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A study of visuospatial working memory pre- and post-Gonadotropin Hormone Releasing Hormone agonists (GnRHa) in young women

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Abstract

Gonadotropin Hormone Releasing Hormone agonists (GnRHa) produce an acute decline in ovarian hormone production leading to a 'pseudo' menopause. This is therapeutically useful in the management of a variety of gynaecological conditions but also serves as a powerful model to study the effects of ovarian hormones on cognition. Animal and human behavioral studies report that memory is particularly sensitive to the effects ovarian hormone suppression (e.g. post GnRHa). Further, it has recently been reported that ovariectomy in young women increases the risk of cognitive impairment in later life. However, the underlying brain networks and/or stages of memory processing that might be modulated by acute ovarian hormone suppression remain poorly understood. We used event-related fMRI to examine the effect of GnRHa on visual working memory (VWM). Neuroimaging outcomes from 17 pre-menopausal healthy women were assessed at baseline and 8 weeks after GnRHa treatment. Seventeen matched wait-listed volunteers served as the control group and were assessed at similar intervals during the late follicular phase of the menstrual cycle. We report GnRHa was associated with attenuation of left parahippocampal (BA 35) and middle temporal gyri (BA 21 ,22, 39) activation, with a significant group-by-time interaction at left precuneus (BA 7) and posterior cingulate cortex (PCC) (BA 31) at encoding, and with cerebellar activation at recognition in the context of unimpaired behavioral responses. Our study suggests that acute ovarian hormone withdrawal following GnRHa, and perhaps at other times, (e.g. following surgical menopause and postpartum) alters the neural circuitry underlying performance of VWM.

Keywords: Visuospatial memory; Working memory; Ovarian suppression; Estrogen; Functional brain imaging

Introduction

Gonadotropin Hormone Releasing Hormone agonists (GnRHa) down-regulate pituitary gonadotropin-releasing hormone receptors to produce a decline in ovarian hormone production. GnRHa subsequently produces a temporary 'pseudo' menopause which is useful in the management of a variety of gynaecological conditions (Craig et al., 2007). This medically-induced menopausal state also provides a powerful model to study the early effects of ovarian hormone suppression on the brain. This is an important period to investigate as a number of studies suggest that it represents a critical period of brain aging. It has recently been reported, for example, that young women (≤45 years old) who undergo ovariectomy have an increased risk of cognitive impairment or dementia when they are older compared to matched controls (Rocca et al., 2007). It has also been reported that women who take hormone therapy (HT; i.e. estrogen±progesterone) in the period immediately following menopause may have a reduced risk of cognitive impairment and

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dementia in later life (Zandi et al., 2002). However, the biological mechanisms underlying the effects of ovarian hormone loss in younger women on brain regions involved in cognitive domains such as memory remain poorly understood.

Functional magnetic resonance imaging (fMRI) is a technique that has facilitated investigation into the effects of various medical conditions and drugs on brain function. We have recently used a verbal episodic memory task to study the effects of GnRHa on brain function in young women (≤47 years old) (Craig et al., 2007). Our findings suggested that GnRHa administration led to a change in the typical pattern of prefrontal activation during successful encoding, with decreased activation in left prefrontal cortex, anterior cingulate, and medial frontal gyrus. There have been no studies to date that have used a visual working memory (VWM) task as a probe to study the effects of GnRHa. However, studies into the effects of HT on visual and working memory suggest that brain networks involved in processing VWM tasks may be sensitive to the effects of ovarian hormone suppression (Duff and Hampson, 2000; Resnick et al., 2006; Resnick et al., 1997; Smith et al., 2006).

We therefore sought to analyse the effects of GnRHa on the encoding and retrieval components of VWM using the delayed match to sample (DMTS) task. Prior work has reported widespread prefrontal and parietal regions with visual object encoding as well as parahippocampus, cingulate, and the inferior temporal cortex (Brewer et al., 1998; Pessoa et al., 2002). Previous studies also report that regions activated during the visual recognition include prefrontal cortical regions, anterior cingulate, insula, precentral gyrus, inferior temporal gyrus, extrastriate regions and cerebellum (Buckner et al., 1998; Buckner et al., 1996; Pessoa et al., 2002; Picchioni et al., 2007). Hence we sought to determine if GnRHa modulates the response of these brain regions during this widely used VWM task.

Methods

Subjects

We included thirty-four right-handed healthy pre-menopausal women with benign *leiomyomata uteri* (i.e. 'fibroids'). All women were prescribed GnRHa (two Zoladex® 3.6 mg implants) as part of their routine clinical management and provided informed consent as per the Ethics Committee Guidelines.

Subject assessment

All the women were recruited from the gynaecology clinics of two London teaching hospitals and screened to exclude past or present psychiatric disorders using the Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID-I and SCID-II) (First et al., 1997a; First et al., 1997b). Scores on the Beck Depression and Anxiety Inventories (BDI and BAI respectively) (Beck et al., 1988; Beck et al., 1996) were also obtained to quantify sub-clinical symptoms of depression and anxiety. General intelligence and cognitive function were measured using the Wechsler Abbreviated Scale of Intelligence (WASI) (1999) and the Mini Mental State Examination (MMSE) (Folstein et al., 1983). Handedness was determined by the Annett handedness scale (Annett, 1970), and menopausal symptoms were assessed using the Greene Climacteric Scale (GCS) (Greene, 1998) at each visit. Women were excluded if they had an IQ less than 70, a MMSE score less than 27, alcohol/drug abuse, significant medical/neurological problems affecting brain function, or if they were taking regular prescribed medication, were left handed or if they did not have regular menstrual cycles. All subjects also underwent routine blood testing to measure their haematological profile and hepatic, renal, thyroid, and ovarian function.

Delayed Matching to Sample (DMTS) task

Stimulus presentation

Subjects wore MRI-compatible air-conducting headphones and visual stimuli were back-projected by an LCD projector (Proxima Desktop Projector 5500) onto a screen 2.5 m from the subject's head and were viewed 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.

Stimulus materials

Our version of the Delayed Matching to Sample (DMTS) test was adapted from the Cambridge Neuropsychological Test Automated Battery (CANTAB). Each trial consisted of four phases.

Phase 1: During the initial 'encoding' phase, subjects were presented with a complex abstract pattern (the sample) for 5000 ms in the centre of the screen. Subjects were instructed to remember the sample as they would be asked to identify it later.

Phase 2: The next 'maintenance' phase involved a variable delay during which the subject was instructed to hold the sample in memory while maintaining fixation on a central cross. The duration of the maintenance delay varied across trials. Simultaneous trials involved no delay (i.e. the sample and choice patterns were shown together at recognition). In the other trials there was a delay of 4000 ms or 12,000 ms between encoding and recognition, and only the choice patterns were displayed.

Phase 3: In the 'recognition' phase, subjects were shown four patterns in a North, South, East, and West distribution around the central location for 6000 ms and were asked to identify the sample by pressing a joystick in the corresponding direction with their right hand. Each pattern was made up of four sub-elements, each of a different colour. One of the choice patterns was identical to the sample, one was a novel distracter pattern, one had the shape of the sample and the colours of the distracter, and the fourth had the colours of the sample and the shape of the distracter. To discourage strategies based on encoding single quadrants, all four choice patterns had one quadrant in common.

Phase 4: In the final 'delay' phase of the trial subjects were simply instructed to maintain visual fixation on a central cross. This delay was designed to equalise the inter-trial (encoding) interval to 27,000 ms across trials, while randomly varying the inter-stimulus (recognition) interval, with the length of the delay dependent upon the duration of the preceding maintenance phase.

Subjects were trained on 7 practice trials. In the experimental task there were 42 trials, 14 for each maintenance delay (simultaneous, 4000 ms and 12,000 ms), presented in a pseudorandom order in two runs of approximately 10 min each.

Behavioral data

All behavioral data, response accuracy and response latency, were recorded on a personal computer using Visual Basic (Microsoft Corp., Redmond, USA) and analysed in SPSS Version 13.0 (SPSS Inc., Chicago, USA).

Experimental paradigm

The overall study design was an observational, repeated measure, wait-list control design. Consecutive women put on a 6-month waiting list to receive 8 weeks continuous pre-operative GnRHa who met eligibility criteria and agreed to take part in the study were randomly divided into two groups. (The waiting list for surgery enabled randomisation of women into the two groups without delaying treatment, in either group, for purposes of this study). Women in the 'experimental' group ($n=17$) were initially scanned (Time 1) before GnRHa was administered between days 9–13 of their menstrual cycle (i.e. when they were predicted to be in the latter part of the follicular phase associated with high estrogen/low progesterone levels, as estrogen, not progesterone, has been most clearly associated with improving memory). They subsequently received GnRHa and had a repeat scan 8 weeks later (Time 2) when still taking GnRHa. The protocol for the wait-list 'control' group ($n=17$) was identical. However, they