

ORIGINAL ARTICLE

Progesterone selectively increases amygdala reactivity in women

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The acute neural effects of progesterone are mediated by its neuroactive metabolites allopregnanolone and pregnanolone. These neurosteroids potentiate the inhibitory actions of γ -aminobutyric acid (GABA). Progesterone is known to produce anxiolytic effects in animals, but recent animal studies suggest that pregnanolone increases anxiety after a period of low allopregnanolone concentration. This effect is potentially mediated by the amygdala and related to the negative mood symptoms in humans that are observed during increased allopregnanolone levels. Therefore, we investigated with functional magnetic resonance imaging (MRI) whether a single progesterone administration to healthy young women in their follicular phase modulates the amygdala response to salient, biologically relevant stimuli. The progesterone administration increased the plasma concentrations of progesterone and allopregnanolone to levels that are reached during the luteal phase and early pregnancy. The imaging results show that progesterone selectively increased amygdala reactivity. Furthermore, functional connectivity analyses indicate that progesterone modulated functional coupling of the amygdala with distant brain regions. These results reveal a neural mechanism by which progesterone may mediate adverse effects on anxiety and mood.

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Introduction

Changes in the blood concentration levels of progesterone and estradiol are associated with changes in mood regulation¹ and cognition.² For instance, explicit memory^{3–5} and mood^{4–6} deteriorate during pregnancy when progesterone and estradiol levels reach their highest physiological concentrations. Mood is also influenced by the more subtle changes in these hormone levels during the menstrual cycle. The negative mood symptoms in premenstrual dysphoric disorder (PMDD) and premenstrual syndrome (PMS) occur during the luteal phase, when progesterone and estradiol concentrations are high, and disappear a few days after the onset of menstruation, when these hormone concentrations are lowest.⁷ However, these negative mood symptoms develop in the absence of abnormal gonadal steroid hormone concentrations.^{7,8} Furthermore, the administration of progesterone or estradiol after gonadal hormone

suppression produces negative mood symptoms in women with PMS, but not in those without PMS.⁹ The negative mood in PMDD/PMS therefore appears as an abnormal response to normal hormonal changes.¹⁰ The neural mechanism by which these hormones influence mood are, however, unknown.

Animal research has shown that progesterone modulates anxiety, and that these effects are probably mediated by its metabolite allopregnanolone.^{11–13} This neurosteroid potentiates the inhibitory actions of γ -aminobutyric acid (GABA) by modulation of the GABA_A receptor.¹⁴ Consistent with this GABAergic mechanism, progesterone and allopregnanolone administration usually produce an anxiolytic effect^{11,13} by the action on the amygdala.¹⁵ Also pregnanolone, the less potent 5β stereoisomer of allopregnanolone that has a similar effect,^{16,17} can produce anxiolysis.¹⁸ However, it induces anxiogenic effects to aversive stimuli after a period of relative allopregnanolone suppression,¹⁸ which mimics the low allopregnanolone levels during the human follicular phase.¹⁹ As the amygdala is involved in a wide range of emotional behavior, and local infusions of GABA antagonists induce anxiogenic effects,²⁰ the amygdala may mediate the anxiogenic effects of allopregnanolone as well.

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In the present study, we investigated whether a single progesterone administration to healthy women during their follicular phase increases amygdala reactivity. The amygdala is part of a larger emotion circuitry, which is important for the identification of the emotional significance of stimuli, the generation of an affective response and emotion regulation.²¹ We therefore explored whether progesterone's modulation of amygdala activity influences the functional integration of this system. We used an oral administration of micronized progesterone, which increases allopregnanolone and pregnanolone concentrations to a similar extent.²² By administering progesterone instead of comparing neural activity during the luteal (high progesterone and estradiol) and the follicular phases (low progesterone and estradiol), the results of this study provide a mechanistic account for a hormone-brain interaction that is not confounded by (spurious) effects linked to the menstrual cycle.

Materials and methods

Subjects

Eighteen naturally cycling women (mean age 24 years; range: 19–39) participated in this study after signing informed consent. They were healthy as determined by routine physical and laboratory examinations, and had no current psychiatric disorder indicated by a structured interview.²³ They were right-handed, free of medication, did not use hormonal contraceptives and reported no history of psychiatric or somatic disease potentially affecting the brain. This study was approved by the local ethics committee (CMO Regio Arnhem-Nijmegen, The Netherlands).

Design and procedure

The subjects participated twice during the early follicular phase (days 2–7) of different menstrual cycles, when endogenous hormone levels are low. They arrived at ~0815 hours after overnight fast to receive a standardized light breakfast, after which 400 mg of micronized progesterone or placebo was administered orally, in a double-blind, crossover fashion. A venous blood sample was collected before drug administration and the scanning session, which started ~90 min after drug intake. In addition, subjects completed a mood rating questionnaire (MRS)²⁴ just before scanning and a state anxiety questionnaire (STAI)²⁵ about 190 min after drug intake.

Behavioral task

The experimental paradigm consisted of a blocked design, including an emotion condition and a visuo-motor control condition. This paradigm has been used previously to investigate drug effects on amygdala reactivity.^{26,27} It robustly engages the amygdala, by contrasting the response to simultaneously presented angry and fearful face stimuli (<http://www.macbrain.org>) with the response to ellipses (that consisted of scrambles of the same face stimuli). The

results therefore do not show emotion-specific effects, but rather a general response to salient, biologically relevant stimuli.

Two emotion blocks were interleaved with three control blocks, and each 30-s block consisted of six 5-s trials. Each trial consisted of three simultaneously presented stimuli, with the cue stimulus presented above the target and distractor (see Hariri *et al.*²⁶). In the emotion condition, an angry or fearful face was presented on top as cue, and subjects had to indicate by an appropriate button press which of the bottom two faces (one angry and one fearful) matched the cue in emotional expression. The three simultaneously presented faces per trial were from different persons from the same sex. Half the trials presented faces of men and half of women, half of each target emotion (angry or fearful). In the control condition, a horizontally or vertically oriented ellipse was presented as cue above two ellipses (one vertical and one horizontal), and subjects had to select the identically oriented ellipse.

Data acquisition

Scanning was performed with a 1.5 T Siemens Sonata MR scanner (Siemens, Erlangen, Germany), equipped with a standard head coil. Seventy-six T2*-weighted EPI-BOLD images were acquired per subject with an echo time of 30 ms to reduce signal dropout, with each image volume consisting of 33 axial slices (3 mm, 0.5 mm slice gap, TR = 2.290 s, 64 × 64 matrix, FOV = 224 mm, FA = 90°). In addition, a high-resolution T1-weighted structural MR image was acquired for spatial normalization procedures (MP-RAGE, TR = 2250 ms, TE = 3.93 ms, 176 contiguous 1 mm slices, 256 × 256 matrix, FOV = 256 mm).

fMRI data analysis

Image analysis was performed with SPM2 (Wellcome Department of Imaging Neuroscience, London, UK). The first five EPI volumes were discarded to allow for T1 equilibration, and the remaining images were realigned to the first volume. Images were then corrected for differences in slice acquisition time, spatially normalized to the Montreal Neurological Institute T1 template, super-sampled into 2 × 2 × 2 mm³ voxels, and spatially smoothed with a Gaussian kernel of 10 mm FWHM.

Statistical analysis was performed within the framework of the general linear model.²⁸ For each drug condition, the two experimental conditions were modeled as box-car regressors convolved with the canonical hemodynamic response function of SPM2. In addition, the realignment parameters were included to model potential movement artefacts as well as a high-pass filter (cutoff at 1/128 Hz). To account for various global effects, the EPI data were proportionally scaled. Temporal autocorrelation was modeled with an AR(1) process and the parameter estimates were obtained by maximum likelihood estimation²⁹ to allow departures from sphericity. Single-subject parameter images contrasting the

emotion and control conditions were obtained and entered into subsequent random effects analyses. The main effect of the task was assessed with a one-sample *t*-test, and the effect of drug (that is, drug \times task interaction) was assessed with a paired *t*-test. In addition, the effects of drug on the functional integration of the amygdala was investigated using a functional connectivity analysis.³⁰ The time course of amygdala activity was extracted (that is, the first eigenvariate of a sphere with 6 mm radius around the peak voxel of the right amygdala as identified by the main effect of task), and added as a covariate of interest to the model. Single-subject parameter images containing the regression coefficients were obtained and entered into subsequent random effects analyses. One-sample *t*-tests were used to identify brain regions with a correlated time course, and paired *t*-tests were used to identify the effects of drug on functional connectivity with amygdala. Statistical tests were family-wise error (FWE) rate corrected for multiple comparisons across the whole brain or the region-of-interest (ROI), using a small volume correction,³¹ unless stated otherwise. The bilateral amygdala ROI was anatomically defined using the WFU Pickatlas,³² and the bilateral face responsive regions in the fusiform gyri were defined as spheres with 14 mm radius around previously reported Talairach coordinates³³ that were transformed into MNI-space (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>). Furthermore, mean amygdala activity in both drug conditions was extracted from the bilateral amygdala ROI for additional correlation analyses.³⁴

Serum analysis

Progesterone was measured with Delfia progesterone kits (Wallac Oy, Turku, Finland) according to the manufacturer's instructions. Allopregnanolone was measured with radioimmunoassay (RIA) after diethyl-ether extraction and celite chromatography (recovery 78%). The antiserum was directed against 3 α -hydroxy-20-oxo-5 α -pregnan-11-yl carboxymethyl ether-BSA with low cross reactivity and a gift from Dr Robert H Purdy (Department of Psychiatry, College of Medicine, University of California, San Diego, CA, USA). The intra-assay coefficient of variation was 6.5% and inter-assay coefficient of variation of was 8.5%.³⁵

Results

The baseline plasma concentrations of progesterone and allopregnanolone did not differ significantly between the progesterone and placebo condition (both $P > 0.2$). The progesterone administration increased the progesterone concentration from the follicular to the luteal phase range (mean \pm s.e.m., from 1.94 ± 0.29 to 16.83 ± 6.17 nmol/l, $t(16) = 2.39$, $P = 0.03$), and increased the concentration of allopregnanolone from 0.60 ± 0.05 to 24.98 ± 7.30 nmol/l ($t(16) = 3.35$, $P = 0.004$). This allopregnanolone level is similar to that during early pregnancy.^{36,37} However, progesterone had no significant effect on the mood²⁴

or state anxiety²⁵ questionnaires (all $P > 0.2$) and did not significantly modulate response accuracy or reaction times in the behavioral task (all $P > 0.05$). These factors therefore appear to have little explanatory value in relation to the observed differences in brain activity between the progesterone and placebo conditions.

The functional magnetic resonance imaging (fMRI) results show that the emotion condition yielded larger responses than the control condition in the amygdala, ventral visual stream (ranging from the primary visual cortex to the fusiform gyrus), inferior frontal gyri, cerebellar vermis and supplementary motor area ($P < 0.05$, corrected; see Table 1 and Figure 1). Critically, progesterone increased the right amygdala response ($P < 0.05$, corrected; see Table 1 and Figures 2 and 3). A similar effect was also present in the left amygdala, although at a less conservative threshold (see Table 1). In contrast, progesterone did not significantly influence neural activity in other brain areas.

To explore the relation between amygdala reactivity and allopregnanolone levels, state anxiety and mood across subjects, additional correlation analyses were performed. While progesterone reliably increased amygdala reactivity in the within-subjects comparison, no significant correlations between allopregnanolone levels and amygdala activity were observed across subjects during the progesterone or placebo conditions. However, progesterone modulated the relation between amygdala activity and mood. While amygdala activity was positively correlated with the MRS subscales alertness ($r = 0.66$, $P = 0.003$) and contentedness ($r = 0.53$, $P = 0.025$) during the placebo condition, no such relation was observed during the progesterone condition ($P > 0.1$).

The functional connectivity analysis identified various brain regions that were functionally coupled with the right amygdala. Brain regions with a positive correlation with amygdala activity included regions in the medial temporal lobe (including the left amygdala and both hippocampi), the basal ganglia, orbitofrontal cortex, temporal pole, thalamus, inferior temporal gyri, pons and fusiform gyri. Brain regions in the midbrain and cerebellar vermis showed a negative correlation with amygdala activity ($P < 0.05$, corrected; see Table 2).

Progesterone decreased functional connectivity of the fusiform gyrus with the amygdala ($P < 0.05$, corrected). Furthermore, the results indicate that progesterone increased functional connectivity of the dorsal anterior cingulate cortex with the amygdala at a less conservative threshold ($P < 0.001$, uncorrected; see Table 2 and Figure 4).

Discussion

The results show that a single progesterone administration to healthy women in their follicular phase selectively increases amygdala reactivity. The progesterone administration significantly increased the

Table 1 Cluster maxima for brain regions with a larger response during the emotion than the control condition (main effect of task), and for brain regions that are modulated by progesterone (drug \times task interaction)

	MNI coordinates			Cluster size	t	P-value ^a
	x	y	z			
<i>Main effect of task</i>						
Right inferior occipital and temporal cortex	26	-90	-10	3613	17.9	<0.001
Left inferior occipital and temporal cortex	-26	-92	-12	3138	14.1	<0.001
Right amygdala	22	-4	-16	125	9.0	<0.001
Left amygdala	-22	-10	-16	164	8.5	<0.001
Right inferior frontal gyrus	44	10	32	575	8.4	<0.001
Left inferior frontal gyrus	-44	10	28	240	8.4	<0.001
Cerebellar vermis	2	-74	-32	63	7.0	0.002
Supplementary motor area	0	10	60	41	6.9	0.002
Left inferior frontal gyrus	-56	22	-4	22	6.7	0.005
<i>Drug \times task interaction (progesterone > placebo)</i>						
Right amygdala	26	-6	-22	14	5.8	0.001 ^b
Left amygdala	-28	-6	-22	—	2.9	0.005 ^c

^aP-values are corrected for multiple comparisons across the whole brain ($P < 0.05$, $k \geq 10$).

^bP-value corrected for multiple comparisons across the amygdala ($P < 0.05$).

^cPeak voxel (P -value is uncorrected for multiple comparisons).

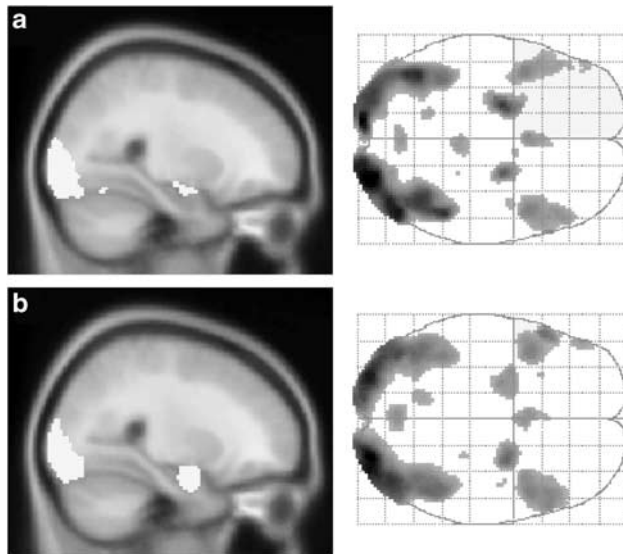


Figure 1 Larger amygdala responses to salient, biologically relevant stimuli than the control condition in the placebo (a) and the progesterone condition (b). The sagittal slices on the left ($x = 26$) and the maximum intensity projections on the right are thresholded at $P < 0.001$, uncorrected for multiple comparisons.

plasma concentration of progesterone as well as that of its metabolite allopregnanolone, which potentiates the inhibitory actions of GABA.¹⁴ Because it is this neurosteroid that mediates the acute effects of progesterone,^{11,13} the observed activity increase of amygdala is probably mediated by the neuroactive metabolites allopregnanolone and/or pregnanolone.

The amygdala is critically involved in a wide range of emotional behavior,³⁸ including fear and anxiety,²⁰

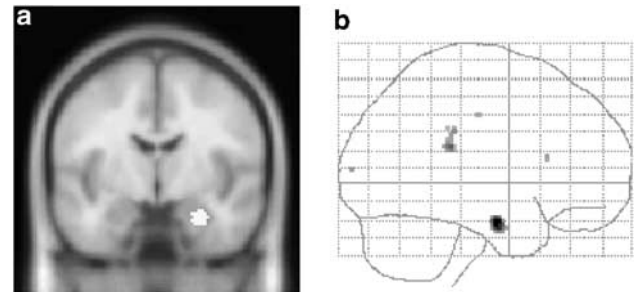


Figure 2 A single progesterone administration increases the amygdala response. A coronal slice (a) shows the increased right amygdala reactivity ($y = -6$) in the progesterone condition. The maximum intensity projection (b) shows the selectivity of the effect. The figures are thresholded at $P < 0.001$, uncorrected for multiple comparisons. Note that the same effect was observed in the left amygdala at a less conservative statistical threshold.

and it displays a pathological pattern of responsiveness in certain anxiety³⁹ and mood disorders.⁴⁰ A previous animal study, in which a relatively large dose of allopregnanolone was infused into the central nucleus of the amygdala, has shown that allopregnanolone acts on amygdala to mediate anxiolysis.¹⁵ Although the present study does not show an anxiogenic effect of allopregnanolone, the results suggest a neural mechanism by which allopregnanolone could increase anxiety and worsen mood (that is, by increasing amygdala activity).

Progesterone decreased functional connectivity of the amygdala with the fusiform gyrus, a brain region preferentially involved in the processing of faces.^{33,41} The amygdala projects back to all levels of the ventral visual stream,⁴² and it influences activity in this brain

region during face perception,⁴³ suggesting that progesterone decreases the back projections of the amygdala to the fusiform gyrus. However, because functional connectivity is a correlational method, this result may also reflect the influence of the fusiform gyrus on the amygdala by feed-forward projections. Furthermore, although the functional integration of the emotion circuitry with the amygdala was largely unaltered by progesterone, the results indicate that

progesterone increased functional coupling of the dorsal anterior cingulate gyrus (dACC) with the amygdala. The dACC is activated during the cognitive evaluation of threatening stimuli which reduces amygdala activity,⁴⁴ and is thought to support the

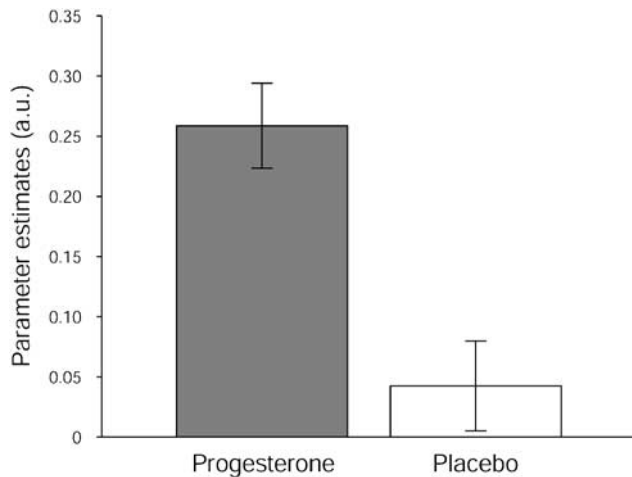


Figure 3 Mean (\pm s.e.m.) amygdala reactivity in the progesterone and placebo condition (26, -6, -22).

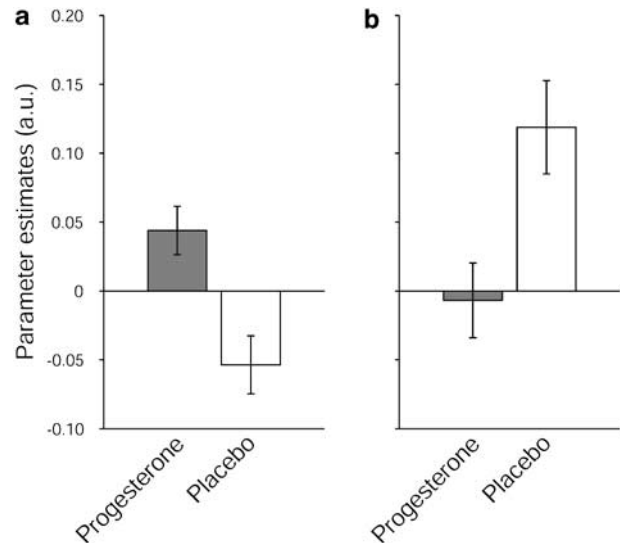


Figure 4 Progesterone modulates functional connectivity of the (a) dorsal anterior cingulate cortex (10, 24, 40) and (b) right fusiform gyrus (42, -60, -6) with the amygdala (mean \pm s.e.m.).

Table 2 Cluster maxima for brain regions that are functionally connected with the right amygdala, and for brain regions whose connectivity shows an interaction with progesterone

	MNI coordinates			Cluster size	t	P-value ^a
	x	y	z			
<i>Positive correlation</i>						
MTL, basal ganglia, OFC, temporal pole, thalamus	-24	0	-16	14 025	18.8	<0.001
Right inferior temporal gyrus	62	-54	-8	98	8.6	<0.001
Right inferior occipital gyrus	40	-88	-2	82	7.6	0.001
Pons	12	-32	-42	479	7.1	0.002
Left inferior temporal gyrus	-52	-64	-8	39	6.3	0.012
Left middle temporal gyrus	-62	-46	-8	10	6.0	0.026
Left fusiform gyrus	-48	-64	-10	93	5.5	0.001 ^b
Right fusiform gyrus	52	-58	-10	56	5.1	0.002 ^b
<i>Negative correlation</i>						
Midbrain	-4	-26	-14	151	8.2	<0.001
Cerebellar vermis	0	-52	-12	57	5.4	0.003
<i>Progesterone > placebo</i>						
Anterior cingulate cortex	10	24	40	9	4.7	<0.001 ^c
<i>Placebo > progesterone</i>						
Right fusiform gyrus	42	-60	-6	10	5.5	0.010 ^b

MTL, medial temporal lobe; OFC, orbitofrontal cortex.

^aP-values are corrected for multiple comparisons across the whole brain ($P < 0.05$, $k \geq 10$).

^bP-values corrected for multiple comparisons across the region-of-interest ($P < 0.05$).

^cP-value uncorrected for multiple comparisons ($P < 0.001$).

cognitive control of emotion (that is, reappraisal).⁴⁵ This suggests either a progesterone-induced change in dACC regulation of amygdala activity, or conversely, the influence of the amygdala on regulatory processes. However, this result should be interpreted with caution, because the effect did not remain significant after correction for multiple comparisons.

Although progesterone consistently increased amygdala reactivity in a within-subject comparison, no significant correlations between allopregnanolone levels and amygdala activity were observed across subjects. However, serum allopregnanolone levels do not reflect the (regionally specific) availability of this and other neuroactive metabolites in the brain, and individual differences in neurosteroid sensitivity may obscure a relation between neurosteroid levels and amygdala reactivity when assessed across individuals. Furthermore, while amygdala activity was positively correlated to alertness and contentedness in the placebo condition, which are two subscales of the mood-rating scale that was used, no correlations with state anxiety and mood were observed in the progesterone condition. The absence of a relation between amygdala reactivity and state anxiety and mood in the progesterone condition could reflect the limitation of this study to assess across-subject correlations, because the study was designed as a within-subjects investigation. In addition, the effects of progesterone on mood are probably mediated by interactions within a larger emotion circuitry.⁴⁶ The absence of a large change in the functional integration of the emotion circuitry may, therefore, explain the absence of a significant change in mood or anxiety.

Two related mechanisms could explain the paradoxical allopregnanolone-induced amygdala activity increase. First, the hormonal milieu appears to determine the acute effects of the neuroactive progesterone metabolites. A study in female mice showed that an otherwise anxiolytic dose of pregnanolone increases anxiety to an aversive stimulus after a period of relative allopregnanolone suppression, which was accomplished by administering a 5α -reductase inhibitor for 3 days that attenuates the metabolic transformation of progesterone to allopregnanolone.¹⁸ This approach was used to mimic the prolonged low allopregnanolone concentration during the human follicular phase,¹⁹ the menstrual cycle phase during which the women in this study were investigated.

Second, allopregnanolone induces a nonlinear behavioral response.^{47–49} Low doses of allopregnanolone increase aggressive behavior in mice, whereas higher doses decrease aggression.⁵⁰ Moreover, the addition of a low dose of progesterone to the treatment with estradiol during hormonal replacement therapy increases negative mood, but higher doses do not.⁵¹ These negative mood symptoms are related to allopregnanolone levels in a bimodal fashion, as these symptoms are only present at moderate, but not low or high allopregnanolone

concentrations.^{35,51} Furthermore, allopregnanolone levels are lower in PMS patients that respond to antidepressant or placebo treatment than nonresponders.⁵² In the present study, an increased responsiveness of the amygdala was observed after increasing the progesterone and the allopregnanolone concentrations from the follicular phase to levels that are naturally occurring during the luteal phase and early pregnancy, respectively.^{36,37} The increased amygdala response might therefore be specific for this concentration change, while higher supraphysiological concentrations might eventually decrease amygdala activity,¹⁵ in parallel with increased sedation in humans.⁵³ These results therefore show that changes in progesterone level that are within the physiological range can increase amygdala activity.

These two mechanisms are not mutually exclusive but may interact, because the probable progesterone dose-dependent amygdala response is probably modulated by the hormonal milieu. In this context, it is important to note that during natural hormone fluctuations during the menstrual cycle, high progesterone levels occur only in the presence of increased estradiol levels. Thus, the threshold for amygdala reactivity probably changes over the menstrual cycle. This suggestion is supported by studies showing that the response of healthy women to a pregnanolone dose is larger in the luteal than the follicular phase.⁵⁴ Furthermore, women with PMS experience more severe symptoms during cycles with high luteal phase progesterone and estradiol levels,⁵⁵ and higher estrogen doses increase negative mood symptoms during the progestin phase of hormonal replacement therapy.⁵⁶

The mechanism by which allopregnanolone could increase amygdala activity is not well understood. However, the paradoxical allopregnanolone-induced amygdala activity increase could reflect the disinhibition of the principal neurons of the amygdala via inhibition of the inhibitory interneurons,⁴⁹ a mechanism that has been demonstrated for the disinhibitory actions of dopamine.⁵⁷ Neurosteroid action is brain region and neuron-specific, and neurons of the central nucleus of the amygdala appear relatively insensitive to allopregnanolone.⁵⁸ This heterogeneity in neurosteroid sensitivity could be mediated by regional differences in receptor subunit composition, phosphorylation and steroid metabolism.⁵⁸ Specifically, allopregnanolone inhibits the $\alpha 4\beta 2\delta$ GABA_A receptor, which reduces tonic inhibition and thereby increases excitability. Because this receptor is highly sensitive to neurosteroids, inhibition of this receptor at relatively low neurosteroid concentrations can induce paradoxical effects,⁵⁹ and may contribute to amygdala disinhibition.

The amygdala has many (largely reciprocal) connections to brain areas that are involved in sensory processing, visceral functioning, emotional behavior and mood.⁶⁰ The progesterone-induced amygdala activity increase could therefore affect the processing in many other brain regions relevant for mood regulation. Studies with depressed patients suggest

that negative mood is generated by increased activity of brain structures that support the identification of the emotional significance of stimuli and the generation of an affective response (for example, the amygdala, insula, ventral striatum and ventral prefrontal cortex), and decreased activity of brain structures supporting emotion regulation (for example, the dorsal prefrontal cortex and hippocampus).⁶¹ The menstrual cycle has been shown to modulate activity in several of these brain regions,^{62–65} suggesting that progesterone and estradiol may influence mood by modulating this emotion circuitry. The results of the present study show that progesterone increases amygdala activity and indicate that it increases functional coupling with the dACC, without affecting the response amplitude in other brain regions. The results of our study therefore suggest that progesterone and/or allopregnanolone modulates amygdala activity, and may, thereby, change the functionality of a larger emotion circuitry.

The amygdala is involved in a wide range of emotional behavior, including social cognition⁶⁶ and the stress response,⁶⁷ which appears to be modulated by progesterone. For example, the modulation of the preference for faces during the menstrual cycle appears to be mediated by progesterone,^{68,69} as well as the enhancement of the hypothalamus–pituitary–adrenal (HPA) axis response to stressors during the luteal phase.^{70,71} Our results suggest that progesterone could modulate these processes by increasing the responsiveness of the amygdala.

The present study shows that allopregnanolone can have paradoxical effects on amygdala activity in healthy women, without influencing anxiety or mood. However, this mechanism could mediate the negative effects of allopregnanolone on anxiety and mood in susceptible women. Whereas the administration of progesterone or estradiol after gonadal hormone suppression does not produce mood changes in healthy women, it produces negative mood symptoms in women with PMS.⁹ Furthermore, PMS patients have a different sensitivity to pregnanolone during the high progesterone luteal phase,⁵⁴ suggesting that allopregnanolone could affect amygdala activity differently in patients with PMDD/PMS. Because the amygdala is pathologically activated in certain anxiety³⁹ and mood disorders,⁴⁰ we speculate that allopregnanolone might increase amygdala activity to a larger extent in women with PMDD/PMS than in healthy women as observed in this study, which could explain part of the negative mood symptoms in PMDD/PMS and possibly other gonadal hormone-related mood disorders.

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