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Effects of sex, menstrual cycle phase, and endogenous hormones on cognition in schizophrenia

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ABSTRACT

Background: In women with schizophrenia, cognition has been shown to be enhanced following administration of hormone therapy or oxytocin. We examined how natural hormonal changes across the menstrual cycle influence cognition in women with schizophrenia. We hypothesized that female patients would perform worse on "female-dominant" tasks (verbal memory/fluency) and better on "male-dominant" tasks (visuospatial) during the early follicular phase (low estradiol and progesterone) compared to midluteal phase (high estradiol and progesterone) in relation to estradiol but not progesterone.
Methods: Fifty-four women (23 with schizophrenia) completed cognitive assessments and provided blood for sex steroid assays and oxytocin at early follicular (days 2–4) and midluteal (days 20–22) phases. Men were included to verify the expected pattern of sex differences on cognitive tests.
Results: Expected sex differences were observed on "female-dominant" and "male-dominant" tasks ($p < 0.001$), but the magnitude of those differences did not differ between patients and controls ($p = 0.44$). Cognitive performance did not change across the menstrual cycle on "female-dominant" or "male-dominant" tasks in either group. Estradiol and progesterone levels were unrelated to cognitive performance. Oxytocin levels did not change across the menstrual cycle but were positively related to performance on "female-dominant" tasks in female patients only ($p < 0.05$).
Conclusions: Sex differences in cognitive function are preserved in schizophrenia. Oxytocin levels do not change across the cycle, but relate to enhanced performance on female dominant tests in women. Physiological levels of oxytocin may thus have a more powerful benefit in some cognitive domains than estrogens in schizophrenia.

1. Introduction

Intervention studies demonstrate a beneficial effect of short-term hormone therapy on clinical symptoms and cognitive performance in premenopausal women with schizophrenia (Kulkarni et al., 1996, 2002, 2008; Akhondzadeh et al., 2003; Louza et al., 2004; Ko et al., 2006a; Bergemann et al., 2008; Ghafari et al., 2013; Huerta-Ramos et al., 2014; Kulkarni et al., 2014). Hormone therapy was found to specifically enhance verbal memory and fluency in premenopausal women with schizophrenia (Ko et al., 2006a) suggesting that these cognitive abilities might also be influenced by endogenous hormone levels. Physiological levels of estradiol and progesterone are higher during the midluteal phase of the menstrual cycle compared to the early follicular phase and have been shown in some studies to influence cognitive abilities in healthy women (Hampson, 1990a,b; Maki et al., 2002; Hampson et al., 2014). Little is known about how these variations in endogenous levels of sex hormones might influence cognition in women with schizophrenia. Oxytocin may also have beneficial effects on cognition in schizophrenia (Feifel et al., 2012; Frost et al., 2014). Whether endogenous levels of oxytocin are related to cognitive performance in women with schizophrenia and whether there are cycle-related variations in these relationships is unknown. Examining these relationships in schizophrenia is important because there is an overlap in the cognitive abilities that are impaired in schizophrenia, that improve with hormone therapy in healthy women (Hogervorst and

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Bandelow, 2010) and in schizophrenia (Ko et al., 2006a; Bergemann et al., 2008; Huerta-Ramos et al., 2014), and that favor women over men (e.g., verbal memory) (Kramer et al., 1988).

In this study, we examined sex differences in cognition in patients with schizophrenia and controls, and then evaluated whether cognitive performance varies across the menstrual cycle in women with and without schizophrenia in relation to levels of estradiol, progesterone, and oxytocin. The primary outcomes were "male" and "female" dominant cognitive domains that show reliable advantages in one sex compared to the other (Rubin et al., 2008). Women show an advantage in verbal memory, verbal fluency, visual scanning, and fine motor skills whereas men show an advantage in visuospatial abilities (Kramer et al., 1988, 1997; Mann et al., 1990; Snow and Weinstock, 1990; Schmidt et al., 2000; McCurry et al., 2001; Weiss et al., 2003, 2006; Halari et al., 2005). Based on previous studies, we hypothesized that both patients and controls would show the expected sex differences in these cognitive domains and that the magnitude of those sex differences would be preserved in schizophrenia. We also hypothesized that female patients and controls would show enhancements in "female-dominant" abilities during the midluteal compared to follicular phase, but the opposite pattern on "male-dominant" abilities. Based on evidence in healthy women, we expected those changes to relate to estradiol but not progesterone. Lastly, in exploratory analyses, we examined the relationship between cognitive performance and endogenous levels of oxytocin predicting that higher levels of endogenous oxytocin would be positively associated with cognitive abilities more generally.

2. Methods

2.1. Participants

Participants included 50 patients (23 women) and 58 controls (31 women). Participants were 18 to 40 years of age and spoke English as their first language. Diagnosis of schizophrenia or schizoaffective disorder depressed type was confirmed with a Structured Clinical Interview for DSM (SCID). All women were regularly menstruating (28 ± 5 days) and were not taking any oral contraceptives. Exclusion criteria for all participants were: history of head trauma or other neurological disorder; history of substance abuse/dependence, excluding cigarettes; high intake of phytoestrogens ($\geq$3 servings of soy/day or supplements); conditions resulting in abnormal gonadal hormone secretion; significant medical illness; and use of sex hormone treatments. Controls were also excluded if they were taking medications known to influence the central nervous system or had an Axis I psychiatric disorder (based on SCID interview). Exclusion criteria for females included atypical menstrual cycle length ($>$ or $<28 \pm 5$ days) and pregnancy/lactation within the previous year.

Controls were recruited from the community, and patients from outpatient clinics and residential facilities in the Chicago metropolitan area. Patients [schizophrenia (68%), schizoaffective disorder-depressed type (32%)] were clinically stable, and reported stable medication regimens for the prior three months. Most patients (84%) were prescribed second generation antipsychotics. Antipsychotic medication dosages ranged from 40 to 1133 mg/day chlorpromazine equivalents (Woods, 2003) (median dosage, 400 mg/day). Forty-six percent of patients were taking antidepressants and 4% were taking mood stabilizers. Written informed consent was obtained from all participants. Study procedures were approved by the UIC Institutional Review Board.

2.2. Measures

2.2.1. Female-dominant tests

Verbal learning and memory were assessed with the California Verbal Learning Test (CVLT) (Delis et al., 1987). Verbal fluency was assessed with phonemic, semantic, and rhyme fluency tests. On the fluency task, participants generated as many words as possible in 60 s that began with a particular letter (phonemic), were animals or supermarket items (semantic), or rhymed with a particular cue word. Parallel forms of these verbal tests were administered to minimize practice effects. Data for outcome measures employed are in Table 2. Processing speed was assessed with the WAIS-R Digit Symbol Substitution Subtest (DSST; Wechsler, 1987) and fine motor skills with the Grooved Pegboard Test (GPEG; Reitan and Wolfson, 1985).

Previous studies report sex differences in favor of females on verbal memory (Kramer et al., 1997, 1988), verbal fluency (Bolla et al., 1990; Rahman et al., 2003; Weiss et al., 2003, 2006 Halari et al., 2005), DSST (Mann et al., 1990; Snow and Weinstock, 1990; McCurry et al., 2001), and GPEG (Schmidt et al., 2000; McCurry et al., 2001).

2.2.2. Male-dominant test

Visuospatial abilities were assessed using the card rotations test (Wilson and Vandenberg, 1978). Participants view individual sample line drawings of a geometric figure and eight alternatives that show the sample in two or three-dimensional rotations of the drawing. Men show an advantage on this task compared to women (Sanders et al., 1982).

2.3. Procedures

Participants were assessed in two separate sessions, approximately 42 days apart. Women were evaluated during the early follicular phase (days 2–4; low estradiol/progesterone) and the midluteal phase (days 20–22; high estradiol/progesterone), where "day 1" was the first day of menstrual bleeding. As described previously, phase was validated with estradiol and progesterone levels using commercial kits (estradiol by double-antibody radioimmunoassay; progesterone by "Coat-a-Count" coated tube RIA, Diagnostic Products, Los Angeles, CA) (Rubin et al., 2010). Serum prolactin (for determination of possible hyperprolactinemia, >30 ng/ml) was measured using two-site immunoenzymometric assay (TOSOH Bioscience, CA) (sensitivity = 1 ng/ml, intra-assay CV = 1.5%). Phase at first session was counterbalanced across female participants, and testers were blind to menstrual cycle phase. Men were also tested in separate sessions approximately 42 days apart. Given that half the women were randomly assigned to follicular phase first and half to luteal phase first, half of the men were randomly assigned to have data from their first session reversed with that of the second session. This methodological approach reduces confounds related to carry over effects. Plasma hormone assays for free testosterone and oxytocin were performed as described previously (Rubin et al., 2010).

2.4. Statistical analyses

For the first aim regarding sex differences in cognitive function, the primary outcomes of interest were the "female-dominant" composite z-score and the "male-dominant" score. To create these, raw scores on each individual cognitive test were transformed into standardized z-scores using data obtained from the healthy controls (males and females combined) at the first cognitive assessment (selected to avoid confound of practice effects) and then averaged together to create a composite representing "female-dominant" cognitive abilities. To reduce the number of statistical comparisons, we only examined verbal memory, verbal fluency, processing speed, and fine motor skill composite measures to follow-up on significant findings. Since we only administered one "male-dominant" task, the "male-dominant" score was the z-score for the card rotations test. For the analysis of sex differences at Session 1, the two male and female scores were used in a multivariate analysis of covariance (MANCOVA) where group (patient, control) and sex were the between-subjects variables and age was the covariate.

For the second aim addressing whether "female-dominant" and "male-dominant" abilities change across the menstrual cycle, mixed

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