Impairment of the Production of Delta Sleep in Anorectic Adolescents

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Objective: Total sleep time and slow-wave sleep (SWS) are frequently reported to be reduced in anorectics. A preliminary study showed that slow-wave activity (SWA, 0.5-4.5 Hz) is decreased in anorectic adolescents. The present study investigates whether this reduction is the result of the increased sleep fragmentation or is dependent on an intrinsic weakness of SWA-producing mechanisms.

Design: Statistical analysis of spectral electroencephalogram data recorded during sleep from a group of anorectics and a control group.

Setting: Polysomnographic data were recorded in single rooms in the hospital for 1 night following an adaptation night.

Participants: 20 adolescent anorectic girls (13.9 ± 2.0 years) and 12 age-matched control subjects.

Interventions: Refeeding and psychotherapy.

Measurements and Results: Anorectics had an increase of wakefulness after sleep onset, a higher number of arousals, and a reduction of SWS and SWA during total sleep time. No relationship between the reduction of SWA and duration of illness was found, while a relationship between SWA decrease and the level of emaciation (body mass index) was present. The analysis limited to the first non-rapid eye movement sleep cycle did not show any difference between the 2 groups in the number of awakenings and arousals. Nevertheless, anorectics showed a reduction of SWS and SWA.

Conclusions: Sleep of anorectic patients seems to be characterized by an impairment of SWA-producing mechanisms independent of the increased sleep fragmentation. This is probably related to the primary pathophysiological characteristics of the illness but could also reflect secondary functional and anatomic alterations of the brain.

Key Words: anorexia nervosa, sleep, delta activity, arousals, depression

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INTRODUCTION

THE PRESENCE OF DEJECTION AND DESPAIR IN SUBJECTS WITH EATING DISORDERS LED RESEARCHERS TO INVESTIGATE THEIR SLEEP WITH THE AIM OF FINDING A POSSIBLE RELATIONSHIP BETWEEN AFFECTIVE AND EATING DISORDERS ON THE BASIS OF SIMILARITIES IN THEIR POLYSOMNOGRAPHIC PATTERN. Some authors have reported a shorter rapid eye movement (REM) latency in a population of anorectic patients.1 Their suggestion was to alert therapists to a possible lurking depression in subjects with eating disorders; sleep could be a means to facilitate the recognition of an affective disorder. However, further studies revealed that REM sleep parameters in anorectic and bulimic patients were largely indistinguishable from those found in age-matched healthy controls.2-4 The majority of studies regarding the polysomnographic characteristics of sleep in patients with anorexia nervosa report both qualitative and quantitative differences with respect to normal subjects: slow-wave sleep (SWS) is reduced, and parameters indicative of sleep instability and discontinuity, such as number of awakenings, wakefulness after sleep onset (WASO) and stage 1 sleep, are increased both in percentage and duration.5,9

In the last few years, it has been shown that sleep stages are insufficient to investigate in detail sleep features such as continuity and intensity. The application of techniques of computerized sleep electroencephalograph (EEG) analysis has revealed that non-REM (NREM) sleep stages represent an arbitrary subdivision of a continuous process. Delta activity, as measured by spectral analysis or period amplitude analysis,9 rather than SWS, is thought to be the parameter able to represent the major indicator of NREM sleep intensity. Slow-wave activity (SWA, 0.5-4.5 Hz) predominates in the first NREM sleep cycle, and it is homeostatically related to the quantity of prior wakefulness.10 In good sleepers, the waning of SWA is achieved progressively during successive cycles, thus indicating an optimum balance between the periodic prevalence of synchronizing mechanisms, leading to the production of SWA, whose strength declines during sleep, and desynchronizing ones (REM-inducing and wakefulness-inducing mechanisms) whose relative strength increases toward the end of sleep. A reduction of SWA may be interpreted as due to a strong sleep fragmentation, which is able to interfere with the dynamic build up of the synchronization processes, an intrinsic feebleness of the synchronization processes itself, or a deficit of accumulation of homeostatic pressure (process S1,2,3) during wakefulness preceding sleep.

In a preliminary study conducted in a small sample of anorectic subjects, SWA was found to be reduced with respect to control subjects.4 However the increase of WASO and of the number of awakenings detected in anorectic patients did not allow the authors to conclude whether the reduction of SWA was the consequence of the sleep fragmentation or if it was due to an intrinsic weakness of SWA-producing mechanisms.

Considering that SWS is chiefly gathered in the first cycle, while awakenings increase progressively toward the end of the sleep period, we have focused our analysis both on the total sleep time and on the first sleep cycle, extending our polysomnograph-
ic study to a larger group of anorectic adolescents. Since the standard staging rules do not highlight sleep fragmentation caused by transient arousals lasting only a few seconds, we also included a scoring of arousals as proposed by the American Academy of Sleep Medicine.\textsuperscript{14}

**PATIENTS AND METHODS**

**Sample**

The study included 20 consecutive patients (mean age ± SD = 13.9 ± 2.0 years) admitted to our hospital after a first clinical examination during which they were diagnosed with restricting type anorexia, following Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. Duration of the illness was 14.0 ± 10 months (range from 3-42 months) (Table 1). None of the patients had a concurrent major depression, anxiety, or other mental disorders; a psychiatric interview was conducted using a semistructured diagnostic interview (Kiddie-SADS-Present and Lifetime Version [K-SADS-PL]). Sleep examination was performed during the first week after admission. All patients, as based on history, were drug free for at least 2 weeks before sleep recordings; they also received no drug therapy during this period (the standard protocol for anorectic patients in our hospital was based on refeeding and psychotherapy). Twelve healthy adolescents (age ± SD = 14 ± 2 years) matched for age and sex, constituted the control group: they were selected from a pool of voluntary subjects, mainly coming from the authors’ families, for this and other studies (Table 2). Their history and psychiatric interview (obtained by 1 trained child psychologist [MS] using the Kiddie-SADS-Present and Lifetime Version) did not reveal any episode of sleep, eating, or mood disorder. None of them reported current sleep or other neurologic

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<th>Duration of the illness, months</th>
<th>Education</th>
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disturbances. Sleep examination of the control group was performed in the same conditions adopted for the patient sample.

The body mass index (BMI, kg/m²), which indicates the value of corpulence, was measured. We have expressed it in terms of the BMI corresponding to the 50th percentile because of the variation of its normal value in this age range. All patients were 69% ± 13% of expected BMI; controls were 106% ± 7.6% (Tables 1 and 2).

After a complete description of the study was provided to all subjects (both patients and controls) and their parents, written informed consent was obtained.

Sleep Recordings and Visual Scoring

Patients and controls were lodged and recorded in single rooms, adopting a standard sleep routine that did not allow more than 9 hours of nocturnal sleep, approximately from 10 PM to 7 AM, with small variations for the subjects’ usual sleep/wake rhythms (which were rated as normal). Sleep was recorded on tape during 2 consecutive nights with an ambulatory device (Brain Spy CH24, Micromed s.r.l., Treviso, Italy). The first night served for adaptation, while only the second night was considered for the study. Daytime naps were not permitted, and this was monitored by the hospital staff under the control of 1 author (EZ).

The EEGs were derived from C3-A2 and C4-A1. The low-pass filter was set to 40 Hz, while the high-pass filter was set to 0.5 Hz. The submental electromyogram and electrooculogram were also recorded. Data recorded on tape were digitized off line with a sampling rate of 128 Hz and a 0.78-µV resolution. Using a software for sleep analysis developed in our laboratory (Institute of Molecular Bioimaging and Physiology, CNR, Genoa, Italy and Center for Sleep Medicine, DISM, University of Genoa, Italy), digitized recordings were visually scored by a trained sleep neuropsychiologist (MGB), blinded to group condition, on computer monitor in 20-second epochs according to modified criteria of Rechtschaffen and Kales. Considering that traditional scoring criteria do not allow the assessment of transient arousals of short duration (less than 15 seconds), we integrated the standard scoring procedure with a microstructure analysis of sleep EEG, as suggested by the American Sleep Disorder Association. This analysis allowed us to individuate brief arousals (minimal duration of 3 seconds) characterized by abrupt changes in EEG frequency, which may include theta, alpha, and/or frequencies greater than 16 Hz but not spindles. Arousal were recognized automatically by a specific software program, then the whole recording was inspected in order to validate the arousal analysis and individuate and mark EEG segments containing artifacts. The number of arousals in the first NREM sleep cycle and the arousal index (number of arousals per hour) in total sleep time was calculated. The first NREM sleep cycle was defined from sleep onset (the first consecutive minute of stage 2 sleep) to the beginning of the first REM episode. Scoring data were stored in the computer linked to the traces, hence power spectra and scoring of the recordings were automatically synchronized.

Power Spectral Analysis

Digitized EEG derived from C3-A2 was assessed by a fast Fourier transform for consecutive 2-second epochs (decimation in frequency fast Fourier transform algorithm, Sande-Tukey; Tukey window tapering). The resulting spectra were averaged every minute. Power spectra were divided into spectral segments corresponding to 0.5 to 4.5, 5.0 to 7.5, 8.0 to 12.0, 12.5 to 16.0,
The EEG segments containing wakefulness, arousals and other artifacts (as recognized by our software and confirmed by a subsequent visual inspection) were carefully discarded.

Statistics

Total Recording Period

The main objective of this study was to verify the differences in SWA between patients and controls. Data derived from spectral analysis were compared by means of univariate analysis of variance with or without repeated measures between diagnostic groups, performed for each frequency band. Statistical analysis was performed on log-transformed data of absolute power values. The Spearman correlation coefficient was used to examine the relationship between SWA and BMI and between SWA and duration of the illness within the patient group: this nonparametric test for correlation was chosen in order to avoid strict assumptions about underlying data distribution. The significance level for the rejection of the null hypothesis was set to .01 to take into account the multiplicity of tests. However, the analysis was also extended to conventional sleep parameters, in order to describe the global trend of data during the total recording period: differences between patients and controls were expressed as t values and associate probability levels.

First Cycle

Differences between sleep parameters were evaluated as for the whole night. Concerning spectral analysis, we considered the temporal evolution of SWA during the first NREM sleep cycle. In order to combine meaningful data from all recordings, the time was standardized with reference to the length of the first NREM episode. The duration of the first NREM episode was set to 100 for each subject, each episode was divided into 10 equal bins, and the averaged power was calculated for each bin. The standardized time-scale transformation involved a linear transformation that did not affect the shape of power evolution within each episode. The hypothesis of significant differences in the temporal evolution of SWA within the first NREM sleep cycle was tested by means of a 2-factor analysis of variance with bins and group (anorectics and controls) as factors.

RESULTS

Total Recording Period

The time of sleep onset and of sleep end was not different in the 2 groups. Anorectic patients showed an increased number of awakenings, a higher arousal index, and more WASO, as well as decreased SWS (both in percentage and duration). A reduction of REM latency, although not statistically significant (P < .07), was present (Table 3).

Anorectics showed an overall reduction in the spectral power values, statistically significant for SWA (F1,30 = 8.5, P < .001) and theta activity (F1,30 = 7.6, P < .01) (Figure 1). In the patient group, no correlation between SWA and illness duration was found, while a correlation between SWA and BMI was present (Spearman R18 = 0.56, P < .01).

Figure 1—Electroencephalogram spectral power values for each consecutive frequency bin (mean values and SEM). Values of anorectics are expressed as percentage of control subject mean values (anorectics, continuous lines; controls, dotted lines). Anorectics showed a significant reduction in the spectral power values of slow-wave activity and theta activity.

Table 3—Sleep stages during nocturnal sleep in anorectics and controls

<table>
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<tr>
<th></th>
<th>Anorectics</th>
<th>Controls</th>
<th>P values</th>
</tr>
</thead>
<tbody>
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<td>REM latency, min</td>
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<td>95.0 (30.2)</td>
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</tr>
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<td>Awakenings, no.</td>
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<td>0.2 (0.40)</td>
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<tr>
<td>AI/TST, no.</td>
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<td>&lt; .001</td>
</tr>
<tr>
<td>WASO, min</td>
<td>60.1 (48.5)</td>
<td>2.1 (4.1)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>TST, min</td>
<td>425.8 (69.2)</td>
<td>467.4 (31.1)</td>
<td>NS</td>
</tr>
<tr>
<td>S1, min</td>
<td>34.2 (26.4)</td>
<td>8.0 (4.2)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>S2, min</td>
<td>194 (53.7)</td>
<td>196.1 (27.1)</td>
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<tr>
<td>SWS, min</td>
<td>88.2 (21.1)</td>
<td>145.2 (26.4)</td>
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<tr>
<td>REM, min</td>
<td>115.4 (58.8)</td>
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<td>NS</td>
</tr>
<tr>
<td>S1, %</td>
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<tr>
<td>S2, %</td>
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<td>REM %</td>
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</tr>
<tr>
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<td>06:45 AM (27 min)</td>
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Data are presented as mean (SD) Percentages of sleep stages are referred to total sleep time (TST). REM refers to rapid eye movement; AI, arousal index; S, sleep stage; WASO, wake after sleep onset; S, sleep stage; SWS, slow-wave sleep (stage 3+4).
First Cycle

No differences were found between the 2 groups for the amount of stage 1, stage 2, WASO, and the number of arousals. The SWS was significantly reduced in anorectic patients (Table 4). The analysis of the temporal evolution of SWA within the first NREM sleep cycle revealed a significant effect of group (F_{1,300} = 213.3, P < .001) and time (F_{9,300} = 78.8, P < .001) and of their interaction (F_{9,300} = 9.99, P < .001). Control subjects reached and maintained higher levels of SWA, as compared with anorectic subjects (Figure 2).

DISCUSSION

The analysis of sleep parameters referred to the total recording period indicates both qualitative and quantitative differences in sleep structure between anorectics and controls. SWS is heavily reduced, and parameters indicative of sleep discontinuity, such as number of awakenings, arousals, and WASO, are increased, thus indicating an impaired sleep soundness. These results confirm our previous findings in a smaller population of anorectics\(^4\) and are in accordance with other previously published studies.\(^7,9\) As for REM latency, anorectic patients showed a reduced REM latency that was in nearly significant at conventional statistical levels. The partial overlapping of these results with those regarding depressed patients underlines the difficulties in separating and defining the 2 groups.

Previously published data have reported that, once the comorbidity with depression has been ruled out, there is no evidence indicative of a significant shortening of this parameter in anorectic patients.\(^3,4,20,21\) However, it must be stressed that, although our interview could not rule out mood differences between the groups that were below the criteria levels. Overall EEG power, and especially mean SWA values and theta frequency power values during the total recording period, were reduced in anorectic patients. SWA has also been shown to be reduced in depressed patients.\(^10\)

The analysis of sleep parameters referred to the first NREM cycle showed a reduction of SWS in anorectic subjects, though no differences in regard to the number of arousals, awakenings, and WASO were found. Nevertheless, the analysis of the temporal course of SWA within the first NREM sleep cycle revealed a reduction of SWA in anorectics. The development of deep sleep is considered to result from organized neural processes underlying EEG microstructural fluctuations during the transition from light to synchronized sleep.\(^22\) A high level of EEG synchrony (lower frequencies with higher amplitudes) is associated with a lower level of arousal. High levels of desynchronizing mechanisms, reflected by an increase of awakenings and arousals, can reduce the level of delta activity production, as has been demonstrated in several sleep disorders such as periodic limb movement disorder and obstructive sleep apnea.\(^17\)

Our results suggest that the mechanisms underlying sleep intensity are affected in this pathology and give evidence of an intrinsic weakness of EEG-generation mechanisms and, particularly, of SWA-producing ones in anorectic patients. A reduction of SWA, or delta activity as measured by period amplitude techniques, has been found in different psychiatric diseases such as depression and schizophrenia.\(^10,23-27\) In depressed patients, the low level of SWA during sleep has been interpreted as the consequence of a reduction of process S accumulation during wakefulness.\(^28\) This interpretation seems to be supported by the observation that the deficiency in SWA is not dependent on an increase in the number of awakenings during sleep.\(^25\) As for this point, anorectic patients seem to differ from depressed ones. In fact, it is unlikely that the decrease of SWA occurs as a consequence of a reduced accumulation of sleep pressure due to the presence of naps. In our study, this possibility can be ruled out for the days spent in the hospital because the continuous monitoring of the EEG and the patient behavior during the day excluded the presence of naps. Instead, a long-term influence of particular sleep/wake and nap patterns cannot be excluded due to a limitation of our study, that is, the lack of an in-depth control of the of patients during the 2 weeks prior to hospitalization.

The integrity of the thalamocortical and cortical circuitry is essential for SWA production. In schizophrenia, a reduction of thalamic volume\(^29\) and synaptic density\(^30\) have been proposed to explain the reduction of delta production during sleep.\(^31\) Moreover, with the aid of magnetic resonance spectroscopy, an association between decreased brain anabolic processes and decreased SWS has been observed in psychotic patients.\(^27\) These findings have been interpreted as the result of an accelerated aging of the brain in these patients or as a consequence of alterations in cortical synaptic development presumed to underlie the pathophysiology of functional psychoses, although the age differences make the analogies with our patients at least debatable.

A reduction of cerebral metabolism both during wake and sleep could express itself with a decrease of SWA production during

![Figure 2](image-url)
sleep. SWS is believed to be the EEG correlate of the thalamocortical and cortical neuron activity that exhibits fluctuations in the membrane potential in the slow-frequency range during NREM sleep. Anorexia nervosa is characterized by both serious psychiatric symptoms and organic alterations, and the attribution of the SWA deficit to 1 of these factors is difficult. We believe that the reduction of SWA found in anorectic adolescents could reflect both functional and anatomic alterations of the brain of these patients.

Functional investigations and morphologic analysis of the anorectic brain have reported subcortical and brain hypometabolism of glucose and cortical and subcortical pseudoatrophy, respectively. Such alterations seem to be only partially reversible after weight gain. Clinical data seem to support the hypothesis of a strong relationship between SWS integrity and state of nutrition. Although the significance of these morphologic and functional alterations of the brain in anorectic patients is still unclear, different pathogenic mechanisms can be proposed: inhibition of brain protein biosynthesis, hypercortisolism (commonly associated with anorexia nervosa) causing cerebral dehydration and atrophy, or direct brain damage. Moreover, estrogen deficiency, a condition peculiar to anorectic girls, is known to produce a remarkable deficit of SWA, though it is reversible with a replacement therapy. However no correlation, but simply an association, can be demonstrated between the severity of the anorexia and modification of the above parameters; on the contrary, our data demonstrate a correlation between SWA reduction and BMI, which could be considered as an indirect indicator of the organic severity of this pathology, thus indicating that the reduction of SWA could depend at least partially on the level of emaciation. On the other hand, the lack of a relationship between SWA and duration of the illness suggests that the reduction of SWA could also be a feature primary to anorexia nervosa. To our knowledge, this is the first demonstration of a significant correlation between a biologic parameter and the severity of anorexia nervosa.

In conclusion, our results suggest that, independent from the presence of perturbing factors, such as awakenings and arousals, the sleep of anorectic patients is characterized by an impairment of delta sleep production. Such an impairment, frequently found in other psychiatric disorders, seems to be in part primary to the psychiatric illness and in part dependent on the neurologic implications of the state of malnutrition: this hypothesis should be verified by studying the correlation between clinical remission and EEG after refeeding. Such a study has never been carried out and is being currently planned by our group.

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