates of depression and anxiety disorders than men (Kessler, 1993), and in schizophrenia, these sex differences in affective functioning are exacerbated (Goldstein and Link, 1988; McGlashan and Bardenstein, 1990). Thus, an understanding of sex differences in affective arousal circuitry dysfunction in schizophrenia may provide clues to understanding sex differences in psychiatric disorders in general. Finally, brain regions implicated in the arousal circuitry also regulate the hypothalamic-pituitary-adrenal (HPA) and -gonadal (HPG) systems, which are dysfunctional in schizophrenia. Thus, this mini-review will argue that understanding the etiology of affective arousal deficits in schizophrenia is intimately connected with characterizing the role of neuroendocrine dysfunction and sex effects in schizophrenia. Further, the etiology of these dysfunctions begins during fetal development when the vulnerability for schizophrenia occurs (Goldstein and Walder, 2006).

Normal sex differences in the anatomy of emotion

The limbic system has been implicated in animal, human lesion and imaging studies in the anatomy of emotion (Derryberry and Tucker, 1992; LeDoux, 1998; Mesulam, 1990). Traditionally, subcortical limbic regions included the amygdala, hypothalamus, hippocampus, and anterior and medial dorsal nuclei of the thalamus, and cortical regions included the cingulate gyrus, orbitofrontal cortex, insula, temporal pole, and entorhinal cortex. The amygdala and hypothalamus integrate inputs from the cortical sensory association areas, and information from the viscera of the
Two recent fMRI studies showed that aversive stimuli activated the amygdala, anterior cingulate gyrus, and/or orbitofrontal cortex significantly more in men than in women (McClure, 2004; Wrase, 2003), even though subjective ratings of stimuli were similar (McClure, 2004). Two recent fMRI studies showed that aversive stimuli activated the amygdala, anterior cingulate gyrus, and/or orbitofrontal cortex significantly more in men than in women (McClure, 2004; Wrase, 2003), even though subjective ratings of stimuli were similar (McClure, 2004). Finally, girls aged 7–10 years exhibited greater arousal to aversive stimuli than same-aged boys, suggesting a sex difference in the development of the arousal circuitry in response to such stimuli (McManis, 2001).

Relationship of limbic system anatomy to neuroendocrine function

The limbic system is highly sensitive to hormonal influence (Herzog, 1999; Holmes and Donaldson, 1987; Logothetis, 1959) and highly vulnerable to pre- and perinatal injury (Falconer, 1974; Jensen, 1991). Limbic regions, such as the amygdala, hippocampus, cingulate gyrus and posterior orbitofrontal cortex, have strong reciprocal relationships with the endocrine system (Herzog, 1989). They have regionally distributed high concentrations of steroid receptors (Pfaff and Keiner, 1973; Stumpf, 1972), are sexually dimorphic (McEwen, 1999), show electrophysiologic (Sawyer, 1972), and neuroprotective as well as neurotoxic responses to steroids (Frye, 1995), and they play an important role in the modulation of endocrine secretion (Herzog, 1989).

The notion that limbic dysfunction, key to the nature of schizophrenia (Benes and Berretta, 2001; Epstein, 1999), may promote the development of endocrine dysfunction is well illustrated by work on temporolimbic epilepsy (TLE), in particular that of Dr. Andrew Herzog (Drislane, 1994; Herzog, 1986, 2002; Sperling, 1986; Zolovick, 1972). The corticomedial and basolateral amygdaloid divisions have separate output tracts (the stria terminalis and the ventral amygdalofugal pathway), which can exert opposing modulatory influences on pituitary hormonal secretion (Kaada, 1972; Zolovick, 1972), reproductive function (Kaada, 1972; Zolovick, 1972), and the resting membrane potentials of individual ventromedial hypothalamic neurons (Dreifuss, 1986). In stimulation studies in female rodents, the corticomedial division increases, while the basolateral division suppresses gonadotropin secretion (Kaada, 1972), and ablation leads to anovulation (Edwards, 1999; Kaada, 1972). Together, clinical and animal experimental findings suggest that disruption of the normal temporolimbic modulation of hypothalamic-pituitary function may disrupt gonadal hormonal secretion and promote the development of reproductive endocrine disorders. Animal and clinical studies have also implicated the amygdala in reproductive endocrine dysfunction in men (Herzog, 2002) and the hippocampus in relation to reproductive endocrine steroids and adrenocorticosteroids (McEwen, 1999). We hypothesize that, in schizophrenia, neuroendocrine abnormalities will be significantly associated with functional brain deficits in regions activated by stress response stimuli and will differ between the sexes.

In fact, the affective arousal circuitry implicates the so-called “stress hormones”, which involve three chemical messengers, corticotropin releasing hormone (CRH) released from the hypothalamus, including VMN and PVN, adrenocorticotropic hormone (ACTH) released from the pituitary, and glucocorticoids, i.e., cortisol in humans, from the adrenal gland. CRH and glucocorticoid receptors are located in numerous brain regions, including the central amygdala, VMN, VMN, anterior cingulate gyrus, and PPN in the affective arousal circuitry. Animal experiments have demonstrated that the PPN is an important relay station for the integration of endocrine and somatosensory information to central amygdala and bed nucleus of the stria terminalis (Carrer, 1978; Lopez and Carrer, 1985a, b). Further, the PPN, PVN and VMN have projections to each other as well as to the central amygdala (Arnault and Roger, 1987; Berk and Finkelstein, 1982; Jones, 1976; Kita and Oomura, 1982a, b; Simmerly and Swanson, 1986). Co-localization of androgen receptor and FOS, which is a marker of activation, implicates the PPN in the control of mating behaviors (Greco, 1996). In addition, local anesthesia and electrical stimulation confirm that the PPN controls sexual receptivity (Carrer, 1978; Hansen and Kohler, 1984; Lopez and Carrer, 1982; Lopez and Carrer, 1985a, b, 1988; Wedemeyer, 1999). It is also an important relay to PVN, VMN, and central amygdala for suckling stimuli that induce neuroendocrine events (e.g., prolactin release, lactation, and release of oxytocin (Factor, 1993; Hansen and Kohler, 1984) and it enhances the effect of GABA on eating and maternal aggression (Keever, 1988, Niehoff and Kuhar, 1983) and other male behaviors (Keever, 1988).

Thus, these brain regions form a system that are poised to integrate arousal, neuroendocrine responses and affect. Hypothalamic nuclei, such as PVN and VMN, are involved in the regulation of HPA hormones, have connections with brainstem regions, and are responsible for ANS function, adrenal and ovarian function and aggression, sexual and maternal behaviors (Swaab, 2003a, b, 2004). The hypothalamus integrates activity of the ANS and the neuroendocrine system (Fuchs, 1985). The central amygdala modulates pituitary hormone secretion and reproductive functions, as described in detail above (Arnado, 1993; Kaada, 1972; Zolovick, 1972) and is involved in emotion, aggression and fear/threat response. Medial/Orbital prefrontal (e.g., anterior cingulate gyrus) cortex provides frontal cortical influence over autonomic and endocrine function (Price, 1999) and an integrative function between bodily states and goal-directed behavior.

In our recent fMRI study, we demonstrated that activations of brain regions that form part of the arousal circuitry are modulated by menstrual cycle stage (Goldstein, 2005) suggesting a relationship between HPA and HPG hormones. In fact, ERα and ERβ are located in the central amygdala, VMN, PVN and PPN (Bao, 2005; Keever, 1988; Österlund, 1999; Österlund, 2000a, b; Stumpf, 1975). Although previous work demonstrated excitatory effects of estrogen on neuronal activity, it also has inhibitory effects, and, through its receptors (ERα, and...
Schizophrenia and the anatomy of affect

Although there are few functional imaging studies characterizing abnormalities in the functional anatomy of affect in schizophrenia, there is an extensive behavioral literature on emotion in schizophrenia (Berenbaum and Oltmanns, 1992; Cedro, 2001; Docherty, 1994; Habel, 2000; Heimberg, 1992; Hoschel and Ire, 2001; Kohler, 2000; Penn, 2000; Quirk, 1998; Schneider, 1995a, b; Shaw, 1999; Silver and Shlomo, 2001; Streit, 2001). Schizophrenia has been associated with deficits in emotion recognition and emotion discrimination using face stimuli (Heimberg, 1992; Hempel, 2003; Kohler, 2000; Schneider, 1995a, b; Silver and Shlomo, 2001; Streit, 2001), and emotional experience and expression during mood induction tasks (Berenbaum and Oltmanns, 1992; Cedro, 2001; Epstein, 1999; Habel, 2000; Penn, 2000; Quirk, 1998; Schneider, 1995a, b; Shaw, 1999; Sweet, 1998). These affective deficits were unaffected by the patients’ level of cognitive ability, suggesting that affective disturbances were not accounted for by the many cognitive dysfunctions associated with schizophrenia. Further, some of the same affective deficits have been found in first-degree relatives of schizophrenia patients (Docherty, 1994; Toomey, 1999), suggesting that they were part of the vulnerability for schizophrenia and not due to medication or psychosis effects per se.

The relationship of brain activity deficits in the arousal circuitry with symptomatology has been somewhat inconsistent across studies. Some studies reported that patients with so-called deficit schizophrenia showed greater reductions in emotion expression and recognition than nondeficit schizophrenia (Kring and Neale, 1996; Kring, 1993; Schneider, 1995a, b), although not consistently (Shaw, 1999; Sweet, 1998). Other studies have demonstrated that brain activity deficits in this circuitry are affected by psychotic symptomatology (Epstein, 1999; Phillips, 1999; Taylor, 2002). The inconsistencies in studies may be due to the lack of control for sex effects, since men with schizophrenia are more likely to exhibit the deficit state than women, and women more likely to exhibit paranoid delusions (Goldstein and Link, 1988), suggesting that brain mechanisms underlying affective disturbances may be differentially affected in men and women.

Although there are few functional imaging studies of affect in schizophrenia, brain activations related to emotion recognition and experience differed between schizophrenia and normal controls. Functional imaging studies of emotion discrimination and mood induction have demonstrated deficits in activations of frontal cortex, insula, and amygdala, unaccounted for by medication effects (Phillips, 1999; Schneider, 1998; Streit, 2001) or visual perception deficits (Phillips, 1999). Further, these brain activity deficits were correlated with autonomic arousal (Wik and Wiesel, 1991) and modulated by valence (Crespo-Facorro, 2001; Schneider, 1998). These brain regions have been found to be normally sexually dimorphic (see section above) and to have a high density of sex steroid and glucocorticoid receptors, thus suggesting a potential role for gonadal and adrenal hormones in understanding affective disturbances in schizophrenia and their association with one’s gender.

There are at least nine functional imaging studies investigating aversive affective arousal (or the stress response) in schizophrenia. In studies that directly compared schizophrenia with normal controls, schizophrenia showed significantly reduced activations in amygdala, orbitofrontal cortex and anterior cingulate gyrus (Epstein, 1999; Hempel, 2003; Paradiso, 2003; Taylor, 2000, 2002; Williams, 2004), with only one study reporting increased activation in anterior cingulate gyrus (Taylor, 2002). A reduction in amygdala activation (particularly in the right hemisphere) in schizophrenia compared with normal controls was found in response to negative or aversive stimuli in emotion recognition and emotion induction tasks (Hempel, 2003; Schneider, 1995a, b; Taylor, 2000), and, in the left hemisphere, to emotion discrimination in general (Gur, 2002a, b). Further, it was recently demonstrated that although there was reduced activation in amygdala and anterior cingulate gyrus in schizophrenia compared to normal controls, there was increased arousal (operationalized as increased electrodermal activity) demonstrating a disjunction between the ANS and central nervous systems (CNS) in schizophrenia (Williams, 2004). Findings suggested that there is a dysregulation of feedback between the ANS, amygdala and prefrontal cortex, which should contribute to regulating arousal (Williams, 2004). This is consistent with behavioral findings in schizophrenia showing greater arousal (indicated by electrodermal response), but less expression of emotion, indicating a disjunction between experience and expression (Kring and Neale, 1996). We would argue that hormonal abnormalities in schizophrenia, in part, explain the dysregulation between the ANS and CNS and differentially by sex. This is supported by (1) our previous MRI work showing significantly larger hypothalamic volume (implicating the PVN) in schizophrenia, particularly among women (Goldstein, in press); (2) the fact that these brain regions are critical in the regulation of HPA activity; and (3) studies demonstrating overactivity of the HPA system in schizophrenia (Breier, 1988; Risch, 1992; Roy, 1986; Walder, 2000; Walker and Diforio, 1997).

Schizophrenia and neuroendocrine function

Studies of schizophrenia, including our own, have demonstrated abnormalities in gonadal hormone levels, i.e., estrogen (Canuso et al., 2001; Haffner, 1991; Kulkarni, 2001; Seeman and Lang, 1990) and endocrine function (with rates of dysfunction reported from 50 to 75%) (Beaumont, 1974; Ghanadian, 1982; Reicher-Rossler, 1994; Sullivan and Lukoff, 1990). Although women with schizophrenia are reported to have diminished levels of estrogen (Oades and Scheper, 1994; Reicher-Rossler, 1994), the etiology of low estrogen levels is still unknown. Recent studies suggest an inverse relationship between estrogen levels and clinical symptoms, and a positive relationship between estrogen and cognitive performance in women with
1998; Tronche, 1999). There is also a wealth of preclinical studies demonstrating the impact of adverse fetal exposures on the HPG axis, resulting in disruptions in the normal sexual dimorphisms of the brain, such as in the hypothalamus and amygdala (De Vries, 2004; Kawata, 1995; Matsumoto and Arai, 1997; McCarthy, 1993; Rhem, 1999). Further, studies have shown that these adverse fetal effects have consequences for interactions between altered HPA and HPG systems (Chrousos, 1998) and that the effects of prenatal stressors on the brain are, in part, mediated by neurotransmitter systems that interact with glucocorticoids and gonadal steroid receptors (McCarthy, 2002; Sockel and Walker, 2001). Thus, we have hypothesized that adverse fetal events will affect fetal HPA and HPG hormonal programming by their impact on shared brain regions that will produce vulnerability to sex differences in adult brain abnormalities, HPA and HPG axis dysfunctions, psychoses and related psychotic mood disorders.

The article following this one (by Koenig) describes the encouraging progress being made in developing animal models for schizophrenia. However, most of the animal work does not consider sex and hormonal status or systematic contributions of abnormalities in the HPA and HPG axes to understanding schizophrenia. This review has argued that these factors constitute part of the endophenotypes that define the nature of schizophrenia and thus should be considered in the etiology of the disorder. Future translational studies of animal model experiments combined with human-level studies will contribute to the next generation of knowledge by considering the confluence of the role of hormones, genetic and epigenetic factors, and arousal circuitry deficits in understanding sex differences in schizophrenia. Further, we would argue that understanding the vulnerability for sex differences in adult brain abnormalities and neuroendocrine deficits in schizophrenia may not be specific to schizophrenia, and thus may provide the field with knowledge about the impact of one’s sex on a number of adult-onset disorders with fetal origins in clinical medicine.

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