Spectral EEG sleep profiles as a tool for prediction of clinical response to antidepressant treatment

Sleep and depression

Two qualitatively different brain states characterize normal human sleep: non–rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is further subdivided into four stages: stage 1 is the lightest and stage 4 the deepest. Stages 3 and 4 are often defined as δ sleep or slow-wave sleep (SWS) due to the occurrence of slow (0.5-3.5 Hz) "delta" waves. REM sleep (also called paradoxical sleep) alternates with NREM throughout the night in recurrent NREM-REM cycles of about 90 min. Sleep-wake regulation is classically viewed as resulting from the interaction of two regulating processes (homeostatic [S] and circadian [C]).[1] In this model, the propensity to sleep or be awake at any given time is a consequence of a sleep debt (Process S) and its interaction with signals coming from the circadian clock located in the suprachiasmatic nucleus (Process C).

In 1982, Borbely and Wirz-Justice[2] suggested that the characteristic sleep disturbances of major depressive patients reflect a homeostatic Process S deficiency, ie, a failure to accumulate SWS pressure during the daytime, leading to sleep initiation and maintenance difficulties, and early emergence of REM sleep. Indeed, characteristic sleep EEG changes such lengthening of sleep latency, sleep disruption, and disturbances in REM sleep organization have been consistently identified in depressive illness.[3] Spectral analysis of NREM sleep in major depressed patients has shown lower δ activity (power spectra in the δ wave) in NREM sleep[4-6] and decreased δ incidence particularly in the first non-REM period,[7] supporting the "Process S" deficiency hypothesis. Using spectral analysis of the sleep-onset period, we have recently brought support to this hypothesis: we found that homeostatic sleep regulation processes are partially maintained in primary insomniacs, but not in major depressed patients with insomnia.[8]

Sleep EEG and antidepressant response

Some studies have shown that the clinical response to various antidepressant therapies could be predicted by sleep electroencephalography (EEG) parameters. For instance, the amount of REM sleep suppression observed after the first dose of antidepressant may predict ultimate clinical response.[9,10] REM rebound following antidepressant withdrawal was also found predictive of antidepressant response. Kupfer et al[11] demonstrated that the antidepressant response to two consecutive days of pulse loading of clomipramine followed by placebo was positively correlated with the amount of REM rebound. Similarly, Gillin et al[9] noted that patients who improved during treatment with amitriptyline exhibit a clear REM sleep rebound during withdrawal, whereas patients with no improvement show no such REM sleep rebound. Induction of cytokine synthesis and fever has been shown to suppress REM sleep and improve mood in patients with major depression.[12] Finally, some studies showed that increased REM activity (ie, more rapid eye movements occurring during REM sleep) identify depressive patients who do not respond to psychotherapy and may warrant somatic treatment.[13,14]

The results of some studies cast doubt on the value of REM suppression as a predictor of antidepressant response. For instance, data suggest that effective long-term pharmacotherapy of recurrent major depression with imipramine[15] or nortriptyline[16] is associated with

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higher REM activity than that observed in patients relapsing while receiving these drugs. Other studies were unable to demonstrate a consistent relationship between REM decreases and the alleviation of depression during treatment with antidepressants.[17-19] The REM suppressant effect may play an important role in the mechanism underlying treatment response, but is insufficient for use in prediction.

It is also not clear whether changes in NREM sleep, including SWS, are related to improvement in depression. Quantification of NREM sleep changes by visual scoring of sleep EEG in terms of changes in duration or proportion may be insufficient for detection of such a relationship. A more accurate method may be to investigate whether clinical response is related to drug-induced modification of sleep microstructure. For instance, the number of transient polysomnographic activations suggestive of an awake state (ie, microarousal) occurring during stage 2 observed after the first doses of doxepine was found to be positively associated with antidepressant response.[20] Other studies have shown that methods involving spectral analysis of NREM sleep are useful for prediction of clinical responsiveness to antidepressants.

Power spectral analysis and antidepressant response

A classical way to describe an EEG signal is in terms of frequency of the common EEG bands. One of the most useful methods to decompose EEG signals into frequency components is Fourrier analysis, and the fast Fourrier transform (FFT) algorithm has been extensively used in EEG analysis. In FFT spectral analysis, signal intensity is calculated per bandwidth and a power spectral density can be obtained for each frequency band of interest.

Predicting clinical response through the sleep EEG spectral analysis of depressed patients has received little interest to date. The few studies on the topic showed that high pretreatment δ activity[5,21] and redistribution of δ activity to the earlier part of the night may predict ultimate clinical response.[22] For instance, we have shown a clear relationship between baseline sleep EEG spectral density values and clinical response *(Figure 1)*. Another study has shown that different forms of δ activity can distinguish between acute depression and the risk of recurrence in previously recovered patients. On the basis of fundamental studies[23] showing that the δ bandwidth

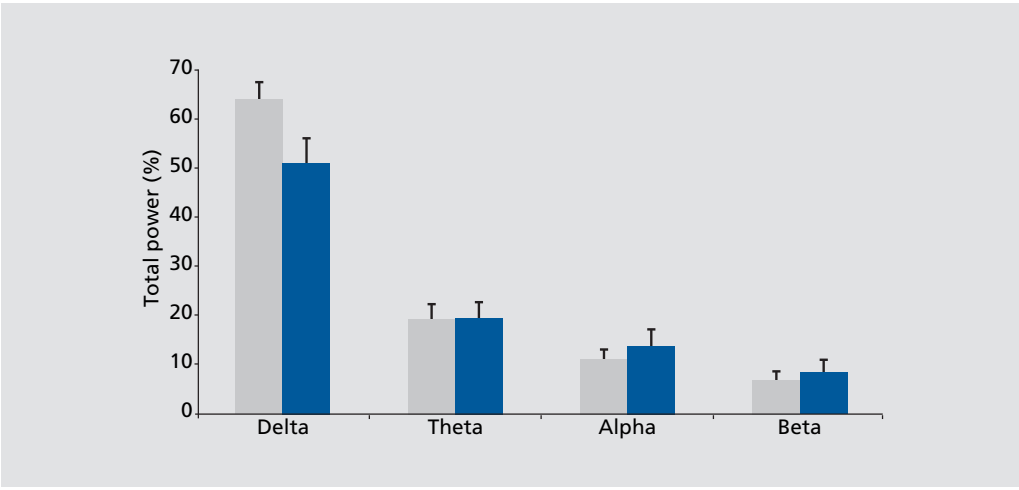

Figure 1. Electroencephalography (EEG) spectral analysis baseline parameters in responders (gray) and nonresponders (blue).

(thought to be generated in thalamic nuclei) also contains slow oscillations (0.5-1 Hz) originating in the cortex, Buysse et al[24] demonstrated that high δ activity (2-3 Hz) was more related to the acute depressive state, while the lower frequencies (0.5-1 Hz) were linked to risk of recurrence. Other research efforts focused on the significance of α frequency during REM sleep. In a topographic study, we found that REM α power spectra are reduced after antidepressant administration in healthy volunteers *(Figure 2)*,[25] a finding that needs to be extended to depressed patients in order to assess its potential predictive value.

Another promising direction for future research is the study of change in dynamic relationships, or coherence, between frequency ranges.[26] Coherence evaluates the strength of covariation between two frequency rhythms: if two frequencies have high coherence, they are likely to be controlled by the same or similar timing mechanism. In this context, Armitage et al[27] reported that β and δ rhythms were less coherent in depressive patients than in healthy controls, and Röschke et al[28] suggested that 4 weeks' administration of paroxetine in healthy volunteers significantly increased coherence between β and δ frequencies.

Conclusion

Clinical research on the influence of antidepressant drugs on sleep microarchitecture will become increasingly important for interpreting the effects of antidepressants on sleep physiology and for the development of new antidepressant therapies. In this regard, spectral EEG sleep profiles represent a promising tool for the prediction of clinical response to antidepressant treatment.

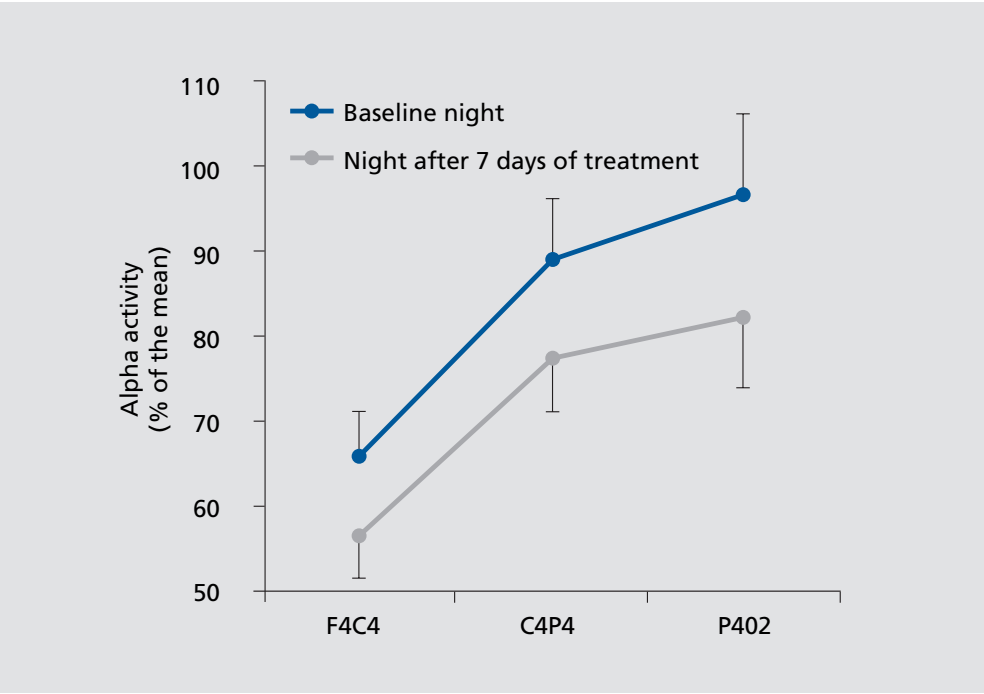

Figure 2. Effects of fluoxetine 20 mg on topographical alpha activity distribution during rapid eye movement (REM) sleep. F4C4, frontocentral derivation; C4P4, centroparietal derivation; P4O2, parieto-occipital derivation.

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