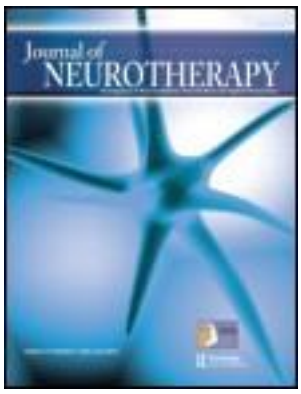

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Neurofeedback Treatment of Restless Legs Syndrome and Periodic Leg Movements in Sleep

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NEUROFEEDBACK TREATMENT OF RESTLESS LEGS SYNDROME AND PERIODIC LEG MOVEMENTS IN SLEEP

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Restless leg syndrome (RLS) and periodic limb movements in sleep (PLMS) are prevalent and chronic movement disorders that result in sleep deprivation and impaired quality of life. Although there is no single pathophysiological explanation, EEG studies commonly implicate alpha activity as being involved. This article presents the first case reports of the treatment of RLS and PLMS with neurofeedback (EEG biofeedback). The encouraging results warrant further controlled research.

INTRODUCTION

Restless leg syndrome (RLS) was perhaps first noted by Willis (1672) and began being studied in the 1940's (Ekbom, 1945). Although long ignored, RLS has been documented to be common (Hening et al., 2004; Lavigne & Montplaisir, 1994; Phillips et al., 2000; Rothdach, Trenkwalder, Haberstock, Keil, & Berger, 2000) and to have a very aversive impact on quality of life (Montplaisir, Walters, Allen, & Hening, 2003; Reimer & Flemons, 2003). RLS is different from periodic limb movements in sleep (PLMS), but the two conditions overlap.

In RLS there are uncomfortable leg sensations prior to falling asleep and during sleep, causing an almost irresistible urge to move the legs (American Academy of Sleep Medicine, 2005). PLMS is associated with periodic episodes of repetitive and very stereotyped limb movements that occur during sleep (mostly NREM sleep; Allen et al., 2003; American Academy of Sleep Medicine, 2005). A large epidemiological study evaluating the simultaneous presence of PLMS and sleep complaints found a 3.9% prevalence in 18,980 persons from the general population between age 15 and 100 (Ohayon & Roth, 2002), although other estimates of prevalence have ranged from 5 to 20% (Allen et al., 2003). Reviews of these conditions have been published by Allen and Earley (2001), Chokroverty, Hening, and Walters (2003), and Hening (2002).

Most patients with RLS also suffer with PLMS (Lugaresi, Cirignotta, Coccagna, & Montagna, 1986), although one can exist without the other. Periodic leg movements (PLM) are short-lasting movements of the arms or legs occurring every 20 to 40 s (Coleman, 1982) during sleep and wakefulness. They are present in 86% of patients suffering from RLS (Montplaisir et al., 1997). Allen et al. (2003) presented the findings of a National Institutes of Health consensus conference that RLS is a condition occurring in cognitively intact adults with complaints of four major symptoms: (a) an urge to move, associated with abnormal sensation; (b) symptoms induced or aggravated by rest; (c) relief that occurs with activity; and (d) intensification in the latter part of the normal day or evening. Research has found a genuine circadian fluctuation of symptoms (Hening et al., 1999; Trenkwalder et al., 1999), and the arms as well as the legs can be involved (Michaud, Chabli, Lavigne, & Montplaisir, 2000), as well as occasionally other parts of the body.

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RLS and PLMS are generally considered chronic conditions (Allen & Earley, 2000). One third of patients in one study (Walters et al., 1996) had an onset of symptoms before the age of 10. Depression and anxiety are not an uncommonly result from the chronic sleep debt (Lustberg & Reynolds, 2000; Neckelmann, Mykletun, & Dahl, 2007; Picchietti & Winkelman, 2005; Saletu et al., 2002).

These conditions are considered to be associated with a heterogeneity of causes (Trenkwalder & Paulus, 2004) with no single pathophysiological explanation accounting for all the features. For example, problems have been found with functioning of the thalamus, brainstem (Etgen et al., 2005), cerebellum (Bucher, Seelos, Oertel, Reiser, & Trankwalder, 1997), and motor cortex. It has been found that iron metabolism abnormalities play a role in the pathophysiology of RLS (Allen & Earley, 2001), and a lower level of iron in brain tissue has been found in human (Connor, Boyer, & Menzies, 2003) and animal studies (Roskams & Connor, 1994), although large individual differences exist in iron concentrations in the brain, even in the absence of neurological conditions (Jellen, Beard, & Jones, 2009). This may be due to impaired regulation of transferring receptors, which may indirectly affect the dopamine system, and some relief from RLS has been found with dopaminergic drugs, whereas in contrast it becomes worse when dopamine antagonists are given (Stiasny, Oertel, & Trenkwalder, 2002). Genetics have also been clearly implicated (Gasser, Winkelman, & Dichgons, 2003), particularly related to the dopamine receptor system, and in one survey more than 50% of patients knew of one or more first-degree relatives affected by RLS (Walters et al., 1996). An increased incidence of RLS has been found in patients with uremia (Hui et al., 2002; Winkelman, Chertow, & Lazarus, 1996), ADHD (Walters, Silvestri, Zucconi, Chandrashekariah, & Konofal, 2008), pregnancy, diabetes, rheumatoid arthritis, and polyneuropathy (O'Keeffe, 1996).

Cyclic arousals associated with alpha activity appear to commonly be present (Akpinar, Aydin, & Kutukcu, 2007; Taher, Jones, Singleton, Meekins, & Smith, 1999), which make it difficult for the brain to shift into deep delta sleep. This alpha intrusion into sleep prevents patients from obtaining enough stage 3 and stage 4 sleep, resulting in sleep deprivation. This problem suggests a dysfunction of thalamic alpha generators. Thus, there appears to be a complex dynamic interaction between cortical and subcortical mechanisms in RLS and PLM. One study (Schober et al., 2004) found RLS patients had far greater event-related synchronization in 14–20 Hz and 20–32 Hz frequencies in central areas compared with healthy control subjects. They interpreted this finding 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 cortical areas controlling the hand and feet. One EEG study (Trenkwalder et al., 1993) did not find cortical potentials prior to periodic leg movements during the daytime, which was interpreted as supporting that restless leg movements were involuntary and associated with a subcortical origin.

In summary, PLMS/RLS is a complex movement disorder with involvement of subcortical and cortical areas of the brain, the dopamine system (although the etiology appears different than what is found with Parkinson's disease), and impaired iron metabolism (which is likely indirectly affecting the dopamine system).

Treatments for RLS and PLM

The primary treatments for these conditions (Trenkwalder et al., 2008) are primarily medications. Those considered most efficacious are levodopa, ropinirole, pramipexole, cabergoline, pergolide, and gabapentin. Clonazepam does not have good research evidence of effectiveness, but has been compared with cognitive behavioral therapy (Edinger et al., 1996). They produced equal improvements in measures of sleep–wake times, but clonazepam produced greater declines in PLM arousals per hour. Exercise is considered investigational as are folic acid, magnesium, oral iron, and many other medications (Trenkwalder et al., 2008).

Neurofeedback has been found to influence the sleep EEG, for example, increasing sleep spindles and reducing sleep latency through reinforcing the sensorimotor rhythm (e.g., Berner, Schabus, Wienerroither, & Klimesch, 2006; Hammer, Colbert, Brown, & Ilioi, 2011; Hoedlmoser et al., 2008; Sterman, 2000; Sterman, Howe, & MacDonald, 1970). Therefore, when two patients inquired about possible neurofeedback treatment for RLS and PLM, it was presented to them as an experimental option and informed consent was obtained. This article presents the first two published cases of the use of neurofeedback in the treatment of RLS and PLM.

CASE 1

Joe was a 45-year-old man who had an onset of RLS more than 20 years previously. It had been diagnosed with a sleep lab evaluation, and he also suffered with PLM. The severity of his conditions had been worse in the past 12 years. He estimated that he only obtained 5 hr of sleep nightly. His symptoms were severe enough that every 60 min he would have to get out of bed and would do leg lift exercises and push-ups before returning to bed. His condition had resulted in depression, which he said at times reached 6 or 7 (on a 0–10 scale where 0 represented feeling no depression and 10 represented being ready to commit suicide), but averaged a 5. He said that he felt that he could not endure the RLS and PLM any longer and rated the severity of these symptoms a 10. He indicated that he was having a migraine an average of once a week. He also rated problems with anxiety as a 5 and with being withdrawn from others an 8. He was taking no medications.

Vigilance-controlled EEG was digitally recorded from the patient with recording electrodes placed according to the 19 standard regions defined by the International 10/20 System of electrode placement, referenced to linked ears. All electrode impedance levels were below 2 KOhms, with no interelectrode differences of more than 500 ohms, and ear references that were balanced. The recordings were of good quality, and the eyes-open and eyes-closed EEG was edited to reduce artifact and then the digitally stored EEG was subjected to quantitative spectral analysis. From 10 min of eyes-closed data, 2 min 19 s of artifact-free data were analyzed, and from 6 min 23 s of eyes-open data, 2 min 5 s of eyes-open data were analyzed. The results of spectral analysis from 1–32 Hz were displayed as computed color-graduated topographic maps and compared via a *Z*-score transformation to a database of normal subjects, the FDA registered NeuroGuide QEEG database. Split-half reliability of eyes-closed and eyes-open data were .99, and test–retest reliability was .95 and .96. Figure 1 displays a Laplacian analysis of the eyes-closed data. Eyes-open data were comparable. Absolute power excesses were seen in alpha (primarily 9–12 Hz) and beta frequency bands with the alpha excess localizing centrally, and the excess beta and high activity (the latter is not seen in Figure 1) along the midline (Cz-Pz).

Treatment consisted solely of using the Low Energy Neurofeedback System (LENS) (Hammond, 2007; Larsen, 2006; Ochs, 2006). LENS is a distinctive and passive form of neurofeedback that produces its effects

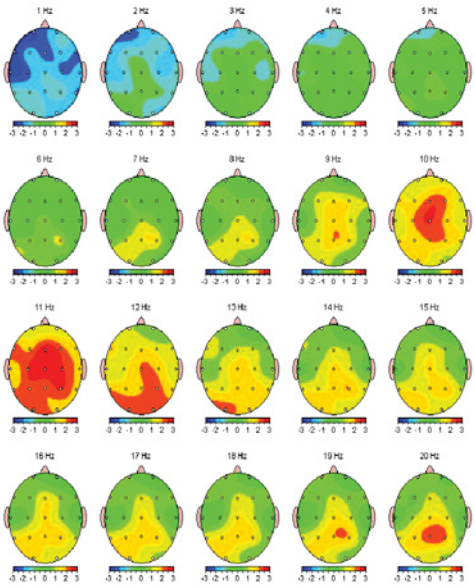

FIGURE 1. Case 1 Quantitative EEG. (Color figure available online.)

through feedback that involves a very tiny electromagnetic field, which has a field strength of 10^{-18} watts/cm^2. This feedback, which is only 1/400th the strength of the input we receive from simply holding a regular cell phone to the ear, is delivered in 1-s intervals at a time down electrode wires while the patient remains motionless, usually eyes closed. This feedback adjusted 16/s to remain a certain number of cycles per second faster than the dominant EEG frequency.

Based on QEEG findings, Joe's treatment was individualized using LENS programs that focused feedback on the 9–12 Hz and 7–12 Hz frequency ranges. The amount of feedback was gradually increased until from Session 9 onward he was receiving approximately 200 s of feedback in each session. For the initial four sessions a standard LENS treatment procedure was followed, rotating through all 19 electrode sites. Subsequently, treatment was done at seven electrode sites in each session, focusing on electrode sites Fz, Cz, C3, C4, and Pz primarily, but also in four sessions providing feedback at T3 and T4. No side effects were experienced during the course of treatment, which consisted of a total of 20 neurofeedback sessions. Treatment frequency was twice a week.

As Joe appeared for the second neurofeedback session he indicated that he sensed ''a change in well-being.'' After four sessions he reported feeling ''amazed.'' He said that instead of awakening after approximately 1 hr and having to exercise before he could go back to sleep, he was now sleeping 6 hr without awakening. He referred to the changes as ''profound'' and ''unbelievable.'' After six sessions he reported being able to relax and read a book in the evening, and indicated that he had not found it necessary to exercise during the night for 2 weeks (since the fourth session). Following nine sessions he reported awakening only once, saying the disturbing sensations were ''slightly there'' but that he was able to go right back to sleep. At this time he described how prior to neurofeedback treatment he would often be sitting on the edge of the bed in the middle of the night feeling ''full of despair and hopeless,'' but that he had not experienced this in the past month. Following 10 sessions he said that the restless legs and limbs were not awakening him at all and he had no need to exercise in the night. After 15 sessions the patient said that the only reason he continued to rate RLS and PLM symptoms a .5 was because he occasionally experienced a restless feeling during the day but that he felt ''absolutely no problem'' with regard to sleep. People at work had noticed that his work had improved. It is interesting that given the link between sleep deprivation and weight gain (Lyytikainen, Rahkonen, Lahelma, & Lalluka, 2011), he noted that he had lost weight, and it was observable.

After 19 sessions the patient indicated that he had not experienced a migraine in 2 months. His ratings of RLS/PLM symptoms had declined from 10 to 0 during the night and 1 during the day. Anxiety declined from 5 to 1, being withdrawn from other people decreased from 8 to .5, and his depression from 5 to 0. On 3-month follow-up his symptom rating remained the same, with the exception that during the day he rated sensations of RLS as a 2. He continued to remain asymptomatic during the night and to sleep without awakening with RLS/PLM symptoms and without exercising in the night. His weight losses were being maintained. However, on 6- and 9-month follow-ups he reported that the RLS was returning on average every other night with a severity of 8. He continued to rate RLS sensations a 2 during the day, and he had maintained emotional-behavioral changes, rating being withdrawn .5, depression 0, and anxiety a 1. The 9-month follow-up occurred when he returned for some reinforcement sessions. After just one LENS session he indicated a week later that he would already rate a 2-point decrease in RLS/PLM severity ratings.

CASE 2

Jay was a 72-year-old man who had suffered with severe RLS with an onset in his 40 s. His father began having RLS in his 40 s and his grandfather also suffered with RLS. Jay had

been prescribed Sinemet for a number of years and then was switched to Mirapex. He was also taking Ambien. Each night he would awaken every 60 to 90 min and have to exercise (walk around the block or on a treadmill) before going back to sleep. A QEEG evaluation was done using the NeuroGuide database. Two min 18 s of artifacted eyes-closed data (split-half reliability = .99; test–retest reliability = .98) and 1 min 30 s of artifacted eyes-open data (split half reliability = .98; test–retest reliability = .95) were analyzed. He showed a pattern similar to Case 1. As may be seen in a Laplacian analysis of the data (Figure 2), he had excess alpha, beta, and high beta (not seen in Figure 2) at central, midline, and parietal electrode sites.

Treatment consisted of 12 sessions of LENS neurofeedback over a 2½-week period. The feedback was done following a traditional LENS map sequence with treatment at seven electrode sites per session, proceeding sequentially from where overall amplitude and variability were lowest toward where they were highest. After four sessions over a 2-week period, as he came for his fifth session he reported that he had not experienced RLS for three nights. After 11 sessions, he reported that he had only experienced RLS once in the previous 14 days. On 9-month follow-up he indicated that he continued to take Ambien and Mirapex before bed (because of experiencing RLS while relaxing prior to bed) but that RLS never awakens him.

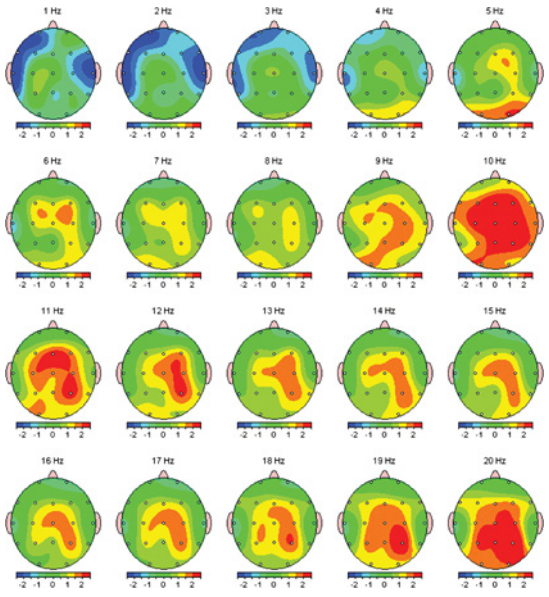

FIGURE 2. Case 2 Quantitative EEG. (Color figure available online.)

Jay lived in a distant state and his treatment occurred while in Salt Lake City visiting relatives. Nine months after his original treatment he was visiting again and he requested another 11 LENS sessions simply for purposes of reinforcement, but not because of any symptomatic reoccurrence. During these sessions a LENS program was used that focused on the dominant frequency in the 7–12 Hz range but which utilized two channel sequential training with electrodes at Fz-Pz and P3-P4 or C3-C4. On 24-month follow-up from when he first entered treatment, Jay was still never awakened by RLS. He continues to take Mirapex and Ambien before bed, but only awakens once at night to urinate and sleeps 8½ hr nightly.

SUMMARY AND CONCLUSIONS

Results in these two consecutive cases suggest that neurofeedback has potential as a therapeutic modality to be added to treatment regimens for RLS and PLM. As this article is being written, the author is treating a third case using LENS neurofeedback, and after 13 sessions (while she remains on Requip medication) she rates her symptoms as 75% improved. In all three of these cases the rapid and very significant improvements from LENS treatment were similar, although in one of the two cases just reviewed the changes have not completely endured and he has returned for some reinforcement sessions. The case where neurofeedback effects were not maintained was one where neurofeedback was the sole treatment for 20 sessions, whereas in the other case the patient remained on medication and had a total of 23 treatment sessions, which included 11 sessions where LENS two channel sequential montage training wad done. The LENS two channel sequential training meant that feedback was being provided at four electrode sites, which has been hypothesized (Hammond, Harper, O'Brien, & Dogris,

2010) to require more subcortical involvement in the training.

Further clinical experience and research is necessary to determine (a) when neurofeedback is the sole treatment, will it require a larger number of treatment sessions, sequential training, or periodic reinforcements for therapeutic effects to be enduring; (b) will the addition of neurofeedback to other forms of treatment promote greater therapeutic gains than medical treatment alone; and (c) will other types of neurofeedback (e.g., QEEG-guided neurofeedback or Live *Z*-score Training) produce similar improvements in RLS and PLM, and may an additional focus on inhibiting high beta along the midline improve outcomes? It may be possible in some cases that underlying pathophysiological conditions (e.g., that result in an iron deficiency) may need to be remedied before changes brought about by neurofeedback can be maintained. Because these conditions can lead to high blood pressure (at least during sleep), heart disease, and stroke (Walters & Rye, 2009), and because obstructive sleep apnea and upper airway resistance syndrome can masquerade as RLS/PLM (Natarajan, 2010), it is important for clinicians to be sure that patients are being followed medically.

The tremendous relief that these patients have reported as a result of neurofeedback does suggest that even if a few occasional neurofeedback reinforcement sessions were required and it was necessary for patients to remain on medication, many patients who suffer with RLS and PLM may find that neurofeedback can provide them with a greater relief of symptoms than they are obtaining with traditional medical treatments alone. Based on results in these uncontrolled case reports, the potential of neurofeedback with RLS and PLM should be explored further with controlled research.

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