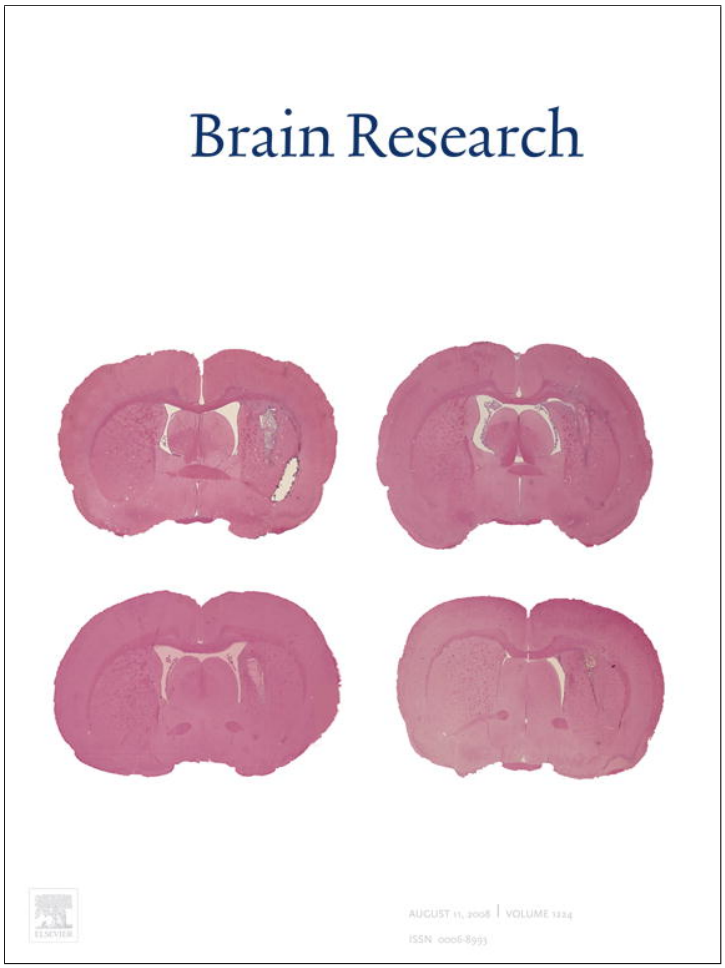

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Research Report

Menstrual cycle phase modulates cognitive control over male but not female stimuli

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ABSTRACT

Evolutionary selection pressures have been one of the factors proposed to underlie sex differences in inhibitory control. Consequently, inhibitory control may vary as a function of the menstrual cycle and may be modulated by the stimuli being processed if these stimuli are related to reproductive success. We used functional MRI to study women's brain activation across the menstrual cycle on a GO/NOGO response inhibition task using attractive male and female faces as stimuli. We detected brain activity changes for both successful inhibitions and errors of commission that were unique to the male stimuli during the follicular phase of the menstrual cycle. That is, when pregnancy was possible women had superior inhibitory brain function and heightened detection of inhibitory failures when processing male stimuli. Moreover, we show that individual differences between females in sexual desire and social risk taking negatively correlate with error-related brain activity to the male stimuli during the follicular phase of the menstrual cycle. These results suggest an interaction between hormonal influences and stimulus-specific effects in producing an endophenotypic outcome predicted by evolutionary psychology, and suggest that the functioning of the brain's monitoring system can predict individual differences in both traits and real-world risk-taking behaviours.

1. Introduction

Parental investment theory (Trivers, 1972) postulates that many psychological differences between the sexes derive from different evolutionary pressures particular to the investment of resources in finding a mate vs. parenting. Theorists (Bjorkund and Kipp, 1996) have proposed that the greater parenting demands placed on females and the advantage of forming stable bonds with males, confer a selection advantage on those females with the ability to suppress sexual interests in other males or aggressive tendencies towards one's own offspring. Consequently, greater selection pressures on female ancestors

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Abbreviations: fMRI, functional magnetic resonance imaging; male-fol, male stimulus-follicular phase; fem-fol, female stimulus-follicular phase; male-lut, male stimulus-luteal phase; fem-lut, female stimulus-luteal phase; STOPS, successful inhibitions; ERRORS, errors of commission; IFG, Inferior Frontal Gyrus; HISD, Hurlbert Index of Sexual Desire, DOSPERT, Domain-Specific Risk Taking; CNS, central nervous system; cAMP, Cyclic adenosine monophosphate; PFC, prefrontal cortex; LH, Lutenising Hormone; SENSE, SENSitivity Encoding; ROI, regions of interest; ANOVA, analysis of variance

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resulted in contemporary intellectual and behavioural functioning, with women demonstrating greater inhibition abilities on tasks related to reproduction and childrearing, such as inhibiting sexual urges, being more selective about sexual partners, and being able to delay gratification (Buss and Schmitt, 1993; Syoms, 1979; Trivers, 1972).

Despite the vast number of functional neuroimaging studies, surprisingly little research has investigated the neural basis of sex differences in brain activation patterns underlying cognitive–affective processing and how these differences might be modulated by the menstrual cycle. Studies have reported that female preference for male characteristics varies with the probability of conception across the menstrual cycle, with women manifesting more attraction to men with masculine traits during the late follicular phase of the menstrual cycle (when fertility is high), than at other times (Jones et al., 2005a and Penton-Voak et al., 1999) These studies support the existence of beneficial adaptations whereby ancestral females increased their reproductive success by increasing attraction to masculine traits in men when fertility probability was high (Penton-Voak et al., 1999) and increasing preferences for people believed to be trustworthy (DeBruine et al., 2005), to be free of contagion (Fessler, 2002; Flaxman and Sherman, 2000; Jones et al., 2005b) and to display social cues associated with relationship commitment (Gangestad et al., 2002) when fertility had a low probability.

Protopopescu et al.(2005) reported that inhibitory control does vary across the cycle but neuroscientists have yet to determine if this modulation is stimulus-specific. Cycling menstrual changes in mating strategy (i.e., women preferring different features in males across the cycle) coupled with parental investment theory suggest that selection might favour human females in inhibitory domains directly related to mate selection and parenting, and that this favourable inhibitory brain function might be influenced by pregnancy potential and may also be stimulus-specific. The present experiment hypothesised that inhibitory control may vary as a function of the menstrual cycle and may be further affected by the stimuli being processed if these stimuli are related to reproductive success. More specifically, we hypothesise that evolutionary pressures have conferred women with superior inhibitory control despite increased attractiveness to male characteristics (Jones et al., 2005a and Penton-Voak et al., 1999) during the follicular period of their menstrual cycle (when pregnancy is possible) and that this advantage, being specific to reproductive success, may be specific to male stimuli. This hypothesis was tested via a GO/NOGO task. Additionally, the relevance of variations in these control mechanisms across the menstrual cycle was assessed by determining whether individual differences in sexual desire and risky behaviours correlated with brain activity.

These hypotheses were tested using the capability of functional neuroimaging to detect brain activation differences between late follicular (days 10–14) and midluteal (days 21–24) phases of the menstrual cycle that might not be easily observable with behavioural measures alone. In this repeated measures design 15 healthy, right-handed, premenopausal females completed a GO/NOGO task in which the stimuli were attractive male and female faces that required multiple button press responses and occasional and unpredictable response inhibitions when the same stimulus was repeated on successive trials (Fig. 1). Here we show that the brain's cognitive control mechanisms facilitate information processing in a stimulus-specific manner that interacts with the menstrual cycle. We couple these findings with negative correlations between the brain's monitoring system and individual differences in both trait measures of sexual desire and real-world measures of risky social behaviours.

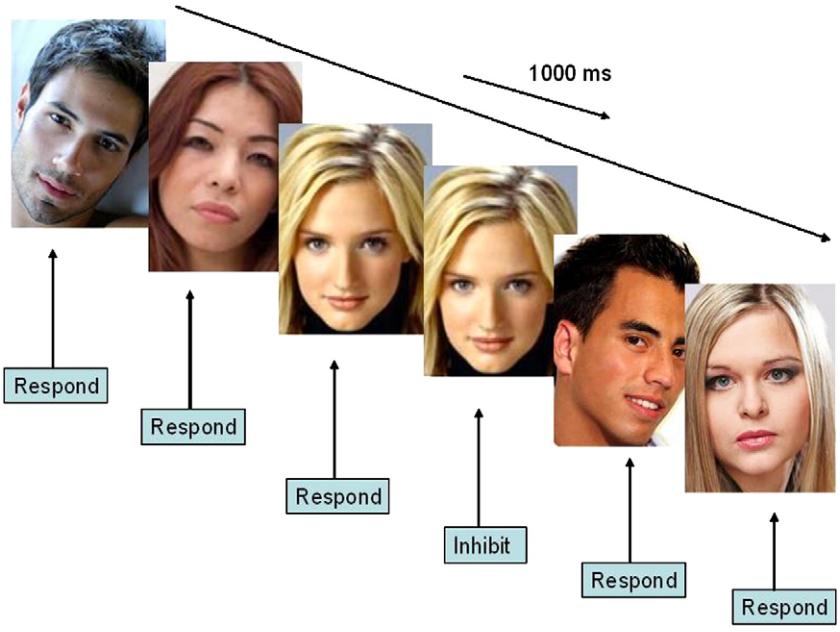

Fig. 1 – Illustration of GO/NOGO task. The male and female stimuli were presented serially at 1 Hz and subjects were required to make a button press response to each stimulus. Responses were to be withheld when the same stimulus was repeated. Each stimulus was presented for 900 ms and the inter-stimulus interval (a blank screen) was 100 ms.

2. Results

2.1. Behavioural results

A series of 2 (Phase: Follicular vs. Luteal)>0.05; Fig. 2A). Error of commission (ERRORS) response times revealed no significant main effects (all Ps≥0.05; Fig. 2B) but there was a significant Phase>0.05; Fig. 2C) however there was a Phase effect with increased reaction times during the follicular phase ($F=6.64$, *df* 1/14, $P<0.02$. Participants provided attractiveness ratings of the faces after each scan session and these ratings also did not differ or interact between Phases or Stimuli (all Ps≥0.05; Fig. 3).

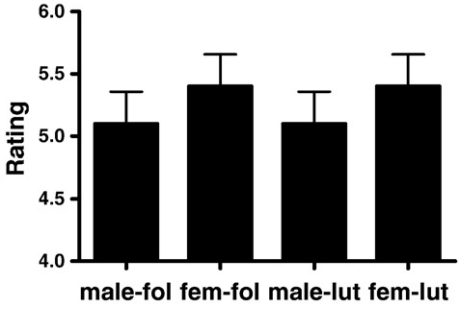

Fig. 3 – Attractiveness rating results. Attractiveness ratings of male and female faces that were rated on a Likert scale that ranged from 1 to 9, with 9 representing extremely attractive and 1 representing not at all attractive. There was no effect of menstrual cycle. Phase or face Stimulus on attractiveness ratings (Phase $F=0.01$, *df* 1/14, $P\geq0.05$; Stimulus $F=1.31$, *df* 1/14, $P\geq0.05$; interaction $F=0.01$, *df* 1/14, $P\geq0.05$, treating Phase and Stimulus as within-subject factors).

2.2. Neuroimaging results

Successful inhibitions (STOPS) activated a number of brain areas (Table 1) that have previously been identified as structures in the neural circuitry of inhibition (Garavan et al., 2002, 2003; Li et al., 2006a,b) including studies using affective stimuli (Chambers et al., 2006; Protopopescu et al. 2005). The Culmen revealed a Phase effect (Phase $F=7.76$, *df* 1/14, $P\leq0.01$) with increased brain activation during the follicular phase, while the Cuneus revealed a Stimulus effect (Stimulus $F=5.41$, *df* 1/14, $P\leq0.04$) with increased brain activation during the luteal phase (see S2 for full statistical details). In addition to STOP-related activity in parietal, temporal and cerebellar regions, there was also robust activity in right ventral Inferior Frontal Gyrus (IFG), a region that imaging, lesion and transcranial magnetic stimulation studies have shown to be a core brain region for inhibitory control ((Aron and Poldrack, 2006; Aron et al., 2003; Fassbender et al. 2004; Chambers et al. 2006) The right IFG was the only area to show a significant Phase × Stimulus interaction (F (1, 14) = 6.5, $P\leq0.02$) with activity significantly reduced when inhibiting to the mal-fol compared to the fem-fol condition (F (1, 14) = 12.3, $P\leq0.00$) (Fig. 4). No other pair wise contrasts were significant (see S2 for full statistical details)).

ERRORS are common on a task of this sort in which a prepotent motor response must be countermanded. ERRORS produced robust activation in the Anterior Cingulate Cortex (ACC), a key structure in monitoring performance (Carter et al., 1998), and additionally in parietal, frontal and sub cortical regions (Table 1). A Phase effect was evident in the Superior Temporal Gyrus (Phase $F=17.12$, *df* 1/14, $P\leq0.00$) with increased brain activation during the follicular phase (see S2 for full statistical details). No region showed a significant interaction between Phase and Stimulus, including the ACC (F (1, 14) = 3.8, $P\leq0.07$). However, the ACC was the only region to show a Stimulus effect for ERRORS (F (1, 14) = 5.0, $P\leq0.04$) showing greater activity for errors to male faces than to female faces. Moreover, despite the absence of a significant interaction, planned comparisons revealed the stimulus effect to be specific to the follicular phase (F (1, 14) = 6.0, $P\leq0.03$) and not at all present in the luteal phase ($F<1$). In contrast to the IFG results for STOPS, in which mal-fol activity was smaller than fem-fol activity, the ACC activity for ERRORS was greater for mal-fol compared to fem-fol (Figs. 5A, B). In addition, male-fol activity was also significantly greater than male-lut activity

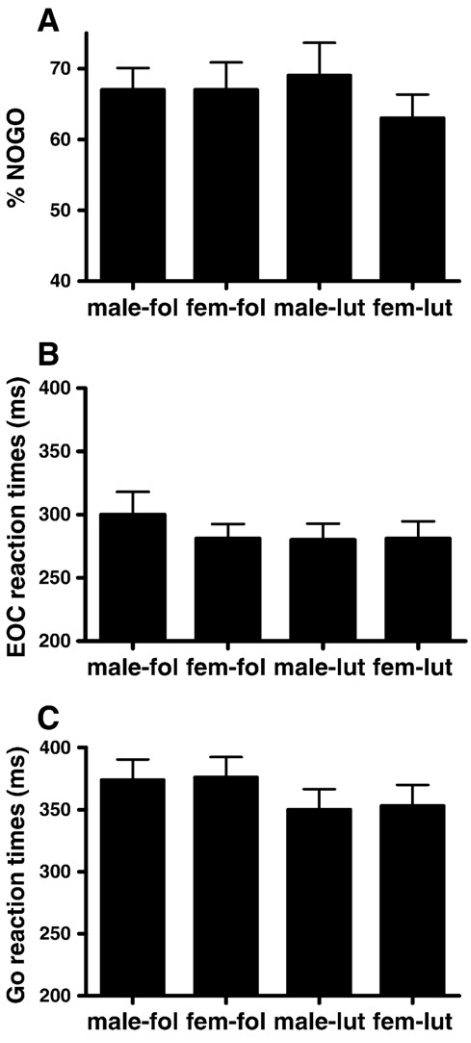

Fig. 2 – Behavioural performance results. Behavioural performance measures. (A) ERROR percentages; (B) ERROR reaction times; (C) Go reaction times. See S1 for full statistical results.

Table 1 – Cerebral foci for NOGO activation

Structure	Broadmann area	Hemisphere	Volume (μl)	Centre of mass		
				X	Y	Z
STOPS						
Inferior frontal gyrus**	47	R	806	37.5	16.4	−8.8
Inferior parietal lobule	40	R	547	43.7	−60.8	41.4
Superior temporal gyrus	38	L	396	−45.4	13.5	−10.0
Superior temporal gyrus	22	R	289	60.7	−51.0	14.1
Middle frontal gyrus	9	R	242	31.0	45.1	36.2
Supramarginal gyrus	40	R	240	53.8	−46.7	30.8
Superior temporal gyrus	39	L	213	−56.0	−49.4	15.9
Culmen*		L	203	−1.8	−33.5	−14.6
Cuneus (1)+	18	L	194	−19.7	−85.1	13.0
Cuneus (2)	19	L	185	−27.8	−83.3	22.1
ERROR						
Anterior cingulate cortex+	32	R	1722	2.8	26.1	30.6
Insula	13	L	462	−39.6	9.1	−1.4
inferior frontal gyrus	47	R	269	37.3	17.8	−14.8
Lentiform nucleus	34	R	242	27.1	5.7	−5.0
Inferior parietal lobule	40	R	241	51.9	−50.7	42.4
Superior temporal gyrus*	22	L	215	−59.5	−39.4	21.5

*Phase effect; +Stimulus effect; **Phase × Stimulus interaction. Positive values are right, superior and anterior to the anterior commissure. See S2 for full statistical results.

(F (1, 14) = 5.0, $P \leq 0.04$). No other pair wise contrasts were significant (see S2 for full statistical details)). These results indicate a heightened performance monitoring reaction for failures to inhibit GO response "approach" behaviour to males that was specific to the follicular phase.

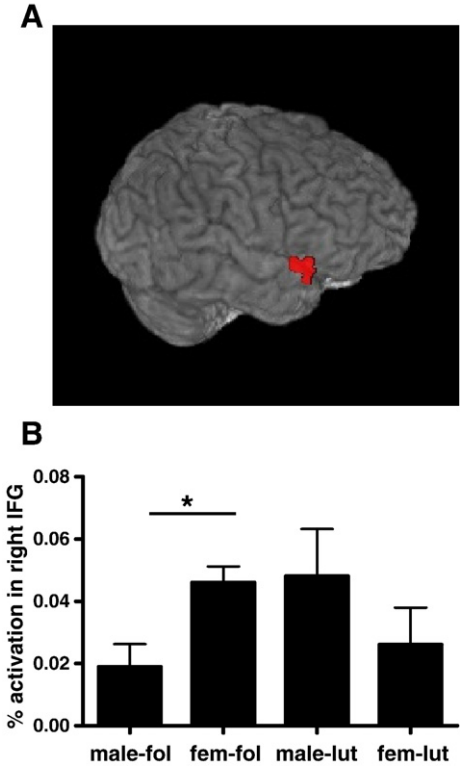

Fig. 4 – IFG brain activation. (A) Right IFG (–37, –16, –9) activation during successful response withholds (STOPS). (B) There were no main effects of menstrual cycle phase or stimulus on STOPS but there was a significant interaction in which mal-fol activation was lower than fem-fol activation.

2.3. *Psychometric correlations*

We assessed the relevance of variations in these control mechanisms across the menstrual cycle by determining whether individual differences in sexual desire, assessed by the Hurlbert Index of Sexual Desire (HISD) (Apt and Hurlbert, 1992), correlated with brain activity. ACC activation for mal-fol ERRORS correlated negatively with sexual desire (Fig. 5C). That is, the error-related brain mechanism that would appear to be sensitive to reproductive, evolutionary effects showed a reduced response in those with higher trait-levels of sexual desire. Moving beyond sex-specific behaviours, ACC activity in this same male-fol condition also correlated negatively with the social subscale of the DOSPERT (Domain-Specific Risk Taking) (Ann-Renee Blais, 2006) which involves a self-report measure of risky social behaviours such as disagreeing with an authority figure at work or starting a new career in your mid-thirties (Fig. 5D). These correlations were not found for activity levels in any other condition nor for any other brain region.

3. Discussion

This study examined whether inhibitory control may vary as a function of the menstrual cycle in a stimulus-specific manner related to reproductive success. In the absence of performance differences we found selective reactions of critical brain regions for inhibiting and registering inhibitory errors to males that were specific to the follicular phase confirming our hypotheses and suggesting that the neurobiology of important cognitive control mechanisms vary in accordance with predictions derived from evolutionary theory. Here we

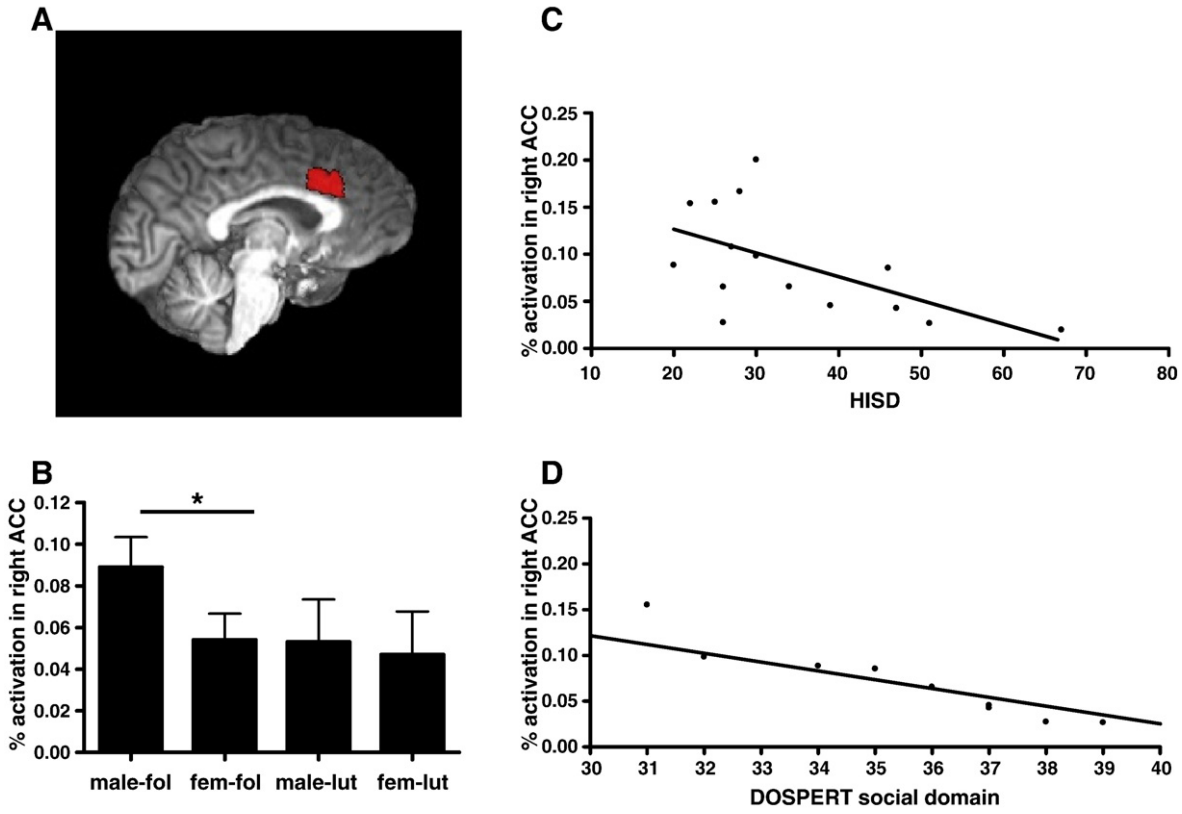

Fig. 5 – ACC brain activation. (A) Significant activation was found in the right ACC (–37, –16, –9) for errors of commission. (B) There was a significant interaction driven by greater activation in the mal-fol condition relative to the fem-fol condition. Right ACC activation in the mal-fol condition correlated negatively with the Hurlbert Index of Sexual Desire ($r = -0.58$, $P \leq 0.02$; C) and with the social subscale of the Domain-Specific Risk Taking questionnaire ($r = -0.73$, $P \leq 0.00$; D).

show that brain activation differences were specific to male stimuli during the follicular phase of the menstrual cycle where IFG activity was significantly reduced during successful inhibitions while an enhancement of ACC brain activity was manifested for inhibitory errors. Even though the task did not yield performance differences, it did succeed in producing an endophenotypic activation measure that would appear to be more sensitive than the behavioural measure for detecting differences in inhibitory control. The expectation is that a more sensitive behavioural measure would reveal performance differences. Note, however, that the absence of performance differences can be advantageous as potential cofounding factors that are secondary to the performance differences such as error-related frustration are eliminated from our within-group comparisons.

In the absence of performance differences, reduced IFG activity of this kind suggests greater ease or neural efficiency in inhibiting. Previous studies of the menstrual cycle using a variety of measurement modalities have demonstrated enhanced memory processing, fine-motor coordination, and increased rapid eye movement latency in the follicular phase (see e.g. Armitage and Yonkers, 1994; Hampson, 1990; Maki et al., 2002). Previous functional studies that used non-sexual stimuli have shown mixed results with activity levels for inhibition being either reduced in the follicular phase or unaffected by menstrual cycle when subjects processed positive and negative words (Amin et al., 2006; Protopopescu et al., 2005). The current results suggest that menstrual influences on brain function may be modulated by the stimuli employed which may help clarify some of the discrepancies in the extant literature. The findings reported here of enhanced ACC brain activation indicate a heightened performance monitoring reaction for failures to inhibit a GO response (an "approach" behaviour) to males that was specific to the follicular phase. We also investigated the relevance of behavioural monitoring across the menstrual cycle by assessing whether sexual desire and risk taking correlate with ACC activation. The psychometric correlations reported here suggest that the functioning of the ACC-mediated monitoring system can predict individual differences in both trait measures of sexual desire and real-world measures of social risk taking. While the precise description of the ACCs function in monitoring behaviour is still a matter of some considerable investigation, there is nonetheless a reasonable consensus that it performs an evaluative function of either one's performance, a task's demands or one's effort/arousal in responding to those demands (Brown and Braver, 2005; Critchley et al., 2001; Magno et al., 2006). Given this important yet broad role it is plausible that reduced activity in this region may also be relevant to important facets of social interaction including, for example, the risky decision-making of adolescents (Bjork et al., 2007).

Progesterone and oestrogen levels vary across the menstrual cycle: oestrogen levels rise during the follicular phase and reach their peak approximately 24 h prior to ovulation, whereas

progesterone levels are low during the follicular phase and peak in the midluteal phase (Fillingrim and Ness, 2000). As scientists (e.g. Buffet et al., 2001) have verified that the concentrations and ratios of circulating sex hormones oscillate throughout the menstrual cycle and influence the central nervous system (CNS) in a large number of varied ways the menstrual cycle effects reported here may be related to hormonal influences. Cholinergic (Gibbs et al., 1998; Lucey et al., 1991; Tseng et al., 1997), glutamatergic (Gazzaley et al., 1996 and Woolley et al., 1997), GABAergic (Murphy et al., 1998), serotonergic (Biegon et al., 1983; Moses et al., 2000; Pecins-Thompson et al., 1996; Sumner and Fink, 1997) noradrenergic (Tseng et al., 1997), and dopaminergic neurotransmitter (Pasqualini et al., 1995) and (Pasqualini et al., 1996) systems all respond to sex hormones. Dopamine is of particular interest here given its role in both response inhibition (Hester et al., 2004) and the ACC error response (Holroyd and Coles, 2002). Oestrogen and progesterone have direct and opposing actions on dopaminergic neurotransmission. Preclinically, oestrogen increases dopamine synthesis (Pasqualini et al. 2005; 2006), turnover and release (Becker and Beer, 1986), and dopamine receptor density (Hruska and Silbergeld, 1980 and Rance et al., 1981b), as well as decreasing monoamine activity which reduces the degradation of dopamine (Luine et al., 1975). In contrast, progesterone appears to down-regulate dopamine systems (Shimizu et al., 1993), leading to the suggestion that the results reported in this study may be influenced by the facilitatory effect of oestrogen on the dopaminergic system during the follicular phase of the menstrual cycle. Although there is less evidence that normal menstrual cycle fluctuations would have similar effects on components of the neurotransmitter systems, a recent study links menstrual cycle influences on response inhibition to oestrogen levels (Amin et al., 2006). As hormone levels were not verified which limits inferences characterising the rapidly changing levels of ovarian steroid hormones inferences are only speculative.

One limitation of the present study is the reliance on human subjects to record their menstrual cycle status as hormone levels were not measured. In our study our only biological marker was LH but as a significant LH surge occurs in only a small window of time, approximately 24–36 h prior to ovulation (Buffet et al., 2001), a negative LH test is not necessarily indicative of low oestrogen levels which are elevated from days 10 to 14 of a normal 28 day menstrual cycle. We found no brain activation differences between participants who tested positive on LH to those who tested negative. Exploration of the effects of cyclic hormonal fluctuation at multiple time points would help to understand the full range of ovarian steroids influence on cognitive–affective processing. When directly comparing studies that investigate menstrual cycle hormonal phase effects, conflicting results may manifest if methodological differences exist, such as slightly different specified time frames, different stimuli modalities, and incorporating different brain activation baseline measures into functional brain analysis.

Fluctuating changes in oestrogen and progesterone are not, however, sufficient explanations for the observed changes in activity in the right IFG and ACC as the phase effects here differed according to the stimulus being processed. This suggests that the hormone-neurotransmitter interactions described above facilitate information processing in a stimulus-specific manner. Arising from evolutionary demands to be selective when sexual activity could yield offspring, the brain's cognitive control mechanisms may be attuned to respond to sexual conspecifics. Despite female preference for masculine characteristics in men when fertility probability is high (Jones et al., 2005a and Penton-Voak et al., 1999) these influences may be "counteracted" to some extent by superior inhibitory brain function and heightened detection of inhibitory failures. The suggestion here is that selection pressures on female ancestors resulted in both an increased attraction to advantageous traits (e.g., increased preference for heritable immunity to infectious disease; Penton-Voak et al., 1999) and an increased ability to be selective and cautious when committing to a sexual encounter (e.g., selecting mates that will also provide resources for the females and their offspring; Bjorklund and Kipp, 1996).

This stimulus-specific interaction between menstrual cycle phase and stimulus type produces an endophenotypic outcome predicted by evolutionary psychology. Our findings can contribute to the development of models of brain function that integrate the effects of stimulus modality, stimulus complexity, contextual differences, stimulus, hormone effects, and other individual differences. Even though previous studies have indicated the influence of stimulus on neural activity underlying seemingly straightforward cognitive tasks, overall, conflicting results have been reported (Amin et al., 2006; Protopopescu et al., 2005). Incorporating menstrual cycle fluctuations into these studies might explain these discrepancies. As cognitive control is believed to be central to many psychological disorders, many of which have different prevalences in males and females (Eme, 2007; Kessler et al., 2005; Neuman et al., 2005), the present results may also have implications for understanding the biological basis of these clinical conditions. Our results suggest that measures of brain function, perhaps by being closer to genetic influences than observable behaviour, can provide a testbed for psychological evolutionary theory.

4. Experimental procedures

4.1. *Participants*

15 healthy right-handed regularly cycling premenopausal participants who were not using contraceptives for at least 6 months participated in the experiment (mean age 22.5, range: 18–39; menstrual cycle length range: 23–32 (12 participants reporting 28 days while the remaining participants reported 23, 30, and 32 days). The subjects were pre-assessed to exclude those with a prior history of neurological or psychiatric illness. Participants were recruited through public advertisement. All participants gave informed consent and the study was approved by the School of Psychology in Trinity College Dublin. The group completing the post-scan mail questionnaire comprised 12 of the 15 participants who completed both fMRI testing sessions.

4.2. *Task design*

Participants took part in two fMRI scans, during which they completed a GO/NOGO task involving male and female attractive faces. For participants who reported a 28 28 day

cycle follicular phase scans took place between days 10 and 14 of the menstrual cycle and luteal phase scans took place between days 21 and 24 of the menstrual cycle. These time frames were adjusted for three participants with longer menstrual cycles. Here, the length of time from the Lutenising Hormone (LH) surge to the next mensus was taken as 14 days (Buffet et al., 2001; Jukic et al. 2007). For example, for a 32 32 day cycle follicular phase scans took place between days 14 and 18 of the menstrual cycle and luteal phase scans took place between days 25 and 28 of the menstrual cycle. Consequently, given the counterbalancing of scans between subjects, there was a longer interscan interval if the luteal scan was first. Two versions of the task, each with 60 male and 60 female faces, were used in order to avoid performance being influenced by stimulus repetition. The tasks were created using the E-prime stimulus presentation programme (Psychology Software Tools, Pittsburgh, PA). Both task version and which phase of the menstrual cycle was imaged first were counterbalanced across sessions. One hour prior to the follicular phase scan the *in vitro* qualitative detection of LH was determined via urinalysis (Clearview easy LH, Unipath LTD, Bedford, UK). Only 8 of the women tested positive, perhaps as a significant LH surge occurs in only a small window of time, approximately 24–36 h, prior to ovulation (Buffet et al., 2001).

The stimuli were attractive male and female faces that were collected from multiple web sources. The emotional expressions were neutral and any distracting items such as accessories (e.g. jewelry, sunglasses) or skin blemishes were removed. The male and female stimuli were presented serially at 1 1 Hz and subjects were required to make a button press response to each stimulus. Responses were to be withheld to NOGO stimuli: a NOGO occurred when the same stimulus was presented twice in succession (see Fig. 1).The female stimuli NOGO trials served as control trials for the male stimuli NOGO trials (i.e., the stimuli had similar dimensions, characteristics, and response demands) and the two NOGO trial types were randomly interspersed among the GO trials. The inter-stimulus interval was 100 100 ms and each stimulus was presented for 900 900 ms. Participants were instructed to try to respond while the stimulus was on screen and responses and response speed were recorded. During fMRI scanning, participants were presented with 960 targets (GO stimuli) and 120 lures (NOGO stimuli) resulting in 1080 events in total with each face appearing eight times as a GO trial and once as a NOGO trial. The event-related design of this experiment allowed the NOGOs to be distributed unpredictably throughout the stimuli stream. This ratio resulted in an average interval between NOGOs of 9 s. The entire run which lasted 22 min consisted of 4 blocks of 240 events followed by 4 rest periods, each of 1 min duration. Directly after the scanning session subjects rated each face for attractiveness on a Likert scale from 1 to 9, with 9 representing extremely attractive and 1 representing not at all attractive. This task was also created using the E-prime stimulus presentation programme (Psychology Software Tools, Pittsburgh, PA) (Fig. 1).

Prior to scanning, subjects completed the Hurlbert Index of Sexual Desire (HISD) (1990., 2002). The HISD consists of 25 items endorsed with a choice from 0 (all of the time) to 4 (never) with overall scores ranging from 0 (lower desire) to 100 (high desire). Beck (1995) noted that this scale has good construct validity, test–retest reliability ($r=0.86$ across two weeks), and internal consistency (alpha=0.89) (Beck, 1995). An 11-item questionnaire that queried menstrual cycle details such as average length of menstrual cycle, sexual interests such as ideal relationship status, and sexual orientation, was also administered.

Following scanning sessions a post-scan mail questionnaire survey was conducted where the Risk Taking Scale of the Domain-Specific Risk Taking (DOSPERT) questionnaire (Ann-Renee Blais, 2006) was completed. The risk-taking scale evaluates behavioural intentions, originating from five domains of life (ethical, financial, health/safety, social, and recreational risks) using a 7-point rating scale. One of the questions was removed from the scale ("investing 5% of your annual income in a very speculative stock") as it was not relevant to our population and euros were substituted for dollars. Subjects also completed a questionnaire on sexual history and sexual risk taking that included questions such as, relationship status, number of sexual partners, and contraception usage. Information on alcohol use and influence was also collected.

4.3. *Imaging parameters*

All scanning was conducted on a Philips Intera Achieva 3.0 T MR system (Best, The Netherlands) equipped with a mirror that reflected a 640 5 s of standard scout images to adjust head positioning, followed by a reference scan to resolve sensitivity variations. Imaging used a parallel SENSitivity Encoding (SENSE) approach (Pruessmann et al., 1999) with reduction factor 2. 180 high-resolution T1-weighted anatomic MPRAGE axial images (FOV 230 230 mm, thickness 0.9 9 mm, voxel size 0.9 6 min), to allow subsequent activation localization and spatial normalization. Thirty-two non-contiguous (10% gap) 3.5 5 mm axial slices covering the entire brain were collected using a T2* weighted echo-planar imaging sequence (TE=35 35 ms, TR=2000 ms, FOV 224 224 mm, 64 64 mm matrix size in Fourier space).

4.4. *Time-series analyses*

The fMRI data were analysed using the AFNI software package (Cox, 1996). Time-series data were motion-corrected using 3D volume registration (least-squares alignment of three translational and three rotational parameters). Activation outside the brain was removed using edge detection algorithms. Deconvolution techniques calculated event-related activation for successful response inhibition (STOPS) and errors of commission (ERRORS). Separate haemodynamic response functions at 2 2 s temporal resolution were calculated. A multiple regression analysis was used to derive estimates for the time-point parameters of the haemodynamic response functions, by estimating the signal contributed by each individual event type to the overall time series. In the present analysis regressors for both ERRORS and STOPS for each cyclic phase and stimulus were entered, and the regression estimated the signal contributed by each of these events over and above that accounted for by the ongoing task (GO trials). The haemodynamic response functions were then modelled voxelwise

with a gamma-variate function using non-linear regression (Garavan et al., 1999; Ward et al. 1998). An area-under-the-curve measure of the gamma-variate model was expressed as a percentage of the tonic baseline activity and served as the activation measure for the event-related responses. Activation maps were warped into a standard stereotaxic space (Talairach et al., 1998) and spatially blurred with a 4.2-mm full-width at half-maximum isotropic Gaussian filter after performing a second edge detection on the skull stripped brain. ERROR and STOP activation maps for each condition (male stimulus-follicular phase (male-fol), female stimulus-follicular phase (fem-fol), male stimulus-luteal phase (male-lut), and female stimulus-luteal phase (fem-lut)), were determined with one-sample *t* tests against the null hypothesis of zero activation changes (i.e. no change relative to tonic task-related activity). Significant voxels passed a voxelwise statistical threshold ($t=4.14045$, $P\leq 0.005$) and were required to be part of a larger 185 185 μl cluster of contiguous significant voxels. Thresholding was determined through Monte Carlo simulations and resulted in a 1% probability of a cluster surviving due to chance. The activation maps were then combined deriving one OR map of all significant STOP activations across conditions and one OR map of all significant ERROR activations across conditions. An OR map includes the voxels of activation identified as significant from any of the constituent maps. The mean activation for clusters in the combined maps was calculated for each subject and condition for the purposes of a whole brain analysis.

4.5. *Statistical analysis*

Performance analysis calculated the percentage of STOPS and GO trial and ERROR trial response times for each condition. Data are expressed as mean±SEM and analysed with the computerized package SPSS (version 12) for statistical analysis. Statistical significance was determined by 2×2 ANOVAs that compared measures during the follicular and luteal phases of the menstrual cycle for male and female stimuli, followed by *post hoc* multiple comparison tests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.brainres.2008.05.061.

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