Nova Acta Leopoldina NF *88*, Nr. 332, 189-206 (2003)

Temporal Scales of Cortical Interactions

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With 6 Figures

keywords

synchronicity, neuronal interaction, statistical analysis, unitary events

Abstract

Higher brain functions are attributed to the cortex. Over the years it became clear that information is encoded not only in the responses of individual neurons but also in the joint activity of populations of neurons. Based on theoretical studies it has been proposed that the temporally coordinated spiking activity of many neurons is a relevant variable for information processing (VON DER MALSBURG 1981, ABELES 1982b) and that cortical neurons organize dynamically into coherent functional groups (»cell assemblies«, HEBB 1949) that are distinguished by the coordinated activity of the participating neurons. Our research focuses on the development of analysis strategies for the identification of neuronal interactions and assembly activity. We attempt to decipher the spatial and temporal scales of dynamical neuronal interactions, and their relations to the external world (stimuli and/or behavior).

In order to identify neuronal assemblies, simultaneously recorded neuronal spiking activity needs to be analyzed with respect to temporal structure. To that end we developed the »unitary event« analysis method (GRÜN et al. 2002a, GRÜN et al. 2002b) that detects the presence of conspicuous spike coincidences and evaluates their statistical significance. The analysis of simultaneously recorded neuronal activity in monkey primary motor and frontal cortex uncovered context-dependent, rapid changes in the patterns of coincident spike activity during performance of a delayed-pointing task (RIEHLE et al. 1997) or a delayed localization task (VAADIA et al. 1989, AERTSEN et al. 1991, VAADIA et al. 1991), respectively. Spike synchronization occurred accompanied by discharge rate modulations and in the absence of spike rate modulations depending on the details of the experimental protocol. The temporal precision of such synchronized events is in the range of a few ms (GRÜN et al. 1999). Data suggest that the composition of significant coincidence patterns changes depending on the computational demands (GRÜN et al. 2002b), which may be taken as an indication that different assemblies are activated in relation to behavior.

In the unitary event analysis a number of different time scales have to be considered and affect different parameters of the signal. Here we specifically address the different temporal scales and give interpretations in respect to the dynamics of the neuronal processes.

Zusammenfassung

Die Verarbeitung höherer kognitiver Leistungen wird der Großhirnrinde zugeordnet. In den letzten Jahren stellte sich heraus, daß die neuronale Informationsverarbeitung im Cortex nicht nur durch Aktivitäten einzelner Neuronen getragen wird, sondern insbesondere auch durch aufeinander abgestimmte, gemeinsame Aktivität von Neuronenverbänden. Auf der Basis theoretischer Untersuchungen wurde die zeitlich abgestimmte Spikeaktivität mehrerer Neuronen als relevante Variable der Informationsverarbeitung vorgeschlagen (VON DER MALSBURG 1981, ABELES 1982b) und mündet in der Hypothese, daß sich cortikale Neuronen dynamisch in funktionelle Gruppen (»cell assemblies«, HEBB 1949) formieren, welche sich durch koordinierte Aktivität der teilnehmenden Neuronen auszeichnen. Unsere Forschung konzentriert sich auf die Entwicklung von Analysestrategien, die es erlauben, neuronale Wechselwirkungen und die Aktivität neuronaler Ensembles zu identifizieren. Dabei werden die

räumlichen und zeitlichen Skalen dynamischer Wechselwirkungen und deren Bezüge zur äußeren Welt (Reize und/oder Verhalten) untersucht.

Um neuronale Ensembles zu identifizieren, muß gleichzeitig abgeleitete Spikeaktivität in Hinsicht auf ihre zeitliche Struktur untersucht werden. Hierfür haben wir die »Unitary Event« Analysemethode entwickelt (GRÜN et al. 2002a, GRÜN et al. 2002b), welche auffällige, koinzidente Spikeaktivität detektiert, und auf Signifikanz untersucht. Die Analyse gleichzeitig abgeleiteter neuronaler Aktivität, gemessen im Motorcortex und Frontalcortex von Affen, brachte kontextabhängige, schnelle Änderungen von Koinzidenzmustern während der Ausführung eines »delayed-pointing task« (RIEHLE et al. 1997) bzw. eines »delayed localization task« (VAADIA et al. 1989, AERTSEN et al. 1991, VAADIA et al. 1991) zu Tage. Spikesynchronisation trat sowohl mit als auch ohne gleichzeitiger Ratenmodulationen auf, und variierte je nach experimentellem Protokoll. Die zeitliche Präzision der synchronisierten Ereignisse beträgt nur wenige ms (GRÜN et al. 1999). Die Daten zeigen auch, daß sich die Zusammensetzung der signifikanten Koinzidenzmuster in Abhängigkeit von den Anforderungen ändern kann (Grün et al. 2002b), und deuten darauf hin, daß unterschiedliche neuronale Ensembles in Abhängigkeit vom Verhaltenskontext aktiviert werden.

Im Rahmen der Unitary Event-Analyse werden eine Reihe von Zeitskalen berücksichtigt, die jeweils einen anderen Aspekt des neuronalen Signals betreffen. In dem hier vorliegenden Beitrag liegt der Schwerpunkt auf der Darstellung obengenannter Zeitskalen, und deren Interpretation in Hinsicht auf die Dynamik der zugrundeliegenden neuronalen Prozesse.

1. Introduction

Higher brain functions are attributed to the cortex, a highly interconnected network composed of about 10^{10} neurons. Each single neuron receives spike inputs from about 10^4 other neurons and projects its output spikes to about the same number of other neurons (BRAITENBERG and SCHÜZ 1991). Initially, recording techniques were limited to recordings from one channel at a time. Here, the recording was optimized to obtain the spikes from a single neuron only, or the spikes where left unidentified (e. g. in recordings from nerve fibers). Due to this limitation and also guided by early considerations about the integrative properties of the neuron (SHERRINGTON 1906, ECCLES 1957) researchers concentrated on reproducible changes in the spike rate. ADRIAN (1928) observed that the spike rate of neurons is related to changes in the environment and concluded that the intensity of sensation is proportional to sensory spike rates. Single neurons with their specific characteristics became the building blocks of cortical processing (BARLOW 1972, BARLOW 1992, for reviews see MARTIN 1994, MARTIN 2000). This approach led to fundamental insights into the neuronal mechanisms of brain function (e. g. LETTVIN 1959, HUBEL 1968) and to important theoretical works on information processing by neuronal networks (MCCULLOCH and PITTS 1943). The influential book by MINSKY and PAPERT (1988) pointed out the limitation of this concept (see also VON DER MALSBURG 1986b).

The parallel and distributed architecture of the cortex suggested the investigation of the collective properties of neural networks. HEBB (1949) proposed that ensembles of neurons, »cell assemblies«, constitute the units of neuronal processing. In this view, functional groups are formed by the coherent activity of the participating neurons. This hypothesis provided the conceptual framework for successful theoretical work on neural networks (e. g. HOPFIELD 1982, RUMMELHART et al. 1986, AMIT 1989, AMIT 1997). These models exhibit multiple attractor states, the attractors being groups of neurons with elevated spike rates. A prominent example from the experimental literature is the demonstration of representation of information by ensembles of neurons (GEORGOPOULOS et al. 1988, GEORGOPOULOS et al. 1989).

In parallel, however, conceptual difficulties of the representation of assembly membership by spike rate were pointed out (VON DER MALSBURG 1981, VON DER MALSBURG 1986b). The notion was developed that, alternatively, assembly membership could be expressed in the temporal organization of spiking activity (VON DER MALSBURG 1981, ABELES 1982, VON DER MALSBURG 1986a, GERSTEIN et al. 1989, PALM 1990, ABELES 1991, SINGER 1993). Consequently, neuronal processing should be reflected in dynamical changes of spike time correlation. Dynamic modulations of spike correlation at various scales of precision have, in fact, been observed in different cortical areas: visual

(ECKHORN et al. 1988, GRAY et al. 1989, for reviews see ENGEL et al. 1992, AERTSEN et al. 1993, SINGER and GRAY 1995, ROELFSEMA et al. 1996, SINGER et al. 1997, SINGER 1999), auditory (AHISSAR et al. 1992, EGGERMONT 1992, DECHARMS et al. 1996, SAKURAI 1996), somato-sensory (NICOLELIS et al. 1995, LAUBACH et al. 2000, STEINMETZ et al. 2000), motor (MURTHY and FETZ 1992, SANES and DONOGHUE 1993, RIEHLE et al. 1997, HATSOPOULOS et al. 1998), and frontal (AERTSEN et al. 1991, ABELES et al. 1993, VAADIA et al. 1995, PRUT et al. 1998, GRÜN et al. 2002b).

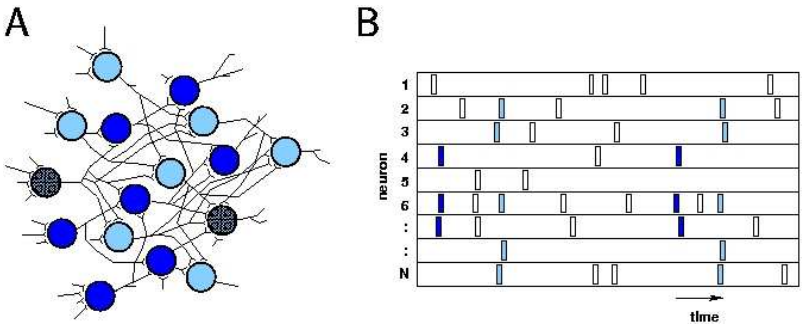

Fig. 1 Cell assemblies. A. Sketch of a piece of the cortical network containing two cell assemblies. The neurons composing the network are indicated by filled circles (black, gray and hatched), the thin lines sketch the connectivity between the neurons. One assembly is composed of the neurons marked in black, the other by the neurons marked in gray. Hatched disks mark neurons that are members of both assemblies. B. Sketch of the spiking activity of N simultaneously recorded neurons. Part of the recorded neurons are members of the indicated assemblies in A., others are »background« neurons. During the observation interval both assemblies are activated twice, e. g. by a sequence of two different stimuli presented shortly one after the other. Assembly 1 (neurons marked black) is activated first by activity entering the net through the black and hatched neurons on the lower left and is propagating through the subnet composing that assembly. The activation of the assembly is visible by the synchronous activity of recorded member neurons (here numbered as 4,6,7). Later the other assembly (neurons marked gray) is activated by a stimulus entering the network through the gray and hatched neurons on the upper left, expressed by the synchronous spiking activity of recorded member neurons (2,3,6,N-1,N). Interestingly, one neuron (6, corresponding to the hatched neuron on the left) exhibits synchronous activity with neurons of both assemblies. It multiplexes its activity in time while being member of different assemblies. The neuron's assembly membership is expressed by the partner neurons with which it exhibits synchronous activity.

The correlations observed in neuronal data cannot be attributed to the underlying network structure alone (AERTSEN et al. 1989, 1991). Parameter changes seem to be able to drive the network into different dynamical regimes or activate different sub-networks. Thus, it was proposed that depending on the behavioral demand neurons organize dynamically into functional groups, which should be reflected in the temporal structure of the spike activity of the neurons involved (sketched in Fig. 1). In order test this hypothesis and to detect the activity of cell assemblies and their interactions, neuronal activity has to be analyzed for correlation structures. For the analysis of spike coincidence patterns in such simultaneously recorded spike trains we developed the »unitary event« analysis (GRÜN 1996, GRÜN et al. 2002a, 2002b). The method allows to uncover excessive coincident spike events among simultaneously recorded neurons. Such conspicuous coincidences are referred to as »unitary events«, and are defined as those joint spike constellations that occur significantly more often than expected by chance. The functional significance of unitary events was tested by investigating their occurrence and composition in relation to sensory stimuli and behavioral events. We were able to define a measure, the joint-surprise, that indicates the presence of an unexpected spike constellation in a time resolved manner. Conspicuous spike patterns can be marked at the point of their occurrence in time. The result is a visualization of the correlation structure of the data as a function of time. The

appearance and disappearance of spike patterns can be compared with the stages of the experimental protocol. The time course of pattern occurrence can also be compared to the time course of other time varying features of the data, such as the spike rate. Recordings from awake animals performing a behavioral task enable the experimenter to observe the correlation structure while the neurons are carrying out computational tasks. Various time scales and their interactions are made explicit in the mathematical formulation of unitary event analysis. In this contribution, we use unitary event analysis, which will be introduced in the next section (section 2), as a framework to discuss the multiple time scales that enter our analysis and may be relevant for cortical processing. Section 3 discusses how temporal coordination is distinguished from changes in spike rate. The following section (section 4) analyzes the time scale of synchronous spiking in cortical data. Section 5 demonstrates that the time courses of rate modulation are often independent from the modulation of fine temporal coordination.

2. Detection and statistical evaluation of spike coincidences: Unitary Event Analysis

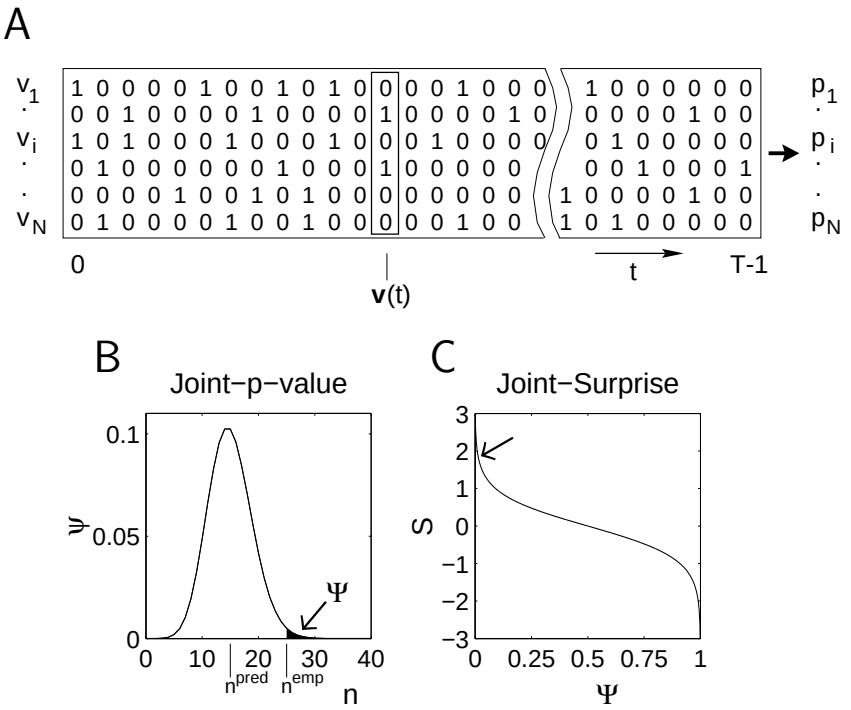

Fig. 2 Unitary Event Analysis. A. Representation of N parallel neuronal spike trains as binary processes. Each horizontal row, consisting of 0's and 1's, represents a realization of a single process v_i observed for T time steps. The 1's mark the occurrences of spike events. The joint activity across the processes at each instant in time can be expressed by a vector **v**(t), as indicated for one example. The empirical firing probability per bin p_i of each single process is evaluated as the marginal probability: the number of spikes in the observation time interval, divided by the number of time steps. B. Distribution of joint-spike events for significance estimation. The black shaded area under the Poisson distribution (with n^{pred}=15) ranging from n^{emp}=25 to ∞, indicates the joint-p-value Ψ as the cumulative probability to get n^{emp} coincidences or an even larger number. For this particular example, the joint-p-value equals 0.0112. C. The joint-surprise S shown as a logarithmic scaling function of the joint-p-value. The transformation converts significant joint-p-values to positive numbers, non-significant values to values around 0, and large joint-p-values, indicating significant lack of coincident events to negative values. The value of the joint-surprise corresponding to the joint-p-value in the example in B. is S=1.9459. Figure modified after GRÜN et al. 2002a.

We developed a method that detects the presence of conspicuous spike coincidences and evaluates their statistical significance (GRÜN 1996, GRÜN et al. 2002a, 2002b). Briefly, the detection algorithm works as follows: The simultaneous observation of spiking events from N neurons can be described mathematically by the joint process, composed of N parallel point processes. By appropriate binning, this can be transformed to an N-fold binary process, the statistics of which are described by the set of activity vectors reflecting the various (0,1)-constellations that occurred across the recorded neurons (Fig. 2A). Under the null-hypothesis of independently firing neurons, the expected number of occurrences of any activity vector and its probability distribution can be calculated analytically on the basis of the single neuron firing rates. The expected joint-probability of an activity vector is given (assuming statistical independence) by the product of the corresponding firing and non-firing probabilities. To test the significance of coincident events we developed a new statistical measure: the »joint-p-value« Ψ. For any particular spike activity vector, this joint-p-value measures the cumulative probability of observing the actual number of coincidences (or an even larger one) by chance (Fig. 2B):

$$\Psi\left(n^{emp}\,\middle|\,n^{pred}\right) = \sum_{n=n^{emp}}^{\infty} \psi\left(n, n^{pred}\right).$$

In order to enhance visual resolution at the relevant low-probability values of Ψ for excessive or lacking coincidences we transform Ψ to a logarithmic scale thereby deriving the joint-surprise measure (Fig. 2C):

$$S = \log \frac{1-\Psi}{\Psi},$$

a measure closely related to the surprise measure defined by PALM (1981). Thus, we can calculate for a stationary data set the significance of any joint-activity constellation across the N neurons and identify those neurons that exhibit significant (e. g. at a significance level of 5%: $S(\Psi) \geq S(\alpha=0.05)$) synchronous activity presumably indicating signatures of assembly activity (for details see GRÜN et al. 2002a).

3. Temporal precision of coincident events

The time resolution of data acquisition in extracellular spike recordings is typically 1 ms or better. To define a coincident event implies to know the time scale on which spike events are coincident. Since spikes do not code information by amplitude or shape of the spike we can assume the duration of a spike signal (1–2 ms) as a lower bound. During the last decade there was an intensive debate if neurons could operate on a time scale smaller than a few tens of ms, since neurons were considered to be »noisy« and as units that integrate the spikes over a relatively large time window before emitting a spike. This view is supported by the relatively long time constants of the membrane potential (tens of ms). Note, however, that the degree of this temporal noise has long been questioned (e. g. ABELES 1981) and is still under debate (e. g. BRYANT and SEGUNDO 1976, MAINEN and SEJNOWSKI 1995, SHADLEN and NEWSOME 1998, DIESMANN et al. 1999). There is experimental evidence from cross-correlation-, JPST- and, particularly, from spike pattern analysis, that the timing accuracy of spiking events which might be relevant for brain function can be as precise as a few ms (ABELES et al. 1993, NOWAK et al. 1995, RIEHLE et al. 1997). Similar suggestions come from modeling studies (DIESMANN et al. 1999).

To detect the relevant time scale of synchronous events in experimental data, we systematically vary the allowed temporal width to detect coincident events and evaluated their significance assuming independence. A straight forward approach to allow synchronous events on a less precise time scale than the time resolution of the data is to section the observation interval into short disjunct time slices (»bins«) and consider spikes from different neurons as coincident if they occur within such a time bin. Although coincident spiking events can reliably be detected by using such a discretized process

(disjunct binning), the method loses sensitivity for higher temporal jitter of the coincident events (GRÜN et al. 1999). This is mainly due to the non-linear effect of binning and clipping of the single spike trains, on the one hand, and the application of the same binning grid over multiple spike trains, on the other.

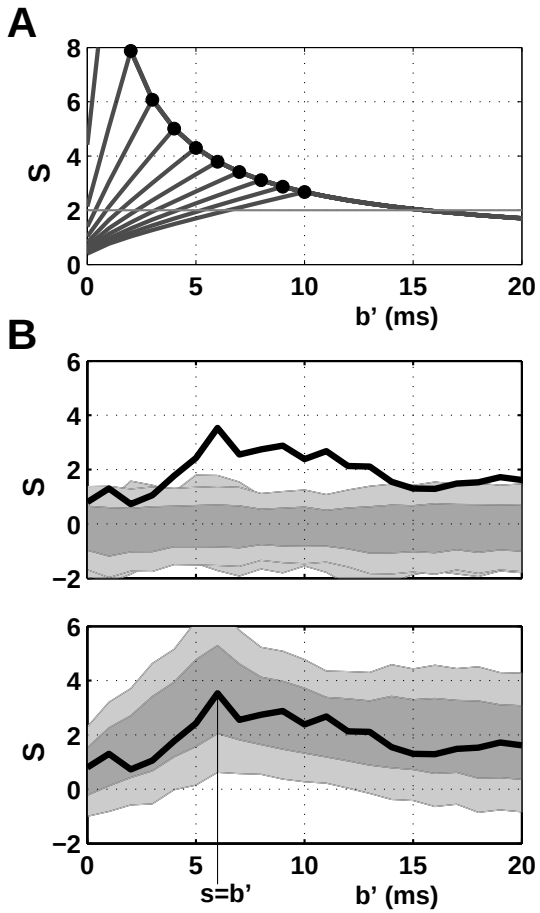

Fig. 3 Temporal precision of coincident activity. A. The detectability of coincident events and their temporal jitter is illustrated for two parallel processes, composed of two independent contributions: background (Poisson processes) and coincident activity with a given homogeneous temporal jitter. For various coincidence widths (from s = ± 1 …10) the joint-surprise (S) is calculated for increasing analysis widths (b' = ± 0 … 20). For a given temporal jitter s, the joint-surprise as a function of b' (gray curves) exhibits a maximum at the corresponding analysis jitter (s = b') (marked by filled black circles). For s = ± 1 the maximum of S equals 11.6 at b' = ± 1 (not shown here). The line at S = 2 marks the significance level of 1%, i.e. S(α=0.01). Data sets were assumed to have the parameters: duration in time as the experimental data shown in B. (33 trials of 800 ms) with a time resolution of h = 1 ms; background firing probability for both neurons: p_r = 0.03, coincidence firing probability of p_c = 0.0029. B. Temporal precision of neuronal spike trains and its comparison with simulated processes. The analysis results expressed by the joint-surprise (S) for increasing shift width b' of two simultaneously recorded neurons are shown and compared to simulated data. The top graph shows, for control purposes, the simulation experiment performed without injected coincidences, firing probabilities correspond to the measured marginals of the neurons (p_1 = 0.0321, p_2 = 0.0359). In the bottom graph, coincidences were injected with a coincidence width of s = ± 6 ms, corresponding to the analysis bin width b' at the maximum of the joint-surprise. The coincidence probability (p_c = 0.0029) and the background probabilities of the two neurons (p_{r1} = 0.0291 and p_{r2} = 0.0329) were calculated based on the model as assumed in A. (see for details GRÜN et al. 1999). Results from simulations are shown as gray bands. The width of the light gray band represents 95 %, the dark gray band 70 % of 30 repetitions of the simulation experiments. Each simulation had the same duration in time as the experimental data (33 trials of 800 ms) with a time resolution of h = 1 ms. In the upper panel, the light gray band (representing 95 % of the simulation

experiments) is well below the threshold for significance of 1 %, i. e. S(0.01)=2, demonstrating the low probability of the significance measure to generate »false alarms«. Figure modified after GRÜN et al. 1999.

As an alternative approach, we worked out the »multiple shift« method that overcomes the need for binning, and thereby treats the data in their (original) high time resolution (GRÜN et al. 1999). Technically, coincidences are detected by shifting the spike trains against each other over the range of allowed coincidence width and integrating the number of exact coincidences (on the time resolution of the data) over all shifts. In calibration studies we analyzed the sensitivity of the method and the reliability to detect near-coincidences with a given underlying coincidence width. Therefore we simulated data sets in which independent spike trains with a given background rate were »injected« with coincident spikes of a given coincidence width (tolerance) into both trains. For a given data set we varied the analysis coincidence width systematically and evaluated the significance for each coincidence width. It turned out that the significance is maximal, if the analysis bin width corresponds to the underlying jitter (see Fig. 3A).

Thus, we used the method to estimate the underlying »jitter« in experimental data. Neuronal data were taken from a pair of simultaneously recorded neurons (time resolution: h = 1 ms) from the primary motor cortex of a behaving monkey involved in a visuo-manual pointing task (see BASTIAN et al. 1998, GRAMMONT and RIEHLE 1999 for experimental details). The results of the analyses of the experimental data using various shift widths (b') are shown in Figure 3B (solid lines). The joint-surprise function, however, shows a clear peak at b' = 6 ms. In Figure 3B (top) the experimental results are compared to control surrogate data (shown in gray), in which no coincidences were injected. The rates for the simulations were set to correspond to the marginal firing rates of the neuronal data. Simulation results of 30 repetitions (each consisting of 33 trials) are shown as gray bands. The experimental results clearly deviate from the simulation results, indicating that neuronal spike trains do not correspond to the assumption of independence.

As discussed above, according to our model the maximum of S in the experimental data indicates the coincidence width of the underlying data as s = b', i. e. here 6 ms. Next, surrogate data with injected coincidences were compared to the experimental results. We extracted the coincidence width for the simulation at the maximum of the joint-surprise (here: 6 ms). The firing probabilities of the neurons, measured as the marginal probabilities, were assumed to be a measure for the sum of coincident and background activity. Using the measured marginal probabilites for the two neurons, we obtained estimates for the probability for coincident firing and the »uncorrelated« background firing probabilities. Figure 3B (bottom) illustrates the comparison of experimental and simulated data using the derived parameters. The experimentally derived joint-surprise function shows basically the same curve as obtained from the surrogate data. The experimental curve lies within the range of about 1 σ of the simulated data (dark gray band), indicating that our model predictions are consistent with the experimental data.

4. Dynamics of synchronous spiking events

In order to account for non-stationarities in the discharge rates of the observed neurons, modulations in spike rates and coincidence rates are determined on the basis of short data segments by sliding a fixed time window (typically 100 ms wide) along the data in steps of the coincidence bin width. This timing segmentation is applied to each trial, and the data of corresponding segments in all trials are then analyzed as one quasi-stationary data set, using the appropriate rate approximation. Besides the effect that this approach corrects for non-stationary rate variation in time, it also allows us to analyze synchronous activity and its potential modulation as a function of time. Excess coincident activity may occur in a short interval, »triggered« by some external or internal event. When the neuronal processes are

observed over repeated trials, the coincident activity appears to some degree locked to certain points in time. We have shown in a modeling study (GRÜN 1996) that loose locking of synchronous activity, e. g. to trial onset, does not contradict precise temporal coordination of the spiking activity related to the assembly activity. Loose locking rather reflects a loose onset of the correspondingly triggered assembly activity. For optimal detection of unitary events using the sliding window procedure, the width of the analysis window has to be adjusted to the temporal spread of the synchronous events. As worked out in detail in GRÜN et al. (2002b), the shape of the joint-surprise function can indicate the optimal window width, such that the window width can be adjusted accordingly. Further details and calibration of the unitary event analysis technique are described in (GRÜN 1996, GRÜN et al. 2002b). Recent extensions of the approach are discussed in (ROY et al. 2000, PAULUIS and BAKER 2000, GÜTIG et al. 2002). Note that the time window fulfills two different purposes: rate estimation and obtaining a large enough coincidence count for significance testing. In general, both tasks may require windows of different size. Even if the spike rates are known a limited number of trials require a certain window size.

4.1 Temporal modulation of synchronous activity

We tested the hypothesis that such precise synchronization of individual action potentials among groups of neurons in the monkey motor cortex is involved in dynamically organizing the cortical network during the planning and execution of voluntary movements (RIEHLE et al. 1997). We found that simultaneously recorded activities of neurons in monkey primary motor cortex indeed exhibited context-dependent, rapid changes in the patterns of coincident action potentials during performance of a delayed-pointing task. Accurate spike synchronization occurred in relation to external events (visual stimuli, hand movements), commonly accompanied by discharge rate modulations, however without precise time-locking of the spikes to these external events. Accurate spike synchronization also occurred in relation to purely internal events (stimulus expectancy; Fig. 4), where firing rate modulations were distinctly absent. These findings indicate that internally generated synchronization of individual spike discharges may subserve the cortical organization of cognitive motor processes. The clear correlation of spike coincidences with stimuli and behavioral events underlines their functional relevance (FETZ 1997, RIEHLE et al. 1997).
Taken together, these findings demonstrate the existence of precise synchronization of individual spike discharges among selected groups of neurons in the motor cortex. This synchronization is associated with distinct phases in the planning and execution of voluntary movements, indicating that it indeed plays a functional role. Moreover, these findings suggest that under behavioral conditions as investigated in this study, the brain uses different strategies in different contextual situations: In order to process a purely cognitive, i. e. an internal and behaviorally relevant event, neurons preferentially synchronize their spike occurrences without changing, at the same time, their firing rates. By contrast, when processing an external, behaviorally relevant event, neurons tend to synchronize their spikes and modulate their firing rates at the same time. Thus, precise synchronization of spike events and modulation of discharge rate may serve different and complementary functions. They act in conjunction at some times, not at others, depending on the behavioral context (RIEHLE et al. 1997).

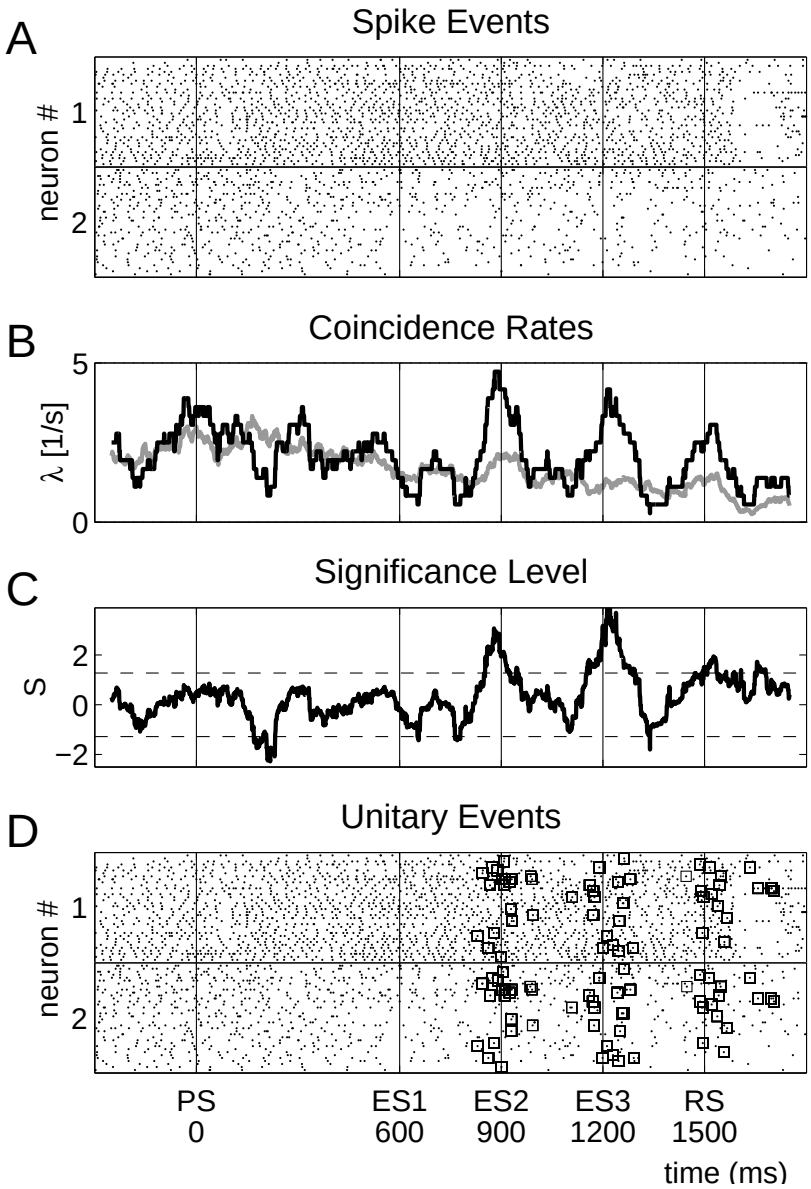

Fig. 4 Temporal modulation of synchronous activity. Unitary event analysis of the spiking activity of two simultaneously recorded single neurons from motor cortex of awake behaving monkey. The monkey was involved in a delayed pointing task, where the duration of the preparation period (after the preparatory signal (PS) up to the reaction signal (RS)) for the movement was selected randomly from 4 possible durations (PP; 600, 900, 1200, 1500 ms) from trial to trial. The 36 trials with longest PP duration (1500 ms) were pooled in this example. Thus the monkey could expect the RS to occur at three successive moments (ES1, ES2, ES3) before it actually occurred at RS. Results of the unitary event analysis in sliding windows of 100 ms over a time interval of 2100 ms, starting at 300 ms before PP and lasting until 300 ms after PS. A. Conventional raster displays of spike discharges of two neurons. Each dot represents an action potential, and each row of action potentials depicts the spiking activity in a single trial. B. Comparison of measured and expected coincidence rates. The measured coincidence rate (black curve) was derived the same way as the firing rates by sliding a box car of 100 ms in steps of 1 ms over the data. Coincident events were detected with an analysis width of $s = \pm 2$ ms. The expected coincidence rate (gray curve), based on the null-hypothesis of independent firing was calculated as the product of the individual firing rates (see for details GRÜN et al. 1999). C. For each time window, the joint-surprise value was computed by comparing the empirical number of coincidences with the expected number (see Fig. 2). D. Whenever the joint-surprise exceeded a fixed threshold (here: $S(\alpha = 0.05)$) this defined an epoch with significantly more coincidences than expected by chance. These precise coincidences were marked as unitary events and are indicated by squares in the raster displays. Reprinted (excerpted) with permission from RIEHLE et al. Science *278*, 1950–1953 (1997). Copyright 1997 American Association for the Advancement of Science.

4.2 Task dependent composition of coincident spiking activity

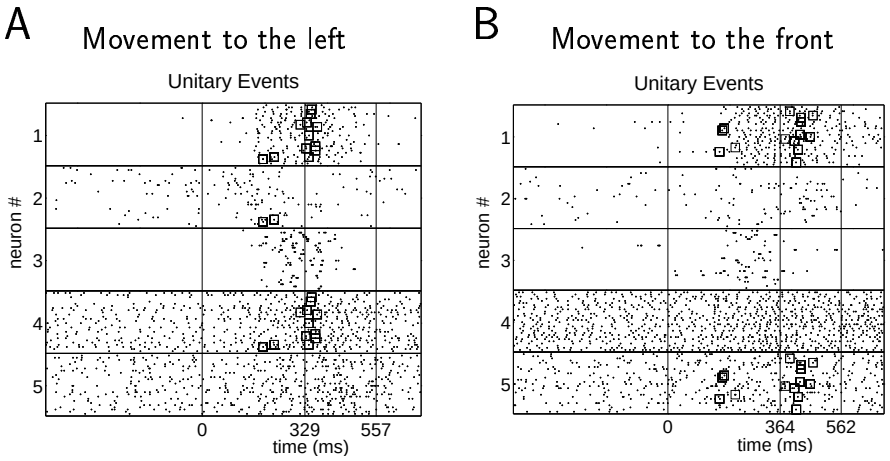

Fig. 5 Task dependence of the composition of coincident spiking activity. The dot displays show the spiking activity of five simultaneously recorded neurons (labeled 1 to 5) from the frontal cortex of a monkey involved in a delayed localization task (28 trials). A. and B. represent two different behavioral conditions: A. movement to the left, B. movement to the front. Unitary event analysis was performed in sliding windows of 60 ms, and with a significance level of $\alpha = 0.01$. Coincident events were detected in disjunct bins with a bin width of 3 ms. Data were taken from segments starting 500 ms before and ending 700 ms after the GO signal (vertical line at time 0 ms). Average times of behavioral events (monkey leaves central key, monkey hits the target) are indicated by vertical lines. In A. the monkey leaves the central key at 329 ms and hits the target at 557 ms after the GO signal, in B. leave at 364 ms, and hit target at 562 ms. Unitary events (marked by squares) occur at about the time when the monkey leaves the center key, i. e. at different times in the two conditions. The composition of the correlated spiking activity differs in the two behavioral conditions: related to a movement to the left neuron 1 and 4 are correlated, and related to the movement to the front neuron 1 and 5 are correlated., i. e. neuron 1 seems to switch the partner neuron depending on the behavioral context. Figure modified after GRÜN et al. 2002b.

In the second experimental study we discuss, Rhesus monkeys were trained in a »delayed localization« paradigm with two basic tasks (localizing and non-localizing, an example of the latter is shown in Figure 5). In both tasks, the monkey receives a sequence of two stimuli (visual and auditory) out of five possible locations. After a waiting period, a »GO« signal instructed the monkey to move its arm in the direction of the stimulus relevant in the current trial. In the localizing task, the relevant spatial cue was selected by the color of the GO signal. In the non-localizing task, an indicator light between blocks of trials informed the monkey about the reinforced direction for arm movement. Thus, in the latter case, the animal had to ignore the spatial cues given before the GO signal. In the behavioral task analyzed here (non-localizing), neither the spatial cues before the GO signal nor the GO signal itself could be used to determine the correct behavioral response (see VAADIA et al. 1989, AERTSEN et al. 1991, VAADIA et al. 1991 for further details). The activity of several (up to 16) neurons was recorded simultaneously in the frontal cortex by using six microelectrodes during task performance. In each recording session, the microelectrodes were inserted into the cortex with inter-electrode distances of 300–600 μm. Isolation of single units was aided by six spike sorters that could isolate activity of 2–3 single units, based on their spike shape (ABELES and GOLDSTEIN 1977). The spike sorting procedure introduced a deadtime of 600 μs for the spike detection.

Using data from this study, we found that coincident activity in the frontal cortex can be specific to movement direction. We parsed the data of five neurons according to the movement direction, and analyzed each of these sub-sets separately. Figure 5 shows the analysis results for two movement directions (A: to the left; B: to the front); for the three other movement directions there was no significant activity. For each of the two movement directions, there is mainly one cluster of unitary events (besides some sparsely spread

individual ones), occurring at the onset of the movement. The clusters of unitary events differ, however, both in their neuronal composition and in their timing. During movement to the left, significant coincidences occur between neurons 1 and 4, for movement to the front they occur between neurons 1 and 5. The timing of the unitary events differs. Both occur shortly after the monkey left the center key (equivalent to reaction time), which differs for the two movement directions (mean reaction time indicated by a line in A: 329 ms after the GO signal, in B: 364 ms after the GO-signal). Thus, unitary events appear to be locked better to the behavioral event than to the external event (GO). The analysis of the same five neurons during the localizing task, where the color of the GO-signal contained the information about the reinforced type of stimulus (data not shown) did not reveal any indications for unitary events related to movement direction. Note, that neuron 1 is participating in significant coincident activity in both movement directions, however with another coincidence partner in each. This is indicative of a common membership of neuron 1 in two different cell assemblies, one of which is activated depending on the movement direction.

4.3 Changes of temporal precision as a function of time

In order to study the temporal aspects of neuronal activity during preparatory processes for arm movements, Rhesus monkeys were trained to perform a multi-directional pointing task (RIEHLE et al. 2000). The animal sat in a primate chair in front of a vertical panel on which seven touch sensitive light emitting diodes (LEDs) were mounted, one in the center and six placed equidistantly on a circle around it. In each trial, two signals were presented successively. The first, the preparatory signal (PS), provided prior information about the target which had to be pointed after the occurrence of the second, the response signal. First, the center target was lit and the animal had to press it for initiating the trial. Then, after a fixed delay of 500 ms, the preparatory signal was presented by illuminating one of the targets in green. After another delay (preparatory period), during which the animal still had to continue to press the center target, the color of the peripheral target turned red. This served as a response signal (RS) requesting from the animal to perform the movement to the indicated target. During performance of the task multiple single neurons were recorded and analyzed using the unitary event analysis. For analysis of the time course and modulation of synchronous activity, the joint-surprise values were obtained using the sliding window analysis. In order to observe the temporal precision of synchronous activity, and its potential change during the preparatory period, the allowed temporal precision of synchronous events was varied using the multiple shifts method (GRÜN et al. 1999).

The analysis of the data revealed two main results. First, synchronous spiking activity in motor cortex during preparation for action is not maintained at a significant level for more than 100–200 ms. Periods of synchrony, however, may occur several times during the trial, with a more or less regular (oscillatory) pattern. Second, for many pairs of neurons, the temporal precision of synchronicity changes over time (comparable to the example shown in Figure 6). If such changes occur, temporal precision typically increases during the preparatory period to be highest towards its end. One possible interpretation is that the increase of temporal precision of synchronous activity facilitates the efficiency of the motor output.

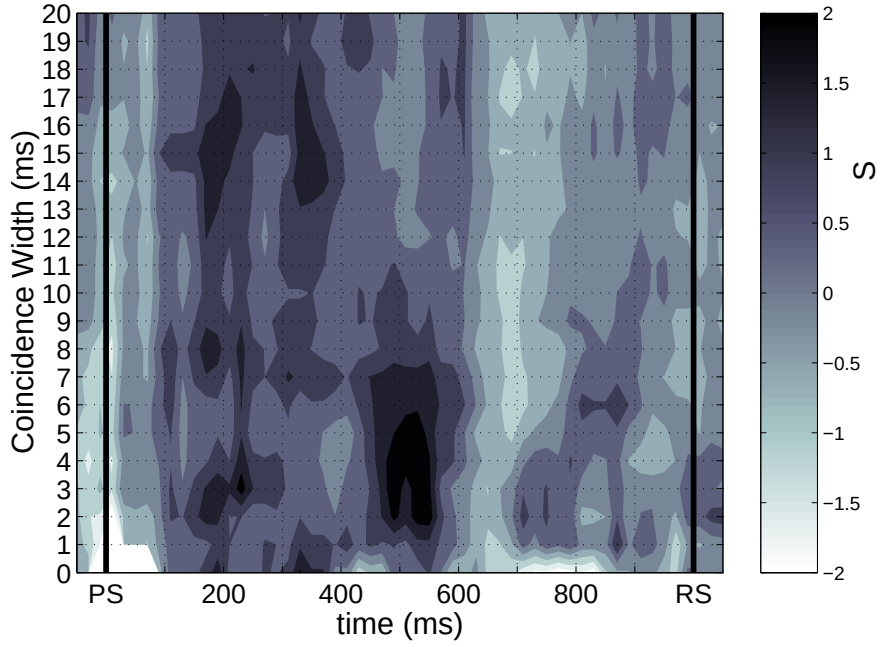

Fig. 6 Temporal precision of coincident spiking events as a function of time. Two simultaneously recorded neurons from a behaving monkey during performance of a delayed multi-directional pointing task. Recording site was primary motor cortex. With the preparatory signal (PS) the monkey was provided with prior information about the target position (1 out of 6; here: movement direction 4) where he had to point at after presentation of the response signal (RS). During the preparatory period (from PS to RS, fixed duration: 1000 ms) the monkey had to sit still, keep the initiating button pressed and the preparatory signal (illuminated in GREEN) was still on. As it turned red it indicated the response signal. The same spike trains were analyzed for varying coincidence widths ranging from b' = ± 0 … 20 ms (vertical). For each coincidence width, the significance level (joint-surprise) was calculated separately. The gray code indicates the joint-surprise values, ranging from -2.19 (white) over 0 (light gray) to 2.42 (black). For symmetry, values were clipped at -2 and 2. The level of statistical significance was $\alpha = 0.05$ for excess coincidences, which corresponds to S = 1.27, correspondingly for lacking coincidences S = -1.27. For calculation of the joint-surprise as a function of time, a sliding window of 100 ms was shifted along the spike trains in steps of 20 ms. Significant coincidences only occurred during the first half of the preparatory period with increasing precision, reaching the strongest synchronicity value at 500 ms with a precision of 2–4 ms (black spot). Figure modified after RIEHLE et al. 2000.

5. Conclusions

We have shown for a number of experimental data sets that several time scales seem to play a role in cortical processing. In order to detect unitary events, we differentiate rate (typically estimated on a time scale of tens to hundreds of ms), and temporal coordination of spiking activity typically on a ms time scale. If synchronous activity occurs more often than expected by chance given the rates, neurons are commonly involved in a fast and active dynamic process.

The temporal precision of significant synchronous activity is in the range of some few ms, an observation that was also found in spatio-temporal spike patterns or in cross-correlation analysis (e. g. MUNK et al. 1995, NOWAK et al. 1995, PRUT et al. 1998). Theoretical work, where the propagation of aperiodic synchronous spiking activity in neural networks is studied, show that the temporal precision of synchronous activity is a function of the rise time of the membrane potential (DIESMANN and AERTSEN 2001), which is in the range of a few ms (e. g. FETZ et al. 1991). Other models explain the occurrence of

synchonous activity in recurrent networks of oscillators. More theoretical studies are required that help to make the link between the connectivity and activity in the neuronal network. Both together define the functional connectivity, i. e. the relationship between neurons in terms of their activity, given the network structure.

The distinction between rate and synchronous activity also depends on the definition of the temporal precision of a synchronous event. If the »coincidence« width is rather in the range of tens or hundreds of ms, one would speak about spike rate correlation or spike count correlation. We found that there can be considerable rate covariation. However, interestingly, rate covariation may occur simultaneously but independent from spike synchronization (GRÜN et al. in press).

If the expected number of coincidences is estimated on the basis of rate averages across non-stationary rates, the danger of falsely detecting coincident activity as significant is enhanced (GRÜN et al. 2002b). Therefore, we introduced the sliding window procedure to account for the non-stationarity in firing rates of the neurons. Interestingly, this procedure helped us to uncover another phenomenon, indicating the dynamics of computational processes in time. Unitary events occur mostly only in short time windows, and are typically not constant throughout trial duration. Unitary events exhibit »loose locking« of synchronous activity to a trigger event, which does not necessarily correspond to an external behavioral trigger, but presumably rather to »internal« trigger events. Unitary events may be locked to purely internal events, as, e. g., the expectation of a signal (RIEHLE et al. 1997). Thus the timing structure of the modulation of synchronous activity is a reflection of the behavioral design in the experiment. However, also the opposite may be true: data from experiments in which no temporal structure is provided during the preparatory period may also show modulation of synchronous activity (RIEHLE et al. 2000). In the context of the given experiment this could be interpreted as internal »rehearsal«.

Both time scales seem to be relevant for cortical processing; measures derived for the different temporal scales seem to indicate context specific and complementary processes (RIEHLE et al. 1997). In the respective study we have shown, that in motor cortex internal processes seem to be reflected by synchronous activity on a fine temporal scale, whereas stimulus-related unitary events are accompanied by rate changes. However, it is not clear whether this can be generalized to all cortical areas. It is even suspected that the closer to the periphery, the stronger the »locking« to the external changes.

Another prominent activity structure in the cortex are oscillatory features of the signals. Depending on the state of the brain (sleep or awake etc.) there are differing dominant frequencies in mass signals like EEG or LPF. Single units do not obviously exhibit the same oscillatory behavior, and the question arises where does the oscillatory signal come about. There are studies that suggest (KÖRNER et al. 1999, SINGER 1999), that oscillations serve as a timing grid in order to structure the time axis to disentangle different computational processes. Thus, synchronous activity would be limited by the oscillatory period. We are currently studying the interaction of oscillatory activity and synchronous activity.

Acknowledgements

We thank Gordon PIPA and Stefan ROTTER for stimulating discussions. This report summarizes results from a number of ongoing collaborations, and extends an earlier review by part of the authors (AERTSEN et al. 2001). Partial funding was received from the *Deutsche Forschungsgemeinschaft* (*DFG*), the *Human Frontier Science Program* (*HFSP*), the *German-Israel Foundation for Research and Development* (*GIF*), and the *Volkswagen Foundation* (*VW*).

References

ABELES, M.: Local Cortical Circuits: An Electrophysiological Study. Studies of Brain Function. Berlin, Heidelberg, New York: Springer-Verlag 1982a

ABELES, M.: Role of cortical neuron: Integrator and coincidence detector? Israel J. Med. Sci. *18*, 83–92 (1982b)

ABELES, M.: The quantification and graphic display of correlations among three spike trains. IEEE Trans. Biomed. Eng. *30*, 236–239 (1983)

ABELES, M.: Corticonics: Neural Circuits of the Cerebral Cortex. 1st edn. Cambridge: Cambridge University Press 1991

ABELES, M., BERGMAN, H., MARGALIT, E., and VAADIA, E.: Spatiotemporal firing patterns in the frontal cortex of behaving monkeys. J. Neurophysiol. *70*, 1629–1638 (1993)

ABELES, M., and GOLDSTEIN, M. H.: Multispike train analysis. Proc. IEEE *65*, 762–773 (1977)

ADRIAN, E. D.: The Basis of Sensation. London: Christophers 1928

AERTSEN, A., and ARNDT, M.: Response synchronization in the visual cortex. Curr. Op. Neurobiol. *3*, 586–594 (1993)

AERTSEN, A., DIESMANN, M., GEWALTIG, M. O., GRÜN, S., and ROTTER, S.: Neural dynamics in cortical networks – precision of joint-spiking events. In: Complexity in Biological Information Processing. vol. 239 of Novartis Foundation Symposium. pp 193–204. Wiley, Chichester 2001

AERTSEN, A., GERSTEIN, G., HABIB, M., and PALM, G.: Dynamics of neuronal firing correlation: Modulation of 'effective connectivity'. J. Neurophysiol. *61*, 900–917 (1989)

AERTSEN, A., VAADIA, E., ABELES, M., AHISSAR, E., BERGMAN, H., KARMON, B., LAVNER, Y., MARGALIT, E., NELKEN, I., and ROTTER, S.: Neural interactions in the frontal cortex of a behaving monkey: signs of dependence on stimulus context and behavioral state. J. Hirnf. *32*, 735–743 (1991)

AHISSAR, M. E. A., BERGMAN, H., and VAADIA, E.: Encoding of sound-source location and movement: activity of single neurons and interactions between adjacent neurons in the monkey auditory cortex. J. Neurophysiol. *67*, 203–215 (1992)

AMIT, D. J.: Modeling Brain Function. Cambridge, New York: Cambridge University Press 1989

AMIT, D. J., and BRUNEL, N.: Model of global spontaneous activity and local structured activity during delay periods in the cerebral cortex. Cereb. Cort. *7*, 237–252 (1997)

BARLOW, H.: The biological role of neocortex. In: AERTSEN, A., and BRAITENBERG, V. (Eds.): Information Processing in the Cortex. pp 53–80. Berlin, Heidelberg, New York: Springer-Verlag 1992

BARLOW, H. B.: Single units and sensation: a neuron doctrine for perceptual psychology? Perception *1*, 371–394 (1972)

BASTIAN, A., RIEHLE, A., ERLHAGEN, W., and SCHÖNER, G.: Prior information preshapes the population representation of movement direction in motor cortex. NeuroReport *9*, 315–319 (1998)

BRAITENBERG, V., and SCHÜZ, A.: Anatomy of the Cortex: Statistics and Geometry. Berlin: Springer-Verlag 1991

BRYANT, H. L., and SEGUNDO, J. P.: Spike initiation by transmembrane current: a white-noise analysis. Proc. R. Soc. Lond. B *194*, 211–223 (1976)

DECHARMS, R. C., and MERZENICH, M. M.: Primary cortical representation of sounds by the coordination of action-potential timing. Nature *381*, 610–613 (1996)

DIESMANN, M., GEWALTIG, M. O., and AERTSEN, A.: Stable propagation of synchronous spiking in cortical neural networks. Nature *402*, 529–533 (1999)

DIESMANN, M., and AERTSEN, A.: Parameter space of synfire activity. Breisach, Germany: Proc 6th Tamagawa Dynamic Brain Forum 2001

ECCLES, J. C.: The Physiology of Nerve Cells. Baltimore: Johns Hopkins Press 1957

ECKHORN, R., BAUER, R., JORDAN, W., BROSCH, M., KRUSE, W., MUNK, M., and REITBÖCK, H. J.: Coherent oscillations: A mechanism of feature linking in the visual cortex? Biol. Cybern. *60*, 121–130 (1988)

EGGERMONT, J. J.: Neural interaction in cat primary auditory cortex. II. Effects of sound stimulation. J. Neurophysiol. *71*, 246–270 (1992)

ENGEL, A. K., KÖNIG, P., SCHILLEN, T. B., and SINGER, W.: Temporal coding in the visual cortex: new vistas on integration in the nervous system. TINS *15*, 218–226 (1992)

FETZ, E. E: Temporal coding in neural populations. Science *278*, 1901–1902 (1997)

FETZ, E. E., TOYAMA, K., and SMITH, W.: Synaptic interactions between cortical neurons. In: PETERS, A. (Ed): Cerebral Cortex. vol. 9. pp 1–47. New York: Plenum Publishing Corporation 1991

GEORGOPOULOS, A. P., KETTNER, R. E., and SCHWARTZ, A. B.: Primate motor cortex and free arm movements to visual targets in three-dimensional space. II. Coding of the direction of movement by a neuronal population. J. Neurosci. *8*, 2928–2937 (1988)

GEORGOPOULOS, A. P., LURITO, J. T., PETRIDES, M., SCHWARTZ, A. B., and MASSEY, J. T.: Mental rotation of the neuronal population vector. Science *243*, 234–236 (1989)

GERSTEIN, G. L., BEDENBAUGH, P., and AERTSEN, A.: Neuronal assemblies. IEEE TransBiomed Eng. *36*, 4–14 (1989)

GRAMMONT, F., and RIEHLE, A.: Precise spike synchronization in monkey motor cortex involved in preparation for movement. Exp. Brain. Res. *128*, 118–122 (1999)

GRAY, C. M., and SINGER, W.: Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. Proc. Natl. Acad. Sci. USA *86*, 1698–1702 (1989)

GRÜN, S.: Unitary Joint-Events in Multiple-Neuron Spiking Activity: Detection, Significance, and Interpretation. Reihe Physik. Band 60. Thun, Frankfurt/Main: Verlag Harri Deutsch 1996

GRÜN, S., DIESMANN, M., and AERTSEN, A.: Unitary events in multiple single-neuron spiking activity: I. Detection and significance. Neural. Comp. *14*, 43–80 (2002a)
GRÜN, S., DIESMANN, M., and AERTSEN, A.: Unitary Events in multiple single-neuron spiking activity. II. Nonstationary data. Neural. Comp. *14*, 81–119 (2002b)
GRÜN, S., DIESMANN, M., GRAMMONT, F., RIEHLE, A., and AERTSEN, A.: Detecting unitary events without discretization of time. J. Neurosci. Meth. *94*, 67–79 (1999)
GRÜN, S., RIEHLE, A., and DIESMANN, M.: Effect of across trial non-stationarity on joint-spike events. Biol. Cybern. (in press)
GÜTIG, R., AERTSEN, A., and ROTTER, S.: Statistical significance of coincident spikes: Count-based versus rate-based statistics. Neural. Comp. *14*, 121–253 (2002)
HATSOPOULOS, N. G., OJAKANGAS, C. L., PANINSKI, L., and DONOGHUE, J. P.: Information about movement direction obtained from synchronous activity of motor cortical areas. Proc. Natl. Acad. Sci. USA *95*, 15706–15711 (1998)
HEBB, D. O.: Organization of Behavior. A Neurophysiological Theory. New York: John Wiley & Sons 1949
HOPFIELD, J. J.: Neural networks and physical systems with emergent collective computational abilities. Proc. Natl. Acad. Sci. USA *79*, 2554–2558 (1982)
HUBEL, D. H., and WIESEL, T. N.: Receptive fields and functional architecture of monkey striate cortex. J. Neurophysiol. *195*, 215–243 (1968)
KÖRNER, E., GEWALTIG, M. O., KÖRNER, U., RICHTER, A., and RODEMANN, T.: A model of computation in neocortical architecture. Neural Networks *12* (7–8), 989–1005 (1999)
LAUBACH, M., WESSBERG, J., and NICOLELIS, M. A.: Cortical ensemble activity increasingly predicts behaviour outcomes during learning of a motor task. Nature *405*, 567–571 (2000)
LETTVIN, J. Y., MATURANA, H. R., MCCULLOCH, W. S., and PITTS, W. R.: What the frog's eye tells the frog's brain. Proc. I R E *47*, 1940–1951 (1959)
MAINEN, Z. F., and SEJNOWSKI, T. J.: Reliability of spike timing in neocortical neurons. Science *268*, 1503–1506 (1995)
MALSBURG, C. VON DER: The correlation theory of brain function. Internal report 81-2, Max-Planck-Institute for Biophysical Chemistry, Göttingen, FRG (1981)
MALSBURG, C. VON DER: Am I thinking assemblies? In: PALM, G., and AERTSEN, A. (Eds.): Brain Theory. pp 161–176. Berlin: Springer-Verlag 1986a
MALSBURG, C. VON DER: Frank Rosenblatt: Principles of neurodynamics: Perceptrons and the theory of brain mechanisms. In: PALM, G., and AERTSEN, A. (Eds.): Brain Theory. pp 245–248. Berlin: Springer-Verlag 1986b
MARTIN, K. A. C.: A brief history of the »feature detector«. Cereb. Cort. *4*, 1–7 (1994)
MARTIN, K. A. C.: The pope and grandmother – a frog's-eye view of theory. Nat. Neurosci. *3*, 1169 (2000)
MCCULLOCH, W. S., and PITTS, W.: A logical calculus of the ideas immanent in neural nets. Bull Math. Biophys. *5*, 115–137 (1943)
MINSKY, M. L., and PAPERT, S.: Perceptrons: An Introduction to Computational Geometry. expanded edn. Cambridge, Massachusetts: MIT Press 1988
MUNK, M. H., NOWAK, L. G., NELSON, J. I., and BULLIER, J.: Structural basis of cortical synchronization. II. Effects of cortical lesions. J. Neurophysiol. *74*, 2401–2414 (1995)
MURTHY, V. N., and FETZ, E. E.: Coherent 25- to 35- Hz oscillations in the sensorimotor cortex of awake behaving monkeys. Proc. Natl. Acad. Sci. USA *89*, 5670–5674 (1992)
NICOLELIS, M. A. L., BACCALA, L. A., LIN, R. C. S., and CHAPIN, J. K.: Sensorimotor encoding by synchronous neural assembly activity at multiple levels in the somatosensory system. Science *268*, 1353–1358 (1995)
NOWAK, L. G., MUNK, M. H., NELSON, J. I., JAMES, A., and BULLIER, J.: Structural basis of cortical synchronization. I. Three types of interhemispheric coupling. J. Neurophysiol. *74*, 2379–2400 (1995)
PALM, G.: Evidence, information and surprise. Biol. Cybern. *42*, 57–68 (1981)
PALM, G.: Cell assemblies as a guidline for brain reseach. Conc. Neurosci. *1*, 133–148 (1990)
PAULUIS, Q., and BAKER, S. N.: An accurate measure of the instantaneous discharge probability, with application to unitary joint-event analysis. Neural. Comp. *12*, 647–669 (2000)
PRUT, Y., VAADIA, E., BERGMAN, H., HAALMAN, I., SLOVIN, H., and ABELES, M.: Spatiotemporal structure of cortical activity: Properties and behavioral relevance. J. Neurophysiol. *79*, 2857–2874 (1998)
RIEHLE, A., GRAMMONT, F., DIESMANN, M., and GRÜN, S.: Dynamical changes and temporal precision of synchronized spiking activity in monkey motor cortex during movement preparation. J. Physiol. (Paris) *94*, 569–582 (2000)
RIEHLE, A., GRÜN, S., DIESMANN, M., and AERTSEN, A.: Spike synchronization and rate modulation differentially involved in motor cortical function. Science *278*, 1950–1953 (1997)
ROELFSEMA, P., ENGEL, A., KÖNIG, P., and SINGER, W.: The role of neuronal synchronization in response selection: A biologically plausible theory of structured representations in the visual cortex. J. Cogn. Neurosci. *8*, 603–625 (1996)
ROY, A., STEINMETZ, P. N., and NIEBUR, E.: Rate limitations of unitary event analysis. Neural. Comp. *12*, 2063–2082 (2000)
RUMMELHART, D. E., MCCLELLAND, J. L., and the PDP Research Group: Parallel Distributed Processing, Explorations in the Microstructure of Cognition: Foundations. Vol. 1. Cambridge, Massachusetts: MIT Press 1986
SAKURAI, Y.: Population coding by cell assemblies – what it really is in the brain. Neuroscience Research *26*, 1–16 (1996)

SANES, J. N., and DONOGHUE, J. P.: Oscillations in local field potentials of the primate motor cortex during voluntary movement. Proc. Natl. Acad. Sci. USA *90*, 4470–4474 (1993)
SHADLEN, M. N., and NEWSOME, W. T.: The variable discharge of cortical neurons: Implications for connectivity, computation, and information coding. J. Neurosci. *18*, 3870–3896 (1998)
SHERRINGTON, C. S.: Integrative Action of the Nervous System. New Haven: Yale University Press 1906
SINGER, W.: Synchronization of cortical activity and its putative role in information processing and learning. Annu. Rev. Physiol. *55*, 349–374 (1993)
SINGER, W.: Striving for coherence. Nature *397*, 391–393 (1999)
SINGER, W.: Neural synchrony: a versatile code for the definition of relations. Neuron *24*, 49–65 (1999)
SINGER, W., ENGEL, A. K., KREITER, A. K., MUNK, M. H. J., NEUENSCHWANDER, S., and ROELFSEMA, P. R.: Neuronal assemblies: necessity, signature and detectability. TICS *1*, 252–261 (1997)
SINGER, W., and GRAY, C.: Visual feature integration and the temporal correlation hypothesis. Annu. Rev. of Neurosci. *18*, 555–586 (1995)
STEINMETZ, P., ROY, A., FITZGERALD, P., HSIAO, S., JOHNSON, K., and NIEBUR, E.: Attention modulates synchronized neuronal firing in primate somatosensory cortex. Nature *404*, 187–190 (2000)
VAADIA, E., AHISSAR, E., BERGMAN, H., and LAVNER, Y.: Correlated activity of neurons: A neural code for higher brain functions? In: KRÜGER, J. (Ed.): Neuronal Cooperativity. pp 249–279. Berlin: Springer-Verlag 1991
VAADIA, E., BERGMAN, H., and ABELES, M.: Neuronal activities related to higher brain functions – theoretical and experimental implications. IEEE Trans. Biomed. Eng. *36*, 25–35 (1989)
VAADIA, E., HAALMAN, I., ABELES, M., BERGMAN, H., PRUT, Y., SLOVIN, H., and AERTSEN, A.: Dynamics of neuronal interactions in monkey cortex in relation to behavioural events. Nature *373*, 515–518 (1995)

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