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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 better on "female-dominant" tasks (verbal memory/fluency) and worse 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.

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Contributors

Drs. Rubin and Maki conceived the idea and methodology for the study. Dr. Carter developed the methodology to explore oxytocin and served as an advisor and resource on this project for understanding oxytocin. Dr. Sweeney served as an advisor on this project and provided his expertise in schizophrenia. Drs. Pournajafi-Nazarloo and Drogos ran the oxytocin assays and helped interpret the data. Dr. Sweeney provided his expertise in schizophrenia, and all authors were involved in data interpretation and manuscript preparation. Dr. Rubin conducted the statistical analyses and wrote the first draft. Drs. Rubin, Maki, and Sweeney exchanged multiple versions of the manuscript. All authors approved the final version.

Conflict of Interest

Dr. Sweeney is a consultant to Pfizer, BMS, Takeda, and Lilly and had a research grant from Janssen. Dr. Maki received honoraria from the American Nutraceutical Association and research support from the Soy Health Research Program. Dr. Rubin declares that, except for income received from their primary employer, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest. There are no conflicts of interest for the other authors.

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.

Keywords

sex differences; estrogen; menstrual cycle; cognition; schizophrenia; oxytocin

1. Introduction

Intervention studies demonstrate a beneficial effect of short-term hormone therapy on clinical symptoms and cognitive performance in premenopausal women with schizophrenia (Akhondzadeh et al., 2003; Bergemann et al., 2008; Ghafari et al., 2013; Huerta-Ramos et al., 2014; Ko et al., 2006a; Kulkarni et al., 2002; 2008; 1996; Kulkarni et al., 2014; Louza et al., 2004). 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; Hampson et al., 2014; Maki et al., 2002). 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 Bandelow, 2010) and in schizophrenia (Bergemann et al., 2008; Huerta-Ramos et al., 2014; Ko et al., 2006a), 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 (Halari et al., 2005; Kramer et al., 1988; 1997; Mann, 1990; McCurry, 2001; Schmidt, 2000; Snow and Weinstock, 1990; Weiss et al., 2003; 2006). 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±5days) 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 (≥ 3 servings of soy/day or supplements); and (4) 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+5days) 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 40–1133mg/day chlorpromazine equivalents (Woods, 2003) (median dosage, 400mg/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 was assessed with the California Verbal Learning Test (CVLT) (Delis, Kaplan, & Ober, 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 seconds 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., 1988; Kramer et al., 1997), verbal fluency (Bolla et al., 1990; Halari et al., 2005; Rahman et al., 2003; Weiss et al., 2003; Weiss et al., 2006), DSST (Mann, 1990; McCurry, 2001; Snow and Weinstock, 1990), and GPEG (McCurry, 2001; Schmidt, 2000).

2.2.1. 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).

2.4. Procedures

Participants were assessed in two separate sessions, approximately 42 days apart. Women were evaluated during the early follicular phase (Day 2–4; low estradiol/progesterone) and the midluteal phase (Day 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, > 30ng/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).

2.5. 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 skills 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 design ANCOVAS were conducted in which Menstrual Phase (follicular, midluteal) was the within-subjects variable, Group and Phase Order (follicular-midluteal, midluteal-follicular) were the between-subjects variables, and age was the covariate. Phase Order was included in the analysis to control for possible carryover effects from low to high estradiol/progesterone conditions or vice versa (Hampson, 1990a, b). Parallel ANOVAs were conducted in men to examine changes in cognition across sessions using the same z-score approach as in the analysis of sex differences. To reduce the number of statistical comparisons, we only examined individual test scores when the “female-dominant” cognitive ability was significant.

Exploratory analyses examined the correlation between absolute endogenous hormone levels and cognitive performance at Session 1 which minimized influence of practice and repeated testing on cognitive performance.

3. Results

Patients and controls did not significantly differ on parental education or ethnicity; however, patients (M=30.9, SD=6.2) were three years older than controls (M=27.7, SD=6.3)($p<0.05$) (Table 1).

3.1. Sex Differences in Cognition in Schizophrenia

Table 2 provides the mean z-scores (with standard error) for the “female-dominant” composite score and the “male-dominant” score as a function of group and sex at Session 1. As expected, there was a statistically significant difference between sexes, validating the designation of tests as “female” or “male”, $F(2, 102)=10.79$, $p<0.001$, Wilk’s $\wedge=0.82$. Follow-up analyses indicated that women (patients and controls) showed an advantage on the “female-dominant” composite ($p<0.01$) whereas men (patients and controls) showed an advantage on the “male-dominant” score ($p<0.05$). Of the “female-dominant” tests, women showed an advantage on all measures (p’s<0.05) except the verbal fluency composite ($p=0.44$). There was no significant Group x Sex interaction indicating that the magnitude of the sex difference did not differ across patients and controls, $F(2, 102)=0.81$, $p=0.45$, Wilk’s $\wedge=0.98$. As expected, patients performed more poorly than controls, $F(2, 102)=28.98$, $p<0.001$, Wilk’s $\wedge=0.63$.

3.2. Changes in Sex Hormones and Sexually Dimorphic Cognitive Abilities across the Menstrual Cycle

As previously described (Rubin et al., 2010), estradiol and progesterone levels were significantly higher during the midluteal versus follicular phase (*p*'s<0.001) whereas testosterone and oxytocin levels were stable across the cycle (p's>0.48)(Table 3). Progesterone levels were also lower in patients compared to controls (*p*=0.003), but only during the midluteal phase (*p*<0.001). Despite these significant cycle-related changes in estradiol and progesterone, sexually dimorphic cognitive abilities did not change significantly across the menstrual cycle in women with or without schizophrenia (Table 4).

As previously described (Rubin et al., 2010), in men, only free testosterone levels were lower in male patients compared to controls (p<0.05). As expected, no hormone levels differed as a function of test session in males and sexually dimorphic cognitive abilities did not differ significantly across sessions (Table 5).

3.3. Correlational Analyses between Sex Hormones and Sexually Dimorphic Cognitive Abilities

At Session 1, levels of estradiol and progesterone were not associated with cognitive performance in women with or without schizophrenia. However, in female patients, higher levels of oxytocin were associated with better performance on the "female-dominant" composite (r=0.46, p=0.04; Figure 1), but not the male dominant test, even after controlling for age (r=0.52, p=0.02). A follow-up analysis of individual tests comprising the female composite suggested that those effects were driven by verbal memory (CVLT long delay free recall, r=0.45, p=0.04) and semantic fluency (r=0.46, p=0.04). Oxytocin was not associated with cognitive performance in female controls. There were no significant associations between sex hormones and the "female-dominant" composite or "male-dominant" score in men with or without schizophrenia. A similar pattern of correlations were demonstrated when scores from both sessions were averaged.

4. Discussion

In the present study, we sought to examine hormonal correlates of cognitive function in schizophrenia by comparing performance of male and female patients and controls after grouping tests according to their typical sex difference. We sought to determine whether those sex differences are preserved in schizophrenia, change across the menstrual cycle in schizophrenia, and related to physiological levels of sex hormones and oxytocin. Consistent with findings from healthy individuals, (Halpern, 1986; Kimura and Hampson, 1993) and in schizophrenia (Fiszdon et al., 2003; Gur et al., 2001; Halari et al., 2006; Rubin et al., 2008; Sota and Heinrichs, 2003), our findings suggest that we were justified in grouping tests according to "female-dominant" and "male-dominant" abilities and that this pattern of sex-related cognitive abilities is preserved in individuals with schizophrenia.

Contrary to prediction, cognitive performance was unrelated to variations in sex steroid hormones across the menstrual cycle in women with or without schizophrenia. The absence of a midluteal phase enhancement on "female-dominant" abilities and an early follicular enhancement on "male-dominant" abilities in the present study is consistent with a recent

meta-analysis in healthy individuals (for a review see, Sundstrom Poromaa and Gingnell, 2014) and in a small study of women with psychosis (Thompson et al., 2000). These findings suggest that these sex-related biases in cognitive ability may be established early in life rather than being maintained by hormone levels – at least as pertains to normal physiological variation in hormone levels and the magnitude of change in them that occurs during the menstrual cycle. Typical cycle-related changes in cognitive abilities are subtle and maybe influenced by genetics (Egan et al., 2001; Jacobs and D'Esposito, 2011) or possibly altered by other hormonal effect such as cortisol (Andreano et al., 2008; Duchesne and Pruessner, 2013; Espin et al., 2013).

Higher levels of oxytocin were associated with better "female-dominant" abilities in women with schizophrenia, although levels of estradiol and progesterone were not associated with cognitive performance. These findings in female patients are consistent with two studies from male-dominant samples of patients with schizophrenia, including a study demonstrating enhanced verbal learning and memory performance with adjunctive intranasal oxytocin (Feifel et al., 2012) and a recent study showing a positive association between endogenous oxytocin levels and processing speed (Frost et al., 2014). Our results suggest that previous findings in men may generalize to women. We did not find associations between endogenous oxytocin levels and verbal memory in men, perhaps men need a higher level of oxytocin to enhance verbal memory compared to women or alternatively perhaps the previous findings in male-dominant samples were driven by women. These findings also add to the growing literature that oxytocin in patients with schizophrenia often shows sex-specific associations in both clinical symptom presentation and emotion perception (Rubin et al., 2011; Rubin et al., 2010; Strauss et al., 2015). In women with schizophrenia, oxytocin may confer direct benefit to "female-dominant" cognitive abilities by acting on the neural substrates of those abilities (e.g., hippocampus) or alternatively might benefit those cognitive abilities indirectly through effects on clinical symptoms.

Oxytocin is directly related to brain function and behavior, possibly via the autonomic nervous system (Gimpl and Fahrenholz, 2001) which regulates emotion and state (Sequeira et al., 2009). Conversely, estrogens effects are more global, structural, and based at least in part on protein synthesis; so some, but not all of estrogens influences would be expected to be slow (Marino et al., 2006). Oxytocin in contrast may have more direct effects and thus induce more rapid changes in physiological and behavior states which may underlie the capacity for improvements in cognitive functioning. The reason why oxytocin may have sex-biased effects on only "female-dominant" abilities requires further study. Assessment of "female-dominant" abilities was more extensive in our study, which may have enhanced our ability to see effects in this domain. Or, oxytocin might have a specific effect on female abilities as studies with other hormones have shown with supra-physiological dosing of hormone administration. It is noteworthy that the oxytocin effects were present in female patients but not controls, suggesting that a facilitative role of oxytocin on cognition may be more evident in cognitively compromised women with schizophrenia, which would be consistent with a potential therapeutic role for oxytocin therapy in the disorder.

The present study has several limitations. First, we had a limited sample size. Second, the "male dominant" composite included only one test, albeit assessing the domain with the

greatest male cognitive advantage. Future studies with a more comprehensive assessment of "male-dominant" skills is needed to better determine whether oxytocin has a general impact on cognition or one that is greater in female tasks. Third, we measured peripheral levels of sex steroid hormones and oxytocin. Peripheral hormone levels are imperfect markers of central hormone levels which may in part explain the lack of associations between peripheral estradiol and progesterone and cognition. While hormone levels are measurable in CSF (Walf et al., 2011), such studies are not always practical and are invasive. However, peripheral hormone levels have been shown to be related to cognitive function in menstrual cycle studies in healthy women (Maki et al., 2002; Mordecai et al., 2008) and in patients with schizophrenia (Hoff et al., 2001; Ko et al., 2006b). Finally, our focus was only on naturally cycling women who had regular menstrual cycles. Menstrual cycle abnormalities are common in females with schizophrenia, particularly among those taking antipsychotics. Smaller studies suggest that these abnormalities can range in patients anywhere from 26–78% (Haddad and Wieck, 2004). Thus, it has yet to be determined whether these associations in women with regular cycles are generalizable to women without menstrual abnormalities.

5. Conclusions

In sum, the present study demonstrates that individuals with schizophrenia show expected sex differences in cognitive performance but this performance is unrelated to sex steroid hormone levels across the menstrual cycle. Our findings add to a growing literature showing that cognitive changes across the menstrual cycle are often difficult to detect and might not be as reliable as the changes in clinical symptoms and social cognition in schizophrenia (Rubin et al., 2011; Rubin et al., 2010). Moreover, improvements in symptoms across the menstrual cycle do not seem to co-occur with cognitive benefits for women with schizophrenia. Higher levels of oxytocin were related to enhanced performance on female tests in women with schizophrenia. These findings suggest that sex steroid hormones have limited effects in modulating sexually dimorphic cognitive abilities in premenopausal women with and without schizophrenia. However, oxytocin may represent a novel therapeutic target for not only social cognition but cognitive functioning more generally, particularly in women with schizophrenia. Oxytocin, but not estrogens relation to sex-biased cognitive abilities may have implications for cognition-enhancing treatments for schizophrenia, especially for female patients.

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References

Akhondzadeh S, Nejatisafa AA, Amini H, Mohammadi MR, Larijani B, Kashani L, Raisi F, Kamalipour A. Adjunctive estrogen treatment in women with chronic schizophrenia: a double-blind, randomized, and placebo-controlled trial. Prog Neuropsychopharmacol Biol Psychiatry. 2003; 27(6):1007–1012. [PubMed: 14499318]

Andreano JM, Arjomandi H, Cahill L. Menstrual cycle modulation of the relationship between cortisol and long-term memory. Psychoneuroendocrinology. 2008; 33(6):874–882. [PubMed: 18468808]

Bergemann N, Parzer P, Jaggy S, Auler B, Mundt C, Maier-Braunleder S. Estrogen and comprehension of metaphoric speech in women suffering from schizophrenia: results of a double-blind, placebo-controlled trial. Schizophr Bull. 2008; 34(6):1172–1181. [PubMed: 18156639]

Bolla KI, Lindgren KN, Bonaccorsy C, Bleecker MLJCP. Predictors of verbal fluency (fas) in the healthy elderly. J Clin Psychol. 1990; 46(5):623–628. [PubMed: 2246370]

Duchesne A, Pruessner JC. Association between subjective and cortisol stress response depends on the menstrual cycle phase. Psychoneuroendocrinology. 2013; 38(12):3155–3159. [PubMed: 24055042]

Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A. 2001; 98(12):6917–6922. [PubMed: 11381111]

Espin L, Almela M, Hidalgo V, Villada C, Salvador A, Gomez-Amor J. Acute pre-learning stress and declarative memory: impact of sex, cortisol response and menstrual cycle phase. Horm Behav. 2013; 63(5):759–765. [PubMed: 23587533]

Feifel D, Macdonald K, Cobb P, Minassian A. Adjunctive intranasal oxytocin improves verbal memory in people with schizophrenia. Schizophr Res. 2012; 139(1–3):207–210. [PubMed: 22682705]

Fiszdon JM, Silverstein SM, Buchwald J, Hull JW, Smith TE. Verbal memory in schizophrenia: sex differences over repeated assessments. Schizophr Res. 2003; 61(2–3):235–243. [PubMed: 12729875]

Frost K, Keller W, Buchanan R, Gold J, Koenig J, Ossenfort K, Katz A, Strauss G. C-14Plasma Oxytocin Levels are Associated with Impaired Social Cognition and Neurocognition in Schizophrenia. Arch Clin Neuropsychol. 2014; 29(6):577–578. [PubMed: 25176857]

Ghafari E, Fararouie M, Shirazi HG, Farhangfar A, Ghaderi F, Mohammadi A. Combination of estrogen and antipsychotics in the treatment of women with chronic schizophrenia. Clinical schizophrenia & related psychoses. 2013; 6(4):172–176. [PubMed: 23302446]

Gimpl G, Fahrenholz F. The oxytocin receptor system: structure, function, and regulation. Physiological reviews. 2001; 81(2):629–683. [PubMed: 11274341]

Gur RC, Ragland JD, Moberg PJ, Bilker WB, Kohler C, Siegel SJ, Gur RE. Computerized neurocognitive scanning: II. The profile of schizophrenia. Neuropsychopharmacology. 2001; 25(5):777–788. [PubMed: 11682261]

Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. Drugs. 2004; 64(20):2291–2314. [PubMed: 15456328]

Halari R, Hines M, Kumari V, Mehrotra R, Wheeler M, Ng V, Sharma T. Sex differences and individual differences in cognitive performance and their relationship to endogenous gonadal hormones and gonadotropins. Behav Neurosci. 2005; 119(1):104–117. [PubMed: 15727517]

Halari R, Mehrotra R, Sharma T, Ng V, Kumari V. Cognitive impariment but preservation of sexual dimorphism in cognitive abilities in chronic schizophrenia. Psychiatry Research. 2006; 141:129–139. [PubMed: 16427141]

Halpern, DF. Sex differences in cognitive abilities. Lawrence Erlbaum Associates; Hillsdale, NJ: 1986.

Hampson E. Estrogen-related variations in human spatial and articulatory-motor skills. Psychoneuroendocrinology. 1990a; 15(2):97–111. [PubMed: 2359813]

Hampson E. Variations in sex-related cognitive abilities across the menstrual cycle. Brain Cogn. 1990b; 14(1):26–43. [PubMed: 2223043]

Hampson E, Levy-Cooperman N, Korman JM. Estradiol and mental rotation: relation to dimensionality, difficulty, or angular disparity? Horm Behav. 2014; 65(3):238–248. [PubMed: 24394702]

Hoff AL, Kremen WS, Wieneke MH, Lauriello J, Blankfeld HM, Faustman WO, Csernansky JG, Nordahl TE. Association of estrogen levels with neuropsychological performance in women with schizophrenia. Am J Psychiatry. 2001; 158(7):1134–1139. [PubMed: 11431236]

Hogervorst E, Bandelow S. Sex steroids to maintain cognitive function in women after the menopause: a meta-analyses of treatment trials. Maturitas. 2010; 66(1):56–71. [PubMed: 20202765]

Huerta-Ramos E, Iniesta R, Ochoa S, Cobo J, Miquel E, Roca M, Serrano-Blanco A, Teba F, Usall J. Effects of raloxifene on cognition in postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. Eur Neuropsychopharmacol. 2014; 24(2):223–231. [PubMed: 24342775]

Jacobs E, D'Esposito M. Estrogen shapes dopamine-dependent cognitive processes: implications for women's health. J Neurosci. 2011; 31(14):5286–5293. [PubMed: 21471363]

Kimura, D.; Hampson, E. Neural and hormonal mechanisms mediating sex differences in cognition. In: Vernon, PA., editor. Biological approaches to the study of human intelligence. Ablex Publishing Corporation; Norwood, New Jersey: 1993. p. 375-397.

Ko YH, Joe SH, Cho W, Park JH, Lee JJ, Jung IK, Kim L, Kim SH. Effect of hormone replacement therapy on cognitive function in women with chronic schizophrenia. International journal of psychiatry in clinical practice. 2006a; 10(2):97–104. [PubMed: 24940959]

Ko YH, Joe SH, Cho W, Park JH, Lee JJ, Jung IK, Kim L, Kim SH. Estrogen, cognitive function and negative symptoms in female schizophrenia. Neuropsychobiology. 2006b; 53(4):169–175. [PubMed: 16763376]

Kramer JH, Delis DC, Daniel M. Sex differences in verbal learning. Journal of Clinical Psychology. 1988; 44:907–915.

Kramer JH, Delis DC, Kaplan E, O'Donnell L, Prifitera A. Developmental sex differences in verbal learning. Neuropsychology. 1997; 11(4):577–584. [PubMed: 9345701]

Kulkarni J, De Castalla A, Downey M, Taffe J, Fitzgerald P. Estrogen- a useful adjunct in the treatment of men with schizophrenia? Schizophrenia Research. 2002; 53(3 Suppl 1):10.

Kulkarni J, de Castella A, Fitzgerald PB, Gurvich CT, Bailey M, Bartholomeusz C, Burger H. Estrogen in severe mental illness: a potential new treatment approach. Arch Gen Psychiatry. 2008; 65(8):955–960. [PubMed: 18678800]

Kulkarni J, de Castella A, Smith D, Taffe J, Keks N, Copolov D. A clinical trial of the effects of estrogen in acutely psychotic women. Schizophr Res. 1996; 20(3):247–252. [PubMed: 8827850]

Kulkarni J, Gavrilidis E, Wang W, Worsley R, Fitzgerald PB, Gurvich C, Van Rheenen T, Berk M, Burger H. Estradiol for treatment-resistant schizophrenia: a large-scale randomized-controlled trial in women of child-bearing age. Mol Psychiatry. 2014

Louza MR, Marques AP, Elkis H, Bassitt D, Diegoli M, Gattaz WF. Conjugated estrogens as adjuvant therapy in the treatment of acute schizophrenia: a double-blind study. Schizophr Res. 2004; 66(2–3):97–100. [PubMed: 15061241]

Maki PM, Rich JB, Rosenbaum RS. Implicit memory varies across the menstrual cycle: estrogen effects in young women. Neuropsychologia. 2002; 40(5):518–529. [PubMed: 11749982]

Mann VA, Sasanuma S, Sakuma N, Masaki S. Sex differences in cognitive abilities: A cross-cultural perspective. Neuropsychologia. 1990; 28(10):1063–1077. [PubMed: 2267058]

Marino M, Galluzzo P, Ascenzi P. Estrogen signaling multiple pathways to impact gene transcription. Current genomics. 2006; 7(8):497–508. [PubMed: 18369406]

McCurry SM, Gibbons LE, Uomoto JM, Thompson ML, Graves AB, Edland SD, Bowen J, McCormick WC, Larson EB. Neuropsychological test performance in a cognitively intact sample of older Japanese American adults. Archives of Clinical Neuropsychology. 2001; 16(5):447–459. [PubMed: 14590159]

Mordecai KL, Rubin LH, Maki PM. Effects of menstrual cycle phase and oral contraceptive use on verbal memory. Horm Behav. 2008; 54(2):286–293. [PubMed: 18455727]

Rahman Q, Abrahams S, Wilson GD. Sexual-orientation-related differences in verbal fluency. Neuropsychology. 2003; 17(2):240–246. [PubMed: 12803429]

Reitan, RM.; Wolfson, D. The Halstead-Reitan Neuropsychological Test Battery: Theory and clinical interpretation. Neuropsychology Press; Tucson: 1985.

Rubin LH, Carter CS, Drogos L, Jamadar R, Pournajafi-Nazarloo H, Sweeney JA, Maki PM. Sex-specific associations between peripheral oxytocin and emotion perception in schizophrenia. Schizophr Res. 2011; 130(1–3):266–270. [PubMed: 21684122]

Rubin LH, Carter CS, Drogos L, Pournajafi-Nazarloo H, Sweeney JA, Maki PM. Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. Schizophr Res. 2010; 124(1–3):13–21. [PubMed: 20947304]

Rubin LH, Haas GL, Keshavan MS, Sweeney JA, Maki PM. Sex difference in cognitive response to antipsychotic treatment in first episode schizophrenia. Neuropsychopharmacology. 2008; 33(2): 290–297. [PubMed: 17392734]

Sanders B, Soares MP, D'Aquila JM. The sex difference on one test of spatial visualization: a nontrivial difference. Child Dev. 1982; 53(4):1106–1110. [PubMed: 7128257]

Schmidt SL, Oliveira RM, Rocha FR, Abreu-Villaca Y. Influences of handedness and gender on the grooved pegboard test. Brain and Cognition. 2000; 44(3):445–454. [PubMed: 11104536]

Sequeira H, Hot P, Silvert L, Delplanque S. Electrical autonomic correlates of emotion. Int J Psychophysiol. 2009; 71(1):50–56. [PubMed: 18723054]

Snow WG, Weinstock J. Sex differences among non-brain-damaged adults on the Wechsler Adult Intelligence Scales: A review of the literature. J Clin Exp Neuropsychol. 1990; 12(6):973–876.

Sota TL, Heinrichs RW. Sex differences in verbal memory in schizophrenia patients treated with "typical" neuroleptics. Schizophr Res. 2003; 62(1–2):175–182. [PubMed: 12765758]

Strauss GP, Keller WR, Koenig JI, Sullivan SK, Gold JM, Buchanan RW. Endogenous oxytocin levels are associated with the perception of emotion in dynamic body expressions in schizophrenia. Schizophr Res. 2015; 162(1–3):52–56. [PubMed: 25620121]

Sundstrom Poromaa I, Gingnell M. Menstrual cycle influence on cognitive function and emotion processing-from a reproductive perspective. Frontiers in neuroscience. 2014; 8:380. [PubMed: 25505380]

Thompson K, Sergejew A, Kulkarni J. Estrogen affects cognition in women with psychosis. Psychiatry Res. 2000; 94(3):201–209. [PubMed: 10889284]

Walf AA, Paris JJ, Rhodes ME, Simpkins JW, Frye CA. Divergent mechanisms for trophic actions of estrogens in the brain and peripheral tissues. Brain Res. 2011; 1379:119–136. [PubMed: 21130078]

Wechsler, D. Wechsler Memory Scale—Revised. Psychological Corporation; San Antonio, TX: 1987.

Weiss EM, Kemmler G, Deisenhammer EA, Fleischhacker WW, Delazer M. Sex differences in cognitive function. Pers Individ Dif. 2003:863–875.

Weiss EM, Ragland JD, Brensinger CM, Bilker WB, Deisenhammer EA, Delazer M. Sex differences in clustering and switching in verbal fluency tasks. J Int Neuropsychol Soc. 2006; 12(4):502–509. [PubMed: 16981602]

Wilson, JR.; Vandenberg, SG. Sex differences in cognition: Evidence from the Hawaii family study. In: McGill, DA.; Dewsbury, DA.; Sachs, BD., editors. Sex and behavior. Plenum; New York: 1978. p. 317-335.

Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry. 2003; 64(6):663–667. [PubMed: 12823080]

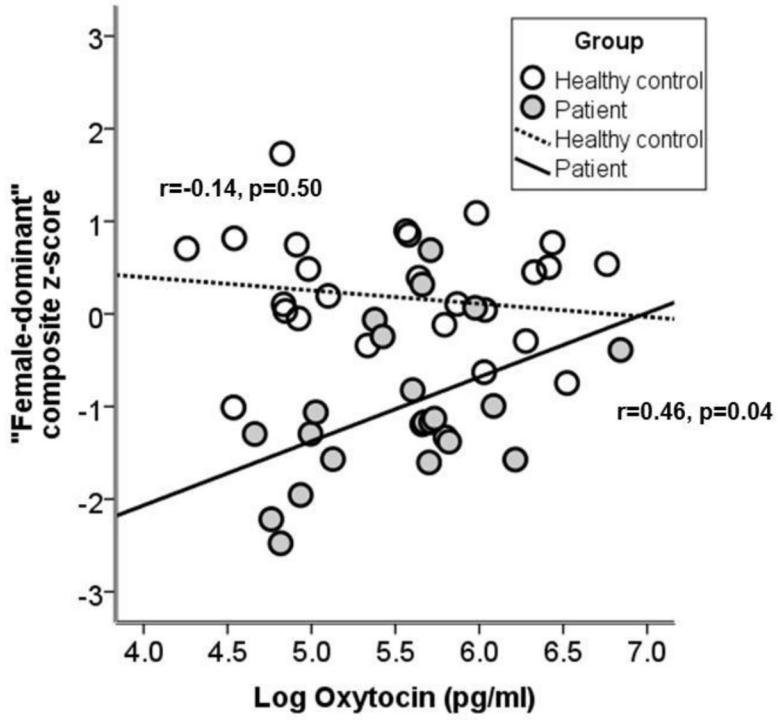

Figure 1.

Higher levels of peripheral oxytocin are associated with better “female-dominant” abilities in women with schizophrenia at Session 1.

Table 1

Demographics and Clinical Characteristics

	Women		Men	
	Patients (n = 23)	Healthy Controls (n = 31)	Patients (n = 27)	Healthy Controls (n = 27)
Variables	**M (SD)**	**M (SD)**	**M (SD)**	**M (SD)**
Age *G*	30.65 (5.73)	27.55 (6.67)	31.19 (6.60)	27.93 (5.99)
Parental SES	3.00 (0.95)	3.13 (1.34)	3.14 (1.08)	3.33 (1.30)
Race, n (%)				
White, non-Hispanic	7 (31)	9 (29)	4 (15)	12 (44)
African-American, non-Hispanic	11 (48)	14 (45)	16 (59)	8 (30)
Hispanic or Latino	4 (17)	3 (10)	4 (15)	1 (4)
Other	1 (4)	5 (16)	3 (11)	6 (22)
SCID diagnosis, n (%)				
Schizophrenia	13 (57)		21 (78)	
Schizoaffective (depressed type)	10 (43)		6 (22)	
Duration of Illness in years†	12.96 (5.50)		11.39 (7.89)	
First Generation Antipsychotics, n (%)	3 (13)		5 (19)	
Second Generation Antipsychotics, n (%)				
Risperidone±	6 (26)		9 (33)	
Clozapine	2 (9)		3 (11)	
Olanzapine	3 (13)		2 (7)	
Quetiapine	3 (13)		4 (15)	
Ziprasidone	3 (13)		2 (7)	
Aripiprazole	3 (13)		2 (7)	
Chlorpromazine mg equivalents *S*	320 (255)		484 (288)	
Antipsychotic + antidepressant, n (%)	13 (56)		10 (37)	
Antipsychotic + mood stabilizer, n (%)	1 (4)		1 (4)	
Hyperprolactinemia,>30 ng/ml, n (%)	5 (22)		6 (24)	
PANSS total score	61.51 (8.46)		65.30 (11.35)	

Note. Parental SES higher scores reflect higher SES; SCID = Structured Clinical Interview for DSM; PANSS = Positive and Negative Syndrome Scale.

† In years since initial treatment for psychosis.

± Higher propensity to elevate prolactin levels compared to other second generation antipsychotics.

G Main effect of group was significant at $p<0.05$.

S Main effect of sex was significant at $p<0.05$.

Table 2

Estimated means (SE) and Effect Size (*d*) of z-scores on Cognitive Measures adjusted for age as a Function of Test, Sex, and Group at Session 1.

	Patients			Controls			Overall Effects	
	Women (n = 23)	Men (n = 27)	*d*	Women (n = 31)	Men (n = 27)	*d*	Group	Sex
Test	**M (SE)**	**M (SE)**		**M (SE)**	**M (SE)**			
Female-dominant tests								
Female composite	−1.03 (0.16)	−1.35 (0.15)	0.41	0.22 (0.14)	−0.25 (0.15)	0.60	***	**
CVLT composite	−0.50 (0.19)	−0.91 (0.18)	0.44	0.33 (0.17)	−0.36 (0.18)	0.73	***	**
Total (Trials 1–3)	−0.63 (0.21)	−1.01 (0.20)	0.37	0.34 (0.18)	−0.36 (0.20)	0.68	***	**
Free recall short	−0.47 (0.20)	−0.86 (0.19)	0.40	0.35 (0.17)	−0.38 (0.19)	0.76	***	**
Free recall long	−0.38 (0.20)	−0.88 (0.19)	0.51	0.30 (0.18)	−0.34 (0.19)	0.64	**	**
Verbal Fluency composite	−0.56 (0.18)	−0.66 (0.16)	0.11	0.08 (0.15)	−0.07 (0.16)	0.18	***	ns
Digit Symbol	−1.16 (0.19)	−1.75 (0.18)	0.64	0.24 (0.16)	−0.36 (0.17)	0.68	***	***
Grooved Pegboard composite	−1.51 (0.25)	−2.04 (0.23)	0.44	0.19 (0.21)	−0.20 (0.23)	0.33	***	*
Male-dominant test								
Card Rotations	−0.84 (0.18)	−0.54 (0.20)	0.31	−0.27 (0.18)	0.30 (0.19)	0.57	***	*

Note.

*** $p<0.001$;

** $p<0.01$;

* $p<0.01$;

d=standardized mean-difference effect size. CVLT = California Verbal Learning Test. Also, note that z-scores were calculated by creating within-test z-scores first. The mean of the z-scores for a multi-variable test such as the CVLT is not 0 for the controls as one would expect if all scores were converted to z-scores based on the scores for the total healthy sample. For all tasks, positive numbers indicate better performance. A MANCOVA examining the female composite and card rotations test controlling for age indicated a significant effect of sex overall ($p<0.001$) and for each of the scores (p's<0.05). There was no significant interaction Group x Sex interaction ($p=0.45$).

Table 3

Endogenous Serum Hormone Levels (M and SD) in a Function of Menstrual Cycle Phase (early follicular, midluteal) in Female Patients and Healthy Controls.

	Group				p-values		
	Patients (n = 23)		Controls (n = 31)				
	Early Follicular	Midluteal	Early Follicular	Midluteal	Menstrual Phase	Group	Menstrual Phase x Group
Phase	M (SD)	M (SD)	M (SD)	M (SD)			
17-β-Estradiol (pg/ml)	42.47 (21.95)	120.82 (57.04)	42.48 (21.64)	121.67 (48.63)	<0.001	0.96	0.95
Progesterone (ng/ml)	0.78 (0.48)	5.69 (4.77)	0.77 (0.40)	11.19 (7.21)	<0.001	0.003	0.002†
Free Testosterone (pm/L)	17.02 (17.19)	16.91 (13.86)	15.68 (19.74)	13.59 (8.60)	0.74	0.45	0.88
Oxytocin (pg/ml)	284.35 (187.50)	321.88 (229.45)	327.75 (231.76)	316.16 (174.70)	0.49	0.67	0.29

Note.

† Patients had lower values than controls during the midluteal phase.

Table 4

Estimated Means (SE) and Effect Size (*d*) of z-scores on Cognitive Measures adjusted for age as a Function of Menstrual Cycle Phase in Women (Follicular Versus Midluteal) and Group (Patients, Controls).

	Patients (*n* = 23)			Controls (*n* = 31)			Overall Effects	
Test	Follicular M (SE)	Midluteal M (SE)	F vs. M *d*	Follicular M (SE)	Midluteal M (SE)	F vs. M *d*	Group	Phase
Female-dominant tests								
Female composite	−1.05 (0.16)	−1.14 (0.16)	0.12	0.26 (0.14)	0.25 (0.14)	0.01	***	ns
Male-dominant test								
Card Rotations	−0.65 (0.24)	−0.71 (0.25)	0.05	−0.02 (0.20)	−0.09 (0.21)	0.06	*	ns

Note.

*** $p<0.001$;

** $p<0.01$;

* $p<0.01$;

F = Follicular; M = Midluteal; *d*=standardized mean-difference effect size; Composite scores were first created by computing within test z-scores followed by between-test z-scores. Therefore, the composite scores will not sum to 0 as typically expected. For all tasks, positive numbers indicate better performance. There were no significant group x phase interactions (p's>0.39).

Table 5

Estimated means (SE) and Effect Size (*d*) of z-scores on Cognitive Measures adjusted for age as a function of Session in Men (A Versus B) and Group (Patients, Controls).

	Patients (*n* = 27)			Controls (*n* = 27)			Overall Effects	
	A	B	A vs. B	A	B	A vs. B	Group	Session
Test	**M (SE)**	**M (SE)**	***d***	**M (SE)**	**M (SE)**	***d***		
Female-dominant tests								
Female composite	−1.27 (0.15)	−1.31 (0.16)	0.05	−0.19 (0.16)	−0.17 (0.16)	0.02	***	ns
Male-dominant test								
Card Rotations	−0.32 (0.20)	−0.35 (0.20)	0.03	0.38 (0.18)	0.39 (0.18)	0.01	*	ns

Note.

*** $p<0.001$;

** $p<0.01$;

* $p<0.01$;

A = Session A; B = Session B; *d*=standardized mean-difference effect size; Half of the men completed Session A first, and half completed Session B first. Composite scores were first created by computing within test z-scores followed by between-test z-scores. Therefore, the composite scores will not sum to 0 as typically expected. For all tasks, positive numbers indicate better performance. There were no significant group x session interactions (p's>0.50).