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Sex differences, hormones, and fMRI stress response circuitry deficits in psychoses

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ABSTRACT

Response to stress is dysregulated in psychosis (PSY). fMRI studies showed hyperactivity in hypothalamus (HYPO), hippocampus (HIPP), amygdala (AMYG), anterior cingulate (ACC), orbital and medial prefrontal (OFC; mPFC) cortices, with some studies reporting sex differences. We predicted abnormal steroid hormone levels in PSY would be associated with sex differences in hyperactivity in HYPO, AMYG, and HIPP, and hypoactivity in PFC and ACC, with more severe deficits in men. We studied 32 PSY cases (50.0% women) and 39 controls (43.6% women) using a novel visual stress challenge while collecting blood. PSY males showed BOLD hyperactivity across all hypothesized regions, including HYPO and ACC by FWE-correction. Females showed hyperactivity in HIPP and AMYG and hypoactivity in OFC and mPFC, the latter FWE-corrected. Interaction of group by sex was significant in mPFC ($F=7.00$, $p=0.01$), with PSY females exhibiting the lowest activity. Male hyperactivity in HYPO and ACC was significantly associated with hypercortisolemia post-stress challenge, and mPFC with low androgens. Steroid hormones and neural activity were dissociated in PSY women. Findings suggest disruptions in neural circuitry-hormone associations in response to stress are sex-dependent in psychosis, particularly in prefrontal cortex.

1. Introduction

Schizophrenia has been associated with deficits in emotion recognition, discrimination (Heimberg et al., 1992; Schneider et al., 1995; Kohler et al., 2000; Streit et al., 2001), and experience (Berenbaum and Oltmanns, 1992; Schneider et al., 1995; Quirk et al., 1998; Epstein et al., 1999; Penn et al., 2000). These deficits, first recognized by Bleuler, were found in non-psychotic first-degree relatives (Docherty et al., 1994; Toomey et al., 1999), suggesting they represent vulnerability for schizophrenia (Phillips and Seidman, 2008; Phillips et al., 2011). Functional magnetic resonance imaging (fMRI) and positron emission tomography studies of emotional arousal in schizophrenia, particularly response to negatively-valenced stimuli or the so-called stress response, have consistently shown increased activation in hippocampus, amygdala and anterior cingulate cortex, coupled with decreased activation in prefrontal cortex (Wik and Wiesel, 1991; Epstein et al., 1999; Phillips et al., 1999; Crespo-Facorro et al., 2001; Taylor et al., 2002; Paradiso et al., 2003; Williams et al., 2004; Fernandez-Egea et al., 2010; Habel

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et al., 2010; Li et al., 2010), although this pattern was not consistent across all studies (Habel et al., 2010; Taylor et al., 2002). In fMRI studies, blood-oxygen-level-dependent (BOLD) signal changes in anterior cingulate cortex have been related to severity of delusions (Holt et al., 2011) and amygdala with affective symptoms (Strakowski et al., 2011), suggesting the need for analyses of traits as well as disorder per se to understand brain activity associated with the stress response.

Brain activity (BOLD) response to tasks of negative valence stimuli regardless of type of emotion have been associated with physiologic responses, such as autonomic arousal (Wik and Wiesel, 1991) and hypercortisolemia (Collip et al., 2011), underscoring their validity as defining the nature of a "stress response task". These brain activity responses in schizophrenia were not explained by visual deficits (Phillips et al., 1999; Reske et al., 2009; Anticevic et al., 2010), medication (Schneider et al., 1998; Phillips et al., 1999; Streit et al., 2001), or cognition (Ursu et al., 2011). However, sex differences in brain activity to negative valence stimuli have been associated with steroid hormone fluctuations in healthy females and in schizophrenia.

Functional MRI studies have shown hyperarousal to negatively valenced stimuli in healthy women compared to men (Borod et al., 1993; George et al., 1996; Lang et al., 1998; Bradley et al., 2001; Cahill et al., 2001; Canli et al., 2002; Wager et al., 2003; Wrase et al., 2003; McClure et al., 2004; McRae et al., 2008; Domes et al., 2010). The magnitude of hyperarousal varied across the menstrual cycle in women, with attenuation of hyperactivity in response to stress during mid-cycle compared with early follicular (McManis et al., 2001; Wrase et al., 2003; McClure et al., 2004; Goldstein et al., 2005; Derntl et al., 2008; McRae et al., 2008; Andreano and Cahill, 2010; Goldstein et al., 2010b) and increased prefrontal and anterior cingulate cortices during the luteal phase, when progesterone was heightened (Ossewaarde et al., 2011; Wang et al., 2007). Menstrual cycle variation contributed to understanding sex differences in response to stress in that men resembled women in early follicular (Goldstein et al., 2010b), a pattern also seen in rodents (Figueiredo et al., 2002). Hyperactivity of hypothalamus in healthy men vs. women was consistent across studies, controlled for menstrual cycle status and negatively correlated with estradiol levels (Goldstein et al., 2010b; Andreano and Cahill, 2010). Further, sex differences in laterality in this circuitry were demonstrated (Pardo et al., 1993; Cahill et al., 1996; George et al., 1996; Canli et al., 1999; Hamann et al., 1999; Damasio et al., 2000; Schneider et al., 2000; Cahill et al., 2001; Canli et al., 2002). Together, studies of sex differences in the healthy brain underscore the need to investigate sex differences in this circuitry systematically in psychoses, given the abundance of evidence demonstrating disrupted stress responses in these disorders.

Brain regions that respond to negatively valenced stimuli also regulate the hypothalamic-pituitary-adrenal (HPA) and HP-gonadal (HPG) systems, which are dysregulated in schizophrenia (Goldstein, 2006). Gonadal hormones, such as estradiol, modulate risk of psychotic illness across the lifespan (Goldstein and Walder, 2006). Likewise HPA dysregulation, at the adrenal, pituitary and central nervous system levels, contribute to the pathophysiology and etiology of schizophrenia (Holtzman et al., 2013; Koolschijn et al., 2008; Walker et al., 2002). Hippocampus, amygdala, hypothalamus, and anterior cingulate cortex are linked to endocrine function and neuroprotective and neurotoxic responses to reproductive steroid exposures (Herzog, 1989). Glucocorticoid receptors are located in the hippocampus, hypothalamus, prefrontal and anterior cingulate cortices, areas that are dense in sex steroid hormone receptors (Pacak et al., 1995; Koob, 1999). The hypothalamus, hippocampus and amygdala are involved in the regulation of HPA and HPG hormones, and anterior cingulate, medial, and dorsolateral prefrontal cortices influence autonomic and endocrine function (Price, 1999) integrating bodily states and goal-directed behavior. These brain regions are some of the most highly sexually dimorphic regions in the brain, demonstrating in vivo sex differences in brain volumes and brain activity in healthy populations (Filipek et al., 1994; Witelson et al., 1995; Giedd et al., 1996; Murphy et al., 1996; Paus et al., 1996; Passe et al., 1997; Rabinowicz et al., 1999; Nopoulos et al., 2000; Goldstein et al., 2001; Williams et al., 2005; Derntl et al., 2008; McRae et al., 2008; Domes et al., 2010; Mather et al., 2010), and schizophrenia (Gur et al., 1999; Frederikse et al., 2000; Goldstein et al., 2002, 2007; Mendrek, 2007).

We previously argued that there is shared pathophysiology between sex differences in stress response circuitry deficits and endocrine dysregulation in schizophrenia that originate during key fetal periods of sexual differentiation (Goldstein, 2006). Our hypotheses are based on the premise that normal sexual dimorphisms go awry in the development of schizophrenia (Goldstein et al., 2002), resulting in sex differences in adult stress response and neuroendocrine function. We hypothesize that *sex differences* in abnormalities in this circuitry are shared with other major psychoses, such as bipolar psychoses, whose etiologic origins begin in fetal development during this sensitive period. Thus, we predict participants with psychoses compared with healthy controls will demonstrate elevated BOLD signal in subcortical stress response circuitry regions and hypoactivity in cortical inhibitory regions. Furthermore, we expect the level of hyperactivity will be greater in men than women, and associated with elevated cortisol and low gonadal hormone deficits (low free androgens in men with psychoses; low estradiol in women with psychoses). Finally, although analyses are exploratory given our sample sizes, we predict shared sex-dependent stress response deficits in non-affective and affective psychoses.

2. Methods

2.1. Sample

Participants for this study were selected from adult offspring of a community sample of women who were originally recruited during their pregnancies 45 years ago, and have been followed by our team over the last 20 years, studies known as the New England Family Studies (NEFS) (Goldstein et al., 2010a, 2014a). In a series of case-control and high risk studies, we identified offspring participants (in their mid-forties) with psychoses. Expert diagnosticians (J.G., L.S. and J. Donatelli, Ph.D.) reviewed all information collected from systematic diagnostic interviews (First et al., 1996) and medical records, if available, to determine final best estimate diagnoses (Goldstein et al., 2010a; Seidman et al., 2013), resulting in 114 cases with DSM IV psychoses and 108 comparable controls (Goldstein et al., 2013).

We recruited 32 participants (50% women) with psychoses and 39 healthy controls (~44% women) for this functional MRI (fMRI) study of sex differences in stress response circuitry and hormonal deficits in psychoses. Approximately 20% were non-New England Family Study subjects but were recruited using the same criteria and from the same community catchment area and were not different on any sociodemographic or clinical characteristic than the rest of the sample. "Psychoses" included so-called "non-affective psychoses" (schizophrenia, schizoaffective, depressed type and psychosis not otherwise specified) and "affective psychoses" (bipolar disorder with psychosis, schizoaffective disorder, bipolar type) (see Table 1), a categorization that has been previously validated in multiple studies (Faraone and Tsuang, 1985; Kendler et al., 1985; Goldstein et al., 2010a) and successfully applied by our group and others (Goldstein et al., 2010a). Healthy controls were adult offspring from the New England Family Study for whom parents and grandparents and parents' and controls' siblings were free of any known lifetime history of psychosis, bipolar, schizotypal, recurrent major depressive disorder, suicide attempts, or psychiatric hospitalizations, as described previously (Goldstein et al., 2010a). Human subjects and methods approval were at Harvard University, Brown University, Partners Healthcare system, and local psychiatric facilities. Written consent was obtained from all study participants, and subjects were compensated for their participation.

2.2. Sample description

Clinical and demographic characteristics are presented in Table 1. There were no significant differences between cases and healthy controls within sex, except for younger age of female cases compared with healthy women. (Given this, analyses controlled for age.) Of the 16 men with psychoses, 44% were classified affective, 56%