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Functional anatomy of visuo-spatial working memory during mental rotation is influenced by sex, menstrual cycle, and sex steroid hormones

S. Schöning [a,b,1], A. Engelien [a,b,c,1], H. Kugel [d], S. Schäfer [a,b], H. Schiffbauer [d], P. Zwitserlood [e], E. Pletziger [a,b], P. Beizai [a,b], A. Kersting [a], P. Ohrmann [a], R.R. Greb [f], W. Lehmann [g], W. Heindel [d], V. Arolt [a], C. Konrad [a,b,*]

[a] *Department of Psychiatry, University of Münster, Germany*
[b] *Interdisciplinary Center for Clinical Research (IZKF), University of Münster, Germany*
[c] *FNL, Department of Psychiatry, Weill Medical College, Cornell University, New York, NY, USA*
[d] *Department for Clinical Radiology, University of Münster, Germany*
[e] *Department of Psychology, University of Münster, Germany*
[f] *Department of Obstetrics Gynecology, University of Münster, Germany*
[g] *Department of Psychology, University of Magdeburg, Germany*

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Abstract

Recent observations indicate that sex and level of steroid hormones may influence cortical networks associated with specific cognitive functions, in particular visuo-spatial abilities.

The present study probed the influence of sex, menstrual cycle, and sex steroid hormones on 3D mental rotation and brain function using 3-T fMRI. Twelve healthy women and 12 men were investigated. Menstrual cycle and hormone levels were assessed. The early follicular and midluteal phase of the menstrual cycle were chosen to examine short-term cyclical changes.

Parietal and frontal areas were activated during mental rotation in both sexes. Significant differences between men and women were revealed in both phases of menstrual cycle. In men we observed a significant correlation of activation levels with testosterone levels in the left parietal lobe (BA 40). In women, a cycle-dependent correlation pattern was observed for testosterone: brain activation correlated with this male hormone only during the early follicular phase. In both cycle phases females' brain activation was significantly correlated with estradiol in frontal and parietal areas.

Our study provides evidence that fMRI-related activity during performance of cognitive tasks varies across sex and phases of the menstrual cycle. The variation might be partly explained by better task performance in men, but our results indicate that further explanations like basic neuronal or neurovascular effects modulated by steroid hormones must be considered. Both estradiol and testosterone levels may influence fMRI signals of cognitive tasks, which should affect selection of subjects for future fMRI studies.

Keywords: Cognition; Functional magnetic resonance imaging; Mental rotation; Visuo-spatial working memory; Sex differences

1. Introduction

Better performance of men compared to women on tests of spatial abilities is well documented in the (neuro)psychological literature (Linn & Peterson, 1985; Voyer, Voyer, & Bryden, 1995). This holds in particular for the Mental Rotation Test (Peters et al., 1995; Shepard & Metzler, 1971; Vandenberg & Kuse, 1978). Mental rotation implies the active manipulation of objects in mind which is based on visuo-spatial memory functions (visuo-spatial sketchpad) (Baddeley, 1992). During the last 35 years, stable effects concerning sex differences in mental rotation have been reported to the advantage of men (Geiser, Lehmann, & Eid, 2006; Lehmann, 2000; Masters & Sanders, 1993). However, it still remains unclear which

* Corresponding author at: Department of Psychiatry, IZKF Research Group, University of Münster, Albert-Schweitzer-Str.11, D-48149 Münster, Germany. Tel.: +49 251 83 57214; fax: +49 251 83 56612.
E-mail address: konradc@uni-muenster.de (C. Konrad).
[1] These authors contributed equally to the present work.

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biological and/or environmental factors may underlie women's poorer task performance. Among influencing factors, sex hormones seem to be of major relevance, with both human and animal studies providing evidence for a biological explanation (Christiansen, 2001; Collaer & Hines, 1995; Kimura, 2002; Lacreuse, 2006). Other potential factors contributing to this gender effect include environmental influences, such as learning effects, or sex stereotypes.

Effects of sex hormones, especially testosterone, have been investigated in several behavioural studies (Hooven, Chabris, Ellison, & Kosslyn, 2004). Studies on testosterone supplementation in testosterone-deficient states, in transsexuals, and in healthy women suggest a positive influence of testosterone on visuo-spatial abilities and spatial memory (Collaer, Geffner, Kaufman, Buckingham, & Hines, 2002; Hines et al., 2003; Orwoll et al., 2006; Van Goozen, Slabbekoorn, Gooren, Sanders, & Cohen-Kettenis, 2002). A single sublingual administration of 0.5 mg testosterone is sufficient to improve visuo-spatial abilities in healthy young women (Aleman, Bronk, Kessels, Koppeschaar, & van Honk, 2004). Spatial memory in women may also benefit from testosterone intake (Postma et al., 2000). Cherrier et al. reported an enhancement of spatial and verbal memory after 6 weeks of intramuscular testosterone in elderly men (advanced age is known to be associated with a state of relative testosterone deficiency) (Cherrier et al., 2001). Working-memory function might also be improved by testosterone supplementation (Janowsky, Chavez, & Orwoll, 2000). Female-to-male transsexuals demonstrate enhanced performance on tests of visuo-spatial ability after 3 months of androgen treatment, while male-to-female transsexuals perform less well under androgen deprivation (Slabbekoorn, van Goozen, Megens, Gooren, & Cohen-Kettenis, 1999; Van Goozen, Cohen-Kettenis, Gooren, Frijda, & Van de Poll, 1994, 1995).

Taken together, these studies suggest a positive correlation between testosterone and spatial abilities, with an almost linear increase in several studies. However, other studies found a curvilinear relationship or sex-specific associations between testosterone and cognitive abilities (Moffat & Hampson, 1996; Muller, Aleman, Grobbee, de Haan, & van der Schouw, 2005; Thilers, Macdonald, & Herlitz, 2006). This suggests that an optimal hormonal state for performance is not necessarily associated with the highest levels of testosterone.

Modulating effects of sex steroid hormones on visuo-spatial abilities are not limited to testosterone. Estradiol also exerts effects on some aspects of memory and attention in animals (Lacreuse, 2006), as well as on several cognitive processes in humans (Maki & Resnick, 2001). Effects of female sex hormones on cognitive abilities have been demonstrated by variations along the menstrual cycle. Women might perform better in spatial tests during the menstruation, as compared to other phases of the menstrual cycle in which estradiol and progesterone are present in higher concentrations (Hampson, 1990a, 1990b; Hausmann, Slabbekoorn, Van Goozen, Cohen-Kettenis, & Gunturkun, 2000; Silverman & Phillips, 1993).

Using modern functional imaging techniques, the neural networks underlying mental rotation and visuo-spatial working memory processes have been investigated during the last decade, and still new questions arise, e.g. concerning the influence of rotation angle on imagined spatial transformation (Keehner, Guerin, Miller, Turk, & Hegarty, 2006) and of social variables (Berns et al., 2005). As a main result, the parietal cortex emerged as a core region for mental rotation processes, e.g. (Alivisatos & Petrides, 1997; Jordan, Heinze, Lutz, Kanowski, & Jancke, 2001; Richter, Ugurbil, Georgopoulos, & Kim, 1997; Tagaris et al., 1996). This was to be expected from neuropsychological work showing selective deficits in mental rotation in patients with parietal lesions (Ditunno & Mann, 1990; Tomasino & Rumiati, 2004; Tomasino, Vorano, Skrap, Gigli, & Rumiati, 2004). In addition, precentral, medial frontal, and temporal regions are part of the mental rotation network (Barnes et al., 2000; Cohen et al., 1996; Kosslyn, Thompson, Wraga, & Alpert, 2001; Richter et al., 2000). Of interest here, sex and menstrual cycle were probed in some previous studies among other factors influencing these networks and their functions. The overall regional pattern of activations seems to be similar in men and women, and task-related activation differences occur within these cortical regions (Jordan, Wustenberg, Heinze, Peters, & Jancke, 2002; Thomsen et al., 2000; Weiss et al., 2003). Remarkably, these differences persist when behavioural measures are comparable for both sexes (Jordan et al., 2002; Weiss et al., 2003).

In only very few recent imaging studies, the cycle phase was taken into account at all (Gizewski, Krause, Wanke, Forsting, & Senf, 2006; Halari et al., 2006). To the best of our knowledge, almost no available fMRI study examined men as well as the same women in two different phases of their menstrual cycle. An exception is the study of Dietrich et al. who investigated two phases of menstrual cycle in six females and six males and reported no sex differences for the low estradiol phase, but prominent differences for the high estradiol phase (Dietrich et al., 2001). Moreover, previous fMRI studies are limited in that the cycle phase was determined by self-reports only, and not by serum hormone analysis. Halari et al. (2006) found that males activated the left middle temporal gyrus and the right angular gyrus more than women during menstruation in addition to the regions of the mental rotation network. Gizewski et al. investigated females in the ovulatory cycle phase and found stronger activation in frontal and parietal cortex in men, whereas females showed stronger activation of the other frontal areas and left fusiform gyrus (Gizewski et al., 2006). Despite the limitations discussed above, these studies indicate that the phase of menstrual cycle plays an important role and needs to be considered.

Our functional MRI study was designed to investigate the influence of sex, phase of the menstrual cycle, and sex steroid hormone levels on cognitive performance and related fMRI signals. In order to probe sex differences, a sexually dimorphic mental rotation task was used. To overcome limitations of many previous studies, women were investigated in two well-defined phases of their menstrual cycle, confirmed by sex steroid level analysis. Moreover, every participant underwent substantial clinical and neuropsychological testing, to control for possible confounding factors. In brief, this study was designed to probe the following three hypotheses: (a) Mental rotation performance and fMRI signals during mental rotation are related to