Advances in Clinical Neurophysiology
(Supplements to Clinical Neurophysiology, Vol. 57)
Editors: M. Hallett, L.H. Phillips, II, D.L. Schomer, J.M. Massey

Chapter 46

The genetics of oscillations in the human brain

B. Porjesz*, K. Jones and H. Begleiter

Department of Psychiatry, Box 1203, SUNY, Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, NY 11203 (USA)

Recording brain electrical activity using scalp electrodes provides a noninvasive, sensitive measure of brain function in humans. These neuroelectric phenomena may be recorded during the continuous electroencephalogram (EEG) when the subject is at rest, and not involved in a task, or one may record the time-specific event-related brain potentials (ERPs) during specific cognitive tasks. These techniques yield spatiotemporal activity maps (i.e. brain activity as it occurs in both space and time).

The EEG consists of the activity of an ensemble of generators producing rhythmic activity in several frequency ranges. In the purely resting state, these oscillations are seemingly random; however, with the application of sensory stimulation, they become coupled and act together coherently. This synchronization and enhancement of EEG activity gives rise to an "evoked" (phase-locked) or "induced" (non-phase locked) rhythmicity. This rhythmicity may also occur without defined physical stimulation, but may be triggered by cognitive operations. The superimposition of these multiple event-related oscillations (EROs) of different frequencies underlies the ERP, and represents multiple sensory and cognitive functions.

Basic dynamics in the brain are governed by the brain's natural oscillations, namely: delta (1.0–3.0 Hz), theta (3.5–7.5 Hz), alpha (8.0–11.5 Hz), beta (12.0–28.0 Hz), and gamma (28.5–50.0 Hz). It is becoming increasingly obvious that these oscillations provide basic links to brain functions, especially for communication and associative functions, and that multiple oscillatory responses provide integrative brain functions. Complex functions are, as a rule manifested by several superimposed oscillations with various degrees of amplitude, durations, and delays. EROs are considered to be different from the ongoing "idling rhythms", since a process-related "partial-phase resetting" occurs in different EEG frequency bands in response to sensory or cognitive stimulation (e.g. Basar, 1980; Makeig et al., 2002). Evidence suggests that ERP features arise from oscillatory changes due to sensory or cognitive processes which influence the dynamics of ongoing EEG rhythms of different frequency bands (Basar-Ergolu and Basar, 1991; Shurmann et al., 1995; Yordanova and Kolev, 1996; Karakas et al., 2000a, b; Basar-Ergolu et al., 2001; Demilralp et al., 2001; Shurmann et al., 2001).

It should be noted that various cognitive processes have been attributed to different frequency rhythms

* *Correspondence to*: Bernice Porjesz, Department of Psychiatry, Box 1203, SUNY, Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, NY 11203, USA.
Tel: (718) 270-2024; Fax: (718) 270-4081;
E-mail: bp@cns.hscbklyn.edu

of oscillatory responses. For example, delta responses are assumed to mediate signal detection and decision-making (Basar et al., 1999; Shurmann et al., 2001), while the theta rhythms are associated with cognitive processes such as conscious awareness, recognition memory, and episodic retrieval (e.g. Klimesch et al., 1994, 2001a, b; Doppelmayr et al., 1998; Basar et al., 2001c). The slow alpha rhythm (8–10 Hz) has been reported to be modulated by the attribution of attentional resources (Basar et al., 1997; Klimesch, 1997; Klimesch et al., 1998) whereas the fast alpha activity (10–12 Hz) has been found to mediate semantic memory processes as well as stimulus-related aspects (e.g. Klimesch et al., 1994, 1997a, b). Faster oscillations such as beta and gamma may be involved in sensory integrative processes (e.g. Basar-Ergolu et al., 1996a, b: Schurmann et al., 1997; Basar et al., 2001a, b).

Brain oscillations represent important correlates of human information processing and cognition. They represent traits less complex and more proximal to gene function than either diagnostic labels or traditional cognitive measures. Therefore these oscillations may be utilized as phenotypes of cognition, and as valuable tools for the understanding of some complex genetic disorders. It should be noted that the heritability of these oscillations obtained under a resting condition is estimated to be between 80% and 90% (Van Beijsterveldt et al., 1996).

1. Beta frequency

A major program of research in our laboratory is to elucidate the genetic underpinnings of human oscillations at rest and under specific cognitive operations. We have begun this program of research by searching for genes associated with the beta rhythm. The beta rhythm is typically obtained in an alert individual, is distributed over the scalp and has a lower voltage than alpha. A large study of resting beta power in alcoholics and their offspring was undertaken by the Collaborative Study on the Genetics of Alcoholism (COGA) (Rangaswamy et al., 2002, 2003). Eyes-closed EEG of 307 alcohol-dependent subjects and 307 unaffected age and gender matched control subjects were compared. The data from 19 leads were transformed into bipolar values and the EEG power spectrum was subdivided into three bands: Beta 1 (12–16 Hz), Beta 2 (16–20 Hz) and Beta 3 (20–28 Hz). Increased Beta 1 and Beta 2 absolute power was observed in alcohol-dependent subjects compared to controls at all loci over the scalp, but was most prominent in the central region. It should be noted that the increase in beta power in abstinent alcoholics is also present in their offspring- individuals at risk to develop alcohol dependence.

Higher concordance rates in the spectral characteristics of resting eyes-closed EEG have been reported from monozygotic twin pairs compared to dizygotic twin pairs; the largest twin study to date estimates the heritability of spectral beta power to be 86% (Van Beijsterveldt et al., 1994, 1996). Although the data on the heritability of EEG frequencies are quite compelling, the genes influencing EEGs have not been identified. More recently, studies from our laboratory have examined the potential genetic underpinnings of the beta frequency of the human EEG. We performed a total genome scan using a computer algorithm called SOLAR (Sequential Oligogenic Linkage Analysis Routines, Almasy and Blangero 1998) to assess genetic linkage (i.e. the closer together two gene loci are, the more frequently they are inherited together or linked). This method yields a Logarithm of Odds (LOD) ratio, indicating the likelihood that there is linkage between a genetic marker locus and the phenotype (e.g. beta power); a LOD score of 3.00 corresponds to an odds ratio of 1000 : 1 and is considered to be significant. The linkage analysis of the beta frequency was based on 1553 individuals in 250 families, with a total of 351 polymorphic microsatellite markers distributed across the genome. We found significant genetic linkage (Beta 1, LOD = 3.39; Beta 2, LOD = 5.01; Beta 3, LOD = 2.17) between the beta frequency of the human EEG and a cluster of $GABA_A$ receptor genes on chromosome 4 (Porjesz et al., 2002). Combined linkage/linkage disequilibrium (SOLAR) to test the association

TABLE 1

COMBINED LINKAGE/LINKAGE DISEQUILIBRIUM OF BETA 2 EEG PHENOTYPE AND *GABRB1* MICROSATELLITE MARKER ON CHROMOSOME 4. ESTIMATES THE STRENGTH OF LINKAGE DISEQUILIBRIUM BETWEEN THE GENOTYPED MARKER AND THE QTL. PROVIDES STRONG EVIDENCE FOR ASSOCIATION BETWEEN *GABRB1* MARKER LOCUS AND BETA PHENOTYPE AND SUGGESTS THAT GENE IS IN OR NEAR *GABRB1* (PORJESZ ET AL., 2002). SNP ANALYSIS ACROSS THE CLUSTER OF $GABA_A$ RECEPTOR GENES ON CHROMOSOME 4 INCLUDING *GABRA2*, *GABRA4*, *GABRB1* AND *GABRG1* INDICATES THAT THE LINKAGE/LINKAGE DISEQUILIBRIUM FINDINGS ARE DUE TO *GABRA2*, THE ALPHA 2 SUBUNIT OF THE $GABA_A$ RECEPTOR GENE

Trait	Linkage LOD score	Combined Linkage/ Linkage Disequilibrium LOD Score	Rho_d	Association *p*-value
Bipolar Beta 2 Power	5.01	6.53	0.57	0.004

between the Beta 2 EEG phenotype and the $GABA_A$ receptor gene cluster on chromosome 4 was highly significant for association (LOD increased from 5.01 to 6.53; $p = 0.004$ for association) (Table 1).

With the use of multiple single nucleotide polymorphisms (SNPs) across this cluster of $GABA_A$ receptor genes on chromosome 4, that includes *GABRA2*, *GABRA4*, *GABRB1* and *GABRG1*, we were able to specifically identify that it was variations in the *GABRA2* receptor gene that accounts for the linkage/linkage disequilibrium findings with the beta frequency. Thus, variations in *GABRA2* (the gene encoding the alpha 2 subunit of the $GABA_A$ receptor) affect brain oscillations and are directly involved in the level of neural excitability (balance between excitation and inhibition). There is a strong relationship between the GBA2E7 SNP in the *GABRA2* receptor gene and Beta 2 EEG power. It is interesting to note that individuals who are homozygous for the rarer genotype (15%) of the GBA2E7 SNP have significantly increased EEG beta 2 compared to individuals with all other genotypes. These individuals are more likely to manifest CNS disinhibition.

It has been demonstrated that the beta rhythm is due to a balance in networks of excitatory pyramidal cells and inhibitory interneurons involving $GABA_A$ action as the pacemaker (Whittington et al., 2000). Fast synaptic inhibition in the mammalian central nervous system is mediated largely by activation of $GABA_A$ receptors (Tobler et al., 2001). $GABA_A$ actions are a fundamental requirement for both gamma (30–80 Hz) and beta oscillations to occur, and blockade of these receptors results in loss of synchronization (Haenschel et al., 2000). Beta rhythms can synchronize over long temporal delays between more spatially distant brain loci than gamma rhythms (Kopell et al., 2000). Although the recording of electrical oscillations from a neural population reflects the firing of multiple excitatory pyramidal cells, the mechanism underlying beta and gamma oscillations depends on the firing patterns of a network of inhibitory interneurons (Faulkner et al., 1999; Kopell et al., 2000), gated by their mutually induced $GABA_A$ action (Whittington et al., 2000). Our genetic results indicate the importance of $GABA_A$ receptor genes in the modulation of beta oscillations in the human brain.

2. Theta and delta oscillations

In addition to the study of genes involved in spontaneous oscillations recorded during rest, we have undertaken to examine the genetic underpinnings of oscillations recorded during event-related potentials (ERPs) under different task conditions. Here, we will focus on oscillations underlying the P3 component obtained to an infrequent target stimulus in a visual oddball paradigm. It is well established that ERPs are not unitary phenomena,

but represent averaged electrical neural activity that emanate from multiple sources in the brain, and consists of superimposed oscillations of different spectral EEG characteristics. These event-related oscillations (EROs) are temporally related to the sensory and cognitive processing of the stimulus and can either be evoked (i.e. phase locked to the event) or induced (not phase locked) (Basar et al., 1999). While the EROs are in the same frequency bands as spontaneous resting EEG, these active EROs are functionally different than spontaneous resting rhythms. The faster the ERO frequency, the more local the synchronization of this neural activity (Von Stein and Sarnthein, 2000). Local resonances (gamma) reflect sensory synchronization (i.e. feature binding) between macrocolumns and produce very high frequency oscillations, above 30 Hz. Regional resonances (beta and alpha) reflect multimodal synchronization (e.g. between adjacent temporal and parietal cortex) between macrocolumns, several cms apart. Global resonances (theta and delta) reflect synchronization between widely separated areas (long fibers); for example, frontal and parietal interactions during working memory (Lubar, 1997). Different scales of cortical integration require different frequencies; faster frequencies lose synchronization over long distances (Kopell et al., 2000).

There is compelling evidence in the literature that the P3 component of the ERP is primarily the outcome of theta and delta oscillations during stimulus and cognitive processing (Basar-Eroglu and Basar, 1992; Yardonova and Kolev, 1996; Basar et al., 1999; Karakas et al., 2000). Delta oscillations primarily underlie the P3 component of the ERP, while theta oscillations are involved in both the P3 and the N2 components. The P3 component consists of superimposed delta and theta oscillations at approximately 60–40% proportions, respectively, with a higher proportion of delta at posterior sites, and theta at frontal sites (Karakas et al., 2000). The maximum power of active theta is frontal, increasing 50% during the performance of an oddball task to the target stimulus. Reciprocal synchronization occurs in the theta range between hippocampus and frontal and parietal regions of the brain.

There are several approaches to elucidate the possible mechanisms of the ERP components, such as P3. One approach taken in this study is to examine the genetic underpinnings of various oscillations which make up these ERP components. It is proposed that the genetic underpinnings of ERPs, and thus underlying evoked oscillations, are likely to stem from regulatory genes which control the neurochemical processes of the brain, and therefore influence neural function.

We examined the ERO mean energy calculated via the S-transform time frequency algorithm (Stockwell et al., 1996) extracted within a time-frequency region of interest (TFROI) corresponding to the P3 time window, and across the delta and theta frequency bands. These energy estimates were averaged across three scalp regions (frontal, central, and parietal) as illustrated in Fig. 1. The TFROI mean energy region-wise features were derived using targets and non-targets separately.

Figure 2a depicts the grand averaged data across the entire dataset (1337 individuals) for the target case at the Cz channel. The data were averaged in time across trials per individuals, and then averaged across individuals to produce the grand mean ERP. The Hilbert transform of the individual trial S-transform was averaged across trials per individual, and then averaged across individuals. The P3 theta band TFROI is illustrated in Fig. 2b and closely corresponds in time to the occurrence of the grand mean P3 ERP.

The initial genome-wide linkage scan of the theta band P3 window TFROI data revealed significant linkage (LOD=3.5) on chromosome 7 between the markers D7S1837 and D7S509 at 171 cM with the frontal group of electrodes. The central and parietal electrode groups showed weaker but suggestive linkage with the same feature. A cholinergic muscarinic receptor gene, CHRM2, is located within the quantitative trait locus (QTL) and appears to be the most likely candidate to account for these linkage findings. These linkage findings implicate the possible role of CHRM2 in the generation and modulation

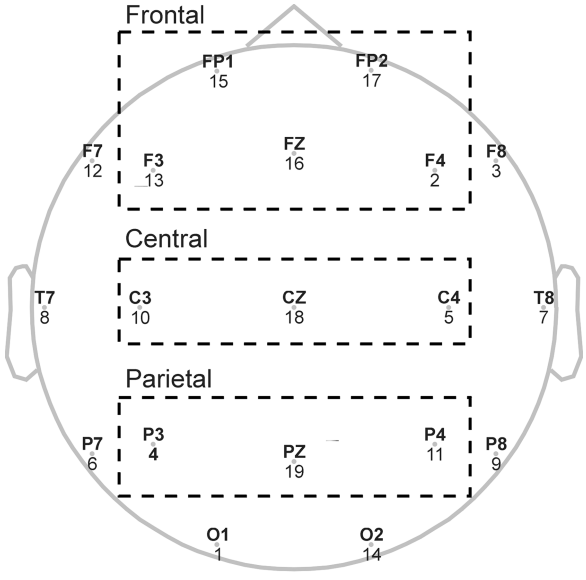

Fig. 1. Aerial view of the scalp with the nose up (top) designating the positions of the electrodes in the 10–20 international system. F, frontal; C, central; P, parietal; O, occipital; T, temporal. Odd numbers indicate leads on the left side of the head, even numbers indicate leads on the right side of the head and Z indicates zero or midline. For the genetic analysis measures on individual leads were averaged into the three scalp regions (frontal, central, and parietal), indicated by dashed rectangles.

of evoked oscillations. The muscarinic cholinergic receptors belong to a larger family of G protein-coupled receptors. Muscarinic receptors influence many effects of acetylcholine in the central and peripheral nervous system and hence are expected to have a direct influence on P3 generation (Frodl-Bauch et al., 1999). Moreover, the cholinergic muscarinic genes have a major role to play in memory and cognition (Calabresi et al., 1998; Comings et al., 2003).

To test whether the observed theta band linkage findings were directly influenced by the CHRM2 gene on chromosome 7, three single nucleotide polymorphisms were genotyped in and around the candidate gene (RS2350786, M16404, and RS1378650). It should be noted that only the M16404 SNP lies within the gene itself. Estimates of linkage disequilibrium, quantified by Lewontin's D′ and d^2,suggest that SNPs M16404, and RS1378650 are in high linkage disequilibrium (LD) (0.79–0.97) with each other, whereas RS2350786 shows only moderate LD with the other SNPs (0.44–0.67); we therefore do not expect independent results from the SNPs in high LD.

Estimates of measured genotype linkage disequilibrium between the QTL and the CHRM2 SNPs were obtained with the Caucasian sample only in order to avoid stratification problems. Additive model LD p values for target case theta band frontal, central and parietal region phenotype data are illustrated in Table 2. For this phenotype, the frontal and central regions show significance with RS2350786 SNP (0.014 and 0.013 respectively), while the parietal region shows borderline significance with this SNP (0.043). The other SNPs (which are in high LD with each other) did not show additive model significance, while the addition of a non-additive component did not improve the results.

The delta band power included in the P3 component showed weak linkage signals at the CHRM2 gene location (170 cM) on chromosome 7. Measured genotype analysis with the 3 CHRM2 SNPs revealed highly significant additive model LD between the target case central and parietal regions and SNPs M16404 and RS1378650 (p values between 0.0006 and 0.0059). Since both of these SNPs are in high LD with each other we expect similar findings. Addition of a dominance component to the measured genotype model did not improve the results. Non-target data did not demonstrate significant additive and dominant measured genotype model effects. As we only obtained significant LD for the target, but not non-target case, this suggests that the CHRM2 gene has functional significance associated with cognitive processing of the target case in the visual oddball paradigm.

Our results strongly support the role of acetylcholine in the generation of N2 (theta oscillations), and in the P3 component (delta and theta oscillations). The function of acetylcholine has been demonstrated with regard to stimulus significance (Perry et al., 1999), selective attention (Mitrofanis et al., 1993). Administration of cholinergic agonists and antagonists have yielded modified memory performance,

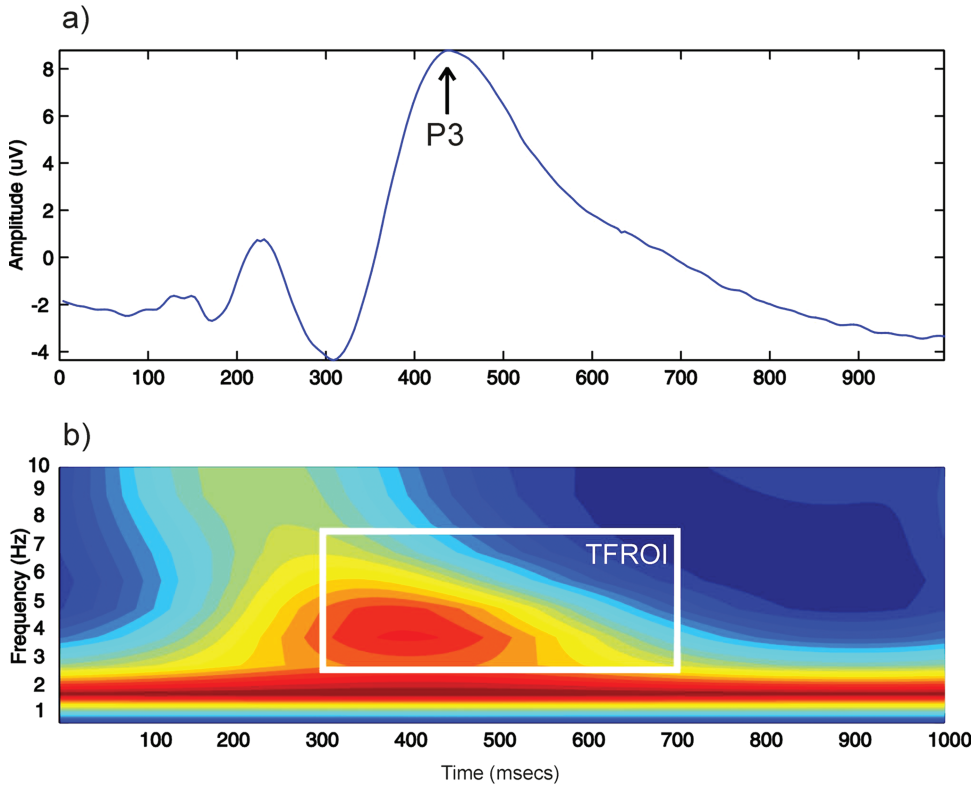

Fig. 2. (a) Plot of the target case visual evoked grand mean evoked potential for ~1300 individuals of the COGA genotyped dataset (CZ). The P300 component is observed to occur between 300 and 700 msecs, and is primarily constituted from delta and theta band energy. (b) Time-frequency representation of the target case visual evoked ERP energy distribution for CZ, calculated using the S-transform. The S-transform distribution was calculated on individual trial data and averaged within individuals, then across individuals. An example time-frequency region of interest (TFROI) is depicted for the P3 time window and the theta frequency band. Mean values calculated within the TFROI per individual are used for genetic analysis.

and modified P3 amplitude in humans (Hammond et al., 1987; Dierks et al., 1994; Potter et al., 2000).

In vitro studies with rat hippocampal slices have suggested that the presence of a cholinergic agonist induces oscillations in the delta, theta and gamma frequency range. In vitro administration of moderate amounts of the muscarinic agonist carbachol in the rat hippocampus induces synchronized delta oscillations, whereas higher concentrations produced short episodes of theta oscillations (Fellous and Sejnowski 2000; Tiesinga et al., 2001). Carbachol induced delta rhythms were not observed concurrent with carbachol-theta. It is important to note that our theta and delta phenotypes did not provide associations with the same CHRM2 SNPs. These data imply that the theta and delta systems may be quite distinct. The different brain regions associated with theta (frontal) and delta (parietal) offers some support for this oscillatory distinction. In addition, it is important to note that theta and delta peak at somewhat different times. Comparable with concentration-dependent carbachol induced oscillations described by Fellous and Sejnowski (2000), the production of theta may be evoked by high concentrations of muscarinic activity whereas the delta band oscillation may be the result of significantly reduced muscarinic activity. This could potentially explain the fact that different SNPs may be involved in the generation of

TABLE 2

LINKAGE AND ADDITIVE MODEL MEASURED GENOTYPE LINKAGE DISEQUILIBRIUM RESULTS FOR THE THETA BAND P300 WINDOW TARGET CASE ERO PHENOTYPE, USING THE CAUCASIAN-ONLY DATA SUBSET (1067 INDIVIDUALS FROM 210 FAMILIES). LINKAGE DISEQUILIBRIUM ANALYSIS WITH ADDITIVE MODEL MEASURED GENOTYPE DATA REVEALS SIGNIFICANT ASSOCIATION OF THE FRONTAL AND CENTRAL REGION PHENOTYPE WITH SNP RS2350786. LINKAGE ANALYSIS CONDITIONAL ON THE ADDITIVE MODEL MEASURED GENOTYPE DATA RESULTS IN ABOUT 10% DECREASE IN FRONTAL, CENTRAL AND PARIETAL PEAK LOD SCORES WITH THE SAME SNP

Region	SNP	LOD score	LOD score with covariate	Percent decrease	Additive model
Frontal	RS2350786	2.62 (171 cM)	2.32	12%	0.014*
	M16404		2.62	–	0.43
	RS1378650		2.62	–	0.14
Central	RS2350786	1.47 (163 cM)	1.32	10%	0.013*
	M16404		1.47	–	0.41
	RS1378650		1.47	–	0.066
Parietal	RS2350786	1.97 (163 cM)	1.75	11%	0.043*
	M16404		1.97	–	0.71
	RS1378650		1.97	–	0.22

theta and delta. Our findings indicate the importance of cholinergic receptor genes in human cognition via modulation of neuroelectric oscillations.

3. Conclusion

Genetic analysis of human brain oscillations helps to identify genetic loci underlying the functional organization of human neuroelectric activity. As reviewed above, we have identified genetic loci underlying brain oscillations that involve neurotransmitter systems of the brain, namely GABAergic and cholinergic systems. The advent of genomics and proteomics and a fuller understanding of gene regulation will open new horizons on the critical electrical events so essential for human brain function.

References

Almasy, L. and Blangero, J. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am. J. Hum. Genet.*, 1998, 62: 1198–1211.

Basar, E. *EEG-brain dynamics: relation between eeg and brain evoked potentials*, New York, Elsevier, 1980.

Basar, E., Schurmann, M., Basar-Eroglu, C. and Karakas, S. Alpha oscillations in brain functioning: an integrative theory. *Int. J. Psychophysiol.*, 1997, 26: 5–29.

Basar, E., Basar-Eroglu, C., Karakas, S. and Schurmann, M. Are cognitive processes manifested in event-related gamma, alpha, theta and delta oscillations in the EEG? *Neuroscience Lett.*, 1999, 259: 165–168.

Basar, E., Schurmann, M., Demiralp, T., Basar-Eroglu, C. and Ademoglu, A. Event-related oscillations are 'real brain responses' – wavelet analysis and new strategies. *Int. J. Psychophysiol.*, 2001a, 39: 91–127.

Basar, E., Basar-Eroglu, C., Karakas, S. and Schurmann, M. Gamma, alpha, delta and theta oscillations govern cognitive processes. *Int. J. Psychophysiol.*, 2001b, 39: 241–248.

Basar, E., Schurmann, M. and Sakowitz, O. The selectively distributed theta system: functions. *Int. J. Psychophysiol.*, 2001c, 39: 197–212.

Basar-Eroglu, C. and Basar, E. A compound P300–40 Hz response of the cat hippocampus. *Int. J. Neurosci.*, 1991, 60: 227–237.

Basar-Eroglu, C., Basar, E., Demiralp, T. and Schurmann, M. P300 response: possible psychophysiological correlates in delta and theta frequency channels. A review. *Int. J. Psychophysiol.*, 1992, 13: 161–179.

Basar-Eroglu, C., Struber, D., Basar, E. and Stadler, M. Frontal gamma-band enhancement during multistable visual perception. *Int. J. Psychophysiol.*, 1996a, 24: 113–125.

Basar-Eroglu, C., Struber, D., Schurmann, M., Stadler, M. and Basar, E. Gamma-band responses in the brain: a short review of psychophysiological correlates and functional significance. *Int. J. Psychophysiol.*, 1996b, 24: 101–112.

Basar-Eroglu, C., Demiralp, T., Schurmann, M. and Basar, E. Topological distribution of oddball 'P300' responses. *Int. J. Psychophysiol.*, 2001, 39: 213–220.

Calabresi, P., Centonze, D., Gubellini, P., Pisani, A. and Bernardi, G. Blockade of M2-like muscarinic receptors enhances long-term potentiation at corticostriatal synapses. *Eur. J. Neurosci.*, 1998, 10: 3020–3023.

Comings, D.E., Wu, S., Rostamkhani, M., McGue, M., Lacono, W.G., Cheng, L. S-C. and MacMurray, J.P. Role of cholinergic muscarinic 2 receptor (CHRM2) gene in cognition. *Molecular Psychiatry*, 2003, 8: 10–13.

Demilrap, T.A., Istefanopulos, Y. Basar-Eroglu, C. and Basar, E. Wavelet analysis of oddball P300. *Int. J. Psychophysiol.*, 2001, 39: 221–227.

Dierks, T., Frolich, L., Ihl, R. and Maurer, R. Event related potentials and psychopharmacology. Cholinergic innervation of P300. *Pharmacopsychiatry*, 1994, 27: 72–74.

Doppelmayr, M., Klimesch, W., Schwaiger, J., Auinger, P. and Winkler, T. Theta synchronization in the human EEG and episodic retrieval. *Neuroscience Lett.*, 1998, 257: 41–44.

Faulkner, H.J., Traub, R.D. and Whittington, M.A. Anaesthetic/amnesic agents disrupt beta frequency oscillations associated with potentiation of excitatory synaptic potentials in the rat hippocampal slice. *Br. J. Pharmacol.*, 1999, 128: 1813–1825.

Fellous, J.-M. and Sejnowski, T. Cholinergic induction of oscillations in the Hippocampal slice in the slow (0.5–2 Hz), theta (5–12 Hz) and gamma (35–70 Hz) bands. *Hippocampus*, 2000, 10: 187–197.

Frodl-Bauch, T., Bottlender, R. and Hegerl, U. Neurochemical substrates and neuranatomical generators of the event-related P300. *Neuropsychobiology*, 1999, 40: 86–94.

Haenschel, C., Baldeweg, T., Croft, R.J., Whittington, M. and Gruzelier, J. Gamma and beta frequency oscillations in response to novel auditory stimuli: A comparison of human electroencephalogram (EEG) data with in vitro models. *PNAS*, 2000, 97(13): 7645–7650.

Hammond, E.J., Meador, K.J., Aung-Din, R. and Wilder, B.J. Cholinergic modulation of human P3 event related potentials. *Neurology*, 1987, 37: 346–350.

Karakas, S., Erzengin, O.U. and Basar, E. A new strategy involving multiple cognitive paradigms demonstrates that ERP components are determined by the superposition of oscillatory responses. *Clin. Neurophysiol.*, 2000a, 111: 1719–1732.

Karakas, S., Erzengin, O.U. and Basar, E. The genesis of human event-related responses explained through the theory of oscillatory neural assemblies. *Neuroscience Lett.*, 2000b, 285: 45–48.

Klimesch, W., Schimke, H. and Schwaiger, J. Episodic and semantic memory: an analysis in the EEG theta and alpha band. *Electroencephalogr. Clin. Neurophysiol.*, 1994, 91: 428–441.

Klimesch, W. EEG-alpha rhythms and memory processes. *Int. J. Psychophysiol.*, 1997, 26: 319–340.

Klimesch, W., Doppelmayr, M., Pachinger, T. and Ripper, B. Brain oscillations and human memory performance: EEG correlates in the upper alpha and theta band. *Neuroscience Lett.*, 1997a, 238: 9–12.

Klimesch, W., Doppelmayr, M., Schimke, H. and Ripper, B. Theta synchronization and alpha desynchronization in a memory task. *Psychophysiology*, 1997b, 34: 169–176.

Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T. and Schwaiger, J. Induced alpha band power changes in the human EEG and attention. *Neurosci. Lett.*, 1998, 244: 73–76.

Klimesch, W., Doppelmayr, M., Stadler, W., Pollhuber, D., Sauseng, P. and Rohm, D. Episodic retrieval is reflected by a process specific to an increase in human electroencephalographic theta activity. *Neurosci. Lett.*, 2001a, 302: 49–52.

Klimesch, W., Doppelmayr, M., Yonelinas, A., Kroll, N., Lazzara, M., Rohm, D. and Gruber, W. Theta synchronization during episodic retrieval: neural correlates of conscious awareness. *Cognit. Brain Res.*, 2001b, 12: 33–38.

Kopell, N., Ermentrout, G.B., Whittington, M.A. and Traub, R.D. Gamma rhythms and beta rhythms have different synchronization properties. *PNAS*, 2000, 97(4): 1867–1872.

Lubar, J.F. Neocortical dynamics: implications for understanding the role of neurofeedback and related techniques for the enhancement of attention. *Appl. Psychophysiol. Biofeedback*, 1997, 22(2): 111–126.

Makeig, S., Westerfield, M., Jung, T.P., Enghoff, S., Townsend, J., Courchesne, E. and Sejnowski, T.J. Dynamic brain sources of visual evoked responses. *Science*, 2002, 295: 690–694.

Perry, E., Walker, M., Grace, J. and Perry, R. Acetylcholine in mind: a neurotransmitter correlate of consciousness? *Trends Neurosci.*, 1999, 22: 273–280.

Mitrofanis, J. and Guillery, R.W. New views of the thalamic reticular nucleus in the adult and in the developing brain. *Trends Neurosci.*, 1993, 16: 240–245.

Porjesz, B., Almasy, L., Edenberg, H., Wang, K., Chorlian, D.B., Foroud, T., Goate, A., Rice, J.P., O'Connor, S., Rohrbaugh, J., Kuperman, S., Bauer, L., Crowe, R.R., Schuckit, M.A., Hesselbrock, V., Conneally, P.M., Tischfield, J.A., Li, T.K., Reich, T. and Begleiter, H. Linkage disequilibrium between the beta frequency of the human EEG and a GABAa receptor gene locus. *PNAS*, 2002, 99: 3729–3733.

Potter, D.D., Pickles, C.D., Roberts, R.C. and Rugg, M.D. Scopolamine impairs memory performance and reduces frontal but not parietal visual P3 amplitude. *Biol. Psychology*, 2000, 52: 37–52.

Rangaswamy, M., Porjesz, B., Chorlian, D.B., Wang, K., Jones, K.A., Bauer, L.O., Kuperman, S., O'Connor, S., Rohrbaugh, J., Reich, T. and Begleiter, H. Beta power in the EEG of alcoholics. *Biol. Psychiatry*, 2002, 51: 831–842.

Rangaswamy, M., Porjesz, B., Chorlian, D.B., Wang, K., Jones, K.A., Kuperman, S., Rohrbaugh, J., O'Connor, S., Bauer, L.O., Reich, T. and Begleiter, H. Resting EEG in offspring of male alcoholics: Beta frequencies. *Intl. J. Psychophysiol.*, 2003, in revision.

Schurmann, M., Basar-Eroglu, C., Kolev, V. and Basar, E. A new metric for analyzing single-trial event-related potentials (ERPs) application to human visual P300 delta response. *Neuroscience Lett.*, 1995, 197: 167–170.

Schurmann, M., Basar-Eroglu, C. and Basar, E. Gamma responses in the EEG: elementary signals with multiple functional correlates. *Neuroreport*, 1997, 8: 531–534.

Schurmann, M., Basar-Eroglu, C., Kolev, V. and Basar, E. Delta responses and cognitive processing: single trial evaluations of human visual P300. *Int. J. Psychophysiol.*, 2001, 39: 229–239.

Stockwell, R.G., Mansinha, L. and Lowe, R.P. Localization of the complex spectrum: The S-transform. *IEEE Trans. on Sig. Proc.*, 1996, 44: 998–1001.

Tiesinga, P.H.E., Fellous, J-M., Jose, J.V. and Sejnowski, T.J. Computational model of carbachol-induced delta, theta and gamma oscillations in the Hippocampus. *Hippocampus*, 2001, 11: 251–274.

Tobler, I., Kopp, C., Deboer, T. and Rudolph, U. Diazepam-induced changes in sleep: Role of the alpha 1 GABA(A) receptor subtype. *Proc. Nat. Acad. Sci. (USA)*, 2001, 98(11): 6464–6469.

Van Beijsterveldt, C.E.M. and Boomsma, D.I. Genetics of the human electroencephalogram (EEG) and event-related brain potentials (ERPs): A review. *Hum. Genet.*, 1994, 94: 319–330.

Van Beijsterveldt, C.E.M., Molenaar, P.C.M., DeGeus, E.J. and Boomsma, D.I. Heritability of human brain functioning as assessed by electroencephalography. *Am. J. Hum. Genet.*, 1996, 58: 562–573.

Von Stein, A. and Sarnthein, J. Different frequencies for different scales of cortical intergration: from local gamma to long range alpha/theta synchronization. *Intl. J. Psychophysiol.*, 2000, 38(3): 301–313.

Whittington, M.A., Traub, R.D., Kopell, N., Ermenttrout, B. and Buhl, E.H. Inhibition-based rhythms: experimental and mathematical observations on network dynamics. *Intl. J. Psychophysiol.*, 2000, 38(3): 315–336.

Yordanova, J. and Kolev, V. Brain theta response predicts P300 latency in children. *Neuroreport*, 1996, 7: 277–280.