

Spatially organized spike correlation in cat visual cortex

Denise Berger^{a,b}, David Warren^c, Richard Normann^c, Amos Arieli^d, Sonja Grün^{b,e,*}

^aNeuroinformatics, Institute of Biology - Neurobiology, Free University, Berlin, Germany

^bBernstein Center for Computational Neuroscience, Berlin, Germany

^cDepartment of Bioengineering, University of Utah, Salt Lake City, USA

^dDepartment of Neurobiology, Weizmann Institute of Science, Rehovot, Israel

^eComputational Neuroscience Group, RIKEN Brain Science Institute, Wako City, Japan

Available online 16 November 2006

Abstract

Inspired by optical recordings from visual cortex which show maps of orientation selectivity, and the finding that very similar patterns of population activity occur when the neurons fire spontaneously [T. Kenet, D. Bibitchkov, M. Tsodyks, A. Grinvald, A. Arieli, Spontaneously emerging cortical representations of visual attributes, *Nature* 425 (2003) 954–956], we approach the question of how the concept of cortical maps may be related to the concept of temporal coding. To this end we analyzed parallel spike recordings performed using a 10×10 electrode grid covering an area of $3.6 \text{ mm} \times 3.6 \text{ mm}$ of cat visual cortex for occurrence of spike correlation.

We calculated all possible pairwise correlations between multi-unit activities (MUA) by cross-correlation and extracted significantly correlated pairs using a boot-strap procedure. The MUAs involved in correlated pairs were typically involved in more than a single correlated pair. Using methods of graph theory we found that the whole set of correlated MUAs decomposes into a small number of groups of MUAs that have a high degree of the overlap of mutually correlated pairs.

Mapping these groups back onto the spatial arrangement of the recording electrodes revealed that these also correspond to spatially segregated clusters. The spatial scale of this correlation map is in agreement with the scale of orientation tuning maps found by optical imaging.

© 2006 Elsevier B.V. All rights reserved.

Keywords: Spike synchronization; Maps; Visual cortex

1. Introduction

Most cells in the primary visual cortex are selective for orientation and respond best, i.e. by increasing their rates, to their optimal stimulus. Neurons located in different columns but with same stimulus preference coherently show high activity during the same, optimal stimulus, as indirectly shown by optical imaging. Moreover, it has been shown that the firing rate of a spontaneously active single neuron strongly depends on the instantaneous pattern of the ongoing population activity in a larger cortical area [10]. Very similar patterns of population activity were observed, both when the neuron fired spontaneously and

when driven by its optimal stimulus [5]. On the other hand, the temporal coding hypothesis suggests that coordinated spiking activity on a fine temporal scale should occur in the nervous system [6] and is suggested to be used for information coding. Accordingly, modern theories of the primary visual pathway contain spatial and temporal aspects accounting for the observed cell behavior in order to explain visual information processing.

We therefore approach the question of how the concept of temporal coding of single neurons are related to the overall functional architecture. More specifically, we ask if correlated neurons are arranged in a specific spatial organization that may be related to maps of orientation tuning. Parallel spike recordings based on using a 10×10 electrode grid (Utah electrode array, Bionic Technologies, Inc., Salt Lake City, UT, USA) covering an area of $3.6 \text{ mm} \times 3.6 \text{ mm}$ of cat visual cortex [11] allow us to address the question of the relation of correlated neuronal

*Corresponding author. Computational Neuroscience Group, RIKEN Brain Science Institute, 2-1 Hirosawa, Wako-Shi, Saitama, 351-0198, Japan.

E-mail address: gruen@brain.riken.jp (S. Grün).

activity to the distance and the spatial arrangement of the recording sites. Data were recorded from area 17 of anesthetized cat during spontaneous activity, and under full-flash treatment with two different stimulus intensities. We first analyze the simultaneous multi-unit recordings for pairwise correlations using cross-correlation analysis and evaluate their significance using boot-strap techniques. In a next step, we identify groups of correlated pairs that are highly mutually intra-correlated. Finally, mapping these groups back onto the electrode positions and thereby to cortical space, allows us to relate their spatial arrangement to the spatial scales found for orientation tuning maps.

2. Methods and results

2.1. Detection of correlated spiking activity

We analyzed the spiking activities that were recorded from the grid of electrodes (Fig. 1) for pairwise correlations, during spontaneous activity (SP; no stimulus) and during full-flash stimulation with two different intensities. We segmented epochs of high intensity (HI) and low intensity (LI) into two separate data sets and analyzed them separately. For simplicity we restricted ourselves to the evaluation of the multi-unit activities (MUA), and requested a minimal firing rate of 1 Hz for further consideration. This left us with 80 parallel MUA spike trains during SP and 83 during LI and HI for further analysis. From these we computed cross-correlations (CCH, [7]) of all possible pairs in the different stimulus conditions. To evaluate the significance of the correlation, we used a boot-strap method that accounts for the firing rate changes of the neurons. Methods that rely on trial repetitions (e.g. [1]) cannot be used here since under the spontaneous condition we have only one trial. Thus we generated surrogate data sets (100) that account for the

firing rate changes in the data by dithering the individual, original spike times within a given time interval [3]. Dithering is performed for each individual spike of each of the parallel MUAs. Each spike was dithered by random placement (equal probability) within a time interval of predefined width positioned symmetrically around the original spike time. Since the widths of the peaks in the original cross-correlograms were typically in the range of 30–50 ms, the dither time interval was chosen such (70 ms) to destroy the temporal correlation while keeping slow rate variations.

For each surrogate data set we computed the cross-correlation in the same way as for the experimental, original data, which finally resulted in a mean cross-correlogram of all surrogates including the standard deviations for each delay τ (Fig. 1C). Spike correlation between two MUAs is considered significant, if the center peak of the smoothed CCH (box car kernel of 10 ms width) exceeds two standard deviations (i.e. a significance level of 5%) of the surrogate data. Then a pair is called correlated. A total of 148/3160 pairs were significant during SP, 78/3402 during HI and 203/3402 during LI.

2.2. Groups of inter-correlated pairs

Representing the pair correlations in form of an undirected graph, in which each MUA is represented as a node, and existence of correlation by an edge between the two involved MUAs, we found that the connection degree of edges per node was typically larger than two, i.e. a single MUA is typically correlated with more than two other MUAs simultaneously. This led us to identify cliques of correlated pairs, i.e. groups of all-to-all mutually correlated MUAs. Table 1 shows for the case of LI how often a clique of k nodes, i.e. MUAs, were found. Surprisingly, we found cliques with up to $k = 9$ nodes were found. In addition, we noticed that cliques often have mutually overlapping

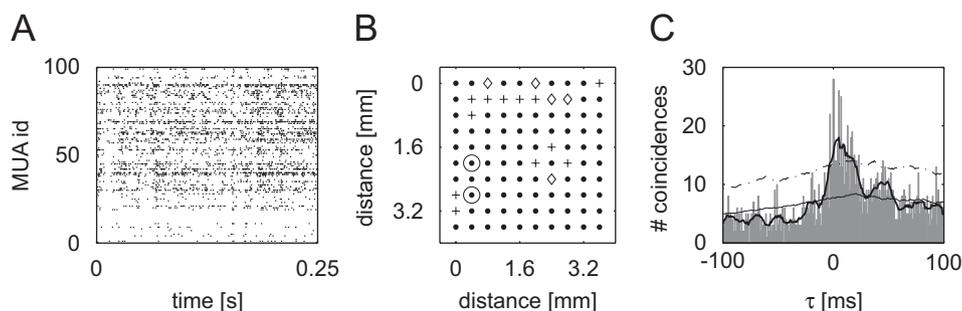


Fig. 1. (A) Dot display of MUA spiking activity under low intensity stimulation measured simultaneously by a grid of electrodes (see B). MUA id corresponds to the electrode position numbered from upper left to lower right, each line from left to right. (B) Electrode recording grid. 10×10 Utah electrode array covering $3.6 \text{ mm} \times 3.6 \text{ mm}$ of the cortex with an inter-electrode distance of $400 \mu\text{m}$. Electrodes marked by a diamond were broken and did not deliver any signal. MUA signals with rates below 1 Hz were not considered for further analysis (corresponding electrode positions marked by crosses). (C) Cross-correlogram of 2 MUAs (recorded from electrode 52 and 72, marked by circles in B). Raw cross-correlogram (gray) computed on the time resolution of $h = 1 \text{ ms}$. The thick black line shows the smoothed CCH (kernel width: 10 bins of h). The thin black line indicates the mean of the predictor, the dashed-dotted line the significance level (mean plus twice the standard deviation). If the center peak of the smoothed cross-correlogram exceeds the significance level, the pair of MUA is considered to be significantly correlated.

members. This led us to define groups of highly intra-correlated MUAs (GIC) according to the following conditions: (1) only cliques with a minimum of $k = 3$ members were considered and, (2) cliques are requested to have a minimal overlap of one member. Interestingly, as a result the graph decomposed into only a small number of completely disjoint subgraphs (3 during SP, 2 during HI and 4 during LI). The GICs contained 4, 13, and 19 MUAs during SP, 7 and 15 MUAs during HI and 14, 3, 11 and 21 during LI (see Fig. 2). Although cliques were requested to

have a minimal overlap of one member, we actually find that each N-clique within a GIC has an overlap of $N - 1$ nodes of other cliques, if at least one other clique with $M \geq N$ nodes exists. A single MUA may be involved in up to 15 pairwise correlations.

2.3. Spatial organization of correlated activity

Now we address the question how the GICs are spatially arranged. Therefore, we map the members of the identified groups back onto the recording grid and mark members of a group by filled circles of a specific gray level (Fig. 3A). Interestingly, the different GICs form separated, compact clusters in space. Thus, the groups of MUAs that are highly intra-correlated also form localized groups in space. Two of the clusters (medium gray corresponding to GIC 1 and light gray corresponding to GIC 4, cf. Fig. 2) also included

Table 1

k	2	3	4	5	6	7	8	9
#	23	18	9	8	2	2	3	1

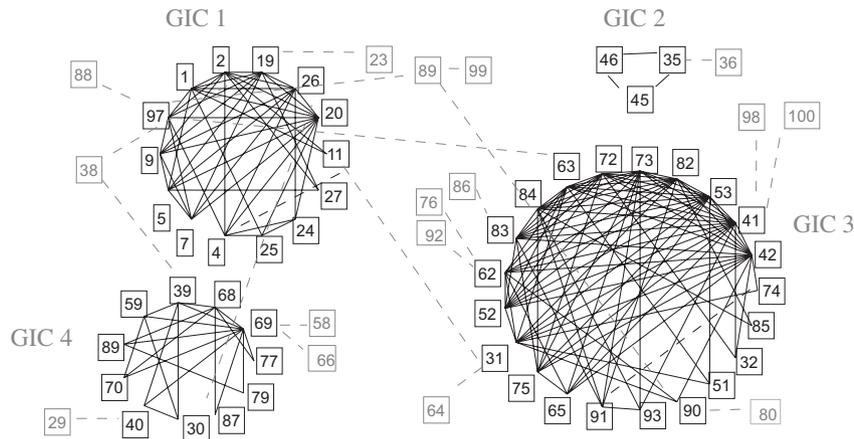


Fig. 2. Graph of all significant pairwise MUA correlations under LI stimulation. Each MUA is indicated by a square that includes the id of the MUA. These represent nodes, and edges indicate an existing correlation between the two connected MUAs. The four circles of nodes show groups that are composed of different cliques. Conditions to form groups are: a minimal clique size of $k = 3$ and a minimal overlap between cliques of 1. The resulting groups (GIC1–GIC4) contain 14, 3, 11 and 21 MUAs, and are composed of 41, 3, 21 and 91 pairwise correlations, respectively. Additional squares (gray) mark nodes that do not fulfill the above criteria, i.e. do belong to cliques of only $k = 2$ members, and thus do not belong to one of the groups. MUAs 52 and 72, for which we have shown the cross-correlation in Fig. 1C, are both members of GIC 3.

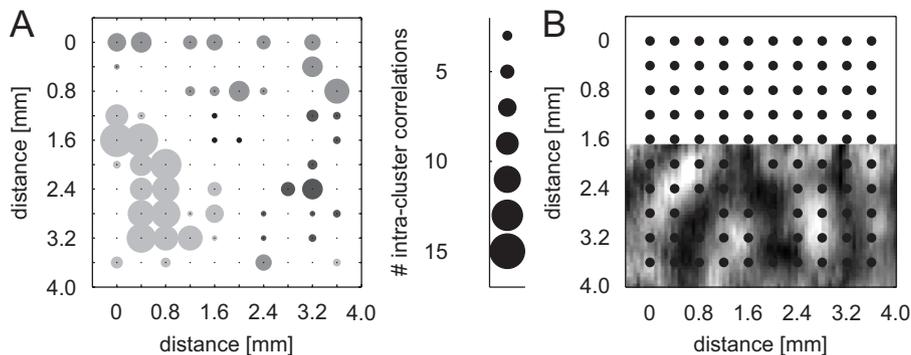


Fig. 3. (A) Spatial arrangement of groups of highly intra-correlated MUAs for the same data as shown in Fig. 2 during LI. The array marks the electrode grid used for the recording. Filled circles of a specific gray color indicate electrode positions of MUAs that are identified as members of a GIC. The radii of the filled circles indicate the number of correlations the MUAs were involved in (see marker bar on the right). GICs result in spatial clusters: GIC1 corresponds to the medium gray cluster (top, horizontal), GIC2 to the black cluster (center), GIC3 to the dark gray cluster (right, vertical) and GIC4 to the light gray cluster (left, vertical). (B) Comparison of spatial scales. Optical imaging orientation map for one stimulus orientation (full field grating; modified from [5]) including the electrode grid used in our study are both shown on the same scale.

one remotely located MUA. Note, that also the remote MUAs are included in multiple correlations with the rest of the MUAs of the corresponding GIC. Circle radii indicate number of MUAs the indicated MUA is correlated to. Our findings clearly show that the spatial organization of correlations are not randomly or homogeneously distributed in space, but rather cluster in certain spatial domains. The spatial scale of the GICs is directly comparable to the spatial scale of orientation maps found by optical imaging (Fig. 3B). Across the different stimulus conditions the number of correlated MUAs differ (see Section 2.1): during HI or SP less MUAs appear to be correlated as compared to LI. As a consequence, in these conditions a lower number of GICs are found (see Section 2.2). However, group memberships stay mainly the same across different conditions.

Variation of the dither width had a minor impact on the results. For a smaller dither width as used for the former analysis (30 ms), a smaller number of correlations appeared to be significant. The involved MUAs formed the same spatial clusters as for larger dither widths, but with less degree of connectivity and less members. For increasing dither widths, the clusters became more and more pronounced. Beyond a dither width of 70 ms, cluster members and degree connectivity remained stable.

3. Discussion

This study investigated the spatial organization of correlated activity in cat visual cortex. Multi-unit activities were recorded by a grid spanning an area of $3.6 \times 3.6 \text{ mm}^2$ allowing us to investigate the relation of correlated MUA pairs to spatial structure. On average 5% of all possible pairs were significantly correlated. To capture the correlation structure, we constructed a graph with each MUA being a node and assigning edges to significantly correlated MUAs. This led to the finding that the large number of pairwise correlations (about 185) separate into a low number of groups (2–4) of highly intra-correlated MUAs with 3–21 members per group (GICs). By mapping the detected GICs back onto cortical space, we found that the members of the individual GICs also clustered in space revealing a relationship between correlation pattern and spatial pattern. The occurrence of correlation between pairs of MUAs appeared to be distance dependent. When adjacent, they occurred most frequently, increasingly less up to about 3 mm, and then again increasingly more (Fig. 4).

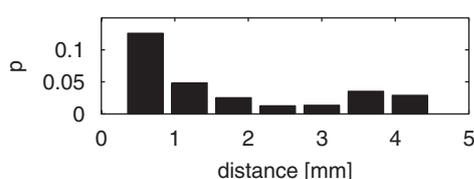


Fig. 4. Distance dependence of correlations. The histogram shows as a function of electrode distance the probability of finding correlated MUA pairs (during LI, same data as shown in Figs. 2 and 3).

Moreover, the spatial extent of the GICs corresponds to the spatial scale of the orientation tuning map obtained by optical imaging (see Fig. 3B, [5]), as well as by electrophysiological imaging maps [12]. Thus we conclude that our results in respect to the extent and spatial arrangement of the clusters are in agreement with the spatial organization reported in visual cortex contained by optical imaging [4].

Ts'o et al. [9] investigated cross-correlations between cortical neurons in respect to long-range horizontal connections, i.e. distances of up to several mm. Their study suggests a high degree of inter-connectivity between cells having the same orientation preference within as well as between columns, thereby strongly supporting our interpretation of our results. Das et al. [2] investigated short-range interactions and observed that neighboring cells in a range of up to 500–800 μm show spike correlations independent of the orientation preference. However, we found correlations on a scale of distance. The GICs have spatial extents that exceed this short-range interactions in all but one GIC. Furthermore, an additional important difference between their experiments and ours are the type of stimulus. Here, we investigated spontaneous activity as well activity under full-flash treatment, whereas Das et al. used isolated optimal bars in the receptive fields of the neurons. More comparable to our results is the study by Tsodyks et al. [10] who found orientation maps under spontaneous activity that is related to the tuning of the individual cortical neurons and concluded that the underlying functional architecture is associated to tuning properties. Another important observation, adding credence to the possibility that our observed GICs reflect the underlying connection network in area 17 is that these correlation maps are highly similar for the three recording conditions. We conclude that the observed correlation patterns cannot be considered to be random, in view of the overall number of correlations. Indeed, the correlations between MUA pairs appear to be well organized, particularly when distance dependent correlations are compared to orientation tuning in distinct columns. Since an orientation stimulus was not used here, MUA correlation cannot definitively be ascribed to orientation tuning. Nevertheless, we propose that these correlations of neuron pairs are linked according to orientation tuning.

For a categorical affirmation these results would have to be verified using an adequate experimental paradigm using oriented stimuli. We also aim to address in future the temporal dynamics in the correlation patterns of the clusters. Since Kenet et al. [5] found different orientation maps to be activated dynamically and systematically during spontaneous activity, we expect the GICs to be dynamically correlated and alternately active. Another open question is related to the order of spike correlations. Due to the limitation of the cross-correlation method to be restricted to pairwise correlations only, we could not determine if the MUAs involved in more than one pair actually reflects the existence of higher-order correlations,

i.e. spike correlation patterns that involve more than two neurons at a time (e.g. [8]).

Acknowledgments

Partial funding by the BMBF (BCCN Berlin, grant 01GQ0413), the Stifterverband für die Deutsche Wissenschaft, and the Volkswagen Foundation. This work was carried out while Sonja Grün was based at the Freie Universität in Berlin, Germany.

References

- [1] A. Aertsen, G. Gerstein, M. Habib, G. Palm, Dynamics of neuronal firing correlation: modulation of “effective connectivity”, *J. Neurophysiol.* 61 (5) (1989) 900–917.
- [2] A. Das, C. Gilbert, Topography of contextual modulations mediated by short-range interactions in primary visual cortex, *Nature* 399 (1999) 655–661.
- [3] N. Hatsopoulos, S. Geman, A. Amarasingham, E. Bienenstock, At what time scale does the nervous system operate?, *Neurocomputing* 52–54 (2003) 25–29.
- [4] M. Hubener, D. Shoham, A. Grinvald, T. Bonhoeffer, Spatial relationships among three columnar systems in cat area 17, *J. Neurosci.* 17 (23) (1997) 9270–9284.
- [5] T. Kenet, D. Bibitchkov, M. Tsodyks, A. Grinvald, A. Arieli, Spontaneously emerging cortical representations of visual attributes, *Nature* 425 (2003) 954–956.
- [6] J. Nelson, P. Salin, M. Munk, M. Arzi, J. Bullier, Spatial and temporal coherence in cortico-cortical connections: a cross-correlation study in areas 17 and 18 in the cat, *Vis. Neurosci.* 9 (1) (1992) 21–37.
- [7] D. Perkel, G. Gerstein, G. Moore, Neuronal spike trains and stochastic point processes. II. Simultaneous spike trains, *Biophys. J.* 7 (4) (1967) 419–440.
- [8] G. Schneider, S. Grün, Analysis of higher-order correlations in multiple parallel processes, *Neurocomputing* 52–54 (2003) 771–777.
- [9] D. Ts’o, C. Gilbert, T. Wiesel, Relationships between horizontal interactions and functional architecture in cat striate cortex as revealed by cross-correlation analysis, *J. Neurosci.* 6 (4) (1986) 1160–1170.
- [10] M. Tsodyks, T. Kenet, A. Grinvald, A. Arieli, Linking spontaneous activity of single cortical neurons and the underlying functional architecture, *Science* 286 (1999) 1943–1946.
- [11] D. Warren, E. Fernandez, R. Normann, High-resolution two-dimensional spatial mapping of cat striate cortex using a 100-microelectrode array, *Neurosci.* 105 (1) (2001) 19–31.
- [12] D. Warren, A. Koulakov, R. Normann, Spatiotemporal encoding of a bar’s direction of motion by neural ensembles in cat primary visual cortex, *Ann. Biomed. Eng.* 32 (9) (2004) 1265–1275.



PD Dr. Sonja Grün was born in 1960 in Germany, where she obtained her Diploma in Physics (Eberhard-Karls University Tübingen). She did her Ph.D. work in the field of computational neuroscience at the Ruhr-University Bochum, Germany, and at the Weizmann Institute of Science, Rehovot, Israel, and obtained her Ph.D. in physics (Ruhr-University Bochum). After her post-doctoral work at the Hebrew University in Jerusalem, Israel, she worked as a senior fellow at the Max-Planck Institute for Brain Research in Frankfurt/M, Germany. From 2002 to 2006 she was an Assistant Professor for Neuroinformatics/Theoretical Neuroscience at the Free University in Berlin, Germany and was a founding member of the Bernstein Center for Computational Neuroscience in Berlin. Since 9/2006 she is the head of a research unit at the RIKEN Brain Science Institute in Wako, Japan. Her main interests are in statistical neuroscience, which includes modeling of stochastic processes and the development of data analysis techniques for multiple parallel neuronal time series.



Denise Berger was born in 1980 in Germany. In 2005, she received her M.Sc. in bioinformatics from the Free University in Berlin, Germany. Currently, she is working on her Ph.D. thesis in the field of Computational Neuroscience at the Free University in Berlin, and is a member of the Bernstein Center for Computational Neuroscience in Berlin (BCCN). Her current interests are in statistical neuroscience and the analysis of massively parallel electrophysiological data.