Interactions Among Neuronal Oscillations in the Developing and Adult Brain

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Cover: Synchronized alpha and gamma oscillations in human brain. (Modified from *The Journal of Neuroscience*, April 13, 2005. Volume 25, number 15.)

Original Publications

This Thesis is based on the following articles, referred to in the text by their Roman numerals. Some unpublished results are also presented in the text.

I   Palva JM, Palva S, Kaila K (2005) Phase synchrony among neuronal oscillations in the human cortex. *J. Neurosci.* **25**, 3962-3972.

II   Vanhatalo S, Palva JM, Holmes MD, Miller JW, Voipio J, Kaila K (2004) Infraslow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep. *Proc. Natl. Acad. Sci. USA,* **101**, 5053–5057.

III   Palva JM, Lämsä K, Lauri S, Rauvala H, Kaila K, Taira T (2000) Fast network oscillations in newborn rat hippocampus *in vitro*. *J. Neurosci.* **20**, 1170–1178.

IV   Vanhatalo S, Palva JM, Andersson S, Rivera C, Voipio J, Kaila K (2005) Slow endogenous activity transients in the immature human cortex. *Eur. J. Neurosci.*, *in press*.

Table of Contents

Abstract

At the neuronal population level, temporally correlated activities can be observed as network oscillations and synchrony. In the mammalian brain, oscillations in specific frequency bands are thought to have distinct functional roles, although the precise identities of these functions have largely remained under debate. In the adult brain, fast network oscillations in beta- (14–30 Hz) and gamma- (30–80 Hz) frequency bands appear to provide a means for integrating anatomically distributed processing and have hence been associated with psychological-level phenomena such as feature binding and object representation, as well as with perception, attention and short-term memory. The physiological basis of this notion rests on the fact that the synchronized firing of action potentials involved in such fast oscillations is very powerful both in entraining neuronal target populations as well as in inducing synaptic plasticity.

Cognition and brain function in general, however, also involve greater time scales, from "cognitive quanta" of ~100–150 ms to >10 s fluctuations in psychophysical task performance. Interestingly, the cognitive quanta may be linked to neuronal oscillations in the theta- (4–8 Hz) / alpha- (8–14 Hz) frequency bands and the very slow fluctuations, respectively, to ~0.1 Hz oscillations presented in this Thesis. How do the neuronal phenomena with these widely separated time scales interact?

The studies in this Thesis show that cross-frequency phase and amplitude interactions are abundant in both the developing and adult brain. Neuromagnetic recordings from the adult human subjects revealed that throughout the range from 3 to 80 Hz, oscillations with frequency ratios of 1:2–1:4 were partially 1:n phase synchronized. In these subjects, mental arithmetic tasks enhanced specifically the 1:2–1:4 phase synchronies among oscillations in gamma-, beta-, and alpha-frequency bands. The amplitudes of all observed oscillations were also weakly coupled, but the cognitive tasks suppressed these correlations. In direct-current coupled electroencephalogram (DC-EEG) of sleeping adults, another form of cross-frequency phase interaction was observed. The amplitude envelope of oscillations from 1 to 30 Hz was strongly modulated by the phase of a novel infraslow oscillation with a frequency ranging from 0.02 to 0.2 Hz. Such nestedness is classically known to take place between rat hippocampal gamma (20–100 Hz) and theta (4–12 Hz) oscillations. In *in vitro* recordings from newborn rat hippocampus, pyramidal cell spiking reached population rates of > 100 spikes/s. This population activity was observed in bursts recurring at 20–80 Hz during the endogenous activity transients that dominate the activity of developing cortical structures. Finally, in DC-EEG of preterm human babies, large-amplitude oscillations in several distinct frequency bands from 0.1 to 30 Hz were concentrated into massive activity transients that in many aspects were similar to those observed in newborn rat cortex.

In the light of these data, the cross-frequency phase interactions in the adult brain appear to have a fundamental role in cross-hierarchical and -functional integration and modulation. In the developing cortex, the precise temporal patterning and nested oscillations within the population bursts could underlie spike-timing dependent shaping of network connectivity with the same coding strategies that later in life are utilized in feature integration and higher cognitive operations.

Abbreviations

AC	Alternating current
CF	Cross frequency
CNS	Central nervous system
DC	Direct current
EEG	Electroencephalography
GABA	Gamma-amino butyric acid
IPSP	Inhibitory post-synaptic potential
ISO	Infraslow oscillation
KCC2	Potassium-chloride cotransporter isoform 2
L5	Layer 5
MEG	Magnetoencephalography
PLF	Phase-locking factor
SAT	Spontaneous activity transient
SNR	Signal-to-noise ratio

Foreword

In every instant between the birth and death of a human brain, millions of neurons operate in transient synchronized assemblies. Their specific constellations and temporal patterns are influenced by the whole history of past neuronal activities. This spatiotemporal correlatedness of neuronal activities pervades all levels of organization, from pairs of nearby cells to massive networks throughout the brain. Is this correlatedness functionally significant or just an epiphenomenon arising from the neuronal architecture?

As has been proposed many times before, the nervous system has originally evolved simply to coordinate the "output" of the organism, *i.e.*, to select and coordinate the actions that favour the organism's survival in an environment that it probes with its senses.

Here, it is worthwhile to briefly consider the hydra, presumably the first organism known to have a nervous system (see Swanson, 2002). Hydra utilize muscle-like cells to bend its tubular body and to make wave-like movements with tentacles near the mouth opening. The availability of such sophisticated behaviours, active eating and movement by tumbling, must have given these organisms a significant advantage in competition for space and resources. These behaviours originate in a hierarchical nervous system composed of sensory, inter-, and motor neurons coupled by both chemical and electric synaptic transmission. A variety of divergent and convergent axonal projections even produce functional specialization in this "nerve net". As a whole, this system allows sense-guided selection of actions as well as performs the actual coordination of the effector activities to produce coherent movements.

The key point here—often neglected amid the current hype on the role of synchrony in cognitive integration—is that movements are based on the correlatedness of effector activities, which consequently necessitates the correlatedness of the underlying neuronal activities in general. Obviously, this is true for practically any multi-cellular organism. Muscle cells contracting in an uncorrelated manner hardly make up a useful effector system for controlling the movements of the organism.

Albeit this Thesis deals with correlated activity in the rat and human CNS somewhere between the inputs and the outputs, the evolutionary *raison d'être* of phase and amplitude correlations—muscle control—might provide the germane perspective.

1. Introduction

1.1 Observations of correlated neuronal activity

Richard Caton, a Liverpool surgeon, reported a successful recording of electrical potentials from the neocortex of rabbits and monkeys in 1875. In a considerable effort from 1924 to 1929, Hans Berger was the first to witness neuronal mass activity in the human brain — *"Elektrenkephalogramm"* rhythms in the alpha- (8–14 Hz) and beta- (14-30 Hz) frequency bands. In fact, the paradigm of correlating objective brain measures with subjective psychological states dates back to Berger's original work and ideology (see Niedermeyer and Lopes da Silva, 1999). In the 1970s, correlated neuronal activities at smaller scales were observed in multi-site single-unit recordings. Neuronal spiking was found to be significantly cross correlated, but these observations were assumed to reflect a common input to the recorded neurons. Later, however, accumulating evidence suggested that this *synchronous* firing emerged via recurrent interactions in the neuronal network and could not be explained in the context of feedforward chains and common inputs (for review, see Singer and Gray, 1995). Finally, postulates of synchrony acting as an integrative mechanism surged growing interest towards temporally correlated activities.

Specific time scales in the synchronizing neural mechanisms are reflected in the temporal structure of synchrony. Hence, it is not surprising that population synchrony is often associated with oscillatory patterns. In human EEG and magnetoencephalography (MEG, see Hämäläinen et al., 1993), a rich variety of oscillatory and transient phenomena have been described, where each, by definition, reflects a coordinated action of millions of neurons. According to the classical EEG nomenclature, activities are classified into distinct frequency bands; delta (1–4 Hz), theta (4–8 Hz), alpha (8–14 Hz), beta (14–30 Hz), and gamma (30–70 Hz).

More recently, high-frequency (100–200 Hz) (Ylinen et al., 1995) and ultra-fast (~600 Hz) (Curio et al., 1994) population oscillations have also been observed. In addition to these relatively fast neuronal oscillations, very slow (<<1 Hz) fluctuations in neuronal population activity and EEG/MEG power have been observed (Leopold et al., 2003; Staba et al., 2002; Penttonen et al., 1999; Steriade et al., 1993; Simon et al., 2000; Linkenkaer-Hansen et al., 2001; Bullock et al., 1995; Achermann and Borbely, 1997). Moreover, human psychophysical performance (Gilden et al., 1995), discrete sleep events (arousals, spindles, K complexes)

(Achermann and Borbely, 1997; Terzano et al., 1985; Parrino et al., 2000; Amzica and Steriade, 1997), as well as epileptic events (Penttonen et al., 1999; Parrino et al., 2000, Jando et al., 1995) show intermittent fluctuations at corresponding temporal scales (>>1 s). Do these very slow fluctuations arise from the self-organizing dynamics of faster (>1 Hz) activities (cf. Linkenkaer-Hansen et al., 2001) or are they related to actual, very slow neuronal/glial oscillations? Such infraslow oscillations (ISOs) are not detectable in conventional EEG because of the limited lower end of the recording bandwidth (typically >0.5 Hz). Utilizing direct-currect EEG (DC-EEG), which can record frequencies from 0 Hz, the presence of ISOs is demonstrated in the second study of this Thesis (II). In this study, amplitude modulation of the faster activities by ISOs is also shown.

1.2 Functional roles of synchrony

1.2.1 The binding problem

The cerebral functional architecture of most vertebrates, and that of mammals in particular, is characterized by parallel information streams as well as by a hierarchical organization of functionally specialized cortical areas. In this system, sensory data are decomposed into distinct features. For example, in the visual

system color, edge orientation, shape, movement, and many other features are signalled by spatially segregated groups of neurons. Projections of neurons signalling lower-level features converge to neurons higher in the hierarchy that, in consequence, become functionally specialized to signal higher-level features. In the case of behaviourally relevant or frequently occurring feature combinations, even very high-level sensory object categories, such as faces, are represented by specialized groups of neurons. The patterns of connectivity in this hierarchy become "hardwired" during the first years of life (Singer, 1995). The usability of such *feedforward* or *labelled-line* coding, however, is limited by the "combinatorial explosion"; there are simply not enough neurons in the brain to represent each possible combination of features in sensory data. While the decomposition of sensory data and its hierarchical recomposition into feature conjunctions appears to be the foundation of all information representation in the cerebral cortex, real-world feature conjunctions or perceptual objects are thus necessarily represented in a highly distributed manner. A major challenge in neuroscience, often called the *binding problem*, has been to elucidate the mechanisms that underlie the integration of this *spatially* distributed processing and signal the relatedness of neurons coding the different features of a

given object (Singer, 1999). In short, the binding problem could be crystallized as follows:

> "How do we consciously perceive *objects* when neurons only signal *features*?".

The binding problem is thus central to brain sciences in general: it addresses the gap between neurobiological and psychological levels[1].

1.2.2 Synchrony in beta/gamma bands

Theoretical (for review, see von der Malsburg, 1999) as well as empirical (Gray et al., 1989) findings suggest that the binding problem—at least at the level of visual feature binding—is solved by synchronization of neurons into transient oscillatory assemblies (Singer, 1999; Varela et al., 2001). A body of evidence suggests that the firing of neurons signaling different features of the same object is synchronized, whereas the firing of these neurons is uncorrelated if they discharge in response to separate perceptual objects. The data also reveal that such "feature-binding" spike synchrony is often periodic and typically involves frequencies above 20 Hz (Engel and Singer, 2001). Indeed, spike

synchrony and synchronous field potential oscillations in the beta- and gamma-frequency bands have been implicated in feature binding (Gray and Singer, 1989) and, more generally, in large-scale integration (Roelfsema, 1997; for review, see Singer, 1999) in cat and monkey cortices. In EEG and MEG recordings from human cortex, gamma band oscillations (Tallon-Baudry et al., 1996; 1999; Palva et al., 2002) and synchrony (Rodriguez et al., 1999) appear to share the functional role of the smaller-scale gamma-band synchrony deduced with animal experiments.

Interestingly, beta- and gamma-band oscillations have also been detected during short-term memory maintenance when sustained activation of neural representations is required (Tallon-Baudry et al., 1998; 2001; Pesaran et al., 2002). It is known that integrated object representations, rather than individual features, are retained in limited-capacity short-term memory (Luck and Vogel, 1997). The observation of pronounced fast oscillations during memory retention is thus in line with the idea that these oscillations underlie the binding necessary for neural object representations (Tallon-Baudry & Bertrand, 1999). It is hence appealing to assume that neuronal assemblies engaged in beta and gamma oscillations underlie the representation of the

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[1] One also should note that although it was introduced in the context of feature binding, the concept of binding problem is generalizable to large-scale integration and inter-network communication *per se* (*cf.* Singer et al., 1999; Varela et al., 2001).

contents of short-term memory or, more generally, the *contents of sensory awareness*.

1.2.3 Oscillations in the alpha band – idling, inhibition or processing?

Alpha-frequency band oscillations are unequivocally the most salient phenomenon in awake human EEG. The attenuation of occipito-parietal alpha activity by eye opening, visual stimuli, and visual scanning (Berger, 1929; 1930), inspired the idea of alpha oscillations having an *idling* function (Adrian & Matthews, 1934). In analogy with an idling car engine, alpha oscillations were thought to reflect the mechanism underlying an "alert but still" brain state[2]. This notion was supported also by reduced sensorimotor ~10 Hz oscillation amplitudes upon somatosensory stimuli and movements (Pfurtscheller et al., 1996; Pfurtscheller and Lopes da Silva, 1999).

However, an accumulating body of evidence contradicting the idling hypothesis rooted another line of hypotheses on alpha function. Observations of enhanced alpha amplitudes during tasks demanding the suppression of sensory inputs, such as mental arithmetic, mental imagery, and working memory tasks, were interpreted in the context of *intake-rejection* hypothesis (Ray & Cole, 1985a, b). Here, the function of alpha was to inhibit sensory information processing. This notion was elaborated by Klimesch (1996, 1997) who proposed that large alpha amplitudes[3] reflect inhibition and disengagement of "task irrelevant" cortical areas whereas small alpha amplitudes[4] are correlated with active processing in "task relevant" areas. This idea was supported by studies showing that parieto-occipital alpha oscillations in EEG are larger in amplitude over the hemisphere ipsilateral[5] to the attended visual hemifield (Worden et al., 2000) and that these, presumably visual-cortex-related, oscillations are also strengthened by attention directed to the auditory modality (Foxe et al., 1998; Fu et al., 2001). According to this *inhibition* hypothesis, the large alpha oscillations in these studies

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[2] This line of thinking irresistibly invokes behaviourist connotations, *i.e.*, the view of the brain as a stimulus-response machine that is doing nothing, *idling*, when not processing stimuli.

[3] Increased amplitudes may stem from enhanced synchronization of the underlying neuronal population. Hence the term *event-related synchronization* (ERS) is commonly used in this context. However, amplitude and synchrony are mathematically orthogonal, and studies using explicit quantification of (phase) synchrony have shown that amplitude and synchrony can change independently (see, *e.g.*, Rodriguez, et al., 1999; Schoeffelen, et al., 2005). Hence the terms ERS and ERD (footnote 4) are inaccurate or even misleading.

[4] *"Event-related desynchronization"* (ERD).

[5] Because of the crossing over of the optic track, left visual field is primarily processed in the contralateral (right hemispheric) visual cortex, where largest event-related responses are also observed.

reflect the suppression of unattended stimuli. This concept may also be supported by *in vivo* data indicating that alpha oscillations are suppressed during the period of stimulus-processing, which is associated with beta/gamma synchrony (Roelfsema, 1997).

However, a wealth of recent data call for explanations other than the idling or inhibition hypotheses. Intracranial and EEG/MEG data on human neocortical oscillations show that in addition to theta- (Raghavachari et al., 2001; Halgren et al., 2002), also alpha-band (Halgren et al., 2002; Jensen et al., 2002) oscillations are modulated during short-term memory retention period. Stimulus-locked alpha-band oscillations are stronger during short-term memory retention than during baseline in intracranial recordings (Halgren et al., 2002). Moreover, increasing memory load is correlated with increasing amplitudes of non-stimulus locked alpha-band oscillations (Jensen et al., 2002). Another recent MEG study showed that the amplitude of early (~0–200 ms after stimulus onset) alpha oscillations in the visual cortex is larger for the attended than unattended stimuli (Yamagishi et al., 2003). Attentional modulation in the alpha band is also evident in the pre-stimulus period; *large* parietal but

intermediate[6] sensorimotor alpha-band oscillations are correlated with the conscious perception of weak somatosensory stimuli (Linkenkaer-Hansen et al., 2004). These data thus appear to link alpha-band oscillations to the mechanisms of short-term memory and attention. However, changes in the EEG/MEG oscillation amplitude are difficult, if not impossible, to interpret in terms of what features in the activity of the underlying neural networks would have changed. Amplitude thus might not be the best indicator in the evaluation of an oscillation's functional significance.

A number of studies that are not based on oscillation amplitude imply that alpha-band oscillations could indeed be intimately involved in higher cognitive functions such as attention and working memory. In the seminal work by von Stein et al. (2000a), non-stimulus locked alpha-frequency band neural synchrony between cat cortical areas 7 and 17[7] was prominent in responses to expected but not to novel objects, thus clearly indicating a role for alpha-band synchrony in top-down modulation (von Stein et al., 2000a; see also Fanselow et al., 2001; Mima et al.,

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[6] Note that, in contrast with the observations, the inhibition hypothesis predicts that *small* sensorimotor alpha oscillations should have been correlated with enhanced processing.

[7] Area 7: the primary visual cortex. Area 17: a visual association area high in functional hierarchy.

2001). Furthermore, in the data of von Stein et al. (2000a), both the time lags (area 17 preceded area 7) and the laminar profile of coherence (deep layers of 17 were coherent with superficial layers of 7)[8] were strikingly suggestive of alpha-band mediated top-down activity. Moreover, temporal intervals corresponding to alpha-frequency-band periodicity have been observed in a number of psychophysical studies on cognitive integration windows (for review, see Van Rullen and Koch, 2003). In humans, large-scale alpha-band stimulus locking[9] is observed for consciously perceived stimuli but not for those escaping perception, whereas the unperceived stimuli did evoke stimulus locking in theta- and beta-frequency bands (Palva et al., 2005). Interestingly, this study also showed that the offset of stimulus locking, in each frequency band, was associated with the onset of an amplitude decrease in that frequency band. Hence, an amplitude decrease *per se* cannot be taken to imply that the activities in that frequency band are *not* actively involved in task execution.

Attention has been suggested to be a prerequisite for both consciousness and short-term memory (see, *e.g.*, Lamme, 2003). The studies discussed above imply that the alpha-frequency band oscillations are involved in all three of the above. A considerable amount of data suggests that, unlike beta and gamma, theta and alpha oscillations are not related to feature integration *per se* (see Singer, 1999; Howard et al., 2003). Hence, in contrast with the *content*-mediating beta- and gamma-band oscillations, it is appealing to posit that the neuronal synchrony in theta- and alpha-frequency bands is involved in the mechanisms of top-down modulation, attention, and other *context*-defining (Llinás et al., 1998) functions.

1.2.4 Binding problem revisited

The mechanisms underlying the integration of *spatially distributed* processing and feature representation—central to the classical binding problem—are likely to include *temporal correlation* of neuronal activities: spike synchrony. However, as discussed in 1.2.2 and 1.2.3, functional specialization is obvious also in the *frequency domain*. Moreover, because of axonal conduction times, the spatial extent[10] of oscillating network sets the maximum oscillation

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[8] See also chapter 4.5.2.

[9] Stimulus locking here denotes specifically the phase locking of ongoing oscillations to the sensory stimuli.

[10] Note that metric distance, *per se*, is irrelevant for neuronal communication. In fact, the only meaningful measure of distance is the axonal conduction time itself. Of course, for axons with similar diameters and degrees of myelination, the conduction time is directly proportional to the axon's length.

frequency[11]. Roughly taken, slower oscillations thus synchronize over greater cortical distances than faster oscillations (Kopell et al., 2000; von Stein et al., 2000b, but see Bibbig et al., 2001)[12]. Hence, a question of *contents*-to-*context* or *bottom-up*-with-*top-down* binding translates also to a question of how processing on small cortical scales is bound to processing on larger scales.

Taken together, an obvious *cross-scale binding problem* emerges:

"How do the various synchronous assemblies at different levels of functional hierarchy act in concert to support unified cognitive functions?" (I)

This appears to demand dynamic interactions between activities in distinct frequency bands (Lisman and Idiart, 1995; von Stein et al., 2000a; Engel and Singer, 2001; VanRullen and Koch, 2003; Jensen and Lisman, 2005; cf. Hochstein and Ahissar, 2002). So far, the nature of these interactions has remained empirically unresolved.

1.2.5 Cross-frequency interactions

This Thesis work is largely based on the assumption that *amplitude* and *phase* (see section 2.2) provide a basis for the analysis and description of large-scale neuronal network activity reflected in field-electrode, EEG or MEG signals. In terms of amplitude and phase, the traditional *within*-frequency band interactions between two signals are either amplitude-amplitude or phase-phase type[13]. Amplitude interactions are conveniently quantified with ordinary or Spearman's correlation coefficients, and there is, as well, a variety of methods for the quantification of phase correlations or *phase synchrony* (Tass et al., 1998; Lachaux et al., 1999).

As above, also in the case of *cross*-frequency interactions, amplitudes of two distinct frequency bands can be directly correlated. Phase-phase correlations, on the other hand, take the form of *n:m*-phase synchrony, where the integers *n* and *m* give the ratio of the two frequencies and hence indicate the phase locking of *n* cycles of one oscillation to *m* cycles of another oscillation (see Tass et al., 1998). In addition, amplitude-phase interactions can take place, for instance, in the form

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[11] As a rule of thumb, coherent oscillations can accommodate conduction delays of up to one fourth of the oscillation period.

[12] The specific of synaptic mechanisms of oscillatory synchronization, however, are of central importance and can produce unexpected system-level phenomena, such as long-range synchrony of gamma oscillations (Traub et al., 1996a,b; Whittington et al., 1997a).

[13] Amplitude-phase type of a within-frequency interaction is not reasonable because amplitude and phase vary on such different time scales (more than one cycle vs. sub-cycle).

of nested oscillations wherein the amplitude of a faster oscillation is modulated by the phase of a slower oscillation (II).

Nested oscillations are prevalent in the human brain (Schack et al., 2002; Bruns and Eckhorn, 2004; II), in macaque auditory cortex (Lakatos et al., 2005) and in rat hippocampus (see, e.g., Chrobak and Buszaki, 1998). *n:m*-phase synchrony among cortical oscillations *in vivo*, on the other hand, was first reported in (I) and, independently, a bit later by Schack et al. (2005) (cf. Tass et al., 1998; 2003). *In vitro*, 1:2 phase locked interneuronal gamma and pyramidal cell beta oscillations follow high-frequency stimulation in rat hippocampal slices (Whittington et al., 1997b; Traub et al., 1999).

Traditionally, cross-frequency interactions have been inspected with bispectral measures, such as bicoherence (Dumermut et al., 1971; Jeffrey and Chamoun, 1994). Bicoherence has been used to detect non-linear, cross-frequency (CF) phase coupling in cat cortex (Schanze and Eckhorn, 1997; von Stein et al., 2000a) and in the human electroencephalogram (EEG) (Jeffrey and Chamoun, 1994; Shils et al., 1996; Schack et al., 2002). However, like conventional coherence (cf. Tass et al., 1998), bicoherence mixes phase and amplitude correlations, and hence leaves the specific form of

the interaction unclear. Consequently, bicoherence might not be the best tool in the search of the neuronal mechanisms underlying the observed cross-frequency interaction.

The first study in this Thesis (I) addresses the presence of *n:m*-phase synchrony among human cortical oscillations and its putative role in cross-scale binding. *n:m*-phase synchrony would be an attractive means for achieving cross-frequency integration because, unlike nested oscillations, it indicates spike synchrony among the neurons underlying the slow and fast oscillations, and hence preserves the possibility of phase coding in the faster frequency band.

1.3 Synchrony in the developing brain

1.3.1 The wiring problem

All animals that have a CNS, have a developmental period during which their nervous system is constructed in the absence of sensory input. In more complex organisms in particular, such as rats or humans, this period is followed by a prolonged stage during which sensory experience sculpts the brain. However, the degree of elaboration that has emerged prior to the onset of the experience-dependent plasticity is astonishing. Spontaneous neural activity is thought to be largely responsible for the establishment and maintenance of the precise connections within

the developing neural networks (Katz, 1993; Katz and Shatz, 1996). The question of how the developing neurons endogenously establish these connectivity patterns is, in fact, akin to the binding problem (1.2.1). In the adult CNS, there must be a code that allows neurons discharging for one *perceptual* object to be identified as belonging to one assembly that is distinct from another neuronal assembly signalling the another perceptual object. In the developing CNS, neurons that will later process related features (in terms of space and orientation, for instance) become mutually connected while they avoid connections with neurons that will signal unrelated features or information from another sensory modality. Interestingly, as the solution of the adult binding problems appears to involve spike synchrony (Singer and Gray, 1995), the "wiring problem" might be solved by a similar strategy: "neurons that fire together, wire together" (Katz, 1993).

1.3.2 Spontaneous activity in neonatal rat cortex

Intermittent, spontaneous bursts of neuronal activity are a salient feature of the developing CNS (Katz and Shatz, 1996; Ben-Ari, 2002; Feller, 1999; O'Donovan, 1999). The cellular and network mechanisms of endogenous activity in immature cortical structures have been extensively studied in rodents

during the first two weeks of postnatal life (Ben-Ari, 2002; Rivera et al., 2005). This period corresponds roughly to the human developmental time window from the last trimester of pregnancy to early postnatal stage (Clancy et al., 2001; Avishai-Eliner et al., 2002). In both rats and humans, its termination coincides with the inception of navigational senses. In the newborn rat hippocampus, spontaneous activity is characterized by pyramidal cell population bursts known as giant depolarizing potentials (GDPs) and suggested to result from synergistic excitation mediated by $GABA_A$ and NMDA receptors (Leinekugel et al., 1997; Strata et al., 1997). Recent work shows that GDPs are primarily driven by glutamatergic mechanisms, and that GABA plays a "permissive" rather than in "instructive" role in their generation (Sipilä et al., 2005). GDP-like activity is accompanied by slow, globally synchronous Ca^{2+} waves suggested to control the formation of new synapses in the developing hippocampus through the key role of Ca^{2+} in biochemical cascades and gene expression (Durand et al., 1996; Ben-Ari et al., 1997; Garaschuk et al., 1998). The disappearance of these bursts is correlated with the maturation of functional GABAergic inhibition (Ben-Ari, 2002; Khazipov et al., 2004; Garaschuk et al., 2000). This, in turn, is governed by the developmental expression of the

neuron-specific K-Cl cotransporter, KCC2, a molecule that underlies the generation of the cross-membrane chloride gradient, providing the driving force of $GABA_A$ receptor-mediated hyperpolarizing Cl^- currents (Rivera et al., 1999; Yamada et al., 2004; Khirug et al., 2005; Payne, et al., 2003). If temporal correlations are involved in the determination of synapse formation/elimination (Katz, 1993), the time window of spike-time dependent plasticity (see Songs et al., 2000) defines the minimum rate at which populations can be dissociated.

In the adult rat hippocampus, beta- and gamma- (20-100 Hz) (Gray et al., 1989; Bragin et al., 1995; König et al., 1995; Laurent, 1997) as well as high-frequency (100-200 Hz) network oscillations (Ylinen et al., 1995) are exploited in the timing and coordination of neural activity (Ritz and Sejnowski, 1997). Moreover, spike synchrony is essential for the induction of dendritic backpropagating action potentials in target neurons. At least in the adult nervous system, backpropagating action potentials play a role in associative synaptic potentiation (Markram et al., 1997; Traub et al., 1998). The generation of gamma- and high-frequency oscillations in the mature hippocampus relies on AMPA-receptor mediated excitation as well as hyperpolarizing $GABA_A$ receptor-mediated inhibition and GABAergic interneuron networks (Lytton and Sejnowski, 1991; Cobb et al., 1995; Whittington et al., 1995; Ylinen et al., 1995; Fisahn et al., 1998).

In developing hippocampus, however, $GABA_A$ responses are depolarizing (Ben-Ari et al., 1989; Rivera et al., 1999). Because of the putative lack of $GABA_A$ receptor-mediated inhibition in the rat hippocampal pyramidal cells during the first postnatal week (Luhmann and Prince, 1991; Ben-Ari et al., 1997; Leinekugel et al., 1997), developing hippocampal networks were thought to lack the critical synaptic circuitry required for fast population oscillations and synchrony (cf. Traub et al., 1998).

The third study of this Thesis (III) shows that, during the endogenous bursts in developing rat hippocampus, fast (> 100 Hz) neuronal spiking occurs in a gamma-frequency modulated fashion. Moreover, the spiking was negatively correlated with the $GABA_A$-receptor mediated currents implying that by shunting, GABA possibly has an inhibitory function despite its depolarizing nature.

1.3.3 Human neonatal EEG

Since early 70s, it has been recognized that from a conceptional age of about 24 weeks, the EEG of preterm babies is clearly discontinuous (Dreyfus-Brisac, 1975; for review, see Lamblin et al.,

1999). Thereafter, the EEG activities gradually become more continuous and the burst-like discontinuities are typically not observed in full-term babies anymore. Interestingly, in the corresponding developmental time window, *in vivo* field recordings from rat hippocampus show a very similar transition from discontinuous bursting to adult-like continuous oscillations (Lahtinen et al., 2002; Khazipov et al, 2004).

AC-coupled EEG techniques, which are commonly used in the study of preterm-EEG, set the lower end of the recording bandwidth to ~0.5 Hz. This high-pass filtering prevents the detection of infraslow events (Vanhatalo et al., 2002; 2004) that are the hallmark of endogenous bursts in rodent cortex. Hence, the developmental profile and characteristics of slow activity patterns in immature human cortex have remained unclear.

In the last study of this Thesis (IV), an ISO- (see II) like association of fast (> 1Hz) activities with large and very slow (<< 1 Hz) deflections in preterm DC-EEG is shown. These spontaneous activity transients (SATs) showed a developmental decline similar to that observed for activity bursts in neonatal rat cortex. Moreover, as in rat cortex, the waning of the SAT occurrence was closely associated with emerging KCC2 expression.
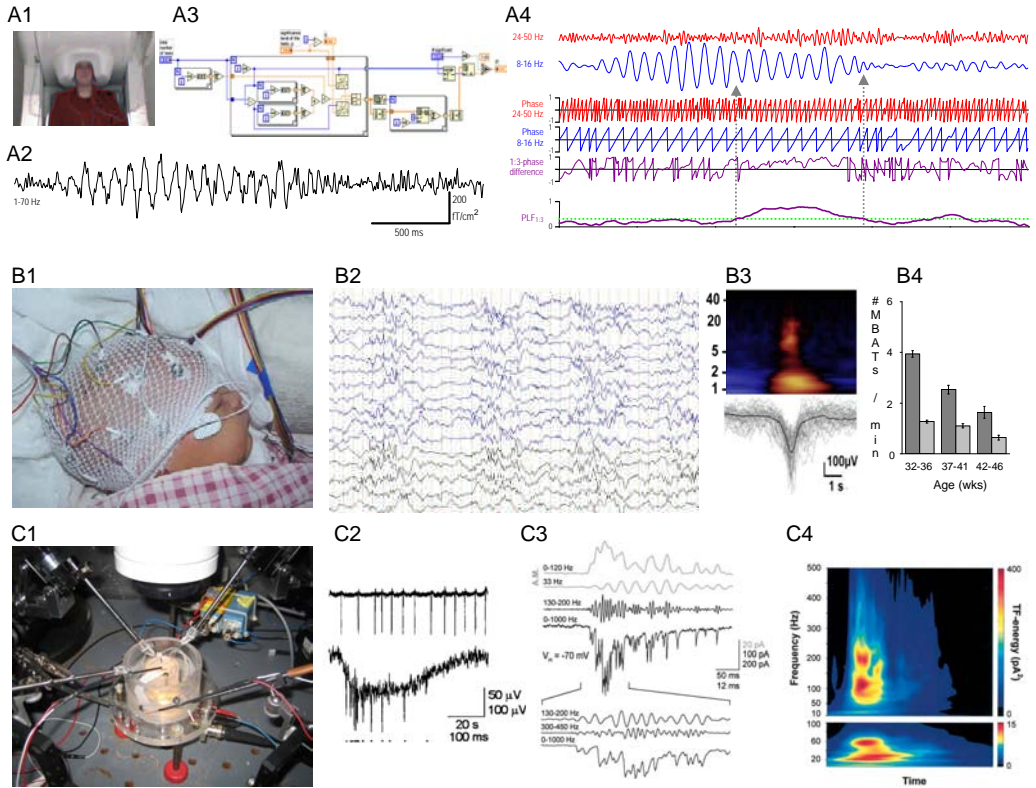
2. Methods

2.1 Measurements

A variety of recording techniques have been used to obtain the data presented in this Thesis (Fig. 1), ranging from *in vitro* field potential and intracellular recordings from newborn rat hippocampi to MEG and DC-EEG of adult and newborn human brains. The materials and methods in these studies are not presented here in detail beyond Figure. 1; the interested reader will find the details in the original publications. However, since much of the novelty in these studies stems from the utilization of relatively new or novel signal analysis methodology, these are presented here in a down-to-earth format. I feel that this is essential also because the concepts of correlation, nested oscillations, and phase synchrony, for instance, are used here in their mathematically defined meaning only.

2.2 Signal analysis

2.2.1 Real vs. complex: Estimation of signal amplitude and phase

In *in vivo* and *in vitro* recordings, a parameter of interest, such as electric potential or magnetic flux, is measured as a function of time. These time series index the temporal evolution of system's state. However, as noted above in the Introduction, electrophysiological signals are

FIGURE. 1 Summary of methods. **A,** Magnetoencephalography (study I). **A1,** MEG recording of a healthy adult subject. **A2,** Broad-band-pass filtered raw data from a posterior gradiometer. **A3,** A minute piece of Labview[TM]-based analysis software which was used in each study of this Thesis. **A4,** Evidence for dynamic 1:3 gamma-alpha phase synchrony in the human brain (for details, see Fig. 1 of I). **B,** Direct-current electroencephalography (studies II and IV). **B1,** DC-EEG recording of a healthy full-term baby. **B2,** DC-EEG raw data showing SATs. **B3,** Averaged time-frequency frequency representations of SATs reveal large-amplitude oscillations in multiple frequency bands nested into very slow deflections (see Fig. 2 of IV). **B4,** Developmental decrease in the occurrence of multi-band activity transients (MBATs) (see Fig. 1 of IV). **C,** *In vitro* electrophysiology (study III). **C1,** Measurement of field potentials and intracellular currents from a rat hippocampal slice. **C2,** A field potential recording from an early postnatal (P6) rat hippocampal slice shows recurrent endogenous bursts. The lower trace shows fast field potential spikes during one burst (see Fig. 1 of III). **C3,** An intracellular recording of a gamma-modulated high-frequency AMPA/kainate-receptor mediated currents during a single population burst. **C4,** An averaged time-frequency representation of 44 bursts (upper panel) shows clear 100 and 200 Hz oscillations. An averaged time-frequency analysis of the oscillation amplitude envelope confirms the presence of conspicuous gamma modulation (see C3) (for details, see Fig. 4 of III).

markedly, albeit transiently, periodic. For rhythmic systems, it can be more informative to inspect the system's state in the complex plane rather than by using the measured *real* values themselves. A complex number z is a pair of real numbers x and y so that

$$z = x + iy, \qquad (1)$$

where x and y are the real (Re z) and imaginary (Im z) parts of z, and

i is the imaginary unit ($i^2 = -1$). It is practical to express (1) in polar coordinates so that when $x = A\cos\boldsymbol{q}$ and $y = A\sin\boldsymbol{q}$,

$$z = A(\cos\boldsymbol{q} + i\sin\boldsymbol{q}) = Ae^{i\boldsymbol{q}}, \quad (2)$$

where A, $A = \sqrt{x^2 + y^2}$, is the modulus (or *amplitude*) of z and $\boldsymbol{q}$, $\boldsymbol{q} = \arctan\dfrac{y}{x}$, its argument (or *phase*).

Hence, the complex form $z(t)$ of a measured signal $x(t)$ represents explicitly the amplitude[14] $A(t)$ and phase $\boldsymbol{q}(t)$ as a function of time, whereas in $x(t)$ the phase and amplitude information are mixed. This explicit representation is essential from the signal analytical point of view. Moreover, one should note the fundamental conceptual difference between $z(t)$ and $x(t)$. The real part $x(t)$ can be (falsely) interpreted so that at the moments of zero crossing (at $\boldsymbol{q} = \pm 0.5\boldsymbol{p}$) the magnitude of the rhythmic phenomenon reflected by the measurement would be zero. In reality, of course, at those moments this magnitude is not zero—the system simply is in a different *phase* than during the peaks of $x(t)$. Hence, unlike $x(t)$ itself, one can use the amplitude of the measured signal, $A(t)$, as an index of the magnitude of the phenomenon under study.

The treatment above left one aspect of this matter unaddressed. How does one obtain the imaginary part $y(t)$ that is needed for $z(t)$ in (1)? At present, two approaches are routinely exploited. One is to use complex wavelets and the other is to use conventional filtering followed by the Hilbert transform.

Morlet wavelet $w(t,f_0)$ is probably the most widely used wavelet in electrophysiological signal analysis. It is given by

$$w(t, f_0) = A\exp\left(\frac{-t^2}{2\boldsymbol{s}_t^2}\right)\exp(2i\boldsymbol{p}f_0 t),$$

(3)

where A is a normalization constant, $\boldsymbol{s}_t = m/2\pi f_0$, m is a constant that defines the compromise between time and frequency resolution, and f_0 is the center frequency of the wavelet. Hence, in time domain, its real and imaginary parts are a cosine and a sine, respectively, of which the amplitude envelope is a Gaussian with a standard deviation of $\boldsymbol{s}_t$. In frequency domain, the Morlet wavelet is also a Gaussian with a standard deviation $\boldsymbol{s}_f$ given $\boldsymbol{s}_f = f_0/m$. Convolution[15],

$$X(t, f_0) = x(t) * w(t, f_0), \quad (4)$$

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[14] "*Amplitude*", as used here, is elsewhere occasionally also referred to as "*amplitude envelope*". The real part $x(t)$ is sometimes called the "*instantaneous amplitude*". The graphical relationship between A and x is easy to see from (2) when $y = 0$ (*i.e.*, at the peaks of the oscillation, $A = x$).

[15] In practise, convolution is conveniently given by multiplication in frequency domain: $F\{X\} = F\{x\}F\{w\}$, where F denotes the Fourier transform.

yields a complex signal $X(t, f_0)$ of which the real part is the 'classical' filtered signal, the modulus is the signal's amplitude envelope in the frequency band centred at f_0 and the argument is the continuous phase in this band.

The other route for obtaining X is by first applying arbitrary[16] band-pass filtering to $x(t)$, then finding the imaginary part $y(t)$ with the Hilbert transform, H, so that $y = \mathrm{H}\{x\}$, and finally applying (1) to obtain $X(t) = x(t) + iy(t)$.

2.2.2 Averaging in time and time-frequency domains

Averaging of electrophysiological signals is widely used to reveal a weak stimulus-locked 'signal' from 'noise'. By averaging, the signal-to-noise ratio (SNR) is improved by a factor of $\sqrt{N}$, where N is the number of averaged trials or epochs. The underlying assumption is that there is a signal *evoked* by a stimulus and that it is superimposed on noise of which both amplitude and phase are uncorrelated with the stimuli.

The complex form of signal representation provides an alternative approach. An average of signal amplitude across trials reveals the mean amplitude dynamics and, for instance, *induced*

oscillations—large amplitude oscillations of which the amplitude is time-locked to the stimulus, but the phase need not be.

The averaging of sig nal phase across trials must be computed in the complex plane. Let us consider the average given by $N^{-1}\sum_i z_i$, where z_i denote the phase values on unit circle of each trial i at some latency t. The argument of this average is the mean phase angle and its modulus is a measure of the distribution of the phases, often called the phase locking factor (PLF).

$$\mathrm{PLF} = N^{-1}\left|\sum_i z_i\right| \qquad (5)$$

For delta-function (*i.e.*, un-) distributed phases, PLF = 1, and for randomly and uniformly distributed phases, PLF $\rightarrow$ 0, when $N \rightarrow \infty$. Thus, in cases where the phase distribution is unimodal, PLF quantifies the distribution's nonuniformity (see Sinkkonen et al., 1995). PLF has been used, for instance, to quantify the phase locking of ongoing neural oscillations to sensory stimuli (Palva et al., 2005).

2.2.3 Estimation of amplitude correlations

Correlation[17] between two observables, say x and y, has been

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[16] In practise, the phase of a bandpass filtered signal is conceptually meaningful only for relatively narrow frequency bands, i.e., roughly oscillatory, zero-mean signals.

[17] The state or relation of being correlated; *specifically:* a relation existing between

traditionally assessed with the correlation coefficient[18]. Correlation coefficient, r, obtains values between 0 and 1, and indexes how well a linear fit $y = a + bx$ describes the dependence of y from x. The square of the correlation coefficient is given by

$$r^2 = \frac{ss_{xy}^2}{ss_{xx}ss_{yy}}, \qquad (6)$$

where ss denote the sums of squared values

$$ss_{xx} = \sum (x_i - \bar{x})^2, \qquad (7)$$

$$ss_{yy} = \sum (y_i - \bar{y})^2, \qquad (8)$$

$$ss_{xy} = \sum (x_i - \bar{x})(y_i - \bar{y}), \qquad (9)$$

where $\bar{x}$ indicates the mean over the data set of x_i. The r^2 has an important physical meaning as giving the proportion of ss_{yy} which is accounted for by the linear fit[19].

The correlation between the amplitudes of signals from two recording sites can be roughly assessed with the correlation coefficient. However, the correlation among oscillation amplitudes is often somewhat non-linear (I, II). A nonparametric

alternative to the correlation coefficient is Spearman's rank correlation coefficient that measures any monotone association between two observables. It is given by

$$r' = 1 - 6\sum \frac{d^2}{N(N^2 - 1)}, \qquad (10)$$

where d denotes the difference in the statistical ranks of x_i and y_i.

The possible non-monotonic correlations as well as the actual shapes of the relations can be characterized by amplitude histograms (I, II) where the amplitude values of y are averaged within the bins of a histogram based on amplitude percentiles of x (see I for normalization and details).

As the temporal evolution of amplitude is independent of frequency, amplitude correlations can be quantified also between oscillations in different frequency bands without complications.

2.2.4 Estimation of phase synchrony

Two processes are said to be phase synchronized if their phase difference is constant or, at least, non-randomly distributed. It is easy to see the phase difference of X and Y is given by the angle of their product

$$XY^* = A_X A_Y e^{i(q_X - q_Y)}, \qquad (11)$$

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phenomena or things or between mathematical or statistical variables which tend to vary, be associated, or occur together in a way not expected on the basis of chance alone. [Modified from *Webster's Unabridged Dictionary*]

[18] Also known as Pearson's correlation.
[19] The slope b of the linear fit is given by ss_{xy}/ss_{xx}. Conversely, the slope b' in $x = a' + b'y$ is given by ss_{xy}/ss_{yy}.

where Y^* denotes the complex conjugate[20] of Y. Several approaches have been developed recently to index the distribution of phase differences over time or over trials. In studies presented in this Thesis (I, II, IV), the phase-locking factor was used (PLF, see (5)). Tass et al. (1998) presented two histogram-based methods utilizing Shannon entropy and conditional probability. The advantage of these over PLF is that they are independent of the shape of the distribution; PLF gives meaningful results only for unimodal distributions. On the other hand, the PLF is very efficient to compute which is relevant when large amounts of data are inspected (as in I). Moreover, PLFs of uncorrelated signals are Rayleigh distributed[21]. Hence, in data devoid of externally evoked correlations, statistics and confidence limits can be estimated (see I) without the computationally demanding Monte Carlo-style shuffling which are used to get the statistics for the histogram-based methods (Tass et al., 1998. For data with, say, stimulus-evoked correlations, shuffling is necessary for PLF-based approaches as well (cf. Lachaux et al., 1999).

Extension of the phase synchrony concept to the cross-frequency case is simple. For oscillations at frequencies f_x and f_y,

the phase difference $w_{n,m}$ is given by

$$w_{n,m} = nq_x - mq_y, \qquad (12)$$

where the integers n and m define the ratio of the frequencies so that $nf_x = mf_y$. The presence of $n{:}m$-phase synchrony is now straightforward to evaluate from the distribution of $w_{n,m}$.

The detection of nested oscillations is also straightforward in this context. Phenomenologically they are observed as the amplitude modulation of a fast oscillation by a slower oscillation. Quantification of this interaction is easy: filtering of the amplitude envelope (see 2.2.1) of the faster oscillation with a filter used for the isolation of the slower oscillation gives the continuous phase of the amplitude fluctuations that can be directly compared with the phase of the slower oscillation. Hence, the analysis problem is reduced to assessment of 1:1 phase synchrony (II, IV). In cases where the modulation is clearly visible (for instance, in the rat hippocampal theta-gamma oscillations), the phase of the amplitude envelope can be obtained directly with Hilbert transform. The omission of filtering improves the temporal resolution and, consequently, the statistical power.

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[20] $z^* = x - iy$, see (1).
[21] J.M.Palva, Master's Thesis, Helsinki University of Technology, 2000.

3. Results

3.1 Phase synchrony among neuronal oscillations in the human cortex.

We addressed the presence of cross-frequency (CF) *n:m*-phase synchrony among ongoing oscillations in human cortex. In neuromagnetic recordings, CF phase synchrony was, indeed, robust and widespread among oscillations throughout the studied frequency range from 3 to 80 Hz. The role of these novel phase interactions in cognition was probed with continuous mental arithmetic tasks. In comparison with the resting state, the retention and summation of items in the working memory during the arithmetic tasks enhanced CF phase-synchrony specifically among alpha (~10 Hz), beta (~20 Hz) and gamma (~30–40 Hz) oscillations. Interestingly, the strongest differences between low- and high task load were observed in phase synchrony between gamma- and alpha-band oscillations. These data thus support the idea that the contents-to-context binding involves phase synchrony between the beta/gamma- and alpha-band oscillations.

3.2 Infraslow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep

We used DC-EEG to examine infraslow oscillations in the human cortex. We found widespread activity with frequency ranging from 0.02 to 0.2 Hz, which has remained hidden from conventional electroencephalography.
Interestingly, the amplitude of faster (> 1 Hz) EEG oscillations, as well as the occurrence of interictal epileptic events and K complexes were locked to the phase of the infraslow oscillation. Hence, similarly to the putative role of slow delta oscillations (0.5-1 Hz) in the modulation of brain excitability, the infraslow oscillations may reflect fluctuations in gross cortical excitability.

3.3 Fast network oscillations in newborn rat hippocampus *in vitro*

We examined the temporal structure of neuronal firing *within* the endogenous population bursts recorded from neonatal rat hippocampal slices *in vitro*. We found that high-frequency spiking (> 100 Hz) by groups of pyramidal cell was modulated by gamma-frequency band rhythmicity. Temporally correlated activities at millisecond time scales thus appear to be found in rat hippocampus already during the first postnatal

week. Non-random within-burst temporal structures may lay the foundation for spike-time dependent plasticity in developing circuits.

3.4 Slow endogenous activity transients in the immature human cortex

Direct-current coupled EEG recordings were used to examine slow endogenous bursts in preterm and full term human babies. The data show that, like in rat hippocampus, in the developing human cortex, discontinuous fast activities (1-30 Hz) are nested in very slow (> 1 s) deflections. These spontaneous activity transients (SATs) were observed only during the pre- and early postnatal stage and they showed a developmental decline reminiscent of that observed for endogenous bursts in neonatal rat cortex. *In situ* analyses showed that the emergence of KCC2 expression in age-matched fetal brain tissue takes place during the gradual attenuation of SAT occurrence. Several lines of evidence thus suggest that SATs are the human homologue for the population bursts (or GDPs) in rodent cortex.

4. Discussion

The studies presented in this Thesis have focused on the characteristics and functional roles of correlated neuronal activities in developing and adult brain. These studies showed that, in addition to the

widely recognized spatial and temporal correlations, neuronal network oscillations are correlated also in the frequency domain. Cross-frequency interactions ranged from > 1 Hz EEG activities nested in very slow and system-scale fluctuations to labile and fine-grained phase synchrony among 10–40 Hz cortical oscillations. Hence, the context of ongoing spatiotemporally and -spectrally correlated activity must be taken into account in the investigation of the mechanisms and functions of distinct neuronal events or activities in specific frequency bands.

The functional significance of the CF interactions in adult brain will probably turn out to be fundamental but diverse: from large-scale regulation and modulation of excitability to cognitive integration, attentional selection and memory multiplexing. Further studies are needed to dissect and identify the specific functional roles CF interactions. In the developing brain, the situation is perhaps even more complicated. The within-burst temporal patterns observed in both rat and human neonates are most likely to influence the shaping of the developing synaptic connectivity. However, both the acquisition of causal evidence and the evaluation of the precise underlying mechanisms will be a long-lasting challenge, as even the elementary

wiring rules and patterns have remained enigmatic to date.

4.1 A role for CF phase synchrony in cross-scale binding

The "temporal correlation hypothesis" (Singer and Gray, 1995; Singer, 1999), based on the concept of within-frequency synchrony, has been successful in explaining neuronal integration at the level of feature binding. While the necessity of CF interactions in higher-level neuronal processing has also been recognized (see, e.g., Lisman and Idiart, 1995; Engel and Singer, 2001; Varela et al., 2001; VanRullen and Koch, 2003), only relatively few studies have addressed their presence and nature. Previous investigations have revealed non-linear CF phase coupling (Jeffrey and Chamoun, 1994; Shils et al., 1996; Schanze and Eckhorn, 1997; von Stein et al., 2000a; Schack et al., 2002) and, more specifically, nested oscillations (Chrobak and Buszaki, 1998; Schack et al., 2002; II; Bruns and Eckhorn, 2004; Lakatos et al., 2005).

Our work (I) was the first to show that among cortical oscillations, CF phase interactions are also found in the form of 1:m-type CF phase synchrony. CF phase synchrony was present in resting state ongoing activity among all frequency bands analyzed, from 3 to 80 Hz. Interestingly, mental arithmetic tasks that posed considerable working memory demands, enhanced specifically the 1:2–1:4 phase synchronies among alpha, beta, and gamma oscillations. These tasks also enhanced 1:1 phase synchrony and slightly also oscillation amplitudes. The spatial patterns of 1:1 alpha, beta and gamma synchronies, however, were distinct from each other and, furthermore, clearly different from the patterns of cross-frequency phase synchrony. The differences in the patterns of 1:1 synchrony support the idea that alpha, beta, and gamma oscillations are all involved in the performance of the mental arithmetic tasks but have dissimilar functional roles (see Singer, 1999; Tallon-Baudry and Bertrand, 1999; von Stein et al., 2000a; Varela et al., 2001; Howard et al., 2003). The robust CF phase synchrony among alpha, beta and gamma oscillations may thus provide a plausible mechanism (see 4.5) to mediate the integration and coordination of this spectrally distributed processing into the cognitive operations required by mental calculation and working memory.

4.2 Is the retention of multiple objects in short-term memory based on synchronized alpha and gamma oscillations?

The mental arithmetic tasks in (I) affected the amplitude, 1:1 phase synchrony, and hemispheric

lateralization of ongoing neuronal activity very similarly to what has been earlier observed in working memory tasks, which is well in line with the notion that the principal task load during easy mental calculation is on the working memory system (for review, see Houdé and Tzourio-Mazoyer, 2003). Nevertheless, the comparison of the mental arithmetic tasks with the resting condition does not allow the dissection of working-memory related activities from those involved in, e.g., the mental calculation, but reveals the overall differences between minimal and near-maximal cognitive load. However, the comparison of low- and high-load arithmetic tasks reveals specifically the components sensitive to the number of items simultaneously retained working memory. Hence the finding of stronger 1:3 gamma-alpha phase synchrony during high-than low-load conditions suggests that synchronized gamma and alpha oscillations are involved in the neuronal mechanisms of working memory. A role for CF phase synchrony in attentional and working memory functions is further supported by the finding that, while 1:1 synchronies were widely distributed over the cortex, beta-alpha and gamma-alpha phase synchronies as well as their task effects were strongest over the right hemispheric parietal regions. The right-hemispheric parietal regions have been shown to have a critical role of in attention and working memory by imaging studies (Corbetta et al., 1998; Kastner and Ungerleider, 2000; Awh and Jonides, 2001; Linden et al., 2003) and by the diversity of attentional deficits, such as neglect, caused by parietal damage (Friedman-Hill et al., 1995; Driver and Vuilleumier, 2001).

The retention of more than one object in short-term memory (or in the focus of attention) supposedly demands multiplexing of the neuronal object representations (Lisman and Idiart, 1995; Jensen and Lisman, 2005). As integrated, coherent object representations are stored in short-term memory, the mechanisms underlying multiplexing must explain how the activity of neural assemblies corresponding to the memorized or attended objects is sustained without compromising the independence of the assemblies or the within-assembly coherence. The brain areas specifically responsible for multiplexing functions (Friedman-Hill et al., 1995) are located, at least partly, in the parietal regions, as suggested again by both imaging studies localizing cortical activity correlated with working memory capacity (Linden et al., 2003; Todd and Marois et al., 2004) and by findings that damage in parietal regions can result in an inability to perceive multiple objects simultaneously (simultagnosia; Friedman-Hill et

al., 1995). In the context of the proposed representation- (Singer, 1999; Tallon-Baudry and Bertrand, 1999) and attention-related (von Stein et al., 2000, VanRullen and Koch, 2003) roles of gamma and alpha oscillations, the data suggest that gamma-alpha 1:3 synchronization well posed to mediate contents-to-context binding of neuronal object representations into working memory and the multiplexing of these object representations.

4.3 Infraslow oscillations in the adult brain

EEG-activities at frequencies below 0.5 Hz have received little attention because of the high-pass filtering nature of the conventional AC-coupled EEG (Voipio et al., 2003; Vanhatalo et al., 2003). We used DC-EEG to address the presence and functional role of <0.5 Hz EEG-fluctuations (II). The observed ISOs turned out to have properties unmatched in the human EEG literature: a frequency range of 0.02-0.2 Hz, a slow apparent propagation over cortical hemispheres, and, most importantly, a strong modulatory link to much faster EEG activities. The phase of ISO and the amplitude of > 1 Hz EEG activities were strongly correlated with strongest > 1 Hz oscillations taking place during the negative[22] deflections of ISO.

Moreover, the occurrence of very brief phenomena, such as interictal epileptic events and K complexes was more probable during the negative than positive deflections of ISO. These data suggest that ISOs reflect slow fluctuations in gross cortical excitability. ISOs may thus underlie the previously observed ~0.1 Hz fluctuations in neuronal population activity in humans (Staba et al., 2002), monkeys (Leopold et al., 2003), cats (Steriade et al., 1993), and rats (Penttonen et al., 1999; Jando et al,. 1995) as well as the long-range coherence (Bullock et al., 1995; Leopold et al., 2003) of this modulation. The slow variability of population activity revealed by micro-scale recordings is well paralleled at the macro level; the amplitudes of 1–30 Hz EEG and MEG oscillations show very slow and spatiotemporally long-range correlated fluctuations (Steriade et al., 1993; Bullock et al., 1995; Achermann et al., 1997; Simon et al., 2000; Linkenkaer-Hansen et al., 2001). Furthermore, the occurrence of both physiological and pathophysiological non-periodic EEG events such as K complexes, arousals (Achermann et al., 1997, Tersano et al., 1985; Amzica and Steriade, 1997) and interictal epileptic events (Penttonen et al., 1999; Parrino et al., 2000; Jando et al., 1995) have all been shown to

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[22] Note that in EEG, the polarity and the magnitude of the signal are dependent on the

choice of reference electrode. These data were referenced to linked mastoids.

exhibit fluctuations at 0.025-0.3 Hz. It should be noted that in our work, ISOs were recorded during sleep.

Future studies should address their presence and modulatory role in awake humans as well, especially as both the magnitude of cortical evoked responses (Prince, 1965), as well as psychophysical performance (Gilden et al., 1995; Palva et al., 2005) are known to show very slow fluctuations. In particular, the extent to which ISOs contribute to the scale-free modulation of theta-, alpha- and beta-band oscillations remains unclear. Does the ISO frequency fluctuate in a scale-free manner across a wide frequency range or do other, even slower phenomena contribute to the very slow amplitude envelope fluctuations (Linkenkaer-Hansen et al., 2001) of these oscillations?

Epileptic activity may be aggravated or triggered during sleep (Basil et al., 2002). Synchronous delta-frequency band (1–4 Hz) oscillations in cat cortex have been suggested to facilitate epileptic activity (Steriade and Contreras, 1995; Amzica and Steriade, 2000). However, in humans, clinical studies have demonstrated a high occurrence of interictal epileptic events also during non-slow-wave sleep (Bazil et al., 2002; Herman et al., 2001; Malow et al., 1998), which is characterized by suppressed delta-frequency band activity. ISOs, on the other hand,

were observed during both slow-wave and non-slow-wave sleep. Our finding of robust locking of interictal events to the phase of ISO during non-slow-wave sleep is hence of particular clinical interest.

4.4 Fast oscillations during an infraslow rhythm in developing cortical structures

4.4.1 GABAergic inhibition and mechanisms of fast oscillations in the newborn rat hippocampus

In the study on neonatal rat hippocampal slices (III), we showed that pyramidal cell discharges give rise to high-frequency population activity. In rat hippocampal pyramidal neurons, GABAergic transmission is depolarizing during the first postnatal week (Ben-Ari et al., 1989), and has been suggested to provide the principal excitatory drive to neonatal neurons together with the NMDA receptor-mediated transmission (Cherubini et al., 1991; Ben-Ari et al., 1997). Nevertheless, our work (III) as well as later studies (Lamsa et al., 2000; Sipilä et al., 2005) showed that AMPA-kainate receptor activation is critical to the excitatory drive. GABA currents, on the other hand, were out-of-phase with the field potential spikes suggesting that they have an inhibitory role. Indeed, massive population bursts observed during the application of bicuculline, a $GABA_A$ antagonist, suggest that by shunting inhibition,

GABAergic transmission restrains both the activity of individual pyramidal neurons as well as the operation of the pyramidal cell population under control conditions (Qian and Sejnowski, 1990; Staley and Mody, 1992; Lamsa et al., 2000).

In the adult hippocampus, gamma oscillations may arise in interneuronal networks that phase both the interneuronal and the pyramidal cell discharges by hyperpolarizing GABA$_A$ergic postsynaptic potentials (Whittington et al., 1995). During the population bursts in neonatal hippocampus, the GABAergic currents occurred predominantly at gamma frequencies suggesting that interneuronal network-gamma oscillations may also take place in the immature hippocampus. Computational models of interneuronal oscillations have emphasized the need for synaptic hyperpolarization in population gamma rhythmicity (Whittington et al., 1995; Traub et al., 1996a,b). However, a recent study showed that mutual GABAergic excitation among interneurons in adult hippocampus can, in fact, co-exist with network beta- and gamma-frequency oscillations (Lamsa and Taira, 2003). Hence, neonatal interneuron networks may generate brief gamma oscillations during spontaneous bursts with mechanisms that are not fundamentally dissimilar to those observed in adult hippocampus. In this case, it is possible that inhibitory GABAergic action contributes to the observed gamma modulation of the pyramidal cell spike bursts.

However, another plausible sources for both the gamma modulation and the gamma-frequency band rhythmicity of GABA-receptor mediated currents are the recently observed intrinsic bursting properties of the immature pyramidal cells (Sipilä et al., 2005). Stereotypical cell-specific spike patterns recurring burst after burst with within-burst inter-spike intervals corresponding to the gamma range would give rise to apparent population gamma rhythmicity in field recordings when the burst onset is synchronized across the participating pyramidal cells. Out-of-phase interneuronal firing evoked by such intrinsically patterned pyramidal cell activity could, in theory, also explain the negative spike-GABA current correlation.

The gamma-modulated pyramidal cell population discharges reached rates of several hundred Hz. This raises a question on the role of gap junctions in the early network activity. In adult hippocampus *in vitro*, phenomenologically reminiscent gamma-modulated high-frequency activity is observed during carbachol- and kainate-induced

gamma oscillations (Traub et al., 2000; 2003). This high-frequency activity is critically dependent on gap junctions (Hormuzdi et al., 2001; Traub et al., 2000, 2003) as are 80–200 Hz oscillations in cats *in vivo* (Grenier et al., 2003) and 200 Hz ripples in rat hippocampus *in vivo* (Ylinen et al., 1995). Intriguingly, Strata et al. (1997) has shown that endogenous bursts in neonatal rat hippocampus are abolished by the blockage on gap junctions. Future studies should hence address the functional roles of gap junctions in fast network activity in the developing rat hippocampus.

Taken together, it appears probable that the intrinsic properties, the synaptic network interactions, as well as gap junctions contribute to the emergence of specific temporal patterns within the endogenous bursts.

4.4.2 Spontaneous activity transients in human babies

DC-EEG recordings of preterm human babies (IV) showed that much of the neuronal activity in the preterm human cortex is concentrated into spontaneous, slow activity transients (SATs), where a prominent slow voltage shift is associated with oscillatory activity in multiple faster frequency bands. SATs were also observed in healthy full term babies although with a reduced frequency of occurrence.

However, the spectral pattern of oscillations co-occurring in SATs remained similar during both continuous and discontinuous sleep as well as throughout the studied developmental period from 32 to 44 conceptional weeks.

The presence of fast bursts nested in slow deflections in the immature human cortex raises the question whether they are homologous to the population bursts in the rodent cortex and hippocampus. Indeed, several lines of evidence support this idea. The developmental transformation of SAT-type EEG into adult-like continuous EEG at around full term parallels the disappearance of prominent burst-like events into continuous activity in rat cortex and hippocampus during the second postnatal week (Ben-Ari, 2002; Khazipov et al., 2004; Garaschuk et al., 2000). In addition, in rodents, the decline of spontaneous bursts takes place during the emergence of hyperpolarizing GABAergic inhibition brought about by the expression of the neuronal K-Cl cotransporter KCC2 (Rivera et al., 1999; 2005). In line with this, we found that the developmental decrease in SAT occurrence was associated with a pronounced increase in the expression of KCC2 mRNA[23] as seen in age-matched

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[23] In native cortical neurons, the developmental rise in KCC2 mRNA level is directly associated with an increased expression of functional KCC2 protein (Rivera et al., 1999; Yamada et al., 2004; Khirug et al., 2005).

fetal human tissue. Furthermore, the nesting of coincident bursts of oscillations in multiple distinct frequency bands into slow deflections was a striking characteristic of both the rat hippocampal bursts (III) and the human SATs (IV). Finally, during human intrauterine development, all sensory cortices are capable of responding to modality-specific stimuli (Grubb and Thompson, 2004; Fulford et al., 2003; Eswaran et al., 2002; Schleussner and Scheider, 2004). In the immature rat primary somatosensory cortex, endogenous network bursts in the form of slow spindle oscillations can be triggered by somatosensory stimuli (Khazipov et al., 2004). Human SATs and rodent population bursts dominate the ongoing neural activity in the developmental time window of intense proliferation of both intracortical and thalamocortical connections (Kostovic and Judas, 2002; Schwartz and Goldman-Rakic, 1991; Mrzljak et al., 1992; Molliver et al., 1973). Both the concentration of synchronous network activities into these endogenous events as well as their interaction with sensory stimuli are in line with the postulated role of this activity in shaping the developing networks.

4.5 Functional significance and 'read-out' mechanisms of CF phase interactions

4.5.1 CF phase interactions as a coding space

All four studies presented in this Thesis have highlighted the functional significance of interactions between neural activities in distinct frequency bands. One (I) demonstrated the presence of cross-frequency amplitude correlations and phase synchrony whereas the rest dealt with different kinds of nested oscillations. In the assessment of the putative functional roles of CF phase interactions, it is essential to consider the cellular level substrates and consequences of the macro-level observations such as oscillations and synchrony.

Spike timing is well known to have a central role in both synaptic integration and plasticity. In the context of the classical binding problem, the concept of 'dynamic binding' posits that the postsynaptic impact of 'bound' presynaptic inputs is greater than the impact of 'unbound' ones (Singer, 1999). Excitatory inputs coinciding within a few milliseconds have much better chances of evoking action potentials in downstream target neurons than asynchronous inputs (König et al., 1996; Singer, 1999) and, importantly, target neurons entrained by one oscillatory

assembly are less susceptible to influences from other sources (Schoffelen et al., 2005). 1:1 phase synchrony can thus be seen as a type of classical winner-take all mechanism where binding is realized by enhanced saliency[24] of the "bound" assembly over other concurrent activities.

Phase synchrony always implies spike synchrony. n:m phase synchrony hence is not only mathematically but also physiologically simply an expansion of the traditional within-frequency synchrony. This is important, because for n:m synchronized oscillations, the slower process operates at a temporal precision that parallels the spike synchrony of the faster process. Thus, for example, a ~10 Hz oscillation could be locked selectively to one coherent ~30 Hz assembly in the presence of other simultaneously active but uncorrelated ~30 Hz assemblies. Moreover, since the timing of afferent spikes *in relation* to the oscillatory cycle is critical, a 10 Hz process could exert a significant influence on one 30 Hz assembly while being ignored by another concurrent 30 Hz assembly that is synchronous but out-of-phase with the first one. Mathematically, the 10 Hz oscillation would be 1:3-phase synchronized with both 30 Hz oscillations, but for the first phase coupling would reflect a physiological interaction. The temporal precision inherent to n:m phase locking thus endow this form of cross-frequency interaction with properties that are relevant in the context of attentional selection, short-term memory multiplexing, and cross-hierarchical bottom-up-top-down integration.

When the frequency separation of two oscillations is greater than about 1:4 (cf. footnote 5 and Fig. 1 and 2 of I), this demand for time accuracy becomes too great for the network mechanisms underlying the slower oscillation. This is evident from the rapid decline in the strength of 1:m phase synchrony with values of m increasing beyond two (see Figs. 1 and 2 in I). However, theoretically and apparently also empirically, nested relationships can take place with arbitrarily large and non-integer frequency ratios. The stereotypical nested oscillations, rat hippocampal gamma- (20-100 Hz) and theta- (4–12 Hz) rhythms, have typically a frequency ratio of roughly ~1:10 (Chrobak and Buszaki, 1996). The nesting of up to 20 Hz EEG activities into 0.02–0.2 Hz infraslow oscillations in (II) shows that frequency ratios of 1:100–1:1000 can also be observed. It is unlikely that this nestedness

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[24] Saliency here may originate from spike synchrony, but is in any case consequently reflected also in enhanced firing rates at higher levels of hierarchy. Hence the traditional *firing rate* coding and the more modern *temporal coding* are, *de facto*, not orthogonal or mutually independent coding dimensions.

per se is significant in neural coding—the infraslow oscillations probably reflect or mediate fluctuations in gross cortical excitability. The fundamental difference between phase synchrony and nested oscillations is that in nested oscillations, the phase of the faster oscillation is independent of the phase of the slower oscillation; only the amplitude envelope of the faster component is locked to the phase of the slower oscillation. The lack of spike synchrony between the two, however, does not preclude the possibility of interesting coding alternatives. For instance, the nesting of synchronous pyramidal cell assemblies discharging in successive gamma cycles into a theta cycle could explain the multiplexing mechanism underlying the 7±1 object capacity of human working memory in the Sternberg task (Lisman and Idiart, 1995; Jensen and Lisman, 1996; Jensen et al., 1996; Jensen and Lisman, 2005; see also van Rullen and Koch, 2004).

Taken together, cross-frequency phase synchrony and nested oscillations add altogether new dimensions and levels of complexity to the possibilities of temporal coding in neuronal networks. It appears likely that, in general, the long distance synchronization of theta/alpha-band oscillations provides a slow "clock-frequency" [25]. The slow cycles would then be subdivided by faster but more local oscillations into 'subcycles' to represent object collections or sequences.

4.5.2 Are layer 5 pyramidal cells cross-frequency coincidence detectors?

Neocortical layer 5 (L5) pyramidal cells, with dendrites spanning all cortical layers, have unique properties that may be important for both the neuronal underpinnings and phenomenological (psychological-level) consequences of CF phase synchrony.

The principal excitatory connections to proximal and basal dendrites of these cells originate from specific thalamic nuclei (Jones, 2002), local layer 4 spiny stellate cells and, overall, from cortical areas at the same level or lower in hierarchy (Felleman and Van Essen, 1991). Inputs to their distal apical dendrites are, conversely, from diverse non-specific thalamic regions (Jones, 2002) as well as from cortical areas higher in hierarchy (Felleman and Van Essen, 1991; Cauller et al.,

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[25] This idea dates back to 1950's when "Wiener proposed that the stable component of the alpha rhythm would function as a brain clock to serve a gating function. Wiener (1948) cites Pitts and McCulloch's (1947) idea of the alpha rhythm as a scanning rhythm (cf. Crick, 1984 and von Stein et al., 2000a!). McCulloch, on the other hand, attributes their idea to Wiener's work (1940) on digital computer design." (Adapted in part from Niedermeyer and Lopez da Silva, 1999, pp. 174.)

1998). L5 pyramidal cells thus receive bottom-up and top-down signals in distinct integrative compartments. Proximal (bottom-up) and distal (top-down) inputs alone, if sufficiently strong, can evoke action potentials or burst firing (Helmchen et al., 1999; Larkum et al., 1999; Williams and Stuart, 1999; Larkum and Zhu, 2002). However, burst firing can be triggered by inputs too weak to cause bursting in separation, if the proximal and distal excitation coincides with a precision of ~5 ms (Larkum et al., 1999). Because bursts have a profoundly stronger impact on postsynaptic neurons than single action potentials (Lisman, 1997; Williams and Stuart, 1999), L5 pyramidal cells can thus detect *and* signal the coincidence of bottom-up and top-down excitation. L5 pyramidal cells can thus mediate cross-hierarchical and -functional integration.

Feedforward / bottom-up excitation typically involves gamma-band rhythmicity (Steriade et al., 1996; Castelo-Branco et al., 1998; Singer, 1999; von Stein et al., 2000a). However, feedback / top-down signals are more likely to have periodicities in the alpha band (von Stein et al., 2000a; Mima et al., 2001; Halgren et al., 2002; Yamagishi et al., 2003) (see also chapter 1.2.3) although the role of gamma oscillations in top-down modulation has also been discussed (for review, see Fell et al., 2003).

L5 pyramidal cells, as well, hardly discharge at rates above 10 Hz, and can entrain each other (Silva et al., 1991) as well as subcortical targets in the brainstem (Nicolelis et al., 1995), and superior colliculus (Brecht et al., 1998) into ~10 Hz oscillations. Furthermore, the regenerative Ca^{2+} action potentials underlying distal dendritic excitation (Helmchen et al., 1999; Larkum et al., 1999; Larkum and Zhu, 2002) are very unlikely to occur at frequencies above ~10 Hz (Larkum and Zhu, 2002). The time window of coincidence detection observed by Larkum et al. (1999) is far smaller than one gamma-oscillation cycle. Hence, proximal and distal inputs that have oscillatory patterning in 20–40 Hz and <10 Hz bands, respectively, can readily induce burst firing *only* when they are phase synchronized in a 1:*m* manner. This indicates that the L5 pyramidal neurons can function as 'read-out devices' for 1:*m* phase synchrony.

This kind of a mechanism would enable an unambiguous and rapid attentional selection (~10 Hz) of target representations (~20–40 Hz) from among other intermittent oscillatory assemblies. Interestingly, although not surprisingly in this context, many of the subcortical targets of L5 pyramidal cells, such as the pulvinar and superior colliculus, have a critical role in attention and

visual orienting (Karnath et al., 2002).

4.5.3 Origins of infraslow oscillations

Deep cortical layers may exhibit endogenous infraslow oscillations both in cortical slices *in vitro* (Sanchez-Vives and McCormick, 2000) and in deafferented cortical slabs *in vivo* (Timofeev et al., 2000). On the other hand, several lines of evidence suggest that large-scale, very slow electric signals are generated by non-neuronal sources, such as the glial cells (Amzica and Steriade, 2000; Laming et al., 2000; Kivi et al., 2000; Dietzel et al., 1989) or the blood-brain barrier (Voipio et al., 2003; Vanhatalo et al., 2003). Multiple cellular- and tissue-level mechanisms are thus likely to underlie the ISOs observed in (II).

ISOs were clearly linked to the amplitudes of faster cortical activities suggesting that they reflect fluctuations in cortical excitability. The direction of causality, however, remains unclear. Does an infraslow oscillation underlie the amplitude modulation of faster activities, or are the amplitude fluctuations of faster activities, and the consequent changes in metabolism and blood flow, reflected in slow changes of scalp potential?

4.5.4 Nested oscillations in developing cortical structures

Nested network oscillations in widely separated frequency bands were one common denominator in rat and human endogenous cortical activity transients (III, IV). It is appealing to speculate that the synchrony and nested oscillations play homologous functional roles in the developing and adult nervous systems; the relational coding schemes that 'solve' the binding (1.2.1) and cross-scale binding (1.2.4) problems in the adult brain (Singer, 1999; Jensen and Lisman, 2005; I) could solve the wiring problem as well (1.3.1). Moreover, as synaptic plasticity is continuously present in all brain activity and intimately involved in cognitive operations of the adult brain (for reviews, see Singer, 1995; Traub et al., 1998), this notion is perhaps not too far fetched.

5. Conclusion

The studies in this Thesis highlight the presence and multiple forms of interactions between neuronal oscillations in different frequency bands. Cross-frequency phase synchrony and nested oscillations are likely to have central roles both in cognition and in the wiring of neuronal circuits.

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7. Acknowledgements