S. Laureys (Ed.)
Progress in Brain Research, Vol. 150
ISSN 0079-6123

CHAPTER 10

Dynamics of thalamo-cortical network oscillations and human perception

Urs Ribary*

Department of Physiology and Neuroscience, NYU School of Medicine, New York, NY 10016, USA

Abstract: There is increasing evidence that human cognitive functions can be addressed from a robust neuroscience perspective. In particular, the distributed coherent electrical properties of central neuronal ensembles are considered to be a promising avenue of inquiry concerning global brain functions. The intrinsic oscillatory properties of neurons (Llinás, R. (1988) The intrinsic electrophysiological properties of mammalian neurons: Insights into central nervous system function. Science, 242: 1654–1664), supported by a large variety of voltage-gated ionic conductances are recognized to be the central elements in the generation of the temporal binding required for cognition. Research in neuroscience further indicates that oscillatory activity in the gamma band (25–50 Hz) can be correlated with both sensory acquisition and premotor planning, which are non-continuous functions in the time domain. From this perspective, gamma-band activity is viewed as serving a broad temporal binding function, where single-cell oscillators and the conduction time of the intervening pathways support large multicellular thalamo-cortical resonance that is closely linked with cognition and subjective experience. Our working hypothesis is that although dedicated units achieve sensory processing, the cognitive binding process is a common mechanism across modalities. Moreover, it is proposed that such time-dependent binding when altered, will result in modifications of the sensory motor integration that will affect and impair cognition and conscious perception.

Gamma-band oscillations and cognitive processing

The excellent correlation between brain gamma-band coherent oscillations and cognitive functions is presently considered a key issue in the study of the electrophysiological basis for higher brain function in humans (Llinás and Ribary, 1993; Crick and Koch, 1996; Schiff et al., 2002) and animals (Steriade, 1993; Gray, 1999). In addition, gamma-band oscillations have been shown to be reset (Ribary et al., 1991) or otherwise modified by sensory stimulation, and to be correlated with normal and altered auditory perception (Joliot et al., 1994; Llinás et al., 1998a; Ribary et al., 2000; Ribary et al., 2004). Because specific findings concerning the relationship between cognition and the temporal organization of the thalamo-cortical system (Kato, 1990; Lindström and Wróbel, 1990) are now well-documented, a very significant area of research with deep implications on the nature of cognitive processes and their abnormalities, is yet to be done.

Over the past two decades, there have been many studies relating to gamma-band oscillatory brain activity (30–50 Hz) in humans and animals during sensory and cognitive processing (Freeman, 1975; Bressler and Freeman, 1980; Galambos et al., 1981; Sheer, 1984; Ribary et al., 1987; Eckhorn et al., 1988; Gray and Singer, 1989; Ahissar and Vaaida, 1990; Ribary et al., 1991; Llinás et al., 1991; Steriade et al., 1991a, b; Engel et al., 1991; Pantev et al., 1991; Llinás and Ribary, 1992; Young et al., 1992; Murthy and Fetz, 1992; Basar

*Corresponding author. Tel.: +1 (212) 263-6561;
Fax: +1 (212) 263-6976; E-mail: urs.ribary@med.nyu.ed

DOI: 10.1016/S0079-6123(05)50010-4

and Bullock, 1992; Llinás and Ribary, 1993; Steriade, 1993; Desmedt and Tomberge, 1994; Singer and Gray, 1995; Traub et al., 1996; Barth and MacDonald, 1996; Neuenschwander and Singer, 1996; Salenius et al., 1996; Lumer et al., 1997; Murthy and Fetz, 1997; Tallon-Baudry et al., 1997; Tallon-Baudry and Bertrand, 1999; Ribary et al., 1999; Knief et al., 2000; Kissler et al., 2000; Jensen et al., 2002a; Palva et al., 2002; Parra et al., 2003) and alterations in aging (Boettger et al., 2002). Freeman and his collaborators implemented multi-channel electric recordings from mammalian olfactory bulb and analyzed the complex spatial distribution of activity during odor discrimination (Freeman, 1975). Basar and co-workers (1987) first reported a 40-Hz auditory response in humans and later identified this distributed property as one of the principal components of the middle latency response of auditory-evoked potentials. Later, Galambos, and co-workers (1981) reported that the human auditory evoked steady-state potentials showed a resonance near 40 Hz and proposed new clinical applications and the extended exploration of cognitive processes. Sheer and his collaborators were the first to record human 40-Hz activity related to cognitive processing, and interpreted the 40-Hz rhythm as an index of a focused state of cortical arousal (Sheer, 1984). Freeman and van Dijk (1987) were the first to report on visual gamma oscillations showing that oscillatory activity in the monkey visual cortex possessed many of the same characteristics as its olfactory counterpart. Gray, from Freeman's laboratory, advanced the field in collaboration with Singer, in parallel with Eckhorn and collaborators, and described stimuli-dependent synchronous oscillations of local field potentials, and multiunit activity at frequencies near 40-Hz activity in the visual cortex of anesthetized cats (Eckhorn et al., 1988; Gray and Singer, 1989). At the single-cell level, gamma band oscillations were demonstrated to be an intrinsic property of cortical inhibitory neurons (Llinás et al., 1991) and of specific and non-specific thalamic neurons studied in vivo (Steriade, 1991a, b). These oscillations occurred coherently at widely separated visual sites within and across both hemispheres (Engel et al., 1991).

Neuronal substrates of human gamma band activity

Analysis of the origin of spatio-temporally coherent transient gamma-band electrical activity in humans during early sensory processing, using magnetoencephalography (MEG), demonstrated specific cortical activations (Pantev et al., 1991) and well-defined cortico-subcortical correlations (Ribary et al., 1991), using combined MEG with magnetic field tomography (MFT), indicating a time shift of 2-3 ms that was consistent with thalamo-cortical conduction times. In particular, MEG/MFT results indicated that the onset of activity at the thalamic level was followed by widespread activation of the thalamo-cortical system (TCS), which resulted in a large coupling of thalamo-cortical gamma band oscillation, organized in space and time (Ribary et al., 1991), which was altered in Alzheimer (AD) patients (Ribary et al., 1989, 1991). In particular, there was also an altered dynamics of steady-state gamma-band oscillations in moderate and severe AD patients, especially at cortical level (Fig. 1). Since our initial MEG findings, several studies have been initiated and confirmed the existence of such thalamo-cortical oscillation by direct recording in animals (Steriade, 1993) as well as the importance of specific and nonspecific thalamo-cortical conjunction (Steriade et al., 1996a, b).

Intracellular recordings from cortical interneurons (Llinás et al., 1991) and thalamic neurons studied in vivo (Steriade, 1991a, b) demonstrated gamma-band activity to be calcium dependent and originate in the dendrites (Pedroarena and Llinás, 1997). Taken together, these studies support the hypothesis that recurrent thalamo-cortico-thalamic activity is involved in organizing and supporting coherent gamma-band oscillations as a general synchronized event during sensory or cognitive processing (Ribary et al., 1987; Llinás and Ribary, 1993; Llinás et al., 1994; Llinás et al., 1998a; Ribary et al., 1999). In addition, mathematical modeling of the thalamo-cortical system (Destexhe and Babloyantz, 1991; Wright et al., 2001; Rennie et al., 2002) showed that the dynamics of the system was turbulent and desynchronized when intrinsic thalamic activity was excluded from the model (Destexhe and Babloyantz, 1991). The onset

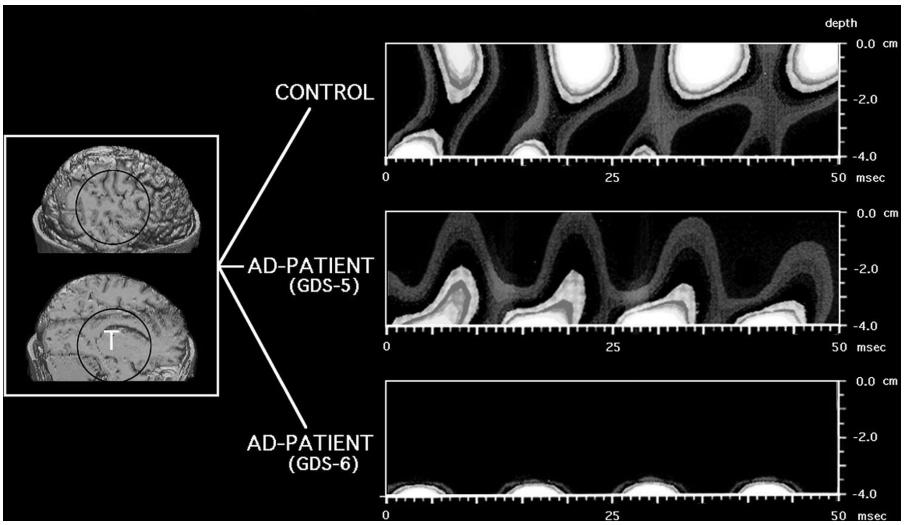

Fig. 1. Magnetic field tomography (MFT) images of steady-state gamma-band activity from a normal elderly adult and two age-matched patients with Alzheimer dementia (AD; moderate AD: Global Deterioration Scale (Reisberg et al., 1982) GDS-5, and severe AD: GDS-6) within the thalamo-cortical system. The location of the cylindrical source space is outlined on the 3D reconstructed MRI scan (left). The top face of the cylinder is close to the temporal area around the auditory cortex, while the bottom face is close to the thalamus (T). The axis of the cylinder is the midpoint of the MEG-probe placement. The MFT images are shown at 1 ms steps within a time window of 50 ms. The onset of activity at the thalamic level precedes the onset of activity at the cortical level by $\approx$ 3 ms. Note the altered gamma-band activation in AD patients, especially at cortical level.

of a pacemaker input organized the system into a more coherent spatio-temporal behavior and indicated further evidence for a coupling of oscillatory activity within thalamo-cortical systems (Steriade et al., 1993a, b; Llinás et al., 1994; Barth and MacDonald, 1996).

Earlier, we indicated that the auditory steady-state gamma-band response also reflected a complex, time-locked sequence of intrinsic network activations involving most probably thalamo-cortico-thalamic pathways, with a focus on temporal sensory areas resulting in increased synchronization of cortical gamma band activity, driven by subcortical areas (Ribary et al., 1988, 1989). A model for the cortico-thalamo-cortical resonance (Fig. 2) and electrophysiological temporal coincidence was proposed (Llinás, 1990; Llinás and Ribary, 1993), which supports gamma-band oscillation at the cortex and was recently demonstrated in vitro using voltage-dependent dye imaging in brain slices of thalamus and cortex (Llinas et al., 2002). Thalamic projection neurons synapse onto GABAergic inhibitory interneurons in layer IV. These interneurons, which have intrinsic membrane oscillations in the gamma band (close to 40 Hz), can elicit inhibitory post-synaptic potential (IPSP) in pyramidal neurons. Such input results in a 40-Hz rebound firing of the pyramidal cells (Pedroarena and Llinás, 1997).

Moreover, input from layer VI pyramidal cells terminate on thalamic neuron dendrites and generate gamma band activation of thalamic projection neurons. This thalamic oscillation is then signaled back to the cortex, establishing a large resonant oscillation between the thalamus and the cortex (Ribary et al., 1991), which can recruit sufficient elements to generate the synchronicity observed at both intracellular and extracellular levels in the cortex and thalamus. In addition to the thalamo-cortical resonance of specific thalamo-cortical neurons, we earlier suggested a second system (Llinás and Ribary, 1993), represented by the intralaminar cortical input to layer I of the cortex and its return-pathway projection via layers V and V1 of pyramidal systems to the intralaminar nucleus, directly and indirectly, via collaterals to the nucleus reticularis. The cells in this system have been shown to oscillate in 40-Hz bursts

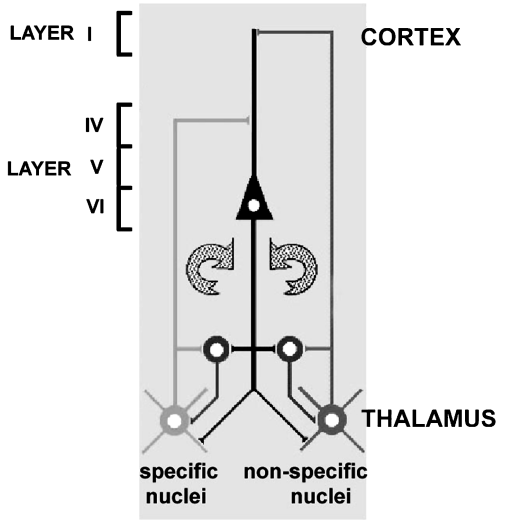

Fig. 2. Diagram of two thalamo-cortical systems proposed to generate gamma-band activity and subserve temporal binding (Llinás and Ribary, 1993). Left: Specific thalamo-cortical circuit: projection of sensory or motor nuclei input to layer IV of the cortex, producing cortical oscillation by direct activation and feed-forward inhibition. Collaterals of these projections produce thalamic feedback inhibition via the reticular nucleus. The return pathway (circular arrow on the right) re-enters this oscillation to specific and reticularis thalamic nuclei via layer VI pyramidal cells. Right: Non-specific thalamo-cortical circuit: Second loop shows nonspecific intralaminar nuclei projecting to the most superficial layer I of the cortex and giving collaterals to the reticular nucleus. Pyramidal cells return oscillation to the reticular and the non-specific thalamic nuclei, establishing a second resonant loop. The conjunction of the specific and non-specific loops is proposed to generate temporal binding.

(Steriade et al., 1993a) and were shown to synapse directly on the apical dendrites of layer V of pyramidal cells (Llinas et al., 2002). (For detailed projections in thalamus, see also Steriade and Llinas, 1988).

Finally, it is also evident from the literature that neither of these two circuits alone can directly relate to cognitive events and conscious perception. Indeed, damage of specific systems produces loss of the particular modality, while damage of the non-specific thalamus produces lethargy and coma (Façon et al., 1958; Castaigne et al., 1980) and disturbances in visual perception (Purpura and Schiff, 1997). As such then, the resonant gamma-band co-activation of both, the specific and non-specific thalamo-cortical system, may contribute to conscious perception (Llinás and Ribary, 1993), and may relate to the binding of sensory information (Gray, 1999).

Network dynamics and sensory perception

It was further proposed that coupling of thalamo-cortical oscillatory activity support the temporal binding mechanism responsible for bringing together information from various sensory modalities into one single percept (Llinás and Ribary, 1993). Indeed, MEG recordings on control subjects demonstrated that such precise timing of thalamo-cortical network activity, originally described during auditory temporal processing (Joliot et al., 1994), was also present in the somatosensory (Sauve et al., 1999) and visual modality (Ramirez et al., 2000, 2002) in the healthy human brain. In particular, we have provided evidence that the reset of the gamma-band magnetic signal correlated with sensory perception, namely with the minimal interval required to identify separate sensory stimuli.

Coherent gamma oscillations vs. auditory perception

The auditory system is known for its excellent time resolution (Teich et al., 1993; Carr, 1993). Indeed, the system can localize sound in space by detecting delays on the order of microseconds (Carr and Konishi, 1990). In addition, neuropsychological and psychophysical observations indicated that the auditory system is capable of tonality discrimination of two stimuli separated by only 1–2 ms (Miller and Taylor, 1948), while 15–20 ms is required for the perceptual identification of two stimuli (Hirsh, 1959).

Using functional brain imaging, such as MEG, earlier data indicated a clear time-locked oscillatory activity in the gamma band in response to one auditory stimulus (Ribary et al., 1991; Pantev et al., 1991; Barth and MacDonald, 1996). This reset was defined as a 2.5 cycle gamma-band oscillation (Joliot et al., 1994). Results further indicated that this coherent gamma-band activity is related to the temporal binding of incoming sensory stimuli (Joliot et al., 1994). In particular, it

was determined that the minimal interval required to identify separate auditory stimuli is correlated with the resetting of the gamma-band magnetic signal. In young subjects, experimental and modeling results indicated a stimulus-interval-dependent response with a critical interval of 12–15 ms (Joliot et al., 1994), which occurred specifically in the gamma range only. At shorter intervals, only one gamma-band response occurred following the first stimulus. With longer intervals, a second gamma-band response appeared, which coincided with the subject's perception of a second distinct auditory stimulus. These results indicated that gamma-band oscillation recorded during the first 100 ms post stimulus represent a functional correlate to the early temporal processing of auditory stimuli.

Specifically, MEG activity was recorded in response to two clicks presented at various interstimulus intervals (ISI). A power spectral analysis of the raw MEG data in response to a single click showed activation at lower frequency (9–10 Hz) and at gamma-band frequency (25–50 Hz) (Joliot et al., 1994). In response to the two clicks with increasing ISI, data indicated a distinct temporal coherent pattern in the gamma range only, and no clear temporal characteristics in the lower frequency range. In particular, data indicated only one gamma-band response following the presentation of two auditory stimuli at ISIs of less than 12 ms. Indeed, the response was identical to that following a single stimulus (Joliot et al., 1994). When the stimuli were presented at longer intervals, a second gamma-band response abruptly appeared. This second response overlapped that elicited by the first stimulus.

To investigate the underlying mechanism of these results we tested two possible models (Joliot et al., 1994): The first model posited that the first stimulus triggers a gamma-band oscillation event and the second stimulus would induce a similar response only after a given time interval. The second model posited that both stimuli produced a separate gamma-band oscillation event, independently of the ISI. The results predicted by the two models were compared with the electrophysiological data obtained from all MEG recording positions. Statistical analysis of nine young subjects (20–40 years old) indicated that the first model fitted the experimental data significantly better than the second one. A two-tailed Student's t-test on the criteria value (x) indicated that the dependent model was not significantly different below the ISI of 14.2 ms for all nine subjects (Joliot et al., 1994).

This finding indicated that at ISIs of 14.2 ms or less, only the first stimulus induced a gamma-band response, while with longer intervals a second reset in gamma-band activity occurred. Thus, in this case each stimulus induced its own gamma-band activity. A similar set of stimuli was presented following MEG recordings, and the perceptual threshold for identifying two clicks was established. Perceptual responses from all subjects indicated that stimuli presented at an ISI longer than 13.7 ms could be identified as two clicks. The interval between stimuli required for the second MEG response and that required for the perception of a second auditory stimulus as a distinct event were not statistically different (interval difference = 1.32 ms, $n = 9$, $p = 0.309$, two-tailed Student's t-test). No regression between the two variables was significant, indicating a cluster-like correlation near 12–15 ms (Joliot et al., 1994). These findings correlated well with neuropsychological and psychophysical observations.

The ability to judge the temporal order of a sequence of sounds was reported to depend on whether the task required actual identification of the individual elements of the sequence or whether it could be performed by discrimination of their global pattern. While the finest acuity for discrimination tasks occurred on the order of 1–2 ms (Miller and Taylor, 1948), the identification of individual elements was on the order of 15–20 ms (Hirsh, 1959). Brain-imaging results coincided closely to the classical ISI required to identify individual stimuli. In addition, other observations concluded that sensory information was processed in discrete time segments (Poppel, 1970; Madler et al., 1991) as low as 12.5 ms (Kristofferson, 1984). This indicated that stimuli coming within one perceptual "quantum" (12–15 ms) were bound into one cognitive event, rather than perceived as separate entities (Llinás and Ribary, 1993).

These findings indicated that gamma-band oscillatory activity is not only involved in primary

sensory processing per se (Pantev et al., 1991), but also forms part of a time conjunction or binding property that amalgamates early sensory information in perceptual time quanta (Llinás and Ribary, 1993). The results further indicated that binding can occur in steps or "quanta" of 12–15 ms, and further support our hypothesis that gamma-band oscillatory activity could serve a broad cognitive binding function of multi-sensory information into a single percept (Llinás and Ribary, 1993).

Coherent gamma oscillations versus somatosensory and visual perception

Furthermore, functional imaging data have shown that this minimal interval to identify two distinct sensory events is similar in other sensory modalities, demonstrating that such precise timing of thalamo-cortical network activity was also present in the somatosensory (Sauve et al., 1999) and visual modality (Ramirez et al., 2000, 2002) and correlated well with the perceptual identification of somatosensory or visual stimuli.

Somatosensory oscillatory cortical representations in the contra-lateral primary somatosensory cortex have been characterized using EEG and MEG (Desmedt and Tomberge, 1994; Sauve, 1999, 2003). Functional somatotopic reorganization in animals and humans has further been observed (Merzenich et al., 1987; Ramachandran et al., 1992; Mogilner et al., 1993; Yang et al., 1994; Elbert et al., 1995). However, relatively few experiments have examined the underlying network dynamics and the binding of somatosensory input. In recent experiments, six sighted and six blind subjects were stimulated with taps of 2 ms duration from two piezoelectric stimulators, held between the thumb and index finger of each hand (Sauve et al., 1999; Ribary et al., 2002). Both hands were stimulated synchronously with one tap each, or with an ISI of 2, 4, 6,…, 26, 30, 34 ms. MEG results indicated a specific time pattern of coherent oscillatory gamma-band activity, which correlated with the perception of somatosensory input (Sauve et al., 1999). In particular, data indicated that the temporal processing of tactile stimuli occurred in discrete time quanta of 12–15 ms, as originally observed in the auditory modality (Joliot et al., 1994).

Recent findings indicated that a similar precise timing of thalamo-cortical networks was also observed in the visual system, responsible for the integration of visual input (Ramirez et al., 2000). The human visual system is hypothesized to code motion in discrete time quanta. To investigate the neurobiological correlates of apparent visual motion perception, we recently designed a paradigm in which the neuromagnetic responses to local apparent motion stimuli were recorded using MEG (Ramirez et al., 2000). Subjects were recorded while stimulated in the periphery with two bars of light separated by 1° at a distance of 45 cm, flashed for 3 ms, with stimulus onset asynchrony (SOA) of 0, 3,…, 27 ms. Psychophysical analysis indicated that the subjects perceived apparent motion more than 50% of the time for SOAs longer than 15–18 ms. For shorter SOAs, subjects perceived two simultaneous bars of light rather than a single moving bar. MEG results therefore indicated that apparent visual motion perception is processed in quanta of 12–15 ms as well, and correlated with increased gamma-band activity in the visual system. Dynamic gamma-band source activations were reconstructed in many of the motion-sensitive visual areas, particularly in area V3A, hMT+, parietal and temporal cortex (Ramirez et al., 2000, 2002; Ribary et al., 2002).

These data further indicated that the same fundamental processing mechanism seems to be functioning for the three sensory modalities, namely a precise timing of thalamo-cortical network activations in the gamma-band in the healthy human brain, in order to bind sensory input into one single percept (Llinás and Ribary, 1993).

Altered gamma oscillations versus altered perception in dyslexia and normal aging

Previous studies have shown that the minimal interval to identify two separate sensory events is altered in subjects with language-based learning disabilities (LLD or dyslexia) (Llinás et al., 1998b; Ribary et al., 2000) and in normal aging (Sauve et al., 2003; Ribary et al., 2004). Such correlation is

observable independently by either psychological means or functional MEG imaging. Also, there is an excellent correlation between these two different measurement techniques (Llinás et al., 1998b; Ribary et al., 2004). As such, MEG imaging may offer an objective measure that is correlated with normal and slightly altered sensory cognitive experience (Nagarajan et al., 1999). We previously proposed that gamma-band binding abnormalities could be one of the neurophysiological correlates of the temporal deficits recorded in LLD (Llinás, 1993). Indeed, in subjects with dyslexia, altered MEG data correlated with a delayed perceptual threshold above 20 ms for the identification of a second auditory stimulus (Llinás et al., 1998b; Ribary et al., 2000), compared to 12–15 ms in healthy controls. This dyschronia is consistent with other findings concerning LLD (Tallal et al., 1993, 1996; Merzenich et al., 1996; Salmelin et al., 1996; Nagarajan et al., 1999; Helenius et al., 1999; Simos et al., 2000; Heim et al., 2000; Benasich and Tallal, 2002; Tallal, 2004). MEG recordings further indicated a large variation in the time interval necessary for the appearance of a second gamma-band wave (Llinás et al., 1998b; Ribary et al., 2000). More specifically, MEG data suggested the existence of two different sub-groups of LLD subjects (Fig. 3).

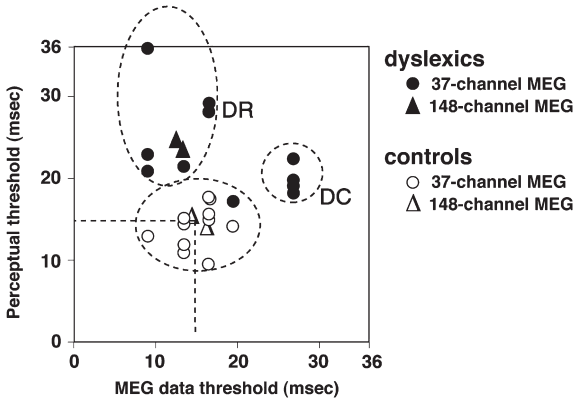

Fig. 3. Altered auditory binding and perception in subjects with language-based learning disabilities (LLD or dyslexia). Perceptual thresholds plotted as a function of MEG thresholds obtained from 16 control (open circles/triangles) and 13 LLD or dyslexic (filled circles/triangles) subjects. Dyschronic (DC) subjects display delayed MEG and perceptual thresholds, while dysrhythmic (DR) subjects display slightly shorter MEG thresholds in conjunction with delayed perceptual thresholds, which may relate to background masking.

Magnetic recordings from one group indicated an increased processing latency for the first stimulus, consistent with increased temporal binding (dyschronia). MEG data recorded from the other group indicated an incomplete processing of the first stimulus and a discontinuity of the binding mechanism resulting in a background masking effect (dysrhythmia). These findings (Ribary et al., 2000) remained the same by using a new state-of-the-art whole head MEG system and by increasing the number to a total of 16 controls and 13 LLD subjects (Fig. 3).

In addition, there is increasing evidence that sensory processing is also altered in the aging brain, although sensory physiological thresholds remain at normal levels. Psychophysical thresholds in many simple auditory tasks deteriorate indeed with age. For example, auditory fusion thresholds for gaps between two long tones have been shown to increase with age, particularly for subjects aged over 60 (McCroskey and Kasten, 1980; Robin and Royer, 1989). Temporal order judgments of auditory stimuli also become less accurate with age (Fitzgibbons and Gordon-Salant, 1998). Such declining auditory acuity has been hypothesized to relate to declining speech processing that has long been evident in elderly subjects. In those studies, however, the discrimination time windows were set above 25 ms. Recent critical discrimination paradigms can produce a more precise measure of perceptual and functional imaging change because the intervals are set between 0 and 36 ms (Ribary et al., 1999, 2004; Sauve et al., 2003).

Preliminary MEG data on elderly subjects that have been tested so far indeed suggested that (1) a distinct gamma-band oscillatory reset within thalamo-cortical systems by sensory stimuli is altered in the aging human brain and (2) an altered reset of gamma-band activity is related to a correlation between delayed MEG thresholds and delayed perceptual thresholds to identify two distinct sensory events during early sensory processing (Sauve et al., 2003; Ribary et al., 2004). In particular, there was a delay of approximately 3–12 ms compared to thresholds in younger control subjects.

Using similar paradigms as mentioned above, two auditory clicks were delivered at different ISIs. MEG activity was recorded and the subjects were asked if they heard one or two clicks (Fig. 4). The gamma-band reset activity was delayed in the five elderly subjects that have been tested (aged 75, 79, 79, 75, 69 years). In particular, at ISIs of 18 ms or more, there was a second reset of gamma-band activity indicating a delayed processing of a second distinct auditory stimulus. Preliminary data further suggested a correlation between delayed perceptual and delayed MEG thresholds in the elderly group. These results strongly suggest a delay during early sensory information processing of sensory stimuli in normal aged subjects.

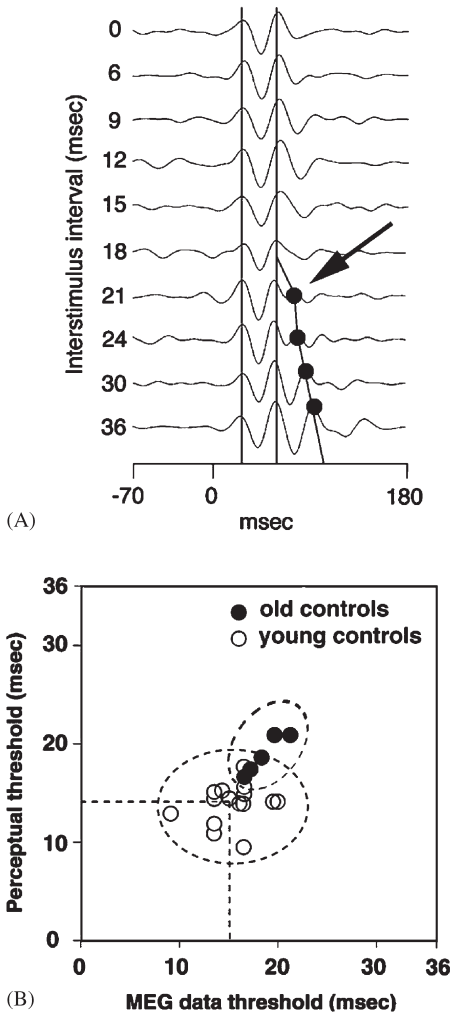

Fig. 4. Altered auditory binding and perception in the aging brain. (A) Effect of increasing the interstimulus interval on MEG activity in the higher (20–50 Hz) gamma band frequency range in an older subject (75 years). As the interval increased >18 ms, a second, delayed gamma band response appeared. (B) Perceptual thresholds plotted as a function of MEG thresholds obtained from 16 younger (20–40 years, open circles) and 5 older (69–79 years, filled circles) subjects. Note that the tendency of an increased MEG threshold is correlated with an increased perceptual threshold.

Network dysrhythmia in neurology and psychiatry

Earlier MEG studies, as mentioned above, provided evidence for a slight dysrhythmia within thalamo-cortical systems in subjects with LLD (Llinás et al., 1998b; Nagarajan et al., 1999). Clearly an alteration of precise timing of thalamo-cortical networks correlated to altered behavioral patterns, namely to altered perception of sensory input (Ribary et al., 1999). In unconscious humans, magnetic resonance imaging (MRI), MEG, and positron emission tomography (PET) data indeed indicated a massive fracture of thalamo-cortical systems, as observed in patients in a vegetative state (Schiff et al., 1999, 2002, this volume). These findings suggested that a dysrhythmia within thalamo-cortical systems could represent a key issue underlying various pathological behavioral symptoms (Llinás et al., 1999). Recent MEG results, combined with findings based on electrical recordings from human thalamus (Jeanmonod et al., 1996, 2001; Sarnthein et al., 2003) and physiological findings on animals (Jahnsen & Llinás, 1984; Llinás et al., 2002), indeed indicated that a severe and sustained dysrhythmia within thalamo-cortical systems could underlie various positive symptoms observed in a subset of neurological and psychiatric patients (Llinás et al., 1999, 2001; Schulman et al., 2000, 2001, 2003; Sarnthein et al., 2003; Jeanmonod et al., 2003; Timmermann et al., 2003).

Spontaneous MEG activity was recently recorded in patients suffering from neurogenic pain, tinnitus, Parkinson's disease, schizophrenia, depression, or refractory obsessive compulsive disease (Llinás et al., 1999, 2001; Schulman et al.,

2000, 2001, 2003). Compared to healthy controls, patients showed increased low-frequency theta rhythmicity in conjunction with a widespread and marked increase of power correlation among high- and low-frequency oscillations consistent with other reports (John et al., 1988; John, this volume). These data indicated the presence of a thalamo-cortical dysrhythmia, which we propose is related to all the above-mentioned conditions (Llinás et al., 1999). Such dysrhythmia can be explained by either excess inhibition or disfacilitation of the thalamo-cortical system in these patients, inducing the generation of low-threshold calcium spike bursts by thalamic cells as seen in animals (Llinás et al., 2001) and humans (Jeanmonod et al., 1996). The presence of these bursts in human thalamus (Jeanmonod et al., 2001) directly relates to thalamic cell hyperpolarization and low frequency generation within thalamus (Jahnsen and Llinás, 1984). This produces coherent theta activity, the result of a resonant interaction between thalamus and cortex. The emergence of positive clinical symptoms is then viewed as resulting from increased gamma-band activation due to decreased inhibition between high- and low-frequency thalamo-cortical modules at the cortical level, which we refer to as the ''edge effect'' (Llinás et al., 1999). This effect is observable as increased correlation between low- and high-frequency oscillations resulting from such inhibitory asymmetry at the cortical level.

The description of such thalamo-cortical dysrhythmias (Llinás et al., 1999) also provides a conceptual framework for evaluating slight alterations in resting brain activity in the normal aging brain or in dyslexia. These alterations are expected to be smaller compared to the severe thalamo-cortical dysrhythmia observed in more invalidating neurological and psychiatrical diseases, or compared to selective fracture of thalamo-cortical networks in unconsciousness (e.g., in vegetative patients; Schiff et al., 2002). In states of thalamo-cortical dysrhythmia, ongoing theta-range (4–8 Hz) thalamic activity serves as the trigger for cortical dysfunction, in which a core region of cortex functions at low frequency, surrounded by a region of activation in the normal waking gamma (25–50 Hz) range (Llinás et al., 2002). In addition, the connectivity of the thalamo-cortical system not only maintains this pathological dynamics, but also causes it to become distributed throughout wide areas of cortex representing a large-scale coupling, which allows such activity to constrain thalamo-cortical dynamics so efficiently. This adds considerable weight to the question of whether some of the slight cognitive deficits of aging and dyslexia are based upon varying degrees of a slight dysrhythmia (Llinás et al., 1998a; Schulman et al., 2003; Ribary et al., 2004).

Fracture of thalamo-cortical networks during unconsciousness

Earlier, we speculated that if the dynamics of thalamo-cortical network oscillations is indeed crucial for early sensory processing relating to perception, then we should expect a massive fracture within these thalamo-cortical systems during unconsciousness (Plum et al., 1998), such as during the vegetative state (Jennett and Plum, 1972). In a series of studies on patients in a vegetative state (Schiff and Plum, 2000), using MRI, PET, and MEG, we indeed found that there was a massive structural damage within thalamo-cortical systems, combined with a massive shutdown of brain metabolism, and a massive shutdown in neural connectivity (Plum et al., 1998; Schiff et al., 1999, 2002; Schiff, this volume). These studies were in accordance with other functional brain imaging studies, demonstrating consistently diffuse and uniformly reduced cerebral metabolic activity (Levy et al., 1987; DeVolder et al., 1990; Tomassino et al., 1995; Rudolf et al., 1999; Laureys et al., 1999). In addition, a selective disappearance of sensory midlatency responses and early evoked potentials were reported in comatose patients (Pfurtscheller et al., 1983) and during general anesthesia (Madler et al., 1991). Recent studies also indicated the importance of coherent gamma-band activity in relation to different functional states during general anesthesia (John et al., 2001; John, this volume).

Recent findings demonstrated that although the vegetative state is characterized by massively reduced brain metabolism and connectivity, some patients may express isolated meaningless fragments

of behavior that can be related to islands of residual metabolic and physiologic brain activity (Schiff et al., 1999, 2002). An earlier case study consisted of such a unique vegetative patient who randomly produced occasional single words (Schiff et al., 1999). In this patient, isolated regions of preserved cerebral metabolic activity and thalamo-cortical transmission associated with remnants of the language system. These findings led us to evaluate additional vegetative patients with multi-modal imaging techniques in order to determine in detail what cerebral activity may remain in patients with catastrophic brain damage. We reported evidence of reciprocal clinical–pathological correlation with regional differences of quantitative cerebral metabolism (Schiff et al., 2002). We also employed MEG to analyze dynamic aspects of source activations in such patients, namely to identify spatio-temporal sources, if any, of brain activations associated to specific frequency bands as seen during normal sensory processing (Regan, 1989; Ribary et al., 1991, 1999; Baumgartner et al., 1995; Llinás et al., 1999). This diagnostic protocol was designed to examine the possible persistence of remaining coherent neuronal network activity. The MEG data from the vegetative patients indicated partially preserved but abnormal, delayed, incomplete or absent coherent dynamic brain activity (Schiff et al., 2002). Restricted sensory representations evidenced by slow evoked magnetic fields and gamma-band activity, were uniquely expressed in each patient, and correlated with isolated behavioral patterns in two patients. These isolated and abnormal residual MEG activations were further correlated with locally preserved metabolic activity. The combination of MRI, PET and MEG techniques allowed us to assess the residual network properties that underlie the expression of meaningless fractional behavior observed in three of the five chronic vegetative patients reported (Schiff et al., 2002; see also Schiff, this volume).

In the intact, normal healthy brain, these modular networks do process selective sources of information and are typically integrated into large, coherent or coupling patterns of activity (Llinás and Ribary, 1993; Friston et al., 1993; Bressler et al., 1993; Zeki and Bartels, 1998; Tononi and Edelmann, 1998.; Van Essen et al., 1998, Singer, 1998; Raichle, 1999; John, 2002; see also John, this volume). These novel findings on patients in a vegetative state (Schiff et al., 2002) collectively provide a foundation for identifying mechanisms underlying complex brain injuries and may lead to more objective diagnostic procedures for the future. In particular, these studies may represent a first step toward characterizing patients with varying degrees of functional recovery beyond the vegetative state. Such steps will be necessary to appropriately risk-stratify patients for future studies of outcome or therapeutic interventions.

Summary: interaction and dynamics of large-scale network oscillations in the normal and pathological brain

All the above-mentioned findings, within the context of the current literature, suggest that non-invasive brain imaging techniques available today and combined with highly sophisticated signal processing and analysis techniques are providing complementary, and very useful information regarding brain structure, and brain function with detailed spatial and temporal constraints. These findings further suggest that these objective brain imaging measurements may already be correlated with various broad cognitive processing and pathological states. A better characterization of underlying extended large-scale networks and the detailed analysis of the temporal dynamics is very important in order to better understand normal human brain function such as perception and memory and the many pathological alterations. Recent improvements in signal processing and analysis techniques (Dale and Sereno, 1993; Makeig et al., 1997, 2002; Pascual–Marqui et al., 1995; Mosher et al., 1999a, b; Gross et al., 2002; Jensen et al., 2002b; Ramirez et al., 2003, 2004; Michel et al., 2004) indeed provide confidence that non-invasive functional human brain imaging techniques may soon be capable of extracting the various network functions (Ribary et al., 1991; Schiff et al., 2002; Gross et al., 2002) and monitoring their detailed network dynamics and interactions in relation to specific cognitive tasks. In addition, specific time sequences or quantal

time windows (Joliot et al., 1994) were already mentioned, in relation to normal or altered early sensory processing, which further suggests that normal brain function may indeed be quantified as non-continuous time sequences (Lehmann et al., 1987; Ribary et al., 1991; Llinás and Ribary, 1993; Michel et al., 2004) based on detailed spatial and temporal constraints. Such a quantification strategy of normal brain function could now be applied in various neurological and psychiatric patient populations, as mentioned here specifically in traumatic brain injury, and the alterations could be specified. I would call such techniques diagnostic brain sequencing procedures. As such then, a "normal" brain sequencing procedure in healthy control subjects would represent an analysis of a normalized series of multiple quantal time windows describing a non-continuous evolution of large-scale network oscillations and couplings, laid out over a time period of several 100 ms and directly correlated to sensory processing and memory. Diagnostic brain sequencing procedures in brain pathologies would then represent a quantitative comparison and a quantitative deviation of such normalized time series having shorter, longer, abnormal, or missing quantal time windows and describing an abnormal non-continuous evolution of large-scale network oscillations and couplings. Detailed analysis of such individual quantal time windows would then specify changes within local networks or between large-scale networks, such as changes in oscillation frequency, changes in spectral power, changes in synchronization, coherence, coupling, etc. Such diagnostic brain sequencing procedures may then lead to better objective diagnostic procedures for various brain pathologies and for better treatment strategies in the future, including dyslexia (Merzenich et al., 1996; Tallal, 2004), neurology (see Schiff, this volume), and psychiatry (Jeanmonod et al., 2003).

Acknowledgments

This review summarizes only a selection of many MEG studies performed at the Center for Neuromagnetism (CNM) at the NYU School of Medicine over the past 16 years in collaboration with many colleagues. Especially, I acknowledge the very inventive and very productive interaction with Dr. R. Llinas and the wonderful interaction with the great team at CNM over all those years, especially with R. Jagow and Drs. E. Kronberg, A. Mogilner, F. Lado, L. Lopez, J. Cappell, J. Schulman, R. Ramirez, K. Sauve, and many others. I further acknowledge the interesting and productive interaction with many collaborators, Drs. N. Schiff, F. Plum, M. Joliot, D. Jeanmonod, J. Volkmann, H. Van Marle, A. Rezai, S. Miller, P. Tallal, S. Ferris, A. Kluger, A. Ioannides, P. Mitra,. P. Kelly, R. Cancro, S. Kolodny, N. Cohen, O. Devinski, S. Pacia, and others. I further acknowledge the MFT analysis by Dr. A. Ioannides for Figure 1.

These studies were supported by many funding sources, especially by NIH, The Charles A. Dana Foundation, The James Watson Foundation, the NYU-GCRC, and 4D-Neuroimaging.

References

Ahissar, E. and Vaaida, E. (1990) Oscillatory activity of single units in a somatosensory cortex of an awake monkey and their possible role in texture analysis. Proc. Natl. Acad. Sci. USA, 87: 8935–8939.

Barth, D.S. and MacDonald, K.D. (1996) Thalamic modulation of high-frequency oscillating potentials in auditory cortex. Nature, 383: 78–81.

Basar, E., Rosen, B., Basar-Eroglu, C. and Greitschus, F. (1987) The associations between 40-Hz EEG and the middle latency response of the auditory evoked potential. Int. J. Neurosci., 33: 103–117.

Basar, E. and Bullock, T. (1992) Induced Rhythms in the Brain, Brain Dynamics Series. Birkhauser, Boston, MA.

Baumgartner, C., Deecke, L., Stroink, G. and Williamson, S.J. (1995) Biomagnetism: Fundamental Research and Clinical Applications. Elsevier, Amsterdam.

Benasich, A.A. and Tallal, P. (2002) Infant discrimination of rapid auditory cues predicts later language impairment. Behav. Brain Res., 136: 31–49.

Boettger, D., Herrmann, C.S. and von Cramon, Y. (2002) Amplitude differences of evoked alpha and gamma oscillations in two different age groups. Int. J. Psychophysiol., 45: 245–251.

Bressler, S.L. and Freeman, W.J. (1980) Frequency analysis of olfactory system EEG in cat, rabbit and rat. Electroenceph. Clin. Neurophysiol., 50: 19–24.

Bressler, S.L., Coppola, R. and Nakamura, R. (1993) Episodic multiregional cortical coherence at multiple frequencies during visual task performance. Nature, 366: 153–156.

Carr, C.E. (1993) Processing of temporal information in the brain. Ann. Rev. Neurosci., 16: 223–243.
Carr, C.E. and Konishi, M. (1990) A circuit for detection of interaural time differences in the brain stem of the barn owl. J. Neurosci., 10: 3227–3246.
Castaigne, P., Lhermitte, F., Buge, A., Escourolle, P., Derouisne, C. and Der Agopian, P. (1980) Paramedian thalamic and midbrain infarcts: clinical and neuropathological study. Ann. Neurol., 10: 127–214.
Crick, F. and Koch, C. (1996) The problem of consciousness. Sci. Am., 267: 153–159.
Dale, A.M. and Sereno, M.I. (1993) Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: a linear approach. J. Cogn. Neurosci., 5: 162–176.
Desmedt, J.E. and Tomberge, C. (1994) Transient phase-locking of 40-Hz electrical oscillations in prefrontal and parietal human cortex reflects the process of conscious somatic perception. Neurosci. Lett., 168: 126–129.
Destexhe, A. and Babloyantz, A. (1991) Deterministic chaos in a model of the thalamo-cortical system. In: Babloyantz A. (Ed.), Self-Organization, Emerging Properties and Learning. Plenum Press, New York.
DeVolder, A.G., Goffinet, A.M., Bol, A., Michel, C., de Barsy, T. and Laterre, C. (1990) Brain glucose metabolism in post-anoxic stroke. Arch. Neurol., 47: 197–204.
Eckhorn, R., Bauer, R., Jordan, W., Brosch, M., Kruse, W., Munk, M. and Reitboeck, H.J. (1988) Coherent oscillations: A mechanism of feature linking in the visual cortex? Biol. Cybern., 60: 121–130.
Elbert, T., Pantev, C., Wienbruch, C., Rockstroh, B. and Taub, E. (1995) Increased cortical representation of the fingers of the left hand in string players. Science, 270: 305–307.
Engel, A.K., Konig, P., Kreiter, A.K. and Singer, W. (1991) Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. Science, 252: 1177–1179.
Façon, E., Steriade, M. and Wertheim, N. (1958). Rev. Neurol. (Paris), 98: 117–133.
Fitzgibbons, P.J. and Gordon-Salant, S. (1998) Auditory temporal order perception in younger and older adults. J. Speech Lang. Hear. Res., 41: 1052–1060.
Freeman, W.J. (1975) Mass Action in The Nervous System. Academic Press, New York.
Freeman, W.J. and van Dijk, B.W. (1987) Spatial patterns of visual cortical fast EEG during conditioned reflex in a rhesus monkey. Brain Res., 422: 267–276.
Friston, K.J., Frith, C.D., Liddle, P.F. and Frackowiak, R.S. (1993) Functional connectivity: the principal-component analysis of large (PET) data sets. J. Cereb. Blood Flow Metab., 13: 5–14.
Galambos, R., Makeig, S. and Talmachoff, P.J. (1981) A 40-Hz auditory potential recorded from the human scalp. Proc. Natl. Acad. Sci. USA, 78: 2643–2647.
Gray, C.M. and Singer, W. (1989) Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. Proc. Natl. Acad. Sci. USA, 86: 1698–1702.
Gray, C.M. (1999) The temporal correlation hypothesis of visual feature integration: still alive and well. Neuron, 24: 31–47.
Gross, J., Timmermann, L., Kujala, J., Dirks, M., Schmitz, F., Salmelin, R. and Schnitzler, A. (2002) The neural basis of intermittent motor control in humans. Proc. Natl. Acad. Sci. USA, 99: 2299–2302.
Heim, S., Eulitz, C., Kaufmann, J., Fuchter, I., Pantev, C., Lamprecht-Dinnesen, A., Matulat, P., Scheer, P., Borstel, M. and Elbert, T. (2000) Atypical organisation of the auditory cortex in dyslexia as revealed by MEG. Neuropsychologia, 38: 1749–1759.
Helenius, P., Uutela, K. and Hari, R. (1999) Auditory stream segregation in dyslexic adults. Brain, 122: 907–913.
Hirsh, I.J. (1959) Auditory perception of temporal order. J. Acoust. Soc. Am., 31: 759–767.
Jahnsen, H. and Llinas, R. (1984) Electro-physiological properties of guinea-pig thalamic neurones: an in vitro study. J. Physiol., 349: 205–226.
Jeanmonod, D., Magnin, M. and Morel, A. (1996) Low-threshold calcium spike bursts in the human thalamus: common physiopathology for sensory, motor and limbic positive symptoms. Brain, 119: 363–375.
Jeanmonod, D., Magnin, M., Morel, A., Siegemund, M., Cancro, R., Lanz, M., Llinás, R., Ribary, U., Kronberg, E., Schulman, J.J. and Zonenshayn, M. (2001) Thalamocortical Dysrhythmia II: Clinical and surgical aspects. Thalamus Related Systems, 1: 245–254.
Jeanmonod, D., Schulman, J., Ramirez, R., Cancro, R., Lanz, M., Morel, A., Magnin, M., Siegemund, M., Kronberg, E., Ribary, U. and Llinas, R. (2003) Neuropsychiatric thalamocortical dysrhythmia: surgical implications. Neurosurg. Clin. N. Am., 14: 251–265.
Jennett, B. and Plum, F. (1972) Persistent vegetative state after brain damage. A syndrome in search of a name. Lancet, 1: 734–737.
Jensen, O., Hari, R. and Kaila, K. (2002a) Visually evoked gamma responses in the human brain are enhanced during voluntary hyperventilation. NeuroImage, 15: 575–586.
Jensen, O. and Vanni, S. (2002b) A new method to identify multiple sources of oscillatory activity. NeuroImage, 15: 568–574.
John, E.R., Prichep, L.S., Friedman, J. and Easton, P. (1988) Neurometrics: Computer assisted differential diagnosis of brain dysfunctions. Science, 293: 162–169.
John, E.R., Prichep, L.S., Kox, W., Valdes-Sosa, P., Bosch-Bayard, J., Aubert, E., Tom, M., diMichele, F. and Gugino, L.D. (2001) Invariant reversible qeeg effects of anesthetics. Consciousness Cogn., 10: 165–183.
John, E.R. (2002) The neurophysics of consciousness. Brain Res. Rev., 39: 1–28.
Joliot, M., Ribary, U. and Llinás, R. (1994) Human oscillatory brain activity near 40 Hz coexists with cognitive temporal binding. Proc. Natl. Acad. Sci. USA, 91: 11748–11751.
Kato, N. (1990) Cortico-thalamo-cortical projection between visual cortices. Brain Res., 509: 150–152.
Kissler, J., Muller, M.M., Fehr, T., Rockstroh, B. and Elbert, T. (2000) MEG gamma band activity in schizophrenia patients and healthy subjects in a mental arithmetic task and at rest. Clin. Neurophysiol., 111: 2079–2087.

Knief, A., Schulte, M., Bertran, O. and Pantev, C. (2000) The perception of coherent and non-coherent auditory objects: a signature in gamma frequency band. Hear Res., 145: 161–168.

Kristofferson, A.B. (1984) Quantal and deterministic timing in human duration discrimination. Annals New York Acad. Sci., 423: 3–15.

Laureys, S., Goldman, S., Phillips, C., Van Bogaert, P., Aerts, J., Luxen, A., et al. (1999) Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. Neuroimage, 9: 377–382.

Lehmann, D., Ozsaki, H. and Pal, I. (1987) Brainstates. Electroenceph. Clin. Neurophysiol., 67: 271–288.

Levy, D.E., Sidtis, J.J., Rottenberg, D.A., Jarden, J.O., Strother, S.C., Dhawan, V., et al. (1987) Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. Ann. Neurol., 22: 673–682.

Lindström, S. and Wróbel, A. (1990) Frequency dependent corticofugal excitation of principal cells in the cat's dorsal lateral geniculate nucleus. Exp. Brain Res., 79: 313–318.

Llinás, R. (1990) Intrinsic electrical properties of mammalian neurons and CNS function. Fidia Res. Foundation Neurosci. Award Lectures, 4: 173–192.

Llinás, R., Grace, A.A. and Yarom, Y. (1991) In vitro neurons in mammalian cortical layer 4 exhibit intrinsic activity in the 10 to 50 Hz frequency range. Proc. Natl. Acad. Sci. USA, 88: 897–901.

Llinás, R. and Ribary, U. (1992) Rostrocaudal scan in human brain: A global characteristic of the 40-Hz response during sensory input. In: Basar and Bullock T. (Eds.), Induced Rhythms in the Brain. Birkhauser, Boston, pp. 147–154.

Llinás, R. (1993) Is dyslexia a dyschronia? Annal NY Acad. Sci., 682: 48–56.

Llinás, R. and Ribary, U. (1993) Coherent 40-Hz oscillation characterizes dream state in humans. Proc. Natl. Acad. Sci. USA, 90: 2078–2081.

Llinás, R., Ribary, U., Joliot, M. and Wang, X.J. (1994) Content and context in temporal thalamocortical binding. In: Buzsaki G., Llinas R., Singer W., Berthoz A. and Christen Y. (Eds.), Temporal Coding in the Brain. Springer, Heidelberg, pp. 251–272.

Llinás, R., Ribary, U., Contreras, D. and Pedroarena, C. (1998a) The neuronal basis for consciousness. Phil. Trans. R. Soc. London, 353: 1841–1849.

Llinás, R., Ribary, U. and Tallal, P. (1998b) Dyschronic language-based learning disability. In: VonEuler C., Lundberg I. and Llinás R. (Eds.), Basic Mechanisms in Cognition and Language. Elsevier Science, New York, pp. 101–108.

Llinás, R., Ribary, U., Jeanmonod, D., Kronberg, E. and Mitra, P.P. (1999) Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc. Natl. Acad. Sci. USA,, 96: 15222–15227.

Llinás, R., Ribary, U., Jeanmonod, D., Cancro, R., Kronberg, E., Schulman, J.J., Zonenshayn, M., Magnin, M., Morel, A. and Siegemund, M. (2001) Thalamocortical dysrhythmia I: functional and imaging aspects. Thalamus Rel. Syst., 1: 237–244.

Llinas, R.R., Leznik, E. and Urbano, F.J. (2002) Temporal binding via cortical coincidence detection of specific and nonspecific thalamocortical inputs: a voltage-dependent dye-imaging study in mouse brain slices. Proc. Natl. Acad. Sci. USA, 99: 449–454.

Lumer, E.D., Edelman, G.M. and Tononi, G. (1997) Neural dynamics in a model of the thalamocortical system I. Layers, loops and the emergency of fast synchronous rhythms. Cere. Cortex, 7: 207–227.

Madler, C., Keller, I., Schwender, D. and Poeppel, E. (1991) Sensory information processing during general anaesthesia: effect of isoflurane on auditory evoked neuronal oscillations. Br. J. Anaesthesia, 66: 81–87.

Makeig, S., Jung, T.P., Ghahremani, D., Bell, A.J. and Sejnowski, T.J. (1997) Blind separation of event-related brain responses into independent components. Proc. Natl. Acad. Sci. USA,, 94: 10979–10984.

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

McCroskey, R. and Kasten, R.N. (1980) Assessment of central auditory processing. In: Rupp R.R. and Stockdell K.G. (Eds.), Speech Protocols in Audiology. Grune & Stratton, New York, pp. 339–389.

Merzenich, M.M., Nelson, R.J., Kaas, J.H., Stryker, M.P., Jenkins, W.M., Zook, J.M. and Cynader, M.S. (1987) Variability in hand surface representations in areas 3b and 1 in adult owl and squirrel monkeys. J. Comp. Neurol., 258: 281–296.

Merzenich, M.M., Jenkins, W.M., Johnston, P., Schreiner, C., Miller, S.L. and Tallal, P. (1996) Temporal processing deficits of language-learning impaired children ameliorated by training. Science, 271: 77–81.

Michel, C.M., Murray, M., Lantz, G., Gonzalez, S. and Grave de Peralta, R. (2004) EEG source imaging. Clin. Neurophysiol., 115: 2195–2222.

Miller, G.A. and Taylor, W.G. (1948) The perception of repeated bursts of noise. J. Acoust. Soc. Am., 20: 171–182.

Mogilner, A., Grossman, J.A.I., Ribary, U., Joliot, M., Volkmann, J., Rapaport, D., Beasley, R.W. and Llinas, R. (1993) Somatosensory cortical plasticity in adult humans revealed by magnetoencephalography. Proc. Natl. Acad. Sci. USA, 90: 3593–3597.

Mosher, J.C., Leahy, R.M. and Lewis, P.S. (1999a) EEG and MEG: forward solutions for inverse methods. IEEE Trans. Biomed. Eng., 46: 245–259.

Mosher, J.C., Baillet, S. and Leahy, R.M. (1999b) EEG Source localization and imaging using multiple signal classification approaches. J. Clin. Neurophysiol., 16: 225–238.

Murthy, V.N. and Fetz, E.E. (1992) Coherent 25-35 Hz oscillations in the sensorimotor cortex of awake behaving monkeys. Proc. Natl. Acad. Sci. USA, 89: 5670–5674.

Murthy, V.N. and Fetz, E.E. (1997) Oscillatory activity in sensorimotor cortex of awake monkeys: synchronization of local field potentials and relation to behavior. J. Neurophysiol., 76: 3949–3967.

Nagarajan, S., Mahncke, H., Salz, T., Tallal, P., Roberts, T. and Merzenich, M.M. (1999) Cortical auditory signal processing in poor readers. Proc. Natl. Acad. Sci. USA, 96: 6483–6488.

Neuenschwander, S. and Singer, W. (1996) Long-range synchronization of oscillatory light responses in the cat retina and lateral geniculate nucleus. Nature, 379: 728–733.

Palva, S., Palva, J.M., Shtyrov, Y., Kujala, T., Ilmoniemi, R.J., Kaila, K. and Naatanen, R. (2002) Distinct gamma-band evoked responses to speech and non-speech sounds in humans. J. Neurosci., 22: RC211.

Pantev, C., Makeig, S., Hoke, M., Galambos, R., Hampson, S. and Gallen, C. (1991) Human auditory evoked gamma-band magnetic fields. Proc. Natl. Acad. Sci. USA, 88: 8996–9000.

Parra, J., Kalitzin, S.N., Iriarte, J., Blanes, W., Velis, D.N. and Lopes Da Silva, F.H. (2003) Gamma-band phase clustering and photosensitivity: is there an underlying mechanism common to photosensitive epilepsy and visual perception? Brain, 126: 1164–1172.

Pascual-Marqui, R.D., Michel, C.M. and Lehmann, D. (1995) Segmentation of brain electrical activity into microstates: model estimation and validation. IEEE Trans. Biomed. Eng., 42: 658–665.

Pedroarena, C. and Llinás, R. (1997) Dendritic calcium conductances generate high-frequency oscillation in thalamocortical neurons. Proc. Natl. Acad. Sci. USA, 94: 724–728.

Pfurtscheller, G., Schwarz, G., Pfurtscheller, B. and List, W. (1983) Computer assisted analysis of EEG, evoked potentials, EEG reactivity and heart rate variability in comatose patients. Elektroenzephalogr Elektromyogr Verwandte Geb., 14: 66–73.

Plum, F., Schiff, N., Ribary, U. and Llinas, R. (1998) Coordinated expression in chronically unconscious persons. Phil. Trans. R. Soc. London, 353: 1929–1933.

Poppel, E. (1970) Excitability cycles in central intermittency. Psychol. Forsch., 34: 1–9.

Purpura, K.P. and Schiff, N.D. (1997) The thalamic intralaminar nuclei: role in visual awareness. Neuroscientist, 3: 8–14.

Raichle, M. (1999) The neural correlates of consciousness: an analysis of cognitive skill learning. Phil. Trans. R. Soc. London, 353: 1889–1901.

Ramachandran, V.S., Rogers-Ramachandran, D. and Stewart, M. (1992) Perceptual correlates of massive cortical reorganization. Science, 258: 1159–1160.

Ramírez, R.R., Horenstein, C., Kronberg, E., Ribary, U. and Llinás, R. (2000) Quantal apparent motion perception and its neuro-magnetic correlates in striate and extrastriate visual cortices. Soc. Neurosci. Abstr., 26: 670–670.

Ramirez, R., Kronberg, E., Ribary, U. and Llinás, R. (2002) Gamma-band and recurrent visual sources correlate with apparent motion perception. Soc. Neurosci. Abstr., 28: on CD ROM.

Ramirez, R.R., van Marle, H.J.F., Kronberg, E., Ribary, U. and Llinas, R. (2003) Large-scale integration, synchronization, and coherent brain dynamics in single trials. NeuroImage, 19: S34(505).

Ramirez, R., Jaramillo, S., Moran, K. A., Ribary U. and Llinas, R. R. Single trial neuromagnetic source dynamics. (2004) Soc. Neurosci. Abstr., 30 (on CD ROM).

Regan, D. (1989) Human Brain Electrophysiology: Evoked Potentials and Evoked Magnetic Fields in Science and Medicine. Elsevier Science, New York.

Reisberg, B., Ferris, S., de Leon, M.J. and Crook, T. (1982) The global deterioration scale (GDS): An instrument for the assessment of primary degenerative dementia. Am. J. Psychiat., 139: 1136–1139.

Rennie, C.J., Robinson, P.A. and Wright, J.J. (2002) Unified neurophysiological model of EEG spectra and evoked potentials. Biol. Cyber., 86: 457–471.

Ribary, U., Weinberg, H., Brickett, P., Ancill, R.J., Holliday, S., Kennedy, J.S. and Johnson, B. (1987) Imaging of EEG and MEG (magnetoencephalography) for the estimate of sources in the human brain responsive to antidepressant drugs. Soc. Neurosci. Abstr., 13: 1268–1268.

Ribary, U., Weinberg, H., Johnson, B., Ancill, R.J. and Holliday, S. (1988) EEG and MEG (magnetoencephalography) mapping of the auditory 40-Hz response: A study of depression. Soc. Neurosci. Abstr., 14: 339–339.

Ribary, U., Llinás, R., Kluger, A., Suk, J. and Ferris, S.H. (1989) Neuropathological dynamics of magnetic, auditory, steady-state responses in Alzheimer's disease. In: Williamson S.J., Hoke M., Stroink G. and Kotani M. (Eds.), Advances in Biomagnetism. Plenum Press, New York, pp. 311–314.

Ribary, U., Ioannides, A.A., Singh, K.D., Hasson, R., Bolton, J.P.R., Lado, F., Mogilner, A. and Llinas, R. (1991) Magnetic Field Tomography (MFT) of coherent thalamo-cortical 40-Hz oscillations in humans. Proc. Natl. Acad. Sci. USA, 88: 11037–11041.

Ribary, U., Cappell, J., Mogilner, A., Hund, M., Kronberg, E. and Llinás, R. (1999) Functional imaging of plastic changes in the human brain. Adv. Neurol., 81: 49–56.

Ribary, U., Joliot, M., Miller, S.L., Kronberg, E., Cappell, J., Tallal, P. and Llinás, R. (2000) Cognitive temporal binding and its relation to 40 Hz activity in humans: Alteration during dyslexia. In: Aine C., Okada Y., Stroink G., Swithenby S. and Wood C.C. (Eds.), Biomag96. Springer, Berlin, pp. 971–974.

Ribary, U., Llinás, R., Jeanmonod, D., Kronberg, E., Sauvé, K., Ramirez, R.R., Schulman, J.J., Horenstein, C. and Van-Marle, H.J.F. (2002) Normal and dysrhythmic thalamo-cortical networks in the auditory, somatosensory and visual modality and their relation to neuro-psychiatric syndromes. In: Novak H., Haueisen J., Giessler F. and Huonker R. (Eds.), BIOMAG 2002. VDE Verlag, Berlin, pp. 198–200.

Ribary, U., Ramirez, R., Sauve, K., Schulman, J., Jaramillo, S., Llinas, R.R. (2004) Altered thalamo-cortical network dynamics and sensory binding during normal aging. Soc. Neurosci. Abstr., 30 (on CD ROM).

Robin, D.A. and Royer, F.L. (1989) Age-related changes in auditory temporal processing. Psychol. Aging, 4: 144–149.

Rudolf, J., Ghaemi, M., Ghaemi, M., Haupt, W.F., Szelies, B. and Heiss, W.D. (1999) Cerebral glucose metabolism in acute and persistent vegetative state. J. Neurosurg. Anesthesiol., 11: 17–24.

Salenius, S., Salmelin, R., Neuper, C., Pfurtscheller, G. and Hari, R. (1996) Human cortical 40 Hz rhythm is closely related to EMG rhythmicity. Neurosci. Lett., 213: 75–78.

Salmelin, R., Service, E., Kiesila, P., Uutela, K. and Salonen, O. (1996) Impaired visual word processing in dyslexia revealed with magnetoencephalography. Ann. Neurol., 40: 157–162.

Sarnthein, J., Morel, A., von Stein, A. and Jeanmonod, D. (2003) Thalamic theta field potentials and EEG: high thalamocortical coherence in patients with neurogenic pain, epilepsy and movement disorders. Thalamus Rel. Syst., 2: 231–238.

Sauve, K., Wang, G., Rolli, M., Jagow, R., Kronberg, E., Ribary, U. and Llinás, R. (1999) Binding of somatosensory stimuli in sighted and blind subjects. Neuroimage, 9: 848–848.

Sauvé, K., Ribary, U. and Llinas, R. (2003) Early, high amplitude intra- and inter-hemispheric gamma-band currents in sensory cortex correlate with reaction times in individual trials in young and old subjects. Soc. Neurosci. Abstr., 29: 172.15 (on CD ROM).

Schiff, N.D., Ribary, U., Plum, F. and Llinas, R. (1999) Words without mind. J. Cognitive Neurosci., 11: 650–656.

Schiff, N.D. and Plum, F. (2000) The role of arousal and 'gating' systems in the neurology of impaired consciousness. J. Clin. Neurophysiol., 17: 438–452.

Schiff, N.D., Ribary, U., Moreno, D.R., Beattie, B., Kronberg, E., Blasberg, R., Giacino, J., McCagg, C., Fins, J.J., Llinas, R. and Plum, F. (2002) Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. Brain, 125: 1210–1234.

Schulman, J.J., Zonenshayn, M., Ramirez, R.R., Mogilner, A.Y., Rezai, A.R., Kronberg, E., Ribary, U., Mitra, P.P., Jeanmonod, D. and Llinás, R. (2000) Differences in MEG patterns produced by central and peripheral pain. Neuroimage, 11: 164–164.

Schulman, J.J., Horenstein, C., Ribary, U., Kronberg, E., Cancro, R., Jeanmonod, D. and Llinás, R. (2001) Thalamocortical dysrhythmia in depression and obsessive-compulsive disorder. Neuroimage, 13: 1004–1004.

Schulman, J.J., Ramirez, R., Cancro, R., Ribary, U. and Llinas, R. (2003) Thalamocortical dysrhythmia in schizoaffective disorder. Soc. Neurosci. Abstr., 29: 714.10 (on CD ROM).

Sheer, D. (1984) Focused arousal 40 Hz EEG and dysfunction. In: Ebert T. (Ed.), Self Regulation of the Brain and Behavior. Springer, Berlin, pp. 64–84.

Simos, P.G., Breier, J.I., Fletcher, J.M., Bergman, E. and Papanicolaou, A.C. (2000) Cerebral mechanisms involved in word reading in dyslexic children: a magnetic source imaging approach. Cereb. Cortex, 10: 809–816.

Singer, W. (1998) Consciousness and the structure of neuronal representations. Phil. Trans. R. Soc. London, 353: 1829–1840.

Singer, W. and Gray, C.M. (1995) Visual feature integration and the temporal correlation hypothesis. Ann. Rev. Neurosci., 18: 555–586.

Steriade, M. and Llinas, R.R. (1988) The functional states of the thalamus and the associated neuronal interplay. Physiol. Rev., 68: 649–742.

Steriade, M., Curro Dossi, R., Pare, D. and Oakson, G. (1991a) Fast oscillations (20–40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. Proc. Natl. Acad. Sci. USA, 88: 4396–4400.

Steriade, M., Curró Dossi, R., Paré, D. and Oakson, G. (1991b) Fast oscillations (20–40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. Proc. Natl. Acad. Sci. USA, 88: 4396–4400.

Steriade, M. (1993) Central core modulation of spontaneous oscillations and sensory transmission in thalamocortical systems. Curr. Opin. Neurobiol., 3: 619–625.

Steriade, M., McCormick, D.A. and Sejnowski, T.J. (1993a) Thalamocortical oscillations in the sleeping and aroused brain. Science, 262: 679–685.

Steriade, M., Curró Dossi, R. and Contreras, D. (1993b) Electrophysiological properties of intralaminar thalamocortical cells discharging rhythmic (~40 Hz) spike-bursts at ~1000 Hz during waking and rapid-eye movement sleep. Neuroscience, 56: 1–9.

Steriade, M. and Amzica, F. (1996a) Intracortical and corticothalamic coherency of fast spontaneous oscillations. Proc. Natl. Acad. Sci. USA, 93: 2533–2538.

Steriade, M., Amzica, F. and Contreras, D. (1996b) Sychronization of fast (30–40 Hz) spontaneous cortical rhythms during brain activation. J. Neurosci., 16: 392–417.

Tallal, P., Miller, S. and Fitch, R.H. (1993) Neurobiological basis of speech: A case for the preeminence of temporal processing. Annal NY Acad. Sci., 682: 27–47.

Tallal, P., Miller, S.L., Bedi, G., et al. (1996) Language comprehension in language-learning impaired children improved with acoustically modified speech. Science, 271: 81–84.

Tallal, P. (2004) Improving language and literacy is a matter of time. Nat. Rev. Neurosci., 5: 721–728.

Tallon-Baudry, C., Bertrand, O., Wienbruch, C., Ross, B. and Pantev, C. (1997) Combined EEG and MEG recordings of visual 40 Hz responses to illusory triangles in human. Neuroreport, 8: 1103–1107.

Tallon-Baudry, C. and Bertrand, O. (1999) Oscillatory gamma activity in humans and its role in object representation. Trends Cogn. Sci., 3: 151–162.

Teich, M.C., Khanna, S.M. and Guiney, P.C. (1993) Spectral characteristics and synchrony in primary auditory-nerve fibers in response to pure-tone acoustic stimuli. J. Stat. Phys., 70: 257–279.

Timmermann, L., Gross, J., Butz, M., Kircheis, G., Haussinger, D. and Schnitzler, A. (2003) Mini-asterixis in hepatic encephalopathy induced by pathologic thalamo-motor-cortical coupling. Neurology, 61: 689–692.

Tomassino, C., Grana, C., Lucignani, G., Torri, G. and Ferrucio, F. (1995) Regional metabolism of comatose and vegetative state patients. J. Neurosurg. Anesthesiol., 7: 109–116.

Tononi, G. and Edelmann, G.M. (1998) Consciousness and complexity. Science, 282: 1846–1851.

Traub, R.D., Whittington, M.A., Stanford, I.M. and Jeffereys, J.G.R. (1996) A mechanism for generation of long-range synchronous fast oscillations in the cortex. Nature, 383: 621–624.

Van Essen, D.C., Drury, H.A., Joshi, S. and Miller, M.I. (1998) Functional and structural mapping of human cerebral cortex: solutions are in the surfaces. Proc. Natl. Acad. Sci. USA, 95: 788–795.

Wright, J.J., Robinson, P.A., Rennie, C.J., Gordon, E., Bourke, P.D., Chapman, C.L., Hawthorn, N., Lees, G.J. and Alexander, D. (2001) Toward an integrated continuum model of cerebral dynamics: the cerebral rhythms, synchronous oscillation and cortical stability. BioSystems, 63: 71–88.

Yang, T.T., Gallen, C., Schwartz, B., Bloom, F.E., Ramachandran, V.S. and Cobb, S. (1994) Sensory maps in the human brain. Nature, 368: 592–593.

Young, M.P., Tanaka, K. and Yamane, S. (1992) On oscillating neuronal responses on the visual cortex of the monkey. J. Neurophysiol., 67: 1464–1474.

Zeki, S. and Bartels, A. (1998) The autonomy of the visual systems and the modularity of conscious vision. Phil. Trans. R. Soc. London, 353: 1911–1914.