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# Influence of adenosine receptors in the striatum during sleep deprivation on declarative memory consolidation

***Are striatal adenosine receptors involved in declarative memory consolidation during sleep deprivation?***

**Pre-master Thesis**

Stan Huisman (S3797732)
Supervisor: Robbert Havekes
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**Abstract:** Sleep is one of the most important aspects of life. Nearly in a third of our life, we spend asleep. Research tries to figure out the purposes of sleep, like in memory consolidation. The hippocampus is one of the important brain structures for memory consolidation. During sleep deprivation, this process is disrupted in the hippocampus. Like the hippocampus, the striatum is also involved in memory consolidation. Both brain structures are closely linked, so the focus of this thesis was on striatal adenosine receptors and their influence on memory consolidation. The reviewed studies showed that $A_1R$ prevents memory consolidation due to inhibition of AC. $A_{2A}R$ stimulate AC and cause trouble in memory retrieval, but it is not certain if they obstruct memory processing and encoding. More investigation to proteins involved in memory processing and encoding is needed to reveal more about $A_{2A}R$ and memory.

## 1 Introduction: What is sleep?

Memory processing is known in both the hippocampus and striatum. Due to sleep deprivation, the hippocampus is less active in memory consolidation as without sleep deprivation. But does the striatum take over the hippocampus and are adenosine receptors involved in this process?

Sleep is an important, yet complicated process that even nowadays is not well understood. Humans spend around a third of their life asleep and without sleep we become tired and our brain functions less well, suggesting it is important. Sleep is a state wherein the body is not active, and the mind is unconscious (Brinkman, 2018). There are several theories trying to identify the purpose of sleep. It plays a role in emotional regulation, metabolic functions, removal of toxic waste and macromolecule biosynthesis. Sleep is also thought to contribute to memory functions and synaptic plasticity (Vyazovskiy, 2015). The hippocampus and striatum play a key role in these memory functions.

Sleep exists of two stages: non-rapid eye movement (NREM) and rapid eye movement (REM). NREM sleep is divided into N1, N2, and N3, where N3 is the deepest stage of sleep, also known as slow wave sleep (SWS) (Eugene, 2015). Both stages alternate during sleep. During NREM sleep, brain activity is decreased, just like heart rate and blood pressure. During REM sleep brain activity increases in motor and

sensory areas and heart and blood pressure are increased. During REM sleep the eyes show rapid eye movement (Vyazovskiy, 2015). The basal forebrain, cerebral cortex, and hypothalamus play a key role to fall asleep and during sleep. These regions, mainly the ventrolateral preoptic nucleus (VLPO) in the hypothalamus, produce the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and galanin, which inhibit firing of cells involved in wakefulness. Including neurons that contain orexins, a neuropeptide produced by the lateral hypothalamic area, which activates orexin neurons, monoaminergic and cholinergic neurons and prevents sleep. By inhibiting these activities, arousal is turned down and finally, NREM sleep is initiated (Siegel, The neurotransmitters of sleep, 2004) (Inutsuka, 2013). The pons is critical for initiating REM sleep. Where GABA induces NREM sleep, it inhibits REM sleep due to inhibition of glutamatergic REM active neurons in the lateral dorsal nucleus. Sleep is initiated by other brain structures than the hippocampus and striatum yet sleep shortage influences memory processing (Siegel, REM sleep: A biological and psychological paradox, 2011).

As mentioned above, one of the theories is that sleep is essential for proper brain plasticity, a crucial effect for memory processing. There are two types of long-term memory. Declarative memories, where consciously information about facts or experiences can be retrieved, whereas procedural memories are those of learned skills or habits. Declarative memories mainly target the hippocampus and cerebral cortex whereas procedural memories target mainly the striatum and cerebellum, but also the hippocampus (Brem, 2013).

The hippocampus is involved in declarative memory processes but can be disturbed by sleep deprivation, the lack of sleep (Havekes, 2012). The focus of this thesis is on the involvement of the striatum during declarative memory processing and especially the adenosine receptors in the striatum.

# 2 Sleep deprivation

Adults need between 7-8 hours of sleep a day. However, nowadays lots of people do not get enough hours of sleep and in today's society, it is considered a serious problem. This due to the availability of technological devices such as mobile phones or game consoles. Besides, people try to cram more activities in a daily schedule than we did a few decades ago. Other lifestyle factors can play a role in a shortage of sleep. For example, drug abuse, alcohol or attending university. Psychosocial factors like anxiety or worry play a role as well. Other factors are medical conditions or sleep disorders (Medic, 2017). As already mentioned, memory processes are influenced by sleep deprivation. The functioning of the hippocampus is obstructed during sleep deprivation which can cause a less efficient processing.

## 2.1 Hippocampus and memory processing

The importance of sleep plays a crucial role in memory processing. Memory consists of three stages: encoding, consolidation, and retrieval. Sleep plays a role in long-term memory. The lack of sleep impairs the long-term memory and memory formation but has no significant effect on short-term memory according to several studies (Havekes, 2012). The hippocampus is required for declarative memory consolidation and formation and is sensitive to sleep deprivation, which can disrupt cellular and molecular processes (Havekes, 2012). It exists of the dentate gyrus and 4 subregions cornu amonis (CA) 1-4. CA1 has the highest concentration of NMDA receptors and creates long term potentiation (LTP) for memory consolidation. The CA3 is an input region for the CA1 region (Leuner, 2010) (Wible, 2013). The dentate gyrus is important for spatial memory processing (Dupret, 2008).

Sleep deprivation disrupts memory consolidation via multiple mechanisms (Figure 1). The lack of sleep cause alternation in AMPA and NMDA receptors, due to the modulation of glutamatergic signaling. This leads to a reduced influx of $Ca^{2+}$, while it normally increases $Ca^{2+}$ influx and creates a hippocampal LTP and

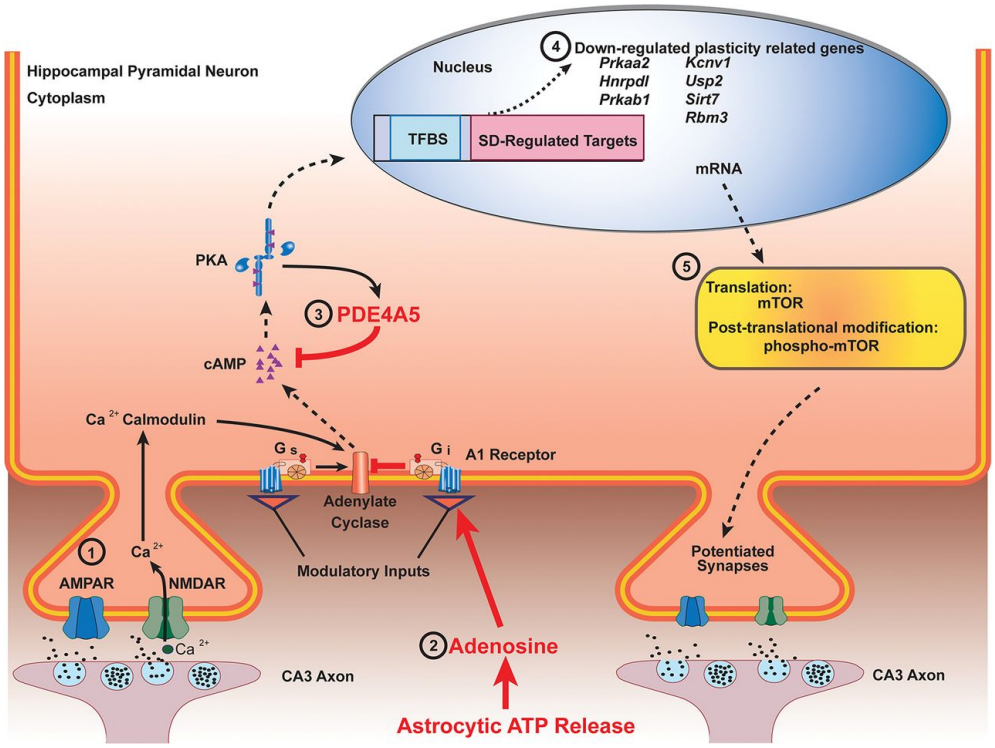


**Figure 1: A schematic overview of signaling pathways in the hippocampus. These pathways are involved in memory consolidation and are influenced by sleep deprivation (Prince, 2013).**

increases synaptic plasticity (Prince, 2013). During wakefulness, adenosine accumulates that regulates the need for sleep. Adenosine can trigger the VLPO, which is involved in sleep-promoting effects (Schwartz, 2008). The increased concentration of adenosine contributes to the $A_1$ adenosine receptor activation, which prevents synaptic transmission. It inhibits adenylate cyclase (AC) and thereby cyclic AMP (cAMP). AC is activated by $Ca^{2+}$. cAMP activates protein kinase A (PKA), which eventually leads to activation of transcription factors. cAMP response element binding protein (CREB), a transcription factor, promotes gene expression for proteins involved in long-term memory consolidation. After sleep deprivation, there is an increased concentration of phosphodiesterase 4 A5 (PDE4A5). This enzyme is responsible for degrading cAMP. Both PDE4A5 and adenosine via an $A_1$ receptor ($A_1R$) cause a decrease in cAMP concentration and a decrease in memory consolidation (Prince, 2013) (Vecsey, 2009). However, via $A_{2A}R$-AC it increases cAMP (Wang, 2019). Further paragraphs tell more about the striatum and adenosine pathways involved in memory consolidation in the striatum.

# 3 Striatum

The striatum represents the main input nucleus of the basal ganglia and exists of subregions, with each a different function. The striatum is made up of the putamen (dorsolateral region), the caudate (dorsomedial region) and the ventral striatum, which is connected to the limbic system, including the hippocampus, amygdala, and medial orbitofrontal and anterior cingulate cortices. The ventral striatum is an important area for learning and is divided into two parts: core and shell (Yuan, 2017) (Van der Meer, 2011). The putamen is connected primarily to sensorimotor cortices via the thalamus. This area is involved in pain processing and movement. It responds to sensory stimuli. Besides, it is necessary for the expression of habitual behavior (Starr, 2011) (Alloway, 2017). The caudate is connected via the thalamus to the prefrontal and parietal association cortices and is involved in encoding connections between conscious actions and their outcome (Liljeholm, 2012) (Alloway, 2017). Studies found that a lesion in the caudate leads to a reduction in planning and problem solving, learning, memories, attention and retrieval (Voelbel, 2006) (Schwartz, 2008) (Poldrack, Striatal activation during acquisition of a cognitive skill, 1999) (Fuh, 1995).

## 3.1 Striatum learning and memory

The ventral striatum is involved in learning. For the learning of motivated behaviors, the caudate is involved which processes the behavior. After this behavior is repeated, the caudate is no longer required, but the putamen takes it over and is needed for the performance of a behavior (Graybiel, 2015). Both the caudate and putamen (together: dorsal striatum) co-operate to form memories for motor skills. Eventually, the ventral striatum is critical for the initial acquisition.

## 3.2 Striatum neurons and receptors

The striatum mainly exists of medium spiny neurons (MSN) or striatal neurons. These cells release GABA, an inhibitory neurotransmitter, at synaptic terminals. Besides MSN, there are many other cell types like cholinergic interneurons and fast-firing GABA interneurons. Cholinergic interneurons are sensitive to reward-predicting stimuli and punishment. The GABAergic neurons are divided into two subtypes: enkephalinergic and dynorphinergic. GABAergic enkephalinergic receptors express adenosine $A_{2A}R$ and inhibitory $D_2R$ and express to the external globulus pallidus (GPe). These two receptors can form heteromers (Orru, 2011). Dynorphinergic receptors express $D_1R$ and inhibitory $A_1R$, which project to the substantia nigra pars reticulata (SNr). The $D_1R$ are $G_s$-protein coupled and are capable of stimulating AC and thereby CREB. $D_1$ and $D_2$ receptors can co-operate to bind a $G_q$-protein and stimulate CREB. Dopamine receptors are capable of inhibiting this process via $G_i$-protein. The $D_1R$ are important for motor functions and motivation (Yuan, 2017) (Nishi, 2011). Adenosine receptors are important for sleep regulation. Adenosine binds an $A_1R$, which then inhibits glutamate of a glutamatergic neuron. The inhibition of an excitatory compound reduces neural activity and induces sleep. Besides, the $A_1R$ inhibits AC binding a $G_i$-coupled protein, causing a decrease in cAMP (Schiffmann, 2007). $A_{2A}R$ are capable of inhibiting histaminergic neurons, activation of sleep-active neurons and modulation of acetylcholine (ACh) release. It can also activate AC via a $G_s$-coupled protein. This plays a role in memory processing (Rodrigues, 2008). Presynaptic $A_{2A}R$ are localized in dynorphinergic MSNs and form heteromers with $A_1R$, which are inhibited by $A_{2A}R$. In low adenosine concentrations, the $A_1R$ receptor is activated, but in higher concentrations both receptors. These results indicate that the $A_{2A}R$ is involved in stimulation of receptors that are needed at memory consolidation (Ferré, 2011). However, $A_{2A}R$ are capable of controlling GABA in both the hippocampus and striatum. They increase the uptake of GABA, but $A_1R$ decrease the uptake. It is suggested that increased inhibitory activity of GABA impairs memory. This would mean that $A_1R$ would improve memory, but it decreases cAMP activity. (Sandeep, 2014) (Díaz-Cabiale, 2002). It is known that the hippocampus and striatum both express adenosine receptors and it is suggested that these structures are co-operative in memory consolidation. The influences of these receptors are further investigated.

# 4 Hippocampus vs Striatum

In the hippocampus and striatum memory processing takes place. In the following chapters, the differences and similarities are reviewed. It is about the coherence of the hippocampus and procedural memory, the striatum, and declarative memory and the involvement of adenosine in the striatum.

## 4.1 Hippocampus and procedural memory

Research indicates that the hippocampus is not only associated with declarative memory, but also procedural memory. Functional magnetic resonance imaging (fMRI) studies showed that there is a competition between the hippocampus and striatum during learning (Poldrack, Competition among multiple memory systems: converging evidence from animal and human brain studies. , 2003). Other behavioral studies were showing evidence of interference between declarative (hippocampus) and procedural (striatum) memory processing, suggesting the existence of sharing a neural network (Albouy,

Hippocampus and striatum: Dynamics and interaction during acquisition and sleep-related motor sequence memory consolidation, 2013). The hippocampus can recruit the striatum for declarative tasks and vice-versa, where the striatum recruits the hippocampus for motor learning (Doeller, 2008) (Gheysen, 2010).

According to studies by Albouy and colleagues, the striatum activation increases after learning of a 'serial ocular reaction time' test (Figure 2A). The bars represent the striatal activity 30 min, 5 h, and 24h after the end of training. After 24 h the striatal activity is at its highest point. Even after sleep deprivation the striatum still shows activity of a retest 72 h after the first 'finger tapping task' (Figure 2B). This indicates that the striatum is active after sleep, but also after sleep deprivation. The hippocampus is mainly activated 24 h after a training session (Figure 2C) and is also active after a retest 72 h after the first training (Figure 2D). However, the hippocampus performance was not enhanced after sleep deprivation (no data available) (Albouy, Hippocampus and striatum: Dynamics and interaction during acquisition and sleep-related motor sequence memory consolidation, 2013)(Albouy, Interaction between Hippocampal and Striatal Systems Predicts Subsequent Consolidation of Motor Sequence Memory, 2013). The 24 h responses were measured overnight, showing that both brain structures cooperate overnight in procedural memory consolidation (Albouy, Both the hippocampus and striatum are involved in consolidation of motor sequence memory, 2008). Another study by Voermans and colleagues showed that the hippocampus and striatum both operate during memory consolidation, but the striatum operates heterogenous: the putamen interacts competitively with the hippocampus, while the caudate operates cooperatively with the hippocampus (Voermans, 2004).

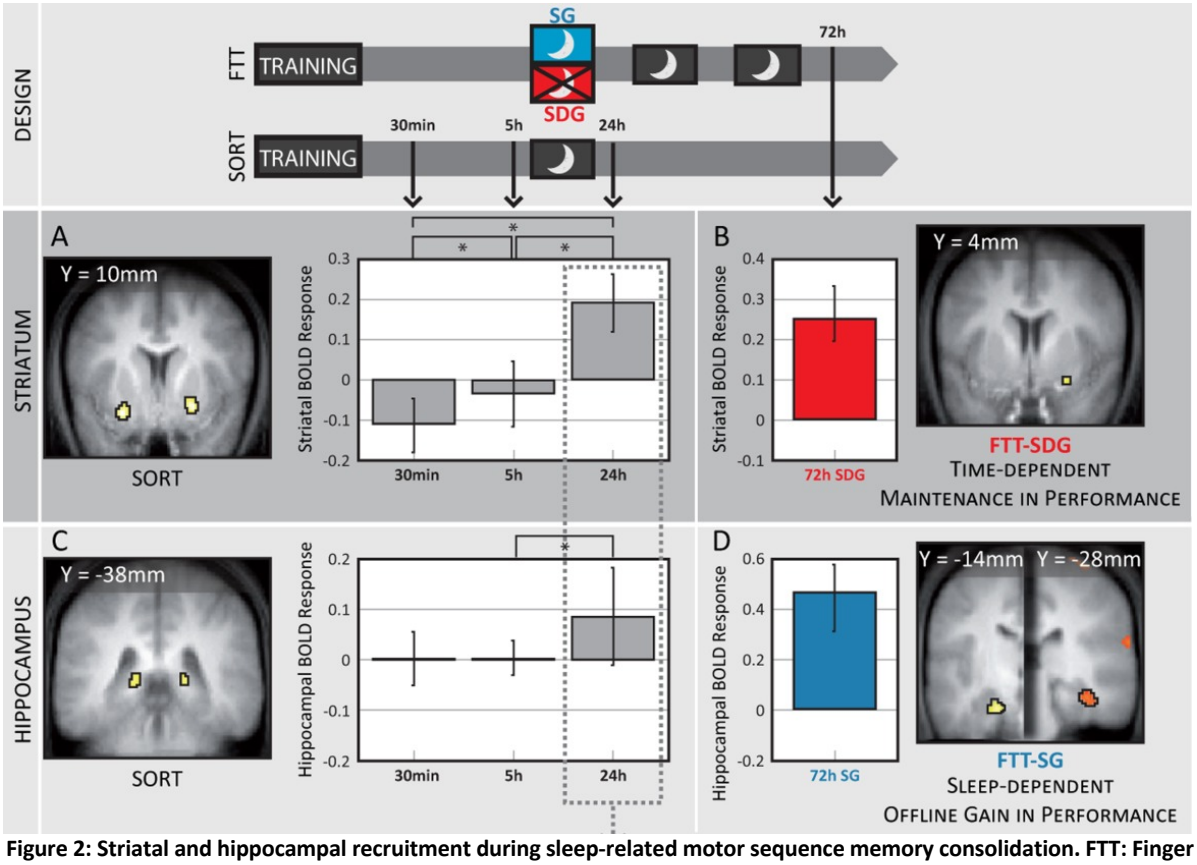


**Figure 2: Striatal and hippocampal recruitment during sleep-related motor sequence memory consolidation. FTT: Finger Tapping Task, SORT: Serial Ocular Reaction Time, BOLD: Blood Oxygen Level Dependent, SDG: Sleep Deprived Group, SG: Sleep Group (Albouy, Hippocampus and striatum: Dynamics and interaction during acquisition and sleep-related motor sequence memory consolidation, 2013).**

## 4.2 Striatum and declarative memory

The hippocampus is involved in procedural memory, which is mainly processed by the striatum. Research indicated that the striatum is involved in spatial memory, which is a hippocampal process. A study by Qing Chang found that rats showed learning based on place (i.e., turning to the correct position relative to room). After more sessions, the rats showed learning based on response instead of place (i.e., turning to correct position to find a reward). At the start of a training, ACh release is increased in the hippocampus. Even when the rats started learning by response, the ACh release in the hippocampus remained unchanged. In the striatum, ACh release increased after the transition from response learning to spatial learning. Both brain structures participate in the same learning task (Chang, 2003).

Other studies in rodents using a maze showed a shift from hippocampal activity to striatal activity when the hippocampus was temporarily inactivated. Again, the spatial strategy shifted towards a response strategy of the striatum and then, in particular, the putamen and caudate. After five hours of sleep deprivation, the rodents preferentially used response strategy instead of the spatial strategy. Here sleep deprivation did not affect training results. Training in a maze showed an increase in phosphorylated CREB in the dentate gyrus, CA1 and CA3 of the hippocampus in rats without sleep deprivation, but not in the striatum. Training after sleep deprivation induced a shift of phosphorylation of CREB from the hippocampus to the striatum. CREB is in both brain structures involved in memory consolidation. (Hagewoud, Sleep deprived mice are capable of spatial T-maze learning despite a reduction in learning-induced hippocampal CREB phosphorylation, 2010) (Hagewoud, Coping with Sleep Deprivation: Shifts in Regional Brain Activity and Learning Strategy, 2010) (Colombo, 2003).

There have been several other studies that indicate that the striatum is also involved in declarative memory based on item recognition. It has even been shown that the putamen, the caudate and ventral striatum are all involved in retrieval of memories of items. However, after showing new items instead of prior shown items, the striatum is more activated, noticing that the striatum is important for declarative memories when cognitive control is required to retrieve a memory (Scimeca, 2012).

## 4.3 Striatum and adenosine

It is known that GABAergic neurons can express both $A_1$ as $A_{2A}$ receptors, depending on neuron class. Both receptors have been reported to regulate sleep. Studies showed that $A_1$ and $A_{2A}$ receptors are causing memory impairment (Pagnussat, 2015) (Oliviera, 2018) (Silva, 2018). The $A_1R$ decreases cAMP in the cytosol and thus phosphorylated PKA (p-PKA) (Yang, 2015). Oliviera and colleagues studied the function of $A_1R$ in sleep deprivation in the hippocampus and striatum using an antagonist (DPCPX). After sleep deprivation, there is a significantly lower concentration of p-PKA in both the striatum and hippocampus (Figure 3). In the hippocampus, DPCPX did not show a significant

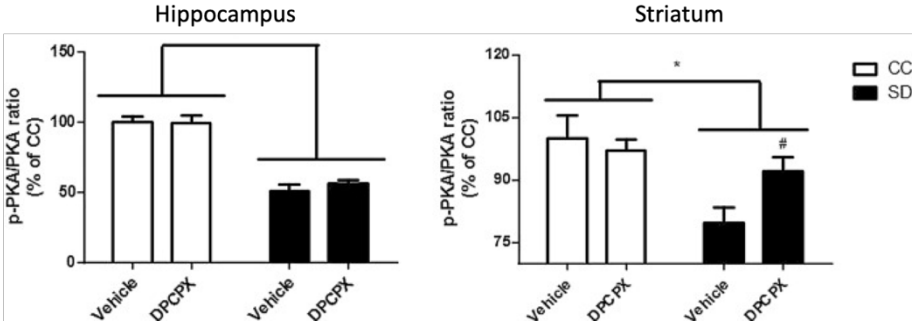


**Figure 3: The ratio of phosphorylated PKA and PKA in the hippocampus and striatum. The hippocampus shows a lower concentration of p-PKA in sleep deprived rats (SD) compared to the cage control rats (CC). In the striatum the vehicle (saline) shows a significant lower ratio, but rats with DPCPX do not (Oliviera, 2018).**

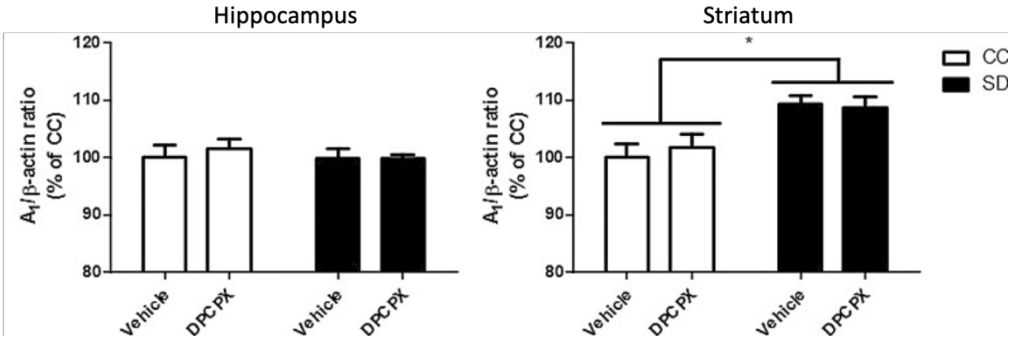


**Figure 4: $A_1$/β-actin (western blot loading control) ratio. The hippocampus shows almost similar ratio between the cage control (CC) and sleep deprived (SD) rats. In the striatum there is a significant difference. The vehicle group got saline injected as placebo (Oliviera, 2018).**

difference in comparison to the vehicle group. In the striatum, the DPCPX antagonized the $A_1R$ leading to a higher ratio of p-PKA. Oliviera did research on memory impairment via $A_1R$. Rats have learned two different tasks that relied on hippocampal functioning. The multiple trial inhibitory avoidance (MTIA) task, which also required the striatum and the contextual fear conditioning (CFC) task, which did not. The rats were sleep deprived and there was a group of rats that got a DPCPX injection.

In the MTIA task sleep deprivation led to memory impairment, but DPCPX prevented this. The results indicate that sleep deprivation leads to impairment of both the acquisition and retention of the task. The rats with DPCPX did not show differences between the sleep deprived rats and the control group. Sleep deprivation also led to an increase of extracellular adenosine in the hippocampus, but not in the striatum, while $A_1R$ expression increased in the striatum, but not in the hippocampus (Figure 4). This indicates that adenosine is signaling in the striatum during sleep deprivation and that it has impact on memory consolidation.

The CFC task was used to verify the results because this task did not involve the striatum. Rats showed a reduced performance in both MTIA and CFC tasks after sleep deprivation, but the $A_1R$ antagonist only prevented impairment in the MTIA task (Oliviera, 2018).

In a study by Pagnussat (Pagnussat, 2015), rats were given three training tasks. The mice were either given a scopolamine (SCO) (induces memory impairment by antagonizing muscarinic $M_1$ receptors), DPCPX ($A_1R$ antagonist), SCH 58261 ($A_{2A}R$ antagonist) or saline + DMSO (control) injection 30 minutes prior to an objective learning task. This was a 0.1; 0.5 or 1 mg/kg dose. The discrimination ratio between objects did not significantly differ much to each other. Only the highest

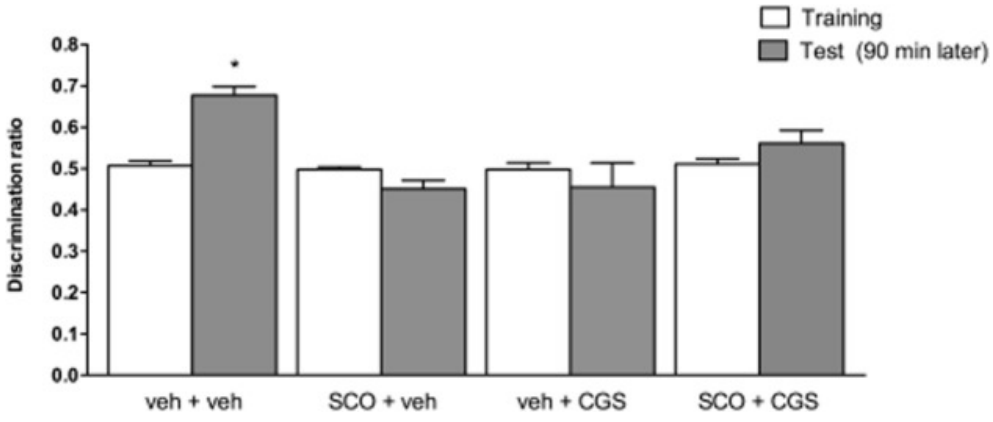


**Figure 5: Object discrimination in mice with SCO, CGS or SCO+CGS. $A_{2A}R$ do not exacerbate scopolamine induced memory impairment. The $A_{2A}R$ causes a lower discrimination ratio. CGS was injected 30 min after SCO. (Pagnussat, 2015)**

dose of SCO led to recognition impairment 90 min after training, but not 24 h after training. So, it had an impact on short-term memory. When given SCO and SCH together, memory impairment is more accentuated.

The study also tested whether $A_{2A}R$ activation exacerbates memory impairment using CGS 26180 ($A_{2A}R$ agonist) (Figure 5). During/after training the mice did not show any discrimination differences. This indicates that it has no effect on the processing and encoding phase. However, 90 minutes later, the control group was better able to discriminate objects. Between SCO, CSG or SCO+CGS there were no differences, except a lower discrimination ratio than the control, which indicates that retrieval is impaired. Another almost similar study on spatial memory by Zhihui obtained results with similarities (Li Z., 2018).

A study by Li (Li W., 2015) focused on working memory and reference memory in mice with an $A_{2A}R$ KO. Four groups of mice were used. A WT, a cross-bred of a WT and $A_{2A}R$ KO, CAG120 and WT, and CAG120 and $A_{2A}R$ KO. The CAG120 line has Huntington's disease and has degeneration in, among other structures, the striatum. The WT mice' working memory improves after three days. The WT-$A_{2A}R$ KO mice already had fewer errors than the WT mice and their working memory also kept improving. The CAG120-WT mice had a working memory deficit, which did not improve. The working memory slightly improved in the CAG120 mice with an $A_{2A}R$ KO (Figure 6A). The reference memory did not alter much and the CAG120 or $A_{2A}R$ KO had no significant effect (Figure 6B). Locomotor skills were also observed. The $A_{2A}R$ is not involved in a locomotor deficit (Figure 6C). Not only mice with an $A_{2A}R$ KO were tested, but also an $A_{2A}R$ antagonist, which showed similar results compared to the knockout. The study showed that retrieval was obstructed but encoding of a learning task was possible.

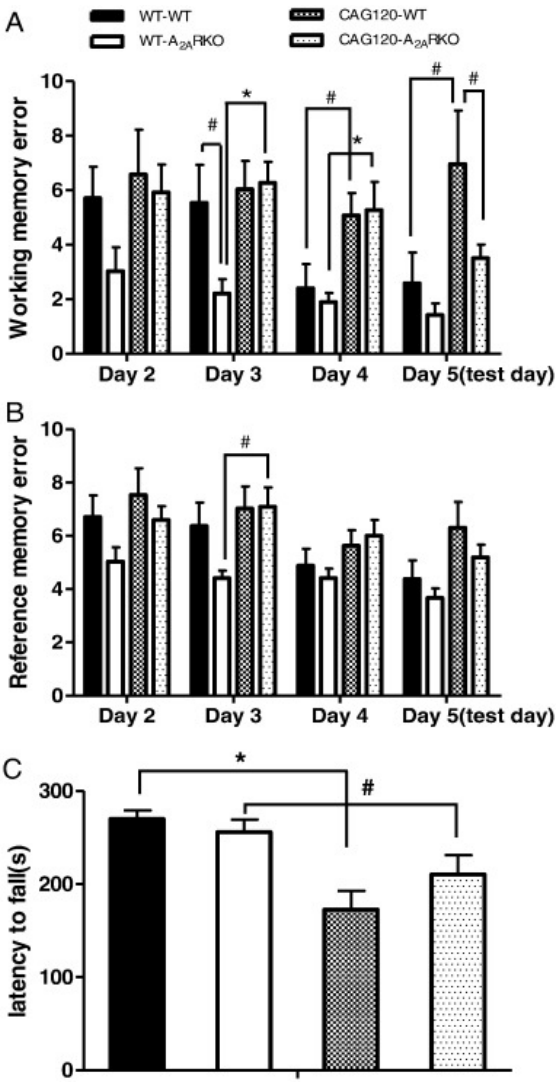


**Figure 6: Deficits of working memory, reference memory and locomotor skills in mice. $A_{2A}R$ causes an impairment in working memory and reference memory. The mice with Huntington disease (CAG120) also showed memory impairments. $A_{2A}R$ does not have an effect on locomotor skills (Li W. , 2015).**

# 5 Discussion

Sleep deprivation can lead to problems with memory processing. It is well known that sleep is important for our memory. During this thesis sleep and sleep deprivation are shortly explained. Furthermore, the function of the hippocampus during memory processing was explained. The functions of the striatum closely connected with memory processing were reviewed, along with their receptors and mostly the adenosine receptors. These functions were compared to the hippocampus using several studies to find out if striatal adenosine receptors are involved in memory processing during sleep deprivation.

The reviewed studies showed that the striatum and hippocampus are closely related and indicated that the brain structures can act

dependently or independently with each other. Both structures express $A_1R$ and $A_{2A}$ receptors and several studies showed that these cause memory impairments. Despite the memory impairments, nothing was mentioned about which areas of the striatum were involved in these impairments and also nothing about which further pathways were involved after stimulating or inhibiting adenosine receptors. Except in a study by Oliviera, PKA was mentioned (Oliviera, 2018).

When taking a look at other adenosine receptors: $A_{2B}R$ induces IL-6 in the striatum, which means it is involved in immunity and not in memory consolidation (Vazquez, 2008). The $A_3R$ in the brain is mainly expressed in inflammatory cells and have, as far as known, no influence on memory consolidation (Choi, 2011). For future studies with learning tasks, GABA, AMPA, NMDA, mGlu5 receptors levels should be measured in the striatum when the $A_{2A}R$ should is induced or inhibited to find out if they are affected. These receptors play a key role in declarative memory formation.

In summary, the hippocampus is an important brain structure for declarative memory consolidation but gets disrupted by sleep deprivation. The striatal adenosine receptors do not take over the consolidation processes. However, both brain structures are closely linked. $A_1R$ is a $G_i$-protein coupled receptor and inhibits synaptic plasticity by reducing $Ca^{2+}$ influx and, therefore, LTP. $A_{2A}R$ activates AC and should, thereby, also activate $Ca^{2+}$ influx. However, studies showed a reduction in memory retrieval, due to $A_1$ and $A_{2A}$ receptors in the hippocampus and striatum, it cannot be said with certainty if the receptor obstructs memory consolidation. So far, it looks like the striatum does not take over the role of the hippocampus during sleep deprivation. More research is needed to fully figure out the connection between the two brain structures.

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