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Review

Functional connectivity and cholinergic modulation in auditory cortex

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ABSTRACT

Although it is known that primary auditory cortex (A1) contributes to the processing and perception of sound, its precise functions and the underlying mechanisms are not well understood. Recent studies point to a remarkably broad spectral range of largely subthreshold inputs to individual neurons in A1 – seemingly encompassing, in some cases, the entire audible spectrum – as evidence for potential, and potentially unique, cortical functions. We have proposed a general mechanism for spectral integration by which information converges on neurons in A1 via a combination of thalamocortical pathways and intracortical long-distance, "horizontal", pathways. Here, this proposal is briefly reviewed and updated with results from multiple laboratories. Since spectral integration in A1 is dynamically regulated, we also show how one regulatory mechanism – modulation by the neurotransmitter acetylcholine (ACh) – could act within the hypothesized framework to alter integration in single neurons. The results of these studies promote a cellular understanding of information processing in A1.

Contents

1. Introduction

Spectral integration is an important function of A1, as indicated by physiological responses of neurons to spectrally complex stimuli (Mendelson and Cynader, 1985; Phillips et al., 1985; Rauschecker and Tian, 2000; Tian and Rauschecker, 2004; Whitfield and Evans, 1965) and behavioral deficits following cortical lesions in animals and humans (Harrington et al., 2001; Kelly and Whitfield, 1971; Ohl et al., 1999; Phillips, 1998; Phillips and Farmer, 1990; Wetzel et al., 1998). Spectral integration by single neurons is represented most simply by frequency receptive fields, which typically are constructed using pure tone stimuli and extracellular recordings of action potentials. Receptive fields thus delineated are "classical", suprathreshold (derived from action potentials) receptive fields that do not reflect the presence of subthreshold inputs. Classical frequency receptive fields are of similar breadth throughout the lemniscal (primary) auditory system (Calford et al., 1983), a finding that seems to suggest A1 does not contribute unique functions to spectral processing. However, when subthreshold (also known as subliminal, surround, nonclassical) receptive fields are considered, spectral integration in A1 neurons may be considerably more extensive than in subcortical neurons (see Section 2). Although the functions of subthreshold inputs are not yet fully appreciated, we have proposed a simple framework of functional connectivity by which spectral integration, including the contribution of subthreshold inputs, may take place in A1 (Kaur et al., 2004, 2005; Metherate et al., 2005). This framework is intended to promote an understanding of the mechanisms and functions of spectral integration in A1, and is reviewed and updated below.

Spectral integration in A1 is dynamic, varying, for example, with behavioral state (e.g., sleep vs. waking) (Edeline et al., 2001) or with attention to spectral cues in a behavioral task (Fritz et al., 2003; Weinberger, 2004). Rapid changes in spectral processing are likely due to physiological mechanisms such as neuromodulation (Edeline, 2003), which also may contribute to lasting changes in frequency representations subsequent to behavioral training (Kilgard

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and Merzenich, 1998; Recanzone et al., 1993). Thus, spectral integration is dynamically regulated, at times rapidly and perhaps continuously. In the second part of this review I will note some mechanisms by which one neuromodulatory agent, the neurotransmitter ACh, can regulate the proposed framework for spectral integration in A1.

2. Breadth of subthreshold inputs to neurons in A1

Studies of classical frequency receptive fields indicate that there is little change in receptive field breadth as one ascends through the lemniscal auditory pathway (e.g., from the central nucleus of the inferior colliculus to the ventral division of the medial geniculate body, MGv, to A1) (Calford et al., 1983), suggesting no change in spectral integration. However, measures of classical receptive fields are based on single- or multi-unit activity (i.e., tone-evoked action potential discharge) and do not take into account the presence or absence of subthreshold responses to stimuli outside the frequency receptive field. It is now well known that classical receptive fields underestimate the breadth of synaptic inputs to cortical neurons. For instance, blockade of GABAergic inhibition results in an expansion of the frequency receptive field (Foeller et al., 2001; Muller and Scheich, 1988; Wang et al., 2000, 2002), indicating the presence of normally-subthreshold excitatory postsynaptic potentials (EPSPs) (but see Kurt et al., 2006). More direct evidence is provided by *in vivo* intracellular recordings, which reveal extensive subthreshold receptive fields (Kaur et al., 2004; Ojima and Murakami, 2002; Tan et al., 2004; Wehr and Zador, 2003). These studies also demonstrate that throughout subthreshold and suprathreshold receptive fields, synaptic responses reflect overlapping ("balanced") inputs from both excitatory and inhibitory neurons that are driven by afferent input. Disruption by GABA receptor blockade of the excitatory–inhibitory balance leads to expansion of classical receptive fields (above). Intracellular studies are complemented by other studies that measure extracellular tone-evoked local field potentials (LFPs, which reflect synchronous synaptic potentials in a local group of neurons), in some cases simultaneously with multiunit spike recordings. These studies show LFP receptive fields that are similar in breadth to intracellular synaptic receptive fields, and in some cases several octaves broader than classical receptive fields at the same recording site (Eggermont, 1996; Galvan et al., 2001; Kaur et al., 2004; Norena and Eggermont, 2002). At higher intensities, the bandwidths of LFP receptive fields often exceed the experimenters' measurement capacity; e.g., a maximum bandwidth of eight octaves in one recent study (Happel et al., 2010). The breadth of intracellular and LFP receptive fields suggests that some neurons in A1 integrate over much, if not all, of the audible spectrum (Happel et al., 2010; Metherate et al., 2005; Schulze and Langner, 1999).

3. Contributions of thalamocortical and intracortical circuits to spectral integration in A1

To examine mechanisms of spectral integration, we focused on how information about characteristic frequency (CF) and spectrally-distant nonCF stimuli – that is, the "center" and one "edge" of a frequency receptive field – converges on single neurons in A1 (CF is the frequency eliciting the lowest threshold response; experimentally, we define nonCF as ~3 octaves from CF so as to maximize differences in underlying circuitry). The relevant circuits – thalamocortical and long-range "horizontal" intracortical pathways – are illustrated schematically in Fig. 1, which also illustrates our hypothesis. The contribution of the thalamocortical pathway is relatively straightforward and involves relaying information mostly about CF and near-CF stimuli from the MGv. Physiological and anatomical studies show that thalamocortical projections link MGv and A1 neurons with similar CFs (Budinger et al., 2000; Imig and Morel, 1984; Winer et al., 1999). Thalamocortical arbors labeled by injections of tracer into small portions of MGv cover regions of A1 containing neurons with similar CFs (Velenovsky et al., 2003), and paired recordings of neurons in MGv and A1 show that cells with correlated discharge exhibit CFs within one-third of an octave (Miller et al., 2001). These data imply that thalamocortical axons project to restricted portions of A1 and do not diverge throughout A1. Thus, direct thalamocortical projections are not responsible for the broad spectral integration observed in physiological studies. Rather, it seems that thalamocortical inputs mediate cortical responses to CF and near-CF stimuli [*Note:* however, this scheme does not incorporate projections from auditory nonlemniscal thalamic regions outside of MGv. Nonlemniscal neurons often have broad receptive fields and project diffusely to superficial layers of temporal cortex; their poorly understood functions may include modulation of cortical excitability (e.g., see discussion in Weinberger, 2004), and also could contribute to breadth of tuning in A1].

According to the framework in Fig. 1, neurons in A1 respond to nonCF stimuli via intracortical horizontal pathways. This scheme is supported by recent findings from several laboratories. One approach has been to deliver into A1 the GABA-A receptor agonist muscimol to inhibit locally generated (cortical), but not afferent (thalamocortical) activity, and then determine the effect on cortical responses to CF and nonCF stimuli. In one study (Kaur et al., 2004), muscimol only partly reduced the initial (first ~10 ms) LFP response to CF stimuli, but fully suppressed longer-latency response components, consistent with inhibition of cortical neurons but not thalamocortical inputs. In contrast, muscimol in some cases fully suppressed all response to nonCF stimuli, suggesting the critical involvement of intracortical pathways. Although a more recent study has questioned the sole use of muscimol to silence cortical activity, and instead suggested simultaneous activation of GABA-A receptors and blockade of GABA-B receptors (Liu et al., 2007), a third study found no difference between the two approaches (Happel et al., 2010). The latter study confirmed that cortical silencing eliminates responses to nonCF, but not CF, stimuli (Happel et al., 2010). Thus, it appears that thalamocortical inputs generate (or, more correctly, initiate) responses to CF stimuli, whereas responses to nonCF stimuli involve intracortical projections from neurons with spectrally-distant CFs (Fig. 1).

Recent studies also show that thalamocortical inputs trigger a rapid and local intracortical amplification of the response to CF stimuli (Happel et al., 2010; Liu et al., 2007), which explains why cortical silencing reduces (partly) the response to CF stimuli. In addition, stimuli within ~1 octave ("near-CF" stimuli) trigger cortical responses that similarly rely on local intracortical amplification of inputs (Happel et al., 2010; Liu et al., 2007).

Although a complete dissociation between the pathways relaying information about CF and spectrally distant stimuli may be unlikely, one prediction of the model (Fig. 1) is that since thalamocortical vs. intracortical projections terminate in different cortical layers, the neural activity elicited by CF vs. nonCF stimuli similarly will have different laminar profiles. Consistent with this prediction, current–source density (CSD) profiles elicited by CF and nonCF stimuli are different, with CF stimuli eliciting major current sinks in lower layer 3 and upper layer 4 (the location of thalamocortical terminals) and nonCF stimuli eliciting current sinks in multiple layers (consistent with intracortical projection patterns) (Kaur et al., 2005). Of course, the model in Fig. 1 is overly simplistic and does not incorporate different cell types, multiple thalamic and corticocortical projections, and a host of other features of the auditory forebrain. Rather, the model is intended to illustrate the general concept as a starting point for understanding connectivity in A1,

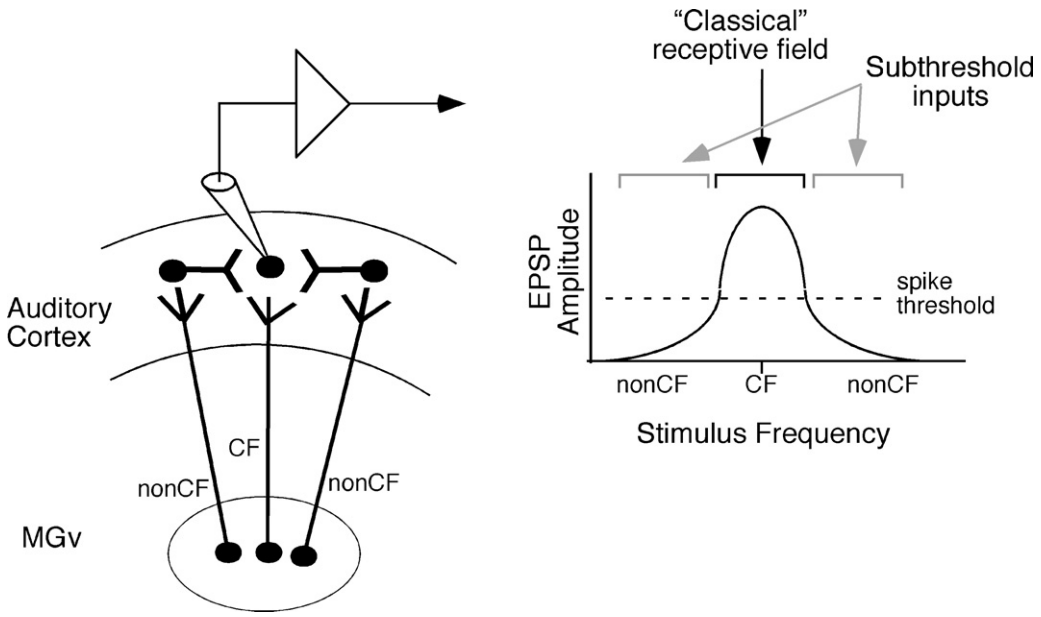

Fig. 1. Schematic (left) of hypothesis that spectral integration by neurons in A1 involves direct thalamocortical inputs carrying information about CF (and near-CF) stimuli and long-distance, intracortical "horizontal" projections carrying information about spectrally-distant (nonCF) stimuli. CF, characteristic frequency; MGv, ventral division of the medial geniculate body. Graph (right) illustrates hypothetical results of intracellular recording from neuron on left responding to tone stimuli, with suprathreshold EPSPs generating the classical receptive field flanked by subthreshold EPSPs elicited in response to higher and lower frequencies.

and to provide a framework for understanding functional modulation and plasticity. The latter issue is reviewed next.

4. Cholinergic modulation of thalamocortical and intracortical connectivity

The final section of this review will touch upon dynamic regulation of processing in A1 via regulation of functional connectivity. Regulatory mechanisms are undoubtedly diverse, but most attention is focused on a subset of neurotransmitters that exert neuromodulatory actions (Edeline, 2003). This section will focus on ACh, a neurotransmitter that plays important roles in arousal, attention, and sensory learning (Hasselmo, 1999; Sarter et al., 2001; Weinberger, 2004). Cholinergic actions at both major subtypes of ACh receptor – nicotinic (nAChR) and muscarinic (mAChR) receptors – may regulate spectral integration in A1. In particular, cholinergic modulation of thalamocortical and intracortical transmission may underlie regulation of spectral processing as reflected in changes to frequency receptive fields.

Many studies of cholinergic modulation *in vivo* have shown that activation of mAChRs enhance cortical responses to sensory inputs (Chen and Yan, 2007; McKenna et al., 1989; Metherate et al., 1988; Sillito and Kemp, 1983; Zhang et al., 2005). A number of cellular effects, not all of which are directly excitatory, contribute to muscarinic modulation of sensory responses. Muscarinic stimulation can increase postsynaptic membrane resistance, and, thereby, responses to afferent inputs, due to decreased conductance of several K^+ channels (Halliwell and Adams, 1982; Krnjevic et al., 1971; Madison et al., 1987; McCormick and Prince, 1986). Accordingly, activation of cholinergic synapses in auditory cortex increases postsynaptic excitability via a slow EPSP associated with increased membrane resistance and decreased after hyperpolarization potentials (AHPs) (Cox et al., 1994; Metherate et al., 1992). Stimulation of cortically-projecting neurons from the nucleus basalis enhances afferent responses in A1 evoked by thalamic (Metherate and Ashe, 1993; Metherate et al., 1992) or acoustic stimulation (Chen and Yan, 2007; Edeline et al., 1994; Zhang et al., 2005), in part by enhancing tone-evoked EPSPs and simultaneously reducing tone-evoked inhibition (Froemke et al., 2007; Metherate and Ashe, 1993; Metherate et al., 1992). The use of the auditory thalamocortical slice preparation (Cruikshank et al., 2002), which preserves the thalamocortical pathway from MGv to A1 along with (unspecified) long-range intracortical pathways, showed that the cholinergic agonist carbachol suppressed intracortical EPSPs while having lesser or no effects on thalamic-evoked EPSPs (Hsieh et al., 2000). Since all of the above effects are blocked by muscarinic receptor antagonists such as atropine, they demonstrate the functional consequences of muscarinic cellular actions for auditory processing in A1.

ACh also acts at nAChRs, which are widely distributed in the auditory system (Morley and Happe, 2000). Studies to date support two main functions of nAChRs in sensory cortex: presynaptic regulation of thalamocortical transmission and postsynaptic excitation of GABAergic interneurons (for review, see Metherate, 2004). Both functions relate to hypothesized mechanisms of spectral integration (Fig. 2). The distribution of nAChRs in cortex varies among species, but generally relates to the widely-held hypothesis that nAChRs regulate thalamocortical transmission in general (Clarke, 2004). Studies in cat and rat show a dense concentration of nAChRs in layers 3–4 where thalamocortical inputs terminate, and also layers 1 and 5/6 (Clarke et al., 1984, 1985; Lavine et al., 1997; London et al., 1985; Parkinson et al., 1988; Prusky et al., 1987; Sahin et al., 1992). In the mouse, nAChRs are less prominent in the middle layers (Marks et al., 1992; Rogers et al., 1998; Ross et al., 2000; Zoli et al., 1998). In addition to cortical locations of nAChRs, in several species (mouse, rat, primate, human) nAChRs are found in the subcortical white matter region containing the auditory thalamocortical pathway, as evidence by positron emission tomography (PET) and radioligand studies (Chattopadhyay et al., 2005; Ding et al., 2004; Easwaramoorthy et al., 2007). Thus, thalamocortical transmission in cat and rat may be regulated by nAChRs located at or near thalamocortical terminals; this mechanism is supported by functional studies (Clarke, 2004; Gil et al., 1997; Lambe et al., 2003). In rodents and primates, nAChRs associated with thalamocortical axons suggest an additional mechanism. Using the auditory thalamocortical slice, we recently showed that activation of nAChRs in the thalamocortical pathway increases axon excitability and regulates thalamocortical relay (Kawai et al., 2007), providing the first functional evidence that ACh – or any neurotransmitter – can act

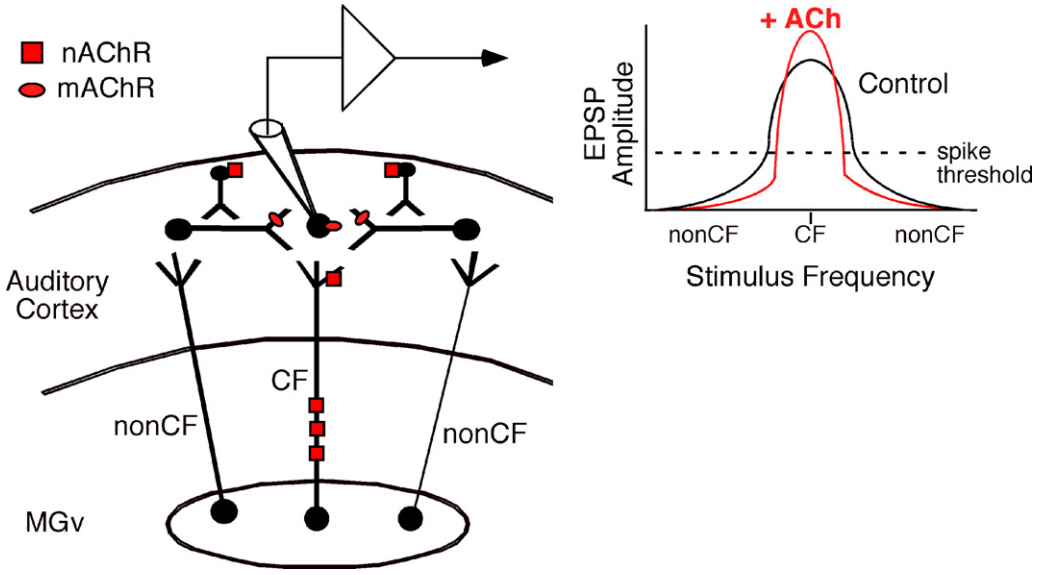

Fig. 2. Hypothesized effect of ACh on receptive fields due to modulation of thalamocortical and intracortical circuits (left). Cellular effects of ACh include those mediated by muscarinic ACh receptors (mAChRs) – including enhancement of postsynaptic excitability and presynaptic reduction of intracortical transmission – and effects mediated by nicotinic ACh receptors (nAChRs) – including enhancement of thalamocortical transmission by axonal and presynaptic receptors on thalamocortical axons, and excitation of cortical GABAergic interneurons. A potential result of these combined actions (right) is to reduce receptive field breadth and enhance responsiveness within the "sharpened" receptive field (red line).

on the myelinated portion of thalamocortical axons. Fig. 2 shows a hypothetical arrangement of axonal and presynaptic nAChRs that individually or together may regulate cortical responses to thalamic inputs.

Other studies have demonstrated rapid nicotinic excitation of postsynaptic neurons, and in sensory cortex, as in other cortical areas, such actions are most prominent in GABAergic interneurons (Alkondon et al., 2000; Christophe et al., 2002; Frazier et al., 1998, 2003; Gulledge et al., 2007; Ji and Dani, 2000; Ji et al., 2001; Jones and Yakel, 1997; Porter et al., 1999). In cortical layer 1, which has the highest density among cortical layers of cholinergic axons and synapses (Mechawar et al., 2000, 2002), nicotinic agonists excite nearly all GABAergic interneurons (Christophe et al., 2002; Gulledge et al., 2007). Notably, activation of nAChRs in layer 1 produces IPSPs in layer 2/3 interneurons but not pyramidal cells, suggesting that nicotinic excitation of layer 1 disinhibits deeper layers. Some GABAergic interneurons in cortical layers 2–5 also can be excited by nicotinic agonists (Gulledge et al., 2007; Porter et al., 1999; Xiang et al., 1998). Interneurons excited by nAChR activation include low-threshold spiking, regular-spiking, late-spiking and irregular spiking neurons, but do not include fast-spiking neurons. Thus, nicotinic excitation of interneurons can shape processing of afferent information by inhibiting some neurons and disinhibiting others.

It is tempting to speculate on the effect of endogenous ACh on A1 function when it is acting simultaneously at multiple nicotinic and muscarinic receptors and receptor subtypes. Although several studies have examined the effects of ACh released endogenously or exogenously in A1, the effects observed have been largely attributed to mAChRs (Ashe et al., 1989; Chen and Yan, 2007; Froemke et al., 2007; McKenna et al., 1988; Metherate et al., 1990). It is hard to reconcile such largely-muscarinic effects of ACh with the high density of nAChRs in A1 and robust effects of selective nicotinic drugs (above) (Gioanni et al., 1999; Kawai et al., 2007; Lavine et al., 1997; Liang et al., 2006). Possible explanations for overlooked nicotinic effects include rapid desensitization of nAChRs or ineffective agonist concentrations at the relevant receptor locations (Metherate, 2004; Role and Berg, 1996). Nonetheless, the studies reviewed above using selective agonists and antagonists suggest that activation of mAChRs would tend to increase postsynaptic excitability while decreasing intracortical transmission via presynaptic receptors, whereas, in contrast, activation of nAChRs may enhance thalamocortical transmission. The role of nAChRs in regulating transmission along intracortical pathways is unknown, but may involve excitation of GABAergic interneurons. Thus, the combined muscarinic and nicotinic actions of ACh could enhance thalamocortical transmission while suppressing intracortical excitatory transmission. Given the hypothesized contribution of thalamocortical and intracortical inputs to frequency receptive fields (Fig. 1), the integrated actions of ACh could produce (Fig. 2): suppression of responses to nonCF stimuli (mediated by intracortical horizontal inputs), facilitation of responses to CF and near-CF stimuli (mediated by thalamocortical inputs), and enhancement of responsiveness to remaining inputs (due to enhanced postsynaptic excitability). The net effect could be to reduce receptive field breadth, lower the threshold to CF stimuli, and enhance responses to stimuli within the "sharpened" receptive field (Fig. 2, right). Note how the increased receptive field selectivity differs from that produced by another neuromodulatory agent, norepinephrine, which can sharpen receptive fields via generally suppressive effects that are greater at nonCF than at CF (Edeline, 2003). Future studies will test the predictions in Fig. 2, but as these examples suggest, understanding the cellular actions of ACh can promote a deeper understanding of the mechanisms regulating auditory processing in A1.

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