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SHORT COMMUNICATION

Reversibility of the effects of acute ovarian hormone suppression on verbal memory and prefrontal function in pre-menopausal women

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Summary
Background: Whilst acute loss of ovarian function is associated with memory deficits, the biological basis of this is poorly understood. We have previously reported that acute loss of function during Gonadotropin Hormone Releasing Hormone agonists (GnRHa) treatment is associated with impaired verbal memory and a disruption of corresponding left inferior frontal gyrus (LIFG) during the encoding stage. In the current study, we provide a critical extension to this work by determining whether this memory deficit is reversible following normalization of ovarian function. To do this we carried out a further imaging study using the same verbal memory recognition task after cessation of GnRHa-induced ovarian suppression.
Method: We used event-related fMRI to study verbal episodic memory performance and brain activation at the LIFG in 13 healthy pre-menopausal women pre-, during, and post-acute ovarian hormone suppression using GnRHa.
Results: Following resolution of acute GnRHa-induced ovarian suppression, verbal recognition scores returned to their initial levels and this restoration was associated with a restored level of left frontal activation during successful encoding of words.
Conclusions: Our findings suggest that the memory deficits associated with acute ovarian suppression are reversed following resolution of normal ovarian function and are associated

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with reversible attenuation of LIFG activation during encoding. These findings lend further support to the hypothesis that memory difficulties reported by some women following acute ovarian hormone withdrawal are reversible and may have a clear neurobiological basis.

1. Introduction

Acute loss of ovarian function leads to memory deficits following both surgical (Sherwin, 1988; Nappi et al., 1999; Farrag et al., 2002) and pharmacological (Sherwin and Tulandi, 1996; Grigorova et al., 2006) menopause. Further, it has been reported that surgical menopause is associated with increased risk for developing Alzheimer's dementia in later life (Nee and Lippa, 1999; Rocca et al., 2007). The cognitive risks of ovariectomy are particularly evident in women who had surgery before natural menopause and did not receive estrogen therapy soon after surgery (Rocca et al., 2007). Early menopause, whether due to surgery or natural menopause, has also been associated with greater longitudinal declines in cognitive function later in life (McLay et al., 2007). In clinical studies, surgical and pharmacological suppression of ovarian hormones produces deficits in verbal memory that are reversed following early treatment with estrogen therapy (Sherwin, 1988; Sherwin and Tulandi, 1996). However, despite the purported links between estrogen and memory (see Sherwin and Henrya, 2008 for review) the biological basis of this relationship is still poorly understood. We have recently reported that verbal recognition success is reduced following acute loss of ovarian function caused by treatment with Gonadotropin Hormone Releasing Hormone agonists (GnRHa). Also, during successful verbal memory encoding this reduction is associated with attenuated activation in left prefrontal cortex—particularly left inferior frontal gyrus (LIFG; BA 44/45) (Craig et al., 2007b) which is a region that has been consistently reported to be central to cognitive processing in language and memory tasks (see Gabrieli et al., 1998 for review). Thus we demonstrated that acute ovarian suppression by GnRHa affects specific brain regions and cognitive functions.

In the present study we address whether the effects of GnRHa on brain function and memory performance are reversible by examining patterns of brain activation following resolution of ovarian function. Specifically, we analysed LIFG activation and verbal memory performance, pre, during GnRHa-induced ovarian hormone suppression, and post-GnRHa during resolution of normal ovarian function. We hypothesized that memory function and activation in LIFG would return to pre-GnRHa levels, indicating that the changes in brain function are indeed reversible.

2. Materials and methods

2.1. Subjects

We studied 13 right-handed healthy pre-menopausal women (39 ± 7 years old) with benign fibroids. This included 10 women from our previous study (Craig et al., 2007b).[1] All women (a) were prescribed GnRHa (two Zoladex® 3.6 mg implants) as part of their routine clinical management and signed informed consent as per the Ethics Committee Guidelines (b) were screened to exclude past and/or present psychiatric problems using the Structured Clinical Interview for DSM-IV Axis I and II Disorders (First et al., 1997a,b) and (c) had an IQ score (Wechsler Abbreviated Scale of Intelligence Manual, 1999) greater than 80 and a Mini Mental State Examination score (Folstein et al., 1983) greater than 27. Women were excluded if they had a history of alcohol/drug abuse, significant medical/neurological problems, if they were taking regular prescribed medication or if they had any blood test results suggesting abnormal endocrine, renal or liver function following routine testing.

2.2. 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. They were informed that the purpose of this task was to help them learn the words which they would later be asked to recognize. At each visit women were presented with 100 words, each for a period of 200 ms, with an inter-stimulus interval of 200 ms.

2.3. 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. The words were presented in the same manner as in the encoding task.

2.4. Stimuli presentation

At each visit women were randomly allocated one of three counterbalanced encoding lists and its corresponding recognition list. The order of words within every list was also randomised for each subject (see McLay et al., 2007).

2.5. Procedure

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

[1] Of the 15 women in the original study four were unwilling to return for a further scanning session post-GnRHa treatment and one woman underwent hysterectomy and bilateral ovariectomy at the time of surgery.

25 min whilst remaining in the scanner. They were subsequently asked to carry out the forced recognition tasks. Each recognition task lasted 10 min with a 5-min delay between tasks.

2.6. Experimental paradigm

The overall study design was a within-group analysis. Women were initially scanned when their ovaries were producing normal levels of ovarian hormones. Scans took place between days 9 and 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 verbal memory, see Section 4). They subsequently received GnRHa, and 8 weeks into GnRHa treatment they underwent further scanning. Approximately 6 months post-surgery when ovarian function returned to normal (i.e. menses had resumed) and women had fully recovered from surgery they had a final scan, again between days 9 and 13 of their menstrual cycle.

2.7. Blood collection, endocrine determinants and MRI scanning methods

See McLay et al. (2007).

2.7.1. Analysis of fMRI data

Data were analysed with XBAM v3.4 (Institute of Psychiatry, London, UK)[2] (see McLay et al., 2007 for details of fMRI analysis). Within this analysis inter-subject variability was treated appropriately (i.e. using mixed and not fixed effects modelling) (Yano et al., 2001). In order to investigate the LIFG as a specific region of interest we used a mask derived from the LIFG (BA 44/45) as defined in the 'parcellated' template constructed by Tzourio-Mazoyer et al. (2002).

The event-related study design enabled us to analyse LIFG activity during the presentation of to-be-encoded words that were subsequently successfully remembered versus those that were forgotten. This is frequently referred to as the 'subsequent memory' or 'Dm' effect and permits a more accurate assessment of the neural correlates of encoding that has been applied to numerous previous memory studies (Rugg, 1995; Otten et al., 2001).

2.7.2. Contrasts

The following contrasts were carried out at the LIFG:

a. *The Dm effect baseline (pre-GnRHa) compared to 8 weeks of GnRHa*: The aim of this contrast was to confirm that brain activation was attenuated at the LIFG post-GnRHa (i.e. as reported in our whole brain analysis, Craig et al., 2007b).
b. *The Dm effect after 8 weeks of GnRHa compared to approximately 6 months post-GnRHa*: The aim of this contrast was to study whether the attenuation of brain function post-GnRHa returned to normal when normal ovarian function was resumed.
c. *The Dm effect at baseline compared to several months post-GnRHa*: The aim of this contrast was to establish the absence of a difference in brain activation at time points when women were not under the influence of GnRHa.

2.8. Additional statistical analyses

Due to a low detectable limit of the hormone assays, Friedman and Wilcoxon rank tests were used to compare plasma hormone levels across time. In order to compare accuracy of encoding and recognition over time we used mixed repeated measure ANOVAs.

3. Results

3.1. Plasma hormone levels

Friedman analyses revealed a significant effect of time for estradiol ($chi^2(2) = 11.091$, $p = .003$), progesterone ($chi^2(2) = 6.741$, $p = .04$) and LH ($chi^2(2) = 12.182$, $p = .001$) (Table 1). Pairwise comparisons using Wilcoxon rank tests showed that women had (a) higher median estradiol concentrations pre- (418 pmol/l) and post- (363 pmol/l) GnRHa compared to during (60 pmol/l) GnRHa treatment ($z = 2.981$, $p = .001$ and $z = 2.981$, $p = .001$) with no significant difference in estradiol concentrations between pre- and post-GnRHa ($z = 0.622$, $p = .289$), (b) higher median progesterone concentrations pre- (10 nmol/l) and post- (7 nmol/l) GnRHa compared to during (5 nmol/l) GnRHa treatment ($z = 2.366$, $p = .016$ and $z = 2.201$, $p = .031$) with no significant difference in estradiol concentrations between pre- and post-GnRHa ($z = -0.140$, $p = .945$) and (c) pre- and post-GnRHa compared to during GnRHa treatment ($z = 2.981$, $p = .001$ and $z = 2.354$, $p = .015$) with a significant median difference in LH concentrations between pre- (7.6 μ/l) and post- (4 μ/l) GnRHa ($z = 2.134$, $p = .031$). However, Friedman analysis did not show a significant effect of time ($chi^2(2) = 4.667$, $p = .114$) for FSH. Despite our attempts to scan women in the follicular phase of the cycle (i.e. between days 9 and 13) the results of blood tests suggested that both pre- and post-GnRHa several women had post-ovulatory hormone profiles.

[2] fMRI analysis, in its most common forms, requires fitting of a time series model at many thousands of intracerebral voxels in a number of individuals. Most assessments of the significance of the resulting model fits in common use in fMRI analysis use normal theory and the validity of the normality assumption is not often tested. Our 'in house' method of analysis, XBAM v3.4 (Institute of Psychiatry, London, UK), makes no such assumptions. Instead, it uses median statistics to control outlier effects and permutation rather than normal theory-based inference. Furthermore our most common test statistic is computed by standardising for individual difference in residual noise before embarking on second level, multi-subject, testing using robust permutation-based methods. This allows a mixed effects approach to analysis. A recent paper by Thirion et al. (2007) has conducted a detailed analysis of the validity and impact of normal theory-based inference in fMRI in large number of subjects. They have found substantial deviations from normality in a significant number (22%) of intracerebral voxels using the most common measure of response size (unstandardised beta) used in fMRI analysis. They recommend a mixed effect rather than simple random effect analysis, permutation-based inference and cluster or parcel level rather than voxel level inference.

Table 1 Plasma hormone concentrations pre-, during and post-GnRHa

	Pre-GnRHa	GnRHa	Post-GnRHa
Median (25%, 75% quartile)			
Estradiol (pmol/l)	418 (245, 696)	60 (30, 89)	363 (238, 651)
Progesterone (nmol/l)	10 (5, 21)	5 (5, 5)	7 (5, 22)
Luteinising Hormone (μ/l)	7.6 (5.2, 16.4)	0.8 (0.8, 0.8)	4 (1.9, 6.3)
Follicular Stimulating Hormone (μ/l)	4.6 (1.7, 10.5)	2.8 (2.2,5.7)	3.5 (2.5, 4.2)

The data expressed in this table highlights the significant drop in ovarian hormone concentrations, particularly estradiol, following GnRHa and the resolution of ovarian function post-GnRHa treatment. The absence of a statistically significant difference between of FSH levels across time does not suggest a failure of GnRHa to suppress ovarian function as GnRHa only suppresses FSH to 'follicular phase levels' (AstraZeneca, 2005). In light of the fact that we attempted to manipulate the study to assess women at the follicular phase of the cycle this finding was predicted at the onset.

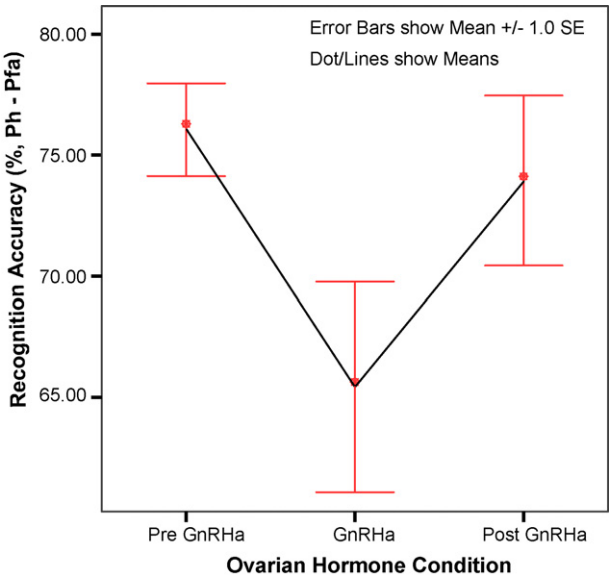

Figure 1 Verbal recognition accuracy as a function of ovarian hormone condition. The graph illustrates the reduced recognition accuracy during GnRHa-induced ovarian suppression compared to normal ovarian function pre- and post-GnRHa treatment. Recognition accuracy was determined by the discrimination measure Pr [Probability hit (Ph) – Probability false-alarm (Pfa)] and expressed as a percentage score.

3.2. Behavioural results

3.2.1. Encoding

A repeated measurement ANOVA of the accuracy of living/non-living responses whilst encoding stimuli revealed that there were no significant main effect for time (i.e. pre-GnRHa, GnRHa, and post-GnRHa) ($F(2,22) = 2.467$, $p = 0.109$).

3.2.2. Recognition memory

Accuracy was calculated by the discrimination measure Pr [Probability of correct-hit (Ph) – Probability of false-alarm (Pfa)]. A repeated measurement ANOVA revealed a significant main effect for time ($F(2,22) = 5.367$, $p = 0.013$). Pairwise comparison showed that accuracy was significant higher pre- and post-GnRHa treatment compared to during GnRHa-induced ovarian suppression ($p = .023$ and .034, respectively). There was no significant difference in accuracy pre- and post-GnRHa treatment ($p = .433$) (Fig. 1).

3.3. fMRI results

a. *The Dm effect baseline (pre-GnRHa) compared to 8 weeks of GnRHa*: There was significant attenuated brain activation at the LIFG post-GnRHa compared to baseline (Fig. 2a).
b. *The Dm effect after 8 weeks of GnRHa compared to several months post-GnRHa*: Also there was significantly attenuated brain activation at the LIFG post-GnRHa

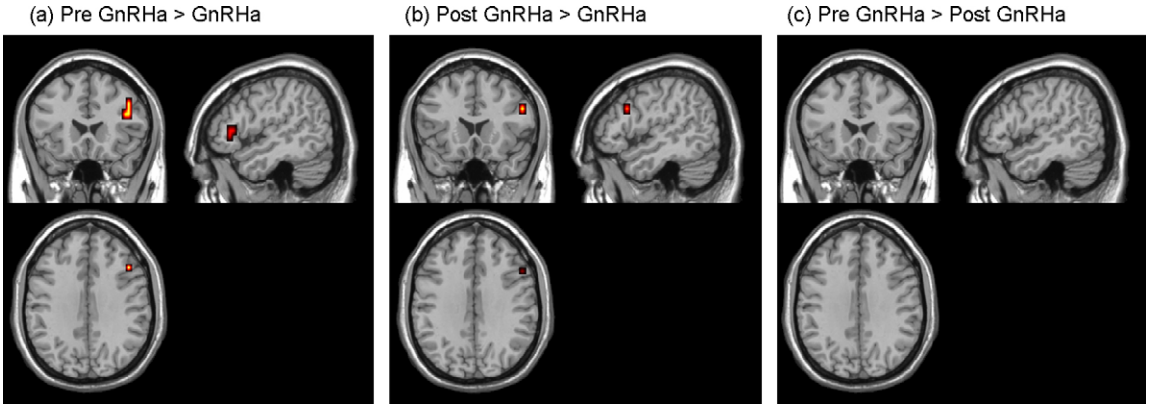

Figure 2 Patterns of brain activation at LIFG ($x = 40$, $y = 26$, $z = 16$) associated with correct verbal recognition as a function of ovarian hormone condition. The figure illustrates reduced LIFG activation following GnRHa-induced ovarian suppression compared to (a) pre suppression and (b) post-suppression (i.e. normal ovarian function) and (c) no significant difference in LIFG activation pre and post-GnRHa.

compared to post-operatively (i.e. following resolution of normal ovarian function) (Fig. 2b).

c. *The Dm effect at baseline compared to several months post-GnRHa*: However there was no significant difference in LIFG activation at baseline and post-operatively, i.e. when women were not under the influence of GnRHa (Fig. 2c).

4. Discussion

We previously reported that acute ovarian hormone suppression, during treatment with GnRHa, is associated with reduced verbal recognition success and LIFG function during successful encoding (Craig et al., 2007b). In the present study we address whether the effects of GnRHa on brain function and memory performance are reversible by including an additional condition examining patterns of brain activation following resolution of ovarian function. Specifically, we analysed LIFG activation and verbal memory performance, pre, during GnRHa-induced ovarian hormone suppression, and post-GnRHa during resolution of normal ovarian function. We report that, resolution of ovarian function (post-GnRHa) is associated with (i) reduced LIFG activation during successful verbal encoding and (ii) reduced recognition success compared to GnRHa. Also there were no significant differences in LIFG activation or recognition performance pre- and post-GnRHa (i.e. during two conditions of normal ovarian function). Taken together these findings lend further support to the hypothesis that memory difficulties reported by some women following acute ovarian hormone withdrawal may have a clear neurobiological basis; one that is manifest during encoding, and involves reduced activation of the LIFG, but which resolves post-treatment with normalized ovarian hormone function.

The specificity of these findings at the LIFG is consistent with previous studies that suggest (i) LIFG sub-serves deep processing of to-be-learned words (Otten et al., 2001), (ii) LIFG activation during encoding is associated with subsequent memory success (Buckner et al., 2000; Staresina and Davachi, 2006) and (iii) LIFG has been consistently reported to be central to cognitive processing in language and memory tasks (see Gabrieli et al., 1998 for review). Although, it could still be argued that our findings are attributable to a non-specific effect arising from impaired attention or behavioural performance we suggest that this is unlikely, since there was no decrement in encoding performance (i.e. in making the living/non-living judgment) across the three time points. Also previous behavioural studies have reported that GnRHa has negative effects on memory with no effects on attention (Sherwin and Tulandi, 1996; Grigorova et al., 2006).

We have previously argued that the reduction in estradiol concentration associated with loss of ovarian function is most likely to account for our findings (Craig et al., 2007b). This is supported by a subsequent study using the same paradigm in young women across the follicular phase of the menstrual cycle which reported a positive correlation between LIFG activation and estradiol concentration (Craig et al., 2008). Although the mechanism(s) by which estradiol modulates prefrontal cortical function is still poorly understood a recent *in vivo* ^{1}MRS study reported that acute loss of ovarian function following GnRHa is associated with a significant increase in prefrontal cortical choline (Cho) (Craig et al., 2007a). Cho, is a marker of neuronal membrane metabolism (Jenden, 1990). These findings therefore suggest that one of the mechanisms via which loss of ovarian hormones modulate prefrontal cortical function may involve differences in neuronal membrane stability. Other mechanisms are likely to include modulation of neurotransmitter systems (see Craig and Murphy, 2007 for review).

Our study has some limitations. First, despite our attempts to scan women at the follicular phase of the menstrual cycle, some women had post-ovulatory hormone profiles either pre- and/or post-GnRHa. Although we have argued above that our findings were probably due to the effects of estradiol on the brain (McLay et al., 2007) we cannot exclude the possibility that variation in the concentrations of other ovarian hormones (e.g. progesterone) influenced our results. Second, the study would have benefited from a separate control group (i.e. as opposed to a within-group analysis). Unfortunately the controls from our earlier study (McLay et al., 2007) also received GnRHa prior to surgery and were therefore not followed up. Finally, the current study reports on the limited effects of acute estrogen deficiency following 2 months of GnRHa as it was not possible modulate this length of time in our study group. It could, therefore, be argued that our findings may not be generalizable to other estrogen deficient states which occur over longer or shorter time frames. Although we have reported that these effects are generalizable over shorter periods of physiological deficiency (i.e. across the menstrual cycle, Craig et al., 2008) and previous studies suggest even greater cognitive deficits following 6 months of GnRHa (Palomba et al., 2004), our study would have benefited from analysing the effects of GnRHa over variable periods of administration.

In summary we report that acute loss of ovarian function using GnRHa is associated with reversible verbal episodic memory deficits and reduced LIFG activation at encoding. These findings lend further support to the hypothesis that memory difficulties reported by some women following acute ovarian hormone withdrawal may have a clear neurobiological basis.

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Conflicts of interest

Dr. Michael Craig is funded by a Medical Research Council (UK) Fellowship and reports no biomedical financial interests or conflicts of interest.

Dr. Paul Fletcher is funded by a Wellcome Trust fellowship and reports no biomedical financial interests or conflicts of interest.

Ms. Daly reports no biomedical financial interests or conflicts of interest.

Professor Mick Brammer reports no biomedical financial interests or conflicts of interest.

Dr. Vincent Giampietro reports no biomedical financial interests or conflicts of interest.

Professor Janice Rymer has received less than $10,000 per year as a member of the Advisory Board for Wyeth-Ayerst and has received less than $10,000 per year in lecture fees from Organon. She does not have any equity ownership/stock options in publicly or privately traded firms.

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