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Premenstrual dysphoric disorder and changes in frontal alpha asymmetry

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Abstract

Objective: Since the clinical picture of premenstrual dysphoric disorder (PMDD) in the Luteal phase of the menstrual cycle is characterized by extreme negative affect, we predicted and obtained a change in frontal cortical EEG alpha asymmetry, which has been shown to be an index of affect. **Method:** We observed two monthly cycles for five women diagnosed as having PMDD and one monthly cycle for five non-PMDD control subjects. **Results:** Asymmetry percent scores for the five PMDD women, and for the five control subjects before and after the Luteal phase were typically within the normal non-depressed range, however the asymmetry scores for the PMDD group fell into the negative range during the Luteal period while the control subjects remained stable. **Discussion:** We predicted alpha asymmetry scores would be affected by the luteal phase in PMDD cases. This hypothesis was clearly confirmed.

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1. Introduction

Premenstrual dysphoric disorder (PMDD) is defined in DSM IV-TM (American Psychiatric Association, 2000) as a disorder which occurs during the last week of the luteal phase of the menstrual cycle (days 15–28 of a 28-day cycle). It is characterized by moderate to severe symptoms

such as depressed mood, self depreciating thoughts, marked anxiety and tension, affective lability, anger and irritability, difficulties in concentration, lack of interest in activities, lethargy, a sense of being overwhelmed, and suicidal ideation. It is differentiated from premenstrual syndrome (PMS), which produces milder physical and emotional symptoms. Approximately 75% of the women with regular menstrual cycles experience PMS as compared to 3 to 15% of women who experience the more extreme dysphoric disorder. (Steiner and Born, 2000; Bronson, 2000; Dalton, 1990,

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1998). The PMDD affective symptoms disappear after the luteal phase, in the beginning of the follicular period, and are distinguished from premenstrual exacerbation of Axis I psychiatric disorders (PME). This latter category includes mood disorders, anxiety disorders, personality disorders, somatoform disorders, bulimia and substance abuse disorder, where the symptoms persist throughout the entire menstrual cycle (American Psychiatric Association, 1994).

In addition to emotional changes, there are neurobiological changes that occur in women who suffer with PMDD. While the symptoms of PMDD may be superimposed on the above-mentioned disorders, the DSM-IV-TM clearly states that they are not merely an exacerbation of these disorders. The cyclic pattern of symptoms must be documented for a period of at least two months. (American Psychiatric Association, 2000).

It is known that in non-PMDD women, the neurotransmitters Gamma-Aminobutyric Acid (GABA) and serotonin peak premenstrually and decline during the follicular phase of the cycle (Blum et al., 1992; Hindberg and Naesh, 1992). In contrast, the normal premenstrual peak serum levels of these substances are absent or blunted during the late luteal phase of the cycle of women with PMDD (Miller, 2002; Kouri and Halbreich, 1997; Halbreich et al., 1996). Both serotonin and GABA mediate inhibitory input to the amygdala (Weiss et al., 2000), a structure frequently implicated in affective phenomena (File, 2000; Nemeroff, 1998; Owens and Nemeroff, 1994), and known to connect to the frontal cortical areas whose EEG asymmetry we may have been recording in relation to affect (see next paragraph and Rosenfeld, 2000). In this study we present data for five depressed women who also met the criteria for PMDD. Comparison data from four previously depressed but non-PMDD women, and one non-depressed and non-PMDD control subject are also presented.

Recent studies have shown that asymmetry in the activity of neurons in frontal cortical areas is a correlate of affect (see review by Davidson, 2000). To briefly oversimplify, we note that Davidson (2000) has theorized that affect is mediated by a conjoint action of a positive emotion/

approach system in the left frontal cortex, and a negative emotion/avoidance system in the right frontal cortex. Thus if right frontal activity exceeds left frontal activity, a depressed affect results, whereas positive affect correlates with relatively greater left frontal cortical activity. Henriques and Davidson (1990) showed that currently depressed persons have left frontal hypoactivation in comparison with never depressed persons. They also demonstrated in Henriques and Davidson (1991), that previously depressed persons in remission, still showed left frontal hypoactivation in comparison with never depressed persons. This finding suggested that a brainwave trait for depression was identified. The finding was replicated and extended by Gotlib et al. (1998) and Baehr et al. (1999) and Baehr et al. (2001). Since the alpha frequency in the brain indexes cortical idling (Hughes, 1994), alpha may be used as an inverse index of cortical activation. The relative amounts of left and right frontal alpha should thus correlate with affect, and indeed, asymmetry indices have been reliably used as metrics of affect (Rosenfeld, 2000; Baehr et al., 1998).

Since the clinical picture of PMDD in the luteal phase of the menstrual cycle is characterized by extreme negative affect, we predicted a drastic change in frontal cortical EEG alpha asymmetry of PMDD cases during the luteal phase, in the direction of greater right than left cortical activation, i.e. more left than right alpha activity.

2. Method

EEG was passed through a computer driven amplification system, which calculated EEG asymmetry from F3 and F4 electrodes. The asymmetry score is defined on a moment-to-moment basis as $(F4 - F3)/(F4 + F3)$. F4 and F3 represent alpha magnitude at those two sites in the 10–20 system, respectively. Cz was reference and the left earlobe was grounded. We are aware that use of the Cz reference is controversial (Reid et al., 1998; Hagemann et al., 1998; Davidson, 1998). We use it here as it is the reference initially used by the Davidson group to demonstrate correlation of frontal EEG asymmetry and affect, and which we too have used in obtaining the best diagnostic and

clinical effects (Rosenfeld, 2000). EEG was recorded and analyzed on a Lexicor Corp. Neuro-search unit. This system computed Fast Fourier Transforms on Blackman–Harris windowed analog signals over 1 s epochs (Harris, 1978). The sampling rate was 128 Hz. An asymmetry index for the entire recording session is the percent of time (PCT) the alpha asymmetry score is >0 . We have shown previously that PCT scores $<58\%$ are associated with depressed affect (Baehr et al., 1998). Higher scores indicated normal and elated affect. It was found that PCT was a more reliable session index of asymmetry than mean asymmetry score (explained in Baehr et al. (1998). We therefore employ PCT here to index session asymmetry.

The nature of the investigation was explained to the subjects and they all gave written consent to allow their data to be used in this study. Before medical and/or behavioral treatment (see below), the five outpatient PMDD cases, and four of the five control cases (from the clinical psychology private practice of Elsa Baehr and Rufus Baehr), met the DSM IV-TM (American Psychiatric Association, 2000) criteria for major depressive disorder. That is, over a consecutive two week period they experienced depressed mood or loss of interest most of the day. In addition they had four or more of the following symptoms: significant weight loss or change of appetite, excessive or inadequate sleep patterns, loss of energy, daily feelings of worthlessness or inappropriate guilt, difficulty in thinking and concentrating, and either psychomotor retardation or agitation. The fifth control subject, a volunteer from a local church group, did not have a history of depression.

All the experimental and control subjects, with the exception of the normal non-PMDD control, were stabilized by successful treatment for depression with behavioral treatment alone, or behavioral treatment and medication by the time of the EEG recorded here. This accounts for non-Luteal scores all being in the non-depressed range in PMDD cases, as well as all scores for non-PMDD controls. The PMDD group included two cases treated with only a behavioral protocol (EEG Biofeedback; see Rosenfeld, 2000), and three other cases treated with the behavioral protocol plus the medications, Fluoxetine Hydrochloride, Bupropion Hydrochloride

and Sertraline Hydrochloride. Their ages were 43, 46, 48, 49 and 50, all still menstruating. In the three medicated PMDD patients, medications commenced 2–10 years before therapy and remained constant for the 2-month period in which EEG and mental functions were observed. All patients' behavioral treatment regimens were likewise consistent during the observation period. The non-PMDD control group included four patients and one non-treated normal control. Three patients were treated with a behavioral protocol only, and two patients were treated with the behavioral protocol plus the medications, Hypercium Perforatum (St. John's Wort), and Zoloft. In the two medicated patients, medication commenced 1–3 years before therapy and remained constant during treatment. The single non-depressed, non-PMDD control received neither treatment nor medication. Control ages were 24, 36, 43, 45 and 52.

The data for five diagnosed PMDD cases were gathered through two cycles of their menses. In these cases we had exact data on when their periods began and ended, and therefore we knew the dates of the Luteal and non-Luteal phases of their menses. The same was true for the one normal non-PMDD control subject. Data for the other four controls were gathered retrospectively, and we lacked the exact dates of the menses, but we had EEG data from 3 days each within one cycle in which the dates were separated by 7 days. Since PMDD symptoms last from about a week before to a few days after the menstrual period (Endicott, 2000; Klock, 1999; Ling, 2000), it is highly probable that at least one of the dates for each of these control cases was from the Luteal phase.

All patients' behavioral treatment regimens were likewise consistent during the observation period. One patient charted her mood changes during the luteal phase the others discussed their feelings; with a clinical psychologist who recorded these reactions in process notes. The most prominent emotional symptoms of the PMDD luteal phase included abrupt negative changes in self-perception, obsessive thoughts, emotional lability and suicidal ideation. The non-PMDD group reported emotional symptoms during the luteal phase that were characterized by mild irritability and tension.

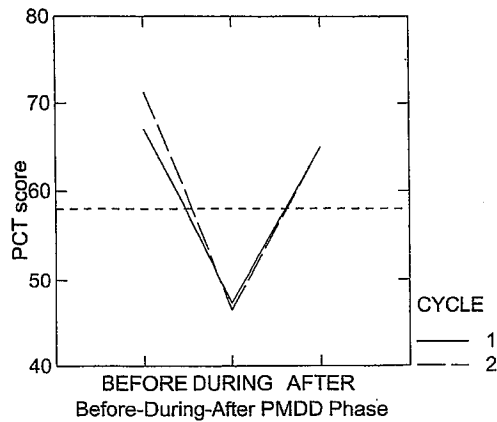


Fig. 1. Mean PCT (asymmetry) scores as a function of menstrual phase in two cycles of five PMDD patients. Horizontal dashed line=PCT=58%, the cutoff for depression vs. non-depression found in Baehr et al. (1998).

3. Results

In Fig. 1, we have plotted the means over the five PMDD patients though two cycles each of the PCT scores before, during, and after the PMDD-Luteal phases of their menstrual cycles. The non-Luteal scores, in the mid 1960s, are well above the indicated cut-off score for depression of 58% (based on Baehr et al., 1998). The figure also shows, however, that during the PMDD symptom phase of the Luteal cycle, the mean scores in both cycles drop to approximately 47%, i.e. well into the depression region. Figs. 2–6 show similar plots for each individual case and cycle, and attest to the robustness of the effect with each patient showing the dip into and out of the depressed range of the PCT score from before to during to after the Luteal phase of their cycles. Statistical confirmation of these visual impressions was provided by a two-way, repeated measures 2x3 analysis of variance (ANOVA) on the effects of Cycle (first and second) and Phase (of cycle: Before vs. During vs. After). The main effect of phase yielded $F(2,8)=24.7, P<0.008$, (Geiser-Greenhouse-corrected). The effects of cycle and the interaction were not significant with each P -value >0.6 .

In Fig. 7, we present data from the non-PMDD control cycles for the four cases in which we did not know the identities of the Luteal data points,

but assumed they were sampled in at least one of the three observations recorded in each case. Superimposed upon these individuals' data is the mean curve over both cycles and five PMDD cases as shown in Fig. 1. There is variation in these controls, but nothing approaching that seen in the PMDD cases, who, in contrast, show drastic dips into the low depressed range. Data from the one non-PMDD control case in which we were able to obtain phase information is shown in Fig. 8 superimposed on the mean curve for the PMDD cases. Fig. 8 conveys the same difference as seen in Fig. 7. Given the constraints of our data set in control cases (i.e. controls were not matched for age and

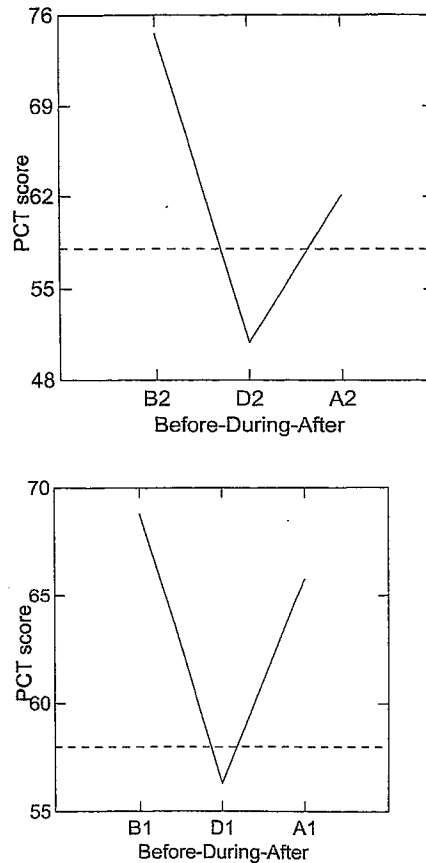


Fig. 2. Case HS. PCT score as a function of menstrual phase; Before (B1 and B2), During (D1 and D2), and after (A1 and A2) PMDD-Luteal phase. Top: cycle 2, Bottom: cycle 1. Horizontal dashed line=58%, depressed/non-depressed cutoff.

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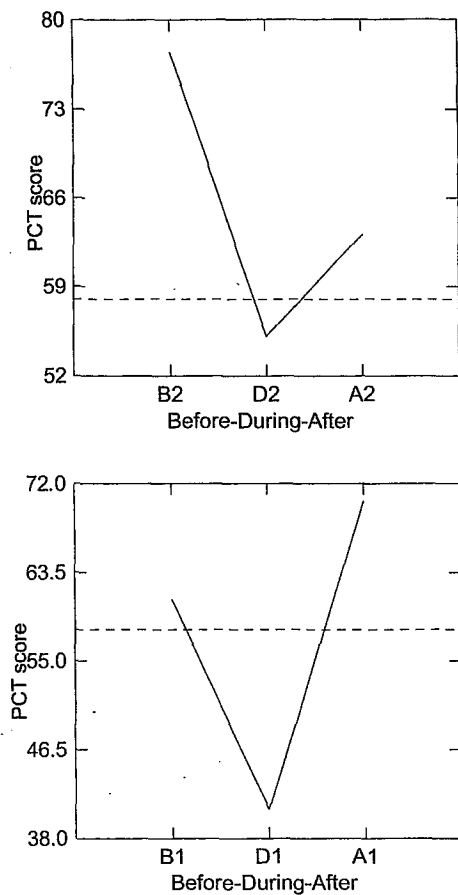


Fig. 3. Case HK. PCT score as a function of menstrual phase; Before (B1 and B2), During (D1 and D2), and after (A1 and A2) PMDD-Luteal phase. Top: cycle 2, Bottom: cycle 1. Horizontal dashed line = 58%, depressed/non-depressed cutoff.

medication), statistical confirmation of the difference between the PMDD vs. non-PMDD cases involved comparison of the differences between *Before* and *During* data for the PMDD cases, with the *maximum* differences obtained between the highest and lowest values of the three values available from controls. Using these maximum differences was the most conservative approach. (It turned out that the known Luteal value for the non-PMDD cases shown in Fig. 8 was also the lowest value of the three data points for this person. The larger value of the two recorded non-Luteal phases was used to compute the difference

for this case). The same maximum differences in controls could be compared with *After* vs. *During* data in PMDD cases, and both of these comparisons were possible also with data from both cycles of the PMDD cases. There were thus four non-orthogonal, *t*-tests performed. The results were: (1) *Before* vs. *During*, cycle 1: Separate Variance $t=4.441$, d.f.=4.1, $P=0.01$, Difference in Means=16.96; (2) *Before* vs. *During*, cycle 2: Separate Variance $t=4.519$, d.f. 4.1, $P=0.01$, Difference in Means=20.1; (3) *After* vs. *During*, cycle 1: Separate Variance $t=2.081$ d.f.=4.0 $P=$

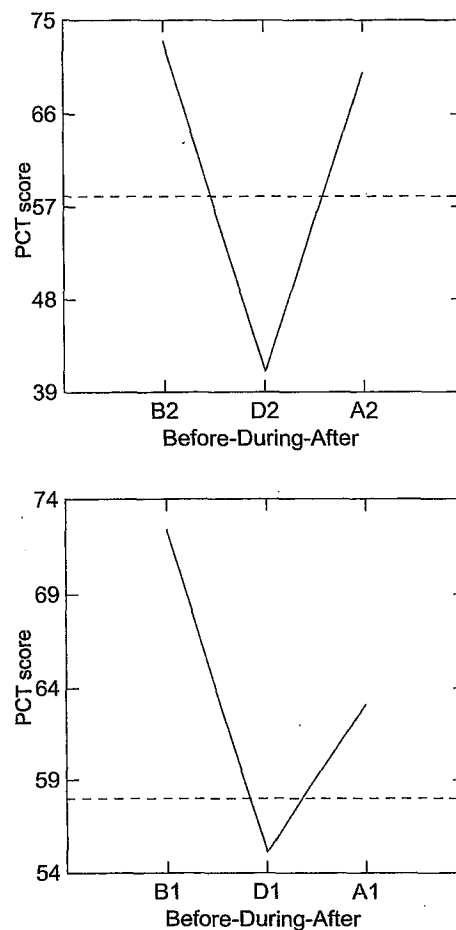


Fig. 4. Case TT. PCT score as a function of menstrual phase; Before (B1 and B2), During (D1 and D2), and after (A1 and A2) PMDD-Luteal phase. Top: cycle 2, Bottom: cycle 1. Horizontal dashed line = 58%, depressed/non-depressed cutoff.

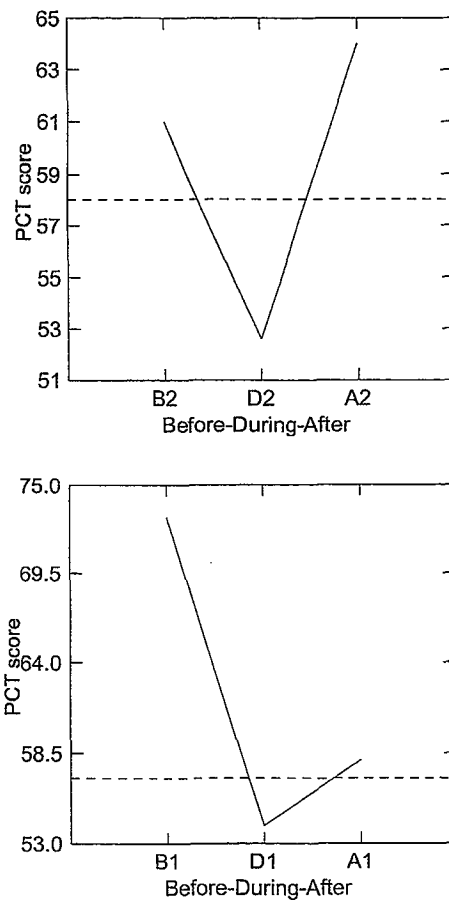


Fig. 5. Case ST. PCT score as a function of menstrual phase; Before (B1 and B2), During (D1 and D2), and after (A1 and A2) PMDD-Luteal phase. Top: cycle 2, Bottom: cycle 1. Horizontal dashed line = 58%, depressed/non-depressed cutoff.

0.105, Difference in Means = 14.0; (4) After vs. During, cycle 2, Separate Variance $t = 2.981$ d.f. = 4.1 $P = 0.04$, Difference in Means = 13.920. Separate variance t -values were computed due to the substantially larger variance of the patient group compared with the variance of the control group. Indeed 19 of the 20 differences obtained from the PMDD cases showed no overlap with the maximum differences in the five non-PMDD controls.

4. Discussion

Since EEG alpha asymmetry is an often reported EEG correlate of affect (Davidson, 2000), and

since the luteal phase of the menstrual cycle in PMDD women is associated with profound affective psychopathology, we hypothesized that alpha asymmetry would be profoundly affected by the luteal phase in PMDD cases. This hypothesis was clearly confirmed. What is the possible basis for this effect? To answer this question, one must look for a connection between unique physiological attributes of PMDD disorder and cerebral asymmetry.

One of the specific effects of PMDD is a profound reduction of Gamma-Amino butyric Acid (GABA) during the luteal phase of the menstrual cycle. (Kouri and Halbreich, 1997; Halbreich et

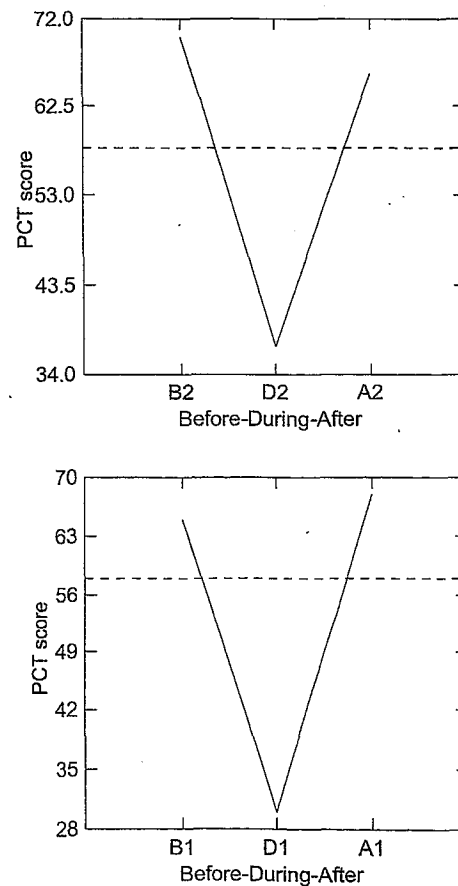


Fig. 6. Case BB. PCT score as a function of menstrual phase; Before (B1 and B2), During (D1 and D2), and after (A1 and A2) PMDD-Luteal phase. Top: cycle 2, Bottom: cycle 1. Horizontal dashed line = 58%, depressed/non-depressed cutoff.

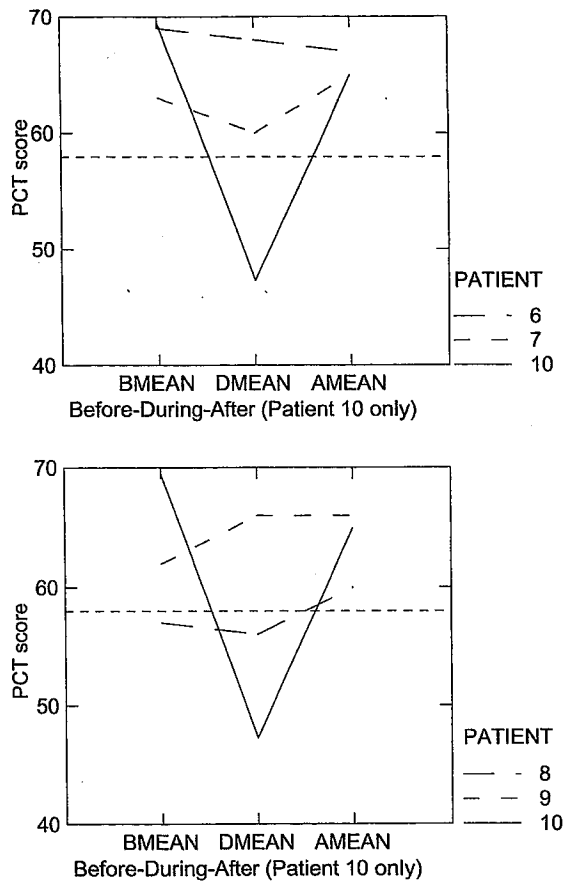


Fig. 7. The solid lines ('PATIENT 10') in each graph above represent means across two cycles in five PMDD cases, as shown separately in Fig. 1, above. The other individual non-PMDD control patients, six and seven in top graph, eight and nine in bottom graph, are superimposed. Before, During, and After have meaning only for PMDD patients. They are three arbitrarily sampled times, separated by 7 days, in control patients six to nine.

al., 1996; Miller, 2002). GABA is known to function as an inhibitory transmitter throughout the nervous system, exerting a tonic inhibitory effect on many neurons including those in the dorsal and ventral regions of the amygdala (LeDoux, 2002; Sahley, 2001). There are also extensive reciprocal connections between the amygdala and the prefrontal cortex, particularly its medial and orbital zones. It is likely that the neural activity in these cortical areas contributes to the EEG, which we recorded in the present study. In normal

subjects greater left-sided prefrontal metabolism is associated with lower metabolic activity in the amygdala (Davidson, 2000).

The amygdala is a structure known to play a key role in the elaboration of negative emotion (Aggleton and Young, 2000; LeDoux, 2000, 2002; Lane, 2000). Moreover, the amygdala is known to show asymmetric responses to different kinds of emotion-relevant input (Thomas et al., 2001a,b; Whalen et al., 2001; Wright et al., 2001). While normal subjects displayed more activity in the right amygdala in response to negative stimuli, depressed subjects with negative affect showed increased activity in both the left and right amygdala (Davidson, 2000). If the inhibitory ability of GABA to keep mildly aversive or even meaningless stimuli from overexciting the amygdala is compromised, as in PMDD, it is possible that normally regulated negative emotions and even non-dangerous stimuli may generate an unwarranted amount of fear and anxiety (LeDoux, 2002; Sahley, 2001; Lane, 2000).

Integrating these factors, we hypothesize that the reduction of GABA seen in the luteal phase of PMDD brings about an asymmetric disinhibition of negative emotional information which is then

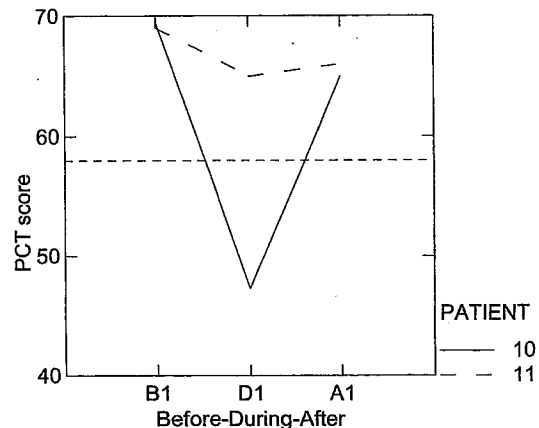


Fig. 8. The solid line ('PATIENT 10') in the graph above represents means across two cycles in five PMDD cases, as in previous figure. The other individual non-PMDD control patient, 11, the one control patient for whom Luteal and non-Luteal data were recorded, is superimposed. B1 = Before, D1 = During and A1 = After the Luteal phase for both plots.

reflected in the cortical asymmetry signature for negative emotion.

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