Before I start, I want to mention that what I will describe is based on a personal interpretation of the scientific literature. I developed these ideas during my collaboration and together with Svetlana Ivanova and her co-workers. I will not describe studies which give the evidence supporting separate aspects of these ideas. Part of our studies have not yet been published. When you are interested you should ask Prof Svetlana Ivanova.
These are my possible conflict of interest. Very limited as you can see.
Before we can start, I want to give a brief introduction to the brain structures which are affected by antipsychotic drugs. The brains consist of a cerebrum, brainstem and cerebellum. The cerebrum consists of an outer layer of cerebral cortex and a sub cortex. The posterior part of the cortex analyses input, the anterior part generates output and the sub cortex regulates the activity of the cortex.
This brings us to the structures which are affected by antipsychotic drugs. This slide shows a summary of these parts of the central nervous system.

- **Extrapyramidal circuits**
  - Caudate: antimanic activity
  - Putamen: Parkinsonism, dystonia, dyskinesia
  - Accumbens: Anti-agitation, akathisia, apathy
- **Temporal lobe**
  - Hippocampal complex: anti-hallucinatory
  - Amygdaloidal complex: anti-delusional
- **Prefrontal cortex**
  - Combating negative and cognitive symptoms
Within the aforementioned structures, certain neurotransmitters play an important role. The extrapyramidal circuits consist of serially connected glutamatergic and GABAergic neurons. Their activity is regulated by dopaminergic, adrenergic and serotonergic neurons.

Within the temporal lobe, serially connected glutamatergic neurons constitute networks. The activity is locally inhibited by GABAergic interneurons. Dopamine, and to a lesser extent, serotonin, regulate the network activity globally.

The same situation exists within the prefrontal cortex, but here dopamine, norepinephrine and serotonin regulate the activity more generally.
Again, very basic information. The cerebrum has an outer cortical layer of about 0.4 cm and an inner component consisting of striatum, hippocampus and amygdala.
The activity is regulated by adrenergic neurons with cell bodies within the brainstem and fibres running to the hypothalamus and spinal cord from the autonomic nuclei, and fibres running to the basal forebrain and anterior cortex coming from the locus coeruleus complex.
Another important player is serotonin or 5-hydroxytryptamine. Cell bodies of the nerve cells can be found in the brainstem and can be divided into two groups: the upper and lower raphe nuclei. Fibres from the upper raphe nuclei run to the basal forebrain, the basal ganglia, the temporal lobe and the frontal cortex.
Dopamine will be mentioned extensively during this lecture. Cell bodies can be found in the ventral tegmental area (area A10) and the substantia nigra, pars compacta (area A9) in the midbrain. Fibres run to the basal ganglia, the frontal cortex and the temporal lobe.
Serotonin, norepinephrine and dopamine are not very abundant. About 2% of the CNS neurons use these neurotransmitters. The majority of the cerebral neurons use either glutamate or GABA as neurotransmitter.
Glutamate is an excitatory amino acid transmitter. It stimulates the post synaptic neurons by binding to either two types of receptors: 1. ionotropic, AMPA, NMDA or kainate, or 2. metabotropic, g-protein coupled receptors, of which 8 subtypes exist.
Ionotropic neurotransmission has an important characteristic named long-term potentiation. During normal activation of a glutamatergic synapse only AMPA receptors are activated. The ion-channels allow a flux of sodium and potassium ions through the membrane which induces depolarization of the postsynaptic membrane. However, during strong stimulation of the synapse, NMDA receptors also become active. Therefore, also calcium ions are released and activate intracellular metabolic processes. This results in an increase of the sensitivity of the synapse for activation, which remains for several weeks or even longer, so the glutamatergic synapse can learn how active or sensitive it should be.
Within the hippocampal complex the process of long-term potentiation can explain how sensory input is recognized. The posterior cortex conveys the sensory input to the hippocampal complex. Within the hippocampus specific input from different spots of the parietal-temporal-occipital association cerebral cortex converges to the same hippocampal neuron and stimulate this neuron simultaneously. Thereafter, LTP induces increased sensitivity of this postsynaptic glutamatergic neuron, which make it easier to stimulate it the next time. This results in a preferred track which is more easily followed within the hippocampal complex when the same sensory input is conveyed to the hippocampus. This sensory input is then recognized as having occurred before.
Also the opposite process can occur: long-term depression or LTD. Here, endocannabinoid transmission plays an essential role. When metabotropic glutamatergic receptors or calcium channels of postsynaptic neurons are activated, they induce synthesis of endocannabinoid from a certain lipid which is released during primary receptor activation (2-archidonoyl-glycerol). These endocannabinoids are released, migrate to the presynaptic part of the synapse and activate g-protein bound cannabinoid type 1 receptors (CB1R). These presynaptic receptors decrease the activity of calcium channels and this results in a long-term decrease of neurotransmitter release upon activation of this presynaptic part of the synapse.
A good example of the process is found within the synapse of glutamatergic cortical pyramidal cells with medium-sized spiny neurons within the striatum. We will see later that the learning ability of these synapses is very important to learn by training to execute certain movement patterns. Within this synapse, activation of dopaminergic, type 2, and cholinergic muscarinic, type 1 receptors, activates the endocannabinoid pathway. This results in down-regulation of the glutamatergic corticostriatal synapse. The activity of this synapse is modified for a long time and this is regulated by dopaminergic and cholinergic input.
On this less schematic picture of these striatal medium spiny neurons we can see that input of the GABAergic projection neurons is formed by glutamatergic fibres coming from the cerebral cortex, dopaminergic fibres coming from the substantia nigra, pars compacta, and striatal GABAergic and cholinergic interneurons. Output of these MSN goes to the globus pallidus and the substantia nigra, pars reticulata.
This output is shown on this slide. Two types of MSN can be distinguished. On the right, the output MSN runs directly to the globus pallidus and substantia nigra, pars reticulata. This direct pathway is stimulated by dopaminergic, type 1 receptors and results in stimulation of the endpoint of the cerebral cortex. When following the pathway on the left, the signal has to make a few steps in between before it reaches the globus pallidus and substantia nigra, pars reticulata. This indirect pathway is inhibited by dopaminergic, type 2 neurons and activation of this indirect pathway results in inhibition of the same spot of the cerebral cortex which is stimulated by the direct pathway, so the direct and indirect pathways can be considered to be the two reins when horse riding to regulate the activity of a certain spot of the frontal cortex. Dopamine always increases the activity of this output cortex, either by activating the direct pathway or by inhibiting the indirect pathway. By LTP and LTD at corticostriatal synapse the extrapyramidal circuit can learn how large the output of the frontal cortex should exactly be.
However, the extrapyramidal circuits have an additional role. Every part of the frontal cortex receives information from many other cortical areas, because different parts of the cerebral cortex are mutually stepwise connected with each other. However, these other cortical areas are also connected with the same spot on the frontal cortex by converging extrapyramidal circuits. This offers the opportunity to learn by LTP and LTD how the influence of these different cortical areas should be adapted to generate a proper output of the frontal cortex.
This slide shows the position of the basal ganglia within the forebrain. As you all know, the basal ganglia consist of the striatum which is formed by caudate nucleus, putamen and accumbens. However, also limbic basal ganglia can be distinguished, consisting of centromedial part of the amygdala, extended amygdala and bed nucleus of stria terminalis. The limbic basal ganglia have a similar role concerning the limbic cerebral cortex as the striatum has with respect of the rest of the neocortex.
Also the proper extrapyramidal circuit show a topographical arrangement. When we only consider the most posterior part of the converging circuits, we can distinguish a motor part connecting the somatosensory cortex with the motor cortex via putamen. Also a cognitive circuit exist, which connects association areas of the posterior cortex with the dorsolateral part of the prefrontal cortex via the caudate nucleus. Finally a motivational circuit exists connecting the limbic cortex with the medial part of the prefrontal cortex via the accumbens nucleus.
This slide shows that dopaminergic fibres coming from different parts of the midbrain run to different parts of the forebrain. Dopaminergic neurons of the ventral tegmental area project to ventral parts of the basal ganglia, frontal cortex and temporal lobe. Fibres of dopaminergic neurons of the substantia nigra, pars compacta, mainly run to dorsal parts of basal ganglia, i.e. caudate and putamen. By the way, this difference is not absolute.
These dopaminergic fibres regulate the activity of the extrapyramidal circuit. By binding to dopamine, type 1 receptors the direct pathway is activated and this results in increased cortical activity. By binding to dopamine type 2 receptors, the indirect pathway is inhibited, and this also results in increased cortical activity. Therefore, dopamine increases output of the frontal cortex.
Dopamine also regulates long-term potentiation and long-term depression. Stimulation of dopamine, type 1 receptors facilitates long-term potentiation of corticostriatal synapses at direct pathway medium spiny neurons. Stimulation of dopamine, type 2 receptors results, either by influencing cholinergic interneurons or at indirect pathway medium spiny neurons, in inhibition of long-term potentiation and facilitation of long-term depression. So far now for dopamine.
Let’s now look into the role of serotonin. This slide shows that several types of serotonin receptors exist, which all have very interesting effects. During this presentation we will specifically consider two different subtypes: i.e. the serotonin, type 2A receptor and the serotonin, type 2C receptor. Both are g-protein coupled or metabotropic receptors.
In g-protein couples receptors, activation of the receptor by a neurotransmitter results in the liberation and falling apart of a g-protein, which dissociation is stabilized by displacing the bound GDP with GTP. This protein fragment thereafter binds an effector protein, which obtains enzymatic activity. This result in the production of a second messenger. This activation is ending with the GTP molecule loses one phosphate atom and becomes GDP again. This takes about 80 milliseconds.
Serotonin, type 2A and type 2C receptor have a unique characteristic, namely constitutive activity. When a serotonin itself is bound, the receptor is activated and this results in increased activity of the postsynaptic neuron. However, certain rest activity is shown by the receptor complex when no serotonin is present. This constitutive activity makes a decrease of the normal activity possible by antagonizing the receptor. Antagonists, therefore, have an effect opposite to serotonin itself. This is called inverse agonism. Important for this lecture is that type 2A receptors have far less constitutive activity than type 2C receptors.
The effects of agonists and antagonists on serotonin, type 2C receptors is shown on this slide. Antagonists like clozapine and mianserin decrease the baseline activity and agonists like serotonin itself increase activity. As type 2A receptors have far less constitutive activity, these receptors are only blocked by clozapine without affecting their baseline activity.
Type 2A and type 2C receptors have almost the same cerebral distribution, but also important differences exist. Serotonergic fibres end on certain GABAergic interneurons which inhibit the activity of dopaminergic terminals. Stimulation of the interneurons results in inhibition of DA release. Within the cerebral cortex these interneurons are stimulated through type 2A receptors. Moreover, serotonergic fibres end on monoaminergic terminals and pyramidal cells, and these fibres are stimulated by type 2A as well as type 2C receptors.
Within the caudate nucleus, putamen and accumbens, the inhibitory GABAergic interneurons are stimulated through type 2c receptors. Serotonin, type 2C antagonist strongly disinhibit dopamine release due to their inverse agonistic activity. In addition, presynaptic terminals and medium spiny neurons are stimulated through type 2A and type 2C receptors. Due to their inverse agonistic activity, type 2C receptor antagonists inhibit the activity of glutamatergic corticostriatal synapses and medium spiny neurons.
Within the midbrain, type 2A receptors stimulate dopaminergic neurons of the ventral tegmental area, which causes dopamine release within the accumbens nucleus and cerebral cortex. Within the substantia nigra type 2C receptors stimulate GABAergic interneurons. Type 2C receptor antagonist increase dopamine release with the caudate and putamen.
When we exaggerate the differences and pose the type 2A antagonists only to block the receptor and type 2C antagonists to decrease their activity acting as inverse agonists, these differences between their distribution cause some interesting differences between their effects. Type 2 antagonists block the inhibition of dopaminergic terminals within the cerebral cortex (directly and terminals coming from the VTA), and have little influence on pyramidal cells within the cerebral cortex and running to the striatum. In addition, within the striatum, medium spiny neurons are denervated but not actively inhibited by type 2A antagonists. Serotonin, type 2C antagonists, however, actively increase dopamine release within the striatum, also by affecting dopamine neurons of the substantia nigra, pars compacta. Moreover the activity of pyramidal cells and medium spiny neurons is actively decreased by type 2C antagonists.
This slide shows you the relationship between the concentration of agonist and/or antagonist on the percentage of receptors bound by them. What you can see is that different substances give different affinity, which results in differences between the concentration, which then results in an occupancy of 50% of the receptors. This concentration is directly related to the value of the binding constant.
When the binding affinity of the classical antipsychotic haloperidol is considered, you can notice that this drug has far higher affinity for dopamine, type 2 receptors in comparison to its affinity to dopamine, type 1 and serotonin, type 2a and type 2C receptors. The higher the figure in his table, the lower the affinity. This drug needs a higher concentration to bind to the receptor. So, when we consider clozapine dopamine, type 2 receptors are only weakly (and also loosely) bound, while serotonin, type 2A and type 2C receptors are strongly affected.
The pharmacological effects of antipsychotics within the striatum are summarized on the following slides. All antipsychotic drugs are dopamine, type 2 antagonists. Within the striatum this characteristic has no influence on the activity of direct pathway medium spiny neurons, because these carry dopamine, type 1 receptors. However, the activity of indirect pathway medium spiny neurons is less decreased by dopamine. This results in more activity of the indirect pathway and therefore inhibition of the frontal cortex, resulting in for example bradykinesia. The blockade of dopamine, type 2 receptors results in extra release of dopamine. This extra dopamine is taken up by the indirect pathway medium spiny neurons and this causes neurotoxic effects due to increased oxidative stress.
Serotonin, type 2A antagonism has little influence within the striatum. These receptors have no effect on GABAergic interneurons and only prevent serotonin from stimulating corticostriatal terminals and medium spiny neurons. They have this effect within both direct and indirect pathways without causing a misbalance between them.
Inverse agonism on type 2C receptors, however, has an entirely different effect. The activity of inhibitory GABAergic interneurons is actively decreased, which results in release of dopamine. This dopamine can only stimulate dopamine, type 1 receptors on direct pathway medium spiny neurons, because the type 2 receptors on indirect pathway medium spiny neurons are blocked. This release results in increased oxidative stress, but at the same time glutamatergic corticostriatal synapses and medium spiny neurons are actively inhibited, because they also carry type 2C receptors. This results in selective stimulation of direct pathway medium spiny neurons causing less Parkinsonism and neuroprotection of indirect pathway medium spiny neurons, causing less dyskinesia.
Summarizing these effects: Parkinsonism is caused by blocking inhibitory dopamine, type 2 receptors. This results in higher activity of indirect pathway medium spiny neurons. Serotonin, type 2A antagonists hardly cause any effect. However, serotonin, type 2C inverse agonism causes increased dopamine release. This selectively stimulates direct pathway medium spiny neurons. Moreover, corticostriatal and medium spiny neurons are inhibited, which mainly affects indirect pathway medium spiny neurons which are not stimulated by dopamine released. This action partly compensates for dopamine, type 2 receptor blockade.
Prevention of tardive dyskinesia is caused by inverse agonism at serotonin, type 2C receptors. Tardive dyskinesia is caused by excess release of dopamine in an attempt to compensate for dopamine, type 2 receptor blockade. This excess dopamine is taken up by these indirect pathway medium spiny neurons, which causes oxidative stress and therefore neurotoxicity. Although serotonin, type 2C inverse agonists induce extra release of dopamine, they also decrease the vulnerability of medium spiny neurons by decreasing the activity of corticostriatal synapses and the stimulation of medium spiny neurons. This protects these cells against neurotoxicity.
The situation becomes a bit speculative when we try to explain the mechanism of dystonia. It has often been suggested that dystonia is caused by a mismatch of the activity of direct and indirect pathway medium spiny neurons. This is probably caused by the compensatory release of dopamine due to the blockade of dopamine, type 2 receptors. This excess can stimulate dopamine, type 1 receptors on direct pathway medium spiny neurons, causing such a mismatch. However, this probably is not the only mismatch. It is tempting to speculate that also the exact collaboration between the direct and indirect pathway is disturbed in the converging extrapyramidal circuits. This exact collaboration is learned during training of the exact execution of complex movements with long-term potentiation and long-term depression. Anticholinergic drugs inhibit acute dystonia by inhibiting the influence of extrapyramidal circuits in general. Atypical antipsychotic drugs may inhibit LTP on the long-term and may prevent novel learning of aberrant movement patterns due to the fluctuating influence of dopamine, type 2 antagonist on indirect pathway medium spiny neurons, which induces tardive dystonia. This LTP inhibiting activity is due to serotonin, type 2C inverse agonism.
This slide summarizes this process. Dystonia is caused by mismatch of direct and indirect pathway activity within extrapyramidal circuit. Anticholinergic drugs switch off the influence of the extrapyramidal circuits. Atypical antipsychotics cause serotonin, type 2C inverse agonism and this disables learning of aberrant movement patterns caused by changing dopamine, type 2 receptor blockade.
Akathisia is something different. Akathisia has two components: a motor and a psychic one. The motor component can be seen as the patient cannot sit or stand motionless and constantly moves about from one position to the other. However, in the opinion of some scientists, and I include myself, the primary aspect of akathisia is a psychic phenomenon which causes these movements. Akathisia is primarily a hyper motivation to get started with doing something against your unpleasant position. This hyper motivation results in an urge to move about, which is accompanied by very unpleasant feelings when you try to resist this. Akathisia is a side effect of all antipsychotic drugs, classical as well as atypical ones. However, its prevalence is lower with atypical drugs. It has been documented that akathisia can result in aggression.
In my opinion, akathisia is caused by a mismatch between the functioning of the core and shell parts of the nucleus accumbens. As we have seen, the accumbens is part of the motivational extrapyramidal circuit. Activation of this circuit results in increased motivation to exhibit behaviour. The two parts of the accumbens motivate for two different types of behaviour. The nucleus accumbens core motivates for behaviour which finally results in improvement of one’s position and well-being. The nucleus accumbens shell stimulates behaviour which makes one try to escape from misery. Both parts are stimulated by dopaminergic fibres from the ventral tegmental area in the midbrain. Within the accumbens the organization is largely the same, so dopamine, type 2 antagonists decrease the activity. This explains why antipsychotics work very well in inhibiting psychomotor agitation and inhibit behaviour. However, the nucleus accumbens shell is also stimulated by adrenergic fibres coming from the locus coeruleus complex. Adrenergic stimulation promotes behaviour that helps you to escape from misery and this is accompanied by feelings of dysphoria. These adrenergic fibres stimulate adrenergic, type beta-1 receptors and this explains why beta-blockers can help to treat akathisia.
The function of the caudate nucleus slightly differs from the role of the putamen. In exaggerated terms, the putamen regulates the activity of the motor circuit, while the caudate regulates the cognitive circuit. This cognitive circuit regulates the speed and magnitude of mental movements, such as reasoning and associating. The cognitive circuit ends within the dorsolateral part of the prefrontal cortex, where for example the working memory, vigilance and the executive functions are regulated. Atypical antipsychotics stimulate the functioning of the dorsolateral prefrontal cortex by causing dopamine release and by directly blocking serotonin, type 2 receptors.
The effects of antipsychotics within the caudate nucleus can explain their antimanic and negative cognitive effects. Mania is accompanied by flight of ideas and the subjective experience that thoughts are racing, as well as distractibility. These behaviours are inhibited by antipsychotic drugs. However, in persons who are not hypomanic or manic, the same effects result in mental slowness. These negative effects are partly compensated for when using atypical drugs due to the serotonin, type 2 antagonistic activity. Their effects are comparable with those on the putamen, but the atypicals also have stimulatory effects on the dorsolateral and medial prefrontal cortex.
This slide shows an overview of these mechanisms. As you can see; the effect within the caudate can explain the anti-manic activity and the effects within the putamen Parkinsonism, dystonia and dyskinesia. Inhibition within the accumbens results in anti-agitation effects and akathisia. The atypical effects on negative and cognitive symptoms of schizophrenia are induced by affecting the functioning of the prefrontal cortex.
The anti-delusional and anti-hallucinatory effects of atypical antipsychotics are accomplished by affecting the temporal lobe. Hallucinations have something to do with the process of recognizing sensory information and delusions with attributing an emotional value to this information. It is necessary to select the most relevant input to respond on. This process is termed incentive salience. This process is disturbed in psychotic patients, and leads to groundless feelings of unsafeness or grandness. Delusions are the ideas which are constructed by the individual to explain these unfounded feelings.
To explain how sensory information is processed within the brain, I will take visual information as an example. Visual information which stimulates the retina is transmitted to the primary visual cortex within the occipital lobe. From there, it is stepwise transported to the association area between the parietal, temporal and occipital lobes. With each step, information from other spots on the retina, and later from other senses is added. Thereafter this information is conveyed to the hippocampal complex, and after recognition sent back to the sensory cortex where the observation is compared with existing memories and as such memorized.
The hippocampal cortex is able to recognize sensory information by long-term potentiation, the process we have dealt with before. It should be realized that every observation results in a unique stimulation pattern of glutamatergic fibres running from the parahippocampal cortex to the hippocampus. This results to a unique track which is followed while passing the hippocampus and returning to the parahippocampal cortex. When the observation has been processed before, this unique track has been sensitized by LTP. This sensitization is the criterion to recognize the observation. It has been observed before.
Dopaminergic neurons of the ventral tegmental area of the midbrain stimulate dopamine, type 2 receptors of the parahippocampal cortex to be more active and sharp when this is very relevant for survival. When this dopaminergic activity is too high, illusions and hallucinations occur. Observations are falsely recognized and possibly recognized without the presence of corresponding sensory input.
In order to explain delusions, we have to describe how animals, including man, select the proper behavioural response. On this slide it is shown that, apart from reflexes, both an explicate and an implicate behavioural response can be distinguished. The explicate response is carefully planned considering all available input. The implicate behavioural response, however, is far more impulsive responding to possible threats or opportunities.
This second response type is partly regulated by the amygdala. The amygdala receives sensory information and attributes relevance to a specific part of this input. Based on this selection, the hypothalamus (or other parts of the emotional brain) is activated to induce a specific type of behaviour; for example ‘run for your life.’ This mechanism can dysfunction, which can be due to a disorder of the medial prefrontal cortex, which task it is to inhibit the amygdala and compensates over activity.
The general idea is that in psychotic persons something goes wrong with the selection of relevant stimuli. Therefore, too much weight is given to a specific part of the sensory input. Dopamine is very important for increasing this type of responding. By stimulating dopamine, type 2 receptors, dopaminergic neurons from the ventral tegmental area within the midbrain stimulate the responsivity and the response conditioning (again by facilitating LTP). The delusion itself is secondary to the feelings. This explains why it takes some time before delusions disappear and why the same delusions occur when the effect of antipsychotics becomes insufficient. Antipsychotics have anti-delusional activity by blocking dopamine, type 2 receptors within the amygdaloid complex.
The effects of antipsychotic drugs within the temporal lobe can be added to those within the basal ganglia and within the frontal cortex. The effects on the hippocampal complex, and particularly the parahippocampal gyrus explain the therapeutic effects on hallucinations. The inhibition of the amygdala to respond to relevant observations explains why these drugs may be effective in delusions.

<table>
<thead>
<tr>
<th>Conclusion: site of action of antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; Extrapyramidal circuits</td>
</tr>
<tr>
<td>• Caudate: antimanic activity</td>
</tr>
<tr>
<td>• Putamen: Parkinsonism, dystonia, dyskinesia</td>
</tr>
<tr>
<td>• Accumbens: Anti-agitation, akathisia, apathy</td>
</tr>
<tr>
<td>&gt; Temporal lobe</td>
</tr>
<tr>
<td>• Hippocampal complex: anti-hallucinatory</td>
</tr>
<tr>
<td>• Amygdaloid complex: anti-delusional</td>
</tr>
<tr>
<td>&gt; Prefrontal cortex</td>
</tr>
<tr>
<td>• Combating negative and cognitive symptoms</td>
</tr>
</tbody>
</table>
These last two slides summarize the receptor interactions which are responsible for the therapeutic and adverse effects of antipsychotics. Classical antipsychotics mediate their effects relatively selectively by blocking dopamine, type 2 receptors. Atypical drugs are also serotonin, type 2A antagonists and type 2C inverse agonists. This explains their effects on cognitive symptoms and their lower potential to induce Parkinsonism and tardive dyskinesia.

### Therapeutic effects

- **Anti-delusional**: DRD2 antagonism
- **Anti-hallucinatory**: DRD2 antagonism
- **Anti-agitation**: DRD2 antagonism
- **Cognitive cortex**: DRD1 stimulation + HTR2A antagonism (not HTR2C)
- **Cognitive caudate**: DRD2 antagonism compensated by HTR2C (not HTRA)
- **Anti- apathy**: DRD2 agonism (and/or prefrontal activation)
My most important conclusion is that the often heard suggestion that serotonin, type 2A receptors are responsible for anti-parkinsonian and anti-dyskinetic effects and serotonin, type 2C receptors are responsible for cognitive effects, is probably erroneous. Moreover, serotonin, type 2C mediated dopamine release is not capable of displacing antipsychotic drug bound dopamine, type 2 receptors. So, in my opinion this is also not a good explanation for the low potential of serotonin type 2 antagonist to induce Parkinsonism and dyskinesia.
Thank you very much. Do you have any questions?