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Alterations in correlated activity parallel ICMS-induced representational plasticity

Hubert R. Dinse,[CA] Gregg H. Recanzone[1] and Michael M. Merzenich[2]

Institut für Neuroinformatik, Lehrstuhl für Theoretische Biologie, Ruhr-University Bochum, ND 04 Box 102148, D-44780 Bochum, Germany; [1]Laboratory of Sensorimotor Research, National Institutes of Health, Bethesda, MD 20892; [2]Keck Center for Integrative Neurosciences, U 76, University of California, San Francisco, CA 94143-0732,USA

[CA] Corresponding Author

WE studied neural interactions by cross correlation analysis during representational plasticity induced by intracortical microstimulation (ICMS). Neuron pairs were simultaneously recorded in area 3b in adult New World monkeys, and in cortical field SI in adult rats. In normal animals, the degree of correlated spontaneous activity corresponded to the extent of receptive field overlap. After several hours of ICMS, the spatial extents of cortex over which correlated activity could be recorded was enlarged several-fold. Mapping experiments revealed that increased correlated activity was only recorded within that cortical sector that was representationally reorganized, indicating a close relationship between cortical reorganization and cooperative processes. Results support the hypothesis that discharge coincidence is crucial for the formation of functionally coupled neural groups, and implicate dynamically maintained groups in the genesis of postontogenetic plasticity.

Key words: Somatosensory cortex; Postontogenetic plasticity; Intracortical microstimulation; Cross correlation; Cortical network; Correlated activity; Neuron assembly; Receptive fields; Synchronization; Simultaneous recordings

Introduction

Cortical neurons have specific response characteristics that are complex consequences of their extrinsic excitatory inputs and intrinsic excitatory and inhibitory connections. Cortical neurons are commonly arrayed in topographically ordered representations resulting in two-dimensional maps. Compelling evidence has been recently accumulating that the somatosensory, auditory, visual and motor systems have a considerable capacity for functional remodeling of these maps in many adult species including humans following central or peripheral lesions or learning and experience related protocols.[1–6] We recently discovered that a few hours' intracortical microstimulation (ICMS)[7] provides a simple means, most likely due to the strong synchronization of local inputs, of generating changes of cortical representations,[8,9] which are comparable in magnitude to those recorded in earlier nerve-, lesion- and behavioral-training experiments.[10] ICMS was also shown to reversibly relocate areal and modality borders.[11]

These findings suggest that the intrinsic network coupling of neuronal populations is subject to modification by either behaviorally or experimentally induced synchronization of inputs.[12–14]

Here we focus on the relationship between dynamic coupling of cortical cells and postontogenetic representational plasticity induced by ICMS. By utilizing simultaneous neuron recordings and cross correlation analysis, we studied the spatial extents and the modifiability of correlated activity to determine how the temporal structure of neuronal discharge and the cooperation between neuron pairs changed in parallel with changes in cortical representational maps.

Materials and Methods

Seventeen adults rats (Sprague–Dawley) and two adult New World monkeys (*Aotus trivirgatus*, *Saimiri sciureus*) were used in these studies. For details of our experimental procedures, see references 9 and 15. Treatment of all animals was within the National Institutes of Health Guide for Care and Use of Laboratory Animals (Revised 1987). After a craniotomy over one hemisphere, the dura mater was resected and the cortex covered with silicon oil. Highly magnified images of the brains were used to mark penetration sites and to reconstruct cortical topographic maps.

Two independent glass NaCl-filled (3 M) microelectrodes were used for recording neuron activity (1–2 MΩ). In some experiments we used solid state multichannel microelectrodes[16] consisting of four active sites arrayed along a straight line separated by distances of 80 μm. Recording contacts had impedences of 1–3 MΩ and were derived at a cortical depth of 700–800 μm from the surface.[9,15]

Intracortical microstimulation (ICMS) was applied through a glass micropipette consisting of capacity-coupled, charge-balanced negative pulses (pulse duration 200 ms, 5 mA amplitude, delivered at 300 pps for 40 ms delivered once per second).[9] Stimuli were monitored by measuring the current across a bleeding resistor. The term 'stimulation site' (ss-RF) is used to designate the penetration site associated with the

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recording electrode used for ICMS; the term 'recording site' (rs-RF) designates the recording site associated with a non-stimulating electrode.

Three protocols were followed in the course of the experiments. Protocol 1 measured the spatial extent of correlated activity recorded simultaneously from pairs of neurons at separated cortical loci in rat SI. First, RF skin locations and RF sizes were defined for the two sampled sites.[9,15] The percentage overlap between the ss-RF and each rs-RF was determined and binned in 25% steps. Spontaneous, on-going activity was recorded (at least 500 spikes per recording channel) and used for calculating cross correlograms for delay times from − 50 to + 50 ms. Correlation strengths (CORR) were expressed as the differences of a weighted measure of peak area between an unshuffled and shuffled correlogram and varied between 0 and 1 for flat correlograms. CORR was plotted as a function of cortical distance and RF overlap before and after ICMS. Also, RF overlap was plotted as a function of cortical distance. Protocol 2 measured correlated activity after controled topographic reorganization induced by ICMS. First, control maps of parts of the hand representation in area 3b of New World monkeys were established by multiple response-sampling penetrations (40 to 50), separated by 100 to 200 mm using a single recording electrode. After several hours of ICMS, the same cortical region was remapped to establish the details and extents of the induced representational changes. Then, the procedure of simultaneous recordings was repeated both within and outside the cortical sectors affected by the ICMS. Protocol 3 measured the time course of ICMS induced changes in three rats. In this series, correlated activity, locations of receptive fields and response latencies to computer controled tactile stimulation[9] applied to the ss-RF were determined every 15–20 min while ICMS was interrupted for these periods.

Results

Distance dependence of correlated activity: Positively correlated activity was measured before and after ICMS for a total of 120 pairs of neurons separated by variable distances recorded within the rat SI hindpaw representation. Under control conditions, correlated activity dropped to chance level at separations of about 200 to 250 μm. After 4 to 8-h periods of ICMS, correlation strength increased for neuron pairs in this central core zone (24 pairs). Most notable, however, was an emergence of correlated activity in spontaneous activity periods for pairs separated by 300 to 800 μm or more (43 pairs). This emergent long-distance functional coupling was similar in strength to that observed for closely spaced neuron pairs in the core zone recorded under control conditions (Fig. 1a). The clear relationship between RF overlap and cortical separation seen under control conditions parallel the distance dependence of CORR (Fig. 1b and Fig. 2). After ICMS, the area over which RFs overlap becomes much larger. However, the relationship between CORR and RF overlap (r = 0.78 pre-ICMS *vs* r = 0.74 post-ICMS) does not change (Fig. 1c).

Characterization of correlograms: All observed correlograms shared some common features. Usually, broad peaks centered symmetrically around zero were encountered. The mean peak halfwidth was 16.4 ms (± 7.2) and the total peak width 27.1 ms (± 9.4). No systematic differences in peak width between the control condition and after ICMS were recorded.

Relationships between correlated activity and map changes: The alteration of correlated activity by ICMS suggests that these changes in neural coupling are related to accompanying cortical map changes. Figure 3A illustrates two examples of paired recordings at different separation distances under control conditions in monkey SM1. Neuron pairs separated by more than 200–250 μm revealed flat correlograms. Figure 3B shows the same cortical sector after 5 h of ICMS. There is a several-fold increase in the zone of complete (shaded) and partial (within the outer line) RF overlap.

These results strongly suggest that changes of correlated activity are restricted to those regions of cortex that underwent reorganization of their skin surface representations.

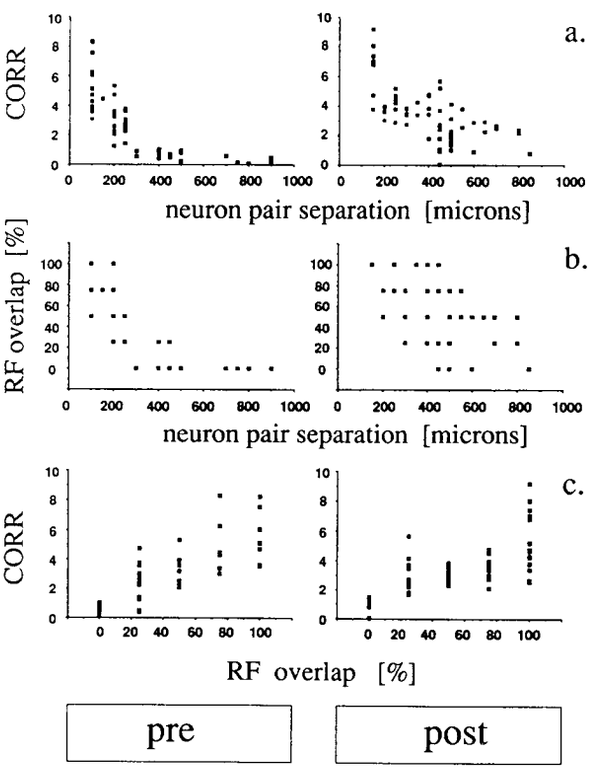

FIG. 1. (**A**) Distance dependence of correlation strength (CORR) before and after ICMS. Neuron pair separations are binned in 50 μm steps with the actual accuracy around 10 to 20 μm. (**B**) Distance dependence of RF overlap between ss-RF and each rs-RFs. Overlap is binned in 25% steps. Same number of data points as in a and c. Due to the binning used, the data points come to overlay each other in some cases. (**C**) Relationship between CORR and RF overlap. Same conventions as in a and b.

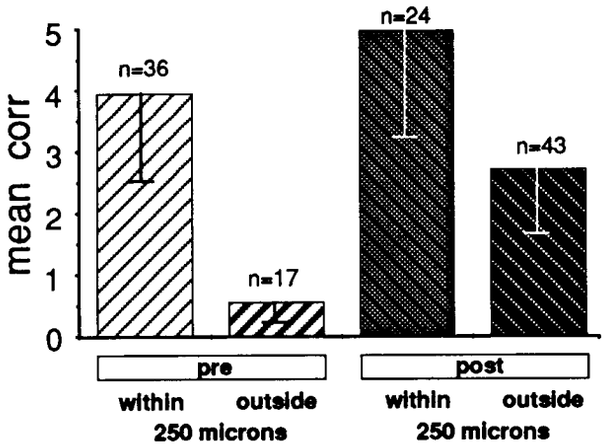

FIG. 2. Mean correlation strength and its standard deviation before and after ICMS. Neuron pairs were subdivided in two groups according to their separation distance (group I: 50–250 μm; group II: > 250 μm). Comparing pre- and post ICMS condition, differences in CORR between neurons separated by more than 250 μm were statistically significant ($p < 0.0001$).

Time course of ICMS-induced changes of correlated activity: A typical example of the time course of the above described effects is shown in Figure 4 which was investigated in three rat experiments. Besides CORR and RF locations, response latency was introduced as a quantitative descriptor of the effects. In all cases, the changes of all three measured parameters paralleled each other providing further argument for the involvement of modifiability of correlated activity in cortical plasticity. A linear regression analysis revealed that CORR was significantly correlated with the following parameters: RF size ($r = 0.927$; $p < 0.03$; df = 6), RF overlap ($r = 0.865$; $p < 0.01$; df = 6) and response latency ($r = 0.979$; $p < 0.001$; df = 6).

Discussion

We have previously shown that ICMS conditioning constitutes a simple means of rapidly modifying the spatial extents of skin representations in area 3b of New World monkeys and SI of rats.[9] Here, we attempt to combine the advantage of short-term ICMS-induced representational plasticity with cross correlation techniques, to address the question of how the coupling of neurons might be modified in parallel with representational plasticity.

In order to measure the degree of the intrinsic cortical network synchronization undisturbed by external stimulation, we focused in this study on the correlation of spontaneous activity epochs. In many cases we used multiple unit activity (2–4 neurons) to calculate cross correlograms[17] in order to increase the number of recording sites in each experiment. Multiple unit correlograms are an indication of the mean correlated activity at the multiple unit recording site. Emergence of correlated activity from zero bears greater significance than do single neuron correlograms, and this method has recently been widely applied in studies of

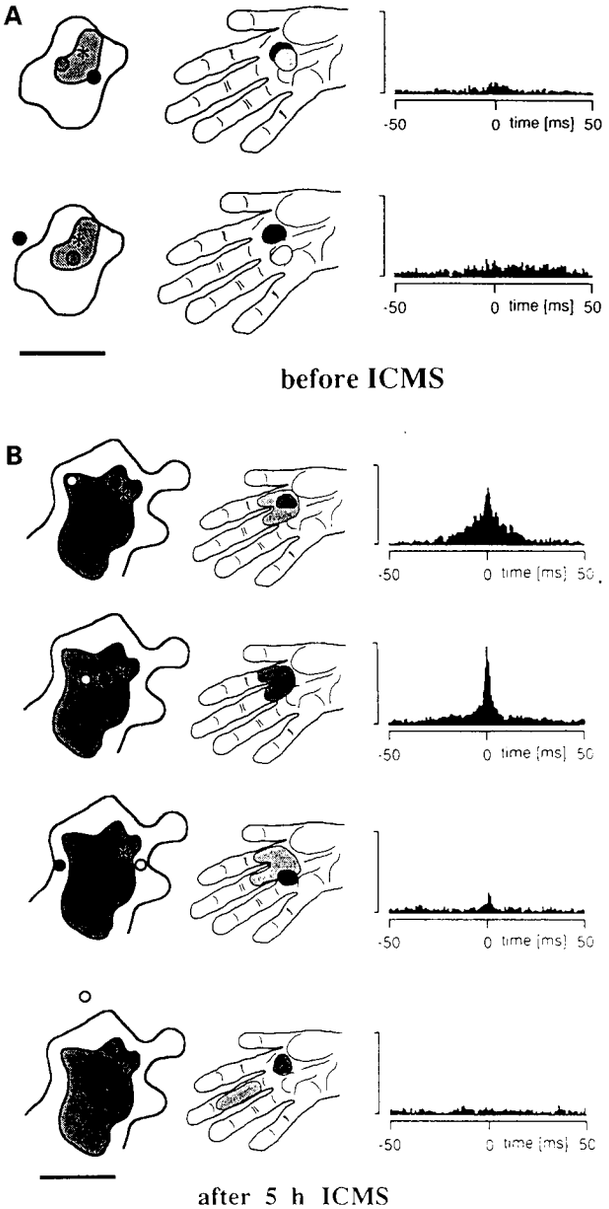

FIG. 3. Relationship between location and separation of recording sites (left), RF positions (middle) and accompanying correlogams calculated on the basis of spontaneous, on-going activity for delay times of – 50 to + 50 ms. The dashed areas indicate recording sites with a complete RF overlap in respect to the stimulation site RF as marked by asterisk. Neurons located in between the dashed areas and the outlined border showed partial overlap of their RFs with the stimulation site RF. Bar is 0.5 mm. (**A**) Control condition before ICMS. Shown are two recording sites at different separations. Closely spaced neuron pairs reveal overlap of their RFs and medium correlated activity (CORR = 2.57). The neuron pair recorded at larger separations shows no RF overlap and flat correlogram (CORR = 0.53). (**B**) After 5 h ICMS. Effects of ICMS on the dimensions of the map are illustrated by the increase of the dashed area that indicates complete RF overlap. Shown are four recording sites at different locations within the altered representation. The values for CORR are (from top to bottom): 3.39, 7.03, 2.28, 0.04. In the second panel from top, both RFs overlap completely.

cortical oscillatory dynamics.[18–20] We rarely found exclusively narrowly peaked correlograms indicating monosynaptic interaction due to direct excitation or common input. In some cases, the correlograms for closely spaced neuron pairs could be interpreted as a superposition of a narrow peak with an additional

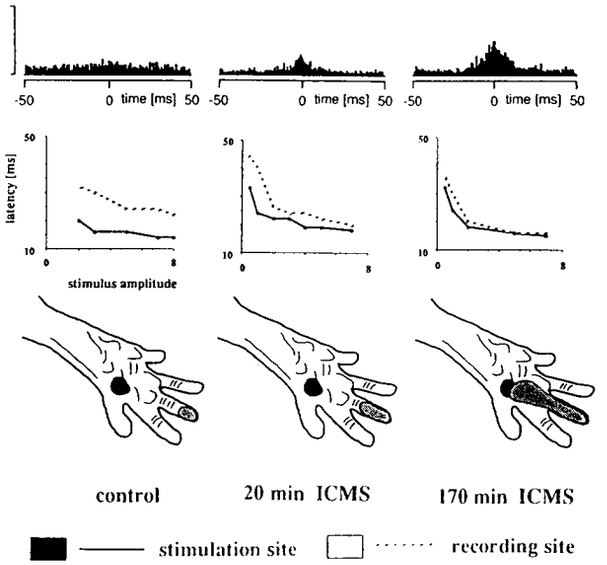

FIG. 4. Time course of ICMS shown for CORR, response latencies and RF locations. Recording separation 0.5 μm. The values for CORR are (from left to right): 0.91, 2.01, 3.10.

broader one. In no case did we observe an oscillatory type of correlation. In our interpretation, the predominance of fairly broad correlograms without delays indicate common excitatory inputs into large, highly interconnected neuron pools, whose weights of interconnections are subject to continuous changes.[10,11,21,22]

After several hours of ICMS, the described spatial patterns of correlation strengths changed considerably, with the spatial extent of the coupled neuronal population increasing asymmetrically around the conditioned site. Similar asymmetric reorganizations had been observed earlier during ICMS induced plasticity.[9] Combined simultaneous recordings and remapping showed very clearly that these changes in CORR were restricted to those regions of cortex that also underwent plastic reorganization. This could be quantitatively shown by the correlation between measures of CORR and RF overlaps. The close association between map changes and topography of correlated activity patterns supports the view that changes of correlated activity are not merely a nonspecific side effect of ICMS, but are causally related. This is further supported by the time course experiments, where gradual changes of correlation strength are paralleled by gradual changes of RFs and their sensitivity profiles. The rapid time-scale of ICMS-induced reorganization showing early effects after only several minutes further reinforce the hypotheses of changes in synaptic efficiency in existing, but dynamically maintained networks.[10–14,21,22] Longlasting anatomical changes, such as axonal sprouting or dendritic spine proliferation on cortical or subcortical level appears rather unlikely.

Although recently ICMS was shown to influence the performance of behaving monkeys,[23] it must be regarded as artificial compared with naturally occurring manipulations. There are, however, several lines of evidence suggesting similar changes do occur under normal circumstances.[15,24] Functional connections between neuron pairs have been demonstrated to be dependent on an associative pairing protocol in behaving monkeys.[21] Using a temporal pairing paradigm, experiments performed in rat SI hindpaw representation have demonstrated changes of RFs and representational maps to occur within a few hours[25] which are comparable to those obtained in the ICMS experiments.

Conclusion

Intracortical microstimulation resulted in significant spatial expansions of regions of correlated activity. These regions coincided with cortical sectors that were representationally reorganized by ICMS. We conclude that these marked changes in functional coupling strengths reflect an enlargement of cooperative cortical cell assemblies that gives rise to the emergence of the representational reorganization typically seen in cortical plasticity experiments.

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