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Physiological variation in estradiol and brain function: A functional magnetic resonance imaging study of verbal memory across the follicular phase of the menstrual cycle

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Abstract

Women frequently complain of memory problems at times in their reproductive lives that are associated with changes in estrogen concentration (e.g. around menopause and childbirth). Further, behavioural studies suggest that memory performance may fluctuate across the menstrual cycle. For example, performance on verbal tasks has been reported to be greatest during phases associated with high estrogen concentrations whereas the opposite has been reported with visuo-spatial tasks. The biological basis of these reported effects remains poorly understood. However, brain imaging studies into the effects of estrogen therapy in postmenopausal women suggest that estrogen modulates the metabolism and function of brain regions sub-serving memory. Furthermore, we have recently reported that acute suppression of ovarian function in young women (with a Gonadotropin Hormone Releasing Hormone agonist) is associated with decreased activation in left prefrontal cortex, particularly the left inferior frontal gyrus (LIFG), during successful verbal memory encoding. We therefore investigated whether physiological variation in plasma estradiol concentration is associated with differences in activity of the LIFG during successful verbal encoding. We hypothesised that higher plasma concentrations of estradiol would be associated with increased brain activity at the LIFG and improved recall performance. Although we did not find a significant relationship between plasma estradiol concentration and verbal recall performance, we report a positive correlation between brain function and estradiol concentration at the LIFG.

Keywords: Estradiol; Menstrual cycle; fMRI; Verbal memory; Left inferior frontal gyrus

Introduction

Women frequently complain of memory problems at times in their reproductive lives that are associated with changes in estrogen concentration (e.g. around the time of the menopause and childbirth) (Mitchell and Woods, 2001). Studies to clarify the possible biological basis of this have generally focussed on the differences between postmenopausal women on and off estrogen therapy (ET), or examined younger women following acute medical or surgical loss of ovarian function. Some of these prior studies reported that verbal, and less consistently visual, memory improved in postmenopausal women taking ET (Jacobs et al., 1998; Kampen and Sherwin, 1994; Maki et al., 2001; Sherwin, 1988; Sherwin and Phillips, 1990; Zec and Trivedi, 2002) (particularly parenteral 17-β estradiol (E2)). Verbal memory deficits have also been reported in women following acute loss of ovarian function, and these deficits have been reversed with estrogen 'add-back' therapy (Newton et al., 1996; Phillips and Sherwin, 1992; Sherwin and Tulandi, 1996; Sherwin and Phillips, 1990). Thus there is increasing evidence that in some women estrogen may affect verbal memory.

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The biological basis of these effects remains poorly understood. However, brain imaging studies in postmenopausal women reported that ET modulates the metabolism and function of brain regions sub-serving memory (e.g. hippocampal, frontal, parietal, and temporal regions) (Maki and Resnick, 2000; Resnick et al., 1998; Shaywitz et al., 1999). Furthermore, we have recently reported that acute suppression of ovarian function (following administration of a Gonadotropin Hormone Releasing Hormone agonist (GnRHa)) in young healthy women is associated with decreased activation in left prefrontal cortex, and particularly the left inferior frontal gyrus (LIFG), during successful verbal memory encoding (Craig et al., 2007). This finding is consistent with reports of an association between LIFG activation at encoding with subsequent memory success (Buckner et al., 2000; Davachi et al., 2003; Jackson and Schacter, 2004; Ranganath et al., 2003; Staresina and Davachi, 2006). Also it suggests that modulation of LIFG function may be an important mechanism through which estrogen affects verbal memory formation.

Several previous studies have reported that hormonal variation across the menstrual cycle is associated with significant changes in brain activity during motor and language tasks (Dietrich et al., 2001; Fernandez et al., 2003; Goldstein et al., 2005) but we are unaware of any brain imaging studies to date that have analysed the relationship between the normal variation in estradiol levels across the menstrual cycle and brain function during a memory task. This is, however, an area of potential interest as behavioural studies suggest that memory performance may fluctuate across the menstrual cycle. For example, high estrogen levels are associated with improved performance on verbal tasks, whereas improved performance on visuo-spatial tasks is associated with lower estrogen levels (Hampson, 1990a, b; Hoff et al., 2001; Rosenberg and Park, 2002; Young-Hoon et al., 2006). We therefore carried out the first study to investigate whether physiological variation in plasma estradiol concentration is associated with differences in activity of the LIFG during successful verbal encoding. We hypothesised that higher plasma concentrations of estradiol would be associated with increased brain activity at the LIFG and improved recall performance. In order to avoid the potentially confounding effect of changes in progesterone levels, we limited our analysis to the follicular phase of the cycle (i.e. when progesterone levels are low (≤ 8 nmol/l) and estradiol levels are rising).

Methods

Subjects

We included 16 right-handed young (26–45 years) pre-menopausal women with regular menstrual cycles. All women signed informed consent as per the Ethics Committee Guidelines of the University of London.

Exclusion criteria

All the women were screened to exclude psychiatric disorders using the Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID-I and SCID-II) (First et al., 1997a,b). Scores on the Beck Depression and Anxiety Inventories (BDI and BAI, respectively) (Beck et al., 1988, 1996) were also obtained to quantify sub-clinical symptoms of depression and anxiety. General intelligence and cognitive status were measured using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) and the Mini Mental State Examination (MMSE) (Folstein et al., 1983). Women were excluded if they: had an IQ less than 70, a MMSE score less than 27, or they were unable to carry out the cognitive tasks we wished to investigate. They were also excluded if they had a history of: alcohol/drug abuse, significant medical/neurological problems affecting brain function, were taking regular prescribed medication (including the contraceptive pill), or did not have regular menstrual cycles. All subjects had routine blood tests prior to the study day to exclude women with significant abnormalities in full blood count; plasma glucose; or liver renal, thyroid, or ovarian function. They also had blood tests on the day of the scan and excluded if their progesterone levels were greater than 8 nmol/l.

Stimulus materials

Stimulus lists were created using nouns randomly selected from the MRC psycholinguistic database (http://www.psy.uwa.edu.au/MRCDataBase/uwa_mrc.htm). Initially two lists were created; a 300-word list composed of 'living' nouns (e.g. apple, liver) and a 300-word list composed 'non-living' words (e.g. chair, mountain). Words ranged in their written frequency of use between 1 and 30 per million (Kucera and Francis, 1967) and were between four and eight letters in length. These lists were then used to create three 100-word encoding lists (A–C) and six 100-word recognition lists. Lists were matched with respect to word length or frequency of use. Encoding lists were made up of 50 words from the 'living' word lists and 50 words from the 'non-living' word list. Each of the two 100-word recognition lists included 50 'old words' from the originally encoded list and 50 'new words' that had not been in the encoded list. The 'new words' included an equal number of 'living' and 'non-living' items. Each of the three encoding lists (A–C) therefore had two associated recognition lists, each made up of 50 'old words' from the encoded list and 50 'new words'. An additional 16 words were selected from the word pool to create a practice list for the study task.

Encoding task

Subjects were asked to decide whether words presented to them represented a 'living' or 'non-living' object by moving a mounted joystick, on their right-hand-side, to the left ('living' object) or right ('non-living' object). They were informed that the purpose of this task was to help them learn the words which they would later be asked to recognise. Women were presented with 100 words, each for a period of 200 ms, with an inter-stimulus interval of 200 ms.

Recognition task

The recognition memory test consisted of the 100 'old-words' that had previously been presented, together with 100 'new-words' (lures) divided into two lists of 100 words presented 5 min apart. For each word, volunteers had to decide whether they had seen the word before during the experiment by moving the mounted joystick, on their right-hand-side, to the left ('old-word') or right ('new-word'). The words were presented in the same manner as in the encoding task.

Stimuli presentation

Each woman was randomly allocated one of the three encoding lists (A–C) and their reciprocal recognition lists. Words were back-projected with an LCD projector (Proxima Desktop Projector 5500) onto a screen 2.5 m from the subject's head in white upper case Times New Roman 48-point font on a black background and were visible to the subject via a prism mounted on the head coil. The paradigms were programmed in Microsoft Visual Basic Professional 6.0 and presented on a PC running MS Windows XP.

Procedure

Before entering the scanner, women were given an explanation about the tasks and undertook a short practice session using a laptop computer to familiarise themselves with the tasks.

Scanning began with a ~20 min structural scan. Volunteers then performed the encoding task which lasted ~10 min. They were then given two unrelated tasks lasting for a period of ~25 min whilst remaining in the scanner. They were