Restless Legs Syndrome: Changes of Induced Electroencephalographic Beta Oscillations—an ERD/ERS Study

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Study Objectives: Primary or idiopathic restless legs syndrome (RLS) is a sensorimotor disorder of unknown neurophysiologic origin.

Setting and Patients: Ten patients with RLS and 10 healthy control subjects were investigated. Postmovement beta oscillations (event-related synchronization, ERS) induced by movement of the right index finger were measured by electroencephalography and analyzed.

Results: We found differences between patients and controls for ERS values at electrode positions C3 and Cz. At C3, the lower beta band ERS (14-20 Hz) in the RLS group was 101.2% compared with 27.5% in the control group (P < .05); in the upper beta band, (20-32 Hz) the findings were 97.8% and 29.0% , respectively, for the RLS and control groups (P < .01). At electrode Cz, no significant difference could be found in the lower beta band, but, for the upper beta band, patients showed significantly higher values than did the healthy control subjects (68.5% vs 25.6%, P < .05).

Conclusions: We interpret these findings as a higher need for motor-cortical inhibition in RLS patients due to an increased level of excitation by motor-cortex activation and input from neighboring functionally interrelated cortical areas (hand and foot region). These results reveal new potentially important findings of the neurophysiologic and pathophysiologic origin of primary RLS.

Key Words: Restless legs syndrome, ERD, ERS, electroencephalography, neurophysiologic/ pathophysiologic origin, pathogenesis

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INTRODUCTION

RESTLESS LEGS SYNDROME (RLS) IS A SENSORIMOTOR DISORDER CHARACTERIZED BY UNPLEASANT CREEPING SENSATIONS IN THE LEGS ASSOCIATED WITH AN IRRESISTIBLE NEED TO MOVE THE LIMBS. It is worse while the affected individual lying down or trying to sleep. The symptoms can be at least partially relieved by moving the limbs.[1,2] Restless legs syndrome is associated in up to 80% of patients with spontaneous periodic limb movements in sleep (PLMS).[3] Restless legs syndrome can be idiopathic (primary RLS) or due to a large variability of conditions or disorders.[4] Primary RLS is associated with a positive family history in up to 60% of cases (transmitted as an autosomal-dominant trait). The diagnosis is based on the exclusion of all possible conditions known to be associated with RLS.[1]

The neurophysiologic and pathophysiologic origin of primary RLS is still unclear. The absence of cortical prepotentials on back-averaging, normal electroencephalogram (EEG) findings[5,6] and an abnormal hyperexcitability along the entire spinal cord[7] argue against the hypothesis of motor-cortical involvement. On the other hand, there is evidence of motor-cortex disinhibition, as suggested by reduced intracortical inhibition[8-10] or an impairment of cortical-subcortical motor structures—in particular of motor-inhibitory pathways,[11]—which supports a cortical origin of primary RLS.

The dynamic behavior of brain oscillatory activity in the EEG at central electrode positions (overlaying the motor-representation areas) is known to be closely related to the states of activation and deactivation of motor-system-neuron populations.[12] Systematic power changes of specific EEG rhythms are defined as event-related desynchronization (ERD) and event-related synchronization (ERS), and an ERD and/or ERS time course describes the changes of signal power within a predefined frequency band over time, relative to a reverence value obtained from the baseline interval.[13] For a brisk hand movement, a typical pattern of ERD and/or ERS can be found over the primary-hand representation area of the contralateral hemisphere. Shortly before and during the execution of the movement, an ERD occurs in the alpha and beta frequency bands for most subjects, and an ERS in the beta frequency range can be expected with a maximum within-1-second after-movement offset. Hand or finger movements are especially suitable for EEG-based motor-system investigations because the relatively large primary-hand representation areas are localized at the top of the rolandic gyrus (area M1), which leads to clear signals. It has been shown that finger movements can also induce specific responses in neighboring interrelated cortical areas like the foot representation area[14] or the supplementary motor area (SMA). This activity is characterized by a differing frequency behavior and invites the investigation of the excitability of cortical neural networks without their direct activation (eg, by foot movements).

Coexistence of reduced excitability of corticospinal neurons with induced beta oscillations as an example of ERS was shown by Chen and

Table 1—Demographic data and history of patients with restless legs syndrome.

Patient	Age, y	Sex	RLS duration, y	Handedness	Family history*
1	40	Woman	10	R	+
2	59	Woman	5	R	+
3	63	Woman	11	R	
4	44	Man	7	R	
5	55	Woman	5	R	
6	29	Woman	10	R	+
7	32	Woman	3	R	
8	34	Man	2	R	
9	24	Man	11	R	
10	66	Man	3	R	+
Mean					
RLS patients	45.5		6.7		
Controls (n, 10)	46.3	4 men; 6 women		R	

*+ refers to positive family history of restless legs syndrome; R, right handed; L, left handed

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Hallett.[15] It is reported to occur in EEG[16-18] and magnetoencephalogram[19] centered within the first second after movement offset. This postmovement beta ERS is of peculiar interest because it shows further interesting features such as somatotopic specificity and origin in the primary motor cortex.[20]

The purpose of the present investigation was to gain further pathophysiologic insights into the motor-cortical involvement in primary RLS. We hypothesize that patients with primary RLS have an increased motor-system excitability that could possibly be reflected by altered ERS.

PATIENTS AND METHODS

Patients

Ten right-handed patients suffering from primary RLS (4 men, 6 women; mean age, 45.5 years) and a sex- and age-matched group of 10 healthy volunteers as controls (mean age, 46.3 years) participated in this study (Table 1). The diagnosis of primary RLS was made according to the International RLS Study Group guidelines.[1] In all patients, the laboratory findings—including blood glucose, serum levels of creatinine, iron/ferritin, thyroid hormones, magnesium, vitamin B12 and folate—were within the normal limits. We performed an electrophysiologic examination and a spinal magnetic resonance imaging study in each patient to exclude peripheral neuropathy, focal radiculopathy, or mononeuropathy of the legs. Medical history and neurologic examination excluded patients with a history of drug or alcohol abuse. None of the patients had ever received medication known to affect the dopaminergic and GABAergic system before the EEG examination. Four patients had a positive family history of RLS.

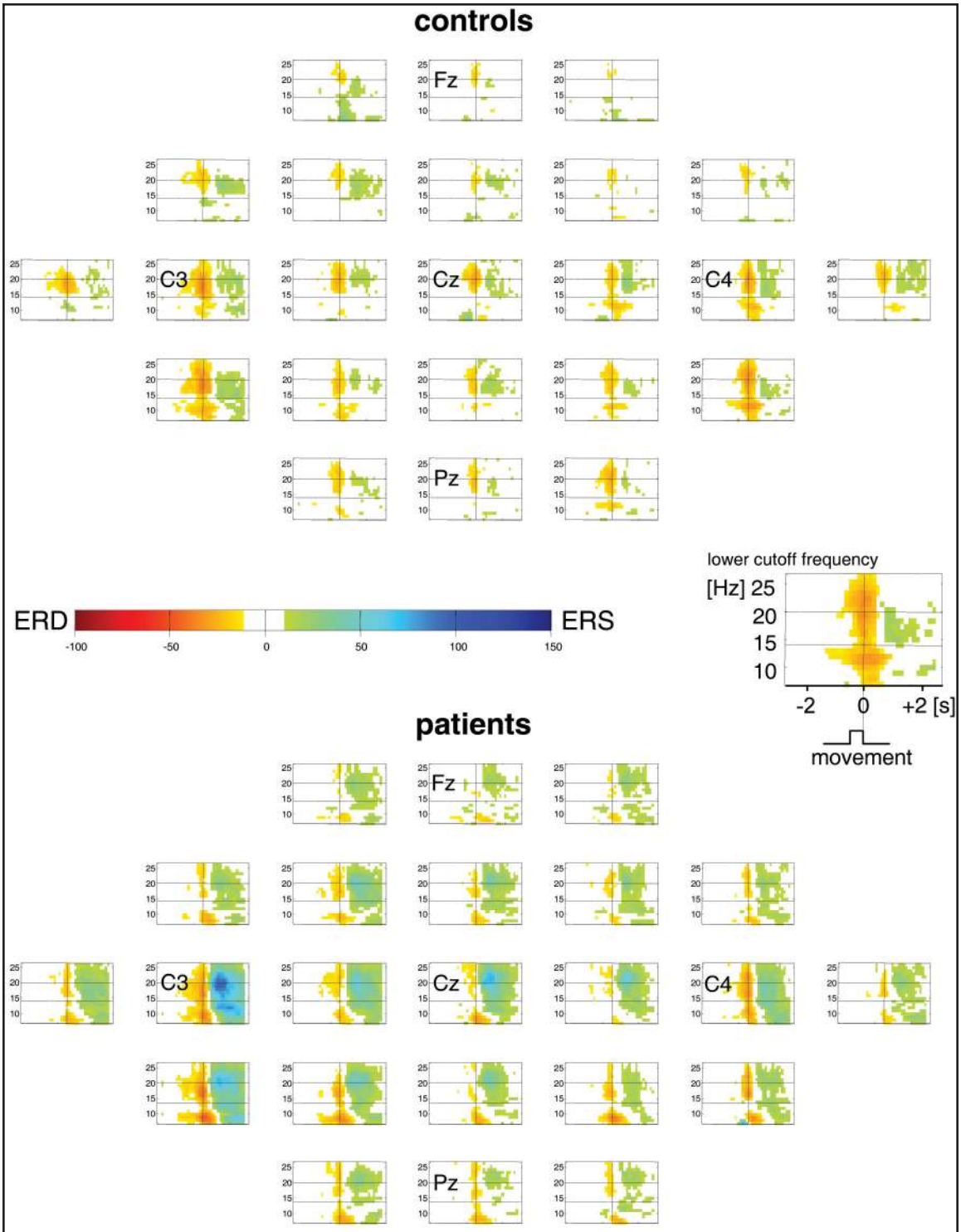

Figure 1—Time-frequency maps of event-related desynchronization (ERD) and/or event-related synchronization (ERS) averaged for controls and patients with restless legs syndrome, respectively. Values between +10% and -10% are not presented (white). Y- scale ticks mark lower cut-off values of corresponding frequency bands. The patient group shows a stronger postmovement ERS, in general, compared to the controls. At electrodes C3 and Cz, this differences occur most prominently.

Electroencephalogram Recordings

The EEG signals were recorded from a grid of 23 Ag/AgCl electrodes referenced to the left mastoid overlying frontal, central, and parietal regions. The regular interelectrode distance was 4 cm and electrode impedances were kept below 5 kOhm. Signals were hardware filtered between 0.5 and 70 Hz, sampled at 256 Hz, and stored together with movement-trigger onsets and offsets.

Experimental Paradigm

Subjects were sitting in a comfortable chair and told to keep their eyes open during the experiment. The task to perform was carefully explained to them, and a few movements were learned before starting. Responding to a "click" appearing in intervals of about 6 seconds, subjects had to perform a brisk movement of the right

index finger, namely to press a microswitch. The finger was resting on the switch between movements. To avoid stress, subjects were expressly told that there was no speed condition and that this was not a reaction-time experiment. Movements and recorded data were monitored by a technical assistant during the recording session. About 100 finger movements were performed by each subject.

Signal Processing and Analysis

Raw data were digitally filtered to a pass band from 3 to 32 Hz (Butterworth IIR-filter, fifth order) and triggered, leading to trials of 5 seconds in length (2.5 seconds before and 2.5 seconds after movement offset). To obtain reference-free data, the local average reference derivation[21] was calculated, and trials containing muscle or ocular activity were visually detected and excluded from further analysis. A lower beta band (14-20 Hz) and an upper beta band (20-32 Hz) were chosen to calculate beta ERD and/or ERS,[22] resulting in time courses of band-power changes, relative to the band power in a reference period (from second 0.2 to 1.2 of each trial). In contrast to the selection of subject-specific frequency bands,[23] we chose fixed bands as the more objective method for the clinical approach. The selection of individual bands often appears quite difficult, especially in the case of low reactivity or multiple peaks in the spectra. For computation of ERD and/or ERS a fast Fourier transform filter was used.[13]

Table 2— Mean values of event-related desynchronization and (event-related synchronization) values for lower and upper beta-frequency bands and electrode positions C3 and Cz

Variable	Control, %	Patients, %	*P* value*
ERD C3 (14-20 Hz)	- 36.4	- 38.4	.824
ERD Cz (14-20 Hz)	- 18.2	- 24.0	.262
ERD C3 (20-32 Hz)	- 31.0	- 29.7	.866
ERD Cz (20-32 Hz)	- 24.4	- 22.2	.798
ERS C3 (14-20 Hz)	27.5	101.2	.026
ERS Cz (14-20 Hz)	28.8	47.5	.251
ERS C3 (20-32 Hz)	29.0	97.8	.010
ERS Cz (20-32 Hz)	25.6	68.5	.027

ERD refers to event-related desynchronization; ERS, event-related synchronization
*Between-group comparisons (analysis of variance) for each of the dependent variables. Statistically significant differences were found for both frequency bands at C3 and for the upper-beta band at electrode Cz.

Statistics

The ERD and/or ERS time courses were time averaged to obtain 4 data points per second. The results for electrode C3 (primary sensorimotor hand area) and electrode Cz (primary sensorimotor foot area and SMA [proper]) of both beta bands were used for statistical comparison between experimental groups by use of analysis of variance (ANOVA). The following variables were used: ERD (the lowest value of the ERD and/or ERS time course within the interval from -750 milliseconds to +250 milliseconds in relation to movement offset) and ERS (the highest value between +250 milliseconds and +1250 milliseconds after movement offset). Additionally, the average absolute band power within the reference period was compared between groups for electrode positions and frequency bands by ANOVA (Table 2).

RESULTS

For the reference power values, no statistically significant differences between groups (controls vs RLS patients) were found at electrode C3 and Cz for both beta bands (ANOVA test). This finding rules out differences in percentage of ERD and/or ERS values due to different reference power values. Similarly, the ERD values did not show any group differences for any of the electrode positions and frequency bands. However, significant differences between groups were found for ERS values. At C3, the lower beta ERS was stronger in the RLS group than in controls (101.2% vs 27.5%, P = .026). In the upper beta band, a more pronounced ERS at C3 was found for RLS patients (97.8%) than for the control group (29.0%, P = .010). At electrode Cz, the lower beta band ERS did not significantly differ between groups, but in the upper frequency band, patients had higher values (68.5%) than did healthy subjects (25.6%, P = .027) (Figures 1 and 2). The numbers of artifact-free trials for patients (mean = 80.5) and controls (mean = 84.7) did not show a significant difference.

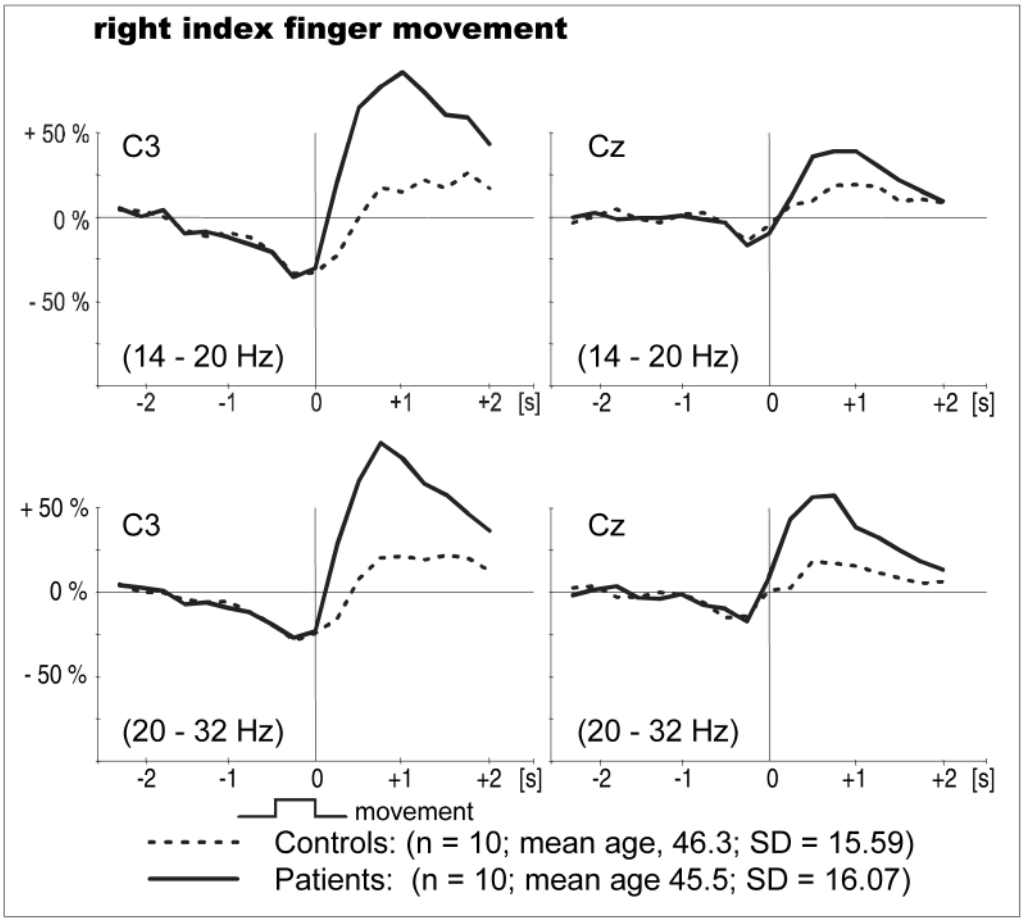

Figure 2—Event-related desynchronization (ERD) and/or event-related synchronization (ERS) curves averaged for controls (dashed line) and patients with restless legs syndrome (black continuous line), respectively. Movement ERD values are quite similar for both groups, but the RLS group shows a more prominent postmovement ERS. At electrode C3, these differences are statistically significant for both beta bands (lower beta band 14-20 Hz, upper beta band 20-32 Hz), but at Cz, this was the case only for the upper beta-frequency band.

DISCUSSION

In this study, it is of particular interest that a significant difference between patients with primary RLS and age-matched controls was found only in the post–movement- induced

beta oscillations (beta ERS) and not in the premovement desynchronization (ERD). This can be interpreted that the preparatory phase before movement onset is not significantly altered by RLS; however, the recovering phase after termination of the movement is affected and accompanied by enhanced magnitudes of induced beta oscillations. One explanation of the increased beta ERS in patients with primary RLS could be that in these patients, due to an increased motorcortex excitability,[8] a larger postmovement inhibition is also present. Such a relationship between a reduced cortical excitability level (inhibition) and the beta ERS was postulated by Chen et al in 1999.[15] In other words, the resetting of the cortical activation in patients with primary RLS needs more inhibition and, therefore, induces stronger beta oscillations.

Remarkable is also the significantly larger beta ERS in the 20 to 24 Hz band at electrode position Cz in the patient group as compared with the control group. Recent studies have shown that reactive peak frequencies for the midcentral region are usually above 20 Hz but are between 16 and 20 Hz for the hand region.[14] The electrode position Cz overlays not only the primary foot representation area but also the SMA. Both areas are in close proximity to and located in the mesial side of both hemispheres. There is increasing evidence that the induced beta oscillations at the electrode position Cz may originate in the SMA. Ohara et al[24] reported on a beta ERD followed by a beta ERS in electrocorticogram recordings from the SMA, and Kaiser et al[25] demonstrated the occurrence of 22- to 28-Hz oscillations in the SMA during self-paced movement. The increased midcentral localized beta ERS underlies perhaps an increased involvement of the foot representation area and/or the SMA in patients with primary RLS compared to controls.

Thus, we interpret our present findings of an increased midcentral beta ERS as a higher need for cortical inhibition in patients with primary RLS due to an increased excitation of midcentral areas by input from neighboring functionally interrelated cortical areas.

Because of the small group size, caution is necessary in the interpretation of these results. In general, the postmovement beta ERS is found in only about 80% of subjects (personal communication, Pfurtscheller). In a similar study on patients with idiopathic Parkinson disease,[26] the control group showed a higher beta ERS in comparison to the control group in the present study. Possible reasons for this could be the slightly different experimental paradigm (self-paced button pressing with the thumb vs stimulus-paced button pressing with the index finger) and the different mean age between the groups (62 vs 46 years).

In conclusion, it can be stated, that the use of EEG reactivity measurements with quantification of induced beta oscillations offers a new tool to investigate cortical-excitability levels on a below-1-second time scale and may, therefore, be suitable to obtain a better insight in the neurophysiologic and pathophysiologic origin of primary RLS.

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