Clinical and Biological Findings in a Case With 48-Hour Bipolar Ultrarapid Cycling Before and During Valproate Treatment

Georg Juckel, M.D.; Ulrich Hegerl, M.D.; Paraskevi Mavrogiorgou, M.D.; Jürgen Gallinat, M.D.; Torsten Mager, M.D.; Peter Tigges, Ph.D.; Stefan Dresel, M.D.; Andreas Schröter, M.A.; Gabriele Stotz, M.D.; Ingeborg Meller, M.D.; Waldemar Greil, M.D.; and Hans-Jürgen Möller, M.D.

Background: The rare cases of patients with 48-hour ultrarapid cycling allow close investigation of mood cycles in affective disorders, because rhythmic changes in psychopathologic state and biological parameters happen very precisely.

Method: A 67-year-old white man who had experienced bipolar 48-hour ultrarapid cycling (DSM-IV 296.80) for several years was studied without any medication and then again studied 4 weeks later during treatment with valproate (1800 mg/day).

Results: Objective and self ratings revealed pronounced manic states 1 day and depressed states the following day, which were found to be accompanied by rhythmic fluctuations in behavior and electroencephalographic parameters, blood cortisol and growth hormone levels (both elevated on depressive days), and urinary metanephrine (dopamine metabolite) and norepinephrine levels (both elevated on manic days). Using single photon emission computed tomography, regional blood flow in the left thalamus was lower than in the right thalamus on the manic day, while symmetric perfusion of the thalamus was found on the depressive day. Under valproate treatment, the patient remitted completely, and significant rhythmic changes in most of the biological parameters were no longer detectable.

Conclusion: The biological findings in this patient with bipolar 48-hour ultrarapid cycling, which correspond to those in other types of affective disorders, suggest that disturbances in the diencephalon-pituitary axis may be especially correlated to pathologic changes of mood.

(J Clin Psychiatry 2000;61:585–593)

Received Feb. 4, 1999; accepted Jan. 16, 2000. From the Department of Psychiatry (Drs. Juckel, Hegerl, Mavrogiorgou, Gallinat, Mager, Tigges, Stotz, Meller, Greil, and Möller and Mr. Schröter) and the Department of Nuclear Medicine (Dr. Dresel), Ludwig-Maximilians-University Munich, Germany.

We greatly appreciate the help of the staff of ward C1 and the Laboratory of Clinical Neurophysiology, as well as Nikolaus Kleindienst, M.A., from the Department of Psychiatry; Klaus Tatsch M.D., from the Department of Nuclear Medicine; and Karl Jacob, M.D., from the Department of Clinical Chemistry, all with the Ludwig-Maximilians-University Munich.

Reprint requests to: Georg Juckel, M.D., Department of Psychiatry, Ludwig-Maximilians-University, Nussbaumstr. 7, 80336 Munich, Germany (e-mail: juckel@nk-i.med.uni-muenchen.de).

Three special forms within the bipolar affective disorders have been described that show rapid mood shifts. So-called rapid cycling is defined in DSM-IV as at least 4 depressive and/or manic episodes or 2 complete bipolar cycles per year, and ultrarapid cycling is characterized by unipolar or bipolar cycles lasting for 48 hours, i.e., showing a constant rhythm of a 24-hour depressed state followed by 24 hours of a euthymic or manic state. In recent years, there have also been reports of ultradian or ultra-ultrarapid cycling, which comprises unipolar or bipolar cycles that occur repetitively in 1 single day.[1] These 3 forms can be regarded as compressed forms of the spectrum of affective illness.[2,3] In each of them, changes of the affective state (depressive, manic, euthymic) happen very precisely and in a short period of time so that they can be observed closely. Therefore, the pathogenetic process of affective illness is likely to be investigated more directly.

Compared with rapid cycling, ultrarapid cycling is extremely rare. Gelenberg et al.[4] counted 8 bipolar and 4 unipolar cases of ultrarapid cycling from 1804 to 1978 in the literature. Until today, only 8 additional cases were reported to our knowledge. In contrast, it is assumed that approximately 15% of all patients with affective disorders show rapid cycling of their episodes.[5] More than 70% of these rapid cyclers are women,[5,6] whereas nearly all cases with ultrarapid cycling are men. Age at onset in ultrarapid cycling has been reported to be older than 60 years.[7] Rapid cycling appears mainly in the third decade of life, and the premorbid history is typically long.[7–9] However, patients having ultrarapid cycling reported short premorbid history and fast acquisition of the 48-hour rhythm. Additionally, such patients often have a pronounced positive family history of psychiatric diseases, whereas a positive family history in patients with rapid cycling is comparable to that in non–rapid-cycling bipolar patients.[5,10–12] Rapid cycling is often associated with alcohol addiction and can be induced by psychotropic substances like antidepressants[13,14]; there seems to be only one case in the literature of developing unipolar ultrarapid cycling

after dibenzepine.[15] Regarding rapid cycling, the change from manic to depressive state occurs slowly, whereas the switch from depressive to manic state often happens suddenly, and the time of day of the switches is variable.[16] In contrast, affective states of ultrarapid cycling switch especially at night, potentially between 1:00 and 3:00 a.m.[17]

Treatment of ultrarapid cycling is difficult, and the response to the different strategies is generally worse than in treating rapid cycling. Sleep deprivation, combined with a treatment of tranylcypromine, was successful in one case with unipolar ultrarapid cycling.[18] In a case with bipolar ultrarapid cycling, the effect of sleep deprivation was not very pronounced.[19] Electroconvulsive therapy (ECT) led to improvement in the case with unipolar ultrarapid cycling induced by dibenzepine.[15] Amitriptyline lessened the amplitude of depressed mood in a case with unipolar ultrarapid cycling, but did not affect the periodicity itself.[20] Trazodone, tranylcypromine, and amphetamines like methylphenidate produced no changes in a unipolar case.[18] A number of other antidepressants and neuroleptics (sulpiride, zuclopenthixol, mianserin, clomipramine, levomepromazine) were ineffective in a bipolar case of ultrarapid cycling.[21] While carbamazepine led only to partial improvement in unipolar and bipolar cases of ultrarapid cycling,[1,18,19] such patients responded well to lithium,[18,20,22,23] but there are conflicting findings.[1] In a bipolar case, the combination of lithium with carbamazepine brought only an unstable relief, but lithium and valproate led to the disappearance of symptoms and stabilization of the patient.[21] Furthermore, valproate alone was very effective in a unipolar case of ultrarapid cycling.[18] There is also one report concerning a good response to the calcium antagonist nimodipine in ultrarapid cycling.[24] To sum up, lithium seems to be a sufficient treatment for ultrarapid cycling, whereas it may be ineffective in simple rapid cycling.[25,26] Valproate is recommended for treating rapid cycling[27,28] and presumably also has favorable effects in ultrarapid cycling.

Because of the rarity of cases, the ultrarapid cycling phenomenon is presently largely unstudied. The cases that have been reported were studied mostly in the acute state. The significance of the biological findings in such cases can be assessed, however, only by comparing the acute state with the state after any sufficient treatment. Therefore, we investigated our patient, who was suffering from a bipolar disorder with ultrarapid cycling of 24-hour depressed states followed by 24-hour manic states, before and during valproate treatment. The patient was examined using neurochemical, neuroendocrinologic, neurophysiologic, and neuroimaging methods. Rhythmic changes of most of these biological measures according to the manic and depressive days and their normalization with clinical remission were expected. A broad range of literature suggests high levels of cortisol and human growth hormone in depressed states as well as high levels of dopamine and norepinephrine in manic states of affective disorders. Mania might also be associated with elevated psychomotor activity combined with unconcentrated and uneven handwriting performance[29,30] as well as with an increased electroencephalogram (EEG) alpha frequency.[31] Neuroimaging techniques (single photon emission computed tomography; SPECT) were focused on mood cycling–related abnormalities in prefrontal cortex, basal ganglia, amygdala-hippocampus complex, and thalamus with lower perfusion in the depressed state.[32,33]

METHOD

Subject

A 67-year-old white man, born the youngest of 4 children in a small town in southwest Germany, was studied. His father, employed by the government, died at 71 years of age owing to an infection; his mother, a housewife, died at 84 years of age owing to cardiac arrest; they were both without any psychiatric disorders. The oldest brother of the patient (74 years old, no profession, unmarried) has suffered from schizophrenia since his 28th birthday and was hospitalized for at least 10 years in a psychiatric hospital. The daughter of the second brother (71 years old, geologist, married, 2 children) has a bipolar disorder and is treated with lithium. The sister of the patient, who died at 62 years of age through complications of diabetes, was also hospitalized for an extended period because of schizophrenia (hebephrenic type). Additionally, an uncle also had contacts with psychiatric institutions, and an aunt of the patient hospitalized in psychiatric hospitals for many years was probably "euthanized" in 1938.

The patient reported that despite poorness and illness in his family, he had had a happy childhood and youth. To his memory, there were no serious somatic or psychological problems in his childhood and youth. He also had no difficulties at school. He studied electrical techniques and physics and worked for nearly 20 years as a leading employee of a French company that detected and claimed mineral oil, most of the time in foreign countries. At the age of 31 years, he married a woman who was 9 years younger than himself and who then became a housewife. Their 3 children (1 son, 2 daughters; 33, 30, and 29 years old; all in academic professions) are physically and psychologically in good health. The patient reported no serious problems in his relationships with his wife and children.

At the age of 44 years, he became professor of electrical measurement techniques. When he was 62 years old, he retired owing to an increasingly unenthusiastic and depressed mood, but he kept his laboratory for further work. In the following year, after a trip to South Africa to visit his brother, during which nothing abnormal occurred, he and his wife noticed that he was very busy one day and despondent the next day. Originally, the patient described himself as a more melancholic type, but he was always

quite active and dynamic as well as interested in many things. Several weeks after that journey, a constant rhythm with 24 hours of hyperthymic mood and 24 hours of hypothymic mood developed. The patient and his wife reported that one day he would be obviously depressed, tearful, inactive, tired, socially withdrawn, and without any appetite and energy; he would speak very rarely and in a monotonic way and feel guilty about his activities on the manic day. On a manic day, he would wake up during the early morning hours (around 4:00 a.m.) in an optimistic mood and with a "thousand plans" for the day. During the whole day he would be very active, always talking and looking for contact with different people without paying attention to the normal borders of social interactions, and he would sometimes spend more money than usual and would be a little bit dysphoric and aggressive. The switches between the 2 different affective states were assumed by the patient and his wife to occur during the night, between 1:00 and 3:00 a.m.

Because of this rhythm during the last 4 years, his life and that of his family has been increasingly impaired. Therefore, he began to consult several medical doctors and psychiatric experts. Reactive or somatic reasons for the unusual mood fluctuations of the patient were not found. Due to different diagnoses, several treatment regimens were tried over these years. The patient was treated with fluspirilen, amitriptyline, alprazolam, trimipramine, fluoxetine, and carbamazepine (discontinued due to skin allergy). All of these treatments were without any sufficient success. Lithium was given for 3.5 months with sufficient plasma levels (0.6–1.0 mmol/L), as controlled by an experienced psychiatrist. As this psychiatrist reported, the lithium treatment was unable to influence the clocklike 48-hour rhythm of manic and depressed states in any regard. Approximately 4 years after the onset of the illness, the patient was first diagnosed as suffering from bipolar disorder with 48-hour ultrarapid cycling (DSM-IV 296.80) by a present author (W.G.) in an outpatient setting, and the patient was then admitted to our hospital 2 months later. During the first days in our hospital, clear depressed states one day and clear manic states the following day were found according to DSM-IV criteria for changed mood, drive, thinking, behavior and somatic symptoms in mood disorders.

The physical examination at admission was without any pathologic findings. The patient reported only to have had some problems with his back including one operation 30 years ago. He never smoked, he reported drinking alcohol only occasionally, and he took no medication regularly. Many additional tests (routine blood and urine examination including immunoelectrophoresis; tests for lues, tuberculosis, sarcoidosis, and autoimmune diseases; cerebrospinal fluid punctation; cranial magnetic resonance imaging; x-ray of chest, spine, and skull; abdomen sonography; electrocardiogram; 24-hour blood pressure measurement) were conducted, and in these investigations, no evidence for any somatic basis for the symptoms was found. Psychological tests of the patient revealed intelligence significantly over the statistical mean value; in these tests, we found no signs of any apparent organic process in the brain that could diminish the cognitive abilities of the patient. The patient was asked to fill out the Minnesota Multiphasic Personality Inventory[34] twice in the unmedicated state. On the manic day, the personality profile was within the norm with relatively high values in the mania subscale. On the depressive day, the personality profile showed depressive-anxious and obsessive-compulsive characteristics with social withdrawal. Pedantic and perfectionistic characteristics of his personality were also seen clinically, but using the Structured Clinical Interview for DSM-III-R,[35] no hints for an Axis II diagnosis could be found.

The patient was studied, using the methods described below, for 8 consecutive days (i.e., 4 cycles) in the unmedicated state, a few days after admission. Until that time, the patient was without any psychotropic or other medication for at least half a year. After this first investigation period, the patient was immediately treated with valproate with increasing dosages. After 4 weeks of treatment, the patient was studied again with the same methods for 8 days. During this study period, the patient took 1800 mg of valproate daily, with a plasma level of 85.7 μg/mL (therapeutic range, 50–120 μg/mL). No other medication or therapeutic intervention was administered to the patient.

The patient gave his written informed consent to all of the investigations after they were fully explained to him, as well as to the publication of all the information and data reported here.

Psychopathologic Ratings

Psychopathologic states were assessed by the Bech-Rafaelsen Melancholia Scale and by the Bech-Rafaelsen Mania Scale[36] twice a day. For each of these scales, the sum score of all items was calculated. For self-rating, the patient was asked to fill out the visual analog scale[37] (German version, 9-cm lines for each of the 6 items) twice a day. The item on the visual analog scale asking for estimation of general mood state was used for further analysis (in all the other items, similar results were obtained). Since there were no significant changes over each day, a mean value per day for each scale mentioned above was calculated.

Motor Activity

Locomotor activity of the patient was registered by a transportable device (Vitaport, Becker, Germany). A small instrument (1 × 1 × 0.4 cm), consisting of a precision sensor (high-developed Piezo element) measuring acceleration movements related to the earth acceleration

(*g*), was fixed at the lower end of the thigh and connected to the Vitaport device. Recordings were conducted repeatedly during the unmedicated and medicated states from approximately 8:00 a.m. until 4:00 p.m.

Handwriting Movements

Handwriting was recorded using a commercially available digitizing graphic tablet (Wacom, Japan) in combination with a personal computer. With a maximum sampling rate of 200 Hz, a spatial resolution of 0.12 mm was obtained. The patient was instructed to write repetitively "aaa" in 4 different sizes (6, 12, 18, and 24 mm). The size was indicated by 2 horizontal lines. To describe the performance quality of skilled handwriting, inversion parameters were found to be sensitive even for small changes in ability[38]: the higher the degree of inversion, the higher the unevenness of a movement concerning acceleration.

Heart Rate, Blood Pressure, and Temperature

Heart rate, blood pressure, and temperature were measured by nurses at 3 designated times per day. Mean values for each day were analyzed.

Blood Parameters

Blood was drawn daily at 8:00 a.m. and anticoagulated with heparin. Cortisol, prolactin, and human growth hormone (hGH) were immediately determined by a luminescence method (ACS apparatus, Kyron, Germany). Due to the extended program, repeated blood samples for whole-day hormone profiles were avoided in order to lessen the burden on the patient and minimize influences on his natural behavior. Thyroid hormone levels including total triiodothyronine (T_3) and free thyroxine (T_4) as well as thyrotropin were measured by an enzyme-linked immunosorbent assay (Boehringer, Germany).

Urine Parameters

The patient was asked to collect urine for 24 hours (due to laboratory reasons, from 7:00 a.m. to 7:00 a.m the following day) several times during the 2 investigation periods (6 collections in total). Urine was prepared with 40 mL hydrochloric acid. The dopamine metabolite metanephrine, epinephrine, norepinephrine, and the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) were immediately analyzed by high-pressure liquid chromatography (HPLC) with electrochemical detection (Biorad and Chromsystem, Germany).

Electroencephalogram

An EEG (Best, Austria) was recorded each day at 1:00 p.m. during the 2 investigation periods under resting conditions. The EEG was analyzed visually by standard international rules. Additionally, power spectral analysis was conducted using a 21-channel bipolar montage. In 4-second segments of P3-O1 and P4-O2 in each recording, which were visually judged as free of artifacts and drowsiness, the dominant frequency and the absolute power in the delta (2–3.5 Hz), theta (3.5–8 Hz), alpha (8–12 Hz), and beta band (12–32 Hz) were determined. Mean values for left and right hemisphere were presented. For technical reasons, the recordings of the second investigation period during valproate treatment could be analyzed only partly.

Auditory Evoked Potentials

Auditory evoked potentials (AEP; Best, Austria) were recorded at 1:30 p.m. each day during the 2 investigation periods. The measurement focused especially on the intensity dependence of AEP (tangential dipole), since this variable is discussed as a valid indicator of the central serotonergic system.[39,40] Five hundred binaural 1000-Hz tones (30 ms duration, 10 ms rise and fall time, interstimulus interval randomized between 1.8 and 2.2 s) with 5 intensities (50, 60, 70, 80, 90 dB sound pressure level) were presented in pseudorandomized form by headphones. Thirty-two–channel data with Cz as reference were collected with a sampling rate of 500 Hz (analog low-pass filter of 70 Hz, high-pass filter of 0.16 Hz) from 200 ms prestimulus to 500 ms poststimulus. One hundred sweeps were recorded for each intensity. After automatic artifact rejection, the remaining sweeps (usually around 90 sweeps) were averaged separately for the 5 intensity levels and entered into dipole source analysis (brain electric source analysis program), using a dipole model developed by the recordings of 60 healthy volunteers. Through this procedure, the 32-channel N1/P2 waves were reduced to the activity of 2 dipoles per hemisphere. The intensity dependence of the tangential dipole, representing mainly activity of the primary auditory cortex,[39] was calculated as the median slope of the slopes of all possible connections between the amplitude values of the 5 intensities. One recording could not be analyzed due to technical reasons.

Single Photon Emission Computed Tomography

A SPECT was conducted twice in the unmedicated state: on 1 manic day and on the following depressive day, at 3:00 p.m. each day. For SPECT acquisition, a triple-headed gamma camera equipped with high resolution fan beam collimators (Picker Prism 3000) was used. The acquisition parameters consisted of a rotational radius of 13 cm or less, 120 projection angles over 360 degrees, and a 128 × 128 matrix with a pixel width of 2.11 mm in the projection domain. Data collection started about 60 minutes after injection of 740 Mbq of ^{99m}Tc ECD (ethyl cysteinate dimer) and lasted for approximately 30 minutes (45 s/projection). Images were reconstructed by filtered backprojection, using a low-pass filter (cut-off frequency 0.3 Nyquist, 4th order). Transverse slices corrected for attenuation according to Chang's method were realigned according to the ac-pc line and documented. Asymmetry of cerebral blood flow was calculated using the region of interest technique compar-

ing corresponding cortical and subcortical areas of both hemispheres.

Statistical Analysis

Statistical analyses were performed using the run test developed by Wald[41] to test whether or not the sequence of the values of each variable over the days was random.

RESULTS

Clinical Findings

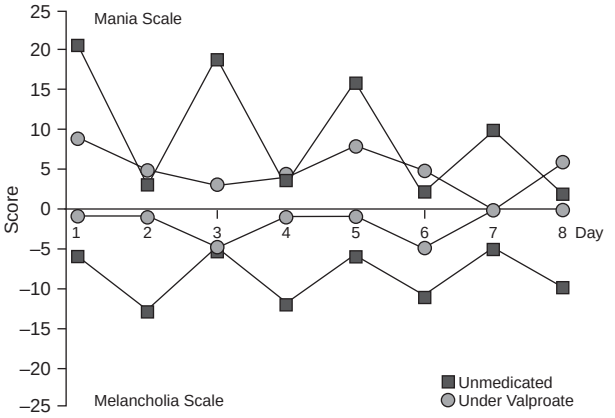
The patient was observed and studied before and during valproate treatment. While being treated with valproate, the patient felt a subjective improvement in his situation within the first days of treatment. During the second treatment week, the amplitudes of the mood fluctuations also became objectively significantly smaller, and the patient became better balanced: on manic days, the patient was more orderly and not so active and full of ideas; on depressive days, the patient was more interested in different things and people and more active and vigorous than before. Increasingly, the patient reported to feel more as he had before the illness. After 4 weeks of treatment, the patient was nearly stabilized and remitted. Neither the patient nor the staff was able to differentiate clinically between the days. Sleep, appetite, mood, and activities were distributed almost completely evenly over the days, and this was confirmed by the wife of the patient. The patient has now been stable for more than 2 years under valproate treatment. Due to occasional side effects of drowsiness and weakness, which were sometimes not acceptable for the patient, he tried to stop valproate, but without success, since 48-hour mood cycles tended to return.

Figure 1 shows the psychopathologic ratings with the Bech-Rafaelsen Mania and Melancholia Scales before and during valproate treatment. In the unmedicated state, there was a clear rhythm of manic (scores up to 21 points) and depressive days (scores down to 13 points). Under valproate medication in the fifth week of treatment, such repetitive changes from day to day were not seen, and the patient's condition as measured by these 2 scales was greatly improved. On the self-rated measurements, mood assessed by the visual analog scales also demonstrated regular changes between manic and depressive days before treatment and no significant fluctuations while under valproate treatment (Figure 2). As self-rating scales and Bech-Rafaelsen Scales revealed, the mood of the patient was judged to be more in the hyperthymic range under valproate treatment, which seems to be in accordance with his original state before illness based on the anamnestic information.

Biological Findings

Objective behavioral parameters also showed rhythmic fluctuations in the unmedicated state of the patient and

Figure 1. Psychopathologic Ratings With the Bech-Rafaelsen Mania and Melancholia Scales in the Unmedicated Days Before Starting Valproate and the Fifth Week Under Valproate Treatment

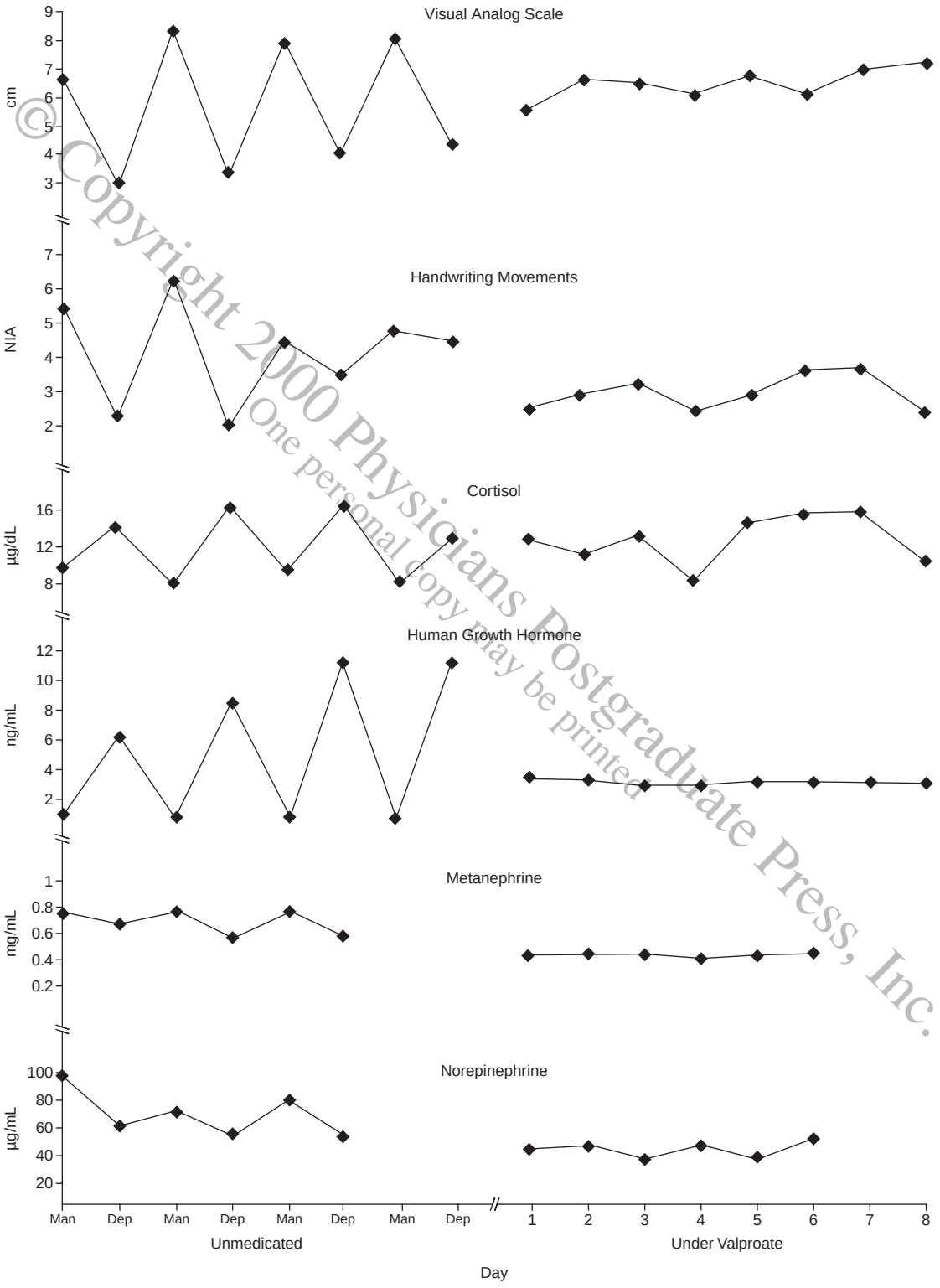


normalization under treatment. Locomotor activity nearly doubled on manic days (mean ± SD = 0.038 ± 0.024*g*) compared with depressive days (mean ± SD = 0.020 ± 0.031*g*). Under valproate in the fifth week of treatment, the locomotor activity was comparable on both the previously manic and depressive days (mean ± SD = 0.016 ± 0.031*g* vs. 0.019 ± 0.029*g*). Concerning handwriting movements (writing repetitively "aaa"), the degree of inversion, i.e., unevenness of these movements, was higher on manic than on depressive days (see Figure 2). This means that smoother and more skilled handwriting was observed in the depressed state of the patient. Under valproate treatment, degree of inversion was lower, and no significant fluctuations were seen.

In the unmedicated state, blood cortisol and hGH levels changed rhythmically daily. Cortisol and hGH showed high values on the depressive days and low values on the manic days (see Figure 2). In contrast, on the urinary parameters the dopamine metabolite metanephrine and norepinephrine showed higher values on the manic than on the depressive days (see Figure 2). In the fifth week under treatment with valproate, there were no such rhythmic fluctuations of cortisol, growth hormone, and metanephrine from day to day. Interestingly, the cortisol values during treatment were rather high, i.e., approximately in the range of the previous depressive days, whereas the hGH values under valproate treatment were rather low. Metanephrine and norepinephrine values were also a little lower under treatment than before, but weak rhythmic changes of norepinephrine were still detectable during valproate treatment.

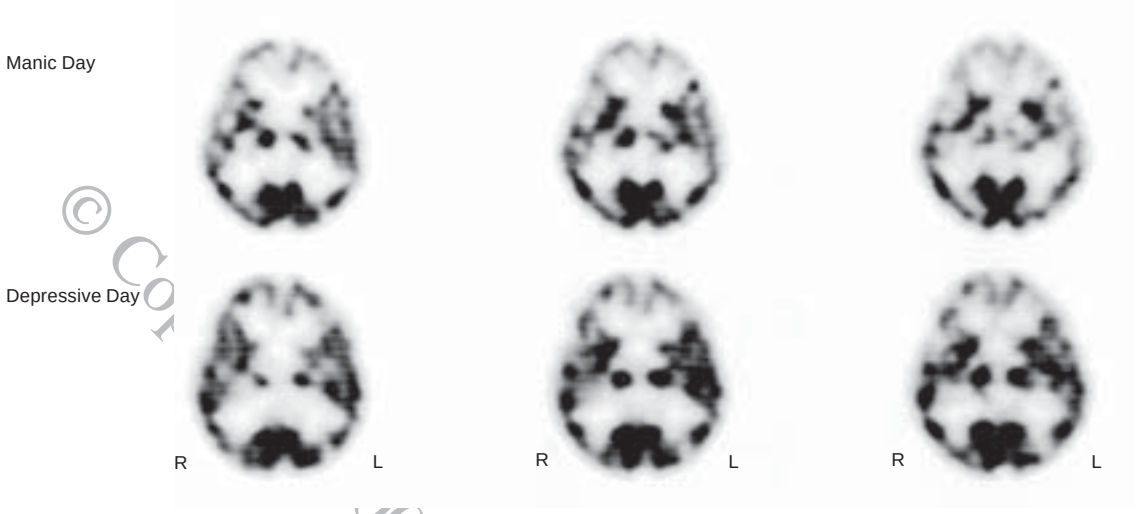
Power spectral analysis of EEG revealed that the dominant alpha frequency changed rhythmically with the psychopathologic state, with higher values on the manic than on the depressive days (range, 8.5–11.25 Hz), whereas the

Figure 2. Mood (visual analog self-rating scale), Behavioral (unevenness of handwriting movements), and Neurochemical Parameters (blood cortisol and growth hormone levels and urine metanephrine and norepinephrine levels) Before and During the Fifth Week Under Treatment With Valproate[a]



[a]Abbreviations: Dep = depressed day, Man = manic day, NIA = number of inversions of acceleration.

Figure 3. Lower Regional Blood Flow in the Left Thalamus Than in the Right Thalamus on the Manic Day in Single Photon Emission Computed Tomography Transverse Sections and Nearly Symmetric Perfusion of the Thalamus on the Depressive Day[a]



[a]Left and right thalamus are the 2 round structures in the middle of each section.

absolute power in the alpha band was lower in the manic than in the depressed state (range, 18.1–41.5 pV^2). No such fluctuations were detectable for any of the other EEG bands. Regarding the few recordings in the fifth week under valproate treatment that could be analyzed, alpha frequency was stable in a range between 9.0 and 9.5 Hz, and alpha power ranged from 14.3 to 20.5 pV^2.

The SPECT results showed that regional blood flow in the left thalamus was significantly lower than in the right thalamus (difference in the mean count rate of 14%) on the manic day, whereas the perfusion of the thalamus appeared symmetrical (left/right difference = 1.3%) on the depressive day (Figure 3). All other brain regions analyzed, such as the prefrontal cortex, the basal ganglia, and the amygdala-hippocampus complex, showed no relevant asymmetries or abnormalities.

The statistical analyses revealed that the values of all clinical and biological variables described significantly changed between the manic and the depressive days during the unmedicated week, while no such significant changes of these parameters (except for norepinephrine) were detectable in the fifth week under valproate treatment.

Finally, several negative findings were also obtained. No rhythmic changes between manic and depressive days were found for prolactin, thyroid hormones (T_3, free T_4, thyrotropin), epinephrine, 5-HIAA, the cardiovascular parameters, or temperature or for the further putative serotonergic parameter, the intensity dependence of the auditory evoked tangential dipole.

DISCUSSION

We presented one of the rare cases of bipolar disorder with persistent 48-hour ultrarapid cycling of manic and depressive states (1 day manic and 1 day depressed) for at least 4 years, which remitted completely under a treatment with valproate alone. Rhythmic changes of biological parameters according to these switches in psychopathologic state also stopped after clinical improvement.

There were no doubts in the diagnosis because repetitively pronounced manic states one day and clear depressive states the following day were observed at our ward and 2 months before on another occasion in an outpatient setting. These observations were in line with the detailed anamnesis of the patient and his wife as well as with reports of other psychiatrists who had seen the patient before. Rhythmic fluctuations of several characteristic biological and behavioral parameters associated with the psychopathology also support the diagnosis of a bipolar disorder with the special feature of 48-hour ultrarapid cycling. The patient showed most of the general characteristics of the ultrarapid cycling illness (male, late and fast onset, positive family history), as given in the introduction. No other reason such as any organic process or personality disorder causing this illness was found. It can only be speculated whether the trip to South Africa had unspecifically triggered the beginning of the ultrarapid cycling.

Treatment with valproate was attempted successfully in 2 previous cases with ultrarapid cycling.[18,21] Additionally, one preliminary report concerns a young boy probably suffering from ultradian rapid cycling (2 hypomanic and 1 depressive state per day) who recovered under the treatment of valproate.[42] During a 4-week treatment with valproate alone, our patient improved promptly and strongly, showing no rhythmic changes in clinical and biological parameters from day to day anymore. This success has persisted now for more than 2 years; attempts to

stop valproate tended to lead again to 48-hour ultrarapid cycling. The patient did not receive any other pharmacologic or nonpharmacologic treatment, e.g., sleep deprivation. Regarding this patient and the 2 patients in the literature treated by valproate, valproate seems to be an effective treatment not only in rapid cycling, but also in ultrarapid cycling. It was reported that valproate seems to have marked efficacy in manic and mixed states of bipolar disorders, but minimal to moderate antidepressant properties.[28,43] Since valproate influenced affective symptoms on both manic and depressive days in our patient, it can be assumed that valproate led to the patient's improvement by more general mood-stabilizing properties. In accordance with the literature,[27] valproate was well tolerated by our patient, who complained only of mild drowsiness and weakness.

Several, but not all, biological parameters studied in this patient changed rhythmically with the psychopathologic switches and were balanced over the days after clinical recovery in the fifth week of valproate treatment. Most of the positive and negative findings in our case of 48-hour ultrarapid cycling correspond to findings in the literature. As the most consistent result in the literature, higher cortisol levels in blood or urine in the depressive than in the manic or euthymic state were found in 48-hour ultrarapid cycling.[19,44–46] An abnormal secretory pattern of cortisol was also observed in a unipolar case of ultrarapid cycling.[4] In contrast to the finding in another case with bipolar ultrarapid cycling,[19] blood hGH levels showed rhythmic variations with psychopathology in our patient. There were also no findings of rhythmic changes in blood levels of thyroid hormones (T_3, free T_4, thyrotropin) by other authors.[4,19,45] Similar to our case, metanephrine and norepinephrine tended to have higher values on manic than on depressive days in a patient with bipolar ultrarapid cycling, whereas epinephrine and 5-HIAA were equal on these days.[45] Visual analysis of EEG in 2 cases with bipolar 48-hour ultrarapid cycling also revealed higher alpha frequency, but less appearance of alpha on manic than on depressive days.[23,47] Using positron emission tomography (PET) instead of SPECT as we did, no differences of nuclide distributions in different brain regions between depressive and manic days in a bipolar ultrarapid cycling case were found, but results concerning the thalamus were not reported.[19] This PET, as well as our SPECT study, is, however, limited because the investigations were conducted on only 2 occasions owing to the risk of a too-high load of radiation. A sequence effect cannot, therefore, be excluded completely, but is not very likely (e.g., patients with epilepsy or vascular diseases often receive 2 perfusion SPECT scans in a short time without showing abnormalities in the thalamus). In contrast to our expectations, the SPECT investigations of our patient with bipolar ultrarapid cycling revealed low perfusion on the manic but not the depressive day in only the thalamus, but not in the other regions of interest. Using PET, decreased regional blood flow in the thalamus was found in normal subjects during induced elated mood states.[48]

Biological rhythmic changes in 48-hour ultrarapid cycling could support knowledge about possible pathogenetic mechanisms in affective disorders, since they seem to be closely related to the rhythmic changes of psychopathologic state in such patients; in our case, the stabilization of the biological parameters under treatment with valproate may be an additional confirmation of the significance of such findings. For example, one of the most consistent neuroendocrine findings in biological psychiatry is hypercortisolism in depression,[49] as patients with ultrarapid cycling also show. In bipolar patients switching from depression to mania, cortisol levels were lower in the manic than the depressive state.[50,51] Regarding anatomical aspects of affective disorders, neuroimaging techniques revealed abnormalities of diencephalic regions such as the thalamus and hypothalamus, especially in bipolar patients.[32,33] There are also some hints that thalamus infarction can induce mania or mood cycles,[52,53] and patients who developed bipolar affective disorder after a brain lesion had their lesions mainly in the caudate and in the thalamus.[54] Since the thalamus is highly involved in the generation of EEG alpha rhythm,[55] the rhythmic changes of alpha frequency and alpha power with the psychopathologic state in the patients with ultrarapid cycling could also be a result of abnormalities in the thalamus of those patients, as our SPECT findings suggest. It can therefore be speculated whether disturbances in the pituitary together with abnormalities in diencephalic structures, resulting in changes of cortisol, hGH, and other biological parameters, are leading to the periodic or clocklike mood shifts in patients with ultrarapid cycling as well as to mood changes in unipolar and bipolar affective disorders.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), carbamazepine (Tegretol and others), clomipramine (Anafranil and others), fluoxetine (Prozac), methylphenidate (Ritalin and others), nimodipine (Nimotop), tranylcypromine (Parnate), trazodone (Desyrel and others), trimipramine (Surmontil).

REFERENCES

1. Kramlinger KG, Post RM. Ultra-rapid and ultradian cycling in bipolar affective illness. Br J Psychiatry 1996;168:314–323
2. Dunner DL, Patrick V, Fieve RR. Rapid cycling manic depressive patients. Compr Psychiatry 1977;18:561–566
3. Maj M, Magliano L, Pirozzi R, et al. Validity of rapid cycling as a course specifier for bipolar disorder. Am J Psychiatry 1994;151:1015–1019
4. Gelenberg AJ, Klerman GL, Hartmann EL, et al. Recurrent unipolar depressions with a 48-hour cycle: report of a case. Br J Psychiatry 1978;133:123–129
5. Coryell W, Endicott J, Keller M. Rapidly cycling affective disorder: demographics, diagnosis, family history, and course. Arch Gen Psychiatry 1992;49:126–131
6. Leibenluft E. Women with bipolar illness: clinical and research issues. Am J Psychiatry 1996;153:163–173
7. Alarcon RD. Rapid cycling affective disorders: a clinical review. Compr Psychiatry 1985;26:522–540

8. Wehr TA, Sack DA, Rosenthal NE, et al. Rapid cycling affective disorder: contributing factors and treatment responses in 51 patients. Am J Psychiatry 1988;145:179–184
9. Kukopulos A, Caliari B, Tundo A, et al. Rapid cyclers, temperament, and antidepressants. Compr Psychiatry 1983;24:249–258
10. Bauer MS, Calabrese J, Dunner DL, et al. Multisite data reanalysis of the validity of rapid cycling as a course modifier for bipolar disorder in DSM-IV. Am J Psychiatry 1994;151:506–515
11. Lish JD, Gyulai L, Resnick SM, et al. A family history study of rapid-cycling bipolar disorder. Psychiatry Res 1993;48:37–45
12. Nurnberger J Jr, Guroff JJ, Hamovit J, et al. A family study of rapid-cycling bipolar illness. J Affect Disord 1988;15:87–91
13. Wehr TA, Goodwin FK. Can antidepressants cause mania and worsen the course of affective illness? Am J Psychiatry 1987;144:1403–1411
14. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 1995;152: 1130–1138
15. Lerer B, Birmacher B, Ebstein RP, et al. 48-hour depressive cycling induced by antidepressant. Br J Psychiatry 1980;137:183–185
16. Erkwoh R, Bräunig P. Biological findings in rapid cycling syndromes. Fortschr Neurol Psychiatr 1991;59:1–11
17. Sitaram N, Gillin JC, Bunney WE Jr. Circadian variation in the time of "switch" of a patient with 48-hour manic-depressive cycles. Biol Psychiatry 1978;13:567–574
18. Churchill CM, Dilsaver SC. Partial sleep deprivation to prevent 48-hour mood cycles. Acta Psychiatr Scand 1990;81:398–399
19. Gann H, Riemann D, Hohagen F, et al. 48-hour rapid cycling: results of psychopathometric, polysomnographic, PET imaging and neuroendocrine longitudinal investigations in a single case. J Affect Disord 1993;28:133–140
20. Gelenberg AJ, Klerman GL. The effects of amitriptyline and lithium on a patient with 48-hour recurrent depressions. J Nerv Ment Dis 1978;166: 365–368
21. Lepkifker E, Iancu I, Dannon P, et al. Valproic acid in ultrarapid cycling: a case report. Clin Neuropharmacol 1995;18:72–75
22. Hanna SM, Jenner FA, Pearson IB, et al. The therapeutic effect of lithium carbonate on a patient with forty-eight hour periodic psychosis. Br J Psychiatry 1972;121:271–280
23. Paschalis C, Pavlou A, Papadimitriou A. A stepped forty-eight hour manic-depressive cycle. Br J Psychiatry 1980;137:332–336
24. Pazzaglia PJ, Post RM, Ketter TA, et al. Preliminary controlled trial of nimodipine in ultra-rapid cycling affective dysregulation. Psychiatry Res 1993;49:257–272
25. Dunner DL, Fieve RR. Clinical factors in lithium carbonate prophylaxis failure. Arch Gen Psychiatry 1974;30:229–233
26. Krüger S, Bräunig P, Young LT. Biological treatment of rapid-cycling bipolar disorder. Pharmacopsychiatry 1996;29:167–175
27. McElroy SL, Keck PE, Pope HG, et al. Valproate in the treatment of bipolar disorder: literature review and clinical guidelines. J Clin Psychopharmacol 1992;12:42S–52S
28. Calabrese JR, Rapport DJ, Kimmel SE, et al. Rapid cycling bipolar disorder and its treatment with valproate. Can J Psychiatry 1993;38:S57–S61
29. Post RM, Stoddard FJ, Gillin JC, et al. Alterations in motor activity, sleep, and biochemistry in a cycling manic-depressive patient. Arch Gen Psychiatry 1977;34:470–477
30. Baig MS, Shen WW, Caminal ER, et al. Signature size in the psychiatric diagnosis: a significant clinical sign? Psychopathology 1984;17:128–131
31. Davis PA. Electroencephalograms of manic-depressive patients. Am J Psychiatry 1941;98:430–433
32. Soares JC, Mann JJ. The anatomy of mood disorders: review of structural neuroimaging studies. Biol Psychiatry 1997;41:86–106
33. Soares JC, Mann JJ. The functional neuroanatomy of mood disorders. J Psychiatr Res 1997;31:393–432
34. Lachar D. The MMPI. Clinical Assessment and Automated Interpretation. Los Angeles, Calif: Western Psychological Services; 1974
35. Wittchen HU, Schramm E, Zaudig M, et al. Structured Clinical Interview for DSM-III-R, German Version 2.0 Manual. Weinheim, Germany: Beltz Verlag; 1990
36. Collegium Internationale Psychiatriae Scalarum. Bech-Rafaelsen Melancholia and Mania Scales. Weinheim, Germany: Beltz Verlag; 1990
37. Aitken RCB. Measuring of feelings using visual analogue scales. Proc Royal Soc Med 1969;62:989–993
38. Eichhorn TE, Gasser T, Mai N, et al. Computational analysis of open loop handwriting movements in Parkinson's disease: a rapid method to detect dopamimetic effects. Mov Disord 1996;11:289–297
39. Hegerl U, Juckel G. Intensity dependence of auditory evoked potentials as indicator of central serotonergic neurotransmission: a new hypothesis. Biol Psychiatry 1993;33:173–187
40. Juckel G, Molnár M, Hegerl U, et al. Auditory evoked potentials as indicators of brain serotonergic activity: first evidence in cats. Biol Psychiatry 1997;41:1181–1195
41. Wald A. Sequential Analysis. New York, NY: Wiley; 1947
42. Kochman F, Ducrocq F, Parquet PJ. Efficacy of valproate/valpromide in ultra-rapid cycling bipolar disorders in children and adolescents [abstract]. Biol Psychiatry 1997;42:249S
43. Calabrese JR, Delucchi GA. Spectrum of efficacy of valproate in 55 patients with rapid-cycling bipolar disorder. Am J Psychiatry 1990;147: 431–434
44. Doerr P, von Zerrsen D, Fischler M, et al. Relationship between mood changes and adrenal cortical activity in a patient with 48-hour unipolar-depressive cycles. J Affect Disord 1979;1:93–104
45. Jenner FA, Gjessing LR, Cox JR, et al. A manic depressive psychotic with a persistent forty-eight hour cycle. Br J Psychiatry 1967;113:895–891
46. Bunney WE Jr, Hartmann EL, Mason JW. Study of a patient with 48-hour manic-depressive cycles, II: strong positive correlation between endocrine factors and manic defense patterns. Arch Gen Psychiatry 1965;12:619–625
47. Harding G, Jeavons PM, Jenner FA, et al. The electroencephalogram in three cases of periodic psychosis. Electroencephalogr Clin Neurophysiol 1966;21:59–66
48. Baker SC, Frith CD, Dolan RJ. The interaction between mood and cognitive function studied with PET. Psychol Med 1997;27:565–578
49. Dinan TG. Glucocorticoids and the genesis of depressive illness: a psychobiological model. Br J Psychiatry 1994;164:365–371
50. Kennedy SH, Tighe S, McVey G, et al. Melatonin and cortisol "switches" during mania, depression, and euthymia in a drug-free bipolar patient. J Nerv Ment Dis 1989;177:300–303
51. Joyce PR, Donald RA, Elder PA. Individual differences in plasma cortisol changes during mania and depression. J Affect Disord 1987;12:1–5
52. Cummings JL, Mendez MF. Secondary mania with focal cerebrovascular lesions. Am J Psychiatry 1984;141:1084–1087
53. McGilchrist I, Goldstein LH, Jadresic D, et al. Thalamo-frontal psychosis. Br J Psychiatry 1993;163:113–115
54. Starkstein SE, Fedoroff P, Berthier ML, et al. Manic-depressive and pure manic states after brain lesions. Biol Psychiatry 1991;29:149–158
55. Andersen P, Andersson SA. Physiological Basis of the Alpha Rhythm. New York, NY: Appleton Century Crofts; 1968