

Changes in Frontal Brain Asymmetry
Associated with Premenstrual
Dysphoric Disorder:
A Single Case Study

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ABSTRACT. *Background.* In a pilot study, Baehr (2001) reports changes in frontal cortical alpha asymmetry during the luteal phase of the menstrual cycle were documented in five depressed women who also

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experienced Premenstrual Dysphoric Disorder (PMDD). In this paper detailed data is presented for one of these subjects and two comparison subjects who were part of the first study. The goal was two-fold: (a) to study how patterns of mood changes during the luteal phase of the menstrual cycle correlated with changes in frontal alpha brainwave asymmetry, and (b) to determine whether treatment strategies, tailored to ameliorate symptoms, would be reflected in brainwave changes.

Method. Neurofeedback, medical interventions, and prospective charting were collected over a period of six months for one patient. These data were compared with data collected for two monthly cycles from two non-PMDD comparison subjects.

Results. The patient responded well to the neurofeedback protocol for depression and was normalizing her scores by the second week in treatment except for setbacks which occurred during the luteal phase of her menstrual cycle. Extreme mood changes correlated with changes in brainwave asymmetry during this period. A combination of neurofeedback and medication worked to stabilize her mood swings and asymmetry scores.

Conclusion. This case study demonstrated how brainwave changes in frontal alpha asymmetry occurred during the luteal phase of the menstrual cycle in a woman who suffered from PMDD. Two comparison subjects, who were undergoing similar treatment for depression but did not suffer from PMDD, had stable alpha asymmetry scores during the entire menstrual cycle. Anomalies in serotonergic and /or gabergic function in the luteal phases of PMDD are pinpointed as possible underlying factors in this disorder. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2004 by The Haworth Press, Inc. All rights reserved.]

KEYWORDS. Premenstrual dysphoric disorder, alpha asymmetry, neurofeedback, depression, EEG biofeedback

INTRODUCTION

The purpose of this paper is to describe a state brain wave change in frontal alpha asymmetry during the luteal phase (days 15-28) of a 28-day menstrual cycle in a patient who was undergoing neurofeedback treatment for depression. The patient was diagnosed as having premenstrual dysphoric disorder (PMDD) in addition to having a major depressive disorder. Treatment strategies included neurofeedback, psy-

chotherapy and medical intervention. In a pilot study, Baehr (2001) reports changes in frontal cortical alpha asymmetry during the luteal phase of the menstrual cycle were documented in five women with PMDD. In this paper data is presented for one of those subjects who are currently receiving medical treatment as well as neurotherapy.

Symptoms of Premenstrual Disorders. Premenstrual mood changes called “premenstrual tension” (PMS) were identified as a syndrome by Greene and Dalton (1953) to describe the psychological and physical symptoms which regularly occur during the luteal phase of the menstrual cycle. Initially there was little recognition of the variety and severity of symptoms that were grouped together under “PMS.” The Diagnostic and Statistical Manual of Mental Disorders (DSM III-R; American Psychological Association, 1987) helped clarify the differences between clinically severe premenstrual symptoms and the milder premenstrual changes with the creation of a new category entitled “Late Luteal Phase Disorder” (LLPDD). Further clarification was made when LLPDD was replaced by “Premenstrual Dysphoric Disorder” (PMDD) in the DSM IV (American Psychiatric Association, 1994) and later expanded in the DSM-IV-TR (American Psychiatric Association, 2000), which specified the research criteria for premenstrual dysphoric disorder (PMDD). Listed in the appendix as a “Depressive Disorder Not Otherwise Specified,” PMDD is defined as a disorder that occurs during the last week of the luteal phase of the menstrual cycle (days 15 to 28 of a 28-day cycle). It is characterized by serious emotional symptoms such as depressed mood, self-deprecating thoughts, marked anxiety and tension, affective lability (suddenly feeling sad or tearful), anger and irritability, difficulties in concentration, lack of interest in activities, lethargy, sleep disturbances, a sense of being overwhelmed, and suicidal ideation. PMDD can be distinguished from premenstrual syndrome (PMS) by the characteristic patterns of symptoms, the severity of the symptoms, and the degree of impairment (DSM IV, 1994; see Box 1). PMS is characterized by mild emotional stress, bloating, swelling of hands and feet, aches and pains, poor concentration, sleep disturbances, and changes in appetite (Garbor, 2003). While estimates vary, approximately 30 to 85% 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 & Born, 2000; Bronson, 2000; Dalton, 1998). The symptoms in both disorders disappear after the menses in the beginning of the follicular period (end of menses to beginning of ovulation), and are distinguished from premenstrual exacerbation (PME) of Axis I psychiatric disorders. This latter category includes

BOX 1. Premenstrual Dysphoric Disorder (PMDD).

In most menstrual cycles during the past year, five (or more) of the following symptoms, with at least one of the symptoms being either (1), (2), (3), or (4), must be present for most of the time during the last week of the luteal phase. The symptoms begin to remit shortly after the onset of the follicular phase, and are absent in the week post menses. The symptoms may be accompanied by suicidal thoughts.

1. Markedly depressed mood, hopelessness, or self-depreciating thought.
2. Marked anxiety, tension, "keyed up" or "on edge."
3. Marked affective lability.
4. Persistent anger or irritability or increased interpersonal conflicts.
5. Decreased interest in usual activities.
6. Difficulty in concentrating.
7. Lethargy, fatigability or marked lack of energy.
8. Marked change in appetite.
9. Hypersomnia or insomnia.
10. Feeling of being overwhelmed or out of control.
11. Physical symptoms such as breast tenderness, or swelling, headaches, joint or muscle pain, bloating, weight gain.

Paraphrased from DSM IV: 311.0, pg. 719.
(American Psychiatric Association, 1994)

mood disorders, anxiety disorders, somatoform disorders, bulimia, and substance abuse disorders where the symptoms may persist throughout the entire menstrual cycle but regularly intensify premenstrually. While the symptoms of PMDD may be superimposed on the above-mentioned disorders, the DSM-IV-TR 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).

Researchers have studied changes in the electroencephalogram (EEG) related to the menstrual cycle; however, none of the EEG studies focused on differences in brain wave asymmetry in PMDD women. The studies failed to distinguish levels of severity in PMS with one excep-

tion (Cantor, 2001). In general, it was found that there was a significant increase in the mean alpha frequency, the mean alpha amplitude, theta activity, absolute power of delta, mild paroxysms (Leary & Batho, 1979; Creutzfeldt et al., 1976), and lower activation of frontal regions during the premenstrual phase (Solis-Ortiz, Ramos, Arce, Guevara, & Corsi-Cabrera, 1994). While these studies did not distinguish between PMS and PMDD, EEG sleep studies comparing women with dysphoric disorders to women with major depressive disorders found that PMDD subjects did not show the same abnormal sleep patterns as the major depressive group (Perry, Mendelson, Duncan, Sack, & Wehr, 1989). Studies of dysphoric women in the late luteal phase with a history of alcoholism were found have more high-frequency alpha in their EEG than subjects without alcoholic relatives or controls (Ehlers, Phillips, & Parry, 1996).

Neurochemical Factors in PMDD. Premenstrual dysphoria may be explained by differences in reproductive hormonal influences on serotonin and gamma-amino butyric acid (GABA). In women without PMDD, serotonin and GABA peak premenstrually and decline during the follicular phase of the cycle (Blum et al., 1992; Hindberg & Naesh, 1992). In women with PMDD, serotonin and GABA levels are normal during the follicular phase but the peaks are absent or blunted during the late luteal phase of the cycle (Miller, 2002; Kouri & Halbreich, 1997; Halbreich et al., 1996).

A consistent pattern has emerged in double blind placebo-controlled studies of medication treatment for PMDD. Antidepressant medications that increase serotonergic functioning (e.g., selective serotonin reuptake inhibitors agents [SSRI] and Clomipramine) are effective (Menkes, Taghavi, & Mason, 1993; Sundblad, Modigh, & Anderson, 1992; Steiner, Steinberg, & Stewart, 1995; Yonkers, 1997; Dimmock, Wyatt, Jones, & O'Brien, 2000). While effective for treating major depression, agents with little or no effect on serotonin (e.g., desipramine, bupropion or maprotiline) are not significantly different from placebo in alleviating PMDD symptoms. This is consistent with findings of hormonally mediated changes in serotonergic functioning across the menstrual cycle in women with PMDD as compared to asymptomatic women (Blum et al., 1992; Hindberg & Naesh, 1992; Halbreich & Tworek, 1993; Kouri & Halbreich, 1997). For PMDD taking antidepressant medication only during the luteal phase of the menstrual cycle (e.g., days 15-28 of a 28-day cycle) is at least as effective as taking medication continuously (Sundblad, Hedberg, & Erickson, 1993; Halbreich & Smoller, 1997; Steiner, Korzekwa, & Lamont, 1997; Young, Hurt,

Benedek, & Howard, 1998; Jermain, Preece, & Sykes, 1999; Freeman, Rickels, & Arredono, 1999). This suggests a different mechanism of action from the antidepressant effects, which can take up to six to eight weeks of continuous use to reach maximum effectiveness. SSRI antidepressants have been shown to rapidly increase the brain's sensitivity to GABA agonists in women with PMDD (Sundstrom & Backstrom, 1998); this could explain the efficacy of luteal phase dosing.

Medical treatment of PMDD works optimally in the context of a multifaceted approach. Calcium supplementation (Thys-Jacobs, Starkey, & Bernstein, 1998), ingestion of complex carbohydrates (Sayegh et al., 1995), aerobic exercise (Steege & Blumenthal, 1993; Aganoff & Boyle, 1994), photo therapy (Lam, Carter, & Misri, 1999), cognitive behavioral therapy (Reading 1992; Christensen & Oe1, 1995), and neurotherapy (Baehr, Rosenfeld, & Baehr, 2001) are approaches with some demonstrated efficacy for alleviating premenstrual dysphoria.

Frontal Asymmetry, Depression and PMDD. Davidson (2000) reviewed a sizeable amount of literature showing that asymmetry in the activity of neurons in frontal cortical areas is a correlate of affect. Davidson has theorized that there is a brain wave signature or trait marker for depression. Thus if right frontal activity exceeds left frontal activity a depressed affect results whereas positive affect results from relatively greater left frontal cortical activity. 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. A neurotherapy protocol designed to increase the magnitude of alpha in the right hemisphere was developed and successfully used for the treatment of depression (Baehr, Rosenfeld, Baehr, & Ernest, 1998; Baehr, Rosenfeld, & Baehr, 1999; Rosenfeld, 2000; Baehr et al., 2001). Normative data gathered from non-depressed subjects confirmed the fact that the right prefrontal cortex was less active than the left prefrontal cortex (percent of time [PCT] score > 58). In Baehr et al. (1998), a PCT score > 58 was associated with normal non-depressed affect. In a recent pilot study (Baehr, 2001), it was demonstrated that PMDD in the late luteal phase of the menstrual cycle is characterized by extreme negative affect (the most prominent symptoms included abrupt negative changes in self-perception, obsessive ideation, and emotional lability) along with drastic changes in frontal cortical EEG alpha asymmetry in the direction of greater left than right activation (PCT < 58). Through two menstrual cycles of the five PMDD subjects, the mean PCT values for both the test

days before and after the luteal phase of the cycles were at approximately 67%, consistently well above the cut-off value for normal (non-depressed) levels.

METHOD

Neurofeedback data and prospective charting were collected over a period of eight months for a patient diagnosed as having PMDD. The goal was two-fold: (a) to study how patterns of mood changes during the luteal phase of the menstrual cycle correlated with changes in frontal alpha brain wave asymmetry, and (b) to determine whether treatment strategies tailored to help ameliorate symptoms would be reflected in brain wave changes.

Subject. Rita, a 49-year-old unemployed professional woman, sought neurofeedback treatment for depression. She had previously been in psychotherapy and had been using Prozac for nine years, but complained that it was no longer effective. She was initially diagnosed as having a major depressive disorder (DSM IV 296.2; see Box 2). During a two-week period she exhibited the following symptoms: diminished interest in daily activity, change in eating habits, loss of energy, sleep problems, and difficulty concentrating and thinking. She also met the DSM IV criteria for premenstrual dysphoric disorder (311.0) as she exhibited markedly depressed mood, feelings of worthlessness, suicidal ideation, and emotional lability during the luteal phase of her menstrual cycle. For example, after beginning neurotherapy she charted daily changes in mood. During the follicular phase of her menstrual cycle she noted that she was feeling good and was noticing beauty in her environment. She also commented that a certain piece of music made her feel happy. In the next few days when she was in the luteal phase she noted that the same music she previously enjoyed now made her feel sad. She was also flooded with negative feelings about herself and expressed suicidal ideation.

Shortly after beginning neurofeedback treatment she began an exercise program and consulted an allergist and nutritionist. In April she was referred to one of the authors for evaluation and medical treatment of PMDD.

Neurofeedback Training for Depression. The patient came in regularly for sessions three times a week beginning in February 2001. She was trained on a protocol designed to increase right frontal alpha asymmetry. The asymmetry score is defined as $(F4-F3/F4+F3)$ where F4 is

BOX 2. Major Depressive Disorder.

Five or more of the following symptoms must be present during the same two-week period, and at least one is either depressed mood or loss of interest.

1. Depressed mood most of the day.
2. Diminished interest in daily activity.
3. Significant weight loss, or change in eating habits.
4. Excessive sleepiness or insomnia.
5. Loss of energy or fatigue.
6. Daily feelings of worthlessness or inappropriate guilt.
7. Difficulty concentrating and thinking.
8. Psychomotor retardation/agitation.
9. Suicidal ideation.

Paraphrased from DSM IV: Single Episode: 296.2, Recurrent Episodes: 296.3, pg. 327 (American Psychiatric Association, 1994)

the alpha magnitude at the right frontal location and F3 is the magnitude at the left frontal side both referenced to CZ with an ear lobe as ground. The EEG data was recorded on a NeuroSearch 24-channel unit (Lexicor Corporation). Fast Fourier transforms (FFTs) were derived on Blackman-Harris windowed analog signals over one second epochs (Harris, 1978). The sample rate was 128. An index based on the percentage of time the alpha asymmetry score was greater than zero was used as the criterion for training with > 58% representing the non-depressed population (Baehr et al., 1998).

During the neurofeedback treatment the subject sat in a reclining chair with her feet up and her eyes closed. She was taught to use self-regulation to maintain a bell tone that signaled when the alpha asymmetry score was greater than zero. Sessions were twenty minutes long. After training was mastered and she was maintaining an asymmetry score of > 58%, she was offered an audio-visual entrainment device consisting of light emitting glasses and headphones that provided beats at selected frequencies to increase stimulation and blood flow to the brain. Occasionally pulsed electromagnetic stimulation consisting of a

small magnet of micro-tesla intensity was placed on her forehead to help deepen her relaxation (Baehr & Lappin, 2000).

RESULTS

By the second week in therapy Rita began normalizing the right frontal alpha asymmetry; however, setbacks in treatment occurred during the luteal phase (days 15-28 of a 28 day cycle) in the months of February, March, and April (Table 1). Rita was referred to one of the authors who prescribed Zoloft with increased dosage during the luteal phase of the menstrual cycle. The improvement in mood and in PCT scores during the luteal phase occurred when the increased dosage of Zoloft became effective (May 2001). For the next three months she was able to maintain a normal PCT score during the luteal phase of the menstrual cycle as well as during the follicular phase.

Comparison Data. Monthly cyclic data is presented for comparison with two other patients: a 24-year-old professional woman and a 47-year old professional woman, who participated in a pilot study (Baehr, 2001) while they were being treated for depression. Neither one exhibited any of the symptoms of PMDD during the luteal phase. The younger patient was taking 150 mg of Zoloft; the older patient was not on medication. Both were initially diagnosed as having a Major Depressive Disorder (DSM IV 296.2) as they exhibited five or more of the following symptoms for a two-week period: depressed mood most of the day, fatigue,

TABLE 1. Changes in Brainwave Asymmetry Percent Scores for Rita During the Luteal Phases of the Menstrual Cycle.

Before Luteal Phase Date	PCT	During Luteal Phase PCT	After Luteal Phase PCT
February	65	30	58
March	70	37	66
March-April	68	47	60
April-May	75	13	58
May-June	61	53	62
June-July	69	56	64

difficulty concentrating and thinking, excessive sleepiness, diminished interest in daily activity, agitation, and suicidal ideation (Box 2). Treatment procedures were identical to those experienced by Rita. Emotional symptoms during the luteal phase were characterized by mild irritability. Both patients had two EEG neurofeedback sessions per week. PCT scores remained relatively stable averaging > 58% during the luteal phase of their menstrual cycles (Table 2).

DISCUSSION

This single case study has allowed us to observe brain wave changes which occurred during the luteal phase of the menstrual cycle in a woman who had successfully trained frontal alpha asymmetry and was not experiencing depression except during this premenstrual period. Comparison data from two other women was used to demonstrate the stability of alpha asymmetry training in women who did not experience PMDD.

This study has helped in the understanding of how a "state" change due to a neurochemical factor could be reflected in brain wave changes. This is an important consideration to be taken into account when practicing neurotherapy. What is a possible basis of the effect? It is known that whereas in asymptomatic women the neurotransmitters gamma-aminobutyric acid (GABA) and serotonin peak premenstrually and decline during the follicular phase of the cycle (Blum et al., 1992;

TABLE 2. Changes in Brainwave Asymmetry Percent Scores for Non-PMDD Control Subjects During Two Luteal Phases of the Menstrual Cycle.

Subject	Age	Before Luteal Phase		During Luteal Phase		After Luteal Phase	
		Date	PCT	PCT	PCT		
MO	47	March-April	72	63	65		
		May-June	60	56	56		
JH	24	Sept-Oct	62	66	62		
		October	66	59	71		

Hindberg & Nash, 1992), 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 & Halbreich, 1997; Halbreich et al., 1996). Both serotonin and GABA mediate inhibitory input to the amygdala (Weiss, Sitcoske-O'Shea, & Post, 2000; Owens, 1994), a structure frequently implicated in affective phenomena (File, 2000; Nemeroff, 1998; Owens & Nemeroff, 1994) and known to connect to the frontal cortical areas whose EEG asymmetry we presumably record. One may speculate that anomalies in serotonergic and/or gabergic function may underlie the affective changes in the luteal phases of PMDD cases, and that these affective phenomena are expressed in frontal EEG asymmetry. A combination of factors including neurotherapy along with serotonergic anti-depressives may help normalize these patients.

We presented only two unsystematic "controls" here. Future research should remedy this deficiency. It would also be of interest to repeat the present observations in women with less severe symptoms and to study the effectiveness of combining neurofeedback and medication in treating this disorder.

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