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# Unilateral whisker trimming in newborn rats alters neuronal coincident discharge among mature barrel cortex neurons

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**Ghoshal A, Lustig B, Popescu M, Ebner F, Pouget P.** Unilateral whisker trimming in newborn rats alters neuronal coincident discharge among mature barrel cortex neurons. *J Neurophysiol* 112: 1925–1935, 2014. First published July 23, 2014; doi:10.1152/jn.00562.2013.—It is known that sensory deprivation, including postnatal whisker trimming, can lead to severe deficits in the firing rate properties of cortical neurons. Recent results indicate that development of synchronous discharge among cortical neurons is also activity influenced, and that correlated discharge is significantly impaired following loss of bilateral sensory input in rats. Here we investigate whether unilateral whisker trimming (unilateral deprivation or UD) after birth interferes in the same way with the development of synchronous discharge in cortex. We measured the coincidence of spikes among pairs of neurons recorded under urethane anesthesia in one whisker barrel field deprived by trimming all contralateral whiskers for 60 days after birth (UD), and in untrimmed controls (CON). In the septal columns around barrels, UD significantly increased the coincident discharge among cortical neurons compared with CON, most notably in layers II/III. In contrast, synchronous discharge was normal between layer IV UD barrel neurons: i.e., not different from CON. Thus, while bilateral whisker deprivation (BD) produced a global deficit in the development of synchrony in layer IV, UD did not block the development of synchrony between neurons in layer IV barrels and increased synchrony within septal circuits. We conclude that changes in synchronous discharge after UD are unexpectedly different from those recorded after BD, and we speculate that this effect may be due to the driven activity from active commissural inputs arising from the contralateral hemisphere that received normal activity levels during postnatal development.

barrels; septa; sensory deprivation; coincident discharge; JPSTH; rats

EXPERIMENTS THAT CREATE ABNORMALLY low levels of activity in a sensory system, either unilaterally or bilaterally during postnatal development, have revealed many negative effects on the maturation of single cell and network properties of sensory cortex. The completely crossed whisker-to-contralateral cortex system provides a highly controllable paradigm for studying the functional repercussions of sensory deprivation. The reduction in activity that accompanies whisker plucking in adult mice leads to a significant depression of metabolic activity in cortical barrels (Durham and Woolsey 1978). Physiologically, the cortical representation of a row of damaged whisker follicles becomes unresponsive or "reassigned" to become responsive to adjacent intact whiskers (Simons et al. 1984). Nontraumatic procedures, such as trimming the whiskers every day or two from the day of birth through 1–2 postnatal mo degrade neuronal responses in the deprived barrels compared with barrels with spared inputs, even in the same hemisphere (Fox 1992; Lee et al. 2007; Simons and Land 1987). Whisker trimming also affects the connections between inhibitory interneurons (Akhtar and Land 1991; Micheva and Beaulieu 1995a, 1995b; Shoykhet et al. 2005), producing an excitatory/inhibitory imbalance that persists for a prolonged period in rat barrel cortex. The imbalance between excitation and inhibition occurs in deprived as well as adjacent nondeprived barrels when a single row of whiskers is trimmed in adult rats, leading to the conclusion that "alterations in the balance of excitation and inhibition in deprived and nondeprived barrel columns underlie the topographic remapping associated with sensory deprivation" (Marik et al. 2010). At a molecular level, many synaptic proteins are markedly up- or downregulated following bilateral whisker trimming (Butko et al. 2013). All of these results are assumed to be an activity-based reorganization of the cortical representation that develops under the influence of experimentally regulated cortical neural activity patterns. These cellular deficits are assumed to underlie the behavioral acuity deficits observed in bilaterally whisker-trimmed rats for 2 mo after birth (Carvell and Simons 1996). By historical accident, behavioral deficits traditionally have been tested following bilateral whisker trimming, while the physiological response alterations assayed to explain the behavioral deficits have often followed unilateral whisker trimming. The assumption was that the two rearing conditions produce identical deficits in cortical function. Current evidence does not support this assumption (Popescu and Ebner 2010).

Unilateral sensory deprivation is a widely studied type of sensory deprivation in rodents, but no one has determined the effect of unilateral deprivation (UD) on the development of spike synchrony in barrel cortex. UD has been shown to degrade cortical circuit properties, especially neural transmission from layer IV to layer II/III (Bender et al. 2003; Rema et al. 2003; Shepherd et al. 2003). Importantly, bilateral whisker deprivation (BD) has been shown to produce dramatically different deficits in the magnitude of responses in barrel cortex compared with those found after UD. Following BD, there is a widespread decrease in magnitude and increase in onset latency of stimulus-evoked neural firing, while UD shifts sensory activation from barrel columns to septal columns around barrels tested both in vivo (Popescu and Ebner 2010) and in vitro

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(Shepherd et al. 2003). Anatomically, UD can lead to an increase in spine density in some locations (Vees et al. 1998), as well as the atypical appearance of inhibitory synapses on dendritic spines (Micheva and Beaulieu 1995b). On the other hand, BD does not produce a significant decrease in spine numbers and spine head diameter (Briner et al. 2010).

In the present study, we analyzed the effect of unilateral whisker trimming of rats for the first 2 postnatal mo on correlated discharge of neurons in barrels and septa of the mature rat barrel cortex. During this period, cortical circuits progress from few synapses in cortex at birth to what should be the full adult complement of cortical synaptic circuitry. Previously, almost all studies related to sensory deprivation have been focused on changes in receptive field architecture, response magnitude, and latency of the neurons. The effect of BD on spike timing and correlation between neurons showed that there are severe deficits in correlated discharge among adult barrel cortical neurons (Ghoshal et al. 2009). Several theories of cortical coding include correlated discharge (neuronal synchrony) within neuronal ensembles as an important component of the neural code (Abbott and Dayan 1999; Eggermont 2001, 2006; Panzeri et al. 2010). The synchrony is degraded more or less throughout all deprived subdivisions of primary sensory cortex following BD (Eggermont 2007; Ghoshal et al. 2009). Thus the results from BD support the conclusion that, like the firing rate properties of neurons, the development of spontaneous spike synchrony is also activity dependent in rat cortex. The effects of BD are shown diagrammatically in Fig. 1, illustrating that activity in all major inputs to the developing cortex are suppressed, including inputs from ipsilateral somatic sensory thalamic nuclei and commissural activity from the contralateral hemisphere.

Based on the differences between UD and BD outlined above and from previous work from our laboratory on firing rate properties (Popescu and Ebner 2010), we tested the hypothesis that the effect of UD on the development of correlated discharge in neural circuits of barrel cortex also would be significantly impaired. Since UD is characterized by normal thalamic activity driving one hemisphere and extremely reduced thalamocortical activity providing inputs to the deprived (analyzed) hemisphere, we further predicted that subareas in the deprived hemisphere (e.g., the septum) receiving more conspicuous inputs from the nondeprived (active) hemisphere may develop a different profile of spike synchrony than areas that do not (e.g., layer IV barrels).

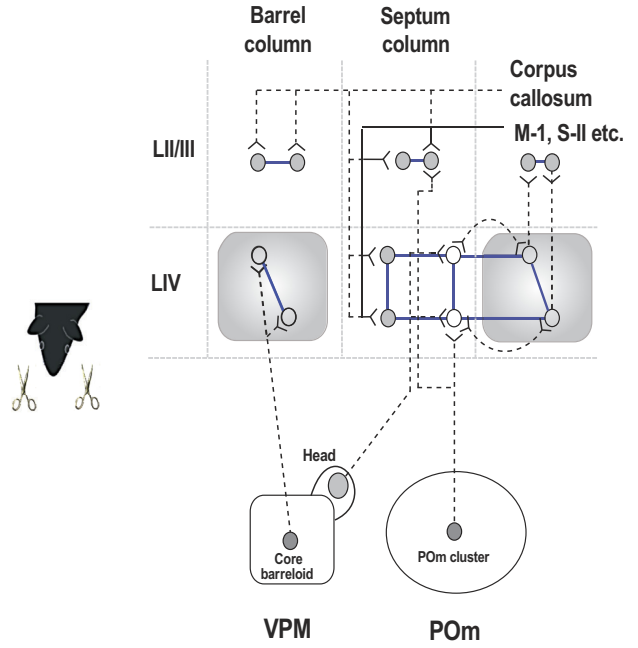


Fig. 1. Effects of bilateral whisker deprivation (BD) that generate an hypothesis for the effects of unilateral deprivation (UD). Previous studies showed that bilateral postnatal whisker trimming results in a pronounced decrease in cortical synchrony. Trimming the whiskers on both sides of the face decreases early sensory activity in both hemispheres. The resultant global low activity during development reduces both the direct thalamic input activity and the activity arising in the contralateral hemisphere conveyed via the corpus callosum. This schema of barrel cortex illustrates the global reduction of inputs during BD (dashed lines) and some of the remaining inputs whose activity levels are unknown under conditions of bilateral whisker trimming (M1, S2, and others). The initial sensory circuits in cortex formed in layers IV and II/III are emphasized in these studies because previous studies have shown strong effects of deprivation in these layers. Since UD silences the direct thalamic inputs to barrel cortex, leaving the commissural activity intact, we tested the hypothesis that UD would produce different changes from BD, with the prediction that synchrony would be preserved in the commissural input zones of barrel cortex. The solid colored lines code the level of correlation strength observed between neuronal pairs after BD, with blue lines signifying low-spike synchrony. VPM, ventral posterior medial nucleus; POm, medial division of the posterior nucleus.

## MATERIALS AND METHODS

All of the experiments performed for this report were approved by the Vanderbilt University Animal Care Committee (Institutional Animal Care and Use Committee) and were in accordance with the guidelines of the National Institutes of Health and the Society for Neuroscience. The animals were housed in an Association for Assessment and Accreditation of Laboratory Animal Care-approved animal facility.

*Sensory deprivation.* Eight Long-Evans rat pups were used in this study, two each from four different litters. Of these, four had all their whiskers cut to the level of the guard hairs only on the right side of the face (whisker-trimmed, a.k.a., unilaterally deprived group, or UD), and four animals were handled the same number of times but not whisker trimmed (whiskers intact, a.k.a., control or CON group). The CON animals are the same animals that were used in Ghoshal et al. (2009), as they were handled and recorded simultaneously with the UD group. In addition, data from the bilaterally whisker-trimmed rats (BD rats) used in Ghoshal et al. (2009) were reanalyzed (data from layer II/III not shown in Ghoshal et al. 2009) for comparison purposes. Whiskers were trimmed to the level of the fur using a head worn loupe for close observation for 60 days beginning at birth: the first 30 days (when the whisker growth rate was faster) the whiskers were trimmed every day, while after postnatal *day 30* the whiskers were trimmed every other day. The whisker-trimmed animals were easily identified for retrimming by having only whisker stubs on one side of the face. During preweaning whisker trimming, the dams nursed the whisker-trimmed UD pups in the same cage with their CON littermates: the dam was removed from the cage before handling the pups. After weaning, same-sex animals were housed in groups of three to five animals, depending on their size. Five days before recording sessions, the whiskers were allowed to regrow to a length sufficient for stimulation without moving the fur, at which time the animals were fully mature (250–350 g, ~2 mo old).

*Surgery and recording.* Surgery and recordings were carried out under urethane anesthesia (1.5 g/kg ip, 30% solution), as described in Ghoshal et al. (2009). In short, we used sets of three quartz glass insulated, platinum/iridium microelectrodes having 2–6 MΩ resistance (Thomas Recording) that were advanced into cortex 305 μm

apart. The electrodes entered through a small opening in the skull and dura, and the neurons analyzed were separated by at least 100 $\mu$m in depth below the cortical surface to reduce the probability of recording twice from the same unit. The recording depth was measured online by Eckhorn microdrive readings. Neurons recorded from 100- to 400-$\mu$m depth from the surface of the brain were considered to be located in LII/III, whereas the neurons recorded from 400–800 $\mu$m from the pial surface were considered to be located in L-IV (Li et al. 2005). The depth locations were later correlated with histological reconstructions of electrode tracks containing microlesions. In all rats, data were collected simultaneously from the three electrodes from each depth. On an average, two to four neurons were recorded from each electrode and were separated into groups according to the histological location of the penetration (Fig. 2). For within-barrel (B-B), above-barrel (AB-AB), within-septa (S-S), and above-septal (AS-AS) groups, neurons recorded from a single electrode were used for analysis, whereas, for barrel-septum (B-S) and above-barrel-above-septum (AB-AS) groups, neuronal pairs from adjacent electrodes were used for analysis. The multiunit analog waveforms were acquired by a Plexon MAP system, digitized at 40 kHz, and stored for offline sorting and analysis. Responses to deflection of each whisker tested were recorded for each vertical location in each penetration. Throughout the experiment, the animals were maintained at stage III, level 3, of anesthesia (Friedberg et al. 1999) using a 10% supplementary dose when necessary. Recording was discontinued when spindling activity was present in the cortex and resumed only after spindling was suppressed by additional anesthesia.

*Whisker stimulation.* Prior to physiological recording, the whiskers in both CON and UD animals were trimmed to just beyond the fur (~5 mm) to keep stimulus distance equal in all animals without moving the guard hairs. We used the same stimulus parameters as in Ghoshal et al. (2009): namely, a piezoelectric stimulator was used to deliver a train of 100 stimuli in a caudal direction at 0.5 Hz, with 600-$\mu$m deflections, 4-ms stimulus duration, and 2-ms rise time using a custom rounded-peak waveform compiled on a DS8000 stimulator (World Precision Instruments) to suppress whisker oscillation. A short wire glued to the end of the piezoelectric wafer was placed as close as possible to the tip of the whisker before stimulation began.

*Histology.* At the end of each recording session, the electrodes were moved to 700 $\mu$m below the pial surface, and electrolytic lesions were produced using a DC current of 1 $\mu$A for 2 min to preserve the insulation on the electrodes. This produced a clearly visible white sphere in cytochrome oxidase (CO) stained, tangential sections of flattened rat brain cortex and was used to assign the electrode penetrations to a barrel or septal column. Lesion depth, in conjunction with microdrive readings during recording and CO chemoarchitecture, was used to assign units to specific locations. Standard histological procedure was used at the end of each experiment: namely, the animals were given a lethal overdose of anesthesia and transcardially perfused using PBS buffer followed by 4% paraformaldehyde in buffer. The fixed brain was removed and postfixed at least overnight before flattening the hemisphere and sectioning at 40 $\mu$m tangential to the cortical surface. Sections then were processed for CO (Wong-Riley 1989).

*Data analysis.* The dataset for CON groups used in Ghoshal et al. (2009) were reanalyzed to compare with the UD group, since the datasets from the UD rats were obtained at the same time as those of the CON rats. The UD and the CON rats were also handled at the same time, and the experiments were performed at the same time as well. Analysis of the supragranular layers of the BD rat dataset that was used in Ghoshal et al. (2009) was not published and is used here for comparison purposes. Moreover, the raw data used for spike synchrony analysis in this paper is the same as the raw data that was collected for the previously published article (Popescu and Ebner 2010), where it was analyzed for firing rate properties. The analysis was restricted to granular layer IV and supragranular layers II/III because the literature indicates that these layers are most affected by deprivation (Bender et al. 2003; Rema et al. 2003; Shepherd et al. 2003). The digitized waveforms obtained from both groups were sorted and analyzed for spike time synchrony using the joint post-stimulus time histogram (JPSTH) method as described in Ghoshal et al. (2009). In short, offline cell sorting was performed using Offline Sorter (Plexon). For each electrode, only cells well separated as three-dimensional clusters and with qualitatively distinctly different waveform shapes were selected for further analysis. We identified the principal whisker as the one that clearly elicited the highest magnitude of response from barrel cells for the B-B and AB-AB locations, and that whisker was stimulated for analyzing synchrony. For B-S and AB-AS pairs, the correlations were computed only on the data collected after the PW stimulation of the barrel neuron in the pair. For the S-S pairs, the best whisker from multiple whiskers was used for the peak correlation coefficient (PCC) analysis and cumulative histograms (see Fig. 4). Only when comparing between "stimulus-evoked" vs. "spontaneous" spike coincidence in the within-septum and above-septum pairs (see Fig. 5) were the stimulus-evoked correlations from all whisker stimulation averaged, and that averaging resulted in

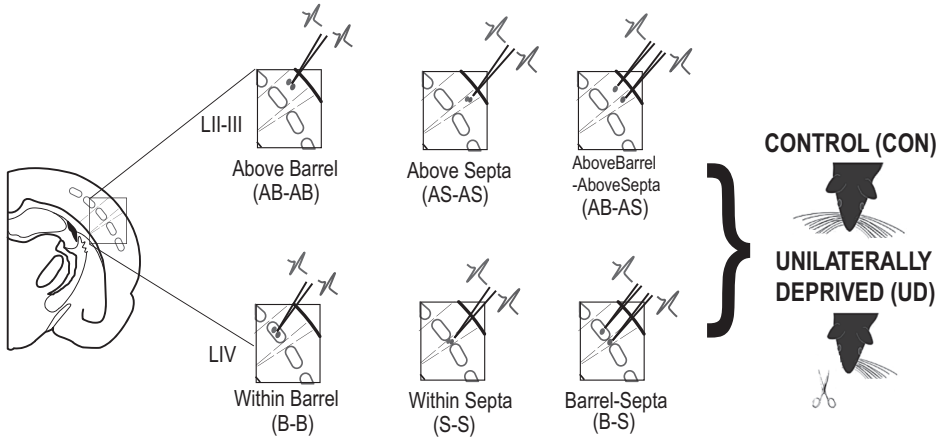


Fig. 2. Experimental design. Pairs of neurons were recorded from control (CON) and UD rat barrel cortex. The simultaneously recorded neuronal pairs were divided into 6 groups based on their location. Neurons recorded from LII/III of a barrel and adjacent septal column were considered as above-barrel (AB-AB) and above-septum (AS-AS) locations. In the above-barrel correlated with above-septum condition (AB-AS), one neuron was located in LII/III of a barrel column, and the other in LII/III of an adjacent septal column. Similarly, when pairs of neurons were recorded in a L-IV barrel or septal column, they were considered as both within a barrel (B-B), both within a septum (S-S), or one in a barrel and another in a septum (B-S) condition. As shown in the figure, neuronal pairs for the B-B, AB-AB, S-S and AS-AS groups were recorded from a single electrode, whereas neuronal pairs for the B-S and AB-AS groups were recorded from 2 adjacent electrodes.

Table 1. *Distribution of different neuronal pairs in L-IV samples*

| | B-B | | | S-S | | | B-S | | |
|---|---|---|---|---|---|---|---|---|---|
| | FS-FS | FS-RS | RS-RS | FS-FS | FS-RS | RS-RS | FS-FS | FS-RS | RS-FS |
| CON | 12 | 48 | 18 | 17 | 64 | 21 | 31 | 58 | 36 |
| UD | 7 | 30 | 13 | 7 | 62 | 33 | 24 | 70 | 55 |

CON, control; UD, unilateral deprivation; B-B, within-barrel; S-S, within-septa; B-S, barrel-septum; FS, fast spiking; RS, regular spiking.

demonstrating a significant septal neuron response. Poststimulus time histograms were constructed using a custom NEX script (provided by Dr. Alexander Kirillov, NEX Technologies, Littleton, MA) and custom software (using MathWorks). JPSTHs were constructed using the methods described by Gerstein and colleagues (1989) using a bin size of 10 ms. Ten-millisecond bins allowed us to analyze coincident discharge over time, especially for the period of relatively low firing during background or so-called "spontaneous" activity. The correlation coefficients were extracted by subtracting the mean values of spike numbers for each neuron in the pair: $\delta n_i^{(k)}(\mu) \equiv n_i^{(k)}(\mu) - \langle n_i(\mu)\rangle$ and $\delta n_j^{(k)}(\nu) \equiv n_j^{(k)}(\nu) - \langle n_j(\nu)\rangle$, respectively, where $n_i^{(k)}(\mu)$ and $n_j^{(k)}(\nu)$ are the numbers of spikes for each time bin across each trial $k$ of each neuron ($\mu$ and $\nu$), and where $\langle n_i(\mu)\rangle$ and $\langle n_j(\nu)\rangle$ are the mean values of spikes in each bin ($i$ and $j$) for each cell ($\mu$ and $\nu$). So that the unconnected part of the correlation is defined as: $\langle \delta n_i(\mu)\delta n_j(\nu)\rangle \equiv \langle n_i(\mu)n_j(\nu)\rangle - \langle n_i(\mu)\rangle\langle n_j(\nu)\rangle$.

When normalized, this value becomes a coefficient of correlation, having values ranging from −1 to +1 (Gerstein et al. 1989). To test the reliability of the normalized JPSTH, we calculated the "shuffled" and "simulated" JPSTHs (Ghoshal et al. 2009). The shuffled JPSTH was generated by shuffling the order of the trials for one of each pair of neurons. The simulated JPSTH was performed on a series of trials with spike trains derived from a nonhomogeneous Poisson process with the rate derived from the actual average spike density function of the neuronal pair. So, for each 1-ms interval we drew a random sample from the uniform distribution [0,1]. If, and only if, the sample was less than the normalized average spike density function value at that interval would a simulated spike be counted. Fifty simulated trials generated from the average spike density function for each pair of neurons was used to calculate the simulated JPSTH. Only pairs showing no correlation for the shuffled and simulated JPSTHs were considered for further analysis. JPSTHs were constructed to determine the correlation coefficient of neuronal spike synchrony between pairs of neurons in CON and UD rats. For each group, the PCC observed between the neuronal pairs in the normalized JPSTH was compared with the simulated PCC and also with the shuffled JPSTH using the paired $t$-test. Only neuronal pairs that had significantly different normalized PCCs than either the simulated or the shuffled PCCs were considered for further analysis.

For each rat group and recording location of neuronal pairs, the average coincidence was calculated from the coincidence histogram in an epoch immediately following the whisker stimulus (0–50 ms, the "stimulus-evoked" epoch), representing the stimulus-evoked response dynamics. Since, in rat barrel cortex, responses of single neurons are back to baseline in roughly 100 ms after a single 4-ms whisker deflection (Armstrong-James et al. 1993), we characterized the average coincidence of a late epoch using 1,950- to 2,000-ms poststimulus as representative of an "essentially spontaneous" background firing period. In a final analysis, the average coincidences were then compared across the early and late epochs within and between barrel and septal locations in each group.

*Statistical analysis.* The nonparametric Wilcoxon rank-sum test was used to determine significant differences (with a critical $P$ value of 0.05) between the cumulative distributions of PCCs. One-tailed unpaired Student's $t$-tests were performed to compare the means of the two rearing groups. Paired one-tailed Student's $t$-test was performed to find the significance of the normalized PCC over simulated and shuffled coefficients and to analyze the difference between the PCC during the early response period and the relatively spontaneous late response epoch. For comparisons between response period and spontaneous periods for CON and UD rats, Bonferroni's correction was applied using a more stringent $P$ value of 0.0125 (0.05/4 comparisons). The $P$ values were rounded to two decimal places, whereas the PCCs were rounded to four decimal places in all cases.

## RESULTS

*Spike synchrony among neuronal pairs in barrel cortex.* Simultaneously recorded pairs of neurons from UD and CON animals were segregated into six groups (Fig. 2), depending on their location in LII/III or L-IV and their location in a barrel or septal column. JPSTHs were constructed to calculate normalized correlation coefficients following the same principle described by Gerstein et al. 1989 (see MATERIALS AND METHODS). In general, the PCCs observed between pairs of barrel cortex neurons in the cross-correlograms were sharp and generally had a time lag close to 0. Moreover, the cross-correlograms did not show oscillations, but periodic fluctuations were seen occasionally in the coincidence histograms. Neurons were also analyzed for their waveform length and grouped into fast spiking (FS; waveform length <750 μs) and regular spiking (RS; waveform length >750 μs). Under our recording conditions, the most common combination was RS-FS neuronal pairs, with a small percentage of RS-RS pairs and even fewer FS-FS pairs. The entire distribution is displayed in a tabular form in Table 1 (L-IV) and Table 2 (LII/III).

Figure 3, *A* and *B*, displays two examples of CON and UD JPSTHs constructed from pairs of neurons located in the supragranular layers of a septal column (a.k.a. "above-septum" location, Fig. *3A*), or a pair of neurons in a barrel (a.k.a. "within-barrel" location, Fig. 3*B*). Figure *3A* (*left*) shows that two above-septal neurons from a CON rat have significant and sharply correlated discharge at 0 lag with a PCC of 0.1325. Figure 3*A* (*right*) shows the correlation of a pair of above-septum neurons from an UD rat. The neurons were in an equivalent location within a supragranular septal zone and showed similar response magnitudes compared with those of the CON neurons: however, they fire synchronously much more often as observed in the JPSTH matrix (frequent correlation occurrences in the diagonal color-coded yellow/red), as well as the coincidence histogram (higher coincidence across time) and in the cross-correlogram peak value (higher peak with a PCC of 0.2725).

In contrast, Fig. 3*B*, *left*, shows the JPSTH of a pair of L-IV barrel neurons in a CON rat with a PCC of 0.1993, and there are negligible differences in the degree of correlated discharge

Table 2. *Distribution of different neuronal pairs in LII/III samples*

| | AB-AB | | | AS-AS | | | AB-AS | | |
|---|---|---|---|---|---|---|---|---|---|
| | FS-FS | FS-RS | RS-RS | FS-FS | FS-RS | RS-RS | FS-FS | FS-RS | RS-FS |
| CON | 2 | 19 | 8 | 0 | 74 | 46 | 7 | 29 | 28 |
| UD | 2 | 18 | 9 | 0 | 79 | 41 | 9 | 24 | 31 |

AB-AB, above-barrel; AS-AS, above-septal; AB-AS, above-barrel-above-septum.

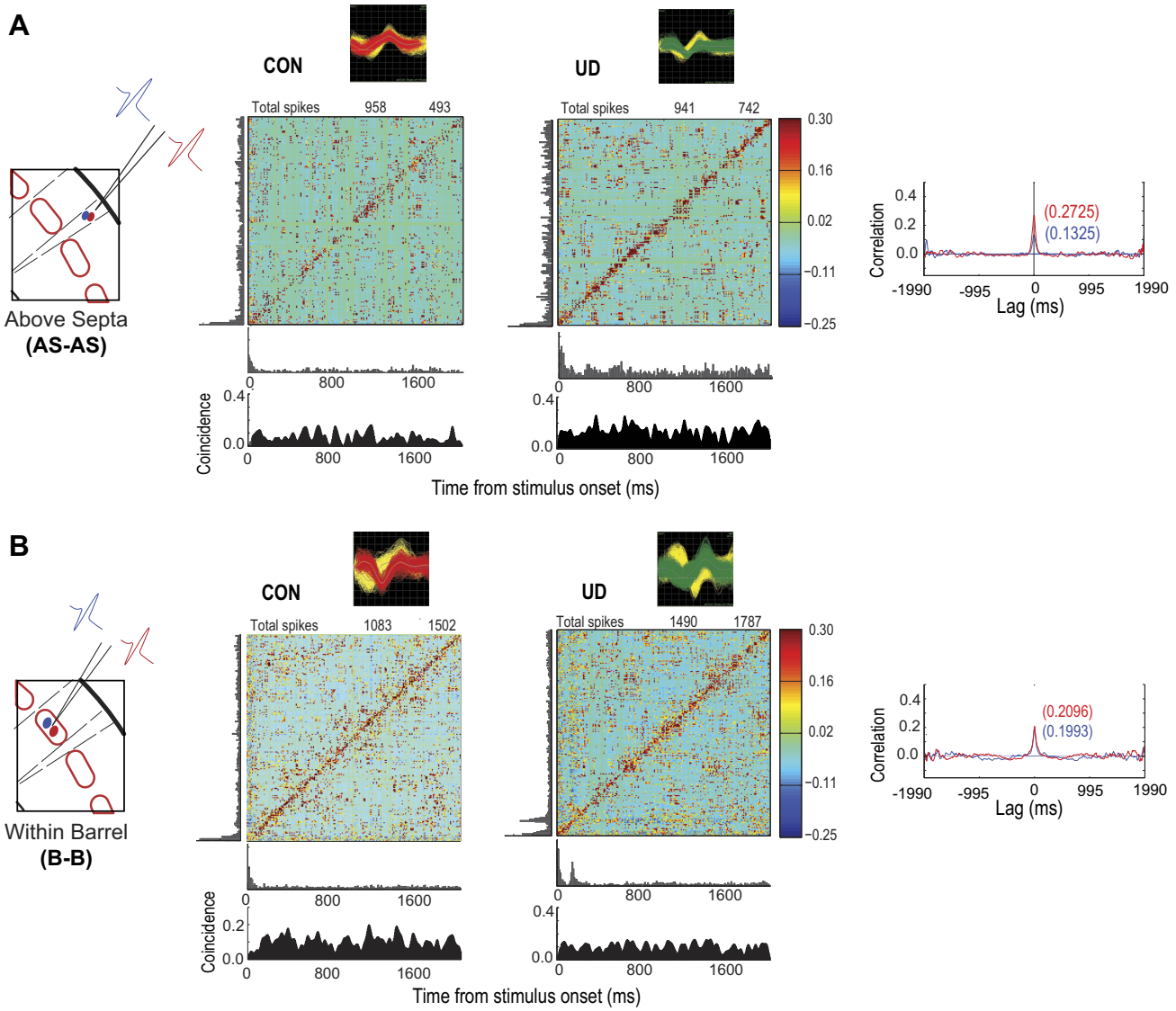


Fig. 3. Typical examples of joint poststimulus time histogram (JPSTH) cross-correlograms. By plotting the time of discharge of two neurons as two poststimulus time histograms on the *X*- and *Y*-axis of a JPSTH matrix, the time and frequency of simultaneous discharge can be calculated and displayed as a cross-correlogram (green background). The poststimulus time histogram (PSTH) for each cell is displayed along the *X*- and *Y*-axis, with the average coincidence over time histogram beneath each JPSTH. In *A*, the two neurons are in LII/III above a septum; and, in *B*, the neuronal pair is located within a single L-IV barrel. The degree of cross-correlation is color coded as shown on the right. Simple examination of the levels of synchrony shows a red diagonal line, indicating that correlated discharge is higher at 0 offset (simultaneous discharge) after UD. In the cross-correlogram on the *right*, the red trace summarizes the UD correlations, while the blue trace summarizes the CON. The peak correlation coefficient calculations for CON and UD are indicated in parentheses in the cross-correlograms. In this example, there is a noticeable increase in spike synchrony above-septa, but not within-barrels after UD.

for a pair of UD barrel neurons (Fig. 3*B*, *right*: PCC of 0.2096). Overall, there was an increase in spike synchrony observed in the UD barrel cortex in all locations tested, except among cells in the L-IV barrel. The greatest increase induced by UD rearing (compared with the CON rats) was observed in the supragranular layers of septal columns.

*Changes in neuronal spike synchrony in the barrel column after UD.* JPSTHs were constructed for 107 CON and 79 UD neuronal pairs that were located in a column of cells in or above a barrel. Of these pairs, 29 CON and UD neuronal pairs were located in the supragranular layers above a barrel (AB-AB pairs) and 78 CON and 50 UD pairs were located within a L-IV barrel (B-B pairs). Figure 4 displays cumulative distributions of the CON (solid line) and UD (dashed line) PCCs for AB-AB (Fig. 4*A*) and B-B pairs (Fig. 4*D*). With UD, there is an obvious and significant shift to the right in the level of correlated discharge between PCCs of AB-AB pairs compared with CON pairs in the same layers ($P = 0.003$, Wilcoxon nonparametric test), indicating that neurons in the supragranular layers of UD barrel cortex fire more synchronously than comparable neurons in normal barrel cortex. Overall, there was an 87% increase of the mean PCC for UD AB-AB pairs compared with the CON group. In contrast, the PCCs of B-B pairs between CON and UD rats were not significantly different ($P = 0.071$, Wilcoxon nonparametric test), indicating that unilateral whisker trimming during the postnatal, developmental, synaptogenesis period does not change the level of correlated discharge within the deprived barrel domains. Changes in AB-AB pairs following BD is displayed in Fig. 6*A*.

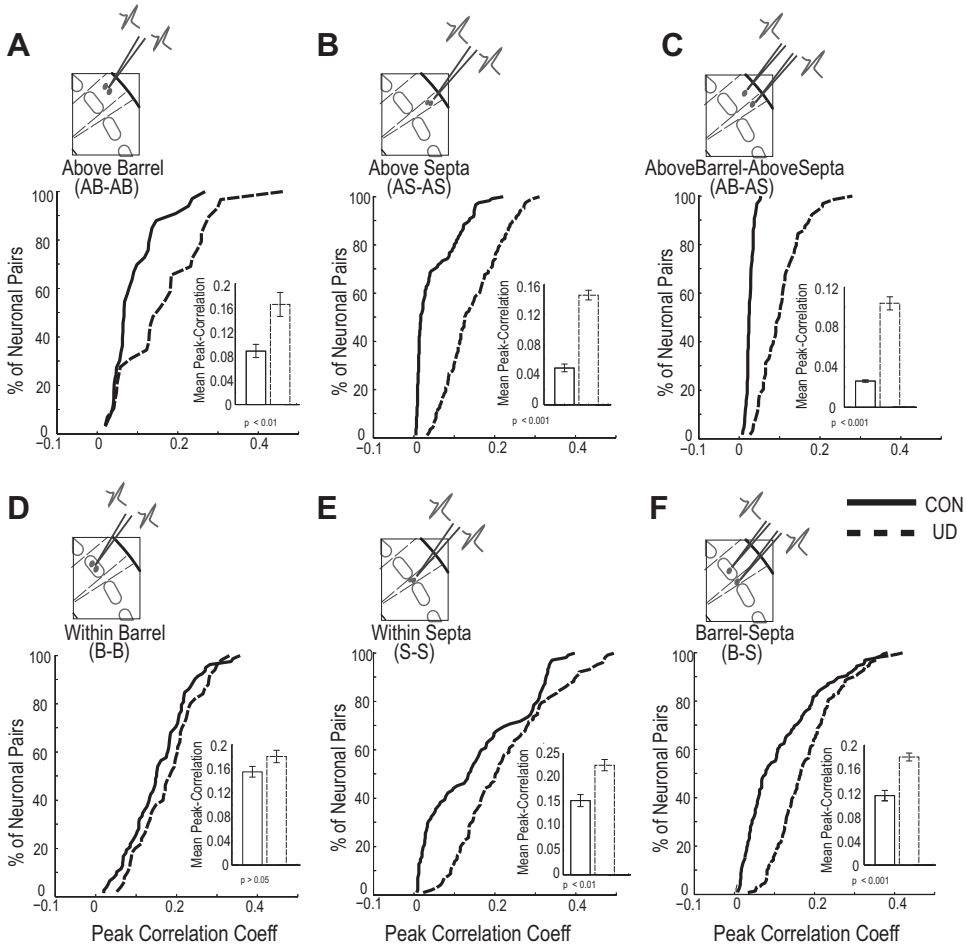


Fig. 4. Population (cumulative) distributions and mean values of peak correlation coefficients for CON and UD rats in each location. Cumulative distributions of peak correlation coefficients are displayed for the CON (solid line) and UD (dashed line) rats when calculated for neuron pairs located in the supragranular (above-septum or above-barrel; *A* and *B*) or granular layers (*D* and *E*). The distribution for correlation coefficients for one cell located in or above a barrel and another in or above a septal column are displayed in *C* and *F*. Each panel includes the mean value as a bar graph for CON (*left*) and UD (*right*) (±SE). The *inset* pictogram shows the recording location of each distribution. Overall, there is a significant increase in correlation strength with UD for all neuron pairs, except for the B-B pairs. [Note: the L-IV control data were reused in this figure from Ghoshal et al. (2009) with permission.]

*Changes in neuronal spike synchrony in septal columns after UD.* Spike synchrony was also calculated for neuronal pairs located in septal columns of CON ($n = 222$) and UD rats ($n = 222$). The neuronal pool in the septal column was also subdivided on the basis of their laminar location, and JPSTHs were calculated for 120 CON and 120 UD neuronal pairs located in LII/III above a septum (AS-AS pairs) and for 102 CON and 102 UD septal pairs in L-IV (S-S). Figure 4, *B* and *E*, shows the cumulative distributions of the CON (solid line) and UD (dashed line) PCCs for AS-AS (Fig. 4*B*) and S-S pairs (Fig. 4*E*). After UD, there is a striking increase in correlated discharge in both LII/III ($P < 0.001$, Wilcoxon nonparametric test) and L-IV ($P < 0.001$, Wilcoxon nonparametric test) of a septal column, as indicated by the range of PCCs in the cumulative distributions. The mean PCC increases by ~200% in UD above septum locations and by 48% in the L-IV septum locations compared with the CON group. Changes in AS-AS pairs after BD is displayed in Fig. 6*B*.

*Changes in synchronized discharge between barrel and septal columns after UD.* JPSTHs were also constructed between neuronal pairs recorded from two electrodes, one of which was located in a barrel column, and the other in an adjacent septal column in CON and UD rats. Figure 4*C* displays the PCC cumulative distribution of CON and UD B-S pairs, specifically when both the neurons were located in the supragranular layers (AB-AS pairs; CON and UD: $n = 64$). The AB-AS correlations are extremely low in CON cortex, but are significantly increased after UD ($P < 0.001$, Wilcoxon nonparametric test). There is a roughly 300% increase in the mean PCC of AB-AS pairs after UD compared with the CON. UD also led to an increase in spike synchrony in the L-IV B-S pairs (CON: $n = 125$; UD: $n = 149$), as shown by the cumulative distributions in Fig. 4*F*. The B-S pair increase in the UD group is highly significant ($P < 0.001$, Wilcoxon nonparametric test of cumulative distributions) with an overall increase of ~56% in the mean PCC compared with the CON group. Thus there is an overall increase in correlated discharge between a barrel column and its adjacent septal column after UD. Changes in B-S pairs after BD is displayed in Fig. 6*C*.

*Differences in neuronal spike synchrony during an early stimulus-evoked period and a later spontaneously active period.* The JPSTH analysis described above was carried out in the entire 2,000-ms window, which encompasses both the stimulus-driven as well as the relatively spontaneously active period of the neuronal pairs. To investigate whether the changes in spike synchrony that were observed with UD were particular to the stimulus-driven period or the spontaneously active period, we calculated the average coincidence during the stimulus-evoked period (0- to 50-ms poststimulus) and a spontaneously active period (1,950- to 2,000-ms poststimulus; just prior to the next stimulus). Figure 5 summarizes the average coincidence in the stimulus-evoked and spontaneously active period. Solid line bars are from the stimulus-evoked period, and dashed line bars from the spontaneously active period. Figure 5 compares the average coincidences within and between the CON and UD rats in the different locations within

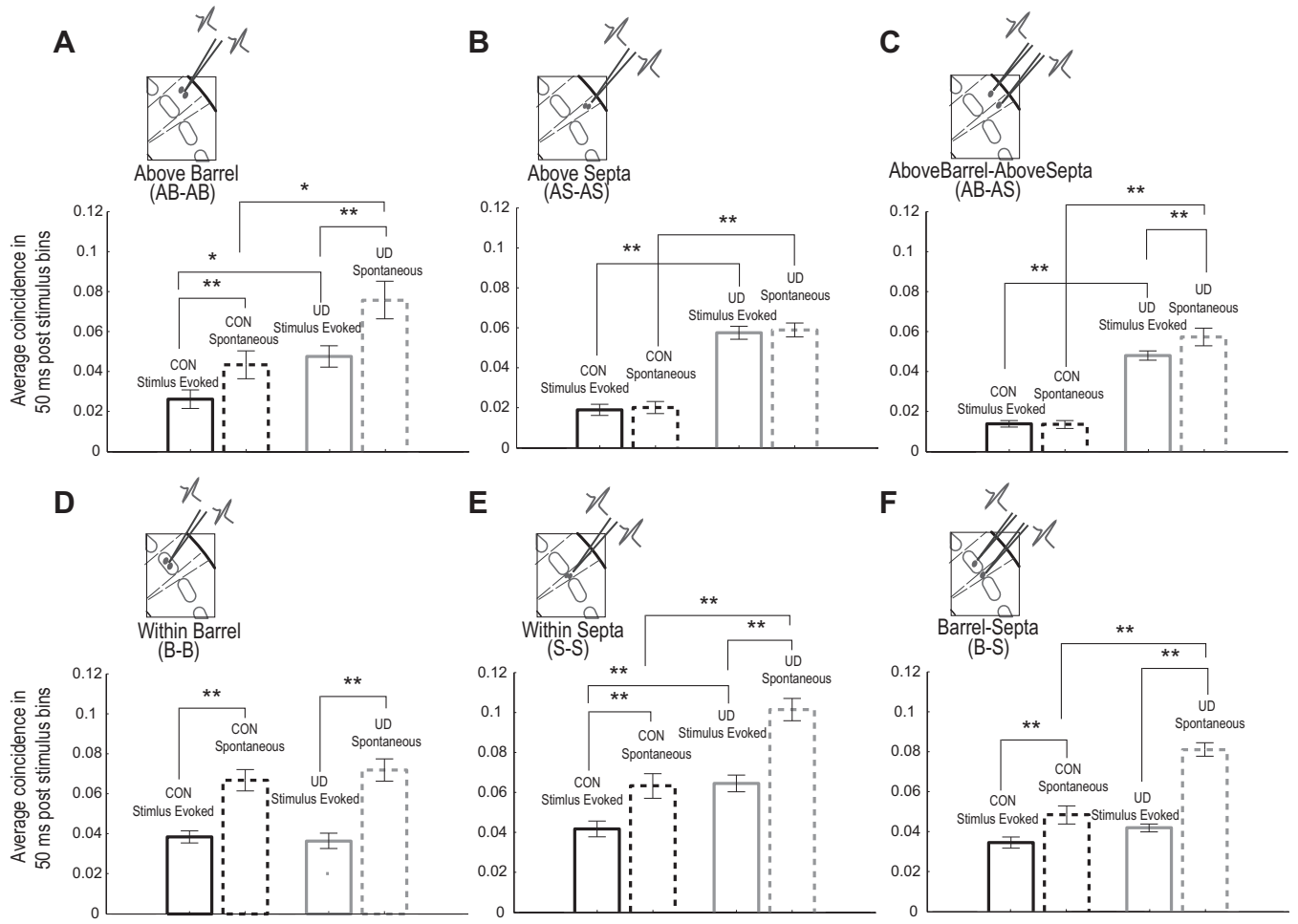


Fig. 5. Average spike synchrony during evoked response periods compared with relatively spontaneous epochs for CON and UD rats. Comparison is shown of the average coincidence of spikes in neuronal pairs in the first 50 ms poststimulus (solid bars; a.k.a. stimulus evoked period) and the "last" 50 ms or 1,950–2,000 ms poststimulus (dashed bars; "spontaneous" period) after principal whisker stimulation in CON (black bars) and UD (gray bars) rats. *A*: AB-AB. *B*: AS-AS. *C*: AB-AS. *D*: B-B. *E*: S-S. *F*: B-S. Above barrels, there is a significant reduction in correlation strength in the CON-evoked response period compared with the spontaneous period, and between CON and UD conditions. The increase in synchrony after UD is evident in both the stimulus-evoked, as well as the spontaneous period. There is an increase in stimulus-evoked coincidence for UD compared with CON rats for all neural pairs, except the B-B (*D*) and B-S (*F*) pairs. On the other hand, an increase in coincidence in the relative spontaneous periods is observed after UD for all areas of barrel cortex, except in L-IV barrels (*D*). Error bars represent SE. $^{**}P < 0.001$. $^{*}P < 0.01$. [The L-IV CON data are from Ghoshal et al. (2009) with permission.]

barrel cortex. The CON rats showed a reduction in PCC during the stimulus-evoked epoch in L-IV B-B, S-S and B-S pairs compared with the PCCs during the spontaneous periods (Fig. 5, *D*, *E*, and *F*; $P < 0.001$ for all, Ghoshal et al. 2009). However, in the supragranular layer of CON rats, only the AB-AB pairs showed this reduction (Fig. 5*A*, CON 0: 50 ms vs. 1,950–2,000 ms, $P < 0.001$). The AS-AS ($P = 0.03$) and AB-AS ($P = 0.481$) neuronal pairs failed to show this significant reduction (Bonferroni's correction; $P > 0.0125$; Fig. 5, *B* and *C*). In UD rats, the stimulus-evoked coincidence was also significantly lower than that of the spontaneous period for the L-IV B-B, S-S and B-S pairs (Fig. 5, *D*, *E*, and *F*, $P < 0.001$). In LII/III, only AB-AB and AB-AS pairs showed significant reduction of coincidence with the response compared with the spontaneous epochs [$P < 0.001$ for both; $P > 0.0125$ (=0.022) for AS-AS; Fig. 5, *A* and *C*]. The increase in neuronal coincidence with UD compared with CON rats was observed in the response period for the septal pairs in L-IV ($P < 0.001$; Fig. 5*E*) and the AB-AB ($P = 0.003$), AS-AS ($P < 0.001$) and AB-AS ($P < 0.001$) in LII/III (Fig. 5, *A*–*C*). Finally, with UD, the average coincidence in spontaneous epochs was increased in all areas of barrel cortex except L-IV barrels compared with CON rats (S-S, B-S, AB-AS, AS-AS: $P < 0.001$; AB-AB: $P = 0.0070.01$; B-B: $P = 0.532$; Fig. 5). Overall, UD produced similar changes in spike synchrony in both the stimulus-driven and spontaneous epochs.

## DISCUSSION

The present results show that UD rearing produces complicated alterations in the coincident discharge of neurons in identified locations within the barrel cortex. The results provide clear evidence that 2 mo of UD experience, a period spanning the onset, peak, and end of the activity-dependent critical period (peak is between 7 and 21 postnatal days) alters the neuronal synchrony that normally develops between neurons in specific cortical circuits. Unilateral whisker trimming produced a significant increase in the amount of coincident discharge in all regions of the barrel cortex, except in the sensory input layer IV barrel domains, which unexpectedly developed CON levels of synchrony. The increase in cortical

synchrony between pairs of neurons was evident both in the early whisker stimulus-evoked response epoch and in a late intertrial epoch dominated by spontaneous activity. The maximum increase in synchrony was observed between neurons in the supragranular layers with a PCC increase of ~200% in locations above a septum (compared with CON), and a 300% increase in synchrony between AB-AB to AS-AS pairs of neurons. Using the same dataset, our laboratory (Popescu and Ebner 2010) previously showed that UD leads to an increase in firing rate in all areas of the barrel cortex, except in L-IV barrels. Moreover, both BD and UD produced unique changes in the firing rate properties (magnitude and latency) of barrel cortex (Popescu and Ebner 2010). Thus it can be concluded that altered single-neuron activity and neuronal spike synchrony are both modified to produce the resultant abnormal cortical sensory processing. Moreover, the UD effects are particularly interesting compared with those following BD because the latter led to a reduction of cortical synchrony throughout L-IV of barrel cortex (Ghoshal et al. 2009). The results show that interfering with sensory activity during early postnatal development has a profound influence on the development of neuronal synchrony in barrel cortex.

Following UD, there is a change in neuronal spike synchrony that occurs in parallel with changes in firing rate of single neurons. Since UD leads to increased firing rates in all areas of the barrel cortex except in L-IV barrels (Popescu and Ebner 2010; Shepherd et al. 2003), this is very similar to the distribution of increased spike synchrony we observed following UD. However, the change in firing rate alone cannot account for the observed changes in spike synchrony. First, the JPSTH method corrects for firing rate differences when calculating neuronal synchrony (see MATERIALS AND METHODS; Gerstein et al. 1989), including the response period where there is an expected increase in neuronal firing rate in response to whisker stimulation. Simulated JPSTHs, in addition, calculate anomalous neuronal synchrony levels between two simulated neurons with the same firing rate but different temporal profiles. Second, if the data from both UD and BD are compared, instances can be found in which the changes in firing rate did not predict the changes observed in neuronal synchrony. For example, Popescu and Ebner (2010) showed that, in LII/III above a barrel, there was a significant decrease in the magnitude of firing rate after BD, but there were no significant changes in PCC observed in LII/III of BD or CON pairs (Fig. 6). Taken together, the data indicate that the changes in neuronal spike synchrony we observe after sensory deprivation are, at least in part, independent of the changes observed in firing rate.

Previously, our laboratory showed that the CON L-IV septal PCC distribution contained multiple peaks (Ghoshal et al. 2009), indicating that there are two to three distinct levels of correlated discharge, and only a subset of CON septal cells has a relatively high correlation (with a PCC of >0.15). Frequency distribution analysis revealed that, after UD, there is a change in the distribution of highly correlated L-IV septal neuronal pairs, with a greater percentage of neuronal pairs showing correlation higher than a PCC of 0.15 (data not shown). We then postulated that the high synchrony observed among normal L-IV barrel neurons and one subset of L-IV septal neurons may be imposed by the dominant lemniscal or paralemniscal thalamic inputs from the ventral posterior medial nucleus (VPM) or the medial division of the posterior nucleus (POm) of the thalamus during the developmental critical period (Ghoshal et al. 2009). The subset of L-IV septal cells that showed highly correlated discharge in CON rats could be a subset of neurons that receive their driving input from the "head" subregion of the VPM thalamic nucleus (Furuta et al. 2009). In short, the driving thalamocortical activity during the developmental period may be responsible for the highly correlated activity observed throughout L-IV of barrel cortex, but not responsible for that seen in LII/III. A revised model emerges based on the assumption that thalamocortical activity during development normally shapes the pattern of correlated discharge observed in adult barrel cortex (Fig. 7*A*). The reorganization induced by UD suggests a commissural hypothesis for the variability of neuronal spike synchrony across the different areas and layers in barrel cortex (Fig. 7*B*).

Thus, following UD rearing, sensory activity in both the lemniscal and paralemniscal pathways are reduced in the hemisphere receiving abnormally low activity from the trimmed whiskers. However, normal sensory activity from the intact whiskers on the other side of the face provides normal drive to the contralateral cortex and indirectly activates the deprived hemisphere via the corpus callosum. In this scenario, the

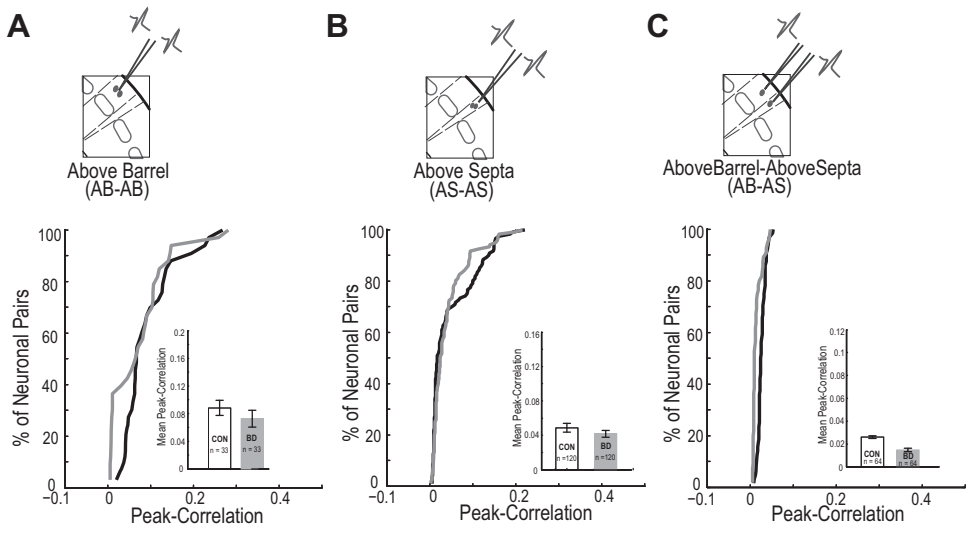


Fig. 6. Cumulative distributions of supragranular neuronal pairs from CON and BD rats. Cumulative distributions are shown of AB-AB (CON and BD, $n = 33$; *A*), AS-AS (CON and BD, $n = 64$; *B*), and AB-AS (CON and BD, $n = 120$; *C*) pairs of CON (black line) and BD (gray line) rats. With BD there is no significant change in correlation strength for the neuronal pair locations in layers II/III. *Inset* bar graphs show the mean (±SE) for each comparison: CON is open bar (*left*), and BD is shaded bar (*right*).

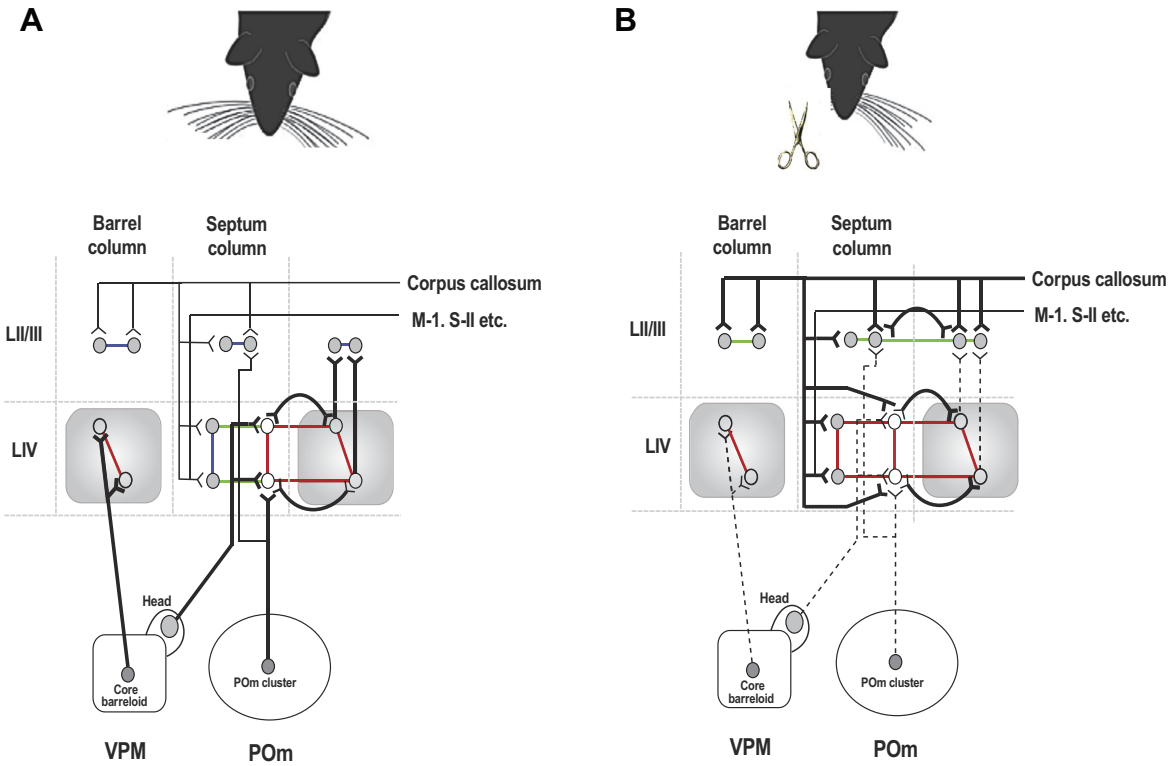


Fig. 7. Model of neuronal spike synchrony development in cortical circuits after CON and UD rearing. *A*: assuming that adult spike synchrony requires repeated volleys of activity during development, active inputs arising from the sensory pathways would provide the dominant activity that leads to high synchrony in L-IV barrels of CON rats. In the L-IV septum, cells receiving inputs from the VPM head cells and/or POm cells drive the subset of septal neurons that develop high levels of correlated discharge. In this construct, the lower correlated septal activity would be normally generated by corticocortical inputs from other cortical areas. *B*: in the UD rats, removal of contralateral whiskers would reduce thalamocortical activity and upregulate the synchrony induced by callosal activity from the normally active hemisphere. That is, the commissural inputs would become the driving circuit for the development of cortical synchrony. Normal activity levels in the callosal inputs would thus be responsible for an increase in correlation strength found in the present study. Heavy black lines indicate known anatomical connections that would be active during UD rearing. The colored lines (red, green and blue) code the level of correlation strength between neuronal pairs, with red highest, green intermediate, and blue lowest.

commissural influence may emerge as the organizing drive in the deprived hemisphere with the initial upregulation being in the septal columns (Popescu and Ebner 2010; Shepherd et al. 2003). Callosal connections between left and right barrel cortex are known to terminate primarily in the supra and infragranular layers, with many fewer terminations in L-IV barrels (Akers and Killackey 1978; Hayama and Ogawa 1997; Ivy and Killackey 1981; Olavarria et al. 1984). Interhemispheric connections are thought to be modulators of bilateral responses in CON animals and appear to develop even higher efficacy in UD rats. The greater efficacy would upregulate the callosal input circuits during the developmental critical period in UD rats and thus would be a logical candidate to account for the sharp increase in spike synchrony within the supragranular layers above both barrel and septal domains of barrel cortex (Fig. 7*B*). In the rat forelimb representation of S1, callosal inputs contact inhibitory neurons preferentially (Pluto et al. 2005), and inhibitory cells are capable of inducing oscillatory activity in cortex (Cardin et al. 2009; Vierling-Claassen et al. 2010). The increase in coincident discharge among neurons in the UD animals that was observed in barrel cortex matched the connection pattern of the callosal inputs, with the callosal-sparse barrels not showing a significant increase in spike synchrony. These findings, therefore, provide further support to the hypothesis that callosal inputs are upregulated when unilateral thalamocortical sensory activity is deficient during the critical period. Moreover, they support the idea that the development of normal cortical synchrony is activity dependent and, therefore, neurons that received the callosal input as the primary input during UD development were more active and thereby may have developed higher synchrony. However, a definitive conclusion about the involvement of callosal inputs in the development of cortical synchrony will require manipulations of callosal input activity during development to directly determine the effect on subsequent neuronal spike synchrony, and such studies have not yet been reported.

Atypical sensory experience during development would be expected to influence the maturation of single-cell and network properties in all sensory systems. Since the classic studies of Hubel and Wiesel, beginning in 1963 (Wiesel and Hubel 1963), the established method for studying cortical function after altered postnatal visual experience has been to block sensory activity from one or both sides of the periphery during critical periods of development. To restrict the deprivation to low activity alone, one or both eyes can be covered during the postnatal period, or the eyelids sutured closed (as distinct from enucleation where the inputs degenerate and the effects cannot be tested later through the deprived pathways). In the rodent whisker pathway, the same distinction is made between surgically removing the whisker pad, cauterizing the whisker folli-

cles or plucking the whiskers from the follicles compared with shortening the whiskers to the level of the fur. Over 50 yr ago, Wiesel and Hubel (1963) reported the effects of monocular sensory deprivation and established in classic studies that there are postnatal "critical periods" during which abnormal monocular sensory experience produces profound deficits in the anatomy and physiology of primary visual cortex, both in cats and primates, that do not occur in adult animals. They compared the effects of monocular deprivation with binocular deprivation (Wiesel and Hubel 1965) and were surprised to find a normal complement of cortical cells in all layers after binocular deprivation, more than one-half of them normally responsive to sensory stimuli. They concluded, "at the cortical level the results of closing one eye depend upon whether the other eye is also closed. The damage produced by monocular closure may therefore not be caused simply by disuse, but may instead depend to a large extent on interaction of the two pathways." An important difference between left and right inputs to visual and somatic sensory cortex is that bilateral inputs lie side by side in each primary visual cortex (ocular dominance columns) and in separate hemispheres in somatic sensory cortex. Since these ground-breaking studies, numerous reports have identified the long-lasting impact of sensory deprivation on magnitude, timing and other cortical circuit properties. Similar comparison difficulties exist with binaural auditory deficits after deprivation (Eggermont 2007; Popescu and Ebner 2010), so that the basic sensory system differences make direct comparisons difficult, given the large number of variables built into deprivation studies: traumatic vs. reversible, complete vs. partial, crossed or bilateral sensory organization, bilateral vs. unilateral, onset of deprivation, duration of deprivation, length of recovery period after deprivation, etc.

Like the visual deprivation studies mentioned above, the changes observed in L-IV after UD were nearly the polar opposite of those after BD. First, following UD, synchrony in L-IV barrels was indistinguishable from that in CONs, but was very significantly reduced following BD. Second, UD led to an increase in highly correlated neuronal pairs in L-IV septa, whereas BD increased the percentage of low-correlation neuronal pairs in the septa. Third, after UD there was a considerable increase in the magnitude of coincident discharge both in above-barrel and above-septal locations, but following BD there were no detectable changes in neuronal synchrony in the supragranular layers of barrel cortex (Fig. 7*A*). Finally, negligible levels of neuronal synchrony were observed in AB-AS pairs in either CON or BD animals. However, after UD robust AB-AS synchrony developed, indicating a possible increase in horizontal connectional strength between barrel and adjacent septal columns in the supragranular layers in UD rats, which are not readily observed in CON rats (Alloway 2008). Such changes with BD only in L-IV can be explained by reduced thalamocortical activity bilaterally and the absence of compensatory activity from a "normal" hemisphere. The clear differences in the single-cell responses (Popescu and Ebner 2010), as well as the ensemble neuronal properties described here between UD and BD, emphasizes how much a primary sensory area is differentially affected by the precise peripheral conditions present during development. The result further emphasizes that neurophysiological evidence from complete or partial whisker deprivation on one side of the face should be interpreted very carefully when comparing deficits that are present after reduction of all whisker activity due to BD rearing.

The hypothetical model (Fig. 7) incorporates most of the changes observed in UD animals. One might expect a reduction in L-IV barrels after UD, since there are no known compensatory anatomical inputs to barrels. Reduction of L-IV barrel activity was found in slice preparations following short-term (postnatal *days 9–14*) UD by Shepherd et al. (2003). However, while Popescu and Ebner (2010) confirmed the shift from normal "barrel-to-above-barrel" to "septum-to-above-septum" transmission after UD, they failed to confirm a reduction in L-IV barrels using in vivo analysis. One possible explanation is that there are compensatory mechanisms occurring at the subcortical level in vivo that prevent the expression of magnitude or cortical synchrony reduction in L-IV barrels, or there could be a failure of barrel cell dendrites to stay within each barrel domain after UD rearing (Harris and Woolsey 1981). Also, active connections from the adjoining upregulated septa could prevent such reductions. With so many alterations in normal circuitry, no single factor can be identified. However, the possibility of exuberant callosal connections spilling over into the L-IV barrels in UD rats cannot be ruled out as an explanation for the absence of reduced synchrony after UD, especially after much longer periods of deprivation in vivo.

Synchrony during the early stimulus-evoked response period (0–50 ms poststimulus) was significantly lower in CON rats than the coincidence measured in a later, relatively spontaneous, period (1,950–2,000 ms poststimulus) for all of L-IV (Ghoshal et al. 2009). This finding correlates with the observation that sensory stimuli actively decorrelate sensory evoked responses (Middleton et al. 2012). Such a relationship occurs in the AS-AS layers in both the stimulus-evoked coincidence and spontaneous period coincidence, but not in AB-AB pairs. It has been postulated that such a reduction in L-IV barrel synchrony following whisker-induced responses could be important for information processing in barrels that depend upon sparse coding (Ghoshal et al. 2009). Since these reductions were absent in L-IV barrel cortex after BD, it was further hypothesized that reduced correlated firing during the response period develops through the influence of the active thalamocortical connections during normal rearing (Ghoshal et al. 2009). Interestingly, although the changes in neuronal synchrony observed with UD were true for both stimulus-evoked and spontaneous coincident discharge, reduction in spike coincidence during the stimulus-evoked period was maintained in the AB-AB neuronal pairs as well as in L-IV. Moreover, the LII/III AB-AS pairs in UD also showed the stimulus-evoked reduction in correlated discharge. This could be a partial explanation for why behavioral disabilities with UD rats are rarely found.

Our results show an upregulation in septal column synchrony after UD, which could be related to the shift from B-to-AB transmission in CON rats to S-to-AS transmission in UD rats (also see Shepherd et al. 2003). This shift in information transfer is postulated to be a consequence of homeostatic plasticity that occurs due to the imbalance of peripheral activity from the ipsilateral intact whiskers vs. the contralateral deprived whiskers as predicted in our hypothesis. Numerous papers show that neurons are equipped with homeostatic mechanisms that allow them to restore their firing rates to CON levels following activity-based changes in firing rate (Burrone et al. 2002; Turrigiano 2007; Turrigiano et al. 1998). This is the

first case of which we are aware that shows that adjustments of the temporal properties in a group of neurons also may be affected by or contribute to such homeostatic mechanisms. Whether such neurophysiological homeostatic mechanisms are the basis of, or important for, the compensatory behavioral skills of UD rats remains to be tested, but our results predict this would be the case.

## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

## AUTHOR CONTRIBUTIONS

Author contributions: A.G., M.V.P., F.F.E., and P.P. conception and design of research; A.G., B.R.L., and M.V.P. performed experiments; A.G., B.R.L., and P.P. analyzed data; A.G., B.R.L., F.F.E., and P.P. interpreted results of experiments; A.G. and B.R.L. prepared figures; A.G. and B.R.L. drafted manuscript; A.G., B.R.L., F.F.E., and P.P. edited and revised manuscript; A.G., B.R.L., M.V.P., F.F.E., and P.P. approved final version of manuscript.

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