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Estrogen treatment effects on cognition, memory and mood in male-to-female transsexuals

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Abstract

Gonadal hormones, particularly estrogens, have been suggested to influence memory and cognitive tasks that show sex differences. Previously, we reported that male-to-female (M–F) transsexuals undergoing estrogen treatment for sex re-assignment scored higher on verbal Paired Associate Learning (PAL) than a transsexual control group awaiting estrogen treatment. The present study used a more robust design to examine further associations between estrogen and cognition. We assessed additional aspects of memory, including visual, spatial, object and location memory, other cognitive abilities that show reliable sex differences, including verbal and visual–spatial abilities, and mood variables that could mediate associations between estrogen and cognition. In addition to comparing groups of individuals on and off estrogen, we used two repeated measures designs (AB and BA). The AB group was tested prior to hormone treatment and then again after treatment had begun; the BA group was tested while on estrogen treatment and then again when hormones had been withdrawn prior to surgery. Few changes in memory or cognition were observed, and changes that were observed were not consistent across study designs. The lack of significant effects did not relate to mood changes or to the sexual orientation of participants. These findings suggest that estrogen treatment associated with sex change for M–F transsexuals has little or no influence on sex-typed aspects of cognition or memory.

Keywords: Estrogen; Memory; Mood; Cognition; Spatial ability; Verbal ability; Transsexual; Sex differences; Hormone replacement; Sex change; Menstrual cycle; Postmenopausal; Gonadal hormones

Differences between males and females have been reported in specific cognitive abilities. On average, males outperform females on certain tests of visual–spatial ability, such as mental rotations, and females outperform males on certain tests of verbal ability, such as verbal fluency (Hyde and Linn, 1988; Collaer and Hines, 1995; Voyer et al., 1995). Females also excel on some tests of verbal memory, such as Paired Associate Learning (PAL) and story recall (Ivison, 1977; DesRosiers and Ivison, 1988; Mann et al., 1990), and on certain spatial memory tasks such as remembering locations of objects (Silverman and Eals, 1992). In contrast, males may excel at retaining other types of spatial information, such as the position of letters in a grid (Kails and Siegel, 1977) or at reproducing designs from memory (Ivison, 1977).

It has been suggested that hormones, particularly androgens and estrogens, may contribute to these cognitive sex differences. In non-human mammals, gonadal hormones guide brain development prenatally or neonatally (Arnold and Gorski, 1984: Collaer and Hines, 1995), permanently influencing behaviors that show sex differences. Hormones also influence the brain at puberty, and postpubertal hormone fluctuations are thought to contribute to sex differences in memory and cognitive abilities (Collaer and Hines, 1995; Hampson and Kimura, 1992). Neural localization of estrogen receptors, particularly in the hippocampus, also suggests a possible hormonal role in cognitive functions involving learning and memory (Loy et al., 1988; O'Keefe and Handa, 1990; Eichenbaum and Otto, 1992).

In non-human mammals, males outperform females on certain aspects of maze learning (Dawson et al., 1975; Gaulin

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and Fitzgerald, 1986; Williams et al., 1990; Galea et al., 1994; Perrot-Sinal et al., 1996; Galea et al., 1996; Bimonte and Denenberg, 2000). In addition, administering estradiol to adult female rats following ovariectomy can enhance performance in the radial maze and the Morris water maze (Luine and Rodriguez, 1994; Williams et al., 1994; Williams, 1996; Packard et al., 1996; Packard and Teather, 1997; Luine, 1997; Daniel et al., 1997; Fader et al., 1999; Sandstrom and Williams, 2001), although some studies have found no influence of estrogen on maze performance in rats (Stackman et al., 1997; Berry et al., 1997).

Estrogen also may relate to memory and cognition in humans. Postmenopausal women have been found to show improved verbal PAL after 6 months of estrogen treatment (Caldwell and Watson, 1952), and estrogen administered following surgical menopause may augment some aspects of verbal, but not visual, memory (Sherwin and Phillips, 1990; Phillips and Sherwin, 1992a; Sherwin, 1996, 2003). However, similar estrogenic effects on memory following menopause are not always found (Barrett-Connor and Kritz-Silverstein, 1993; Binder et al., 2001), and some studies have associated Hormone Replacement Therapy (HRT) with better cognitive function in general in postmenopausal women (Kimura, 1995; Resnick et al., 1997; Hogervorst et al., 1999; Duka et al., 2000; Farrag et al., 2002).

Variation in gonadal hormones over the menstrual cycle also has been linked to memory and cognition. It has been suggested that, in the midluteal phase, when estrogen levels are high, verbal abilities, or other abilities at which females excel, are enhanced and visual–spatial abilities, or other abilities at which males excel, are impaired, whereas the reverse occurs at menses, when estrogen levels are low (Hampson and Kimura, 1988; Hampson, 1990a,b,c; Phillips, 1996; Maki et al., 2002). However, associations of verbal and visual–spatial performance with cycle phase have not always been found (Gordon et al., 1986; Gordon and Lee, 1993; for a review, see Epting and Overman, 1998). In regard to memory, Phillips and Sherwin (1992b) report significantly lower delayed visual memory recall during the menstrual phase compared to the luteal phase, but no differences for other memory tests, such as Digit Span (DS) and PAL.

Transsexual individuals offer one of the few ethical opportunities to study the effect of estrogen treatment on cognitive performance in human males. Genetic males transitioning to live as women (male-to-female (M–F)) transsexuals are treated with estrogen to promote feminization of breast and hip contours (Green, 2005), and this treatment could also influence cognitive performance. One study reported that ten M–F transsexuals showed impaired visual–spatial and improved verbal performance after 3 months of cross-sex hormones (Van Goozen et al., 1995). Although these results were not replicated in two subsequent studies (Slabbekoorn et al., 1999; Van Goozen et al., 2002), one failure to replicate was attributed to studying only homosexual M–F transsexuals (i.e., those erotically interested in men) (Van Goozen et al., 2002). In a prior study, we found that M–F transsexuals taking estrogen showed enhanced performance on PAL, a verbal memory task at which females generally excel, but no change in verbal or visuospatial ability (Miles et al., 1998).

Alterations in mood also have been associated with Estrogen Replacement Therapy (ERT). One study of women with clinically diagnosed depression found that ERT plus fluoxetine reduced depressive feelings more than fluoxetine alone (Schneider et al., 1997). Estrogen also has been associated with positive mood among women in general (Amsterdam et al., 1999). However, Barrett-Connor et al. (1999) measured plasma levels of estradiol, testosterone, estrone, androstenedione, cortisol, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate in postmenopausal women and found only one significant association, a negative relationship between the androgen, DHEA, and depression. A meta-analytic review concluded that HRT ameliorated depressed mood, although different hormone preparations, differences in the length of treatment and the differing measures used to assess mood produced variable effect sizes (Zweifel and O'Brien, 1997).

In summary, studies investigating changes in memory and cognition over the menstrual cycle or with HRT have produced inconsistent results. Similarly, initial results suggested that estrogen treatment improved verbal fluency and impaired spatial ability in M–F transsexuals, but subsequent studies have not replicated these findings, although the failure to replicate could reflect a focus on homosexual M–F transsexuals. Furthermore, one study suggests that estrogen treatment of M–F transsexuals enhances verbal PAL performance, but there are no replication attempts for this result and other aspects of memory have not been investigated. Estrogen may also influence mood, and hormone-related mood changes could mediate relations between hormones and cognition.

In this study, we examined effects of estrogen on cognition and memory, as well as mood, in homosexual and heterosexual M–F transsexuals. To enhance the power of the study, in addition to comparing groups of individuals on versus off estrogen, we used a repeated measures design in which M–F transsexuals were tested twice, either before and then after the initiation of estrogen treatment (AB), or while on estrogen treatment and then after withdrawal of estrogen (BA). The main hypotheses tested were that M–F transsexuals taking estrogen would show enhanced memory and cognitive abilities at which females excel and impaired memory and cognitive abilities at which males excel. No differences were predicted on tasks showing no sex difference.

Methods

Participants

Genetic males ($n=103$) desiring sex re-assignment as females and diagnosed as having Gender Identity Disorder (American Psychiatric Association, 1994) were recruited through the Gender Identity Clinic, Charing Cross Hospital, London, UK, and were paid £10 for participation. For the repeated measures analyses, participants formed 2 conditions, depending on their stage in the treatment process. (1) Off then on (AB) condition: patients were tested first shortly before estrogen treatment began ($n=27$, mean age=37.07 years, SD=8.68) and then again 3 to 12 months later, depending on when clinic visits were scheduled ($n=27$, mean age=37.85 years, SD=8.84); (2) on then off (BA) condition: patients were tested after having been on estrogen for at least 28