Differentiation of women with premenstrual dysphoric disorder, recurrent brief depression, and healthy controls by daily mood rating dynamics

Steven M. Pincus [a,*], Peter J. Schmidt [b], Paula Palladino-Negro [b], David R. Rubinow [b]

[a] 990 Moose Hill Road, Guilford, CT 06437, USA
[b] Behavioral Endocrinology Branch, National Institute of Mental Health, Bethesda, MD 20892, USA

Abstract

Enhanced statistical characterization of mood-rating data holds the potential to more precisely classify and sub-classify recurrent mood disorders like premenstrual dysphoric disorder (PMDD) and recurrent brief depressive disorder (RBD). We applied several complementary statistical methods to differentiate mood rating dynamics among women with PMDD, RBD, and normal controls (NC). We compared three subgroups of women: NC ($n = 8$); PMDD ($n = 15$); and RBD ($n = 9$) on the basis of daily self-ratings of sadness, study lengths between 50 and 120 days. We analyzed mean levels; overall variability, SD; sequential irregularity, approximate entropy (ApEn); and a quantification of the extent of brief and staccato dynamics, denoted 'Spikiness'. For each of SD, irregularity (ApEn), and Spikiness, we showed highly significant subgroup differences, ANOVA $\leqslant 0.001$ for each statistic; additionally, many paired subgroup comparisons showed highly significant differences. In contrast, mean levels were indistinct among the subgroups. For SD, normal controls had much smaller levels than the other subgroups, with RBD intermediate. ApEn showed PMDD to be significantly more regular than the other subgroups. Spikiness showed NC and RBD data sets to be much more staccato than their PMDD counterparts, and appears to suitably characterize the defining feature of RBD dynamics. Compound criteria based on these statistical measures discriminated diagnostic subgroups with high sensitivity and specificity. Taken together, the statistical suite provides well-defined specifications of each subgroup. This can facilitate accurate diagnosis, and augment the prediction and evaluation of response to treatment. The statistical methodologies have broad and direct applicability to behavioral studies for many psychiatric disorders, and indeed to similar analyses of associated biological signals across multiple axes.
© 2007 Elsevier Ltd. All rights reserved.

Keywords: Mood disorders; Premenstrual dysphoric disorder; Premenstrual syndrome; Recurrent brief depression; Approximate entropy; Spikiness

1. Introduction

Most mood disorders are episodic and recurrent; yet, with the exception of seasonal triggers, little is known about the underlying determinants or characteristics of the dynamics of mood state regulation. It is axiomatic in endocrinology that the timing and amplitude of hormonal pulses both conveys regulatory information (beyond that of the mean hormone level) and allows inferences about the regulatory antecedents of the hormonal events (Santen and Bardin, 1973; Veldhuis and Johnson, 1994). Pulse detection algorithms have now been augmented (Pincus and Keefe, 1992; Pincus et al., 1998, 1999) by a statistical technique, Approximate Entropy (ApEn) (Pincus, 1991), that identifies the existence and degree of order and regularity in what otherwise may be viewed as random or disordered serial data. Not surprisingly, ApEn has been applied to mood rating data in one study contrasting three treatment regimens applied to healthy controls, with very significant decrease in mood dynamic irregularity seen for one of

the treatments, despite no differences in mean mood rating among the regimens (Yeragani et al., 2003). Similarly, we asked whether further statistical characterization of mood rating data would enable us to distinguish between two recurrent mood disorders – premenstrual dysphoric disorder (PMDD) and recurrent brief depressive disorder (RBD) – irrespective of knowledge of when menses occurred; i.e., are there replicable characteristics of the mood cycles that may be extracted either to facilitate diagnosis, identify subgroups, or provide independent measures that might predict course or treatment response characteristics.

During the past 20 years, both premenstrual syndrome (PMS) and, to a somewhat lesser extent, RBD have been the subject of extensive study. A severe form of PMS, PMDD is characterized by a mix of mood, physical and cognitive symptoms that occur during the luteal phase of the menstrual cycle, and are associated with significant impairment of function. Approximately 3–8% of women experience PMDD, which has been estimated as resulting in 14.5 million disability adjusted life years annually in the United States (Ginsburg and Dinsay, 2000; Halbreich et al., 2003; Johnson, 1987; Sternfeld et al., 2002). RBD is an affective disorder characterized by depressive episodes occurring at least once a month and lasting for only a few days (Angst and Dobler-Mikola, 1985). It is associated with a substantially increased risk of suicidal behavior (Pezawas et al., 2001; Weiller et al., 1994). Prevalence rates for RBD without mood disorder comorbidity range from 3% to 13% worldwide (Pezawas et al., 2003). Although formal integration of each of PMDD and RBD as a new (DSM-IV) diagnostic category has been relatively recent (American Psychiatric Association, 1994), the essential characteristics of each disorder have been mentioned in the psychiatric literature since the 19th century (Angst, 1994), and in the case of PMS, since antiquity (Endicott, 2000).

Both PMS and RBD are defined not only by the severity of mood symptoms but as well by the timing; PMS symptoms must be confined to the luteal phase, and RBD symptoms must last for several days but not more then two weeks, with episodes occurring approximately monthly. However, in the vast predominance of mood-rating data analyses of these and other mood disorders, only the mean (per-subject) mood rating levels of selected time-periods are considered, either to certify diagnostic state, or to compare distinct cohorts. Notably, other characteristics of these mood-rating time-series remain unevaluated.

Upon visual inspection of mood-rating time-series characteristics of PMDD and RBD subjects, compared to normal controls, we identified three distinct, complementary statistical attributes that we hypothesized would clarify statistical definition of each subgroup. These were overall variability (standard deviation, SD); sequential irregularity (ApEn); and (a quantification of) the extent of brief and staccato dynamics, denoted 'Spikiness'. The purpose of this study was to evaluate this hypothesis, and moreover, to simultaneously demonstrate the feasibility and potential utility of the statistical methodologies in the evaluation of many other psychiatric disorders.

2. Materials and methods

2.1. Subject selection

Women with PMDD or RBD were self-referred in response to advertisements for women with PMS in local newspapers or referred by their physician. Normal volunteer (control) women, NC, were recruited through local advertisement. All women were without current medical illness (as assessed by medical history, physical examination, laboratory tests, and electrocardiogram) and medication free. PMDD was prospectively confirmed by longitudinal ratings for three consecutive cycles. Before entry into the study, prospective participants were screened with a daily visual analogue scale of self-ratings of mood. All PMDD patients experienced at least 5 of the DSM-IV symptoms for PMDD (American Psychiatric Association, 1994) associated with significant functional impairment; additionally, each PMDD patient in the present study showed at least a 30% increase in mean level of sadness or anxiety/irritability or both in the week before menses compared to the week after the end of menses in at least two of three menstrual cycles. Current and past histories of psychiatric disorders were obtained with the SCID (Structured Clinical Interview for DSM-IV) (Spitzer et al., 1990) and the mood disorders module of the SADS-L (Spitzer and Endicott, 1979). PMDD subjects were not permitted to have either a current or recent past (last two years) history of any disorder other than PMDD.

Subjects with a diagnosis of RBD presented with complaints of PMS that were not confirmed with prospective ratings for at least three months. These subjects had periodic, brief depressions unrelated to menstrual cycle phase and satisfied all of the following DSM-IV criteria: (i) depressive episodes occurred about once a month over the previous year (by history); (ii) individual episodes, confirmed with prospective ratings lasted less than two weeks (typically 2–3 days in our subjects); (iii) the episodes did not occur solely in relation to the menstrual cycle. Normal control women also completed two months of prospective ratings, had no evidence of PMS or RBD, and did not meet criteria for either current or past psychiatric illness as determined by the SCID (Spitzer et al., 1990). Individuals with first degree relatives with an Axis I psychiatric disorder were excluded from the normal control group. All patients and controls had cycle lengths between 26 and 31 days, with the exception of two patients, one with a cycle length of 21 days and another with a cycle length of 33 days, and all had a negative urine pregnancy test. The protocols were reviewed and approved by the National Institute of Mental Health (NIMH) institutional review board, and all subjects gave both written and verbal consent to study participation.