Precise synchronization dynamics in cortical networks – feasibility and constraints

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Studies of cortical network function on the basis of multiple single-neuron recordings have revealed neuronal interactions which depend on stimulus and behavioral context. These interactions exhibit dynamics on several different time scales, with time constants down to the millisecond range (Grün et al. 2002a,b, Gütig et al. 2002, 2003, Heck et al. 2002, Riehle et al. 1997, Vaadia et al. 1995). Mechanisms underlying such dynamic network organization are investigated by experimental and theoretical approaches. Our current research focuses on two interrelated aspects: precision and variability of cortical network activity (Arieli et al. 1996, Nawrot et al. 2000, 2003). Starting from previous model work (Diesmann et al. 1999, Gewaltig et al. 2001) in which we investigated conditions for the occurrence of precise joint-spiking events in cortical network activity, I will present recent findings from ongoing experimental and theoretical work in our laboratory (Heck et al. 2000, Hehl et al. 2001, Kuhn et al. 2002, 2003, 2004, Mehring et al. 2003), undertaken to test and expand some of the model predictions. Specifically, I will discuss new findings regarding the feasibility and constraints of precise synchronization dynamics in cortical networks, resulting from a critical evaluation of biological constraints from cortical connectivity and *in vivo* physiology, and dynamical constraints from large-scale network simulations.

Funded by GIF. Further information at http://www.brainworks.uni-freiburg.de

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Ongoing activity and the "state of mind": the role of spontaneously emerging cortical states in visual perception and motor action

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The brain is often described as a system of sequential stations leading from an object that has a fixed internal representation to the behavioral response. According to this classical view of feature detection, each element can be characterized by a fixed response to a specific stimulus. However, even during well-defined cognitive tasks, successive brain responses to repeated identical stimulations are highly variable due to the ongoing cortical activity: even in the absence of external sensory input, cortical activity exhibits highly structured, internally driven ongoing (spontaneous) waves of activity (including in the sensory areas). Therefore, there has been a long-standing debate whether this ongoing activity reflects "brain noise", a nuisance to neural processing or, instead, "states of mind" expressing the brain's internal context.

Bearing these questions in mind, my work focused on the role of the internal ongoing cortical activity and the way it may provide the neuronal substrate for the dependence of sensory information processing on context, behavioral and/or conscious states.

We revealed the spatio-temporal organization of this activity in the mammalian brain, where ephemeral ensembles of hundreds to millions of cortical neurons organize dynamically into instantaneous functional groups by being active together (Arieli 1992, Arieli et al. 1995). The ongoing activity encompasses a set of dynamically switching cortical states. Thus, functional maps that were thought to be purely stimulus-driven were observed to arise instantaneously and completely spontaneously (Kenet et al. 2003). A neuron has a preferred cortical state that corresponds to the pattern of activation over a large cortical area, obtained by using the neuron's optimal stimulus. The neuron is most likely to fire when this pattern (cortical state) emerges, regardless of stimulation, or its absence - when the neuron fires spontaneously (Tsodyks et al. 1999). Furthermore, the ongoing activity affects stimulus driven cortical responses (Arieli et al. 1996) as well as the behavioral response of the animal. This means that the brain does not "average out" the variability found in cortical evoked activity. Rather, this variability has direct impact on the manifest behavior.

Taken together, these findings indicate for the first time that ongoing activity carries established representations of the external world, and therefore could express the brain's internal context, which influences perception and behavior (Fig. 1). Instead of the feature detection view, I propose a dynamic theory, in which the observer's perception of reality in one instant, is interwoven into the ongoing dynamics in the brain in the following instant, the ongoing activity which reflects expectations about the sensory input, thus shaping the intentions and actions of the observer.

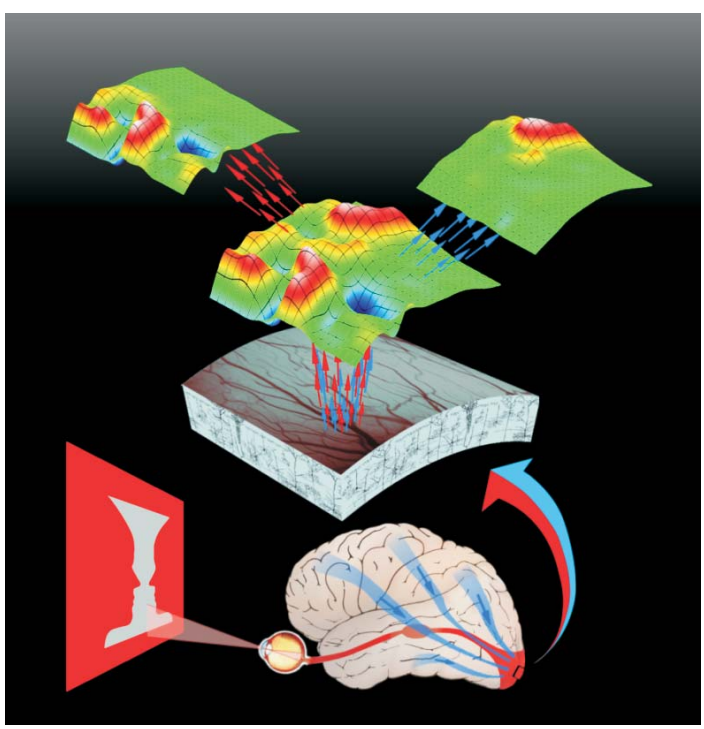

Fig. 1. The visual cortex never responds to a given stimulus the same way twice. The response has a reproducible component which derives from the stimulus itself (red pathway). But this is combined with the ongoing internal activity (blue streams on the cortex) to produce an overall response which varies each time the stimulus is seen. Thus the pattern of activity (lower map) can be decomposed into a deterministic response (top left map) superimposed onto the constantly changing internal brain state (top right map).

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Relative spatio-temporal properties of odor evoked oscillations in turtle olfactory bulb

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Due to the relatively recent advances in multi-site recordings and neuroimaging techniques, the existence of synchronous activity (appearing usually as periodic oscillations) was established experimentally to be widespread in different regions of the cortex across species (Gelperin and Tank 1990, Lam et al. 2000, Laurent and Naraghi 1994, Singer 1999). It is hypothesized that the oscillatory patterning observed in the brain can be a proof of existence of spatio-temporal codes and at the same time, it may underlie their formation (Laurent 1999, Singer 1999, Von der Malsburg 1995, 1999). However, despite its ubiquity, the specific roles and mechanisms of formation of those stimulus evoked oscillations remain still unknown.

One of the most direct observations linking oscillatory patterning with cognitive processing were obtained from the olfactory system and show that in insects the pharmacological disruption of the observed oscillations led to impaired recognition of odorants having similar chemical structure (Gelperin and Tank 1990, Hosler et al. 2000, Stopfer et al. 1997). The olfactory bulb (OB), which represents the first stage of olfactory processing in the vertebrate brain, has a relatively simple cortical structure. The axons of olfactory receptor neurons (ORN) expressing the same type of receptor are sorted and converge onto specific glomerulus to form a chemotopic map in the OB. The glomeruli therefore represent the specific type of receptor and are tuned to specific molecular features of the odorant (Malnic et al. 1999, Mombaerts et al. 1996, Mori et al. 1999).

The combined activity of the excitatory mitral/tufted (M/T) cells constitutes the output of the OB and is modulated through the activity of extensive local neuronal circuits (Wachowiak and Cohen 2001).

It was established relatively early that the presentation of the odorant evokes oscillatory response in the olfactory bulb across different species (Adrian 1942, Gelperin and Tank 1990, Lam et al. 2000, Laurent 1996, Laurent and Naraghi 1994, Laurent et al. 1996). It has been also identified that the observed oscillations are primarily mediated by interaction of the M/T cells and the inhibitory periglomerular and granule cells (Wachowiak and Cohen 2001). Furthermore, it was established that in the insect antennal lobe (corresponding structure to the OB in vertebrates).

We measured the spatio-temporal properties of odor-evoked oscillations in the turtle OB using a voltage sensitive dye, RH 414- and a 464-element photodiode array (Lam et al. 2000, 2003). Optical imaging provides a relatively detailed map of population activity of the dorsal regions of the OB. It is expected that the responses will be seen only to those odorants that activate at glomeruli, from which at least a fraction is located in the dorsal region.

We monitored odor evoked activity in turtles (n = 75). Four distinct signals were detected during and immediately after odorant presentation – slow depolarization and three oscillations. The slow excitation (DC) component appeared just after the onset of stimulus presentation, and lasted for at least 2 s. The DC component encompassed most of the bulb. The oscillatory patterning appeared on top of the DC. For visualization purposes the DC has been reduced through high-pass filtering to allow the focus on properties of the observed oscillations. The three observed oscillations are rostral, middle and caudal oscillations and have different spatial location, latency and frequency. Fig. 1 depicts examples of the observed oscillations and their approximate locations from two experimental animals showing range of typical responses. The rostral oscillation (Fig. 1, trace 1) has

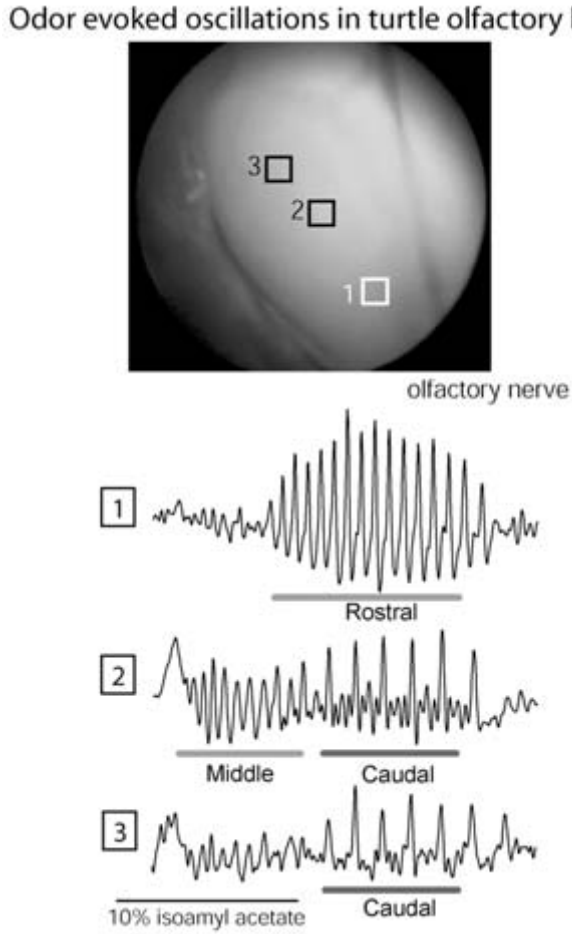

Fig 1. Locations and time courses of odor evoked oscillations in turtle olfactory bulb. Three separate oscillations were detected: rostral, middle and caudal.The locations of the oscillations are overlaid on the picture of the bulb. The numbers assigned to traces on correspond to the numbered squares on the photograph. The slow excitation was filtered out and appears as the large peak before the oscillatory patterning. The temporal characteristics of the three oscillations are described in the text.

about 750 ms average latency and average initial frequency of about 14 Hz. This oscillation has a limited propagation area and does not propagate into the caudal regions of the bulb. The amplitude of the rostral oscillation is usually significantly larger than that of the other two. The middle oscillation (Fig. 1, trace 2) has an average latency of 580 ms and frequency that is similar to that of the rostral oscillation. It appears in the medial-lateral part of the bulb. This oscillation is usually relatively short lived and its magnitude is often smaller than that of the other two oscillations. It is however much more resilient to odor concentration changes than the other two. Lastly, the caudal oscillation (Fig. 1, trace 2 and 3) is usually composed of two phases having different frequencies. It initiates as 14 Hz frequency oscillation and undergoes period doubling to obtain a resulting frequency of 7 Hz. The high frequency phase usually is detected relatively soon after the onset of the rostral oscillation, whereas its slow frequency phase has average latency of 1,100 ms form the odorant onset. The region of its formation is often at least partially overlapping with the region of formation of middle oscillation. The observed spatio-temporal characteristics of the oscillatory response did not depend on the odorant presented. The oscillations were detected for all tested concentrations between 0.03-10% of saturated vapor.

These distinct characteristics of the three oscillations indicate that the three oscillatory patterns may be generated by partially different cell populations. Closer examination of the evoked oscillatory patterns yields additional insight in their interdependencies. Fig. 2 (A and B) shows two examples from two different animals of the response to the same odorant (10% isoamyl acetate). In both cases, the trials had the same duration of odorant presentation, the same odorant as well as odorant concentration. The traces in the respective examples come from a single trial and represent three different spatial locations. There are significant differences between the animals in the response to the same odorant: (i) the latency of all the oscillations on the second example is significantly shorter than those in example one (Fig 2A); (ii) the amplitude, duration and the shape of the envelope of the observed oscillations are significantly different. The differences can be due to slight differences in the placement of the tubing facilitating the airflow through the nasal cavity that would influence the airflow (Scott-Johnson et al. 2003), thickness of the mucose layer or inherent sensitivity to the presented odor, which could be induced by earlier uncontrolled exposure to similar odorant. However, the precise interdependencies between oscillations are preserved indicating a common network mechanisms generating them. Firstly the middle oscillation is generated significantly before rostral oscillation. Then, it gradually decreases before the rostral oscillation starts, or ends abruptly at its onset (Fig. 2B). The caudal oscillation on the other hand is usually significantly phase shifted in comparison to the rostral oscillation (Fig. 2C). In the first example the middle oscillation has a length of 5 cycles. The last cycles are significantly smaller than the middle ones indicating its termination. However, as soon as the rostral oscillation starts to be noticeable, the amplitude of the oscillatory cycles significantly increase (Fig. 2B, trace 3) indicating the beginning of the fast phase of the caudal oscillation. In the second example however, the rostral oscillation starts significantly earlier, during the generation of the middle oscillation. The middle oscillation is initially in phase with the first cycle of the rostral oscillation (arrow I), however on the next cycle it undergoes abrupt phase shift (arrow III), so that its next oscillatory cycle (arrow II) – or the first cycle of fast phase of caudal oscillation – is already phase shifted with respect to that rostral oscillation. In both examples in Fig. 2B the cycles of middle oscillation have a relatively symmetric, "Gaussian" shape as compared to the shape of the cycles of rostral and caudal oscillations. That could indicate a relatively loose synchronization of cell activity within that oscillatory pattern. In many cases the rapid transition shown in the second example did not take place as the middle oscillation initially exhibited the phase

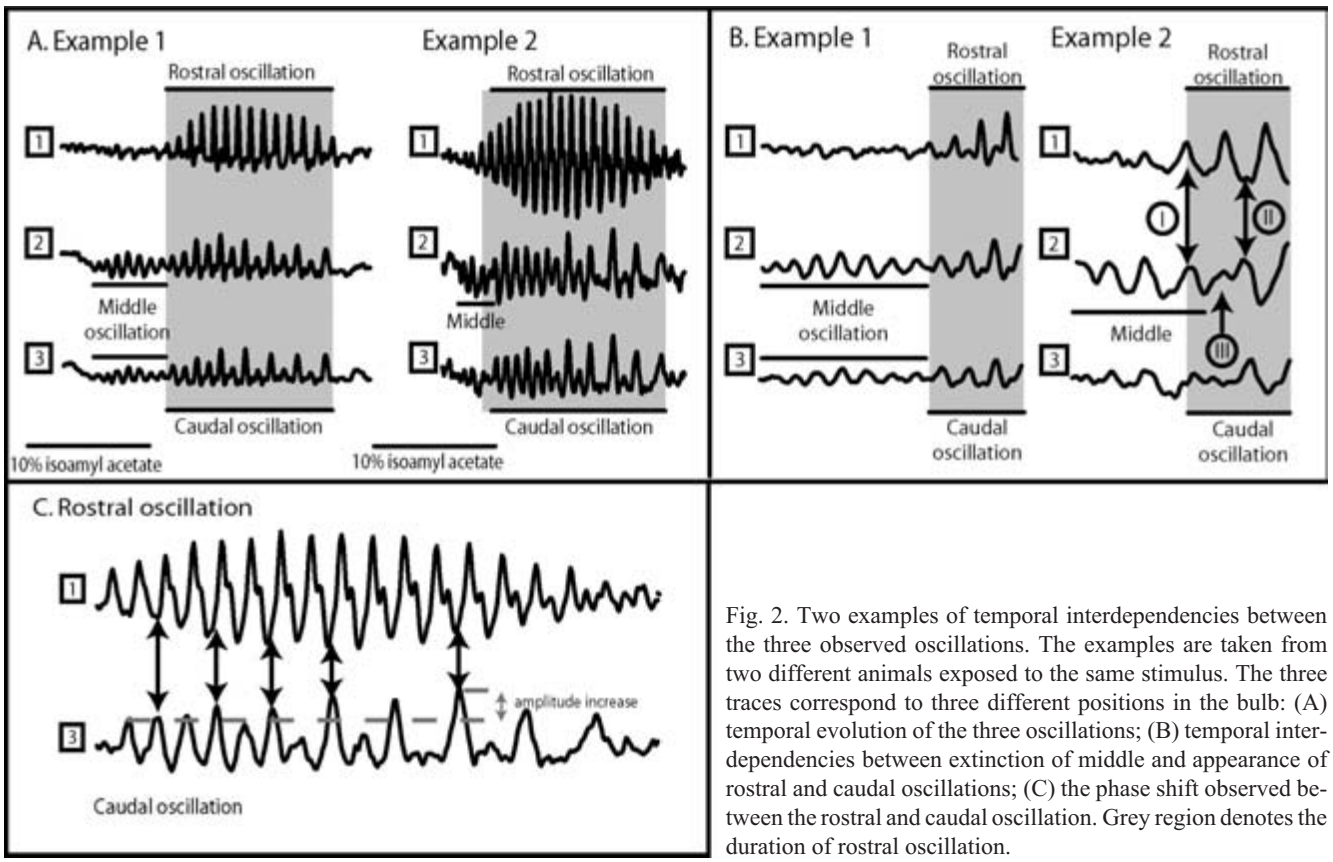

Fig. 2. Two examples of temporal interdependencies between the three observed oscillations. The examples are taken from two different animals exposed to the same stimulus. The three traces correspond to three different positions in the bulb: (A) temporal evolution of the three oscillations; (B) temporal interdependencies between extinction of middle and appearance of rostral and caudal oscillations; (C) the phase shift observed between the rostral and caudal oscillation. Grey region denotes the duration of rostral oscillation.

shift with respect to rostral oscillation or the phase shift was generated through smoother transition over two or more cycles. Moreover, as the caudal oscillations undergoes period doubling one can observe a significant increase in the height of the remaining cycles. This could be explained by increasing number of neurons activating in that particular cycle, indicating that the transition from high frequency phase to low frequency phase could mediated not by the change of firing frequencies of the individual cells but by shifting of its activation to different cycle of the oscillation.

In summary, our results indicate that the three odor evoked oscillations appearing in the turtle olfactory bulb are generated by distinct cell populations but are highly interdependent on each other.

METHODS

Odor evoked responses were monitored in *in vivo* turtle preparation optically, using voltage sensitive dye, RH414 and 464 element photodiode array (Lam et al. 2000, 2003). Turtle was immobilized and tubocurarine d-chloride was injected to further reduce animal movement. The craniotomy was performed on the anesthetized (cooled) animal with additional local anesthetic (1% bupivicane, Sigma). The dura and arachnoid matter were carefully removed to facilitate staining. An optimal die (RH414, Molecular Probes, Eugene OR) was chosen after extensive testing.

The dye solution (0.01-0.1% in saline) was applied to the uncovered bulb for 60 minutes. The remaining dye was washed out and agarose was applied over the bulb to reduce its movement. After the surgery, the turtle was allowed to warm up for over an hour. The odorant was delivered through a constructed olfactometer, copied from (Kauer and Moulton 1974), at concentrations ranging from 0.01% to 10% of saturated vapor, providing a wide range of odor concentration. To facilitate odorant delivery to the olfactory epithelium the air with the odor were drawn into the nose through the tubing installed at the back of the nasal cavity. The odorant presentation lasted between 0.5-2 s. The air was drawn into the nose for at least 0.5 s before the odor delivery, and for 10-15 s after to clear the nasal cavity. The tested odorants were: isoamyl acetate, n-amyl acetate, cineole, hexanal, hexanone, butric acid, corvone, octanol. The largest response was usually detected for the acetates, cineole and hexanal.

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