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Developmentally degraded cortical temporal processing restored by training

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Abstract

Enduring deficits in temporal processing can be induced in the auditory cortex by rearing infant rats in the presence of low frequency–modulated noises. We found that it was possible to restore normal temporal processing, overcoming deficits induced during the critical period, by intensively training developmentally impaired animals as juveniles or young adults. Re-normalized cortical temporal response characteristics were sustained long after training cessation.

Response selectivity of neurons in the mammalian auditory system can be enhanced or degraded by manipulating acoustic experience in early postnatal life¹. Structured (for example, modulated) noise exposure during a critical period of postnatal development disrupts tonotopy and degrades frequency response selectivity for neurons in the primary auditory cortex (A1) of rats². A recent study also demonstrated that structured noise exposure at a consistently low modulation rate results in degraded cortical temporal processing, manifested by weaker responses to higher-rate sounds and by sharply decreased event-by-event response synchronization. These changes in temporal response dynamics induced by sound exposure during the critical period of development endure into adulthood³.

Many natural sounds and most animal communication sounds have complex temporal structures. It has been shown that the auditory cortex is important in the perception of time-varying features of these sounds⁴. A persistent, developmental degradation of cortical dynamics induced via early environmental-sound manipulation presumably impairs the cortical processing of behaviorally important acoustic inputs in later life. In humans, fundamental deficits in temporal processing abilities have been argued to contribute to delayed and impaired language development, and have been shown to put impaired child populations at risk for reading failure^{5,6}.

Earlier studies have shown that it is possible to improve or degrade neuronal response dynamics in the auditory cortex in adult animals and humans using appropriate forms of intensive behavioral training^{7–9}. However, all of these studies were conducted in normal adults. We

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AUTHOR CONTRIBUTIONS

X.Z. conducted the experiments. X.Z. and M.M.M. designed the experiments, analyzed the data and wrote the manuscript.

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sought to determine whether or not these same strategies effectively restore cortical dynamics in a developmentally impaired animal. Using a stimulus target-seeking operant conditioning procedure, we found that perceptual training could completely restore the temporal fidelity of cortical responses to high-rate sound stimuli in juvenile (post-critical period) rats.

We trained noise-reared rats to identify a target auditory stimulus (pulse train of a specific repetition rate) that was presented with varying nontarget auditory stimuli (pulse trains of various repetition rates) for food rewards. The repetition rate of the target pulse train changed daily on a random schedule (all experiment procedures were approved by the Animal Care and Use Committees at the University of California, San Francisco; Supplementary Methods online). In the early days of training, rats continuously nose poked on each trial to receive food rewards, resulting in a high response rate for both target and nontarget (false positive) responses (Fig. 1a). It took an average of ~17 min for rats to finish a training block as a result of frequent 'time-out' periods, during which the house light was turned off and no stimuli were presented. In early training, there were no significant differences in the rate of target or nontarget responses for each block, or in the time required to complete each block (ANOVA, $P = 0.06$ – 0.28), and nose pokes in each block were equally distributed over all of the pulse trains presented (ANOVA, $P = 0.12$ – 0.78 ; Fig. 1a).

The rats learned to identify and selectively respond to a new randomly set target pulse-train rate on each day as training progressed. When the rats had mastered the task, they still continuously nose poked during each training day's initial block, resulting in high rates of both target and nontarget responses (Fig. 1b). Starting from the second block, however, nontarget responses sharply decreased as rats consolidated their identification of the target (ANOVA with *post hoc* Student-Newman-Keuls test, all $P < 0.001$), whereas the target response rate remained high (ANOVA, $P = 0.56$). The time required to complete a single training block also significantly decreased (ANOVA with *post hoc* Student-Newman-Keuls test, all $P = 0.001$). Nose pokes for these blocks sharply favored the target train (ANOVA with *post hoc* Student-Newman-Keuls test, all $P < 0.001$; Fig. 1b). Although noise-reared rats achieved high performance levels at late training days, they showed an initially degraded reception of temporal features of sound stimuli when compared with naive rats (Supplementary Fig. 1 online).

Immediately after ~2 months of training, the representations of temporal modulation rates in A1 of these developmentally impaired rats that received training (referred to as EXP rats) were documented in detail and were compared with data from untrained noise-reared (UNR) rats, equivalently passively stimulated noise-reared rats that were never trained (PNR rats) and age-matched naive control (CON) rats (Fig. 2a and Supplementary Methods). Data were recorded from neurons in the middle cortical layers from 210 sites in 5 EXP rats, 250 sites in 5 UNR rats, 193 sites in 4 PNR rats and 179 sites in 4 CON rats. All subsequent quantitative analyses were conducted on the basis of these samples.

We first derived the temporal modulation-transfer functions (tMTFs) to characterize cortical temporal responses for different rat groups. Most cortical neurons in CON (normally reared) rats could follow repeated stimuli at and below 10 pulses per second (pps), with each successive brief tone evoking about the same number of spikes as the first pulse in the train (Fig. 2b). In contrast, although normalized cortical responses for UNR or PNR rats were increased at 4 pps when compared with CON rats (ANOVA with *post hoc* Student-Newman-Keuls test, both $P < 0.01$), the responses fell off rapidly above 7 pps (ANOVA with *post hoc* Student-Newman-Keuls test, all $P < 0.001$). After training, however, normalized cortical responses for EXP rats were again significantly increased at higher repetition rates (that is, 10–20 pps) and were consistently greater than those recorded from CON rats (ANOVA with *post hoc* Student-Newman-Keuls test, all $P < 0.001$). Normalized cortical responses at lower repetition (that is,

2–7 pps) for EXP rats were comparable to those of CON rats (ANOVA with *post hoc* Student-Newman-Keuls test, all $P > 0.05$).

We quantified the cortical capacity for processing high-rate stimuli by determining the highest temporal rate at which the tMTF was at half of its maximum ($f_{h1/2}$). At first glance, the $f_{h1/2}$ that we obtained for both UNR and PNR rats were lower at most sites than for CON rats, whereas the $f_{h1/2}$ for EXP rats were comparable to those of CON rats (Fig. 2c). To further illustrate these data, we compared distributions for $f_{h1/2}$ obtained from all four rat groups. There was a significantly leftward shift of $f_{h1/2}$ distributions for both UNR and PNR rats compared with CON rats (Kruskal-Wallis with *post hoc* Dunn's test, both $P < 0.001$; Fig. 2d), indicating a reduced rate-following ability for these two developmentally noise-exposed groups. For EXP rats, however, the distribution was significantly shifted to the right compared with UNR and PNR rats (Kruskal-Wallis with *post hoc* Dunn's test, both $P < 0.001$), manifesting a significantly increased rate-following ability resulting from training. The evident, modest rightward shift of the distribution recorded in EXP rats compared with CON rats did not reach statistical significance (Kruskal-Wallis with *post hoc* Dunn's test, $P > 0.05$).

We further compared $f_{h1/2}$ values obtained from different rat groups by binning their characteristic frequency values into three ~1.5-octave-wide categories (Fig. 2d). As expected, average $f_{h1/2}$ values were significantly smaller for UNR and PNR rats than for CON rats across all characteristic frequency ranges (ANOVA with *post hoc* Student-Newman-Keuls test, $P < 0.01$ – 0.001). The average $f_{h1/2}$ values for EXP rats, however, were substantially similar to those of CON rats at low characteristic frequencies (that is, 1–3.1 kHz; ANOVA with *post hoc* Student-Newman-Keuls test, $P > 0.05$) but were significantly greater at middle and high characteristic frequencies (that is, 3.1–30 kHz; ANOVA with *post hoc* Student-Newman-Keuls test, $P < 0.01$).

To determine the temporal fidelity of cortical responses, we calculated vector strength and derived the Rayleigh statistics to assess the statistical significance of the vector strength. Although the average vector strength and Rayleigh statistics as a function of stimulus repetition rates showed the same band-pass characteristics for all rat groups, these curves shifted leftward and peaked at lower repetition rates for both UNR and PNR rats when compared with CON rats (peaked at 4 or 7 pps in UNR and PNR rats versus 10 pps in CON rats; Fig. 2e). Overall, both vector strength and Rayleigh statistics for UNR and PNR rats were larger at low repetition rates (that is, 4 and 7 pps; ANOVA with *post hoc* Student-Newman-Keuls test, $P < 0.05$ – 0.001), whereas they were consistently smaller at higher rates (that is, 10–20 pps; ANOVA with *post hoc* Student-Newman-Keuls test, $P < 0.05$ – 0.001) than in CON rats. Although the vector strength and Rayleigh statistic obtained from EXP rats peaked at the same repetition rates as did CON rats, they were larger at certain higher repetition rates (that is, 15–20 pps for vector strength and 10–20 pps for Rayleigh statistic, respectively; ANOVA with *post hoc* Student-Newman-Keuls test, $P < 0.05$ – 0.001).

Consistent with an earlier study³, rats reared in structured noise that was consistently delivered at low temporal rates had enduring, degraded cortical responses to higher modulation-rate sounds. We trained these noise-reared juvenile and young adult post-critical period rats in a temporal rate-discrimination task over the course of 2 months, initiating training when the rats were 35 d old. We found that degraded dynamic cortical responses and response synchronization for trained animals were alleviated across the range of modulation frequencies that were targeted in training. Indeed, dynamics were driven to an above-normal level in trained versus control rats. This remodeling of cortical temporal processing was paralleled by an alteration in the dynamics of cortical post-stimulation suppression (Supplementary Fig. 2 online). The training-induced cortical changes endured for at least 2 months after training ceased (Supplementary Fig. 3 online). Our results illustrate, for the first time to the best of our

knowledge, the neurological restoration of cortical temporal processing capacities by intensive behavioral training in developmentally degraded juvenile and adult animals. Temporal training in this form had no measurable effect on the spectral response selectivity of A1 neurons (Supplementary Fig. 4 online), supporting the earlier conclusion that learning-based cortical plasticity is restricted to stimulus parameters that are established ‘top-down’ by the task demands¹⁰.

Our results imply that this training must necessarily result in adjustments in the time constants governing post-excitatory synaptic suppression, paired-pulse facilitation and slow inhibitory potentials^{4,11,12}. They show that cortical networks have a wide capacity for adjusting their fundamental sampling-rate characteristics by adjusting the many processes that govern their dynamics and, hypothetically, by selectively strengthening intrinsic circuits that support faster versus slower cycle-by-cycle operations. These results indicate that the manifold processes governing this very elementary dimension of cortical processing are, together, reversible.

In humans, refinements in the central representations of spectral, intensive and temporal aspects of acoustic inputs in developmentally impaired children achieved through intensive training have been argued to facilitate their more accurate encoding of phonemic inputs, thereby improving speech reception and language-processing abilities^{13,14}. We have behaviorally documented the re-normalization of cortical sampling-rate characteristics by intensive training akin to that applied in these rats in language- and reading-impaired children, and have shown that improvements in this very elemental processing ability are correlated with training-induced gains in these children’s more general language and reading abilities¹³. Here we found the probable physiological basis for those positive changes in the sampling-rate characteristics of cortical networks that are so crucial for complex stimulus encoding and found that they can be selectively restored in cortical field A1 by relatively simple forms of training initiated at an older brain age. We have previously demonstrated that perceptual training also refines deteriorated cortical frequency representations that are again induced by early noise exposure¹⁵. All of these findings contribute to the rapidly growing body of studies that reveal the extent to which, and the specific strategies by which, developmentally impaired brains can be corrected in older (post-critical period) children and adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Learning a temporal rate-discrimination task. **(a,b)** Behavioral performance of noise-reared rats on the temporal rate-discrimination task in the early **(a)** and late **(b)** training days. Left, target and nontarget responses for each block during a single training day. The time required for rats to complete each block is also shown (right ordinate). Error bars represent s.e.m. * $P < 0.001$, compared with the first block for both target and nontarget responses. Right, distribution of total responses for each block.

Figure 2.

Cortical temporal responses for different groups of rats. **(a)** Experimental time lines for different groups of rats. Postnatal day 7 or 35 (P7 or P35). **(b)** Average tMTFs of cortical responses to repetitive tone stimuli at different repetition rates. Error bars represent s.e.m. * $P < 0.001$, EXP versus CON. ** $P < 0.01-0.001$, UNR or PNR versus CON. **(c)** Representative auditory cortical $f_{h1/2}$ maps obtained from single rats of different groups. The color of each polygon indicates the $f_{h1/2}$ recorded at that site. Unfilled polygons indicate that the tMTF was not recorded at that site. A, anterior; D, dorsal; ○, non-A1 site; ×, nonresponsive cortical site. **(d)** Cumulative frequency histograms of $f_{h1/2}$ (top) and average $f_{h1/2}$ for each of three characteristic frequency ranges (bottom). * $P < 0.01$, EXP versus CON. ** $P < 0.01-0.001$, UNR or PNR versus CON. **(e)** Average vector strengths (left) and Rayleigh statistics (right) at different repetition rates. * $P < 0.05-0.001$, EXP versus CON. ** $P < 0.05-0.001$, UNR or PNR versus CON.