English summary:

Cholinergic modulation of the medial prefrontal cortex

Our brains are continuously bombarded by a variety of stimuli. To ensure that important information is processed, whereas distracters are filtered out, we need attention. An example of this can be found in driving a car. When we are behind the wheel, we can fortunately maintain our attention on the road and react attentively whenever a potentially hazardous situation occurs. On the other hand, this can result in a lowered ability to participate in a conversation. For passengers in the car, however, the situation is the reverse. They can focus completely on whatever they want, but they probably miss most of what is happening in traffic. Although this might seem trivial, for the brain it is not. In both situations the stimuli are the same. Still the brain has to make sure that in both situations the right information is processed.

In addition to this role of attention in the selection of sensory information that needs to be processed, we also require attention to make sure that we keep our focus, since we never know when we need to act. We continuously miss a big part of what is going on around us and unfortunately this also occurs with important information we want to attend to. The research that is described in this thesis aimed at studying the way our brains allow us to focus continuously on relevant information.

A brain area that is of great importance for maintaining attention is the medial prefrontal cortex (mPFC). Damage to this brain region can result in a reduction in our attentional capacities. During tasks that require a lot of attention, a substance called acetylcholine is released in this part of the brain. This signaling substance, called a neurotransmitter, is being produced by a small group of cells but released throughout most of the brain. Not much is known about what exactly this neurotransmitter does, but we do know that it can bind to two groups of receptors, the nicotinic and the muscarinic receptor, and thereby transmit information. A large part of the research has focused on the effects that acetylcholine has on the mPFC when it binds the first of these two receptors, the nicotine receptor.

The mPFC is, like the rest of the brain, composed of a network of brain cells (neurons). Neurons can be conceptualized as microchips in a computer that can process information and communicate with each other through electrical and chemical signals. There are two major classes of neurons in the mPFC. The two types of neurons in the mPFC have opposing effects. Pyramidal neurons stimulate other neurons with a substance called glutamate. On the other hand, interneurons inhibit each other via another neurotransmitter, called GABA. The balance between these two forces forms the basis of a large part of the information processing that goes on in the brain. The mPFC is also, on top of glutamate and GABA, influenced by other signaling substances, such as acetylcholine. These latter neurotransmitters are called neuromodulators because they modulate the processing of information that occurs in the local circuits. With our research we have tried to gain insight into the way the neuromodulator acetylcholine influences processing in the network of the mPFC. We have done this by manipulating the receptors for acetylcholine and by measuring the effects on behavior and on brain activity. In addition, we have determined the exact source of this acetylcholine. In the remainder of the summary I will describe the findings of these studies.

We started by testing which nicotine receptors are important for attention. We studied the role of nicotine receptors because there are clues that indicate that this type of receptor is very important for attention. For this we tested mice in an attention task. We compared mice that have all of the nicotine receptors with mice that lack specific subtypes of this receptor.

By doing this, we determined that one specific type of receptor, the heteromeric β2-subunit containing receptor, is crucial for normal attention performance. When we put this receptor back in the mPFC, behavior was restored to normal levels. This way we demonstrated that these receptors, specifically in the mPFC, are crucial for attention. This study is described in chapter 2.

The next step of our research was to determine what happens when acetylcholine binds these nicotine receptors. We did this by applying acetylcholine to brain slices that were kept alive and by monitoring the activity of the neural circuits in these brain slices. This way we measured the effects of acetylcholine binding to nicotine receptors. We did this for different elements of the neuronal circuit, such as different celltypes and different layers. Moreover, we have determined the net effect of acetylcholine when all these different elements are stimulated simultaneously. For more information, see chapter 3.

In addition, we have determined the effects of nicotine itself. Our body does not make nicotine itself and our nicotine receptors are normally only stimulated by acetylcholine. However, people that use tobacco administer nicotine to themselves. As a consequence, nicotine receptors are not only stimulated by acetylcholine, but also by nicotine. Interestingly, nicotine can activate these receptors, like acetylcholine, but also interfere with signaling by acetylcholine. For this reason, we wanted to know how nicotine influences neuronal activity in the mPFC and how it changes the response to acetylcholine. This study provided a complex picture in which nicotine stimulated the network to some degree but blocked the effect of acetylcholine at the same time. These effects were strongly dependent on the type of neuron studied, the location in the network and the specific type of nicotine receptor.

Finally, we have determined the source of acetylcholine in the mPFC. It was known that nearly the entire brain receives acetylcholine from a group of cells that are called the basal forebrain. These cells send fibers throughout the brain, but there was little knowledge about which cells in the basal forebrain provide the mPFC with acetylcholine. We studied this and we tested how specific this innervation of fibers is. In other words, we wanted to know whether the basal forebrain cells send their projections to the entire mPFC or whether specific cells project to specific areas of the mPFC. We have studied this by forcing small groups of cells to make a fluorescent protein. After this we determined where in the brain the fluorescent fibers can be found. With this research we demonstrated that the projections are quite specific. Furthermore we demonstrated that there are two kinds of projections of acetylcholine producing cells to the mPFC. This research is described in chapter 5.

With the research described in this thesis we have tried to make a contribution to understand the brain processes that make us able to focus and maintain our attention on something. Our hope is that, if we understand what the role of acetylcholine and its receptors are, we can better treat diseases in which attention is severely affected. Attentional problems are a core symptom of ADHD but are also strongly present in other diseases such as schizophrenia and different forms of dementia. In these diseases it has been found that the acetylcholine system is affected and that nicotine receptor stimulation can improve the attentional capabilities in those suffering from it. A problem, however, is that nicotine is very addictive and that nicotine receptors are involved in many different processes. For this reason it is crucial to learn more about the role of the different types of nicotine receptors and the brain processes in which they play a role. With this research we have aimed to increase our knowledge about the way acetylcholine modulates the mPFC.