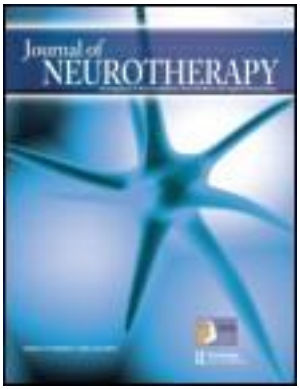


Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience

Comodulation

M. Barry Sterman PhD [a] [b] & David Kaiser PhD [b]

[a] School of Medicine, UCLA

[b] Sterman-Kaiser Imaging Laboratory , Bel Air, CA, USA

Published online: 20 Oct 2008.

To cite this article: M. Barry Sterman PhD & David Kaiser PhD (2000) Comodulation, Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience, 4:3, 73-83, DOI: 10.1300/J184v04n03_05

To link to this article: http://dx.doi.org/10.1300/J184v04n03_05

Comodulation: A New QEEG Analysis Metric for Assessment of Structural and Functional Disorders of the Central Nervous System

M. Barry Sterman, PhD
David Kaiser, PhD

ABSTRACT. A new quantitative EEG metric is described here that examines the temporal correspondence of magnitude modulation between cortical recording sites. It is termed ''comodulation,'' and is applied as a cross-correlation analysis either within-subject or statistically between subject and a control database. Analysis can be performed for any selected frequency band between 1 and 23 Hz and for each of four basic functional states, including eyes closed, eyes open, and two task engagement conditions. The metric is tested here by ap-

M. Barry Sterman is affiliated with the School of Medicine, UCLA. Both Dr. Sterman and Dr. Kaiser are affiliated with the Sterman-Kaiser Imaging Laboratory, Bel Air, CA.

Address correspondence to: M. Barry Sterman, PhD, Department of Neurobiology, UCLA Medical Center (CHS), 10833 Le Conte Avenue, Los Angeles, CA 90085-1763.

Journal of Neurotherapy, Vol. 4(3) 2000

plication to clinical cases where structural alterations and functional disturbances of the brain are documented.

KEYWORDS. QEEG, imaging, comodulation, anterior temporal lobectomy, callosotomy, depression

INTRODUCTION

In the course of conducting numerous quantitative EEG studies of the correlates of human attention and performance, we encountered many unresolved issues and shortcomings associated with QEEG evaluation. These experiences led us to develop a new QEEG analysis program (SKIL Topometric Software System) that addressed these issues and improved the quality and reliability of evaluations. In so doing, we applied a number of new and unique assessment metrics that were dictated by our research interests, and that have ultimately proven quite useful in clinical assessment.

Among the new assessment metrics developed was a topographic quantification of the temporal synchrony between recording sites, a metric that we have labeled "comodulation." Using a multi-site cross-correlation analysis of sequential spectral density estimates in bands between 1 and 23 Hz, this analysis provided a useful perspective on putative thalamocortical modulation of the EEG, and allowed for intuitive mapping and interpretation of quantitative results. Comodulation differs from coherence by evaluating the temporal correspondence of variation in spectral density estimates between sites, rather than coincident frequency and waveform characteristics. It examines the extent of shared modulation in EEG rhythmic activity within the time domain rather than the frequency domain. Comodulation analysis of data in relevant frequency bands has clearly disclosed unique and clinically significant patterns of altered functional interactions in preliminary studies (Sterman & Kaiser, 1999).

METHODS

Comodulation analysis includes both coefficient generation and statistical comparisons to an appropriate database. Cross-correlation of each recording site with all other sites is calculated for a given frequency band and recording condition. These data provide a within-subject analysis of regional correla-

tion, with values ranging from −1 to +1. Cross-correlations of each site with itself produce coefficients of exactly +1.0, while all other comparisons show progressively diminishing correlation with each other as the functional distance between them increases (Figure 1). This analysis, in fact, appears to define the regional localization of function within the cortical mantle.

Statistical comparison of these correlation coefficients with our coefficient database identify those regions where functional homogeneity or heterogeneity deviate from normal. Statistical analyses are available for a given frequency band and a given recording condition. An example of non-deviant statistical comodulation is shown in Figure 2.

FIGURE 1. Mean normative database cross-correlation values between each designated site and every other site for the 8-12 Hz band. Data are from 274 eyes closed recordings. Maximum coefficient of 1.0, shown in black, appears only where each site is correlated 100% with itself.

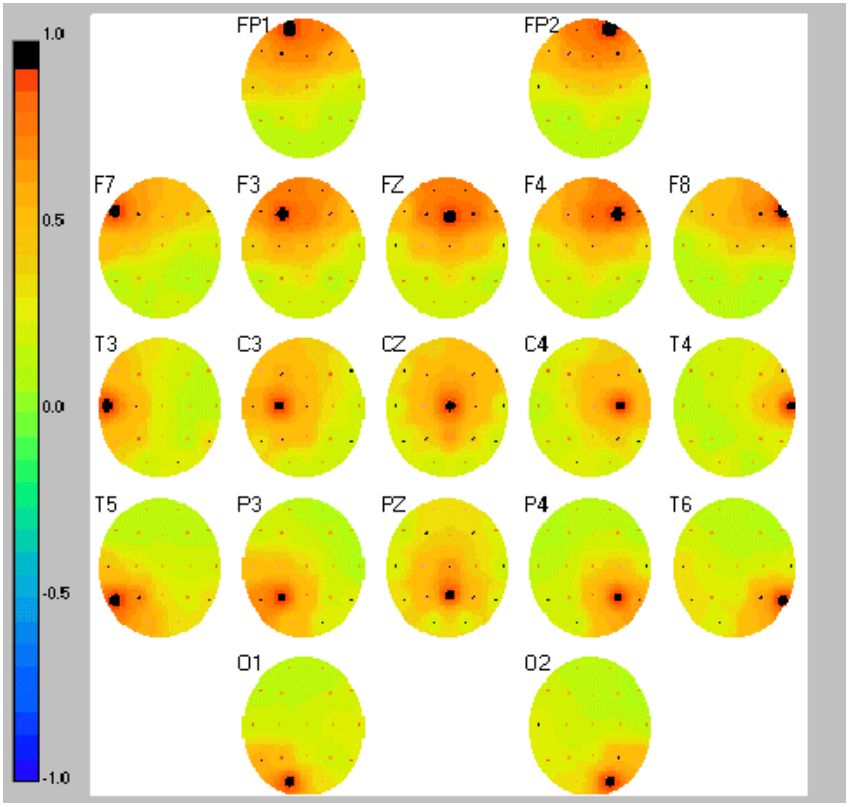
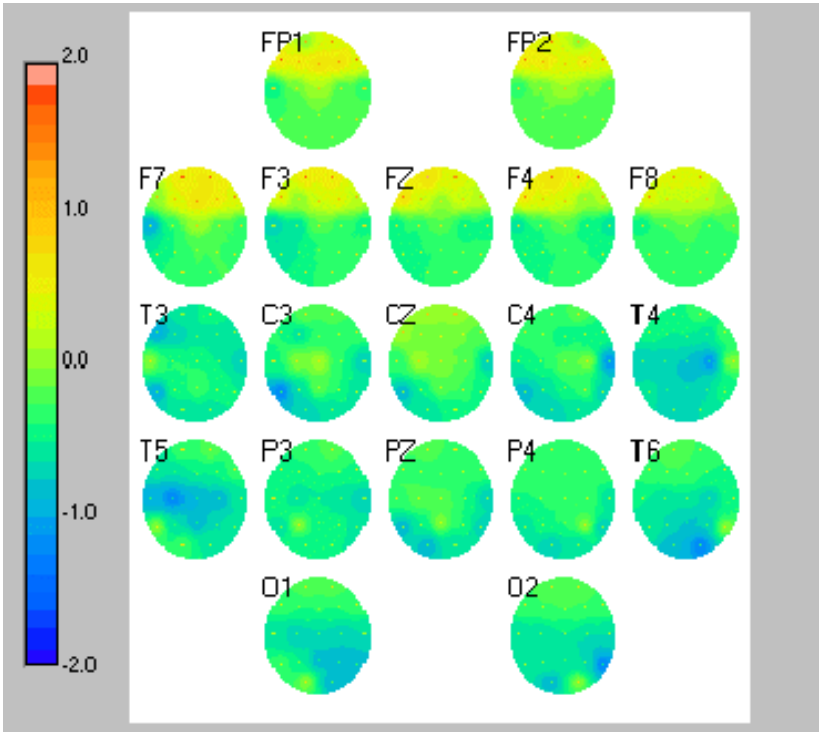


FIGURE 2. Statistical analysis showing mean comodulation at 8-12 Hz in a group of six adult subjects with eyes closed. For this anlaysis color code at left shows database variance scaled to ±2.0 standard deviations. Note that all the values are within normative population range.



Data Collection. EEG data were collected and digitized on a Lexicor NRS-24 recording system with a sampling rate of 128/sec, and high- and low-pass filtering at 1.5 and 37 Hz, respectively. Data files were then transported to a custom program where comprehensive automatic and visual artifact removal was carried out (for details see Sterman, Kaiser & Veigel, 1996). As with coherence, comodulation analysis is extremely sensitive to artifact corruption. The random frequencies of muscle discharge can create signal discrepancies between vulnerable electrode sites and the rest of the montage. Additionally, low frequency artifacts from eye or head movements can likewise create unique patterns of modulation at susceptible frontal and posterior locations. Artifact removal was thus given a high priority. However, where

minor artifact corruption (usually muscle discharge at lateral locations) was persistent the resulting distortions were disregarded.

The temporal continuity of sequential data segments was maintained in FFT analysis by using overlapping 1-sec cosine-tapering windows, with an interval of 250 msec (see Kaiser & Sterman, this volume). Data were collected during eyes closed, eyes open, and two cognitive task conditions. The control database was derived from 274 data sets obtained from carefully screened healthy adult subjects between the ages of 18 and 54 years. With this program a Pearson product-moment coefficient can be calculated between each of the standard 10/20 recording sites and all other sites for any selected frequency band. This metric is expressed as either a within-subject analysis or as a parametric statistical comparison between a given individual or set of individuals and the database, as described above.

RESULTS AND DISCUSSION

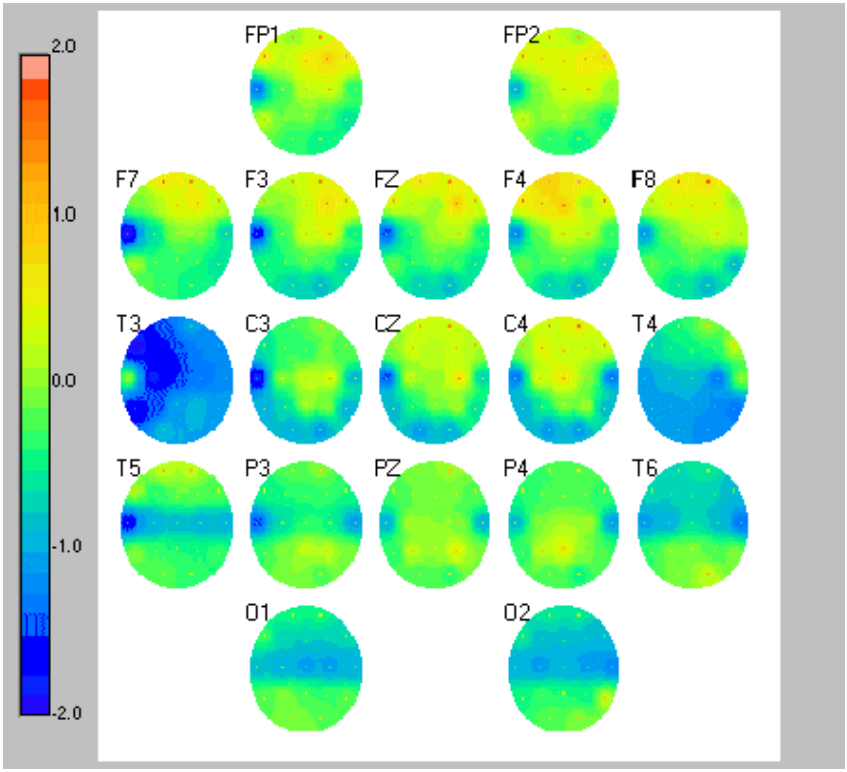
Structural Alterations. The recent application of comodulation analysis within a clinical context has afforded the opportunity to validate the metric with reference to cases where surgical procedures of putative therapeutic value have created documented alterations of brain structure. Two such cases will be reviewed. Both of these cases involved patients with poorly controlled seizure disorders.

In the first case, the anterior portion of the left temporal lobe was surgically removed, a procedure called *anterior temporal lobectomy.* The client was a 43-year-old female with recurring partial-complex seizures. Pharmacological treatment had not provided satisfactory control of these seizures. The clinical justification for this procedure was the assumed elimination of epileptogenic influences originating from this region.

The dominant frequency was slowed to the 7-9 Hz band in this client, a frequent finding in seizure disorder patients. While normally greatest in posterior cortex, the dominant frequency can be generalized, and provides an index of attention, its presence reflecting an ''idling'' or ''standby'' state in thalamocortical networks (Klimesch, Doppelmayr, Schimke, & Ripper, 1997; Pfurtscheller, 1992; Sterman, 1996, 1999a). As such, it discloses an underlying state condition that is normally shared by many cortical systems.

A statistical comparison of the client's dominant frequency comodulation with values from the database is shown in Figure 3, during the eyes closed state. It can be seen that the waxing and waning of magnitude in the 7-9 Hz band is unique at T3, and isolates this site from the rest of the map. From a statistical standpoint, modulation at T3 bears no relationship to modulation in a wide zone of adjacent sites (dark blue area) and little relationship to modulation in the rest of the cortex (remaining blue area). This effect is, of course,

FIGURE 3. Statistical comodulation analysis of the 7-9 Hz band with eyes closed in an epileptic patient after left anterior temporal lobectomy. Dark blue areas represent sites of significantly reduced cross-correlation with the site indicated at the left top of each map.



reciprocal, leading to blue spots at the T3 site on every other cross-correlation map.

From a structural perspective, this analysis identified the surgical lesion with great accuracy. Additionally, however, it exposed another potentially critical functional alteration. Thus, reduced comodulation can be seen also at T4, in relation to adjacent medial and posterior sites. This finding suggests a disturbance in the function of the *intact* contralateral anterior temporal lobe, and raises the possibility of a secondary epileptogenic area, or "mirror focus" (Morrell, 1959, 1985). Such a conclusion would be consistent with the post-operative recurrence of uncontrolled seizures in this patient, the basis

for her interest in neurotherapy. It is interesting to consider what might have been the case had she sought neurotherapy initially, instead of surgery.

The second case involves a 28 year-old female patient with a late-onset mixed seizure disorder, including frequent atonic attacks. The later are characterized by a sudden, intense muscular hypotonia, often leading to abrupt falls with potentially life threatening consequences. Treatment with anticonvulsant medications had proven ineffective in this patient. As a result of the serious risk factor and the bilateral character of EEG seizure discharges, the patient underwent a surgical transection of the anterior and middle corpus callosum, in two phases, a procedure called a *callosotomy.*

While atonic seizures were eventually reduced following this procedure, the patient was severely compromised in terms of cognitive functions, and continued to have these and other seizures, despite medication. Additionally, the EEG during inattention was dominated by very abnormal 3-5 Hz slow background activity, with transient paroxysms and spike-and-wave discharges. These patterns were reduced significantly during meaningful task engagement.

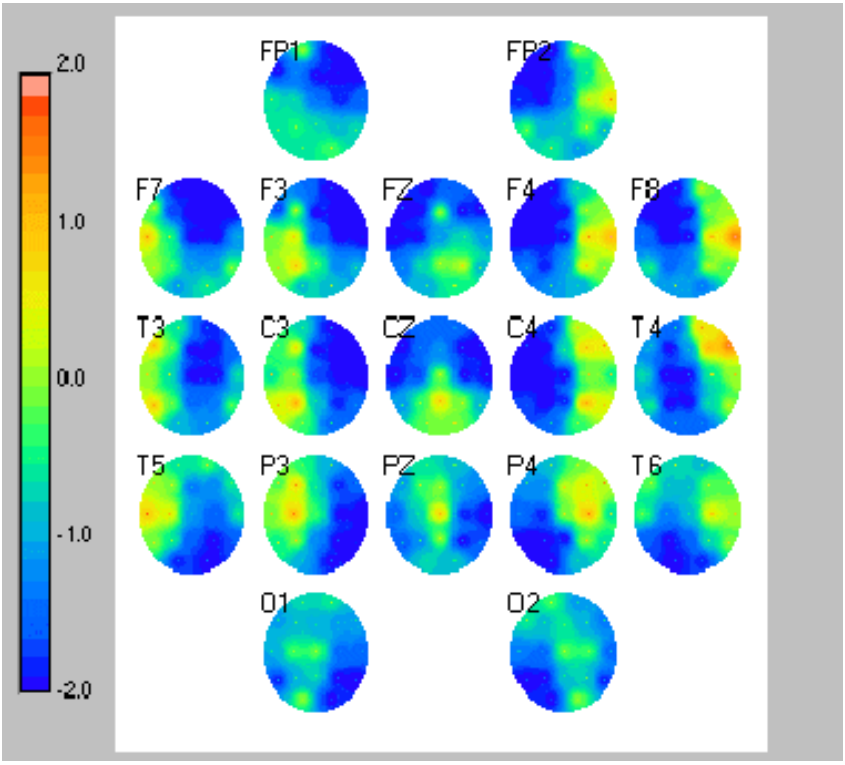
Statistical comparison of her comodulation with the database, focusing on the dominant 3-5 Hz frequency band during the eyes open state, is shown in Figure 4. Comodulation was significantly reduced between hemispheres, as indicated by the dark blue zones contralateral to each cortical region in both hemispheres. This statistically validated image actually depicts a ''split-brain.'' It is characteristic of findings in all tested states, including task engagement.

Of particular interest is the more localized ''disconnect'' noted in pre-frontal and frontal cortex. This pattern has been seen reliably among patients with closed head injuries (Sterman, 1999b). It has been interpreted as reflecting damage to anterior callosal fibers as a result of tissue distortions produced by the head injury, a conclusion supported here where damage is clearly documented.

Functional Alterations. A number of deviant comodulation patterns have also been noted in clinical cases with no observable structural abnormality. These may be interpreted as functional in nature. Perhaps the most interesting of these is a unique pattern involving a pre-frontal and frontal cortex hypercorrelation, manifested in the dominant frequency primarily during inattentive states (Figure 5). It is typically abolished with cognitive engagement. What makes this pattern of particular interest is its consistent and seemingly exclusive appearance in clients with depressive disorders, and its convergence with findings in this population reported by others using different brain imaging methods.

This finding has been limited in our experience to clients with a clinical history of either unipolar or bipolar depression. It has also been limited to the

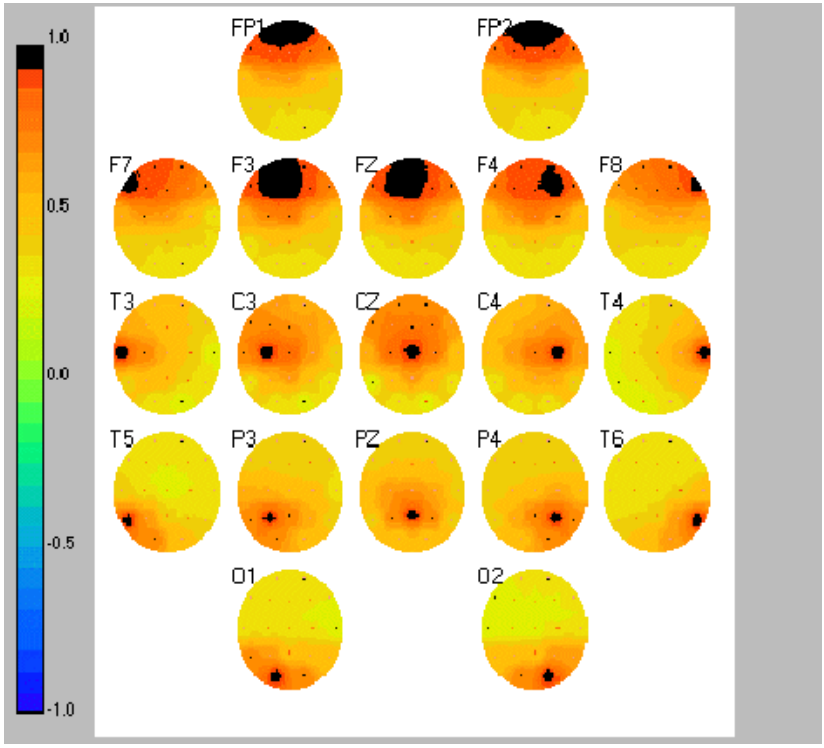
FIGURE 4. Statistical comparison of comodulation in client with nearly complete surgical transection of the corpus callosum. Analysis focuses on an abnormally slowed 3-5 Hz dominant frequency, in this case with eyes open. Note bilateral dissociation (significantly reduced comodulation) between homologous contralateral areas.



dominant frequency, and is usually greatest in the low dominant 8-10 Hz band, as seen in the group data presented in Figure 5. From our perspective, it suggests a deviant frontal inactivation, or *hypofrontality*, as some have termed it (Galynker, Cai, Ongseng, Finestone, Dutta & Sersen, 1998). Our analysis showed that this condition was facilitated by inattention, a fact that has not been explored in other studies. Since it is abolished with task engagement, we believe that it represents a deficit in both the level of frontal activation and functional differentiation.

Such an interpretation is supported by a growing literature from investigators employing other imaging methods to study depression. Thus, using

FIGURE 5. Within-subject cross-correlation analysis of comodulation is shown here averaged among a group of six adult subjects with a clinical history of depression. Expanded pre-frontal and primarily left frontal zones shown in black contrast with the limited expression of maximal auto-correlation seen at all other sites, and disclose deviant hyper-correlation (Sterman, 2000, reprinted with permission).



single photon emission computed tomography (SPECT), Galynker, Cai, Ongseng, Finestone, Dutta, and Sersen (1998) and Drevets, Price, Simpson et al. (1997) both found that blood flow to pre-frontal and left dorsolateral frontal cortex was negatively correlated with the severity of symptoms in depressed patients. They suggest that these frontal areas are metabolically hypoactive in this patient group. Further, Mallet, Mazoyer, and Martinot (1998) found reduced functional connectivity in frontal cortex among depressed patients using fluoro-deoxyglucose positive emission tomography (PET) analysis. Finally, Larson, Davidson, Abercrombie et al. (1998) used PET analysis to examine the relationship between thalamic metabolic rate

and EEG dominant frequency activity. They found a very clear inverse relationship in control subjects, indicating that thalamic cellular activity is indeed reduced in association with dominant rhythmic patterns in the EEG, as the thalamic neural oscillator model dictates. However, in depressed patients this inverse relationship was abolished. They suggest that depressed patients may have a deficit in thalamocortical connectivity. Thus, a disturbance in thalamocortical and corticothalamic frontal regulation in these patients may result in disturbed functional connectivity, or differentiation, with significant affective and cognitive consequences.

CONCLUSIONS

We have described only a few of the interesting and clinically significant findings that have emerged from the use of the comodulation metric. Others will be the focus of future communications. Despite the preliminary nature of some of these findings, they have been consistently confirmed by a growing number of affiliated clinicians using this measure. And in all cases this metric has helped to link EEG findings to underlying substrates because of its approximation of neural-network dynamics.

Perhaps most significantly, these unique findings and the functional clues they provide offer a new direction for neurotherapy applications. The basic principle of EEG normalization can be expanded to include attempts to appropriately re-connect or disconnect areas with disturbed interactions. Clearly, the relevance of QEEG-guided neurotherapy is further supported by this reality. However, this reality will also require an expansion of current methodology and, more likely, the development of new training logic and displays.

REFERENCES

Drevets, W.C., Price, J.L., Simpson, J.R. et al. (1997). Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*, *386*, 824-827.

Galynker, I.I., Cai, J., Ongseng, F., Finestone, H., Dutta, E. & Sersen, D. (1998). Hypofrontality and negative symptoms in major depressive disorder. *Journal of Nuclear Medicine*, *39*, 608-612.

Klimesch, W., Doppelmayr, M., Schimke, H., & Ripper, B. (1997). Theta synchronization and alpha desynchronization in a memory task. *Psychophysiolgy*, *34*, 169-176.

Larson, C.L., Davidson, R.J., Abercrombie, H.C. et al. (1998). Relations between PET-derived measures of thalamic glucose metabolism and EEG alpha power. *Psychophysiology*, *35*, 162-169.

Mallet, L., Mazoyer, B. & Martinot, J.L. (1998). Functional connectivity in depressive, obsessive-compulsive, and schizophrenic disorders: An explorative correlational analysis of regional cerebral metabolism. *Psychiatry Research*, *82*, 83-93.

Morrell, F. (1959). Secondary epileptogenic lesions. *Epilepsia*, *1*, 538-560.

Morrell, F. (1985). Secondary epileptogenesis in man. *Archives of Neurology*, *42*, 318-335.

Pfurtscheller, G. (1992). Event-related synchronization (ERS): An electrophysiological correlate of control areas at rest. *Electroencephalography and Clinical Neurophysiology*, *83*, 62-69.

Sterman, M.B. (1996). Physiological origins and functional correlates of EEG rhythmic activities: Implications for self-regulation. *Biofeedback and Self-Regulation*, *21*, 3-33.

Sterman, M.B. (1999a). Event-related EEG response correlates of task difficulty sleep deprivation, and sensory distraction. In *Event-related desynchronization. Handbook of electroencephalography and clinical neurophysiology: Revised series*, Vol. 6. G. Pfurtscheller and F.H. Lopes da Silva (Eds.). (pp. 233-242). Amsterdam: Elsevier Science B.V.

Sterman, M.B. (1999b). Topographic analysis of spectral density co-variation: A new tool for clinical assessment. Presented at the Society for Neuronal Regulation Conference, Myrtle Beach, SC.

Sterman, M.B. (2000). *Atlas of topometric clinical displays*. Los Angeles: Sterman-Kaiser Imaging Laboratory.

Sterman, M.B. & Kaiser, D.A. (1999). Topographic analysis of spectral density co-variation: Normative database and clinical assessment. *Clinical Neurophysiology, 110 (Suppl. 1)*, S80.

Sterman, M.B., Kaiser, D.A. & Veigel, B. (1996). Spectral analysis of event-related EEG responses during short-term memory performance. *Brain Topography*, *9(1)*, 21-30.