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Gonadotropin hormone releasing hormone agonists alter prefrontal function during verbal encoding in young women

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Summary
Gonadotropin hormone releasing hormone agonists (GnRHa) are commonly used in clinical practice to suppress gonadal hormone production in the management of various gynaecological conditions and as a treatment for advanced breast and prostate cancer. Animal and human behavioural studies suggest that GnRHa may also have significant effects on memory. However, despite the widespread use of GnRHa, the underlying brain networks and/or stages of memory processing that might be modulated by GnRHa remain poorly understood. We used event-related functional magnetic resonance imaging to examine the effect of GnRHa on verbal encoding and retrieval. Neuroimaging outcomes from 15 premenopausal healthy women were assessed at baseline and 8 weeks after Gonadotrophin Releasing Hormone analogue (GnRHa) treatment. Fifteen matched wait-listed volunteers served as the control group and were assessed at similar intervals during the late follicular phase of the menstrual cycle. GnRHa was associated with changes in brain response during memory encoding but not retrieval. Specifically, 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. Our study suggests that the memory difficulties reported by some

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women following GnRHa, and possibly at other times of acute ovarian hormone withdrawal (e.g. following surgical menopause and postpartum), may have a clear neurobiological basis; one that manifest during encoding of words and that is evident in decreased activation in prefrontal regions known to sub-serve deep processing of to-be-learned words.

1. Introduction

Over 3000 analogues of Gonadotropin hormone releasing hormone (GnRH) have been developed and tested (Karten and Rivier, 1986). These are primarily agonists (GnRHa) which down-regulate pituitary gonadotropin-releasing hormone receptors to produce a decline in ovarian hormone production. GnRHa is most commonly used in the management of benign uterine fibroids which are present in 20–30% of women over 30 years of age (Karten and Rivier, 1986). Pre-operative GnRHa administration has been shown to reduce intra-operative blood loss and facilitate more conservative operative techniques (e.g. reducing the need to carry out a midline incision) (Lethaby et al., 2001). GnRHa is also prescribed to facilitate super-ovulation during assisted reproduction (Pinkas et al., 2000) and to treat various other gynaecological conditions including endometriosis, (Shaw and Team, 1992) pelvic pain (Vercellini et al., 1993; Carey and Slack, 1996) dysfunctional uterine bleeding (Coulter et al., 1995), premenstrual syndrome (West and Hillier, 1994), and as a treatment for advanced cancer of the breast (Cheer et al., 2005) and prostate (Wirth and Froehner, 1999).

Recent research in animals (Casadesus et al., 2006) and humans (http://www.secinfo.com/d14D5a.z6483.htm, pp. 55–64) suggest that GnRHa may have beneficial effects on cognition, and Phase III trials are currently underway for the administration of GnRHa (as an adjunct to anticholinesterase drugs) in people with mild to moderate Alzheimer's dementia (http://www.centerwatch.com/trials/trial4063.html). However, most studies suggest that GnRHa has a negative effect on cognition (Varney et al., 1993; Newton et al., 1996). In particular GnRHa has been associated with reduced scores on neuropsychological tests of verbal episodic (Sherwin, 1996) and working (Grigorova et al., 2006) memory. Despite the widespread use of GnRHa (and the reported effects on cognition) the underlying brain networks and/or stages of memory processing that might be modulated by GnRHa remain poorly understood. The one in vivo brain imaging study into the effects of GnRHa on cognition (Berman et al., 1997) reported that GnRHa significantly reduced cerebral blood flow in the dorsolateral prefrontal cortex and the inferior parietal and temporal lobes during an executive function task in young women (most with premenstrual mood disorder). However, there have been no studies into the effects GnRHa on brain function during a memory task—despite this being the cognitive domain that has been most robustly reported to be affected by GnRHa (Sherwin and Tulandi, 1996). We therefore carried out a study to analyse the behavioural and functional effects of GnRHa on verbal episodic memory.

Prior studies of verbal memory have reported that successful encoding is associated with activation in the prefrontal cortex, particularly the left inferior frontal gyrus (Staresina and Davachi, 2006), the cingulate, medial temporal lobe and lateral temporal cortex (Fletcher et al., 2003). Studies have also reported that recognition success is associated with activation in the posterior parietal cortex (PPC), including inferior and superior parietal lobules, and medial structures extending from the precuneus to the posterior cingulate and retrosplenial cortices (Rugg and Yonelinas, 2003; Wagner et al., 2005). We hypothesized that GnRHa would impair verbal memory performance and that this would be associated with functional changes in these brain regions during successful encoding and recognition.

2. Materials and methods

2.1. Subjects

We included 30 right-handed young (26–47 years) healthy pre-menopausal women with benign *leiomyomata uteri* (i.e. 'fibroids') awaiting surgery. All women 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.

2.2. 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) (1999) and the Mini Mental State Examination (MMSE) (Folstein et al., 1975). 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, if they were taking regular prescribed medication or if they did not have regular menstrual cycles. All subjects also underwent routine blood testing to measure their haematological profile, and liver, renal, thyroid, and ovarian function.

2.3. 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 did not differ significantly 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.

2.4. 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 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. They were then given two unrelated tasks lasting for ~25 min whilst remaining in the scanner and subsequently asked to carry out the recognition tasks.

2.5. Recognition task

The recognition memory test consisted of the 100 'old-words' 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.

2.6. Stimuli presentation

Each woman was randomly allocated two of the three encoding lists (A–C) and their reciprocal recognition lists. The order that each lists was presented across the two visits and the order of words within every list was also randomized for each subject. 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.

2.7. 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 took place during the encoding and forced recognition task.

Scanning began with a ~20 min structural scan (see below for details). 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 subsequently asked to carry out the forced recognition tasks. Each recognition task lasted ~10 min with a ~5 min delay between tasks.

2.8. 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 randomization of women into the two groups without delaying treatment, in either group, for purposes of this study.) Women in the 'experimental' group ($n = 15$) were initially scanned 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 verbal memory—see Discussion). They subsequently received GnRHa and had a repeat scan 8 weeks later when still taking GnRHa. The wait list 'control' group ($n = 15$) was also initially scanned at a high oestrogen/low progesterone phase (i.e. between days 9 and 13). However, they were subsequently scanned 8 weeks later (during the same phase of their menstrual cycle) without having received GnRHa during the intervening 8 weeks. The design of the imaging task was an event-related design focusing on two primary contrasts: (1) successfully and unsuccessfully encoded words and (2) successfully and unsuccessfully recognized words. Each contrast was examined as a function of time (baseline, 8 weeks) and group (GnRH, wait list controls).

2.9. Blood collection and endocrine determinants

Blood was collected into tubes without any anticoagulant and allowed to clot. Samples were centrifuged for 15 min at 1500*g* and serum separated within 4 h. Estradiol and progesterone concentrations were quantified using a competitive immunoassays (supplied by Bayer Advia Centaur) using direct chemiluminometric technology [*estradiol intra-assay precision*: level 1 (mean concentration = 242.2 pmol/l), CV = 12.1%, level 3 (mean concentration 642.3 pmol/l) CV = 4%, level 5 (mean concentration = 2377.1 pmol/l, CV = 6.3%); *progesterone intra-assay precision*: level 1 (mean concentration = 12.4 pmol/l), CV = 12.4%, level 3 (mean concentration 22.9 pmol/l) CV = 3.7%, level 6 (mean concentration = 154.9 pmol/l, CV = 2.5%)]. Luteinizing hormone (LH) and follicular stimulating

hormone (FSH) were quantified using two-site sandwich immunoassays (supplied by Bayer Diagnostics Europe) using direct chemiluminometric technology [*LH intra-assay precision*: level 1 (mean concentration = 4.2 IU/l), CV = 2.3%, level 3 (mean concentration 16.4 IU/L) CV = 2.3%, level 6 (mean concentration = 118.2 IU/l, CV = 2.6; *FSH intra-assay precision*: level 1 (mean concentration = 6.9 IU/L), CV = 2.7%, level 3 (mean concentration 23.4 IU/L) CV = 21.2%, level 6 (mean concentration = 144.3 IU/L, CV = 1.2%)].

2.10. MRI scanning methods

Gradient echo echoplanar imaging (EPI) data were acquired on a neuro-optimized GE Signa 1.5 T system (General Electric, Milwaukee WI, USA) at the Maudsley Hospital, London. Consistent image quality was ensured by a semi-automated quality control procedure. A quadrature birdcage headcoil was used for radio frequency transmission and reception.

For blood oxygen level-dependent (BOLD) imaging, 268 T2*-weighted whole-brain volumes were acquired during each of the encoding and forced recognition paradigms at each of 22 near-axial non-contiguous planes parallel to the intercommissural line (slice thickness = 5 mm; gap = 0.5 mm; TR = 2.0 s; echo time = 40 ms; flip angle = 90°; matrix = 64 × 64). At the same time, a high-resolution gradient echo image of the whole brain was acquired in the intercommissural plane consisting of 43 slices (slice thickness = 3 mm; gap = 0.3 mm; TR = 3 s; flip angle = 90°; matrix = 128 × 128). This EPI data set provided almost complete brain coverage.

2.11. Analysis of fMRI data

Data were analysed with XBAM v3.4 (Institute of Psychiatry, London, UK) on a Sun Workstation (Sun Microsystems Inc., Santa Clara, USA).

2.11.1. Individual analysis

The data were first realigned (Bullmore et al., 1999a) to minimize motion related artefacts and smoothed using a Gaussian filter (full width half maximum 7.2 mm). Responses to the experimental paradigms were then be detected by time-series analysis using Gamma variate functions to model the BOLD response. In order to constrain the possible range of fits of physiologically plausible BOLD responses, a constrained fitting procedure (Friman et al., 2003) was used. Following this fitting operation, a goodness of fit statistic was computed at each voxel. This was the ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by the sum of squares due to the residuals (original time series minus model time series). This statistic is called the SSQratio. The percentage change in the BOLD signal at each voxel was also calculated. This was $[(\mathrm{fit}_{max}-\mathrm{fit}_{min})/\mathrm{mean\ signal\ intensity}] \times 100$, where fit_{max} and fit_{min} were the maximum and minimum values of the fitted response for the time series in question.

In order to sample the distribution of SSQratio under the null hypothesis that observed values of SSQratio are not determined by experimental design (with minimal assumptions), the time series at each voxel was permuted using a wavelet-based re-sampling method (Bullmore et al., 2001; Breakspear et al., 2003). This process was repeated 20 times at each voxel and the data combined over all voxels, resulting in 20 permuted parametric maps of SSQratio at each plane for each subject. The same permutation strategy was applied at each voxel to preserve spatial correlational structure in the data during randomization. Combining the randomized data over all voxels yielded the distribution of SSQratio under the null hypothesis. A test that any given voxel is activated at any required type I error was then be carried out by obtaining the appropriate critical value of SSQratio from the null distribution. For example, SSQratio values in the observed data lying above the 99th percentile of the null distribution had a probability under the null hypothesis of $\leqslant 0.01$. It has been shown that this permutation method gives very good type I error control with minimal distributional assumptions (Bullmore et al., 2001; Breakspear et al., 2003).

2.11.2. Group mapping

In order to extend inference to the group level, the observed and randomized SSQratio maps were transformed into standard space by a two stage process involving first a rigid body transformation of the fMRI data into a high-resolution inversion recovery image of the same subject followed by an affine transformation onto a Talairach template (Brammer et al., 1997). By applying the two spatial transformations computed above for each subject to the statistic maps obtained by analysing the observed and wavelet-randomized data, a generic brain activation map (GBAM) was produced for each experimental condition. The median observed SSQratio over all subjects at each voxel (median values were used to minimize outlier effects) were then be tested at each intra-cerebral voxel in standard space (Talairach and Tournoux, 1998) against a critical value of the permutation distribution for median SSQratio ascertained from the spatially transformed wavelet-permuted data (Brammer et al., 1997). In order to increase sensitivity and reduce the multiple comparison problem encountered in fMRI, hypothesis testing was carried out at the cluster level using a method (Bullmore et al., 1999b) initially designed for structural image analysis, and subsequently shown to give excellent cluster-wise type I error control in both structural and functional fMRI analysis. When applied to fMRI data, this method estimated the probability of occurrence of clusters under the null hypothesis using the distribution of median SSQratios computed from spatially transformed data obtained from wavelet permutation of the time series at each voxel (see above). Image-wise expectation of the number of false positive clusters under the null hypothesis was set for each analysis at <1. Consequently, correction for multiple comparisons was not required, as thresholds were set on an image-wide basis, not a voxelwise basis.

2.11.3. Group differences

Analysis of variance was carried out on the SSQratio maps in standard space by first computing the difference in median SSQratio between groups at each voxel. Subsequent inference of the probability of this difference under the null

hypothesis was made by reference to the null distribution obtained by repeated random permutation of group membership and re-computation of the difference in median SSQratios between the two groups obtained from the re-sampling process. As with the GBAM, cluster-level maps were then obtained with the cluster-wise probability equivalent to less than one false positive cluster per image.

2.12. Contrasts

We set up contrasts to determine the following effects:

2.12.1. Encoding task

(a) *The subsequent memory* (*Dm*) *effect at baseline*: In this contrast we compared the encoding trials at baseline that were subsequently correctly recognized with those that were forgotten both irrespective of group and between group. This is frequently referred to as the 'subsequent memory' or 'Dm' effect (Otten et al., 2001). This contrast therefore explored regions of brain activation during encoding that were predictive of subsequent memory success and established that there were no baseline differences between the two groups.
(b) *The Dm effect across time in the control group*: In this contrast we compared the Dm effect at baseline (time 1) with the Dm effect 8 weeks later (time 2). This contrast explored the effect of practice.
(c) *The Dm effect across time in the experimental group*: This contrast compared the Dm effect at baseline (time 1) with the Dm effect 8 weeks later (time 2); i.e. following 8 weeks of GnRHa administration (ovarian suppression). This contrast explored the combined influence of practice and ovarian suppression.
(d) *The group-by-time interaction*: This contrast explored the effects of ovarian suppression on the Dm effect that is not explained by non-specific effects of time or practice.

2.12.2. Recognition task

(a) *Recognition success at baseline*: In this contrast we analysed all trials at baseline (i.e. both dependent and independent of group), and we compared recognition of 'old-words' correctly recognized as having previously been studied (hits) with 'new-words' correctly classified as not previously studied (correct rejections, CRs). This contrast therefore explored group differences at baseline and the regions of brain activation during recognition that were predictive of success.
(b) *Recognition success across time in the control group*: In this contrast we compared recognition success at baseline (time 1) with the recognition success 8 weeks later (time 2). This contrast explored the main effect of practice.
(c) *Recognition success across time in experimental group*: In this contrast we compared recognition success at baseline (time 1) with the recognition success 8 weeks later (time 2). This contrast explored the combined effects of practice and ovarian suppression.
(d) *The group-by-time interaction*: This contrast explored the effects of ovarian suppression on the recognition success that is not explained by non-specific effects of time or practice.

2.13. Additional statistical analyses

Simple *t*-tests were used to compare age, full scale IQ, MMSE, BDI and BAI between groups at baseline. Due to a low detectable limit of the hormone assays, Wilcoxon rank tests were used in the group comparisons of plasma hormone levels across time. In order to compare accuracy of encoding and recognition between the two groups over time we used mixed repeated measure ANOVAs.

3. Results

3.1. Baseline screening tests

At baseline women did not differ on scores on the MMSE, BDI, BAI, age or IQ (Table 1).

3.2. Plasma hormone levels

There were no baseline differences in ovarian hormone or gonadotrophin levels, but oestrogen and LH concentrations were significantly reduced in the experimental group post GnRHa administration (Table 2). 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 at baseline in both groups and in the control group at time 2 some women had post-ovulatory hormone profiles. However, our results were not significantly different when

Table 1 Between group characteristics at baseline.

	Control group (SEM) $N = 15$	Experimental group (SEM), $N = 15$	Test statistic (F)	P	95% Confidence interval of the difference	
Age	40.4 (1.2)	38.1 (1.7)	0.197	0.307	−2.18	6.67
Full scale IQ	94 (3.4)	98 (5.6)	0.181	0.485	−18.27	9.16
mMSE	29.5 (0.3)	29.2 (0.2)	0.163	0.471	−0.45	1.05
BDI	5.4 (1.6)	4 (1.1)	0.536	0.294	−2.06	6.49
BAI	3.2 (1.2)	6.4 (2.2)	0.69	0.320	−7.34	2.50

mMSE, Mini-Mental State Examination; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.

Table 2 Plasma hormone levels.

	Time 1 Median (25%, 75% quartile)	Time 2 Median (25%, 75% quartile)	*z*-score	*P*
Control group				
Estradiol (pmol/l)	650 (285, 958)	377 (201, 948)	−0.722	0.470
Progesterone (nmol/l)	5 (5,34)	10 (5,30)	−0.764	0.445
Luteinising hormone (u/l)	6.9 (3.95, 7.95)	5.1 (3.3, 11.8)	0.000	1.000
Follicular stimulating hormone (u/l)	3.4 (2.85, 6.5)	4.3 (3,7.2)	−0.039	0.969
Experimental group				
Estradiol (pmol/l)	418 (260, 805)	30 (30,70)	−3.180	0.001[a]
Progesterone (nmol/l)	5 (5,15)	5 (5,5)	−1.826	0.068
Luteinising hormone (u/l)	7.85 (4,20.35)	0.8 (0.8, 0.8)	−3.180	0.001[a]
Follicular stimulating hormone (u/l)	4.5 (1.62, 8.17)	3.25 (2.2, 5.7)	−1.153	0.249

[a]NB: The absence of a statistically significant difference between FSH levels across does not suggest a failure of GnRHa to suppress ovarian function. GnRHa only suppresses FSH to 'follicular phase levels' (AstraZeneca, 2005). In light of the fact that we attempted to manipulate the study to assess *all* women at the follicular phase of the cycle this finding would have been predicted at the onset.

these women were excluded and they were therefore included in the final analysis.

3.3. Behavioural results

3.3.1. Encoding

A mixed repeated measurement ANOVA of the accuracy of living/non-living responses whilst encoding stimuli revealed that there were no significant main effects of time ($F(1,28) = 0.107$, $p = 0.746$) and group ($F(1,28) = 0.034$, $p = 0.856$) or a significant interaction between time and group ($F(1,28) = 0.01$, $p = 0.922$.

3.3.2. Recognition memory

Accuracy was calculated by the discrimination measure Pr [probability of a correct-hit (*P* hit) minus probability of a false-alarm (*P* false-alarm)]. A mixed repeated measurement ANOVA revealed a trend for the interaction between group and time ($F(1, 28) = 2.99$, $p = 0.095$, two-tail). There was no main effect for time or group ($F(1,28) = 1.854$, $p = 0.184$ and $F(1,28) = 0.01$, $p = 0.972$. Pairwise comparison showed that there was no change in discrimination over time within the control group ($p = 0.80$, CI: −0.089–0.069), but there was a significantly reduced discrimination within the experimental group ($p = 0.037$, CI: −0.16–0.05)).

3.4. *f*MRI results

3.4.1. Encoding

(a) *Dm effect on brain activation patterns at baseline in both groups*: The Dm effect (i.e. the difference between encoding trials at baseline that were subsequently correctly recognized with those that were forgotten) was associated with significantly increased activation; bilaterally in the lingual and inferior medial and middle frontal gyri (left > right), caudate nuclei, and thalami; and in left anterior cingulate cortex and cerebellum (Figure 1). There were no significant between-group differences at baseline in brain activation during the Dm effect.

(b) *The Dm effect across time in the control group*: There were no significant within-group changes in activation in any brain region.

(c) *The Dm effect following treatment in the experimental group*: Dm-related activation following treatment was significantly reduced compared to pre-treatment bilaterally in the medial frontal gyrus, left inferior frontal gyri and anterior cingulate and right precentral gyrus (Figure 2).

(d) *The effects of ovarian suppression on Dm*: There was a significant group by time interaction. Dm-related activation was significantly reduced across time in women who received GnRHa as compared to women who did not. This interaction was observed; bilaterally at the medial frontal gyrus; in left anterior cingulate, middle and inferior frontal gyri (Figure 3).

3.4.2. Recognition memory

(a) *Recognition success at baseline in both groups*: In both groups activation was increased bilaterally in the inferior parietal lobules, angular gyri, posterior cingulate and superior occipital gyri and left supramarginal gyrus and right superior temporal gyrus. There were no significant between-group differences at baseline in brain activation.

(b) *Recognition success across time in the control group*, (*vii*) *recognition success across time in experimental group and* (*viii*) *differences between group and recognition success across time*: There was no significant change in activation across any brain region within either group, and no group by time interaction.

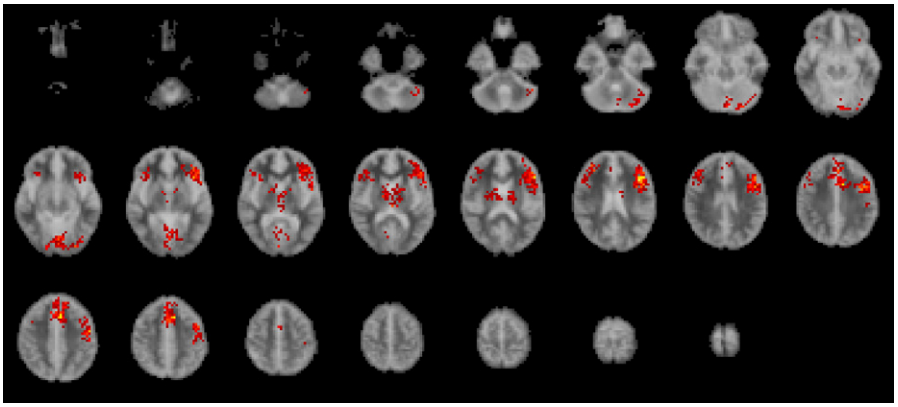


Figure 1 Brain activation associated with successful versus unsuccessful encoding (Dm) in all women at baseline. Encoding of words that were subsequently correctly recognised compared to those that were not recognised (the Dm effect) was associated with significantly increased activation bilaterally in the lingual (BA 17/18) and inferior (BA 44/45/47) medial (BA 8/9) and middle (BA 9/46) frontal gyri (left > right), caudate nuclei, and thalami; and in left anterior cingulate cortex (BA 24/32) and cerebellum.

4. Discussion

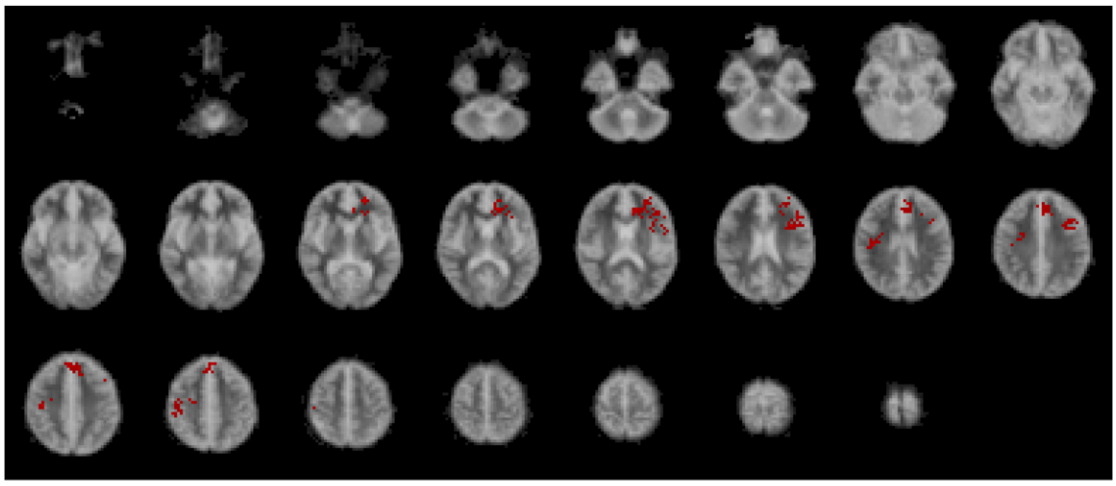
Our aim was to elucidate the effects of GnRHa administration on brain function during a verbal memory task; because previous behavioural evidence suggested specific, and detrimental, effects of GnRHa on verbal memory (Sherwin and Tulandi, 1996). Hence we examined patterns of brain activation before and 8 weeks after GnRHa treatment 15 healthy premenopausal women and contrasted their findings with a wait-list control group over a similar interval. We hypothesized that GnRHa administration would be associated with altered activation in regions important to successful encoding (e.g. the left inferior frontal gyrus, LIFG) and successful retrieval (e.g. the PPC). Also, we used an event-related design that enabled us to interpret modulations in brain responses produced by GnRHa separately from any behavioural confounds (since the elucidation of the Dm effect involves comparing, in all cases, words successfully encoded with words that are unsuccessfully encoded and analysis of the retrieval task compared 'hits' with CRs.

Our results indicated that the key neurobiological change produced by GnRHa administration was at the encoding stage rather than at the retrieval stage. This change was evident in the LIFG, left anterior cingulate and adjacent prefrontal cortical regions. In behavioural analyses, we also found reduced recognition success in women following GnRHa administration, and the interaction between treatment group and time showed a trend ($p<0.10$, two tailed). These behavioural findings are consistent with previous findings of memory decline following GnRHa treatment (Sherwin and Tulandi, 1996) and provide novel insights into the neurobiological basis for the verbal memory impairment associated with GnRHa.

4.1. Analysis of the underlying encoding network disrupted by GnRHa

Our functional imaging findings are broadly consistent with previous studies into brain regions activated during successful verbal encoding in the general population (see Fletcher et al., 2003; Wagner et al., 2005; Staresina and Davachi, 2006 for reviews). In particular at baseline we report activation of brain regions that are typically described during the Dm effect including LIFG and adjacent prefrontal cortical regions and the anterior cingulate. The finding of reduced activation in the prefrontal cortex, especially LIFG, in the between group analysis of the Dm effect across time suggests that GnRHa has a direct effect on the network of regions that are important to successful verbal episodic encoding.

The frontal activation we subsequently observed in both groups associated with the Dm effect at encoding (particularly in the LIFG) may reflect semantic processing of encoded material which is encouraged by the nature of the encoding task (i.e. making a living/non-living judgement). Thus the reduction of left frontal activity following GnRHa may be indicative of reduced semantic processing or reduced processing more generally during the encoding of material into episodic memory and contribute to the subsequent trend towards reduced recognition success. Previous neuroimaging studies have found activation in this same region during word generation tasks, including semantic fluency (Paulesu et al., 1997), and have found activation in this area to be associated with a deeper level of processing at encoding (Otten et al., 2001) and higher confidence (Wagner et al., 1998). Alternatively, it could be argued that our finding of neural disruption at the encoding stage is attributable to a non-specific effect arising from impaired attention or behavioural performance. This is, however, unlikely since subjects showed no decrement in their ability to perform the encoding task (i.e. in making the living/non-living judgment) and previous behavioural studies of GnRHa show negative effects on verbal memory or working memory with no effects on tests of attention (Sherwin and Tulandi, 1996; Grigorova et al., 2006) A recent behavioural study reported declines in working memory tasks mediated by frontal lobes following GnRHa treatment in a group of healthy premenopausal women (Grigorova et al.,



Area	Brain Region	Side	Tal(x)	Tal(y)	Tal(z)	BA	Clusterwise probability	SSQ ratio
Frontal	Anterior Cingulate gyrus	**L**	**-22**	**37**	**9**	**29**	0.001159	0.015048
		L	-18	44	4	32		
		L	-7	30	15	24		
		L	-11	33	9	24		
	Medial frontal gyrus	**L**	**-36**	**19**	**31**	**12**	0.002046	0.031501
		L	-4	41	26	31		
		R	**4**	**37**	**42**	**8**	0.000217	0.03211
		R	7	37	37	8		
	Inferior frontal gyrus	**L**	**-40**	**22**	**20**	**45**	0.000546	0.025734
		L	-32	7	31	44		
	Precentral gyrus	**R**	**40**	**-15**	**26**	**43**	0.002313	0.013416
		R	47	-11	42	6		

Voxelwise significance p = 0.05; Clusterwise significance = 0.0025. Talairach (Tal) coordinates in bold print indicate the most activated voxel within a cluster. Other Talairach coordinates represent other active areas in clusters (derived from decomposition of each cluster into contiguous slices, 5.72 mm diameter in the z dimension).

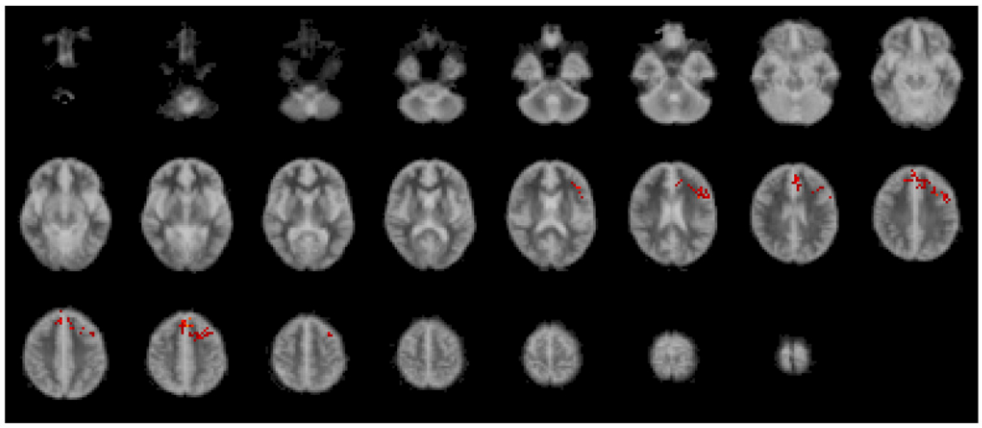
Figure 2 Regional reduction in brain activation from baseline to post-GnRHa associated with successful versus unsuccessful encoding (Dm).

2006). This suggests a possible overlap in GnRHa effects during working memory and encoding into verbal long-term memory.

4.2. Neuroendocrinological basis of the effect of GnRHa on encoding

The changes in brain function reported in this study may have been attributable to the *direct* effects of GnRHa or the *indirect* effects of reduced LH, FSH and/or ovarian hormones on the brain. Distribution studies in rats report that, under normal circumstances, GnRHa does not cross the blood brain barrier (BBB) (Barnfied et al., 1988). This suggests that our findings are likely to be attributable to the indirect effects of GnRHa as ovarian hormones (estrogen and progesterone), FSH, LH all cross the BBB.

A stronger case can be made for implicating reduced estrogen as the key neuroendocrine determinant of memory loss and brain dysfunction. It has been reported that estrogen therapy (ET) increases semantic clustering of words during verbal learning in postmenopausal women (Maki et al., 2001) and randomized trials of ET indicate reliable benefits to verbal memory in younger postmenopausal women, though not in older postmenopausal women (see Maki, 2005 for a systematic review). In imaging studies, ET has been reported to significantly increase (left) frontal activation during working memory tasks (Shaywitz et al., 1999) and fronto-temporal and parietal lobes (Resnick et al., 1998; Shaywitz et al., 1999; Maki and Resnick, 2000; Joffe



Area	Brain Region	Side	Tal(x)	Tal(y)	Tal(z)	BA	Clusterwise probability	SSQ ratio
Frontal	Anterior cingulate gyrus	L	-18	11	42	32		
		L	-29	15	31	24		
	Inferior frontal gyrus	**L**	**-40**	**22**	**20**	**45**	0.000168	0.054103
		L	-40	11	31	44		
	Medial frontal gyrus	L	-4	37	26	9		
		R	**4**	**33**	**42**	**8**	0.000295	0.052231
		R	**4**	**48**	**31**	**7**	0.000473	0.037382
	Middle frontal gyrus	**L**	**-29**	**15**	**31**	**9**	0.000302	0.031086

Voxelwise significance p = 0.05; Clusterwise significance = 0.001. Talairach (Tal) coordinates in bold print indicate the most activated voxel within a cluster. Other Talairach coordinates represent other active areas in clusters (derived from decomposition of each cluster into contiguous slices, 5.72 mm diameter in the z dimension).

Figure 3 The group difference in Dm × time interaction.

et al., 2006) during verbal recognition. In light of these studies, our finding of significant decreases in frontal activation during successful verbal encoding following GnRHa appears likely to be due to reduced estrogen rather than to increased LH or FSH. This interpretation is further supported by a previous behavioural study that reported add-back estrogen treatment reversed verbal memory deficits associated with GnRH treatment (Sherwin and Tulandi, 1996).

Estrogenic effects on behaviours mediated by prefrontal cortex may be due to direct effects of the hormone on this brain region, or the indirect effects of estrogen on neurotransmitter systems that affect prefrontal cortical function (see Craig and Murphy, 2007 for review). Estradiol increases spine number in the prefrontal cortex of ovariectomized young monkeys (Tang et al., 2004). We previously reported that postmenopausal women on long term ET, as compared to treatment naive controls, have significantly greater cholinergic, serotonergic and dopaminergic responsivity to neuroendocrine challenge tests (van Amelsvoort et al., 2001, 2003; Craig et al., 2004). Both animal and human studies have reported that the deleterious effect of scopolamine, a cholinergic antagonist, is reduced by estrogen (Fader et al., 1999; Dumas et al., 2006) Furthermore, a recent *f*MRI study has reported reduced brain activation in the inferior prefrontal cortex during the encoding of face-name associations following scopolamine administration (Sperling et al., 2002). These findings suggest that estrogen-mediated effects on these neurotransmitter systems might partly explain our results.

4.3. Interpretation of the absence of an effect GnRHa on verbal episodic retrieval

Previous event-related fMRI studies of retrieval, contrasting hits with CRs, have described increased activation in similar brain regions to those reported at baseline in this study (Wagner et al., 2005). In particular we report increased activation at the PPC, including the inferior parietal lobules and angular gyri as well as medial structures such as the posterior cingulate. The absence of significant changes in brain activation during retrieval across conditions suggests that GnRHa does not affect activation in brain regions associated with retrieval of studied versus unstudied words. These results were unexpected as previous neuroimaging

studies have reported that estrogen has significant effects on brain regions activated during retrieval (see Sherwin, 2003 for review).

There are a number of possible explanations for the differences in our results, some pertaining to the samples who were studied and others to the methodologies employed. In contrast to our investigation previous imaging studies have, for example, contrasted recognition with a rest condition (Resnick et al., 1998; Maki and Resnick, 2000) or other experimental conditions (Shaywitz et al., 1999). These previous studies also used 'block designs'—whereas we employed an 'event-related' method'. Analysis of trials using blocks of items/words (as opposed to individual items/words) makes it difficult to determine whether or not the effects of estrogen reported by others on specific brain regions are confounded by differences in attention and/or performance. In contrast, our event-related design enabled us to address performance effects by focusing on correct and incorrect memory trials separately. Also, our analysis was subsequently limited to brain responses to 'retrieval success' whereas blocked design studies and PET studies are unable to disambiguate, with confidence, retrieval attempt from retrieval success. We cannot rule out the possibility that GnRHa can affect brain regions underlying retrieval in experimental conditions similar to those used in previous neuroimaging studies (i.e., when analysed in a block design or when analysed regardless of whether a trial was correct or incorrect). Treatment related considerations may also be important. Previous PET studies of episodic verbal memory examined long-term hormone therapy use on verbal retrieval in a sample of older women, with one cross-sectional study and one longitudinal study (Resnick et al., 1998; Maki and Resnick, 2000). The effects of GnRHa on brain regions subserving verbal retrieval may become evident only during late-adulthood or following long-term treatment. Lastly, we employed a more conservative statistical approach than prior studies, because our statistical model took into account multiple comparisons and treated inter-subject variability as a random effect.

4.4. Implications for use of GnRHa as a memory enhancer

Recent animal (Casadesus et al., 2006) and human studies (http://www.secinfo.com/d14D5a.z6483.htm, pp. 56–64) in people with AD have reported positive effects of GnRHa on memory. The mechanism by which reduced LH (i.e. following GnRHa administration) might modulate cognition remains unclear. It has been suggested that it may be via down-regulation of β-amyloid production. The design of this trial—8 weeks in healthy premenopausal women-precludes the possibility of detecting any cognitive benefit due to reduced β-amyloid production. Our finding of deleterious effects of short-term GnRHa use on prefrontal brain regions suggests potential adverse effects in older samples, at least over the short term. Future imaging studies are needed to examine the effects of GnRHa given over longer periods in clinically appropriate groups. This might, for example, include women with mild cognitive impairment (MCI) or early AD.

4.5. Limitations of the study

Our study has several limitations. First, to better understand the neurobiological mechanisms underlying the negative effects of GnRHa on function in prefrontal and other brain areas, it would be helpful to have included an add-back estrogen condition. Secondly, it would have been helpful to have measured subjects' responses in the recognition task to address the possibility that the apparent reduction in brain activity following GnRHa was not directly attributable to an effect of GnRHa, but was indirectly due an increased tendency to guess whether words are new/old in the recognition task. On the other hand, guessing would likely have affected retrieval—and we did not observe effects on retrieval. Lastly, our study may have benefited from analysing the effects of GnRHa over a longer period of administration. Previous studies suggest, for example, that GnRHa may have more profound effects on cognition after 6 months (i.e. leading to reduced scores on the MMSE) (Palomba et al., 2004) but may have beneficial effects in people with Alzheimer's Dementia (i.e. by stabilizing cognitive performance). It has been postulated that the beneficial effects of GnRHa on cognition relate to its effects on reducing LH concentrations in the brain which subsequently leads to reduced β-amyloid deposition (Casadesus et al., 2006). This mechanism has received some support from recent studies which have reported increased β-amyloid deposition in transgenic mice strains which over-express LH (Casadesus et al., 2007). Although this is an area of research that requires further study it is unlikely that the postulated effects of GnRHa on β-amyloid confounded the results of our study.

5. Summary

Our study suggests that the memory difficulties reported by some women following GnRHa and possibly at other times of acute ovarian hormone withdrawal (e.g. following surgical menopause and postpartum) may have a clear neurobiological basis; one that manifest during encoding of words and that is evident in decreased activation in prefrontal regions known to sub-serve deep processing of to-be-learned words. Further research is required to determine the precise mechanism(s) through which GnRHa effects this modulation.

Role of the funding sources

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Conflicts of interest

Dr Craig is funded by a Medical Research Council (UK) Fellowship.

Drs. Michael Craig, Eileen Daly, William Cutter, Vincent Giampietro have not received any money from any pharmaceutical companies for consulting fees or sitting on advisory boards, etc. and do not have any equity ownership/stock options in publicly or privately traded firms.

Dr. Paul Fletcher has received less than $10,000 per year as a member of the Advisory Board for GSK. He does not have any equity ownership/stock options in publicly or privately traded firms.

Dr. Pauline Maki 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 Wyeth-Ayerst. She does not have any equity ownership/stock options in publicly or privately traded firms.

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.

Professor Mick Brammer has not received any money from any pharmaceutical companies for consulting fees or sitting on advisory boards etc. However, he has shares in the Brain Resource Company (Sydney) and is a director of Neurosense ltd UK.

Professor Murphy has received funding from the Medical Research Council (UK), the Wellcome Trust, the Psychiatry Research Trust and Wyeth-Ayerst for research.

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