Tuning the brain by learning and by stimulation of the nucleus basalis

Norman M. Weinberger

Although it is well-established that the cerebral cortex is a substrate for learning, memory and higher cognitive functions, rather less is known about the mechanisms by which experiences are acquired and stored in the cortex. The role of the basal forebrain cholinergic system (BFCS) in learning-induced plasticity is underlined by a recent report by Kilgard and Merzenich[1]. In this article I will discuss the findings of Kilgard and Merzenich in the context of other developments in our understanding of the BFCS and its role in learning-induced plasticity. However, before the discussion I would like to provide some essential background information.

Plasticity in adult primary auditory cortex

The role of learning in the induction and maintenance of physiological plasticity in the adult primary auditory cortex addresses at least three fundamental issues. First, the fact that learning alters primary auditory cortex shows that traditional views of its function as purely sensory are wrong. Second, because plasticity readily develops in the adult, the belief that sensory plasticity is confined to critical developmental stages is incorrect. Third, as explained below, the plasticity is highly selective, suggesting that it has sufficient specificity to be involved in the actual representation and storage of experiences, that is, to serve as a substrate of some of the contents of memory.

Auditory cortical plasticity has been found for learning and memory in a variety of tasks, most extensively in rapid classical conditioning and also during both rapid and slow instrumental conditioning in experimental animals. It has also been found for classical conditioning in humans. In classical conditioning, associative processes generally produce an increased neuronal response to the conditioned stimulus (CS) when subjects learn that this stimulus predicts (i.e. is associated with) a forthcoming unconditioned stimulus (US), such as food or mild electric shock. Recently, the application of sensory physiological approaches has revealed that the augmented response to the CS is part of a highly selective alteration in neuronal receptive fields. For the commonly studied domain of acoustic frequency, the receptive field of an auditory cortical neuron can be represented by discharge rate as a function of frequency. The peak of this frequency tuning function is generally called the 'best frequency' (BF).

Learning-induced receptive-field plasticity in the primary auditory cortex was first reported in 1990 (Ref. 2), in the guinea pig. This study revealed not only increased response to the frequency of the conditioned stimulus but also decreased responses to the original (pretraining) BF and many other frequencies. These opposite changes could produce a shift in frequency tuning, toward or even to the frequency of the conditioned stimulus so that it became the new BF. That is, learning about stimulus relationships involves the specific re-tuning of cortical cells.

This receptive-field plasticity is associative (i.e. requires CS–US pairing), develops very rapidly (in as few as five trials), is highly specific (decreased responses to frequencies as close as 0.1 octave from the CS frequency), is discriminative (increased response to a reinforced frequency, decreased response to a non-reinforced frequency), is extremely long lasting (retained at the longest testing interval of two months), is not caused by arousal to the CS, develops in both classical and instrumental conditioning, and is sufficiently robust to be expressed under deep general anesthesia[3]. These characteristics suggest that the acquired importance of a stimulus is represented by the increased tuning of the cortex to that stimulus.

Across the spatial extent of primary auditory cortex, the overall representation of frequency is the aggregate of best frequencies, yielding a frequency map. This map is tonotopic, that is, shows a systematic gradient of frequency with location on the cortical surface. Because learning can shift best frequencies, a model of associative receptive-field plasticity predicted that the changes in receptive-field tuning would be revealed as an increase in the spatial representation for that frequency in the cortical map, while decreasing the representation of other frequencies[4].

This prediction was verified in a study of instrumental frequency-discrimination training[5]. Owl monkeys were trained to discriminate between different frequencies in order to obtain a food reward. Training was extensive, lasting for many thousands of trials across months. Discriminative performance improved greatly over time. Maps of the primary auditory cortex, obtained later when the animals were anesthetized, revealed a significantly greater area of best tuning for the training frequencies than for non-training frequencies. Moreover, the cortical maps of control animals that received the same type of stimuli while performing a task in another modality did not show an expansion. Finally, the better the discrimination, the greater the cortical area representing the frequencies on which the animal was trained.

The nucleus basalis cholinergic system

These learning-induced changes provided the basis for the recent article of Kilgard and Merzenich[1]. The basal forebrain contains cholinergic neurons, centered on the nucleus basalis (NB), that project to the cortex and affect cortical function largely through the release of acetylcholine acting at muscarinic receptors. This basal forebrain cholinergic system has been implicated in some types of learning by neurophysiological, pharmacological and lesion studies; moreover, Alzheimer's disease is associated with degeneration of the NB and depletion of cortical acetylcholine[6]. Is this basal forebrain cholinergic system a substrate of learning-induced receptive-field and map plasticity?

Kilgard and Merzenich investigated the possibility that the BFCS is necessary for learning-induced plasticity in the auditory cortex of the rat. They paired a tone with stimulation of the nucleus basalis every 8–40 s, 300–500 times a day for 20–25 days (i.e. between 6000 and 12 500 trials in total). The authors reported several changes in the functional organization of the primary

N.M. Weinberger is at the Center for the Neurobiology of Learning and Memory, Bonney Center, University of California, Irvine, CA 92697-3800, USA.

tel: +1 949 824 5512
fax: +1 949 824 4576
e-mail: nmweinbe@uci.edu

 1364-6613/98/$19.00 PII: S1364-6613(98)01200-5

auditory cortex, the most relevant of which are summarized here. First, the tuning of receptive fields was predominantly in the region of the frequency that had been paired with NB stimulation, compared to naïve rats. Second, the area of representation of the paired frequency was substantially expanded (e.g. doubled in size). Third, the degree of change seemed to be a function of the amount of stimulation, as animals receiving the treatment for only one week exhibited a smaller change than those receiving a full course of tone–stimulation pairing. Fourth, application of the specific neurotoxin 192 IgG-Saporin, to destroy basal-forebrain cholinergic cells in two animals prevented the changes in receptive fields and frequency maps.

While the findings are quite consistent with the putative role of the nucleus basalis cholinergic system, this study does not demonstrate unequivocally that the basic phenomena of receptive-field plasticity and expanded representation were due to stimulation of the nucleus basalis, because it did not include a 'tone alone' group, as the authors acknowledge. This would have answered the question of whether or not repeated tones themselves produced the plasticity. Mitigating this problem are some data indicating that changes did not occur for unpaired tones.

In any event, we have previously provided evidence that NB stimulation is necessary for the induction of RF plasticity in the auditory cortex in urethane anesthetized guinea pigs[7]. Two groups were used, each receiving only 40 trials of stimulation in a single session: one with paired tone and NB stimulation and the other with unpaired tone and NB stimulation. Receptive-field changes (increased response to the CS frequency compared to the BF) were found only for the former, indicating not only the need for NB stimulation but also for pairing, within the temporal limits used. This experiment also demonstrated that the effects of NB stimulation, as assessed by change in the auditory cortical electroencephalogram from high voltage slow to low voltage fast waves ('desynchronization') was blocked by systemic or cortical application of the muscarinic antagonist atropine sulphate. Although this study revealed that paired NB stimulation is sufficient to induce RF plasticity, it left open the question of whether the effects are mediated by cholinergic/muscarinic mechanisms because stimulation of the NB might engage separate mechanisms, one affecting the EEG cholinergically, the other affecting receptive-field plasticity noncholinergically.

The link between NB-induced EEG desynchronization and RF plasticity has been strengthened recently by findings of Bjordahl, Dimyan and Weinberger[8]. Their experiment was similar in design to Bakin and Weinberger's earlier experiment[7] but now used awake rather than anesthetized animals receiving paired tone and NB stimulation[8]. As a control, a terminal experiment with animals under urethane anesthesia was run and this revealed that NB stimulation produced EEG desynchronization in only half of the animals, despite the fact that stimulation sites of all animals were intermixed within the cholinegic basal forebrain. However, only the desynchronized animals developed RF plasticity, showing the need for an independent assessment of the effectiveness of NB stimulation. These findings do not show that the cholinergic effects of NB stimulation are necessary for RF plasticity but they do indicate a one-to-one relationship between physiologically-effective stimulation (i.e. desynchronization) and the induction of RF plasticity. Bjordahl *et al.* also found retention of RF plasticity at 24 h, the longest interval tested, indicating that only 40 trials of tone and NB stimulation are sufficient for long-term retention.

Unresolved issues

Together, the experiments of Kilgard and Merzenich and our laboratory do provide fairly strong evidence for the 'NB cholinergic hypothesis'. However, several issues need to be resolved, four of which are now outlined.

Is acetylcholine responsible for receptive-field/map plasticity?

Kilgard and Merzenich reported that two animals which received the cholinergic neurotoxin saporin failed to develop receptive-field and map plasticity. More definitive data are needed to establish that acetylcholine is necessary. A larger sample is required and, more importantly, appropriate histochemical and immunocytological analyses are necessary to directly validate cholinergic depletion[9].

Rate of development of receptive-field and map plasticity?

During conditioning, receptive-field (RF) plasticity developed in only five trials[3]. NB-induced RF plasticity was seen after only 40 trials, the fewest attempted[7,8]. However, map data were not obtained in these experiments. Kilgard and Merzenich obtained data only after at least one week and thousands of trials. Thus, the rate of development of map plasticity is not known. If all RF plasticity produces map plasticity, then the rates of development will be the same. If map plasticity develops more slowly, perhaps requiring many more training trials, then the two aspects of auditory cortical change are likely to involve different mechanisms and subserve different functions. Also, the two forms of plasticity may be differentially sensitive to the temporal parameters of training such as interstimulus and intertrial intervals.

Functions of NB activation

As NB stimulation is used in place of a normal reward or punishment, the issue of behavioral relevance needs to be examined. Kilgard and Merzenich stimulated the NB either 50 ms after or 200 ms before tone presentation. They stated that there were no differences between the results of these procedures and pooled the resulting data. However, the authors concluded that the role of the NB concerns'...labeling which stimuli are behaviorally important' (see also Ref. 4). Thus, a tone followed by NB activation would be more important than a tone that is not followed by NB stimulation. Indeed, this is a key premise of our model[3,4]. In contrast, when a tone follows NB stimulation, as in some of Kilgard and Merzenich's findings, then its behavioral relevance to the subject could not be designated by the preceding NB activation.

Clarification might come from the findings of Edeline and co-workers[10]. These authors reported cholinergically dependent facilitation of auditory cortical responses when NB stimulation precedes a tone. Furthermore, facilitation could be maintained for many minutes. Although receptive fields were not studied, the findings show that the state of the cortex at the time a sound occurs can have a marked effect on cortical processing, possibly leading to long-term changes.

Therefore, NB activation could have two functions. First, the tonic release of acetylcholine that appears to maintain a waking cortical state (indexed by EEG desynchronization) might generally facilitate stimulus processing. This function is modeled by stimulating the NB before presenting the tone. Second, in the waking state, the additional phasic release of acetylcholine, caused by a reinforcing stimulus following a tone, might signal to the cortex that an important event has occurred and promote its specific storage, observed as shifts of RF tuning. This function is modeled by stimulating the NB after presenting the tone. The issue then is whether, as Kilgard and Merzenich report, NB activation preceding a tone actually produces the same type of specific RF plasticity as has previously been established for NB activation that follows a tone[7,8]. If so, then NB activation *per se* cannot uniquely be a signal that labels the importance of an auditory stimulus, as Kilgard and Merzenich currently propose and as we specifically hypothesized in 1990 (Ref. 4).

Types of learning

Two very different paradigms have been used both in behavioral studies and in NB studies of RF/map plasticity. Kilgard and Merzenich used massed pairings at intervals of 8–40 s for 6000–12 500 trials over weeks, some of which occurred while animals were asleep. This is questionable as a realistic behavioral learning situation. Nonetheless, this paradigm might be engaging mechanisms that normally take part in perceptual skill learning, a type of learning that seems to require many trials over a long period of time. Kilgard and Merzenich

probably designed their NB study as a model for the long-term perceptual learning study previously reported by their laboratory[5].

Their paradigm contrasts with our use of only 30–40 spaced trials in a single session, both in behavioral and NB studies. Our focus has been on the initial events in associative learning, not on perceptual learning. Thus our behavioral neurophysiological studies use rapid stimulus–stimulus (tone–shock) learning that is the first stage of association in classical conditioning[11]. Our choice of a relatively small number of spaced trials for NB studies was based on substituting such stimulation for peripheral shock, to determine whether or not NB activation by a conditioned stimulus might be sufficient to induce RF plasticity in rapid associative learning.

Thus, RF plasticity in the primary auditory cortex might be related to two different forms of primary sensory cortical plasticity. Rapidly-developing shifts of tuning might represent the increased behavioral importance of a signal stimulus as part of an initial stage of association. Slowly developing plasticity that requires massing thousands of trials might underlie improvements in perceptual acuity. Whether the second type of plasticity depends on the first is an open question.

Conclusions

Behavioral neurophysiological studies to date are consistent with the idea that the tuning of primary auditory cortex by learning is a substrate for the acquisition and storage of specific aspects of experience. They also support the hypothesis that acetylcholine released in the cortex by activation of the nucleus basalis is sufficient and might be necessary to induce receptive-field and map reorganization. Such plasticity might underlie at least two aspects of cortical information storage, rapidly-developing stimulus associations and slowly-developing improvement of perceptual skills. Several basic issues remain unresolved at this relatively early stage of inquiry. In addition to those discussed above, there remains the overarching issue of whether such cortical plasticity is actually a substrate for cognitive processes. This line of inquiry, while difficult, would shed light on the question of the forms and mechanisms by which some types of information are acquired and stored in the cerebral cortex, and ultimately used as needed for adaptive behavior.

Acknowledgements

This research was supported by the The National Institute on Deafness and Other Communication Disorders, grant numbers DC 02346 and DC 02938.

References

1 Kilgard, M.P. and Merzenich, M.M. (1998) Cortical map reorganization enabled by nucleus basalis activity *Science* 279, 1714–1718

2 Bakin, J.S. and Weinberger, N.M. (1990) Classical conditioning induces CS-specific receptive-field plasticity in the auditory cortex of the guinea pig *Brain Res.* 536, 271–286

3 Weinberger, N.M. (1995) Retuning the brain by fear conditioning, in *The Cognitive Neurosciences* (Gazzaniga, M., ed.), pp. 1071–1089, MIT Press

4 Weinberger, N.M. *et al.* (1990) Retuning auditory cortex by learning: a preliminary model of receptive-field plasticity *Concepts Neurosci.* 1, 91–132

5 Recanzone, G.H., Schreiner, C.E. and Merzenich, M.M. (1993) Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys *J. Neurosci.* 13, 87–103

6 Pepeu, G. and Marconcini-Pepeu, I. (1994) Dysfunction of the brain cholinergic system during aging and after lesions of the nucleus basalis of Meynert *J. Neural Transm. (Suppl.)* 44, 189–194

7 Bakin, J.S. and Weinberger, N.M. (1996) Induction of a physiological memory in the cerebral cortex by stimulation of the nucleus basalis *Proc. Natl. Acad. Sci. U. S. A.* 93, 11219–11224

8 Bjordahl, T., Dimyan, M. and Weinberger, N.M. (1998) Induction of physiological memory in the auditory cortex of the waking guinea pig by stimulation of the basal forebrain *Behav. Neurosci.* 95, 1–13

9 Robertson, R.T. *et al.* (1998) Neonatal treatment with 192 IgG-Saporin produces long-term forebrain cholinergic deficits and reduces dendritic branching and spine density of neocortical pyramidal neurons *Cereb. Cortex* 8, 142–155

10 Edeline, J.M. *et al.* (1994) Non-awaking basal forebrain stimulation enhances auditory cortex responsiveness during slow-wave sleep *Brain Res.* 636, 333–337

11 Lennartz, R.C. and Weinberger, N.M. (1992) Analysis of response systems in Pavlovian conditioning reveals rapidly versus slowly acquired conditioned responses: support for two factors, implications for behavior and neurobiology *Psychobiol.* 20, 93–119

Update/Comment

Comment articles offer short updates and discussions of one or more ground-breaking and important primary research papers. The author of the primary paper has the opportunity of replying to the comment, thus extending the dialogue on their work.

Monitor

Summaries of recently published papers of interest to cognitive scientists. Readers who would like to contribute to this section, by identifying appropriate papers and writing short summaries, should contact the Editor.

Language 'off-line'

Individuals with the rare genetic disorder, Williams syndrome (WMS), are of particular interest to cognitive neuroscientists because of the well-known dissociation between intact language abilities and severely impaired spatial abilities[1]. This dissociation is often used to support claims of an innate, genetically determined grammar module. Some reports have challenged this view, however, and recently Karmiloff-Smith *et al.*[2] provided further evidence that might force a rethink of whether all aspects of language are intact in individuals with WMS. These authors used both 'on-line' (implicit) and 'off-line' (explicit) tasks to examine the processing of receptive syntax. The on-line task, which required monitoring sentences for target words, revealed an impairment in the processing of the specific syntactic construction called subcategorization. This particular syntactic construction is often acquired later in development than other aspects of syntax, and also causes difficulties for second-language learners. Two other aspects of syntax examined on-line were performed normally, whereas all seven types of syntactic construction examined off-line, which required matching sentences to appropriate pictures, were performed very poorly. This study reaches two important conclusions: that there is a need for both on-line and off-line tasks in the investigation of language disorders; and that at least one aspect of language processing in WMS is not intact.

References

1 St George, M. (1998) What studying genetically-based disorders can tell us about ourselves *Trends Cognit. Sci.* 2, 203–204

2 Karmiloff-Smith, A. *et al.* (1998) Linguistic dissociations in Williams syndrome: evaluation of receptive syntax in on-line and off-line tasks *Neuropsychologia* 36, 343–351