Irvine, D. R. F. 2018. Plasticity in the auditory system. *Hearing Research*. **362**: 61-73.

doi: 10.1016/j.heares.2017.10.011

Plasticity in the Auditory System

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Abstract

Over the last 30 years a wide range of manipulations of auditory input and experience have been shown to result in plasticity in auditory cortical and subcortical structures. The time course of plasticity ranges from very rapid stimulus-specific adaptation to longer-term changes associated with, for example, partial hearing loss or perceptual learning. Evidence for plasticity as a consequence of these and a range of other manipulations of auditory input and/or its significance is reviewed, with an emphasis on plasticity in adults and in the auditory cortex. The nature of the changes in auditory cortex associated with attention, memory and perceptual learning depend critically on task structure, reward contingencies, and learning strategy. Most forms of auditory system plasticity are adaptive, in that they serve to optimize auditory performance, prompting attempts to harness this plasticity for therapeutic purposes. However, plasticity associated with cochlear trauma and partial hearing loss appears to be maladaptive, and has been linked to tinnitus. Three important forms of human learning-related auditory system plasticity are those associated with language development, musical training, and improvement in performance with a cochlear implant. Almost all forms of plasticity involve changes in synaptic excitatory – inhibitory balance within existing patterns of connectivity. An attractive model applicable to a number of forms of learning-related plasticity is dynamic multiplexing by individual neurons, such that learning involving a particular stimulus attribute reflects a particular subset of the diverse inputs to a given neuron being gated by top-down influences. The plasticity evidence indicates that auditory cortex is a component of complex distributed networks that integrate the representation of auditory stimuli with attention, decision and reward processes.

Keywords

Attention; Hearing loss; Neuromodulators; Perceptual learning; Stimulus-specific adaptation; Synaptic weights

1. Introduction

The auditory system was traditionally viewed as a hard-wired system, largely specified and determined genetically, and influenced by auditory experience only during restricted “critical” or “sensitive” periods during development (see Hensch (2005) and Knudsen (2004) for reviews). Over the last 30 years or so, however, multiple lines of evidence have demonstrated that it constantly reorganizes itself in response to changes in auditory input or in the significance of particular inputs. This evidence for auditory system plasticity has driven changes in the way auditory cortex is conceptualized: rather than being seen as simply a dedicated auditory processor (the end point of the “lemniscal line” system), it is now seen as a component of complex distributed networks that integrate the representation of auditory stimuli with attention, decision and reward processes

Auditory system plasticity occurs over multiple time scales, from very rapid adaptation to longer-term changes driven by partial hearing loss, and varies in the extent to which it is dominated by the history of sensory input (bottom-up processes) or by the influence of attention, learning, and decision criteria (top-down processes). The various forms of short- and long-term plasticity will be reviewed here, with an emphasis on auditory cortex in mature organisms and on recent findings. More detailed accounts of individual topics can be found elsewhere (e.g., Wright and Zhang, 2009; Irvine, 2010; Weinberger, 2010; Shepard et al., 2013; Malmierca et al., 2014, Schreiner and Polley, 2014; Froemke and Schreiner, 2015; Eggermont, 2017)

2. Stimulus-specific adaptation

Stimulus-specific adaptation is a reduction in the response of a neuron to a repeated stimulus, and is distinguished from firing-rate adaptation by the fact that it does not generalize, or generalizes only weakly, to other stimuli (e.g., Nelken, 2014). SSA was first demonstrated in the auditory cortex (Ulanovsky et al., 2003), but has subsequently been demonstrated in the midbrain and thalamus. In both the inferior colliculus (IC) and the medial geniculate body (MGB), SSA is associated with so-called “lemniscal-adjunct” structures (the external and dorsal cortices of the IC and the medial and dorsal divisions of the MGB) and is weak or absent in the lemniscal-line structures (central nucleus and ventral division, respectively) (Malmierca et al., 2009; Antunes et al., 2010; Duque et al., 2012). At the cortical level, although SSA occurs in the primary auditory cortex (AI) (Ulanovsky et al., 2003), it is stronger and develops more rapidly in non-primary fields (Nieto-Diego and Malmierca, 2016).

SSA has commonly been demonstrated using an "oddball" paradigm, in in which rare signals ("deviants") are embedded in a sequence of common ("standard") signals. Adaptation to the standard stimulus while the response to the deviant remains robust suggests a role for SSA in deviance (or "novelty") detection, and SSA has therefore been investigated as a correlate of the mis-match negativity (MMN) (Näätänen et al. 2005) seen in human evoked potential (EP) and magnetoencephalographic recordings (Fishman and Steinschneider, 2012; Malmierca et al., 2014; Khouri and Nelken, 2015).

The most fully developed account of the mechanisms of auditory SSA in the frequency domain is the adaptation of narrowly tuned modules (ANTM) model developed by Nelken and his colleagues (see Nelken (2014) for review). According to this model, SSA occurs in neurons that integrate multiple inputs, each of which shows simple (firing rate) adaptation. When one of those inputs is repeatedly stimulated, it adapts while the other inputs remain unadapted, thus generating SSA. This model fits well with the fact that SSA is characteristic of lemniscal-adjunct structures, in which frequency tuning is typically broad. However, the ANTM model cannot account for some of the characteristics of SSA as manifested in the AI (Nelken, 2014).

As others have noted, SSA has many properties in common with behavioural habituation to a repeated stimulus (e.g., Netser et al., 2011; Nelken, 2014). It is therefore not surprising that there are similarities between the characteristics of SSA and those observed in earlier studies of habituation in auditory cortical EPs and single-neuron responses (e.g., Westenberg and Weinberger, 1976; Condon and Weinberger, 1991). The mechanisms of auditory cortical habituation have received relatively little attention, but in a recent two-photon calcium imaging study of habituation in the AI of mice, Kato et al. (2015) found that daily periods of repetive stimulation resulted in a decrease in the responses of layer 2/3 pyramidal neurons that was associated with an upregulation in the activity of somatostatin-expressing inhibitory neurons. These changes clearly take place over a much longer time-scale than most forms of SSA, but the relationship between the two effects of repetitive stimulation and the mechanisms that produce those effects merits further investigation.

Habituation is generally regarded as a simple form of learning (Rankin et al., 2009), and SSA (and the MMN) can be considered to reflect a form of learning that allows the organism to ignore irrelevant acoustic events and detect rare (and thus potentially salient) events. A "memory" model of the MMN has been contrasted with models based on afferent adaptation (Näätänen et al. 2005), but as Khouri and Nelken (2015) have pointed out, cognitive and mechanistic accounts of these phenomena are not necessarily mutually exclusive.

3. Plasticity associated with various forms of altered auditory experience

Since the early demonstrations of plasticity in the AI associated with behavioural conditioning (Bakin and Weinberger, 1990) and with partial hearing loss associated with restricted cochlear lesions (Robertson and Irvine, 1989), longer-term auditory system plasticity has been investigated as a consequence of a wide range of manipulations of auditory experience. The vast majority of these studies have been concerned with neuronal frequency selectivity, and this review will largely be restricted to plasticity in the spectral domain. It is important to emphasise, however, that temporal and other response characteristics are also modifiable by experience (e.g. Bao et al., 2004; Polley et al., 2004)

3.1. Auditory learning, memory and attention

Investigations of auditory cortical plasticity associated with changes in stimulus significance have used a variety of associative learning procedures. The nature of the observed changes in neuronal response characteristics has been found to depend critically on the nature of the task requirements presented by the particular learning situation. The most commonly reported effect of classical conditioning with a tonal conditioned stimulus (CS) is an increase in the response at the CS frequency and a decrease in response at the pre-training best frequency (BF), such that the BF shifts towards, or becomes the same as, the CS frequency (see Weinberger (2004, 2010) for reviews). As a consequence, the area of AI comprising neurons with that BF (often described as the “area of representation” of that frequency) is increased. Weinberger and his colleagues have interpreted this change in AI spectral sensitivity as the memory trace underlying learning of the conditioned response, and it has been reported that the magnitude of the increase in area is correlated with performance on the task (Bieszczad and Weinberger, 2010b).

It should be noted here that although the term “area of representation” provides a convenient shorthand for the area occupied by neurons with BF or characteristic frequency (CF) within a given frequency range, it also carries additional, unjustified connotations. It is well established that a given frequency is not represented in the AI solely by the activity of neurons with that CF or BF but in a complex, intensity-dependent fashion across a large proportion of the neurons that respond to that frequency (e.g., Phillips et al., 1994). Despite this caveat, the term will continue to be used here, partly because it has been so widely used in the literature to be reviewed, and partly because of the difficulty of identifying an alternative term that is not excessively unwieldy.

Early evidence indicated that changes in frequency selectivity could occur very quickly (within the first five training trials) (Edeline et al., 1993). Their rapidity has been confirmed in experiments by Fritz and his colleagues (Fritz et al. 2003, 2005) in which ferrets were trained on an avoidance (conditioned suppression of drinking) task to detect a tone of a particular frequency (the target sound) against a background of broadband noise-like reference sounds. An interesting feature of the design of these studies is that the ferrets were initially trained in a test box on the avoidance task for a number of weeks until they reached the criterion, and neurophysiological recordings were subsequently made in repeated test sessions in which the animal was restrained in a different apparatus. In each test session, the tone frequency used as the discriminative stimulus (target) was selected on the basis of the spectro-temporal receptive field (STRF) of the neuron(s) isolated in that session, and thus changed from day to day. The most common result was enhancement of the response at the target frequency, reflecting either increased excitation or decreased inhibition at that frequency. In some of these neurons, the changes in spectral sensitivity were short-lived, the STRFs reverting to their original form when the task was not being performed, while in other cases the changes were longer lasting. While the longer term changes are compatible with their constituting a memory trace, the ephemeral nature of the changes in some neurons suggests that they reflect attention to the particular frequency that is salient in that test session (Fritz et al., 2007).

FIG. 1 ABOUT HERE

In contrast to reports of enhanced responses at the frequency of a conditioned or discriminative stimulus, there have been reports of decreased responses at the target frequency. The first such report was that of Ohl and Scheich (1996) who reported that learning in a frequency-discrimination conditioning task was associated with a decrease in the response of AI neurons at the CS frequency, which resulted in enhancement of contrast sensitivity in that frequency region. More recently, David et al. (2012) examined changes in the STRFs of neurons in the AI of ferrets trained on either an approach or avoidance task, using the same stimuli (target tones in a sequence of noise sounds) (Fig. 1A and B). Performance of the avoidance task was associated with enhancement of the response at the target frequency, as reported previously by Fritz et al. (2003). In contrast, performance on the approach task was associated with a decrease in the response at the target frequency (Fig 1, C and D). As in Fritz et al.'s (2003) study, the changes in the STRFs of most neurons were ephemeral, reversing after completion of the task. This suggests that the changes reflect attention rather than the laying down of a memory trace, but the different direction of the changes in the approach and avoidance tasks also indicates that the nature of the changes depends on reward structure. These and other related studies have led to the recognition that the specific form of both short- and long-term plasticity induced in auditory cortical neurons by conditioning procedures is critically dependent on task structure, the nature of the response required by the task, and learning strategy (e.g., Fritz et al., 2005; Scheich and Brosch, 2013; Bieszczad and Weinberger, 2010a).

For both appetitive and aversive conditioning paradigms, however, the initial stages of learning involve a decrease in auditory cortical inhibition (Letzkus et al., 2011; Sarro et al., 2015). Given the evidence for the role of the cholinergic system in learning-related plasticity (e.g., Ma and Suga, 2005; Weinberger, 2007), it is of interest that the first effect of pairing stimulation of the cholinergic fibres originating in the nucleus basalis (NB) with an acoustic stimulus is a rapid reduction in auditory cortical inhibition (Froemke et al., 2007, 2013; see Section 5)

With reference to the interpretation of changes in auditory cortical receptive fields as a/the memory trace, the importance of auditory cortex for fear conditioning has been a contentious issue (see Grosso et al. (2015) for review). However, studies involving lesion (Boatman and Kim, 2006) or other forms of deactivation (Letzkus et al., 2011; Weible et al., 2014) of auditory cortex have established that cortical activity is necessary for fear conditioning in rodents. It should be noted, however, that these studies do not establish whether particular changes in cortical receptive field properties are a necessary pre-condition of such learning.

The effects of attention and other task-related processes on responses in the AI indicates that auditory cortical processing is modulated by top-down influences from “higher-order” cortical areas mediating attention and related processes. Fritz et al. (2010) reported that the responses of neurons in ferret frontal cortex (FC) to tonal stimuli were modulated during discrimination behaviour on the task(s) previously used to demonstrates AI plasticity, and that there was an increase in the coherence of local field potentials in the AI and the FC during learned behaviour. Activation of FC neurons in the mouse produces changes in AI auditory responses (Winkowski et al., 2013, 2017). As described in Section 5, there is an extensive literature on the effects of various neuromodulatory systems on processing in the AI, and the influences of FC could therefore be mediated by FC projections to the sources of these neuromodulatory systems. However, Winkowski et al. (2017) demonstrated direct projections from the FC to the AI, and found that that optogenetic activation of FC axon terminals in the AI both evoked neural activity in the AI and altered AI responses to acoustic stimuli.

Studies of auditory cortical plasticity associated with learning have concentrated on the AI, but Atiani et al. (2014) reported that changes in tonotopically organized belt areas in the ferret were of much greater magnitude than those in AI. Such studies have also been extended to the AI's afferent and efferent connections with structures outside the auditory system. Classical fear conditioning with an acoustic CS has long been known to depend on connections between the auditory system and the lateral amygdala (LA) (Romanski and LeDoux, 1992), and is known to involve plasticity in the CS pathways to the LA (Bocchio et al., 2017; Kim and Cho 2017). Yang et al. (2016) described increases in boutons formed by LA axons and in dendritic spines of AI layer 5 pyramidal neurons in mice as a consequence of such conditioning. Xiong et al. (2015) reported that corticostriatal synapses in rats were potentiated in a frequency-specific fashion in the course of learning a frequency discrimination task. Synaptic potentials in the striatum were evoked by optogenetic stimulation of AI neurons, so the increase in synaptic efficacy was not merely a reflection of increased AI responses. These observations indicate that plasticity associated with auditory learning and attention is not restricted to the auditory system itself, but occurs at multiple points throughout the networks engaged by auditory behavior.

Finally, although the emphasis here has been on auditory cortical plasticity, it is important to recognize that similar effects of learning and attention have been reported in the medial geniculate body (MGB) and inferior colliculus (IC) (e.g., Edeline and Weinberger, 1991; Slee and David 2015). These forms of subcortical plasticity undoubtedly reflect, at least in part, centrifugal influences from auditory cortex (e.g., Suga and Ma, 2003), but might also involve intrinsic processes.

3.2 Partial hearing loss

Changes in auditory cortical response characteristics as a consequence of partial hearing loss produced by damage to a restricted region of the cochlea provided some of the earliest evidence for auditory cortical plasticity. Plasticity as a consequence of such losses produced by noise trauma and ototoxic drugs has recently been reviewed in detail by Eggermont (2017), and this form of plasticity will therefore be only summarily treated here.

Early studies of such plasticity in the AI of mature (Robertson and Irvine, 1989) and developing (Harrison et al., 1991) animals focused on changes in neuronal frequency selectivity and associated changes in the cortical tonotopic map. Neurons in the region of cortex in which the damaged section of the cochlea would normally be represented develop new CFs at frequencies represented at the edge(s) of the cochlear lesion. As a consequence of this change in frequency tuning, this region is wholly or partly occupied by an expanded representation of the lesion-edge frequency or frequencies (see Irvine (2010) and Eggermont (2017) for reviews). Changes in cortical tonotopy consequent on partial hearing loss have typically been examined some weeks or months after the cochlear insult. On this time scale, studies of injury-induced plasticity in other modalities have found evidence of structural changes associated with cortical reorganization (see Section 5). It is likely that long-term changes of this sort also occur in the AI, but changes in frequency response areas are seen immediately following cochlear trauma. Calford et al. (1993) described complex patterns of expansion and contraction of frequency receptive fields in association with temporary threshold shifts induced by intense pure-tone exposure. The synaptic mechanisms responsible for such changes have been revealed by *in vivo* whole-cell recordings from AI neurons in rats: the strength of inhibition was selectively increased and reduced at different positions with a neuron’s receptive field (Scholl and Wehr, 2008). Rapid changes in frequency selectivity as a consequence of damaging noise exposure have also been described in the mouse AI, and are associated with a reduction in inhibition mediated by parvalbumin-expressing inhibitory interneurons (PVNs) (Resnick and Polley, 2017).

In adult animals, plastic changes in frequency organization as a consequence of partial hearing loss are restricted to the auditory thalamo-cortico-thalamic system (Irvine, 2010), but such changes are also seen in the IC after neonatal lesions (Harrison et al., 1996). In contrast, another form of plasticity produced by cochlear insults - increases in spontaneous firing rates (hyperactivity) and in neural synchrony - occur in the cochlear nucleus and in all higher centres (see Noreña (2011) and Eggermont (2017) for reviews). These changes have been identified as possible generators of tinnitus and hyperacusis (e.g., Noreña, 2011; Robertson and Mulders 2012). As others have pointed out, the perceptual (and emotional) experience of tinnitus undoubtedly depends on the connections of auditory cortex with higher cognitive and affective brain areas (Eggermont, 2015, Rauschecker et al., 2015).

The other forms of auditory system plasticity considered in this review are undoubtedly adaptive, in that they enhance the organism’s ability to extract behaviourally significant information from the acoustic environment. In contrast, plasticity driven by partial hearing loss is almost certainly not adaptive – the changes in frequency selectivity and organization do not in any way compensate for the hearing loss. Indeed, as indicated by their hypothesized association with tinnitus, these forms of plasticity would appear to be maladaptive. They are likely attributable to homeostatic plasticity mechanisms that act to maintain set levels of activity in neural circuits (Turrigiano, 2011), as has been demonstrated in visual cortex after retinal lesions (Keck et al., 2013). Such plasticity, which is mediated by synaptic changes such as synaptic scaling and changes in excitatory/inhibitory balance (Turrigiano, 2011), has also been implicated in the maintenance of sound detection and some aspects of auditory processing in the IC, MGB, and AI of mice after profound cochlear denervation (Chambers et al., 2016a,b)

Finally, the studies of adult plasticity reviewed here have used various forms of cochlear trauma to selectively reduce outflow from the cochlea. An important form of developmental auditory system plasticity is that produced by conductive hearing loss, which has widespread effects throughout the auditory pathway, including cortical synaptic potentials (e.g. Xu et al., 2007; Whitton and Polley, 2011; Mowery et al., 2015), and affects subsequent auditory performance and learning (Caras and Sanes, 2015; von Trapp et al., 2017).

3.3. Perceptual learning

Another form of experience that has been shown to influence processing in auditory and other sensory cortices is practice on tasks involving the detection, discrimination, or identification of sensory stimuli. The improvements in performance that occur with such training are referred to as perceptual learning. The literature on auditory perceptual learning has been reviewed in detail by Irvine (2018; submitted for publication), and the evidence it provides for auditory system plasticity will therefore be only briefly summarised here.

The specificity of many forms of visual perceptual learning (to a region of the retina and/or to a particular stimulus attribute) (e.g. Karni and Bertini, 1997) led to the view that the site of the underlying changes was at relatively early stages of cortical processing (viz., in primary visual cortex (V1)). Subsequent electrophysiological and imaging studies in all major sensory systems have confirmed the occurrence of changes in primary and/or secondary sensory cortices associated with perceptual learning, although the changes described in V1 have been relatively modest (see Watanabe and Sasaki (2015) for review). In contrast to such “early stage” models, other have proposed “late-stage” models in which the improvements depend on decision processes involved in identifying the sensory channels that provide the basis for optimal performance.

The most commonly studied form of auditory perceptual learning in electrophysiological studies in animals has been frequency discrimination, but the nature of the changes in the AI underlying such learning remains unclear. In two studies (Recanzone *et al*., 1993; Polley *et al*., 2006) improvement in frequency discrimination performance was associated with an increase in the area of representation of the frequencies used in training. In contrast, Brown *et al*. (2004) and

Witte and Kipke (2005) found no change in the frequency organization of AI in cats trained on frequency discrimination tasks. Witte and Kipke (2005) in fact reported decreases in the summed response to the training frequencies of auditory cortical neurons in the AI, and in the number of neurons with CF in that range.

There were numerous procedural differences between these four studies that might explain the different patterns of results. Just as changes in the spectral sensitivity of AI neurons produced by auditory conditioning depend critically on a range of task characteristics (Section 3.1), it is likely that changes associated with perceptual learning will vary in a similar fashion. Nevertheless, it should be noted that an increase in the representation of the training frequencies must occur at the expense of the representation of other frequencies, and thus implies the loss of discriminative ability at those other frequencies. No such loss was observed by Brown et al. (2004), and numerous studies of human perceptual learning on frequency discrimination tasks have demonstrated generalization of learning from trained to untrained frequencies (Wright and Zhang, 2009). This issue relates to the more general "stability-plasticity dilemma" which arises for all learning systems (Mermillod et al., 2013) and is discussed below (Section 6).

An alternative possibility, suggested by Reed et al. (2011), is that expansion of the area of representation occurs in the course of training and enables the changes in circuitry that underlie improved performance, but that once these changes have occurred the representation re-normalizes. On this hypothesis, at least some of the different findings described above with respect to perceptual learning involving an enlarged representational area in AI would be attributable to differences in the time during training at which the cortical measures were obtained.

Another account of the mechanisms underlying auditory perceptual learning is suggested by studies of the effects of manipulation of sound localization cues. Hofman et al. (1998) modified the spectral shape cues to sound source elevation in adult human subjects by the insertion of ear moulds. Vertical localization was massively disrupted immediately after insertion of bilateral moulds, but improved greatly over 3–6 weeks experience with the moulds. Surprisingly, when the moulds were removed, participants were immediately able to perform at the levels exhibited prior to the experiment. The learning demonstrated in this study therefore seems to have involved the acquisition of a new representation of the pinna transfer function without disruption of the original representation. A similar rapid switching between representations of auditory space is suggested by studies in which animals and humans learned to localize sounds in the azimuth with one ear occluded, by assigning greater weight to monaural spectral cues, but then responded at normal levels when the occlusion was removed and localization again depended primarily on interaural disparity cues (Kacelnik et al., 2006; Kumpik et al., 2010).

The rapid switching between central processing mechanisms indicated by these findings is reminiscent of a proposal by Li and Gilbert (2008) concerning the mechanisms of visual perceptual learning. They suggest that the critical process underlying perceptual learning relating to a particular stimulus attribute might be that a particular subset of the diverse inputs to a given cortical neuron related to that attribute is gated by top-down influences. An important feature of this hypothesis is that learning related to multiple attributes can be represented in the same neural population (i.e., an expanded representation is not required) and that the organism can switch rapidly between different sets of inputs depending on the task being performed. A similar dynamic multiplexing by individual cortical neurons has been suggested by Fritz and his colleagues to underlie the task dependency of learning- and attention-related changes in auditory cortical STRFs (e.g., Fritz et al., 2007).

Auditory perceptual learning by humans has been investigated for a wide range of stimulus attributes (viz., frequency, level, duration, interaural level and time disparities), and the characteristics of the learning (e.g., its time course, the shape of the learning curve, etc.) are highly attribute dependent (Wright and Zhang, 2009). Studies using various electrophysiological and imaging techniques, have demonstrated that perceptual learning on a range of tasks is correlated with changes in auditory cortical activity. The most commonly reported effect of training on scalp-recorded event-related potentials (ERPs) is an increase in the amplitude of components with latencies in the 100- to 200-ms range, although decreased responses have also been reported (see Alain *et al*. (2007) for review). Larger ERPs could reflect either an increase in the number of responsive neurons or increased synchrony in the discharge of the responding population; furthermore, the ERP components investigated in these studies have multiple generators, including (but not restricted to) primary and belt areas of auditory cortex, so the cortical fields in which the changes occur cannot be specified with certainty.

An important form of human auditory perceptual learning concerns the effects of musical training, and there have been numerous reports of differences between musicians and non-musicians in auditory cortical structure and function (see Herholz and Zatorre (2012) and Strait and Kraus (2014) for reviews). Much of the data on this topic is cross-sectional, and thus cannot establish the direction of causality between the observed cortical and skill differences. However, longitudinal studies have established unequivocally that musical training results in changes in auditory cortical processing mechanisms (Herholz and Zatorre, 2012). In both musicians and trained naïve listeners, improved pitch discrimination ability is associated with increased robustness of the brainstem frequency following response (FFR) (e.g., Carcagno and Plack, 2011; Wong et al., 2007), indicating that perceptual learning also involves changes in subcortical structures. These changes presumably reflect corticofugal modulation of brainstem processing, but could also reflect the fact that cortical activity contributes to the FFR (Coffey et al., 2017).

3.4. Environmental enrichment and other forms of altered acoustic environment

Perhaps the most intensively studied aspect of structural brain plasticity over the last 60 years or more has been the range of cellular and molecular changes seen in the brains of rats raised in enriched environments relative to those of littermates raised in (admittedly often impoverished) standard conditions (e.g. Nithianantharajah and Hannan, 2006). There has been only limited investigation of the effects of generalized environmental enrichment on the response characteristics of auditory cortical neurons, but Kilgard and colleagues (e.g., Engineer *et al*., 2004) have reported that a combination of generalized and specifically acoustic enrichment results in changes in the response strength and the receptive field and temporal processing characteristics of AI neurons in both developing and adult rats.

In contrast to the limited number of studies of the effects of generalized environmental enrichment, there is an extensive literature on the effects of various manipulations of the acoustic environment, particularly during development (see Sanes and Bao (2009), Froemke and Jones (2011), de Villers-Sidani and Merzenich (2011) and Eggermont (2013) for reviews). For example, repeated exposure to tones of a given frequency during critical periods in development results in an enlarged cortical representation of that frequency in AI of rats and mice, and a diminished representational of frequencies flanking the exposure frequency. Conversely, exposure to continuous or pulsed white noise during the developmental critical period disrupts the normal development the tonotopic organization of AI in rodents (Chang and Merzenich, 2003; Zhou et al. 2008). In apparent contrast to the developmental effects of exposure to a restricted range of frequencies, Noreña et al. (2006) reported that long-term exposure of juvenile cats to a stimulus comprising tone-pips in the range 5-20 kHz caused a reduction of the representation of that frequency range and over-representation of neighboring frequencies (but see Eggermont (2013)).

An important finding is that subsequent acoustic environmental enrichment can prevent the consequences of, or promote recovery from, early damaging noise exposure. Noreña and Eggermont (2005) reported that when cats exposed to a traumatizing noise were immediately placed in an enhanced acoustic environment which spectrally matched the expected hearing loss range, the hearing loss was reduced and reorganization of the frequency map did not occur. Similarly, Sturm et al. (2017) reported that acoustic enrichment immediately after noise trauma prevented both the deficits in auditory gap detection produced by the trauma and the reorganization of excitatory and inhibitory circuits in the IC that was associated with the gap detection deficits. Zhu et al. (2014) reported that the degraded frequency discrimination and cortical processing that resulted from developmental noise exposure were partially reversed by a period of rearing in an acoustically enriched environment. The effects of early conductive hearing loss can also be reversed by subsequent exposure to tailored acoustic stimuli (Green et al., 2017). These results suggest the possibility of therapeutic applications of manipulation of the acoustic environment.

The effects of environmental enrichment raise an interesting issue concerning the majority of laboratory studies of sensory system plasticity. Some of the most compelling evidence for developmental plasticity in the auditory system has been provided by changes in the neural mechanisms by which sound localization cues are processed and maps of auditory space are generated in the midbrain (viz. in the IC and the superior colliculus (SC) or optic tectum (OT)). In both barn owls and mammals, interventions during “sensitive” periods in development that alter the relationship between binaural cues and spatial location, or that between visual and auditory space, result in profound changes in these mechanisms (e.g., King et al., 2000; Knudsen, 2002). Although, the prismatic displacement that produces profound effects in development had been reported to have little or no effect in adult barn owls, Bergan *et al*. (2005) found that owls exposed as adults showed much greater effects when they hunted live prey (rather than being fed dead food). This finding suggests, as Keuroghlian and Knudsen (2007) have pointed out, that the plasticity demonstrated in many experiments using laboratory animals is limited by the impoverished conditions under which the animals are maintained.

In this context, it can be noted that perhaps the most remarkable evidence for developmental plasticity driven by the characteristics of the acoustic environment is provided by human language development. In the first year of postnatal life, the human infant’s auditory system is modified to selectively represent the phonetic and prosodic characteristics of its native language (native language neural commitment; e.g., Kuhl and Rivera-Gaxiola, 2008; Werker and Tees, 2005).

3.5. Maternal experience

An intriguing form of change in the significance of an acoustic stimulus occurs when significance is enhanced as a consequence of change in the internal state of the organism. Mouse pups separated from the nest emit ultrasonic distress calls which trigger behaviour (location and retrieval of the pups) in experienced mothers (dams) but not in virgin females without pup experience (Ehret, 2005). Studies of the representation of distress calls in the auditory cortex of dams and virgin females constitute an interesting extension of animal research on auditory cortical plasticity to ethologically significant communication sounds. An appealing feature of this model is that it eliminates the confounding effects of the task, reward, and learning strategy variables which have been shown to contribute to the diversity of effects seen in studies of other forms of auditory cortical plasticity.

Responses of AI neurons to natural or synthesized pup calls are enhanced in a number of respects in dams as compared to virgin females (see Marlin and Froemke (2017) for review). Cohen and Mizrahi (2015) reported that the transition to motherhood resulted in a shift in the best frequency of parvalbumin-expressing inhibitory interneurons (PVNs) in layer 2/3 of mouse AI, but had no effect on the best frequency of pyramidal neurons. In the presence of pup odours, the spontaneous and evoked activity of PVNs was reduced, and this reduction in feedforward inhibition coincided with an increase in the spontaneous and evoked activity of pyramidal neurons. Of interest in terms of the issues considered above with respect to both conditioning and perceptual learning, these changes do not involve an increase in the area of representation of ultrasonic vocalizations (or other ultrasonic signals), either permanently (Shepard et al., 2015) or as a transient phase during maternal experience (Shepard et al., 2016). Marlin et al. (2015; Marlin and Froemke (2017)) have shown that at least some of these effects reflect modulation by oxytocin, and that the effects of oxytocin are lateralized to the left auditory cortex

3.6. Cochlear implantation

It is widely recognized that the remarkable success of cochlear implants in restoring functional hearing in the profoundly deaf, despite the unnatural and degraded input provided by the device, is in large part attributable to brain plasticity (Moore and Shannon, 2009). The speech discrimination performance of post-lingually deaf adult implantees typically improves over the months and years following implantation (e.g., McKay, 2005; Fu and Galvin, 2007). This improvement undoubtedly reflects plasticity in numerous hearing- and language-related brain areas, but there is compelling evidence for changes in auditory cortical responses as a consequence of implant experience. For example, Pantev et al. (2006) reported that in two post-lingually deaf adult implantees, the magnetoencephalographically measured auditory evoked fields (AEFs) with sources located in auditory cortex increased in amplitude (reflecting an increase in the amount and/or synchrony of neural activity) over months following the implant being switched on, and that AEF component configurations were identical or near-identical to those in controls two years post implantation. A similar increase in the amplitude, and decrease in the latency, of auditory evoked potentials (AEPs) over the months following implantation, changes that were associated with an increase in auditory frequency discrimination ability, was reported by Sandmann et al. (2015).

In congenitally deaf children, maturation of AEPs depends on the age of implantation: in early-implanted children (implanted before 3.5 years of age) the latency of the P1 component decreases rapidly and reaches normal levels, but in late-implanted (after 7 years of age) children AEPs remain abnormal even after many years of implant use (Ponton and Eggermont, 2001) These differences correspond to differences in the speech perception and language skills of early- and late- implanted children, and indicate a sensitive period for cochlear implantation (see Kral and Sharma (2012) for review).

There have been numerous studies of the effects of profound deafness and subsequent stimulation via a cochlear implant on central auditory processing mechanisms in animals (see

Fallon et al. (2008) and Kral et al. (2006) for reviews). The cochleotopic organization of AI is rudimentary or absent in congenitally deaf or neonatal-deafened adult cats. In neonatal-deafened cats, environmentally-derived chronic stimulation via a multichannel cochlear electrode, initiated as soon as implantation is possible (at around 2 months of age), results in the maintenance of basic cochleotopy in the adult AI (Fallon et al., 2009). When such stimulation is initiated in adult animals after an extended period of deafness, when cochleotopy has been lost, it can restore normal cochleotopy (Fallon et al., 2014). Analogous effects of experience with cochlear electrical stimulation on temporal processing in the AI of deaf cats have been demonstrated (e.g., Vollmer and Beitel, 2011; Vollmer et al., 2017).

4. Cross-modal Plasticity

It has long been known that loss of one sensory modality can result in enhanced discriminative abilities in other modalities, and that these enhancements reflect, at least in part, changes in sensory cortices (see Merabet and Pascual-Leone (2010) and Lee and Whitt (2015) for reviews). Although primary sensory cortices are known to receive input from other modalities (Ghazanfar and Schroeder, 2006), there is a substantial body of evidence in both humans and animals for enhanced acoustically-evoked activity in visual cortex of the blind, and visually-evoked activity in auditory cortex of the deaf. An intriguing discovery has been that the changes underlying specific aspects of enhanced performance can be localized to specific regions of the reorganized cortex. Lomber et al. (2010) found that congenitally deaf white cats exhibited superior visual localization in the peripheral field, and lower visual movement detection thresholds, than normal-hearing cats. These enhancements were selectively eliminated by reversible deactivation of the posterior auditory field and the dorsal zone, respectively, but neither was influenced by reversible deactivation of the AI or the anterior auditory field (Fig. 2). Cross-modal plasticity is generally considered to involve the unmasking (and presumably increases in the efficacy of) existing connections (e.g., Meredith et al., 2017), and differences between species in patterns of cross-modal connectivity between primary sensory cortices are likely to be reflected in differences in the characteristics of cross-modal plasticity (Meredith and Lomber, 2017).

FIG. 2 ABOUT HERE

Cross-modal influences are not restricted to cases of complete loss of a sensory modality. Humans who suffer brief postnatal visual deprivation (as a consequence of congenital cataracts treated early in the first year of life) show enhanced auditory activation of visual cortex as adults (Collignon et al., 2015). Short periods of visual deprivation in mice (after the critical period) have been shown to result in enhanced responses and frequency selectivity in layer 4 neurons in the AI, changes which involve adjustments of both thalamo-cortical and intracortical circuits (Petrus et al., 2014; Meng et al., 2017).

Although cross-modal plasticity is generally considered to be adaptive, there is evidence to suggest that enhancement of visual input to auditory cortex in the long-term deaf might impact negatively on performance with a subsequently implanted cochlear prosthesis (see Collignon et al. (2011) for review and discussion).

5. Neuromodulatory and synaptic mechanisms of plasticity

The neocortex receives diffuse extrathalamic projections from five different subcortical cell groups, which act to modulate cortical sensitivity and have been implicated in learning-related cortical plasticity (e.g., Metherate, 2011). In terms of their effects on auditory system plasticity, the most extensively studied of these systems are the cholinergic and noradrenergic systems, arising in the NB and locus coeruleus, respectively. Early studies demonstrated that pairing activation of the cholinergic fibres via NB stimulation with tonal stimulation at a particular frequency shifted the tuning of AI neurons towards the stimulation frequency, such that there was an expanded representation of that frequency (see Metherate (2011) and Edeline (2012) for reviews). *In vivo* whole cell recordings have demonstrated that such pairing produces a stimulus-specific rapid reduction in inhibition, followed by an increase in excitation at the paired frequency (Froemke et al., 2007, 2013; Fig. 3). Inhibition subsequently slowly increased to result in restoration of excitatory-inhibitory balance at the neuron's new CF. Froemke et al. (2013) demonstrated that the effects of such pairing can also be seen in behaviour: NB pairing in awake rats led to improved detection and recognition of paired acoustic stimuli.

FIG. 3 ABOUT HERE

In contrast to the changes in frequency selectivity associated with learning and attention, those produced by cochlear lesions do not involve cholinergic modulation (Kamke et al., 2005). This dissociation between bottom-up injury-induced plasticity and top-down learning-related cortical plasticity has been elegantly demonstrated in a study of the effects of cholinergic basal forebrain lesions on the two forms of plasticity in motor cortex. In the same animals, the cholinergic system was found to be necessary for learning-related plasticity but not for injury-related plasticity (Ramanathan et al., 2009). Although animals raised in acoustically enriched environments presumably attend to those environmental events, the fact that this form of plasticity is also independent of the cholinergic system (Percaccio et al., 2007) suggests that it is also predominantly bottom-up.

The fundamental mechanisms underlying most forms of auditory cortical plasticity are changes in synaptic efficacy within existing patterns of connectivity. A remarkable anatomical finding to emerge in parallel with the evidence for auditory cortical plasticity has been that the AI receives input from a remarkable diverse range of intrinsic and extrinsic sources (e.g., Budinger and Scheich, 2009; Lee and Winer, 2011). In contrast to the traditional view of the AI as the end-station of a dedicated lemniscal-line system, projections from the ventral MGB constitute only a small proportion (less than 7% in the cat) of its input (Lee and Winer, 2011). In the frequency domain, AI neurons receive subthreshold input, derived from intrinsic cortico-cortical connections over horizontal fibres, that define "synaptic integration fields" that extend far beyond their classically-defined receptive fields identified in recordings of spiking activity (e.g., Fig. 3; see Metherate et al. (2005) for review), and two-photon imaging of calcium transients has revealed that the individual dendrites of pyramidal neurons receive input over a remarkable range of CFs (Chen et al., 2011). Given this diverse range of inputs, changes in receptive fields and response characteristics can potentially be produced by a wide range of synaptic mechanisms (see Dan and Poo (2006), Feldman (2009) for reviews).

On a longer time scale, studies of injury-induced plasticity in other modalities have found evidence of structural changes associated with cortical reorganization: axonal sprouting of horizontal fibres in the superficial layers (e.g., Yamahachi et al., 2009), increase in the turnover of dendritic spines in the superficial layers (Keck et al., 2008), and shifts in dendritic orientation (Tailby et al., 2005). It is likely that analogous structural changes are involved in injury-induced plasticity in the auditory system.

6. Conclusions

A vast body of evidence accumulated over more than 30 years has established that the auditory system continuously adjusts to changes in stimulus statistics and significance. These forms of plasticity occur at many different levels of the auditory pathway and over many time scales, and in most cases serve to optimize auditory performance. Only in the case of plasticity consequent on cochlear trauma and hearing loss do the changes appear to be maladaptive. Auditory system plasticity is, of course, just one of many forms of brain plasticity manifested throughout the life span, recognition of which has prompted attempts to harness this plasticity for therapeutic purposes (see Cramer et al. (2011) and Collignon et al. (2011) for reviews).

As noted previously, the evidence for these different forms of plasticity in auditory and other sensory systems, given the need alluded to above to maintain a degree of stability of perceptual systems, creates a problem which is directly analogous to the “stability/plasticity dilemma” that has long been recognized in neural network and other models of learning and memory (e.g., Seitz and Watanabe, 2005; Mermillod et al., 2013). Stated in general terms, the nub of this problem is how a neural system can be endowed with the plasticity that allows it to be modified by experience without compromising the stability necessary to execute its previously established functions. An attractive feature of the sort of multiplexing model proposed to explain visual perceptual learning (Li and Gilbert, 2008) and attentional changes (Fritz et al., 2007) (see Section 3.3) is that it avoids this problem, because synaptic weights are not permanently changed but are modulated by higher centres. The feasibility of such models is indicated by modelling studies which suggest ways in which individual neurons can switch their responsiveness between various input signals by adjustment of excitatory – inhibitory balance (e.g., Vogels & Abbott, 2009). The possibility of experimentally testing such switching hypotheses has until recently seemed remote, but the advent of techniques that allow the visualization of simultaneous synaptic events at multiple sites on the dendrites of individual cortical neurons (e.g., Chen et al., 2011) suggests that it might soon be possible to detect such multiplexing. The recent description of an auditory cortico-thalamic circuit that enables rapid switching between feature detection and discrimination (Guo et al., 2017) also indicates that switching mechanisms can be identified.

Acknowledgements

The author's research in this area has been funded by the National Health and Medical Research Council of Australia. The Bionics Institute acknowledges the support it receives from the Victorian Government through its Operational Infrastructure Support Program.

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Figure Legends

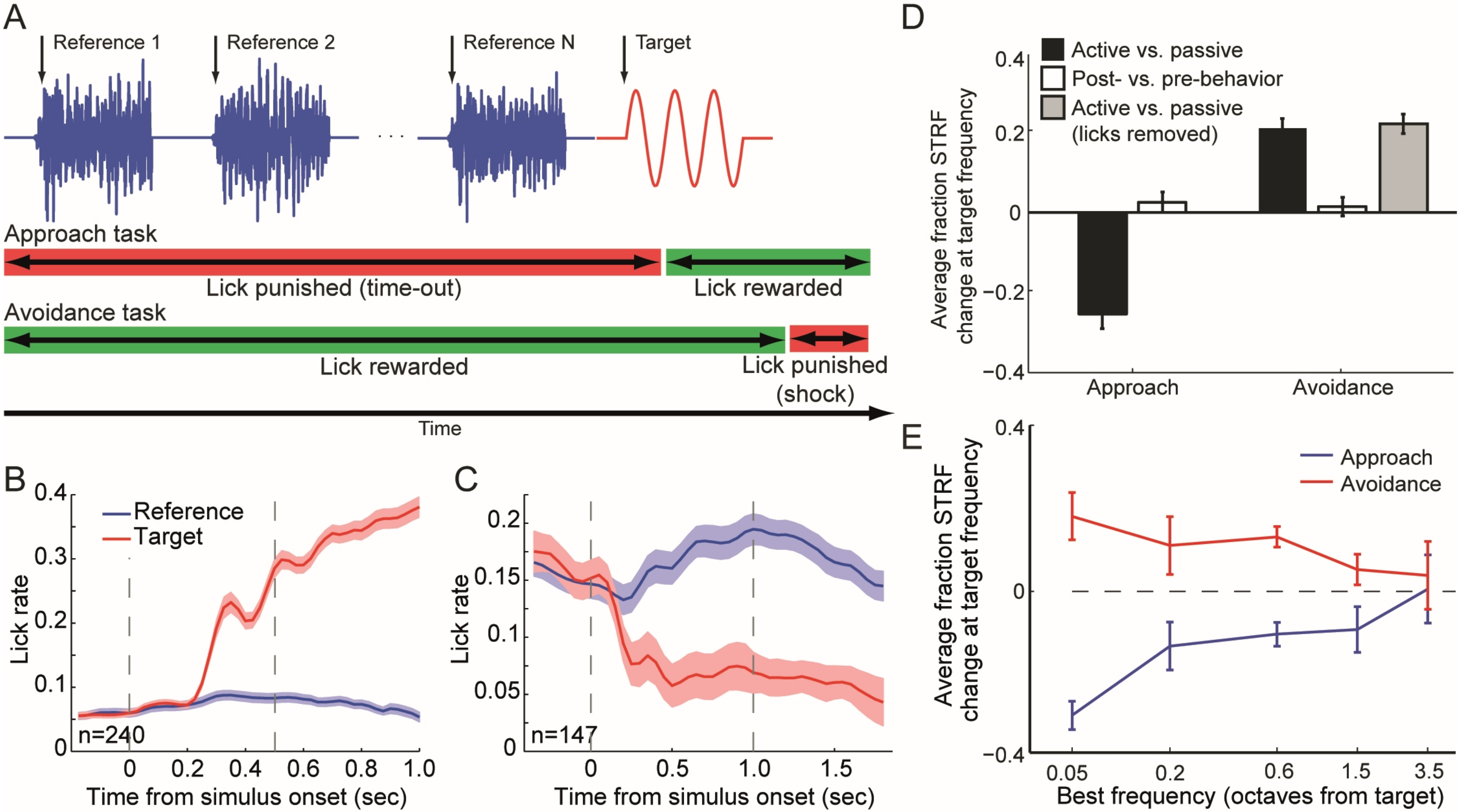
Fig. 1. Neural changes associated with approach and avoidance behaviours. (A) In both tasks, subjects were required to detect a pure tone target (red) after a random number of reference noise sounds (blue). During the approach behavior (timeline, Lower), subjects were positively rewarded with water for licking a water spout 0.1–1.0 s after target onset (green bar) and punished with a timeout for licking earlier (red bar). During avoidance, subjects were rewarded by licking a continuously flowing stream of water during the references and punished with a mild tail shock if they failed to cease licking 0.4 s after target offset. (B) Average behavior during approach experiments, plotted as a function of time after reference (blue) or target onset (red). Shading indicates one standard error (SE) across sessions. Dashed lines indicate stimulus onset and offset. Licking was minimal during references, because these trials were punished as false alarms; it substantially increased after target onset, and these trials were rewarded as hits. A stereotyped lick rate (five licks per second) is reflected by multiple peaks in the target curve. (C) Average behavior during avoidance experiments, plotted as in B. During references, animals maintained an elevated lick rate to retrieve reward. Licking was attenuated 0.2–0.4 s after target onset until after offset, when licking resulted in punishment for a miss. (D) Average STRF change at target frequency during behavior (black bars) and post-behavior (white bars), relative to pre-behavior baseline. The opposite sign changes for approach and avoidance largely reversed after behavior was complete. Data are shown for significantly modulated neurons with passive data recorded both before and after behavior (n = 86 approach, 59 avoidance). The gray bar plots the average STRF change during avoidance, after excluding data 150 ms before and after lick events9 to control for the possibility that licking related noise or middle ear muscle contractions might have produced the observed effects) . Error bars indicate 1 SE across neurons. (E) Average STRF change at target frequency, grouped by the difference between neural BF and target frequency. During approach (blue, n = 86), STRF changes tended to be negative for all neurons, but the greatest decrease occurred when BF was within 0.1 octave of the target frequency. During avoidance (red, n = 87), STRF changes were positive for all BF-

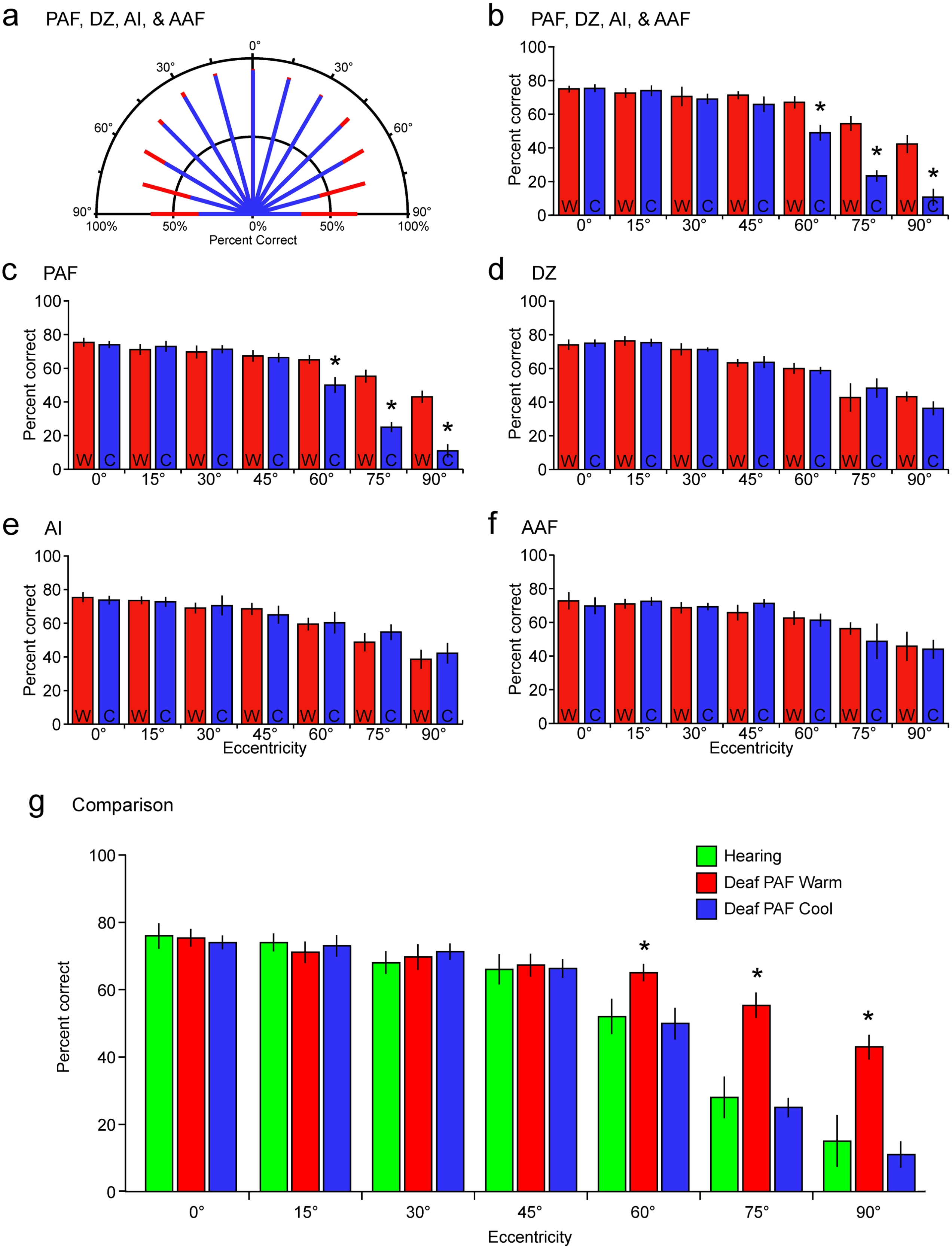
target frequency distances, and the magnitude was also greatest within 0.1 octave of target. Reproduced with permission from David et al. (2012).

Fig. 2. Visual localization task data from deaf cats during bilateral reversible deactivation (by cooling) of different auditory cortical fields: posterior auditory field (PAF), dorsal zone (DZ), AI and anterior auditory field (AAF). (**a**) Polar plot of the visual localization responses of deaf cats while cortex was warm (red) and active, and during simultaneous deactivation of PAF, DZ, AI, and AAF (blue). (**b**–**f**) Histograms of combined data from the left and right hemifields showing mean ± s.e.m. performance for deaf cats while cortex was active (red) and while it was deactivated (blue). Asterisks indicate a significant difference ($P < 0.01$) between the active and deactivated conditions. (**b**) Data from the simultaneous deactivation of PAF, DZ, AI and AAF. (**c**–**f**) Data from individual area deactivations. (**g**) Visual localization data comparing performance at each position for hearing cats (green), deaf cats while PAF was active (red), and deaf cats while PAF was deactivated (blue). *$P < 0.01$ from the hearing and deaf PAF deactivated conditions. Reproduced in modified form with permission from Lomber et al. (2010).

Fig. 3. Example of AI synaptic receptive field modification induced by pairing an acoustic stimulus with nucleus basalis (NB) stimulation. (**a**) Experimental preparation. Rec, recording; Stim, stimulation; (**b**) Example of synaptic tuning curve modification induced by NB pairing. Top, intensity sensitivity at 4 kHz. Bottom, frequency tuning at 30 dB SPL. Responses to the paired stimulus (30 dB SPL, 4 kHz; arrows) are enhanced, whereas responses at peak SPL and best frequency (arrowheads) are reduced. (**c**) Frequency-intensity synaptic receptive field for same cell as in **b**. Top, before (left) and after (right) pairing. Color, EPSC amplitude. Blue lines, threshold. Bottom, change in EPSCs (post-pairing − pre-pairing). Excitation (exc) at paired tone

(circle) increased from −14.8 ± 3.6 pA to −46.8 ± 6.6 pA ($P < 0.01$, Student's paired two-tailed *t*-test); excitation at original best stimulus (80 dB SPL, 16 kHz; square) decreased from −98.6 ± 15.4 pA to −43.3 ± 8.1 pA ($P < 0.01$). Net excitation across stimuli was similar before and after pairing (before, −1.68 nA; after, −1.51 nA; $P > 0.4$). Scale bars: 50 pA, 40 ms. Error bars show s.e.m. Reproduced with permission from Froemke et al. (2013).


A
Reference 1
Reference 2
Reference N
Target
Approach task
Lick punished (time-out)
Lick rewarded
Avoidance task
Lick rewarded
Lick punished (shock)
Time
B
Reference
Target
Lick rate
n=240
0
0.1
0.2
0.3
0.4
0
0.2
0.4
0.6
0.8
1.0
Time from simulus onset (sec)
C
Lick rate
n=147
0
0.05
0.1
0.15
0.2
0
0.5
1.0
1.5
Time from simulus onset (sec)
D
Active vs. passive
Post- vs. pre-behavior
Active vs. passive (licks removed)
Average fraction STRF change at target frequency
0.4
0.2
0
−0.2
−0.4
Approach
Avoidance
E
Approach
Avoidance
Average fraction STRF change at target frequency
0.4
0
−0.4
0.05
0.2
0.6
1.5
3.5
Best frequency (octaves from target)


a
PAF, DZ, AI, & AAF
0°
30°
30°
60°
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90°
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50%
100%
Percent Correct
b
PAF, DZ, AI, & AAF
c
PAF
d
DZ
e
AI
f
AAF
Percent correct
100
80
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Eccentricity
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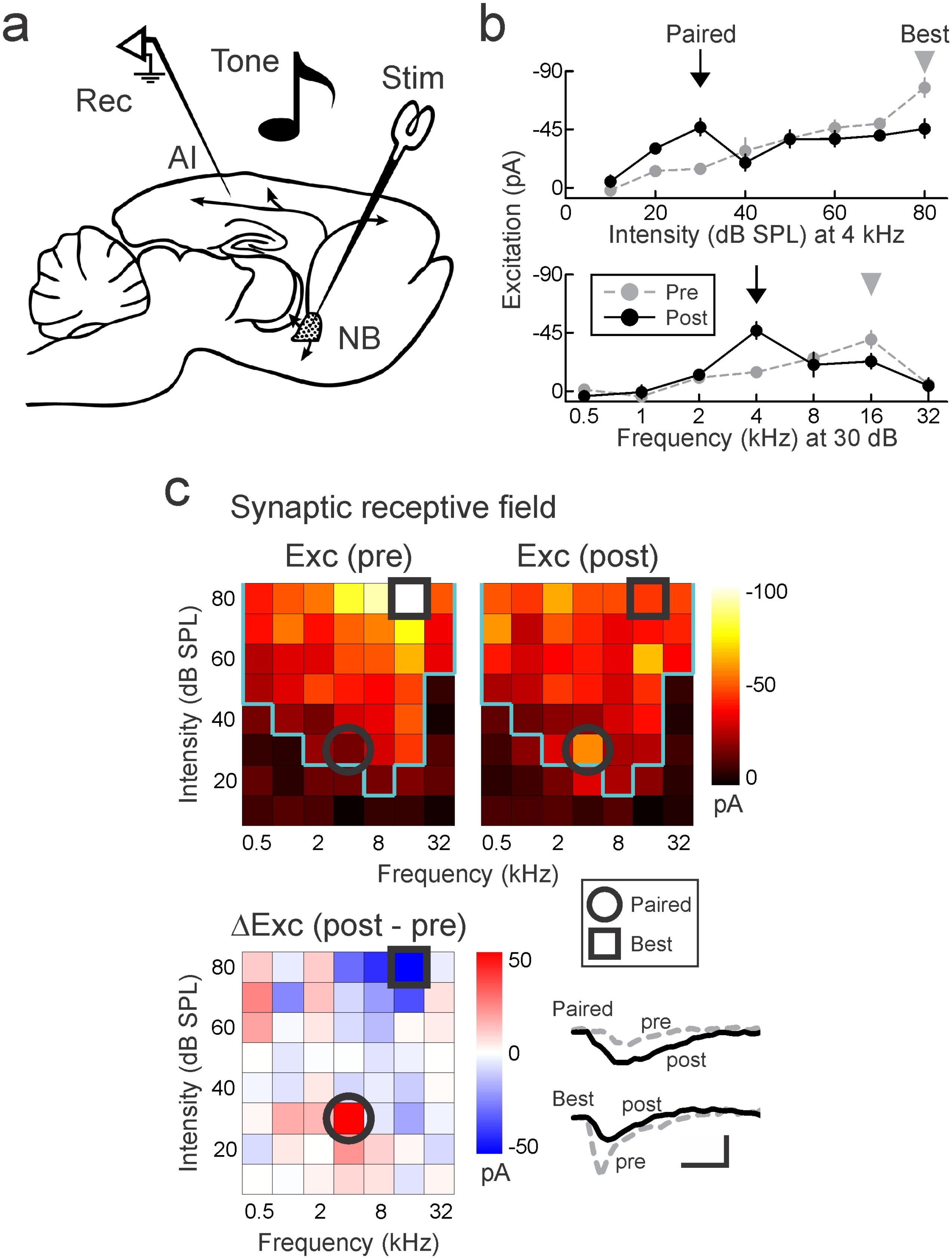
Comparison
Hearing
Deaf PAF Warm
Deaf PAF Cool


a
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Stim
AI
NB
b
Paired
Best
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-45
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0
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40
60
80
Intensity (dB SPL) at 4 kHz
Excitation (pA)
Pre
Post
0.5
1
2
4
8
16
32
Frequency (kHz) at 30 dB
c
Synaptic receptive field
Exc (pre)
Exc (post)
Intensity (dB SPL)
80
60
40
20
0.5
2
8
32
Frequency (kHz)
-100
-50
0
pA
Paired
Best
ΔExc (post - pre)
50
0
-50
pA
Paired
pre
post
Best
post
pre

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