INVITED REVIEW

Darwinian computation with a functional map of the auditory cortexHirokazu Takahashi^{1,2,*}¹*Department of Mechano-Informatics, Graduate School of Information Science and Technology, The University of Tokyo,
7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8656 Japan*²*Research Center for Advanced Science and Technology, The University of Tokyo,
4-6-1 Komaba, Meguro-ku, Tokyo, 153-8904 Japan*

Abstract: Place codes of frequency, or tonotopic maps, are commonly found in the auditory pathway, from the cochlea to the auditory cortex, and thus, are believed to play substantial roles in auditory computation. In contrast, in the auditory cortex, tonotopic activation is clearly observed at the onset responses within 50-ms post-stimulus latency but rapidly decays to long-lasting suboptimal stimuli, suggesting that neural representation is made beyond the tonotopic map. We recently demonstrated in the rat auditory cortex that the degree of response variance is closely correlated with the size of its representational area, suggesting that place coding is an effective strategy to generate diverse response properties within a neural population. We also demonstrated long-lasting sound-induced steady-state local synchrony within the auditory cortex, where neural representation might be made in a different manner from transient tonotopic activation at stimulus onset. These results support the idea of Darwinian computation, where the tonotopic map effectively creates a response variance, while the steady-state synchrony gradually selects the neural population beyond the tonotopic map.

Keywords: Auditory cortex, Neural coding, Microelectrode, Rat

PACS number: 43.64.Qh [doi:10.1250/ast.41.39]

1. INTRODUCTION

Auditory perception undoubtedly emerges from activation of the auditory cortex. While our auditory perception is relatively stable throughout life, the auditory cortex dynamically changes depending on experience and learning. Based on these experimental facts, the principles underlying encoding of sounds with a wealth of plasticity in the auditory cortex has long been discussed.

In particular, map plasticity in the auditory cortex has long been the focus of interests over decades. The development of the place code of frequency, or tonotopic map, in the auditory cortex depends on the auditory environment [1,2], whereas the tonotopic map is originally produced at the level of the cochlea based on its mechanical properties with low flexibility. Some pioneering studies interpreted map plasticity as an evidence that cortical representations encode behaviorally relevant information [3–7]. However, others argued that map plasticity is not always associated with enhanced perceptual ability [8–10] and is sometimes associated with deteriorated percepts [11]. These diverse observations have made it difficult to

understand the roles the tonotopic map plays in computation in the auditory cortex.

A common caveat to the abovementioned studies is that map plasticity has been characterized in the most distinct neural activation following the stimulus onset with a post-stimulus latency within 50 ms under anesthesia. Therefore, another line of recent studies has characterized single-unit activities beyond the onset activities under an awake condition [12–16]. Importantly, the onset activities are occasionally followed by long-lasting sustained activities that last during the stimulus presentation when spectrotemporal characteristics of the stimulus are optimal to a given neuron but usually rapidly decay to most suboptimal stimuli. Despite the notion that such sustained activities undoubtedly play substantial roles in auditory perception, narrow tunings of sustained activities have hampered bridging a gap between the tonotopic map and sustained activities to date.

We here review our recent experiments and discuss about the underlying principle of encoding in the transient onset activities and long-lasting sustained activities in the auditory cortex [17–27]. In our working hypothesis, the Darwinian principle is implemented in the auditory cortex and probably other sensory cortices: the onset activities

*e-mail: takahashi@i.u-tokyo.ac.jp

cover all the possibilities of what to represent, and the sustained activities gradually narrow the possibility through local synchrony.

2. FUNCTIONAL MAP AS A BLANKET OF RESPONSE VARIANCE

Santiago Ramón y Cajal predicted in 1904 that acquisition of new skill, such as playing piano, could be characterized as a two-step learning process: formation of new pathways in the neural circuits and reinforcement and refinement of pre-established pathways. Almost a century later, such two-step plasticity was confirmed in the motor cortex in modern brain imaging studies [28,29]. More microscopically, a large fraction of excitatory neurons developed movement-related activity with a transient increase in dendritic spine turnover in the initial phase of learning, while the fraction of movement-related neurons decreased gradually in the late phase of learning [30]. Similarly, in experience-dependent plasticity in the somatosensory and visual cortices after deafferentation, expansions of receptive fields are followed by shrinkages and use-dependent refinements [31–33]. These observations are reminiscent of the Darwinian principle, which consists of two-step processes, i.e., variation and natural selection. More specifically, the theory of neural Darwinism predicts that variation and selection within neural populations are crucial to cortical computation.

Heterogeneity and variance of neural activities in the cortex could be a sign of the Darwinian principle, which is consistent with the well-established notion of sparse coding [12–14] and complex feature selectivity in the long-lasting sustained activities of the auditory cortical neurons [15,16]. Additionally, recent studies on two-photon calcium imaging with a single cellular resolution has revealed that the tonotopic map was present on a large scale but was fractured on a fine scale, i.e., within a single column, suggesting that groups of nearby neurons with locally shared inputs perform independent parallel computations and create wide variation within the group [34,35].

As a further experimental proof of neural Darwinism in the sensory cortex, we have hypothesized that response variance within a given group (e.g., tonotopic column and functionally delineated field) is closely associated with the size of the corresponding representational area. To test this hypothesis, we have investigated learning-stage-dependent map plasticity in the auditory cortex of rats [17,18,21].

In our previous study [17], we trained rats in nose poking during the presentation of a conditioned stimulus of 20-kHz tone with food pellet rewards. The rates of both hit and false-positive responses increased during the early stage of training, while hit responses continued to increase but false-positive responses decreased thereafter. On day 4, the maximum false-positive rate was observed. Both hit

and false-positive rates reached asymptotes by day 20. We performed microelectrode mapping at the depth of layer 4 in the auditory cortex of isoflurane-anesthetized rats and characterized the tonotopic map in 3 groups: non-trained naïve control group; day 4 group, engaged in training for 4 consecutive days; and day 20 group, underwent training for ≥ 20 days.

At each recording site, frequency response areas (FRAs) were characterized to identify the characteristic frequency (CF) and tonotopic map in the auditory cortex (Fig. 1A). The tonotopic map is then further divided into multiple auditory fields based on tonotopic discontinuity, response latency, and FRA properties (Fig. 1B). These tonotopic and field maps changed dynamically during learning (Fig. 1C) in that tone-responsive area tended to expand at the early stage and shrink after extended training. Interestingly, late-stage shrinkage was significantly correlated with behavioral performance.

Next, we investigated the response variability within the tonotopic map to find links between the response variance and representational area in the map. Despite having an identical CF, some multiunit responses show large FRAs (left column in Fig. 1A), while others show small and uncertain FRAs (right column in Fig. 1A). To quantify such variability among units, we used mutual information (MI) to estimate how a discharge rate at a given site carried information about the frequency of test tones. Qualitatively, small and uncertain FRAs tended to result in small MI. Consistent with the notion of sparse coding in the auditory cortex, MI was typically small. However, the degree of response variance was dependent on CF with more units having large MI in high-CF regions (Fig. 1D). Additionally, MI distribution also depended on the stage of learning such that response variation temporally increased at day 4 and decreased at day 20. These results were consistent with the variation and selection process in neural Darwinism. Consequently, neural representations may become sparse during the later stages of learning [36].

Most importantly, the variance of MI was significantly positively correlated with the representational area delineated by either CF or auditory subfield (Fig. 1E(i)), irrespective of the learning stage. Significant correlation was also observed in the maximum value of MI (Fig. 1E(ii)) but was not obvious in the minimum value (Fig. 1E(iii)) because small MI was commonly observed in all test groups. Furthermore, the learning-induced changes of representational area were also positively correlated with those of MI (Fig. 1E(iv)), suggesting that a gain and loss of representational area are associated with diversification and sparsification of neural responses, respectively. This result adds compelling evidence regarding the functional link between the response variability and representational area

Fig. 1 Map plasticity and response variance. A. Representative frequency response area (FRA). Mutual information (MI) for each unit is indicated in the upper insets. B. Cortical map from naïve, day 4, and day 20 groups. Cortical maps from individual subjects were superimposed with the positional reference of the highest CF location and the aligned flat-skull plane. Abbreviations: A, anterior; P, posterior; D, dorsal; V, ventral. C. Learning-stage-dependent representational area for the CF (i) and auditory subfields (ii). D. MI distribution. Histogram of entire data include the following: (i) naïve ($n = 838$); (ii) day 4 ($n = 965$); and (iii) day 20 ($n = 618$). (b) CF-dependent distribution. On each box, the central mark is the median, and the edges of the box are the 25th and 75th percentiles. The whiskers extend to the most extreme data points. (c) Auditory-subfield-dependent distribution. E. MI distribution on the functional map. (i) Interquartile range (IQR) of MI with respect to representational area with a given property, i.e., CF and auditory subfield. The shapes indicate the test groups: circle, naïve; triangle, day 4; and square, day 20. R and p are Pearson's correlation and its significance level (t -test), respectively. (ii) Maximum value of MI. (iii) Minimum value of MI. (iv) Learning-induced changes in MI IQR (Δ IQR) and representational area (Δ area). These figures were adapted and modified from [17,21].

because the measure of learning-induced change is not biased by the delineation of the test area, i.e., binning of CF.

Thus, within the functional units of computation (e.g., tonotopic columns and auditory fields), the degree of response variability is likely to be comodulated with the representational area according to training and experience. In other words, larger representational areas may help accommodate a heterogeneous population of neurons that emit diverse responses to stimuli. Empirically, representational areas in the sensorimotor cortices are likely to increase with their functional importance [6,7,37]. The auditory cortex of rats had wider ultrasonic, high-frequency regions than low-frequency regions, possibly because ultrasonic sounds are used for vocal communications [38,39]. In contrast, a larger representational area is devoted to low frequencies <10 kHz in the auditory cortex of cats [40] and monkeys [41], whose vocal communications are mediated within these lower ranges that are audible to humans. These biased distributions of functional columns can be considered as experimental evidence of Darwinian computation.

The original theory of neural Darwinism involves selective death of neurons [42], but now we usually assume selective strengthening or weakening of population of synapses [43]. Our and other studies on map plasticity are consistent with the expansion and renormalization model based on Darwinian selection [44]. In this model, the number of neural circuits that respond to task stimuli increases at the early stage, causing heterogeneous circuits to emerge. The late stage of learning constitutes selection of the most efficient neural circuit from the heterogeneous population. By the end of learning, the useful circuit is stabilized, and the cortical map is normalized. This model is also consistent with recent findings in human studies that neural plasticity is transient in motor and perceptual learning [45–47].

The functional map endows neurons in close proximity with shared synaptic inputs and allows mutually independent computations among neurons [34]. Decorrelating neuronal activities from shared inputs is a possible neural mechanism to generate variance of neural patterns [20,48–50]. Paradoxically, the functional map could be capricious in some conditions [51,52]. Thus, the functional map is likely to play an essential role in Darwinian computation, serving as an effective, but not absolutely necessary, structure to generate various response properties within a neural population.

3. SELECTION THROUGH LOCAL SYNCHRONY

As discussed in the previous section, sound stimuli recruit a large number of neurons at the stimulus onsets

within tonotopic columns of given stimulus frequencies. Our experimental finding that response variance was correlated with its representational size in the tonotopic map suggests that place coding is an effective strategy to generate diverse response properties within the neural population. However, following such onset activities, sustained activities were observed in only a small number of neurons but rapidly decayed in the majority of neurons [15,16]. Therefore, it is still challenging to characterize stimulus representation in the sustained activities, despite of the broad consensus on its importance in perception.

Sustained activities may be fine-tuned to the optimal stimulus through cortical interaction between neurons, which is different from classical tuning properties, i.e., feedforward thalamocortical activation at the stimulus onset within 50-ms post-stimulus latency. Large-scale interaction gives rise to a cortical state, which could predict discharges in a single neuron under test and external stimuli [53,54]. These state-dependent discharges are produced by specific spatiotemporal patterns of shared inputs spreading across several millimeters [25,55–57], which should be associated with local synchrony within the auditory cortex. Thus, we hypothesized that sound-induced band-specific power and phase synchrony patterns in local field potential (LFP) could be considered as cortical states underlying sustained activities and represent rich information on test sounds.

We implanted a microelectrode array with a 10×10 grid of recording sites to characterize onset and sustained activities from layer 4 in the auditory cortex of isoflurane-anesthetized rats [23]. Here, the sustained activities were defined as time average of band-specific LFP power and phase locking value (PLV) with a given time window during long-lasting tones with a duration of 30 s. Sparse logistic regression (SLR), one of the machine learning algorithms for classification with sparse parameter estimation, was then applied to determine whether and how the existence of test tone could be predicted from LFP power and phase synchrony patterns. During supervised learning for classification, SLR prunes irrelevant dimensions of data by setting their associated weights to zero [58]. We assumed that the resultant sparse representation would indicate some neural correlates and contribute to understanding of the cortical representation of sustained activities [22,59].

Figure 2A shows the representative organization of the auditory cortex within a 10×10 grid of recording sites. Based on the tonotopic discontinuity, FRA characteristics, and latency, each recording site was classified into the core, belt, and non-auditory regions. The core region includes A1 and AAF, each of which exhibits a posterior-to-anterior or lateral-to-dorsal tonotopic gradient and short peak latency.

Fig. 2 Decoding of tone presence from the onset and sustained activities. A. Representative cortical map within a grid of 10×10 microelectrode array. B. Representative activity patterns under test: (i) onset activity; (ii) high-gamma power in the sustained activity; and (iii) high-gamma phase locking value (PLV) in the sustained activity. C. Decoding performance: (i) onset activity; (ii) band-specific power in the sustained activity; and (iii) band-specific PLV in the sustained activity. These figures were adapted from [22].

The belt region consisted of several subfields with longer latency than that of the core region.

Figure 2B(i) shows the representative spatial patterns of LFP amplitudes in spontaneous activity and the onset activities. As compared with spontaneous activity, auditory-evoked LFPs exhibited several distinct activation foci, depending on the test frequency. Such clear differences between auditory-evoked and spontaneous LFPs led to the high accuracy rate of decoding ($>95\%$) (Fig. 2C(i)).

Figure 2B(ii) shows the representative patterns of band-specific, high-gamma power during sustained activ-

ity, which was less distinct than those during spontaneous activity. Nonetheless, discrimination accuracy between silence and a given tone presence increased with the length of the time window, and the highest accuracy (68.3%) was achieved in the high-gamma band for a time window of 1,000 ms, suggesting that stable synchrony pattern is informative (Fig. 2C(ii)).

Figure 2B(iii) shows the representative PLV patterns, i.e., local synchrony patterns, which have extremely high dimensions of 4,560. Such high dimension makes it difficult to manually extract distinct patterns or informative

pairs of recording sites that represent the existence of a test tone. Nonetheless, SLR was able to discriminate between sound-induced and spontaneous activities from PLV patterns. The highest accuracy (71.3%) was achieved in the high-gamma band for the time window of 1,000 ms, again supporting that stable synchrony patterns within the auditory cortex represent rich information on sounds (Fig. 2C(iii)).

During the supervised learning phase, SLR selected informative recording sites and removed irrelevant recording sites from the discriminator by updating their weights. We examined the selected features in the 20 most successful discriminations of each test frequency and characterized how these informative features are distributed among the tonotopic and field maps in the auditory cortex.

For the onset activity, 2.3 ± 0.96 (mean $\pm$ standard deviation) recording sites were selected. Most of these remaining sites (90.8%) had CFs, which gradually increased with the test frequency. The CFs at the peaks of these histograms almost corresponded to the test frequencies, indicating that the frequency representation of the auditory-evoked LFP is consistent with the tonotopic organization in the auditory cortex.

The sustained activities exhibited similar trends. For high-gamma bandpower, 15 ± 5.9 recording sites remained, and for PLV, 12.5 ± 4.3 pairs of recording sites (i.e., 25 ± 8.6 recording sites) remained. The remaining sites were likely to have CFs that were close to the decoded test frequency, indicating that the frequency representation of the bandpower and PLV also corresponds to the tonotopic organization.

More interestingly, each auditory subfield was likely to contribute differently between the onset and sustained activities. For the onset activity, the core region contributed more to decoding than the chance level, while the belt region had higher contribution during sustained activities. Thus, sparse parameter estimation with SLR revealed that both the onset and sustained activities represent the test frequency according to the tonotopic organization of the auditory cortex but depend on different cortical regions.

At the level of auditory nerves, sustained steady-state firing activities are commonly observed, although these firing rates are reduced by approximately half [60,61]. Such steady-state firings are forwarded to the auditory cortex in a tonotopically organized manner and organize band-specific power and PLV in cortical LFPs, which might underlie sustained activities in a small number of cortical neurons [15,16] and synchronized firing among neurons [56,62].

For both the band-specific power and PLV, the highest decoding performance was achieved in the gamma band, which has long been considered to mediate feature binding and perception in the visual and auditory cortices

[24,25,63–66]. The gamma band synchrony mainly reflects activities of inhibitory interneurons in the cortex [67,68], and the cortical inhibition plays an important role in both sparse coding [12,69,70]. These facts are consistent with our view of neural Darwinism: through inhibition of irrelevant activities during local synchrony, a neural population is selected from a pool of diverse responses recruited in the onset activities.

SLR suggested that the belt cortex, i.e., higher-order auditory areas, was more informative than the core cortex during the sustained activities, while the core was more informative than the belt in the onset activities. The core cortex receives feedforward projection from the ventral division of the medial geniculate body (MGB), the main station of the auditory thalamus, and this thalamocortical projection is a source of the onset activities [71,72]. The belt cortex receives thalamocortical projections from the medial division of the MGB and reciprocal connections within the auditory cortex and with other regions including the basal ganglia, amygdala, and prefrontal cortex [71–80]. Together with these anatomical facts, our results indicate that the computation in the auditory cortex is tonotopically and hierarchically organized, starting from the onset activities in the core cortex and recruiting the belt cortex during the sustained activities for higher-order functions.

4. OUTLOOK

We have discussed so far about the Darwinian principle, which is likely implemented in the auditory cortex for perception and perceptual learning. The principle consists of two steps: diversification and selection of neural responses. At the onset activities, the functional map serves as an effective blanket of response variance through mutually independent computations among neurons with shared synaptic inputs. From the neural population participating in onset activities that cover all the possibilities of what to represent, the sustained activities gradually narrow the possibilities through the gamma-band local synchrony emerging from interaction of inhibitory interneurons.

Thus, we believe that response variance and steady-state synchrony within the functional map play substantial roles in cortical computation. Learning-induced map plasticity in the sensorimotor cortex could be interpreted as a modification of response variance within a given cortical region. Phantom perception, e.g., phantom-limb pain and tinnitus, is often associated with disorganization of functional maps in the sensory cortex [81,82] and probably with maladaptive response variance in an affected region. Furthermore, thalamocortical dysrhythmia has long been considered as a neural mechanism of tinnitus [83,84], and accumulating evidence has indicated to date that tinnitus is associated with increased gamma activities [85–87]. This pathological perception could be relieved by

vagus nerve stimulation, an emerging technology that induces targeted plasticity, which reorganizes the pathological functional maps and modulates gamma synchrony [26,44,88,89].

Our preliminary studies suggest that the steady-state local synchrony within the auditory cortex might play important functional roles, which still remain to be clarified. For example, consonance and tonality modulate the local synchrony in a band-specific manner [90]. Appetitive and aversive learnings also modulate the synchrony differently [91]. Learning-induced map plasticity, which has long been the center of focus in the research field of sensory cortex, is likely involved in the diversification process in the Darwinian principle. Map plasticity outside the behavioral context by pairing tones with stimulation of the cholinergic nucleus basalis did not affect tone discrimination performance but enhance perceptual learning [92]. Therefore, the missing link to better understand how the sensory cortex works might be the selection process in the Darwinian principle, one of the most likely candidates of which is the gamma-band local synchrony emerging from inhibitory neurons.

This work is partly based on results obtained from projects commissioned by JSPS KAKENHI (17K20090, 18H04999), AMED (JP18dm0307009), NEDO (18101806-0), and the Tateishi Science and Technology Foundation.

REFERENCES

- [1] E. F. Chang and M. M. Merzenich, "Environmental noise retards auditory cortical development," *Science*, **300**, 498–502 (2003).
- [2] L. I. Zhang, S. Bao and M. M. Merzenich, "Persistent and specific influences of early acoustic environments on primary auditory cortex," *Nat. Neurosci.*, **4**, 1123–1130 (2001).
- [3] K. M. Bieszczad and N. M. Weinberger, "Representational gain in cortical area underlies increase of memory strength," *Proc. Natl. Acad. Sci. USA*, **107**, 3793–3798 (2010).
- [4] G. Recanzone, C. Schreiner and M. Merzenich, "Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys," *J. Neurosci.*, **13**, 87–103 (1993).
- [5] D. B. Polley, E. E. Steinberg and M. M. Merzenich, "Perceptual learning directs auditory cortical map reorganization through top-down influences," *J. Neurosci.*, **26**, 4970–4982 (2006).
- [6] R. G. Rutkowski and N. M. Weinberger, "Encoding of learned importance of sound by magnitude of representational area in primary auditory cortex," *Proc. Natl. Acad. Sci. USA*, **102**, 13664–13669 (2005).
- [7] N. M. Weinberger, "Associative representational plasticity in the auditory cortex: A synthesis of two disciplines," *Learn. Mem.*, **14**, 1–16 (2007).
- [8] S. K. Talwar and G. L. Gerstein, "Reorganization in awake rat auditory cortex by local microstimulation and its effect on frequency-discrimination behavior," *J. Neurophysiol.*, **86**, 1555–1572 (2001).
- [9] M. Brown, D. R. Irvine and V. N. Park, "Perceptual learning on an auditory frequency discrimination task by cats: Association with changes in primary auditory cortex," *Cereb. Cortex*, **14**, 952–965 (2004).
- [10] J. M. Edeline and N. M. Weinberger, "Receptive field plasticity in the auditory cortex during frequency discrimination training: Selective retuning independent of task difficulty," *Behav. Neurosci.*, **107**, 82–103 (1993).
- [11] Y. K. Han, H. Kover, M. N. Insanally, J. H. Semerdjian and S. Bao, "Early experience impairs perceptual discrimination," *Nat. Neurosci.*, **10**, 1191–1197 (2007).
- [12] T. Hromadka, M. DeWeese and A. Zador, "Sparse representation of sounds in the unanesthetized auditory cortex," *Plos Biol.*, **6**, 124–137 (2008).
- [13] T. Hromadka and A. M. Zador, "Representations in auditory cortex," *Curr. Opin. Neurobiol.*, **19**, 430–433 (2009).
- [14] O. Bar-Yosef and I. Nelken, "The effects of background noise on the neural responses to natural sounds in cat primary auditory cortex," *Front. Comput. Neurosci.*, **1**, 1–14 (2007).
- [15] X. Wang, T. Lu, R. K. Snider and L. Liang, "Sustained firing in auditory cortex evoked by preferred stimuli," *Nature*, **435**(7040), 341–346 (2005).
- [16] X. Q. Wang, "Cortical coding of auditory features," *Annu. Rev. Neurosci.*, **41**, 527–552 (2018).
- [17] H. Takahashi, R. Yokota, A. Funamizu, H. Kose and R. Kanzaki, "Learning-stage-dependent, field-specific, map plasticity in the rat auditory cortex during appetitive operant conditioning," *Neuroscience*, **199**, 243–258 (2011).
- [18] H. Takahashi, A. Funamizu, Y. Mitsumori, H. Kose and R. Kanzaki, "Progressive plasticity of auditory cortex during appetitive operant conditioning," *Biosystems*, **101**, 37–41 (2010).
- [19] R. Yokota, K. Aihara, R. Kanzaki and H. Takahashi, "Learning-stage-dependent plasticity of temporal coherence in the auditory cortex of rats," *Brain Topogr.*, **28**, 401–410 (2015).
- [20] R. Yokota, K. Aihara, R. Kanzaki and H. Takahashi, "Tonotopic-column-dependent variability of neural encoding in the auditory cortex of rats," *Neuroscience*, **223**, 377–387 (2012).
- [21] H. Takahashi, R. Yokota and R. Kanzaki, "Response variance in functional maps: Neural darwinism revisited," *PLoS One*, **8**, e68705 (2013).
- [22] T. I. Shiramatsu, T. Noda, K. Akutsu and H. Takahashi, "Tonotopic and field-specific representation of long-lasting sustained activity in rat auditory cortex," *Front. Neural Circuits*, **10**, 59 (2016).
- [23] T. Noda and H. Takahashi, "Anesthetic effects of isoflurane on the tonotopic map and neuronal population activity in the rat auditory cortex," *Eur. J. Neurosci.*, **42**, 2298–2311 (2015).
- [24] T. Noda, R. Kanzaki and H. Takahashi, "Stimulus phase locking of cortical oscillation for auditory stream segregation in rats," *Plos One*, **8**, e83544 (2013).
- [25] T. Noda, T. Amemiya, T. Shiramatsu and H. Takahashi, "Stimulus phase locking of cortical oscillations for rhythmic tone sequences in rats," *Front. Neural Circuits*, **11**, 2 (2017).
- [26] R. Kano, K. Usami, T. Noda, T. I. Shiramatsu, R. Kanzaki, K. Kawai and H. Takahashi, "Vagus nerve stimulation-induced synchrony modulation of local field potential in the rat cerebral cortex," *Electron. Commun. Jpn.*, **98**(3), 47–56 (2015).
- [27] A. Funamizu, R. Kanzaki and H. Takahashi, "Pre-attentive, context-specific representation of fear memory in the auditory cortex of rat," *PLoS ONE*, **8**, e63655 (2013).
- [28] A. Pascual-Leone, A. Amedi, F. Fregni and L. Merabet, "The plastic human brain cortex," *Annu. Rev. Neurosci.*, **28**, 377–401 (2005).
- [29] A. Karni, G. Meyer, P. Jezard, M. Adams, R. Turner and L. Ungerleider, "Functional MRI evidence for adult motor cortex plasticity during motor skill learning," *Nature*, **377**, 155–158

- (1995).
- [30] A. J. Peters, S. X. Chen and T. Komiyama, "Emergence of reproducible spatiotemporal activity during motor learning," *Nature*, **510**(7504), 263–267 (2014).
 - [31] E. Jones, "Cortical and subcortical contributions to activity-dependent plasticity in primate somatosensory cortex," *Annu. Rev. Neurosci.*, **23**, 1–37 (2000).
 - [32] E. Foeller and D. E. Feldman, "Synaptic basis for developmental plasticity in somatosensory cortex," *Curr. Opin. Neurobiol.*, **14**, 89–95 (2004).
 - [33] K. Fox and R. O. Wong, "A comparison of experience-dependent plasticity in the visual and somatosensory systems," *Neuron*, **48**, 465–477 (2005).
 - [34] S. Bandyopadhyay, S. A. Shamma and P. O. Kanold, "Dichotomy of functional organization in the mouse auditory cortex," *Nat. Neurosci.*, **13**, 361–368 (2010).
 - [35] G. Rothschild, I. Nelken and A. Mizrahi, "Functional organization and population dynamics in the mouse primary auditory cortex," *Nat. Neurosci.*, **13**, 353–360 (2010).
 - [36] A. Gdalyahu, E. Tring, P. O. Polack, R. Gruver, P. Golshani, M. S. Fanselow, A. J. Silva and J. T. Trachtenberg, "Associative fear learning enhances sparse network coding in primary sensory cortex," *Neuron*, **75**, 121–132 (2012).
 - [37] W. Penfield and E. Boldrey, "Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation," *Brain*, **60**, 389–443 (1937).
 - [38] R. J. Blanchard, D. C. Blanchard, R. Agullana and S. M. Weiss, "22kHz alarm cries to presentation of a predator, by laboratory rats living in visible burrow systems," *Physiol. Behav.*, **50**, 967–972 (1991).
 - [39] R. J. Barfield and L. A. Geyer, "Sexual behavior: Ultrasonic postejaculatory song of male rat," *Science*, **176**(4041), 1349–1350 (1972).
 - [40] M. M. Merzenich, P. L. Knight and G. L. Roth, "Representation of cochlea within primary auditory cortex in the cat," *J. Neurophysiol.*, **38**, 231–249 (1975).
 - [41] X. Wang, M. Merzenich, R. Beitel and C. Schreiner, "Representation of a species-specific vocalization in the primary auditory cortex of the common marmoset, temporal and spectral characteristics," *J. Neurophysiol.*, **74**, 2685–2706 (1995).
 - [42] R. Dawkins, "Selective neurone death as a possible memory mechanism," *Nature*, **229**(5280), 118–119 (1971).
 - [43] G. Edelman, "Neural Darwinism, selection and reentrant signaling in higher brain function," *Neuron*, **10**, 115–125 (1993).
 - [44] M. P. Kilgard, "Harnessing plasticity to understand learning and treat disease," *Trends Neurosci.*, **35**, 715–722 (2012).
 - [45] L. Ma, B. Wang, S. Narayana, E. Hazeltine, X. Chen, D. A. Robin, P. T. Fox and J. Xiong, "Changes in regional activity are accompanied with changes in inter-regional connectivity during 4 weeks motor learning," *Brain Res.*, **1318**, 64–76 (2010).
 - [46] K. Molina-Luna, B. Hertler, M. M. Buitrago and A. R. Luft, "Motor learning transiently changes cortical somatotopy," *Neuroimage*, **40**, 1748–1754 (2008).
 - [47] Y. Yotsumoto, T. Watanabe and Y. Sasaki, "Different dynamics of performance and brain activation in the time course of perceptual learning," *Neuron*, **57**, 827–833 (2008).
 - [48] E. Zohary, M. Shadlen and W. Newsome, "Correlated neuronal discharge rate and its implications for psychophysical performance," *Nature*, **370**, 140–143 (1994).
 - [49] A. S. Ecker, P. Berens, G. A. Keliris, M. Bethge, N. K. Logothetis and A. S. Tolias, "Decorrelated neuronal firing in cortical microcircuits," *Science*, **327**(584), 584–587 (2010).
 - [50] A. Renart, J. de la Rocha, P. Bartho, L. Hollender, N. Parga, A. Reyes and K. D. Harris, "The asynchronous state in cortical circuits," *Science*, **327**(587), 587–590 (2010).
 - [51] J. C. Horton and D. L. Adams, "The cortical column: A structure without a function," *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, **360**, 837–862 (2005).
 - [52] D. L. Adams and J. C. Horton, "Capricious expression of cortical columns in the primate brain," *Nat. Neurosci.*, **6**, 113–114 (2003).
 - [53] A. Arieli, A. Sterkin, A. Grinvald and A. Aertsen, "Dynamics of ongoing activity: Explanation of the large variability in evoked cortical responses," *Science*, **273**(5283), 1868–1871 (1996).
 - [54] M. Tsodyks, T. Kenet, A. Grinvald and A. Arieli, "Linking spontaneous activity of single cortical neurons and the underlying functional architecture," *Science*, **286**(5446), 1943–1946 (1999).
 - [55] D. Y. Ts'o, C. D. Gilbert and T. N. Wiesel, "Relationships between horizontal interactions and functional architecture in cat striate cortex as revealed by cross-correlation analysis," *J. Neurosci.*, **6**, 1160–1170 (1986).
 - [56] R. C. deCharms and M. M. Merzenich, "Primary cortical representation of sounds by the coordination of action-potential timing," *Nature*, **381**, 610–613 (1996).
 - [57] K. D. Harris and A. Thiele, "Cortical state and attention," *Nat. Rev. Neurosci.*, **12**, 509–523 (2011).
 - [58] O. Yamashita, M. A. Sato, T. Yoshioka, F. Tong and Y. Kamitani, "Sparse estimation automatically selects voxels relevant for the decoding of fMRI activity patterns," *Neuroimage*, **42**, 1414–1429 (2008).
 - [59] A. Funamizu, R. Kanzaki and H. Takahashi, "Distributed representation of tone frequency in highly decodable spatio-temporal activity in the auditory cortex," *Neural Netw.*, **24**, 321–332 (2011).
 - [60] R. L. Smith and M. L. Brachman, "Operating range and maximum response of single auditory nerve fibers," *Brain Res.*, **184**, 499–505 (1980).
 - [61] L. A. Westerman and R. L. Smith, "Rapid and short-term adaptation in auditory nerve responses," *Hear. Res.*, **15**, 249–260 (1984).
 - [62] J. J. Eggermont, "Firing rate and firing synchrony distinguish dynamic from steady state sound," *Neuroreport*, **8**, 2709–2713 (1997).
 - [63] A. Engel, P. Fries and W. Singer, "Dynamic prediction, oscillations and synchrony in top-down processing," *Nat. Rev. Neurosci.*, **2**, 704–716 (2001).
 - [64] C. D. Gilbert and M. Sigman, "Brain states: Top-down influences in sensory processing," *Neuron*, **54**, 677–696 (2007).
 - [65] N. E. Crone, D. Boatman, B. Gordon and L. Hao, "Induced electrocorticographic gamma activity during auditory perception. Brazier Award-winning article, 2001," *Clin. Neurophysiol.*, **112**, 565–582 (2001).
 - [66] N. Weisz, S. Muller, W. Schlee, K. Dohrmann, T. Hartmann and T. Elbert, "The neural code of auditory phantom perception," *J. Neurosci.*, **27**, 1479–1484 (2007).
 - [67] M. Bartos, I. Vida and P. Jonas, "Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks," *Nat. Rev. Neurosci.*, **8**, 45–56 (2007).
 - [68] X. J. Wang, "Neurophysiological and computational principles of cortical rhythms in cognition," *Physiol. Rev.*, **90**, 1195–1268 (2010).
 - [69] J. Wolfe, A. R. Houweling and M. Brecht, "Sparse and powerful cortical spikes," *Curr. Opin. Neurobiol.*, **20**, 306–312 (2010).

- [70] G. K. Wu, R. Arbuckle, B. H. Liu, H. W. Tao and L. I. Zhang, "Lateral sharpening of cortical frequency tuning by approximately balanced inhibition," *Neuron*, **58**, 132–143 (2008).
- [71] C. C. Lee and J. A. Winer, "Connections of cat auditory cortex: I. Thalamocortical system," *J. Comp. Neurol.*, **507**, 1879–1900 (2008).
- [72] C. C. Lee, A. U. Kishan and J. A. Winer, "Wiring of divergent networks in the central auditory system," *Front. Neuroanat.*, **5** (2011).
- [73] C. C. Lee and J. A. Winer, "Connections of cat auditory cortex: III. Corticocortical system," *J. Comp. Neurol.*, **507**, 1920–1943 (2008).
- [74] M. Roger and P. Arnault, "Anatomical study of the connections of the primary auditory area in the rat," *J. Comp. Neurol.*, **287**, 339–359 (1989).
- [75] M. Malmierca, "The structure and physiology of the rat auditory system: An overview," *Int. Rev. Neurobiol.*, **56**, 147–211 (2003).
- [76] P. Arnault and M. Roger, "Ventral temporal cortex in the rat: Connections of secondary auditory areas Te2 and Te3," *J. Comp. Neurol.*, **302**, 110–123 (1990).
- [77] L. Romanski and J. LeDoux, "Information cascade from primary auditory cortex to amygdala, corticocortical and corticoamygdaloid projections of temporal cortex in the rat," *Cereb. Cortex*, **3**, 515–532 (1993).
- [78] L. M. Romanski, B. Tian, J. Fritz, M. Mishkin, P. Goldman-Rakic and J. Rauschecker, "Dual stream of auditory afferents target multiple domains in the primate prefrontal cortex," *Nat. Neurosci.*, **2**, 1131–1136 (1999).
- [79] L. M. Romanski, J. F. Bates and P. S. Goldman-Rakic, "Auditory belt and parabelt projections to the prefrontal cortex in the rhesus monkey," *J. Comp. Neurol.*, **403**, 141–157 (1999).
- [80] R. Reale and T. Imig, "Auditory cortical field projections to the basal ganglia of the cat," *Neuroscience*, **8**, 67–86 (1983).
- [81] H. Flor, T. Elert, S. Knecht, C. Wlenbruch, C. Pantev, N. Birbaumer, W. Larbig and E. Taub, "Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation," *Nature*, **375**, 482–484 (1995).
- [82] W. Muhlcnickel, T. Elbert, E. Taub and H. Flor, "Reorganization of auditory cortex in tinnitus," *Proc. Natl. Acad. Sci. USA*, **95**, 10340–10343 (1998).
- [83] D. De Ridder, S. Vanneste, B. Langguth and R. Llinas, "Thalamocortical dysrhythmia: A theoretical update in tinnitus," *Front. Neurol.*, **6** (2015).
- [84] R. R. Llinas, U. Ribary, D. Jeanmonod, E. Kronberg and P. P. Mitra, "Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography," *Proc. Natl. Acad. Sci. USA*, **96**, 15222–15227 (1999).
- [85] W. Sedley, S. Teki, S. Kumar, G. R. Barnes, D. E. Bamiou and T. D. Griffiths, "Single-subject oscillatory gamma responses in tinnitus," *Brain*, **135**, 3089–3100 (2012).
- [86] M. Ortmann, N. Mueller, W. Schlee and N. Weisz, "Rapid increases of gamma power in the auditory cortex following noise trauma in humans," *Eur. J. Neurosci.*, **33**, 568–575 (2011).
- [87] W. Schlee, T. Hartmann, B. Langguth and N. Weisz, "Abnormal resting-state cortical coupling in chronic tinnitus," *BMC Neurosci.*, **10**, 11 (2009).
- [88] N. D. Engineer, J. R. Riley, J. D. Seale, W. A. Vrana, J. A. Shetake, S. P. Sudanagunta, M. S. Borland and M. P. Kilgard, "Reversing pathological neural activity using targeted plasticity," *Nature*, **470**, 101–104 (2011).
- [89] J. A. Nichols, A. R. Nichols, S. M. Smirnakis, N. D. Engineer, M. P. Kilgard and M. Atzori, "Vagus nerve stimulation modulates cortical synchrony and excitability through the activation of muscarinic receptors," *Neuroscience*, **189**, 207–214 (2011).
- [90] T. I. Shiramatsu and H. Takahashi, "Neural representation of sound texture in the auditory cortex," *Brain Nerve*, **67**, 679–690 (2015) (in Japanese).
- [91] T. Isoguchi, T. Noda, R. Kanzaki and H. Takahashi, "Phase locking value depending on the emotional valence of sound in rat auditory cortex," *Proc. Aud. Res. Meet. Acoust. Soc. Jpn.*, **41**, 599–604 (2011) (in Japanese).
- [92] A. Reed, J. Riley, R. Carraway, A. Carrasco, C. Perez, V. Jakkamsetti and M. P. Kilgard, "Cortical map plasticity improves learning but is not necessary for improved performance," *Neuron*, **70**, 121–131 (2011).