Whisker row deprivation affects the flow of sensory information through rat barrel cortex

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NEW & NOTEWORTHY Sensory cortical plasticity is usually quantified by changes in evoked firing rate. In this study we quantified plasticity by changes in sensory detection performance using Chernoff information and receiver operating characteristic analysis. We found that whisker deprivation causes a change in information flow within the cortical layers and that layer 5 regular-spiking (L5RS) cells, despite showing only a small potentiation of short-latency input, show the greatest increase in information content for the spared input partly by a significant decrease in spontaneous activity and an increase in a short-latency excitatory conductance.

SENSORY EXPERIENCE dynamically reshapes cortical receptive fields. Subregions of the receptive field can be strengthened or weakened by altering the balance of sensory drive between competing inputs. In layers 2/3 (L2/3), the nature of receptive field plasticity is known to vary with the type of sensory modification set by the experimenters, but for any given pattern of deprivation, the plasticity is relatively uniform in effect across neurons (Feldman and Brecht 2005; Wallace and Fox 1999). In contrast, we recently found that a row-deprivation pattern can cause nonuniform receptive field plasticity in subtypes of layer 5 (L5) pyramidal cells (Jacob et al. 2012). The two main types of pyramidal cells in cortical layer L5 are known as thick tufted or intrinsically bursting (IB) cells and thin slender or regular-spiking (RS) cells (Chagnac-Amitai et al. 1990; Connors and Gutnick 1990; McCormick et al. 1985). In deprived columns of barrel cortex, spared whisker inputs were potentiated in IB cells together with little depression of deprived inputs, whereas RS cell responses to deprived whiskers were depressed without potentiation of spared input (Jacob et al. 2012).

What mechanisms might be responsible for the different reactions of different cell types to the same deprivation pattern? At the cellular level, these include different capacities between cells for particular synaptic plasticity processes such as long-term potentiation (LTP), long-term depression (LTD), and homeostatic plasticity; at the circuit level, these include the dynamic interaction between cells in different layers of the cortical columns, the relative strength of cortical vs. thalamic input differences, and changes in the balance between excitatory and inhibitory inputs. A previous study in mouse barrel cortex has provided evidence Hebbian and homeostatic mechanisms are recruited to different degrees in L5RS and L5IB cells (Greenhill et al. 2015). In this study we have concentrated on the differences that might arise at the circuit level.

To understand the information flow between layers, we recorded intracellularly from all layers and compared spontaneous activity and receptive fields using both conventional measures of activity (subthreshold inputs and suprathreshold outputs) and analysis of Chernoff information induced by whisker stimulation. We also analyzed response latencies to judge the relative dominance of rapid thalamic vs. slower intracortical inputs after plasticity. Finally, in a separate set of experiments, we measured synaptic conductance of evoked postsynaptic potentials (PSPs) in RS and IB cells as a first step toward understanding whether the excitatory inhibitory balance might be responsible for differing expression of potentiation and depression in IB and RS cells, respectively. Although L5RS cell responses did not potentiate above the baseline value...
METHODS

Subjects and whisker deprivation. Experiments were performed at Cardiff University and were approved under the UK Scientific Procedures Act 1986. Recordings were performed in 37 control and 30 deprived Long-Evans male rats. Animals were lightly anesthetized with isoflurane and had the left D-row of whiskers trimmed to length <1 mm (same length as the fur hairs) every 24 or 48 h. Whisker trimming started at postnatal day 32–45 (P32–P45) and was continued for 10 days before recording; the trimmed whiskers were kept and glued to the whisker cut end before stimulation. Control animals were recorded at the same age as deprived animals, but the D-row of whiskers were trimmed and glued on the day of recording. For this reason, recordings from trimmed whiskers were compared with those from control D-row whiskers, whereas the control for the spared whiskers were the C- and E-row whiskers.

Surgery and recording procedures. Anesthesia was induced with isoflurane and maintained with intraperitoneal injection of urethane (1.5 g/kg body wt). Anesthetic depth was monitored by reflex movements, breathing rate, and cortical activity, and if required, additional doses of urethane were injected (0.15 g/kg body wt). Body temperature was maintained at 37°C with a thermostatic heating blanket. The animal was placed in a stereotoxic frame and a 1-mm-diameter craniotomy performed over the D1-2 barrels. A separate craniotomy was made caudally away from the barrel field to insert a carbon fiber electrode; a D1 barrel was maintained at 37°C with a thermostatic heating blanket. The electrodes were calibrated with a laser displacement measurement system (Micro-Epsilon, Ortenburg, Germany). Receptive fields were mapped with a data acquisition interface (CED 1401; Cambridge Electronic Design, Cambridge, UK). The deflection amplitude of each actuator was calibrated with a laser displacement measurement system (Micro-Epsilon, Ortenburg, Germany). Receptive fields were mapped with a data acquisition interface (CED 1401; Cambridge Electronic Design, Cambridge, UK). The deflection amplitude of each actuator was calibrated with the use of independent computer-controlled piezoelectric actuators (Physik Instrumente, Bedford, UK) arranged in a 3 × 3 array (Jacob et al. 2012). The principal whisker and the 8 immediate neighbor whiskers were trimmed to 12-mm length and inserted into short tubes glued to the skull of the animal. When the principal whisker was not at the center of the array in the control animals, the whiskers two rows or two columns apart from the principal whisker were excluded from the analysis. Each element of the stimulator has a very large range of positional adjustments due to gimbal joints, and the actuators were positioned and oriented to maintain the whiskers at their initial resting position and angle unless stimulated. Piezoelectric bender movement was controlled by a whisker stimulator driver (CED 3901) interfaced with a data acquisition interface (CED 1401; Cambridge Electronic Design, Cambridge, UK). The deflection amplitude of each actuator was calibrated with a laser displacement measurement system (Micro-Epsilon, Ortenburg, Germany). Receptive fields were mapped with sparse noise stimuli composed of pseudorandom sequences of ventral/dorsal deflections at 5 Hz (interpolated with a nonstimulation event). Five to 125 sequences (mode 50) were considered, depending on the stability of the recording. Each whisker deflection lasted 30 ms (with a 10-ms plateau phase) to avoid oscillations and was 200 μm in peak amplitude (Fig. 2A).

Cell type identification and location. After recordings were complete, animals were perfused with fixative under deep general anesthetic. Biocytin staining of L5 cells was revealed in coronal sections (300 μm thick) using Vectastain ABC kits (Vector Laboratories, Peterborough, UK). The morphology of a subset of recorded cells was recovered and used to establish a correlation between somatic position and electrophysiology. The actuator was calibrated with a laser displacement measurement system (Micro-Epsilon, Ortenburg, Germany). Receptive fields were mapped with sparse noise stimuli composed of pseudorandom sequences of ventral/dorsal deflections at 5 Hz (interpolated with a nonstimulation event). Five to 125 sequences (mode 50) were considered, depending on the stability of the recording. Each whisker deflection lasted 30 ms (with a 10-ms plateau phase) to avoid oscillations and was 200 μm in peak amplitude (Fig. 2A).

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observed spike train. In the current context, the Chernoff information is simply approximated by

\[
l \approx \max_{\alpha} \left\{ -\sum_{\ell} \log \left[ \frac{(f(t)\Delta)\alpha g(t)\Delta^{1-\alpha}}{1 - f(t)\Delta} \right] \right\}
\]

when the size of the time bin, \( \Delta \), is small enough so that each bin does not contain more than one spike. The maximum of the integral with respect to the parameter \( \alpha \) was computed by discretely sampling the range with step size 0.01. If the difference between firing rate traces \( f(t) \) and \( g(t) \) is small, the Chernoff information becomes equivalent to the Fisher information, a measure widely used in neuroscience to quantify detectability of a small parameter change (Seung and Sompolinsky 1993; Toyozumi et al. 2006). The Chernoff information is more general than the Fisher information because it can also characterize large “distance.” An in-depth explanation about Chernoff information in the neuroscience context is given elsewhere (e.g., Kang et al. 2004).

**Receives operating characteristic.** For each stimulus condition, the overlap between the distributions of spike counts in trials with whisker and without whisker stimulation was calculated using receiver operating characteristic (ROC) analysis. The ROC curve was created by plotting the proportion of stimulus trials whose spike counts were above the threshold against the proportion of null trials whose spike counts were above the same threshold. This was repeated for various thresholds. The area under ROC (AUROC) was calculated by measuring the area under the ROC curve. When the area was below 0.5, the area above the curve was taken instead. A larger AUROC indicates that the two distributions are more separated. This was repeated for variable upper limits of the time window in the range of 6 to 60 ms after the stimulus in 1-ms steps. The lower limit of the time window was 5 ms after the stimulus.

**Initial slope analysis.** The initial slope of the PSPs was defined as the maximum PSP derivative. When the maximum did not correspond to the initial part of the response, the whiskers were excluded from the analysis by visual inspection (29 cells).

**Latency analysis.** Latency was defined as the first time point following stimulation when the time derivative of the evoked PSP crossed a threshold fixed at mean ± 3 SD beyond the time derivative of the spontaneous activity. After visual inspection, latency was corrected if an obvious false positive was detected (3.8% of the cases). In rare cases, the response was small enough that the derivative of the PSP did not cross the threshold but the response was unambiguously visible. In these cases, the latency was taken as the time of the maximum PSP derivative (1.4% of the cases).

**Conductance estimation.** Because voltage clamp cannot be achieved with high-access resistance electrodes, we used current-clamp recording for conductance estimation. A range of current injections was used to maintain the cell hyperpolarized or slightly depolarized. We avoided depolarizations that would recruit the nonlinearities of the current-voltage (I-V) curve, as recommended by Monier et al. (2008). Receptive fields were mapped during random alternation between three to five different levels of current injection (−40 to +20 pA) that always included the zero-current level. Recorded membrane potential traces were median-filtered with a 10-ms window to eliminate residual spikes. For each whisker, at each time point \( t \), a linear regression model \( v(t) = v_0(t) + a(t)I \), where \( v_0(t) \) and \( a(t) \) are regression coefficients relating injection current \( I \) to membrane potential \( v(t) \) was fit to minimize the sum of squared errors in all recordings of the cell with the whisker stimulus. The regression coefficient trace was smoothed \( \hat{a}(t) \) and \( \hat{v}(t) \) and differentiated \( \hat{a}(t) \) and \( \hat{v}(t) \) with respect to time both using the Savitzky-Golay filter. A third-order polynomial was used, and the window length was 5 ms (1 ms for 2 cells with sharp response). The overall results did not change if a 5-ms window was used in all the cells.

First, total conductance and reversal potential were estimated on the basis of the following equations, where \( C \) is the measured capacitance of the cell:

\[
G_{\text{total}}(t) = \frac{1 - a(t)}{\hat{a}(t)} - C \hat{a}(t) \frac{\hat{v}(t)}{G_{\text{total}}(t)}
\]

\[
E(t) = \hat{v}(t) + C \frac{\hat{v}(t)}{G_{\text{total}}(t)}
\]

Leak conductance \( (G_{\text{leak}}) \) and reversal potential \( (E_{\text{rest}}) \) were estimated by averaging −40 to −10 ms before the stimulus onset.

Evoked excitatory \( [G_{\text{ex}}(t)] \) and inhibitory conductances \( [G_{\text{in}}(t)] \) were estimated by solving the following equation:

\[
G_{\text{total}}(t) = G_{\text{ex}}(t) + G_{\text{in}}(t) + G_{\text{rest}}
\]

\[
E(t) = G_{\text{total}}(t) = E_{\text{ex}}G_{\text{ex}}(t) + E_{\text{in}}G_{\text{in}}(t) + E_{\text{rest}}G_{\text{rest}}
\]

where \( E_{\text{ex}} = 0 \) mV and \( E_{\text{in}} = −75 \) mV are excitatory and inhibitory reversal potential, respectively. Evoked reversal potential \( (\Delta E) \) was estimated by subtracting the baseline average \( E_{\text{ref}} \) from \( E \).

**Statistical tests between control and deprived conditions.** We typically recorded one to two cells of a given type per animal. Whiskers were first categorized in three trimmed whisker classes and six spared whisker classes by sorting their response level. We then tested the effect of deprivation on deprived and spared whiskers with a two-way ANOVA using the aligned rank transform (ART; Wobbrock et al. 2011) with cells as independent samples (the number of cells is indicated by \( n_c \)). With ART, ANOVA can be applied without making assumptions about the distribution of the data.

In addition, a bootstrap test was applied to all combinations of a cell and whisker as independent samples (number of whisker-cell pair is indicated by \( n_{WC} \)) for times around the stimulus. The bootstrap test has the advantage of making no assumption about the distribution of data and of being adapted to low sample size. In most cases, the bootstrap method yielded the same level of significance as ART-ANOVA. For each group, the quantity of interest was computed from each of the 1,000 data sets resampled from the corresponding data group, allowing replacement (bootstrap). This provided resampled differences of the quantity of interest, from which we reconstructed a distribution of differences between the groups. The \( P \) value was then calculated by assuming the null hypothesis that there is no statistical difference between the control and deprived conditions. Hence, a one-tailed \( P \) value in this scenario is given by the probability that this difference is either positive or negative. The two-tailed \( P \) value is twice the smallest one-tailed \( P \) value. The \( P \) value vs. deprived groups was considered statistically significant if \( P < 0.05 \). The limits of the confidence interval are defined as 2.5% and 97.5% percentiles of the resampled quantities of interest computed from the group. We tested the difference in mean firing rates (shown in Fig. 2) and the difference in Chernoff information computed on the basis of population average of the PSTHs (shown in Fig. 3). Furthermore, we tested the difference in median membrane potential (shown in Fig. 5) and the difference in median conductance/evoked reversal potential (shown in Fig. 7) to avoid sensitivity of the results to a small number of outliers.

A color bar at the top of each panel in Figs. 2–5 and 7 indicates the time at which the population represented by that color is significantly greater than the other population using the bootstrap test \( (P < 0.05) \). Initial slope and latency distributions shown in Fig. 6 were compared using the Wilcoxon rank sum test or ANOVA.

**Data representation.** In this article, we characterize population statistics using bootstrap resampling (unless we mention otherwise). For the quantity of interest, we quote the bootstrap median (BM), upper confidence interval (UCI), and lower confidence interval (LCI),
which are respectively 50%, 97.5%, and 2.5% percentiles of the bootstrap samples. Likewise, we plot these three percentiles in each panel of Figs. 2–5 and 7.

RESULTS

Intracellular recordings were performed in vivo in the D-row columns of the barrel cortex of juvenile rats (~P30; Fig. 1A). Cortical layers were assessed by the depth from pia (deeper L2/3, mentioned as L3 for simplification, L4, and L5, Fig. 1B). A subset of these cells was studied morphologically (Fig. 1C). L4 cells (n = 5) were categorized into stellate-like or pyramidal-like morphology; L3 cells (n = 4) typically had dendritic branching within L2/3; and L5 cells (n = 43) were either thick tufted or thin slender pyramidal neurons, as found in earlier studies (Simons and Woolsey 1984; Zhu and Connors 1999). L5 cells were further classified as intrinsically bursting (L5IB) or regular spiking (L5RS) according to their firing pattern in response to current injection, and the classes correlated with their morphology (Fig. 1, D and E; Jacob et al. 2012).

Sensory deprivation was induced by trimming the D-row whiskers (Fig. 2A). After 10 days of deprivation, trimmed whiskers were re-glued on the whisker stump for testing cortical responsiveness. Responsiveness was compared with that in control animals, whose whiskers were trimmed and re-glued on the day of recording. To assess changes in the receptive fields of recorded cells rapidly and automatically, we used a whisker stimulator containing 9 piezoelectric bimorph wafers attached to 9 whiskers in a 3 × 3 square grid such that the principal whisker was located at the center of the grid (Fig. 2A). We applied a pseudorandom sequence to stimulate the whiskers, comprising 50 stimuli for each of the 9 whiskers plus a null period of no stimulation, which we used to estimate spontaneous activity (Jacob et al. 2008, 2012). Evoked activity was evaluated by subtracting spontaneous activity and averaging the response over 50 stimuli. Overall, the absolute level of spontaneous and evoked activity reported (Fig. 2) cannot be directly compared with that of other studies due to the use of sharp microelectrodes. However, the relative incidence of each cell type is in agreement with the literature (de Kock et al. 2007).

Effect of deprivation on spontaneous activity. Spontaneous activity was unchanged by deprivation in all but the L5RS cells (Fig. 2B). After whisker deprivation, the mean spontaneous firing rate of L5RS cells located in the deprived row decreased approximately fourfold in row-deprived animals (control: BM = 7.9 Hz, deprived: BM = 2.1 Hz). This difference was highly statistically significant (P < 0.001, bootstrap test) and can be seen in the prestimulus period of the PSTHs (Fig. 2, C and D, L5RS). Spontaneous activity was unchanged for any other cell type studied, including L5IB cells and cells located in other layers (see Fig. 2 and Table 1).

Effect of deprivation on evoked activity. Evoked activity was affected by deprivation, and the amplitude and direction of the effect depended on cell type, layer location, and the identity of the stimulated whisker (trimmed or spared, Fig. 2, C and D). For trimmed whiskers, the mean firing rate decreased to 71%
of control levels in L3 (P = 0.008, ART-ANOVA). In L5, the mean firing rate of RS cells decreased to 36% of control levels (P = 0.0002). The mean firing rate evoked by trimmed whiskers was unaffected by deprivation for cells located in L4 (P = 0.20) and for IB cells in L5 (P = 0.07). In summary, trimming the whiskers led to lower trimmed whisker responses in L3 and L5RS cells but not in L4 and L5IB cells, and the magnitude of the decrease was largest for L5RS cells (Table 1).

For spared whisker responses, the mean firing rate of L5IB cells increased to 139% of control values, which was statistically significant (P = 0.009). However, no other cell types showed changes in spared whisker responses (L3, P = 0.48; L4, P = 0.11; L5RS, P = 0.21) as shown in Fig. 2 and Table 1.

Effect of deprivation on sensory information coding. The information a neuron receives about a stimulus depends in part on differences between the evoked and spontaneous activity. The spontaneous activity of L5RS cells was reduced after deprivation, which suggested that information might change even if spared whisker responses remained constant. Therefore, we investigated deprivation-induced changes in information coding across cortical layers and cell types. We quantified the Chernoff information (Chernoff 1952; Cover and Thomas 1991; Kang et al. 2004), which summarizes detectability of whisker stimulation on the basis of population responses (shown in Fig. 3). For each cell type, the Chernoff information measures a distance between the time-varying population firing rate under evoked and spontaneous conditions, assuming inhomogeneous Poisson spiking of neurons (see METHODS). Although sensory information is generally coded by more than just firing rate (de Ruyter van Steveninck et al. 1997), including pattern of firing such as bursts, such extra features were not prominent in our data, possibly because of the relatively low spiking activity and the sparse stimulation protocol applied in this study. Chernoff information was calculated as accumulating with each 1-ms time bin from 1 to 60 ms poststimulus. Aggregate Chernoff information about the stimulus was contained in the last time window (60 ms) and for each response appeared to reach an asymptote by 60 ms (see Fig. 3). To obtain the Chernoff information in an unbiased way based on rare spiking events, we calculated Chernoff information of the population mean responses rather than the single-cell responses. However, the results were qualitatively similar when the information was calculated for individual cells.
Suprathreshold responses of neurons in different layers of the cortex to stimulation of the whiskers are tabulated along with the spontaneous firing rates. The mean firing rate for evoked responses are estimated over the period 3–103 ms poststimulus after subtracting spontaneous activity. The spontaneous firing rate period is estimated over 40 to 10 ms before the stimulus (Hz). Upper and lower 95% confidence intervals are calculated using the bootstrap method. *P values compare control and deprived values using the aligned rank transform (ART) ANOVA test (evoked) or bootstrap test (baseline). *P < 0.05. T refers to trimmed whisker and S to spared whisker stimulation.

(data not shown). This result suggests that the variability of sensory response in the current experiment was relatively small within each cell type and emphasizes the robust nature of the finding.

In control undeprived animals, Chernoff information was maximal in L4 cells. Whiskers in the same row as the principal whisker, corresponding to the trimmed row in deprived animals, had bootstrapped Chernoff information of BM = 0.36 \( [\text{UCI} = 0.47, \text{LCI} = 0.26, n_{\text{WC}} = 40 (14 \text{ cells})] \). In the flanking rows, which are spared in the deprived animals, Chernoff information reached median BM = 0.15 \( [\text{UCI} = 0.22, \text{LCI} = 0.11, n_{\text{WC}} = 77 (14 \text{ cells})] \). In control animals, Chernoff information for both flanking and same-row whiskers decreased in the order L4 > L3 > L5IB > L5RS.

For all cell types except L5RS cells, the effect of whisker deprivation on Chernoff information matched the changes in evoked firing rate. After deprivation, Chernoff information was unchanged in L4, which retained the greatest information in the column (as with undeprived control animals). For the deprived-row whiskers, Chernoff information was significantly decreased in L3 and L5RS cells [L3: control BM = 0.21, \( n_{\text{WC}} = 30 \) whisker cell pairs (10 cells), deprived BM = 0.11, \( n_{\text{WC}} = 36 (13 \text{ cells}) \), \( P = 0.030 \), bootstrap test; L5RS: control BM = 0.13, \( n_{\text{WC}} = 60 (23 \text{ cells}) \), deprived BM = 0.058, \( n_{\text{WC}} = 58 (21 \text{ cells}) \), \( P = 0.018 \), bootstrap test] and delayed in L5IB cells, but the order by which information decreased by layer remained unchanged.

The situation was different for the spared whisker responses. In L4 cells, Chernoff information was not significantly increased, though it was advanced in time (Fig. 3). In L5 cells, Chernoff information was significantly increased (L5IB spared: \( P = 0.032 \), L5RS spared: \( P < 0.001 \), bootstrap test) and in addition, the increase in information was substantially advanced in time for the L5RS cells. Finally, there was no significant change in spared whisker information in L3 \( (P = 0.27) \). As a consequence, the ordering of information for spared whisker stimulation was reorganized by sensory deprivation such that activity in L5RS cells contained almost as much Chernoff information as in L4 cells (BM = 0.17 vs. 0.24, respectively) and far more than in L3 and L5IB cells (BM = 0.070 and 0.133, respectively). Therefore, sensory deprivation changed the order of information representation for spared whiskers within a deprived barrel column to L4 > L5RS > L5IB > L3.

Although Chernoff information takes into account changes in the time course of neural response, we also used a simpler ROC analysis based on spike count to check the robustness of the finding (Fig. 4). The results of the ROC analysis and the Chernoff information analysis were very similar in that the effect of whisker trimming produced the same direction of change in each case. The only difference was that the spared whisker response of L5IB cells did not show a significant difference under ROC analysis despite the increased spike count. In contrast, L5RS cells, which were of particular interest, showed a robust increase in sensory detection performance by either measure.

Plasticity of subthreshold responses. To explore neuronal mechanisms underlying the deprivation-induced changes in sensory information representation, we analyzed membrane potential in each group of cells. First, we tested for differences in “resting” membrane potential of cells in different layers (Table 2). We found that there was no difference in mean resting membrane potential for cells in L3, L4, and L5IB but that L5RS cells showed a significant hyperpolarization from −60.7 to −65.6 mV in deprived animals \( (P < 0.006 \), bootstrap test). This is consistent with the significant decrease in spontaneous action potential firing rate for L5RS cells (Table 1). Figure 5, A–C, shows example traces and distribution of ongoing membrane potential activity for L5RS cells with and without whisker deprivation. Deprivation did not induce a global shift of the membrane potential distribution toward hyperpolarization, but rather induced greater losses for depolarized membrane potential values.

Next, we analyzed the trimmed whisker-evoked postsynaptic potentials (tPSPs) and the spared whisker-evoked postsynaptic potentials (sPSPs) in L3, L4, L5IB, and L5RS cells (Fig.

### Table 1. Spiking properties

| Layer (Spared/Trimmed) | Control | Deprived |
|------------------------|---------|----------|
|                        | No. of cells | Mean | Lower 95% CI | Upper 95% CI | P Value |
| L3 (T)                 | 10       | 0.677  | 0.439        | 0.896        |        |
| L3 (S)                 | 10       | 0.495  | 0.302        | 0.746        |        |
| L4 (T)                 | 14       | 1.24   | 0.968        | 1.55         |        |
| L4 (S)                 | 14       | 0.71   | 0.541        | 0.889        |        |
| L5IB (T)               | 27       | 0.864  | 0.62         | 1.13         |        |
| L5IB (S)               | 27       | 0.692  | 0.538        | 0.848        |        |
| L5RS (T)               | 23       | 0.685  | 0.485        | 0.887        |        |
| L5RS (S)               | 23       | 0.529  | 0.389        | 0.658        |        |

**Total evoked (3–103 ms), spikes/stimulus**

| Layer (Spared/Trimmed) | Control | Deprived |
|------------------------|---------|----------|
|                        | No. of cells | Mean | Lower 95% CI | Upper 95% CI | P Value |
| L3                     | 13       | 0.482  | 0.254        | 0.69         | 0.00760* |
| L3                     | 13       | 0.417  | 0.289        | 0.557        | 0.4795  |
| L4                     | 12       | 0.932  | 0.601        | 1.32         | 0.19866 |
| L5IB                   | 12       | 0.866  | 0.681        | 1.1          | 0.1124  |
| L5IB                   | 22       | 0.684  | 0.45         | 0.913        | 0.06672 |
| L5RS                   | 22       | 0.959  | 0.792        | 1.13         | 0.00946* |
| L5RS                   | 21       | 0.25   | 0.127        | 0.4          | 0.00022* |
| L5RS                   | 21       | 0.654  | 0.513        | 0.823        | 0.21064 |

**Baseline (−40 to −10 ms), Hz**

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For L4 cells, we observed no changes in the peak tPSP (0.25, ART-ANOVA) or tPSP slope (cells in general, except for a significant slope reduction for L5RS rank sum test). For L3 cells, the decrease in firing rate caused by deprivation is approximately 35% of control values, which is a significant decrease (bootstrap test). This decrease is consistent with the shorter latency spiking response to spared whiskers in this population. We explore later whether this change involves changes in excitatory and inhibitory synaptic conductances.

Plasticity of response latency. The relative latencies recorded in the different groups of neurons provide additional information on how sensory signals are sent to the cortex and how they travel through layers. The latency of response to remote surround whisker stimulation is much greater than the latency of response to whiskeys positioned closer to the center.
of the receptive field (Armstrong James and Fox 1987), and its estimation is more sensitive to noise. Therefore, we considered latency independently for each whisker rather than averaging all trimmed and all spared whiskers as described above. To study the plasticity of PSP latencies, we plotted latencies against the Euclidian distances between the corresponding whisker positions and a center of mass (CM) of the multiwhisker receptive field, which is evaluated using the coordinates of the whisker positions on the face. To estimate the CM independently from sensory deprivation, we used the CM of evoked local field potentials recorded in L4 during the same electrode penetration (Fig. 6A). The selected recording sites had one dominant principal whisker in the D-row that largely defined the center of the receptive field, but it could be offset by secondary inputs from surrounding whiskers. As expected, both latency and variability of latency distribution increased with the distance of the whisker from the receptive field center (Fig. 6B, for all cell types, $P < 0.01$, ANOVA).

In the control condition, latency also increased from L4 and L3 to L5 (respectively for L3, L4, L5 IB, and L5 RS cells: median latency $= 9.6$, 10.3, 11.4, and 13.5 ms; UCI $= 10.3$, 11.2.1, and 14.6 ms; LCI $= 9$, 9.9, 11.1, and 12.4 ms). In the deprived condition (Fig. 6C), the latency of trimmed whisker tPSPs was unchanged for all layers. For spared whiskers, the latency of sPSPs decreased significantly in the entire L5 RS cell’s receptive field ($P < 0.001$, ANOVA) and in L4 mostly away from the receptive field center ($P < 0.01$, ANOVA). Latencies did not change in L3 and L5 IB cells. Interestingly, the latency of sPSPs in L5 RS cells (median $= 10.5$ ms, UCI $= 12.4$ ms, LCI $= 9.2$ ms, $n_{WC}$ $= 83$) was shorter than that in L3 neurons (median $= 12.3$ ms, UCI $= 13.4$ ms, LCI $= 10.6$ ms, $n_{WC}$ $= 80$, $P = 0.05$, ANOVA) and L5 IB cells (median $= 13.2$ ms, UCI $= 14.4$ ms, LCI $= 12.1$ ms, $n_{WC}$ $= 88$, $P < 0.01$, ANOVA) but was not different from that in L4 neurons (median $= 9.3$ ms, UCI $= 10.7$ ms, LCI $= 8.7$ ms, $n_{WC}$ $= 65$, $P = 0.13$, ANOVA). Moreover, latency of the 10% most rapid sPSPs was significantly shorter in L5 RS cells (median $= 5.2$ ms) than in L3 cells (median $= 7$ ms, $P < 0.001$, ANOVA) and in L5 IB cells (median $= 8.4$ ms, $P < 0.001$, ANOVA). This result suggests that short-latency potentiation in L5 RS cells is unlikely to be derived either from L3 or L5 IB cells.

Conductance analysis for L5 cells. To gain some insight into the excitatory and inhibitory components of whisker responses and their plasticity, we repeated sets of stimuli under various levels of injected current to calculate synaptic conductance and reversal potential (Fig. 7A). We recorded conductance for L5 receptive field responses in control and deprived animals. We found that the decrease of latency observed in L5 RS cells was associated with both excitatory ($P < 10^{-4}$ for trimmed whiskers and $P < 10^{-6}$ for spared whiskers, Wilcoxon’s rank sum test) and inhibitory components ($P < 10^{-6}$ for trimmed whiskers and $P < 10^{-5}$ for spared whiskers; Fig. 7B).

For trimmed whisker responses, even though the median excitatory and inhibitory conductance peaks were both decreased (Fig. 7C; $P = 0.018$ for excitatory conductance and $P = 0.018$ for inhibitory conductance, $n_c = 6$ cells, ART-ANOVA), the effects largely canceled one another out to produce no net change in the reversal potential over the same time interval.

For spared whisker responses, both excitatory ($g_E$) and inhibitory ($g_I$) conductance peaks increased significantly ($P = 0.003$ and $P = 0.03$, respectively, ART-ANOVA). The early part of the median excitatory conductance waveform from 10 to 17 ms was the main source of the effect ($P < 0.05$, bootstrap test; Fig. 7C). In addition, the median reversal potential was significantly increased during a similar period from 9 to 26 ms ($P < 0.05$, bootstrap test), and the peak reversal potential was 209% greater in deprived compared with control animals (Table 3: $P = 0.026$, bootstrap test; $P = 0.007$, ART-ANOVA). Both observations confirmed a stronger increase of excitatory conductance than of inhibitory conductance. Because

### Table 2. Membrane potential

| Layer  | No. of cells | Median | Lower 95% CI | Upper 95% CI |
|--------|--------------|--------|--------------|--------------|
| L3 (T) | 14           | 4.94   | 4.16         | 6.87         |
| L3 (S) | 14           | 3.11   | 2.71         | 3.84         |
| L4 (T) | 15           | 6.81   | 5.43         | 7.63         |
| L4 (S) | 15           | 3.68   | 3.11         | 4.59         |
| L5IB (T)| 27           | 4.04   | 3.09         | 4.99         |
| L5IB (S)| 27           | 3.39   | 2.71         | 3.99         |
| L5RS (T)| 23           | 2.83   | 2.03         | 3.91         |
| L5RS (S)| 23           | 2.08   | 1.63         | 2.68         |

| Layer | No. of cells | Mean | Lower 95% CI | Upper 95% CI | $P$ Value |
|-------|--------------|------|--------------|--------------|-----------|
| L3    | 14           | −61.35| −68.35       | −54.57       | 0.162     |
| L4    | 15           | −66.30| −70.70       | −61.74       | 0.122     |
| L5IB  | 27           | −63.69| −69.08       | −56.30       | 0.052     |
| L5RS  | 23           | −60.74| −65.40       | −55.20       | 0.006     |

Membrane potential responses to stimulation of the whiskers (with spikes removed) are tabulated along with the resting membrane potential for neurons in different layers of the cortex. Median membrane potentials for evoked responses and means for resting potential are shown together with the upper and lower 95% confidence intervals, which are calculated using the bootstrap method. $P$ values compare control and deprived values using the ART-ANOVA test (peak) or bootstrap test (resting). *$P < 0.05$. T refers to trimmed whisker and S to spared whisker stimulation.

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the earliest part of the subthreshold waveform is related to the period when spikes are produced in response to whisker stimulation, the increase in reversal potential during the first 30 ms of the response most likely explains the increase in spike firing to the spared whiskers during this period (see above on RS cell suprathreshold responses).

For L5 IB cells, we found no significant difference in the level or latency of total conductance with deprivation. Although all whisker responses showed a trend toward more positive reversal potentials favoring excitatory conductance (data not shown), none were significant (Table 3).

DISCUSSION

We found that plasticity induced by row deprivation alters the distribution of sensory information within and between the different layers of the cortical columns. To summarize, no major changes were observed in L4 cells except for a decrease in latency to the spared whiskers; the only change we observed in L3 cells was a decrease in response to trimmed whiskers; L5IB cells underwent a small depression to trimmed whisker inputs and a global potentiation to spared whiskers; and finally, L5RS cells exhibited a remarkable form of plasticity resulting in the largest change in information that we observed. L5 cells showed a decrease in spontaneous activity, the potentiation of a short latency excitatory input from the spared whiskers and a decreased response to the trimmed whiskers. We discuss below some of the substrates and pathways for L5 plasticity that was clearly distinct from the more conventional effects observed in L4 and L3.
Pathways underlying short-latency responses in L5. There is a long history documenting the short-latency thalamic ventral postemodial nucleus (VPm) input to L5 of the somatosensory cortex. Electron microscopy studies have shown that VPm projections make contact with cells in all layers of the barrel cortex except L2, and in particular on L5 (White 1978; White and Hersch 1982). Short-latency whisker responses, concurrent with those in L4, were observed in L5b almost a quarter-century ago (Armstrong-James et al. 1992), and in vitro studies pioneering the thalamocortical slice preparation concurrently demonstrated VPm input to L5 cells (Agmon and Connors 1992). More recent studies have further documented the presence of thalamic input to L5 in both the mouse and rat (Constantinople and Bruno 2013; Petreanu et al. 2009; Rah et al. 2013; Wright and Fox 2010). In the present study we found that an early component of the RS cells response to whisker stimulation was potentiated by row deprivation and that potentiation was related in time to an increase in an excitatory conductance. Given the latency of the response comes before any other cortical cell responds except those in L4 of the principal barrel, the most likely source of the excitation is a direct input from VPm. At present, it is not clear why short-latency input should potentiate in RS cells and not in IB cells. The original report of Agmon and Connors (1992) suggested that IB cells do not receive thalamic input whereas RS cells do. However, there is evidence of the opposite in the auditory cortex (Sun et al. 2013) and in the barrel cortex (Bureau et al. 2006).

For the thalamic input to account for the increased short-latency component generated by spared whisker stimulation, the VPm input would need to convey excitation to a nonprincipal whisker barrel. There are two possibilities: first, branches of thalamic afferents innervating their principal barrels might grow into the neighboring deprived barrel (Oberlaender et al. 2012) during the 10-day deprivation period; second, the nonprincipal whisker inputs that potentiate might already exist, and there is evidence for this view. Blocking intracortical activity with muscimol and locally disinhibiting the recorded cell reveals double-whisker responses or multiwhisker responses in some L5 cells (Wright and Fox 2010).

Potentially, the short-latency input to L5 RS cells might arise from L4 in the neighboring barrel. There is functional evidence from paired recordings, glutamate uncaging, and optogenetic stimulation studies that L4 projects to L5 (Feld-
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Fig. 7. Plasticity of excitatory and inhibitory conductances in L5RS cells. A1: evoked conductances and reversal potential calculated on a control L5RS cell. Left, PSPs were calculated for different levels of injected currents. Middle, reversal potential (E<sub>rev</sub>). Right, total (G<sub>exc</sub> subtracted) excitatory (G<sub>ex</sub>) and inhibitory (G<sub>in</sub>) conductances. A2: evoked conductances and resting potential calculated on a control L5IB cell. Same conventions as in A1. B: plasticity of latency of inhibitory (top) and excitatory (bottom) conductances to control (black), trimmed (red), and spared whiskers (blue). Same conventions as in Fig. 5. C: plasticity of reversal potential (top), inhibitory (middle), and excitatory (bottom) conductances. Same conventions as Fig. 5, D and E. The bar charts represent areas (scale bars: E<sub>rev</sub>, 0.1 s·mV; G<sub>in</sub>, 0.1 s·nS; G<sub>ex</sub>, 0.04 s·nS) and peaks (scale bars: E<sub>exc</sub>, 5 mV; G<sub>exc</sub>, 4 pS; G<sub>ex</sub>, 1 nS). Error bars indicate 95% confidence interval. *P < 0.05, bootstrap test.

meyer et al. 2005; Petreanu et al. 2009; Schubert et al. 2001). Furthermore, anatomical studies show axons projecting ventrally from L4 spiny stellate cells, mainly in the column, but with some overlap into neighboring columns, including subgranular layers (Lubke et al. 2000; Narayanan et al. 2015). Basal dendritic branches of L5 pyramidal cells spanning into the neighboring barrel could be engaged by axons confined to the home column. Glutamate uncaging studies in row-deprived mouse barrel cortex demonstrate that L4 connections from neighboring spared columns to L5IB in the deprived column can potentiate in response to deprivation (Jacob et al. 2012), but this has not been demonstrated for L5RS cells. Finally, L6 cells, known to display short-latency responses to whisker stimulation (Constantinople and Bruno 2013; de Kock et al. 2007) and to project axons to L5 (Narayanan et al. 2015), are alternative candidates for inducing the short-latency responses in L5RS cells. However, neither L4 nor L6 inputs to L5RS cells were found to potentiate (Jacob et al. 2012).

Pathways underlying spontaneous activity in L5. Information about the principal whisker decreases significantly within the deprived column for all layers except L4, whereas information about the spared whiskers increases for all layers except L3. In addition, spared whisker information builds up in the L5RS cells after stimulation more rapidly than in control cases, partly due to potentiation of a short-latency excitatory input (vide supra) but also due to a decrease in spontaneous activity. Spontaneous activity varies according to the anesthetic level, the sleep states, or, in the awake animal, the conscious state, and it might alter the Chernoff information for the RS cells and other cell types. Urethane anesthesia creates a state of delta-wave activity where the EEG fluctuates at 0.5–4 Hz due to the burst-pause activity of L5 neurons, similar to the condition present in natural slow-wave sleep (Armstrong-James et al. 1985; Armstrong-James and Fox 1988). The burst activity is generated partly by intracortical circuits, particularly via horizontal connections in L5 (Beltramo et al. 2013; Chauvette et al. 2010; Le Bon-Jego and Yuste 2007), and partly by thalamic input originating in principal and intralaminar thalamic nuclei (David et al. 2013; Doi et al. 2007; Fox and Armstrong-James 1986). The decrease in spontaneous activity in the L5RS cells was accompanied by a hyperpolarization in membrane potential, suggesting a decrease in excitatory drive. The decrease in spontaneous activity would not appear to arise from a change in principal thalamic input, because this appears to potentiate in RS cells; it also would not appear to derive from a decrease activity in the L3-to-L5 pathway, because L5 bursts of action potentials persist when activity is abolished in supragranular layers (Beltramo et al. 2013), and some degree of independence was observed between subgranular and supragranular spontaneous activity (Reyes-Puerta et al. 2015). This suggests that a decrease in horizontal connections between L5 cells, which are known to be important for spontaneous bursts of action potentials (Beltramo et al. 2013; Chauvette et al. 2010), are more influential for the decrease in spontaneous activity. In this respect, it is of interest that bursts of action potentials in IB cells tend to precede those in RS cells (Chauvette et al. 2010), which suggests that IB-to-RS cell connections may be depressed by whisker deprivation. Conversely, the IB cells still show normal levels of spontaneous activity, which is consistent with the lack of depression of columnar pathways and potentiation of intracolumnar pathways onto L5IB cells (Jacob et al. 2012).

Compound sources of principal whisker depression. L2/3 provides a major input to L5 across various cortical areas (Hooks et al. 2011). In the barrel cortex, input from L2/3 cells to L5b is important for principal whisker responses in L5b (Wright and Fox 2010). In the current row-deprivation experiments, the input from L2/3 to L5 is depressed within the deprived column, and this is due to two main effects; first, the L4 input to L2/3 is depressed in the deprived column (Glaze-
Excitatory and inhibitory membrane conductances during responses to stimulation of the whiskers are tabulated along with the reversal membrane potential for neurons in L5 of the cortex. Input resistances are also indicated. The median peak of conductances and reversal potentials is shown together with the upper and lower 95% confidence intervals, which are calculated using the bootstrap method. $P$ values compare control and deprived values using the ART-ANOVA test. *$P < 0.05$. T refers to trimmed whisker and S to spared whisker stimulation.

Excitatory conductance, nS

| Layer | Control | | | | Deprived | | |
|-------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|       | No. of cells | Median | Lower 95% CI | Upper 95% CI | No. of cells | Median | Lower 95% CI | Upper 95% CI | $P$ Value |
| L5IB (T) | 6 | 0.823 | 0.696 | 3.44 | 3 | 0.98 | 0.37 | 1.94 | 0.2614 |
| L5IB (S) | 6 | 0.701 | 0.465 | 0.958 | 3 | 1.23 | 0.487 | 2.18 | 0.081611 |
| L5RS (T) | 6 | 1.38 | 0.78 | 2.96 | 6 | 0.771 | 0.342 | 1.31 | 0.018267* |
| L5RS (S) | 6 | 0.55 | 0.268 | 1.15 | 6 | 0.842 | 0.557 | 1.55 | 0.0033439* |

Inhibitory conductance, nS

| Layer | Control | | | | Deprived | | |
|-------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|       | No. of cells | Median | Lower 95% CI | Upper 95% CI | No. of cells | Median | Lower 95% CI | Upper 95% CI | $P$ Value |
| L5IB (T) | 6 | 2.62 | 1.72 | 9.1 | 3 | 0.859 | 0.441 | 5.62 | 0.59498 |
| L5IB (S) | 6 | 0.94 | 0.602 | 1.37 | 3 | 1.65 | 0.911 | 4.08 | 0.092052 |
| L5RS (T) | 6 | 2.49 | 1.39 | 5.36 | 6 | 2.67 | 1.11 | 4.97 | 0.018054* |
| L5RS (S) | 6 | 0.933 | 0.314 | 1.5 | 6 | 2.31 | 0.866 | 4.55 | 0.028516* |

Reversal potential, mV

| Layer | Control | | | | Deprived | | |
|-------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|       | No. of cells | Median | Lower 95% CI | Upper 95% CI | No. of cells | Median | Lower 95% CI | Upper 95% CI |
| L5IB (T) | 6 | 3.88 | 2.9 | 5.45 | 3 | 4.99 | 3.28 | 12.4 | 0.62465 |
| L5IB (S) | 6 | 4.66 | 3.11 | 5.74 | 3 | 5.83 | 4.1 | 7.86 | 0.19963 |
| L5RS (T) | 6 | 3.49 | 2.41 | 6.66 | 6 | 4.19 | 2.67 | 6.3 | 0.7624 |
| L5RS (S) | 6 | 2.66 | 1.85 | 4.14 | 6 | 5.57 | 3.6 | 7.4 | 0.0071428* |

Input resistance, MΩ

| Layer | Control | | | | Deprived | | |
|-------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|       | No. of cells | Median | Lower 95% CI | Upper 95% CI | No. of cells | Median | Lower 95% CI | Upper 95% CI |
| L5IB | 6 | 283 | 126 | 354 | 3 | 150 | 114 | 549 | 0.587 |
| L5RS | 6 | 188 | 113 | 324 | 6 | 175 | 98 | 258 | 0.730 |

Wide plasticity of cortical information flow

excitatory synaptic conductance in superficial layer L4 neurons also target the apical tuft (Petreanu and Svoboda 2009). For significant changes in the L4 cells independent of subtype. A more specific depression of L4 inputs might impact L5 plasticity. One other factor that might contribute to the lower depression of L5IB cells is that the hyperpolarization activated current ($I_h$) is downregulated in the apical dendrites by whisker deprivation, and this effect appears restricted to IB cells (Breton and Stuart 2009). Lower levels of $I_h$ would be expected to increase excitability of the IB cells to their diminished L2/3 input and to some extent counter the circuit effects.

Excitatory vs. inhibitory influences in expression of plasticity. Inhibition is important for induction of plasticity; disinhibition occurs phasically and chronically during the early stages of whisker deprivation in superficial layers (House et al. 2011; Katzel and Miesenbock 2014; Kelly et al. 1999; Li et al. 2014), but its role in expression of barrel cortex plasticity is less well established. For the spared whiskers, both excitatory and inhibitory conductances were found to increase in L5RS cells, although at different latencies, which rules out the idea of disinhibition and supports the idea that potentiation is due to excitatory inputs likely through excitatory synapse potentiation. For the spared whiskers, the increase in $g_E$ preceded that in $g_I$ and therefore allowed excitation to escape the influence of the inhibitory effect and depolarize the cell. For the deprived whiskers, the concomitant increase of $g_E$ and $g_I$ canceled one another out and led to no change. This finding is consistent with previous studies showing that the phase relationship between excitation and inhibition is crucial in creating the response selectivity of neurons in the barrel cortex (Wilent and Contreras 2005). Our results should be interpreted with caution, since all studies estimating conductance from somatic recordings are biased toward perisomatic synapses (Williams and Mitchell 2008). For L5 pyramidal cells, all excitatory input pathways target the perisomatic dendrites in L5, even if VPm neurons also contact oblique dendrites in L4 and L2/3 inputs also target the apical tuft (Petreanu and Svoboda 2009). For
inhibitory inputs, parvalbumin-expressing interneurons target the perisomatic dendrites of L5 pyramidal cells, but somatostatin-expressing interneurons essentially target the apical tuft (reviewed in Naka and Adesnik 2016). The plasticity of inputs from the latter interneuron type cannot be assessed with somatic conductance estimation and need to be explored with alternative methods.

Conclusions. The present analysis shows that when information content is taken into account, a relatively minor spared based input potentiation in L5RS cells, when combined with a reduction in spontaneous activity, retrieves greater information content than potentiation of spared whisker responses in the presence of spontaneous activity for the L5IB cells. In conclusion then, the present data indicate that in addition to differences in underlying plasticity mechanisms induced in L5RS and IB cells due to their different propensities for Hebbian vs. homeostatic plasticity (Greenhill et al. 2015), cortical and subcortical circuit effects act to exacerbate the differences in plasticity in different cell types (Fig. 8). Despite different underlying mechanisms, L5RS and L5IB cells both act to increase the information content of spared whisker responses.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS
V.J. and K.F. conception and design of research; V.J. performed experiments; V.J., A.M., T.T., and K.F. analyzed data; V.J., A.M., T.T., and K.F. interpreted results of experiments; V.J., A.M., and T.T. prepared figures; V.J., T.T., and K.F. drafted manuscript; V.J., A.M., T.T., and K.F. edited and revised manuscript; V.J., A.M., T.T., and K.F. approved final version of manuscript.

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