

# Local Cortical Interactions Determine the Form of Cortical Plasticity

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Received 10 May 1999; accepted 20 May 1999

**ABSTRACT:** Competitive interactions between left and right eye inputs to visual cortex during development are usually explained by the thalamocortical axons competing more or less well for cortical territory during retraction into eye specific domains. Here we review the evidence for competitive and co-operative interactions between cortical columns in barrel cortex which are present several weeks after retraction of thalamocortical axons into barrels. Sensory responses in barrel cortex can be altered by a period of vibrissa deprivation. It was found that responses to previously deprived vibrissae (that had been allowed to regrow) were depressed more if neighboring vibrissae were spared than if all vibrissae were removed simultaneously. Depression of the deprived vibrissa response was greater the closer the cell lay to a spared barrel. It was also found that spared

vibrissae responses were potentiated more if several neighboring vibrissae were left intact than if only a single vibrissae was spared. These results suggest a mechanism of cooperative potentiation, perhaps due to intracortical summation of excitation evoked by neighbouring vibrissa stimulation. Thalamic responses to vibrissa stimulation were unaffected by deprivation indicating a cortical origin. One of the consequences of deprivation was that the speed of transmission between barrels was increased for spared and decreased for deprived vibrissa. These results imply that inherent interactions between cortical columns give rise to a property of competition and co-operativity which amplify the effects of sensory deprivation. © 1999 John Wiley & Sons, Inc. *J Neurobiol* 41: 58–63, 1999

The barrel cortex is a useful cortical area in which to study experience-dependent plasticity. The advantages of studying plasticity in this area include the ease with which the main sensory input, the vibrissae, can be manipulated and the one-to-one correspondence between the vibrissae and the anatomical map of the contralateral vibrissae pad located in layer IV. The columnar organization of the barrel cortex and the receptive fields of the neurons are also relatively simple. The principal vibrissa, which is the topologically related vibrissa for a particular barrel, tends to dominate the receptive fields of neurons within that barrel column. However, most cells also respond to a lesser extent to stimulation of neighboring surround

receptive field vibrissae. The fastest input to the barrel column is provided by the principal vibrissa, while the surround vibrissa input occurs with a slight delay (Armstrong-James and Fox, 1987). The delay is thought to be due to a longer route for synaptic transmission of surround vibrissae information involving intracortical relay between neighboring barrel columns (Armstrong-James et al., 1991; Fox, 1994). During postnatal development, the barrel cortex is highly plastic and neuronal circuits for principal and surround representations are altered according to the animal's history of sensory tactile experience (Simons and Land, 1987; Fox, 1992). The barrel cortex remains plastic into later life, and recent experiments have shown that both the degree and form of whisker deprivation plasticity are highly dependent on the exact pattern of whisker deprivation (Glazewski and

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Fox, 1996; Glazewski et al., 1998; Wallace and Fox, 1999a).

The effect of a particular pattern of deprivation is presumably related to the set of intracortical interactions it produces, which will be slightly different for each pattern. Experiments in the visual and barrel cortex have indeed suggested that the distance between the active and inactive cortical barrel columns is likely play a crucial role in determining the degree of plasticity induced. In the visual system, high levels of plasticity can be induced during the critical period of monocular deprivation. Plasticity levels may be high partly because monocular deprivation sets up a pattern of cortical domains where each neuron in a deprived eye column is not more than 150–200  $\mu\text{m}$  from the nearest open eye column: Each closed eye ocular dominance column is surrounded by open eye ocular dominance columns and the columns themselves are about 300–500  $\mu\text{m}$  wide (Hubel et al., 1977, 1978; Anderson et al., 1988). In the barrel cortex, both potentiation of the spared vibrissae responses and depression of the deprived vibrissae responses are known to decrease with distance from the spared barrel column (Glazewski and Fox, 1996; Glazewski et al., 1998), which suggests that plasticity should be greater if every neuron in a deprived column is close to a spared or active input. Together, these results suggest a mechanism for competition between sensory inputs. In the following sections, we review the evidence for local interactions affecting depression and potentiation of sensory responses, before going on to considering the locus of plasticity and its effect on intracortical transmission.

### PROXIMITY EFFECTS ON VIBRISSAE RESPONSE DEPRESSION

The first indication that depression of the deprived vibrissa response might be partly dependent on the proximity of the neurons to an active barrel came from an experiment in which the animals were given a period of single vibrissa experience (Glazewski and Fox, 1996). In this paradigm, one barrel column receives its normal input from the spared whisker, while the barrel columns surrounding it are relatively quiet because their principal input is missing. The responses of neurons on one side of the barrel closest to the D1 (the spared vibrissa's barrel) were lower to stimulation of the regrown, previously deprived vibrissa compared to cells on the side of the barrel farthest away (see Fig. 8 in Glazewski and Fox, 1996). This result suggests the presence of a mechanism of heterosynaptic depression, where the active

barrel influences the activity of the inactive cortical barrels.

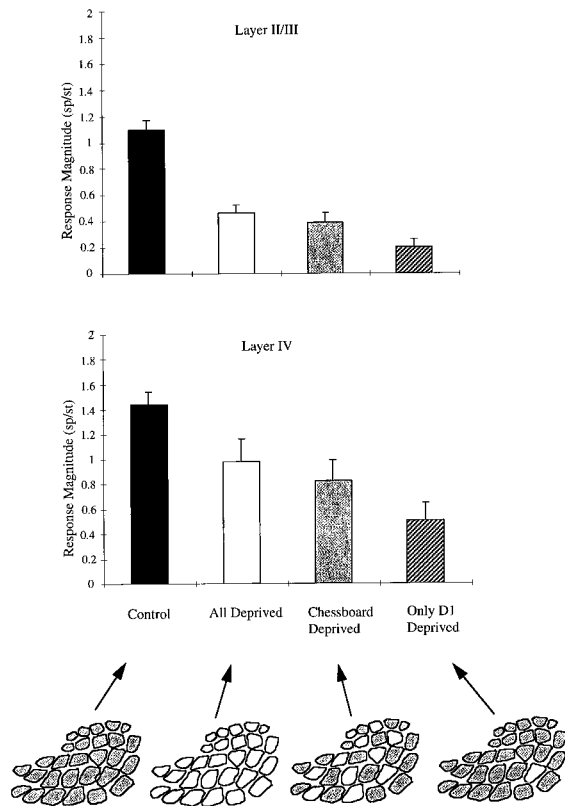
To test this hypothesis further, experiments were performed in which all vibrissae were removed, thus eliminating any explicitly active inputs to the barrels. In a second set of animals a single vibrissa was removed, thereby creating a quiet barrel column surrounded on all sides by normally active barrel columns. The result was that depression was far greater in the case in which a single vibrissa had been deprived than those in which all vibrissae had been deprived (Fig. 1). These results support the view that active inputs are capable of depressing the inactive inputs (Glazewski et al., 1998).

However, some depression did occur in animals deprived of all their vibrissae simultaneously, demonstrating that both homosynaptic and heterosynaptic depression operate in the cortex in tandem (Fig. 1). Depression in layer II/III appears to be mainly homosynaptic, because depression still occurs when all the vibrissae are equally deprived. The greater depression seen in layer II/III when just a single vibrissa is deprived could be explained by passive relay of depression occurring in layer IV, which only occurs to any appreciable extent in the single vibrissa-deprived case. Layer IV behaves differently from layers II/III. The fact that depression only occurs in layer IV when active inputs remain points to a heterosynaptic depression mechanism for this layer.

The influence of active cortical domains on deprived domains can also be demonstrated if a chessboard pattern of vibrissae deprivation is used (Fig. 1) (see next section for description). With a chessboard pattern of deprivation, the number of active inputs is intermediate between the case in which all the vibrissae are deprived and only one vibrissa is deprived. Comparing the three different patterns of deprivation (Fig. 1) reveals that the degree of depression observed in layer II/III and IV correlates with the number of vibrissae left intact. Increasing the number of spared vibrissae leads to a progressive increase in depression.

### COOPERATIVITY EFFECTS ON POTENTIATION OF VIBRISSAE RESPONSE

It is clear that active cortical domains have an effect on inactive cortical domains. To determine whether active cortical domains also influence nearby active domains, we analyzed the effect of chessboard pattern whisker deprivation. In this situation, every other vibrissa is deprived, creating a pattern in the barrel cortex whereby each spared barrel column is sur-

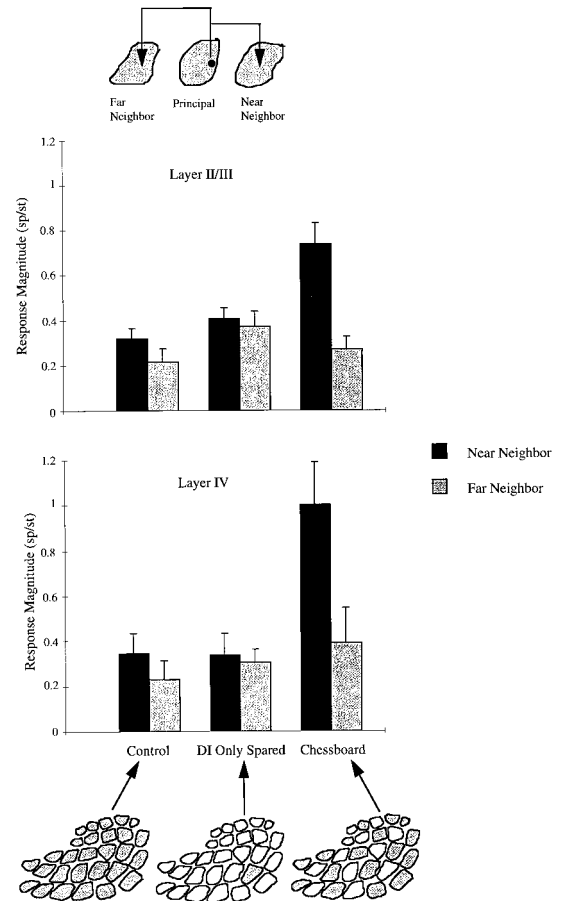


**Figure 1** The effect of varying the number of spared vibrissae on response depression in layers II/III (top) and IV (bottom). The diagrams of the barrel field beneath the histograms represent the pattern of deprivation; deprived vibrissae are represented by white barrels, and spared vibrissae by gray barrels. The graphs show the mean and standard errors between animals for the distribution of responses to deprived principal vibrissa stimulation. Note that depression of the principal vibrissa response is greater if a single vibrissa is deprived (hatched bars, "Only D1 Deprived") than if all vibrissae are deprived simultaneously (white bars, "All Deprived"). Chessboard pattern deprivation results in an intermediate degree of depression (gray bar, "Chessboard Deprived"). The vertical axis denotes the response magnitude for principal vibrissa stimulation (mean  $\pm$  standard error of the mean) averaged across animals (spikes per stimulus).

rounded by four deprived barrel columns, and each deprived barrel column is surrounded by four spared barrel columns (Fig. 1). We compared the effect of chessboard pattern deprivation in which many active domains are present with the case in which a single vibrissa was spared and therefore only one active domain was present.

Figure 2 shows the effects of a chessboard pattern of deprivation after just 7 days. There is significant potentiation of neighboring spared vibrissa responses on the near side of deprived barrels in layers II/III and

IV. Responses to spared vibrissa stimulation in spared barrel columns also potentiate in layer IV (Wallace and Fox, 1999a). In contrast, if only one vibrissa is spared, potentiation is completely absent after 7 days and appears only after 18–20 days (Glazewski and



**Figure 2** Comparison of the effect of sparing a single vibrissa with sparing several vibrissae on potentiation of spared vibrissae responses in deprived barrels. The diagrams of the barrel field denote the patterns of deprivation, (see legend to Fig. 1). As shown by the diagram at the top of the figure, if the cell is located on one side of the barrel column, its near neighbor is the principal vibrissa for the nearest neighboring barrel. The far neighboring vibrissa is the principal vibrissa for the barrel on the opposite side (along the row). Black bars show average responses for the spared near neighbor vibrissa, and gray bars show average response for the far neighbor vibrissae. All recordings are in deprived barrel columns. The chessboard pattern of deprivation produces significant potentiation on the near side of the neighboring barrel in layers II/III and IV compared to control. In contrast, potentiation does not occur on the near or far side if only a single vibrissa is spared. The vertical axis denotes the response magnitude for spared vibrissa stimulation (mean  $\pm$  standard error of the mean) averaged across animals (spikes per stimulus).

Fox, 1996). Furthermore, the potentiation consists of only potentiation of neighboring spared vibrissa responses on the near side of deprived barrels in layers II/III and is absent within the spared barrel (Glazewski and Fox, 1996). Therefore, sparing multiple vibrissae results in more pronounced potentiation after 7 days, and that potentiation includes layer IV.

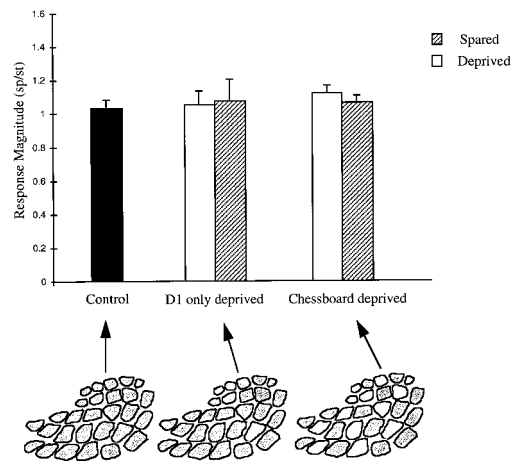
One explanation for why potentiation occurs more readily when several active domains are present is that excitation transmitted intracortically from two simultaneously activated cortical barrel columns can summate in the deprived barrel columns. Intracortical summation would be far less when only one active cortical domain is present; therefore, in this situation potentiation takes 11–13 days longer to occur. This explanation is further supported by recent evidence demonstrating that potentiation depends on neuronal activity in barrel cortex (Wallace and Fox, 1999b).

### EXPRESSION OF PLASTICITY IS CORTICAL, NOT THALAMIC

Is it possible that the deprivation patterns described above give the appearance of cortical plasticity but in reality produce subcortical plasticity which is passively relayed on to the cortex? If this were the case, one could argue that the short latency responses recorded in layer IV appeared to be potentiated owing to potentiation of spared vibrissa responses in the thalamus. One step in the process of pinpointing the origin of plasticity was to make recordings from the thalamus of animals where depression had been accentuated by removing a single whisker, or potentiation had been accentuated by sparing multiple vibrissae. Figure 3 shows that thalamic responses to spared or deprived (regrown) vibrissa stimulation did not change as a result of deprivation. Principal vibrissa responses from the two deprivation paradigms were very similar and virtually identical to control undeprived animals (Glazewski et al., 1998; Wallace and Fox, 1999a). Further evidence comes from studies where cortical postsynaptic activity was blocked in chessboard pattern–deprived animals (Wallace and Fox, 1999b). Blocking postsynaptic cortical activity prevented potentiation, again offering support for a cortical rather than subcortical origin.

### EFFECT OF PLASTICITY ON INTRACORTICAL TRANSMISSION

Inducing plasticity in the barrel cortex causes measurable changes in intracortical transmission. Any

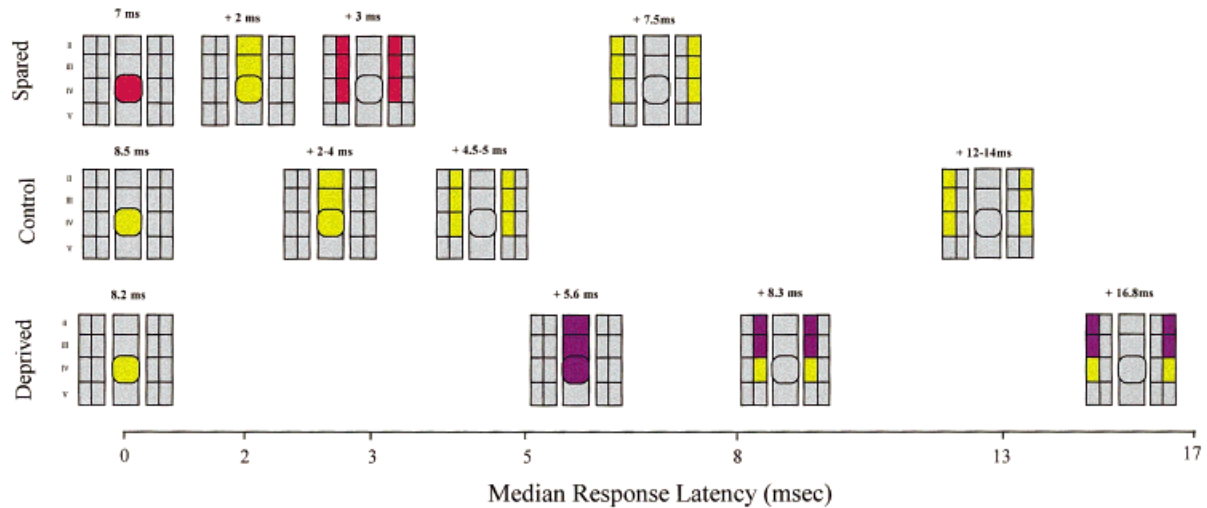


**Figure 3** Effect of vibrissae deprivation on thalamic responses. Responses to stimulation of the spared vibrissae (white bars) and deprived vibrissae (hatched bars) are shown for cases where either a single vibrissa has been deprived (“D1 Only Deprived”) or a chessboard pattern of deprivation has been employed (“Chessboard Deprived”). The graphs show means and standard errors for principal vibrissa responses averaged across animals. Control undeprived animals (black bar) are shown for comparison. There was no significant change in any of the cases compared to control or to each other.

changes in sequence and timing of excitation can be studied by following the spread of activity within the cortex. Two features of the barrel cortex make it possible to follow the flow of excitation following stimulation of a single vibrissa. First, it is possible to relate the anatomical location of a cell within the barrel map and the layer in which the cell is situated, to its receptive field properties. Second, the vibrissae can be stimulated rapidly at a discrete point in time, allowing the timing of responses within the cortex to be measured with an accuracy of milliseconds. Other systems usually rely on electrical stimulation for such accuracy.

Figure 4 shows the effect of chessboard deprivation on the flow of excitation through the cortex. The sequence of activation does not change as a consequence of altered sensory experience. First, layer IV is activated, followed by layers II/III. Then, activity expands to layers II/III and IV of the nearside neighboring barrel column, and then to cells in the far half of the neighboring barrel column. The timing of excitation reaching layer IV is also the same for deprived and spared cases compared with undeprived controls. However, deprivation significantly affects the speed of cortical activation beyond layer IV. The spread of activation is faster for spared vibrissa stimulation and slower for deprived. For spared vibrissa

## Spread of Activity within Barrel Cortex: Sequence and Timing.



**Figure 4** Sequence and timing of excitation within the barrel cortex for spared, deprived, and control vibrissa stimulation. Excitation of a particular group of cells in the cortex is represented at different points in time by a diagram of a coronal section of the barrel field. The principal barrel is shown centrally and its immediate neighboring barrel columns to either side. Time increases from left to right as shown by the latency axis, and the median latencies above each panel. The timing is for response to the principal vibrissa for the central barrel in each case. The difference between the magnitude of the response relative to control is indicated by the color of each location (green = no change, control levels; red = potentiated relative to control; blue = depressed response relative to control). Note that beyond layer IV excitation spreads much faster in response to spared vibrissa stimulation compared to control. Response magnitudes in layer IV and near neighbor responses are potentiated in the active barrel. In contrast, excitation spreads extremely slowly for deprived vibrissae stimulation compared to control. Furthermore, responses are attenuated in all locations except for layer IV surrounding barrels.

stimulation, excitation reaches the far side of the neighboring barrel 4.5 ms earlier than it does in an undeprived control animal. For deprived vibrissa stimulation, excitation reaches the same location 4.8 ms later than it does in controls. Even transmission within the barrel column is slower following deprived vibrissa stimulation. It takes 3 ms longer to activate layer II/III after layer IV has responded in a deprived barrel column than in the control case.

Without fully understanding the normal function of plasticity in the cortex, it is difficult to know what advantages the animal may acquire owing to the cortical changes described above. One possible benefit of the changes in intracortical transmission caused by plasticity may be to improve to integration of information from the neighboring vibrissae. In chessboard-deprived animals, the neighboring vibrissae are farther apart than normal, requiring faster interbarrel transmission if excitation is to summate within a time window similar to that possible in controls (where, of

course, the neighboring vibrissae, and therefore barrel columns, are right next to each other).

## DISCUSSION

The phenomenon of competition has been well documented in the developmental literature. Ocular dominance columns do not expand in favor of one eye or the other unless there is an imbalance of activity between the two eyes (Wiesel and Hubel, 1965). The imbalance can be provided by vision versus lid suture, or even spontaneous activity versus complete lack of retinal activity (Chapman et al., 1986). Competition between thalamic inputs also occurs during development of the barrel cortex (Van der Loos and Woolsey, 1973), and this process is known to depend on postsynaptic cortical activity (Schlaggar et al., 1993).

The experiments reviewed here offer a different view of competitive interactions because the colum-

nar structure and in particular the thalamic afferents are already settled in place before plasticity is induced. Consequently, the intracortical interactions become a dominant feature of both induction and expression of plasticity. This is useful because it allows one to study the effect of intracortical interactions on plasticity in isolation from their interaction with growing thalamocortical axons. Intracortical interactions are an important feature of models of ocular dominance plasticity (Miller et al., 1988) because they help produce the periodicity in eye dominance columns.

We have outlined two mechanisms revealed by these studies that operate in the cortex: namely, heterosynaptic depression and cooperative potentiation. The experiments reviewed above suggest that these mechanisms are most likely to operate via intracortical connections. In addition, it appears important that active domains lie in close proximity to both inactive and active domains for heterosynaptic depression and cooperative potentiation to occur. This is presumably related to the way in which barrel columns are interconnected. Potentiation and depression are accentuated in cases where many active barrel columns lie in close conjunction with less active ones. Since plasticity is observed in the cortex and not in the thalamus, these results are consistent with the hypothesis that plasticity mechanisms are activated most powerfully in the cortex where local areas of activity contrast occur.

In conclusion, if the difference in outcome produced by different patterns of deprivation is accepted as being due to the different patterns of intracortical activity they produce, heterosynaptic depression and cooperative potentiation are likely to operate via intracortical connections. These results emphasize further the fact that to understand cortical plasticity it will be necessary to understand the intracortical connectivity and functional architecture of the cortex.

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