A Possible Mechanism of Learning-Evoked Reorganization of Receptive Fields in the Primary Auditory Cortex: A Role of the Basal Ganglia, Prefrontal Cortex, Hippocampus, Acetylcholine and Dopamine

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Abstract A hypothetical mechanism is advanced that determines a role of acetylcholine and dopamine in the reorganization of receptive fields (RFs) in the primary auditory cortical area A1 evoked by learning with a pure tone with a frequency F. This mechanism is based on dopamine- and acetylcholine-dependent long-term changes in the efficacy of neural connections in the auditory and limbic cortico-basal ganglia-thalamocortical loops. Dopamine, released in response to the tone F and reinforcing signal acting at D1 receptors on striatonigral cells of the dorsal striatum promotes the induction of LTP in the efficacy of inputs from A1 neurons with preferred tuning frequency (PTF) equal or close to F. As a result, basal ganglia (BG) output more strongly disinhibits neurons in the MGB with the PTF close to F, thus promoting a rise in the activity of tonotopically connected MGB and A1 neurons. Simultaneously, LTD is induced at other corticostriatal inputs, leading to inhibition of MGB and A1 neurons with PTF different from F. Voluntary attention promotes RFs narrowing due to a rise in the prefrontal cortex activity and its excitatory input to A1, as well as by dopamine-dependent disinhibition of MGB neurons by the limbic part of the BG that includes the nucleus accumbens. Hippocampus is involved in auditory processing due to its connections with the cortex and projections to the nucleus accumbens. Acetylcholine released by the basal forebrain and pedunculopontine nucleus (that is also under inhibitory control from the BG) modulates RFs due to activity reorganization in the whole network. The complex effect of acetylcholine is determined by location of muscarinic and nicotinic receptors at both pyramidal cell and GABAergic interneurons. Therefore, it depends on ACh concentration and strength of inhibition.

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1 Introduction

It is known that the receptive fields (RFs) of neurons in the primary auditory cortex A1 are modified during learning. Changes are highly specific, selective, quickly formed, and can be maintained during long time, i.e., possess the characteristics of associative memory (Weinberger, 2007). The cholinergic innervation from the basal forebrain has a significant effect on the learning-evoked plastic reorganization in the RFs of A1 neurons. These modifications are also highly specific and have characteristics of associative memory (Weinberger, 2007). The increase in acetylcholine (ACh) release in the neocortex has the same effect on the RF changes during learning as dopamine. Our previous analysis of possible mechanisms for processing of pure tones indicated that dopamine-dependent activity reorganization in the basal ganglia (BG) are involved in the creation of RFs of tonotopically connected neurons in the A1, the ventral part of the medial geniculate body (MGBv), and the central part of the inferior colliculus (ICc), since neurons of the BG output nuclei inhibit neurons of the MGBv and ICc (Silkis, 2015). Only a few models consider that the thalamus is under inhibitory control from the BG and that this inhibition is important for the information processing of ascending sensory information (Cabessa & Villa, 2018). In this paper, we introduce our hypothesis that during learning, a modulation of the cortico-striatal inputs by dopamine, which is released in response to reinforcement and a conditioning signal (CS), a pure tone with the frequency F, as well as modulation of neuronal activity in the neocortex, hippocampus and thalamus by Ach underlie changes in RFs of neurons in the A1 and MGBv.

2 A Hypothetical Mechanism for the Learning-Evoked Changes in the RFs of the A1 Neurons

2.1 Functional Organization of the Cortico-BG-thalamocortical Loops Involved in the Processing of Pure Tones

The information about pure tones entries into the A1 via the ICc and MGBv (bottom-up pathway), and there is a top-down pathway to A1 from the prefrontal cortex (PFC) (Fig. 1). Neurons from the A1 project back into the MGBv and also into the dorsal striatum, where they excite striatonigral (S-N) cells, giving rise to the direct disinhibitory pathway through the BG. S-N cells inhibit neurons of the ventral part of output BG nucleus, the substantia nigra pars reticulata (vSNr). Neurons of the ventral striatum, the nucleus accumbens (NAc) receive excitation from the PFC and contain both S-N cells and striatopallidal (S-P) cells. S-N cells inhibit the ventro-medial part

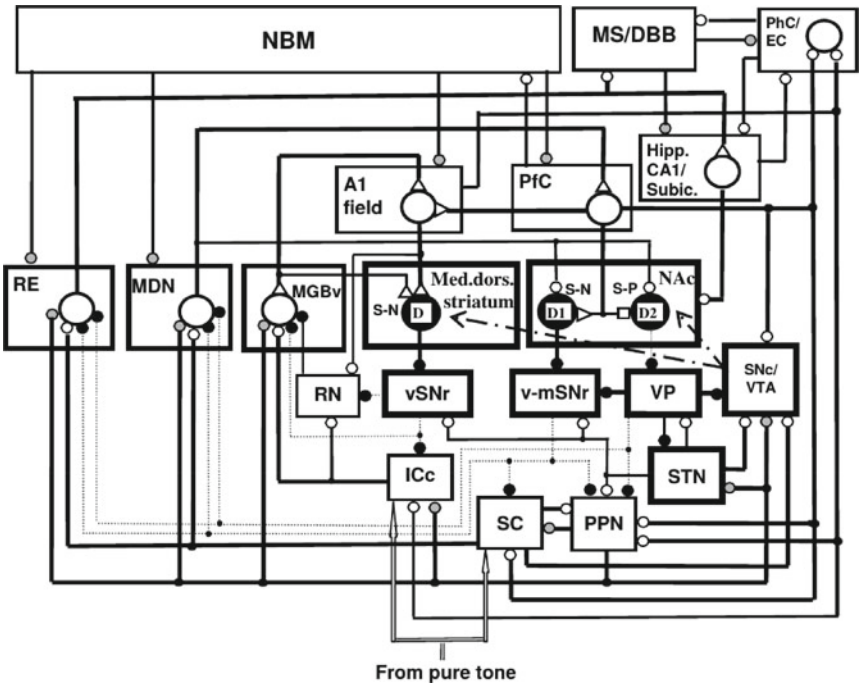

Fig. 1 The scheme of neuronal loops providing pure tone processing, shaping RFs, and their modulation by dopamine and acetylcholine. Cortical areas: A1, PFC, PhC, EC. Thalamic nuclei: MGBv, MDN, RE, reticular, RN. Basal ganglia nuclei: medio-dorsal striatum, NAc, vSNr, m-vSNr, VP, STN. Dopaminergic structures: SNc, VTA. Cholinergic structures: NBM, MS/DBB, PPN. Large light and dark circles, excitatory and inhibitory neurons, respectively; small light, dark and shaded circles, excitatory, inhibitory, and cholinergic inputs, respectively; small triangles and squares, potentiated and depressed excitatory inputs, respectively; arrows, dopaminergic inputs; thick and dashed lines, strong and weak inputs, respectively. Other abbreviations are in the text

of the SNr (v-mSNr), whereas S-P cells, giving rise to the indirect inhibitory pathway through the BG inhibit the ventral pallidum (VP). The output BG nuclei, SNr and VP tonically inhibit neurons in thalamic nuclei (Fig. 1). It is important to note that cortico-BG-thalamocortical (C-B-Th-C) loops are closed and topically organized.

2.2 A Possible Mechanism for the Participation of the BG and Dopamine in Learning-Evoked Plastic Reorganizations of the RFs of the A1 Neurons

Sound stimuli evoke the short-latency responses of dopaminergic cells in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) since there are

inputs from the superior colliculus (SC), pedunculopontine nucleus (PPN), PFC, and subthalamic nucleus (STN) (Fig. 1). Dopamine, acting at D1 receptors on S-N cells, promotes induction of LTP of the efficacy of strong cortico-striatal inputs, and LTD of weak inputs (Silkis, 2001). The strong inputs are formed by those A1 neurons whose preferred tuning frequency (PTF) coincides or is close to F, so they are initially strongly activated by the stimulus, and their excitation of S-N cells allows opening postsynaptic NMDA channels. The inputs to other S-N cells from weakly responsive cortical neurons whose PTF is differed from F are weak, and therefore do not allow opening the NMDA channels (Silkis, 2015). Due to the topical organization of A1-BG-MGBv-A1 loops the dopamine-dependent reorganization of activity in the BG should lead to a disinhibitory action from the SNr on activity of MGBv neurons whose PTF is close to F. At the same time, the inhibition of the activity of MGBv neurons with PTF different from F will be enhanced. As a result, the RFs of tonotopically connected MGBv and A1 neurons will tend to be narrower. Since the neurons of the lateral part of the SN are projected into the ICc, the disinhibitory effect on some of ICc neurons from the BG can enhance the activity of neurons at the low level of auditory processing.

A class of long-range GABAergic cells (not shown in Fig. 1 to simplify) has recently been discovered in the auditory cortex and PFC. They send projections to spiny cells of the dorsal striatum and NAc, and are involved in learning (Lee et al., 2014; Rock et al., 2016). In the NAc, the inhibitory terminals were observed on both S-N and S-P cells. We assume that in the presence of such inhibition, the NMDA channels will be opened on a small number of spiny cells while LTD will be induced at cortical inputs to many other spiny cells. As a result, many thalamic cells will be inhibited, and therefore RFs will be narrower.

Since there are reciprocal connections between the MGBv and A1, the output signals from the BG can influence the efficacy of connections between all elements of talamo-cortical loops. We have earlier shown in in vivo experiments that microstimulation of a group of neurons with PTF F_1 leads to a shift towards to F the PTF of neurons in the adjacent locus of the A1 and in the tonotopically connected MGBv locus with initial PTF F_2. At the same time, we found long-term modification (LTP and LTD) of monosynaptic connections between elements of the thalamo-cortical loop (Sil'kis, 1996).

2.3 A Possible Mechanisms for the Participation of Attention in Plastic Reorganizations of RFs of the A1 Neurons

It is known that learning requires voluntary attention. We proposed that voluntary attention is a part of sensory processing and is triggered by activation of the PFC and dopamine release (Silkis, 2007). The effect of the PFC on the A1 neurons is sufficiently effective. Optogenetic stimulation of the PFC resulted in short-latency excitation of the A1 neurons, and combined stimulation of the PFC with a sound

led to an improvement of the representation of this sound in the A1 as well as sound discrimination (Winkowski et al., 2018). Since attention is normally directed to reinforced CS with the frequency F, we assume that additional PFC action at A1 neurons with the PTF F will cause an additional rise in activity of these neurons. It follows from proposed mechanism that this must be manifested in the better narrowed and intensive RFs of A1 neurons.

2.4 Possible Mechanisms for Participation of the Hippocampus in Plastic Reorganizations of RFs of the A1 Neurons

The hippocampus and adjacent parahippocampal cortex (PHC), that includes the entorhinal cortex (EC) and connects hippocampus with the sensory cortical areas are considered as a part of the brain involved in the perception. Memory of information about individual tones correlates with a rise in the interaction between the hippocampus and the inferior frontal gyrus (Kumar et al., 2016). Removing the medial temporal gyrus led to impaired auditory memory (Fritz et al., 2016). Activity in the hippocampus depends on both the parameters of sound and the source of its location. After prolonged tone presentation, the activity of the place cells in the hippocampus were changed (Goble et al., 2009). It is believed that long-range connections between the auditory cortex, hippocampus, and frontal cortex may underlie the maintenance of tone mapping in the working memory. Closing the loop connecting the hippocampus with the BG is carried out through the midline thalamic nucleus reuniens (RE) that innervates the hippocampal CA1 field (McKenna & Vertes, 2004). The BG influence hippocampal activity since RE is under inhibitory control from the SNr.

In turn, the hippocampus influencing the functioning of the limbic part of the BG since it facilitates the passage of signals from the PFC through the NAc. Normally the spiny cells of the NAc are in the low state of membrane polarization, and the excitation from the PFC is insufficient to spike generation by NAc cells (O'Donnell & Grace, 1995). However, simultaneous signal arriving from the hippocampus and the PFC brings the spiny cells to discharges. Subsequent disinhibition of the RE and mediodorsal nucleus (MDN) by the BG must lead to an increase in the activity of some hippocampal and PFC neurons.

3 The Effect of ACh on Changes in RFs of the A1 Neurons During Learning

The A1 and PFC neurons, as well as the midline thalamic nuclei receive cholinergic innervation from the nucleus basalis of Meynert (NBM). The hippocampal neurons are influenced by cholinergic cells of the medial septum and diagonal band of Broca

(MS/DBB). Sound stimuli statistically significant increased ACh release in both the hippocampus and neocortex (Inglis & Fibiger, 1995). Cholinergic terminals from the PPN innervate the ICc and MGB (Schofield, 2010). Latencies of the PPN neuron responses to sound stimuli is less than 80 ms (Vitale et al., 2019). Due to the direct projections from the PFC to NBM, there is a top-down effect on the Ach release (Sarter et al., 2005). The A1 neurons influence ACh release due to top-down projections to the PPN (Fig. 1).

ACh exerts a complex influence on the RFs of pyramidal neurons in the A1 via muscarinic and nicotinic receptors of various types that are placed on pyramidal cells and inhibitory interneurons in all structures involved in sound processing. According to the unified modulation rules that we formulated earlier (Sil'kis, 2003), the activation of postsynaptic nicotinic receptors and muscarinic M1/M5 receptors should promote the induction of LTP of efficacy of excitatory inputs to a neuron, whereas activation of M2–M4 receptors should promote the induction of LTD. The resulting effect must depend on the strength of the inhibitory input to a pyramidal target cell, as well as on the affinity of the cholinoreceptors, and therefore on the ACh concentration.

During associative Pavlovian learning with a pure tone as the CS, ACh concentration in the A1 consistently increases with the progress of learning. A conditioned stimulation of the NBM and a tone with a frequency F led to changes in RFs of the A1 neurons similar to those evoked by classical learning. In these experiments, RFs of the A1 neurons shifted towards the conditioned tone (Froemke et al., 2007), and the neural representation of this tone in the A1 was expanded (Weinberger, 2007). The PTF of neurons in the MGBv and ICc also shifted toward the frequency of the conditioned tone, the threshold of responses to this tone decreased, and the number of spikes in the response increased (Zhang et al., 2005; Zhang & Yan, 2008). Since these effects disappeared after inactivation of the cortex, it can be assumed that cortico-fugal influence makes a significant contribution to specific rearrangements of neuronal responses in the MGBv and ICc (Villa et al., 1991). The conditioned stimulation of the PPN and a tone with a frequency F also led to a significant shift of the PTF of neurons in the auditory cortex towards the frequency F (Luo & Yan, 2013). Application of muscarinic receptor antagonists has prevented all these effects. Systemic administration of nicotine also increased the responses of A1 neurons with determined PTF and narrowed their RFs, and this effect was obtained at the level of the IC and thalamus (Askew et al., 2017).

However, opposite effects were also observed. In some experiments, the application of ACh or activation of muscarinic receptors promoted a decrease in the responses to the tone matching PTF, and an increase in the responses to tones of different frequencies (Ashe et al., 1989; McKenna et al., 1989). From the point of view of the proposed mechanism, in mentioned experiments, the potentiating effect of ACh on the inhibitory cortical interneurons via M1 receptors prevailed and inhibition was so strong that it masked the potentiating effect of activation of M1 receptor on pyramidal cells. Presumably, the ACh concentration was sufficiently high to affect these receptors.

4 Conclusion

The proposed mechanism for the functioning of C-BG-Th-C loops differs from conventional models in which only strong inputs to the striatum are taken into account by default, and transmission via the direct and indirect pathways through the BG leads to opposite behavioral effects. However, it is inconsistent with the data that S-N and S-P cells are activated by the same cortical or thalamic neuron (Doig et al., 2010), and then the BG through the SNr and thalamus affect the same neocortical neuron. In known models of sensory processing, the RF shaping is explained by plastic reorganizations in the efficacy of connections between neurons in the thalamo-cortical loop, and by the presence of lateral inhibition in the neocortex. It is ignored that the thalamus is under inhibitory control from the BG, and it is unlikely that lateral inhibition can provide any input-specific effect due to the small number of inhibitory interneurons (a few percent) and the large convergence and divergence of their connections. In our model, signal transduction through both BG pathways synergistically lead to disinhibition of one group of connected thalamic and cortical cells, and simultaneous inhibition of other groups (Silkis, 2013). Shaping RFs is naturally performed due to the opposite sign of modification of the efficacy of strong and weak cortico-striatal inputs.

The proposed mechanism of learning-evoked reorganization of RFs in the primary auditory cortex determines the role of the BG, PFC, and hippocampus in pure tone processing. This is also in agreement with the role of C-BG-Th-C loops in controlling the complexity of processing ascending sensory information (Cabessa & Villa, 2014, 2018). Our new model also points out the significant role of CS-evoked dopamine release in shaping the RFs as well as modulatory effect of ACh on RFs of A1 neurons. The understanding mechanism of the effect of these neuromodulators on auditory processing can help in alleviating hearing impairment in some neurological diseases. For example, it was shown that nerve growth factor (NGF)-treatment increased following parameters: choline acetyltransferase activity in the septal area, functional cortico-cortical interactions in the short frequency range, the mean firing rate of MGB neurons, and interactions between pairs of distant MGB neurons (Villa et al., 1996, 2000). If taken into account that observed high MGB activity must promote firing of S-N cells and subsequent disinhibition of thalamic neurons via the BG, and that increased neuronal interactions may reflect LTP in the efficacy of cortico-cortical and thalamo-thalamic connections it is reasonable to assume that NGF has significant potential for the improvement of auditory processing and memory in patients with Alzheimer disease that is characterized by deficiency of ACh.

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