Cholinergic modulation of microcircuits in the cortex

Obermayer, J.M.G.

2019

document version
Publisher's PDF, also known as Version of record

In our daily lives we are continuously bombarded with an overwhelming amount of inputs from our eyes, ears, nose and many more sensory organs. It is even for our brain, which is thought to be the most powerful information processor, not possible to process all this information at once and respond to all these inputs in an appropriate manner. Because of that, our brain has a mechanism called attention that enables it to focus and highlight relevant information. For example, I need attention to stay focused on writing these lines while next to me somebody is loudly speaking with his wife on the phone. Our brain has to determine at any given time point what item to focus on and for this it has to combine external inputs with our internal goals. Since human beings with a damaged medial prefrontal cortex (mPFC) have a reduced capability to stay focused and are easily distracted by external inputs it is thought that this brain area plays an important role for information processing in attention demanding behavior.

When information reaches our brain, it is processed in neuronal networks that are formed by highly interconnected excitatory and inhibitory neurons. The activity of each neuron in these networks is modulated by both excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmission. Also, neuromodulators such as acetylcholine can change the excitability of these networks during cognition and neuronal signal processing. Multiple studies showed that there is a significant increase of acetylcholine concentration in the mPFC when animals perform a task that requires attention demanding behavior. These findings indicate that ACh release in the mPFC is important for attention. Acetylcholine in the cortex is mainly released by cholinergic projections coming from neurons in the basal forebrain. However, there are also local interneurons which express ChAT: an enzyme that is only expressed in neurons that release acetylcholine. There is still a debate whether these cholinergic interneurons could be a local source of ACh.

We found that these interneurons innervate both superficial and deep layers in the mPFC and release ACh and GABA in the mPFC. Activation of these neurons leads as net outcome to an increased excitability of interneurons as well as pyramidal neurons. Since we could see that there are two different sources for acetylcholine in the mPFC, we asked whether these sources might have a different role in the modulation of attention demanding behavior. To answer this question, we used a specific behavioral paradigm with which it is possible to test the attention performance of an animal. By blocking either the release of acetylcholine from projections coming from the BF or from local cholinergic interneurons while the animal was performing the test, we showed that the two sources are in distinct phases relevant for attention behavior.

To understand how cholinergic signaling influences computational processing in the cortex, we investigated whether released acetylcholine modulates different types of microcircuits. We therefore investigated whether synaptic plasticity, a mechanism that is thought to be important for information processing, is modulated by cholinergic signaling. We found that acetylcholine modulates synaptic plasticity differently among the different layers in the mPFC. In the superficial layers, acetylcholine prevents synaptic plasticity, whereas in the deepest layer it augments synaptic strength. We revealed that the augmentation depends on a specific acetylcholine receptor subunit, whose activation leads to increased dendritic depolarization.

In a next step, we wanted to understand how cholinergic signaling is modulating inhibitory microcircuits, which shape the firing behavior of excitatory neurons, a mechanism which is thought to be crucial for cortico-cortical signal processing and cognition. Several circuit motifs have been identified by which interneurons influence the firing behavior of excitatory pyramidal neurons. One of these circuits is called lateral inhibition and enables excitatory neurons to modulate the firing behavior of surrounding excitatory cells. For this, the presynaptic excitatory neuron projects to an interneuron which then projects to the postsynaptic pyramidal neuron. If the presynaptic cell is highly active it can trigger activity in

the interneuron and by this shape the firing activity of the postsynaptic pyramidal neuron. This circuit motif can be modulated by fast spiking- as well as by low threshold spiking interneurons. These two interneuron types project to different areas at excitatory neurons and because of that, they have a different inhibitory effect. Firing activity of interneurons is strongly modulated by acetylcholine and specifically low threshold spiking interneurons are strongly modulated by cholinergic signaling. This raised the question whether cholinergic signaling modulates lateral inhibition. We found that cholinergic signaling augments specifically lateral inhibition that is mediated by low threshold spiking interneurons. This finding indicates that cholinergic signaling can highlight specific inhibitory motifs that modulate the firing behavior of excitatory neurons. Furthermore, we found that the cholinergic modulation of both synaptic plasticity as well as lateral inhibition is evolutionary conserved from mice to human.

In summary, the findings presented in this thesis demonstrate that cholinergic signaling in the mPFC coming from projections from cholinergic neurons in the basal forebrain or from local cholinergic interneurons is relevant for attention demanding behavior. When ACh is released in the mPFC it affects both excitatory and inhibitory circuit motifs which are thought to be relevant for cognitive signal processing for example in memory or attention demanding behavior.