In what way can our knowledge of the role of Ach in sleep and memory consolidation be used to benefit Alzheimer’s research?

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Abstract.

Acetylcholine (ACh) is a neurotransmitter which is involved in cognitive neural processes in the brain. It is also a neurotransmitter which is deficient in Alzheimer’s disease (AD). AD is characterized by a decline of cognitive abilities, as well as atrophy of cholinergic neurons. In this thesis, I examine the ways in which ACh is involved in several cognitive processes. I then investigate how our understanding of these processes could bring us closer to a cure for AD. ACh is essential for maintaining a circadian rhythm. It is deeply involved in memory formation and synaptic plasticity. I also find that in nearly all of these processes, ACh engages in cooperation with non-neural cells, such as astrocytes and microglia. These cells are necessary for maintaining neural health in the brain. These same cells are also deficient in AD. Due to the literary evidence for a large contribution by non-neural cells to cholinergic neural health, I propose that future AD therapy and research attempt to improve the health of the cholinergic system by targeting non-neural cells.

Abbreviations: Central Nervous System (CNS), Alzheimer’s Disease (AD), Acetylcholine (ACh), Slow-Wave Sleep (SWS), Forebrain Arousal System (FAS), Suprachiasmatic Nucleus (SCN), Basal Forebrain (BF), Long-Term Potentiation (LTP), Long-Term Depression (LTD), Acetylcholinesterase Inhibitor (AChEI), Rapid Eye Movement (REM), Brain-Derived Neurotrophic Factor (BDNF)
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Introduction.

Our brain relies on an abundance of signalling molecules to relay information between neurons. These signalling molecules are also known as neurotransmitters. Neurons have long extensions called axons, along which electrical signals can travel. When one such signal reaches the end of an axon, neurotransmitters are released. They bind to receptors on the adjacent cell, and can then trigger a response. Acetylcholine (ACh) is one such neurotransmitter, which fulfils a broad range of tasks in the body and brain. It is the postganglionic neurotransmitter in all peripheral efferent neurons, as well as an important regulator of arousal, attention, and memory. Due to its wide range of functions, it is involved in a wide range of diseases, and is a target for many drugs and therapies. One of the main diseases in which it is involved is Alzheimer’s Disease.

Alzheimer’s Disease (AD) is a disease which has a large impact on our society. It is characterised by dementia, having difficulties with language, spatial orientation, and a general cognitive decline over time, which generally ends in a patient having no real cognitive abilities to speak of. If a patient lives to reach the final stages of the disease, they are often in the foetal position in bed, not responding to the outside world at all. In the modern world, it is the cause of 50-60% of the cases of dementia. Developing a remedy for AD is in the public’s best interest, as the total aggregate cost of treating AD in 2018 is around 277 Billion $ in the United States alone. Several possible causes have been postulated. The main ones are genetics, abnormal extracellular deposits of Amyloid β (Aβ), intracellular Tau proteins, and a decrease in ACh synthesis. There has been no consensus on the cause, though there is agreement on some common risk factors, the main one being one’s age. As one grows older, the chance of acquiring AD increases drastically. Other risk factors include one’s family history, genetics, as well as a few cardiovascular parameters. AD is characterized by, among other things, atrophy of neurons that synthesize and release ACh, otherwise known as cholinergic neurons. This has wide ranging consequences. Due to the pathology of AD, there is ample reason to investigate any potential therapeutic intervention that might involve ACh. As we will see later in this thesis, ACh is an important modulator of memory formation and consolidation, maintaining a steady circadian rhythm, and neuroplasticity. These processes will be the focus of this thesis.

In this thesis, I will cover the role of ACh in the aforementioned cognitive processes, all of which are affected by the loss of cholinergic neurons in AD. I will investigate how ACh is of importance in all of these processes. In doing so, we will gain a deeper understanding of how a deficiency in the cholinergic system might explain the symptoms and problems experienced by AD patients. This will have implications for AD treatment and pathology, and will provide new insights for new possible directions in AD research.

What is the relationship between Acetylcholine, rhythm, and sleep?

Circadian rhythms are processes that show a natural oscillation of approximately 24 hours. They have been shown to exist in nearly all branches of organic life, including insects, and bacteria. There are three criteria that need to be met, in order for something to be counted as a circadian rhythm. The first condition is that the rhythm has to have a free running period that, under constant conditions, will last approximately 24 hours. The second requirement is that the rhythm must be entrainable. Circadian rhythms, when exposed to different light phase rhythms, will adjust to the new light cycle. The third criterium is that the rhythms compensates for temperature. In mammals, the circadian clock is located mainly in the Suprachiasmatic Nucleus (SCN), in the hypothalamus. The brain receives input from environmental cues, known as zeitgebers (literally “time givers” in German). These function as cues for setting our internal clock. This is necessary because the innate rhythm of many organisms is not exactly 24 hours. The main zeitgeber for the
SCN is the retinohypothalamic pathway. This is a neural pathway connecting retinal cells in the eye to the hypothalamus. The retinal cells pass on information to the SCN, mainly pertaining to the intensity of the light. It has been known for some time that nearly all cells, not just the neurons in the SCN, possess their own rhythm, independent of the SCN. Generally, however, the SCN functions as the main regulator of the rhythm of the body.

Acetylcholine exerts influence on the circadian rhythm. As early as 1985, Carbachol (an ACh agonist) was shown to be able to entrain the natural circadian rhythm in hamsters. In more recent years, it has been hypothesised that the interaction between ACh and the SCN mainly stems from the role of ACh in the ‘forebrain arousal system’ (FAS). Optogenetic stimulation of Cholinergic neurons in the Basal Forebrain has been found to promptly induce a shift to REM sleep or waking. In other research it was found that resetting the circadian clock would activate many cholinergic cells. Finally, blocking ACh binding (through atropine) would ensure that phase shifting could not occur. These findings would suggest that ACh is not only a neurotransmitter which plays an intricate role in the regulation of the circadian rhythm, but also essential to its functioning.

It is important to note, however, that the FAS is a different system than the light phases that function as zeitgebers for the SCN. The FAS is a nonphotic system, meaning it is not regulated by light. The findings of Yamakawa et al. paint a picture of ACh as a transmitter which can override the regulation of the retinohypothalamic pathway. For a while, the SCN was viewed as the master of all clocks in the body, but it would seem that ACh has the capability to overturn the rhythm set by the SCN. ACh itself is also released in a circadian fashion. The phasic release of ACh falls in line with the sleep and wake stages of the organism. It was observed that, in cats, the release of ACh would be lowest during slow wave sleep (SWS), and generally higher during REM sleep and waking. There was, however, a large difference in ACh amount released between the different parts of the brain. During REM sleep, the hippocampus would show a near fourfold increase in ACh levels, when holding SWS levels as a baseline. This is markedly higher than levels during waking. The cortex would only show an increase in ACh levels to the same levels as they would be during waking. These findings would suggest that, like all other cells of the body, ACh release is ultimately subject to being controlled by the SCN, but it can also function as an arousal signal to the SCN.

The involvement of ACh in rhythms and the SCN has some implications for its role in AD. Patients of the disease experience disturbances in their circadian rhythm. Additionally, they undergo morphological changes in the SCN. As was already established, AD is characterised by degeneration of cholinergic neurons (explained in the introduction). It is therefore not a stretch of the imagination to presume that the loss of cholinergic neurons in AD is connected to patients having disturbed day/night cycles. For this reason, ACh-targeting drugs are regarded as a potentially rewarding direction for research to take.

How is Acetylcholine involved in memory consolidation?

Several areas of the brain have been identified as part of the memory formation and consolidation system. The most prominent of these areas is the hippocampus. In order for long-term memory formation to occur, certain molecular events need to occur, such as gene transcription and protein synthesis. The main way in which ACh is connected to memory formation is through its relationship with the several stages of sleep.

All of the stages of sleep have their own distinct EEG and ECOG profiles. Slow wave sleep (SWS) is characterized by EEG waves with the lowest frequency, and is also the stage of sleep in which memory consolidation is believed to take place. During this stage of sleep, ACh levels are lowest, and it is believed that this is connected to the formation and retention of memories. It is believed that the levels of ACh during SWS is one of the main determinants of whether memories can be consolidated. Raising their levels during SWS through administration of a reuptake inhibitor will
completely block the consolidation of memories in humans, as was described in an experiment in 2004\textsuperscript{xxix}. Human subjects were either given an ACh antagonist, or a placebo. They then had to take a memory test, to remember word pairs, which they had to repeat at a later time, after getting some sleep. The people who had been given the ACh antagonist, scored significantly worse than the people who were given a placebo. This did not influence their ability to perform at a non-declarative memory task. The results of this study are shown in figure 1. If one has rats running a certain route, and then take measure of which cells fire at which point of the track, these same cells will fire in the same pattern during sleep as they did when running the track\textsuperscript{xxx}. Rasch et al exposed test subjects to a certain odour during a learning task. Exposing the same person to the same smell during SWS will ensure that they perform significantly better at a memory performance related to the learning task than if they had been given no odour\textsuperscript{xxxi}. The results of these studies are summarized in figure 2\textsuperscript{xxxii}. All of this seems like fairly compelling evidence that SWS is the one stage of sleep which is necessary for memory consolidation. There is, however, some research that would seem to contradict this finding. Research done by Genzel et al showed that deprivation of any single stage of sleep, REM or SWS, would not impair memory consolidation in humans\textsuperscript{xxxi}. The authors noted that it was the amount of sleep spindle activity that was significantly correlated with performance at the memory tasks, rather than the amount of any single sleep stage. They therefore suggest that sleep spindle activity is the main determining factor for memory consolidation, instead of SWS. It is important to note that SWS was never completely diminished in their test subjects. For this reason the authors note that SWS might not need to have a particularly long duration in order for memory consolidation to take place.

![Figure 1. Courtesy of Gais et al. Black bars were given physostigmine(an ACh antagonist). White bars were given placebo. People with ACh antagonists performed significantly worse on memory tests than people with placebo.](image)

So as we can see, the exact role of sleep in memory formation is a controversial topic. A recent hypothesis on the role of ACh and the different sleep stages on memory consolidation is the Dual Process Hypothesis\textsuperscript{xxix}. This model states that different stages of sleep are of importance for different kinds of memory consolidation. SWS sleep would mainly function to consolidate declarative memory, whereas REM sleep would serve as consolidation of non-declarative memories. To this end, ACh would need to be low during SWS to accommodate memory consolidation, but need to be in higher concentrations during REM sleep in order to facilitate plasticity\textsuperscript{xxx}. Ackermann takes the Dual Process hypothesis a step further, and suggests that emotional memory, procedural memory, and declarative memory consolidation all have a different
relationship with the different stages of sleep. The exact mechanisms are still up to debate, but it is agreeable to say that ACh does play an essential role in memory consolidation.

Next, we will examine how ACh performs its functions on a cellular level. ACh plays a modulatory role in memory formation, alongside another neurotransmitter, Serotonin (5-HT). When memory formation takes place, a molecular cascade needs to be activated. This is mainly performed by 5-HT\textsuperscript{xxxi}. In short, repeated stimulation by 5-HT will cause a rise in cyclic AMP, which will activate several immediate-response genes. Activation of those genes will cause several long-term molecular changes in the corresponding neurons, which are necessary for formation of long-term memory. The role ACh has to play in this process is one of regulation. Acetylcholine enhances the influence of
afferent input to the cortex, while simultaneously diminishing retrieval mechanisms\textsuperscript{xxxi}. When it’s low, the opposite happens, and the neurons start to become more focused on Long-Term Depression, which is cutting back on connections which are unnecessary for memory formation or consolidation. It would stand to reason that this is why we have wildly differing ACh levels, depending on which stage of sleep we are in. This would fall in line with the hypothesis that different stages of sleep are necessary for the various molecular processes of memory formation, where SWS is mainly for strengthening memories, and REM sleep for cutting back on unnecessary connections.

Neurons are not the only cells in the brain of relevance to memory formation, and the view that non-neural cells are important for memory formation and consolidation has been gaining ground. This hypothesis will be covered in the next part in more detail. Microglia are among the cells needed for proper differentiation of neurons, as well as synapse formation\textsuperscript{xxxi}. Several mechanisms through which astrocytes interact with memory formation have been discovered\textsuperscript{xxxv}. We now know that ACh engages in several interactions with glial cells in the hippocampus, in processes which are essential for memory formation\textsuperscript{xxxv}. It was found that microglia promote synapse formation which is essential for learning\textsuperscript{xxxvi}. The interaction of ACh with neurons and glia is not fully explored. We can, however, induce that ACh is involved in memory formation and consolidation through multiple pathways, neural or otherwise.

What we can discern from this is that memory formation is a delicate process, one that involves many steps, and multiple neurotransmitters to take place. If ACh is missing from the equation, the whole process stops. This is one of the underlying causes of the severe memory deficiency in AD, and that remediating this deficiency will probably have to include a therapy aimed at preserving the health of the cholinergic system in the CNS.

**In what way is neuroplasticity influenced by Acetylcholine?**

In order for the brain to be able to make new memories, it needs to be plastic. It needs to be able to form new neural connections, and to terminate rudimentary ones. There are currently two places in the brain that we know of, where neurogenesis can take place. Out of those two areas, the hippocampus is of particular relevance to this thesis. It is here where the trisynaptic circuit resides. It is where processes of synaptic plasticity take place, which are essential for proper memory formation.

The process of long term changes in synaptic plasticity necessary for memory consolidation is called Long-Term Potentiation (LTP). This is essentially an attempt by the neurons involved to make using a particular synaptic connection more efficient. It a process that can occur at essentially any synapse that is used often. Repeated stimulation can cause an increase of receptors at the receiving dendrite, causing a higher sensitivity. The corresponding axon can also increase the amount of neurotransmitters in its presynaptic vesicles. All of this results in a synapse where more neurotransmitters are released, and is more sensitive, meaning an overall more effective synaptic connection. LTP takes place, among other areas in the brain, in the hippocampus, in the CA1 region\textsuperscript{xxxvii}. This happens, among other things, due to modification of NMDA-R, the receptor that has already been an earlier subject of attention. It has been shown that specific blocking of ACh in the hippocampus will inhibit LTP\textsuperscript{xxxviii}. The effect of ACh on LTP is different for several areas of the hippocampus. In the CA3 region administration of an ACh agonist would depress LTP\textsuperscript{xxxv}, whereas it would facilitate LTP in the CA1 region\textsuperscript{xxxviii}. This is mainly attributable to differences in muscarinic receptor subtypes. These processes are modulated by microglia and astrocytes. These findings suggest that ACh influences neuroplasticity through many different and complex pathways.

A particularly relevant model is the ‘tripartite synapse’ hypothesis\textsuperscript{xli}. This model hypothesizes that cholinergic neurons mainly empower neuroplasticity through their interaction with non-neural cells, called astrocytes. Astrocytes are cells which mainly fill a supportive role in the brain. They mainly
provide structural and metabolic support, and are important for the maintenance of the Blood-Brain Barrier. Until recently, astrocytes were generally regarded as cells that could support neurons, but could not contribute to the process of actually passing on, and storing information. As of late, however, the view has been accepted that Astrocytes are of importance in the synapse. Astrocytes are projected onto by certain neurons and, through CA2+ action potentiation, can then release signalling molecules, known as gliotransmitters, which influence the density of receptors in the synapse. This is done through release of D-Serine, which then modulates the postsynaptic receptor density. This process is summarized in figure 2. Whether this process can influence presynaptic receptors or autoreceptors was not investigated. In the hippocampus, the neurons that excite the astrocytes are cholinergic\textsuperscript{eill}. This interaction will cause a postsynaptic increase in the postsynaptic NMDA receptor(NMDA-R)\textsuperscript{xliii}. It might be reasonable to suspect that this is connected to the low levels of ACh during slow sleep that was covered in the previous part.

Figure 3. Courtesy of Perea et al.' Scheme of the tripartite synapse'. A neuron releases neurotransmitters presynaptically. These neurotransmitters then take two pathways. Some just bind to the postsynaptic membrane, others interact with the nearby astrocyte. This elevates Ca\textsuperscript{2+} levels in the astrocyte, causing it to release gliotransmitters, which then modify postsynaptic density/sensitivity.

The other aspect of brain plasticity is neurogenesis, a process in which ACh also plays a vital role\textsuperscript{xlv}. Neurogenesis mainly takes part in the Dentate Gyrus part of the hippocampus. Neural stem cells in this area express ACh receptors, and stimulation of these receptors will increase neurogenesis. Lower levels of ACh will halt neurogenesis. Much like with LTP and NMDA-R, this process is also modified by non-neural cells. Microglia are necessary for neurogenesis, and mice lacking T-and B-cells have impaired neurogenesis\textsuperscript{xlv}. Due to the involvement of microglia, the term “quad-partite synapse” has been coined by Schafer et al. Overactivation of the immune system will impair neurogenesis, and can even be neurotoxic\textsuperscript{xlv}. These findings, along with the ones from the previous paragraph, would suggest that both ACh and non-neural cells have a role to play in neuroplasticity/neurogenesis, and there is a possibility of interplay between the cholinergic and non-neural cells of the brain. This process is comprehensively summarized in figure 4.
The hippocampus is not the only area of the brain where ACh modifies plasticity. There is a strong consensus that ACh is of particular relevance to cortical plasticity. It has been shown that ACh can induce long lasting changes, when applied to cortical cellsxlvii. There is even evidence to suggest that the exact nature of the elicited effect can differ, depending on which part of the cell the ACh is applied tooxlviii. ACh can induce plasticity through changing in membrane plasticity, changing sensitivity to certain neurotransmitters, causing changes in receptor density, and cause small post-action potential aftercurrents. Already, several groups have attempted to boost ACh-produced plasticity through drugs, or transcranial magnetic stimulationlix. ACh is able to modulate plasticity through interacting with Brain-Derived Neurotrophic Factor(BDNF), a molecule known for its role in neuroplasticity and neurogenesisl. This is also regulated by BF cholinergic neurons. This process is also influenced by non-neural cells. It is likely that these are two fairly independent systems designed to regulate neural and synaptic growth.

What we can gather from this data is that there is increasing evidence that ACh and non-neural cells are part of a cellular interplay, designed among other things, to keep our brain in a healthy state. This is especially relevant to this thesis, because a neuroplasticity deficiency is one of the earlier symptoms of ADli. This calls for further exploration of this relationship between these two systems, as a loss of neuroplasticity is not just limited to AD, but to nearly all diseases that involve forms of cognitive declinelix.
The relationship between Alzheimer’s and Acetylcholine.

Alzheimer’s is a condition in which all of the phenomena described earlier in this thesis are greatly diminished: a normal day/night rhythm, memory formation and consolidation, and neural plasticity. One of the main noticeable changes in the brain with AD is the atrophy of cholinergic neurons. The way to determine the stage of Alzheimer’s is through quantifying the loss of (cholinergic) neurons. When examining the brains of AD patients, the loss of neurons becomes worse as the disease progresses. The disease is broken up in several “Braak” stadia. At the beginning, patients’ memory takes a slight hit, as well as their spatial orientation, along with some motor ability. In the final stages, patients have lost nearly all of their cognitive abilities, and lie on their bed in the foetal position. What is notable, is that one of the areas that loses its cholinergic neurons quickly is the Basal Forebrain. This area of the brain is of relevance, among other things, for arousal and higher cognition. This is one of the reasons why one tends to lose their more sophisticated brain functions in the earlier stages of the disease. It has been hypothesized that the symptoms of Alzheimer’s are essentially the accelerated version of a process that already naturally occurs during ageing. This claim is substantiated by the observation that both ageing and AD are characterized by loss of ACh reuptake by neurons. The subsequent loss of ability to synthesize ACh would cause the cells to autocannibalize membranes which contain Choline, in order to keep up with the need for ACh synthesis. This would lead to a quick demise of these cells, resulting in the loss of numerous cholinergic cells in AD. Many of the symptoms of AD can be traced back to the loss of these neurons. Indeed, AD patients are known to lose spatial orientation, memory function, and circadian rhythms. Due to this relationship between ACh and AD, the main treatments against AD at present are aimed at preserving ACh in the synapse. Four out of five drugs for AD treatment currently approved by the FDA are Acetyl-Cholinesterase Inhibitors (ACHs). Their effect is, however, limited to a slight slowing down of the symptoms. It is safe to say that there is, as of yet, no cure for AD.
Another implicated role of ACh in AD pathology is that higher neural engagement during one’s lifetime staves off AD, at least for a time\textsuperscript{li}	extsuperscript{vii}. It was found that people with higher educational or occupational attainment have a decreased risk of developing AD, or other forms of dementia. This birthed the “cognitive reserve” hypothesis. This states that people who perform jobs that require more neural activity keep their brain more healthy. In doing so, their brain becomes better at combating AD. Admittedly, the line that you can draw between this and ACh is tenuous, but it has some important implications. This does show that there is a non-medical way in which every individual can modify their odds of acquiring AD at a later age.

Again, we find a connection between non-neural cells and the cholinergic system. Astrocytes dysfunction is a common occurrence in AD. This dysfunction can then cause neuro-inflammation, excitotoxicity, a decrease in synaptic plasticity, a dysregulation of neural energy metabolism, and neurovascular dysregulation\textsuperscript{lix}. Most importantly, though, is the fact that astrocytes play an important part in relieving the burden of Amyloid β plaques. Astrocytes can drain Amyloid β from the brain\textsuperscript{lx}, as well as internalize and degrade it(shown in figure 7). What this shows is that Astrocytes are at the forefront of combating AD pathology. In our previous chapters we found a large body of
evidence suggesting that the interaction between non-neural cells and ACh is one of the things that is keeping the brain healthy, capable of learning, as well as refreshing and rebuilding itself. This should be ample reason to focus research and therapy on astrocytes, and other non-neural cells.

Figure 7. Courtesy of Wyss-Cory et al. Astrocytes were incubated with (synthetic) Amyloid, whereupon supernatant or pellets were collected at time points indicated on the x-axis. In both supernatant and pellets, the astrocytes cleared away the plaques over time.

**Discussion.**

The main question on how our knowledge of ACh can be used in AD research has quite a faceted answer. Through our sub questions we have discussed the main relationships between ACh and our memory and rhythmic systems. However, ACh, like any neurotransmitter, is pleiotropic, and has other functions in the brain which we couldn’t cover in this thesis. A fundamental flaw with a piece of literature that attempts to look at any single neurotransmitter or hormone as a cause for a complex disease lies in that these diseases are usually caused by a myriad of factors. As of 2018, there is still no scientific consensus as to what the cause of AD is. Even when it came to our subthemes, there were occasionally conflicting models, an example being the several theories regarding the role of different sleep stages in memory formation. There are, however, some important implications that we can induce from our findings.

The main implication in this thesis has been the relationship not just between ACh and memory systems and neuroplasticity, but an interplay between all of these processes and non-neural cells in the brain. Due to the ACh pathology of AD, many drugs targeting ACh, its synthesis, or its (re)uptake have been created. Their efficacy is, however, minimal, and does very little besides slightly delaying the inevitable. For this reason, I propose that treatment involving non-neural cells are an option which modern AD researchers ought to consider. We have found an intricate interplay between microglia and astrocytes with the cholinergic system, especially in the hippocampus. We also know now that astrocytes have important functions in staving off AD and its symptoms. We do now know that ACh does indeed improve neurogenesis, and that it does so through interacting with microglia. Targeting these cells could go a long way to alleviating many of the more severe symptoms of the disease. It would stand to reason that targeting the non-neural cells could indirectly
have a positively impact on patients’ memory, neuroplasticity, and their ability to maintain a normal circadian rhythm.

Having the aim of targeting non-neural cells would raise the obvious question of how to do so. One of the major difficulties of any medication aimed at the brain is the Blood-Brain Barrier (BBB)\textsuperscript{[1]} Due to this, among other reasons, it is quite difficult for drugs targeting the brain to still be of significant concentration, once it reaches the relevant tissue\textsuperscript{[2]}. A recent technique to circumvent this problem is the development of nanotechnology\textsuperscript{[3]}. It is now possible to treat mice with surfactant-coated nanoparticles, which reach clinically significant doses in their brain tissue\textsuperscript{[4]}. Similarly promising results have been achieved with in vitro models\textsuperscript{[5]}. Recently it was found that nanoparticles are still very limited in their applicability, with the main concern being that in the majority of cases, the drug would still need to be enhanced by several orders of magnitude\textsuperscript{[6]}. It would be in the public’s best interest to work to improve this technique, as projections predict a steady rise in the incidence of Alzheimer’s and other dementia related diseases in the future.

Although it will probably take years to go through the medical research necessary, looking into potential therapies targeting the non-neural cells in the brain would probably be a wise direction for research to take. As we have repeatedly demonstrated, these cells, particularly microglia and astrocytes, are involved in nearly all relevant processes for memory formation and neural plasticity. It would certainly be a good alternative for the current therapies. The problem with neurons is that they are very specialized cells, and that they are essentially impossible to replace, once lost. As such, AChEIs can only slow the loss of neuronal connections. We now know that these non-neural cells do not only help with memory formation, but are important for maintaining neural health\textsuperscript{[7]}. Therapies that could boost the abilities of these non-neurons would probably go a long way to keeping the CNS plastic, and helping it preserve connections that might become lost to AD otherwise. As such, it would be able to serve not as a replacement for AChEIs, but as a supplement.

Another issue is that AD is nearly impossible to detect in its early stages. Once detected, with the current treatments available, therapy is essentially nothing but fighting the symptoms, rather than the cause. It is sometimes difficult to distinguish between symptoms of Alzheimer’s and normal ageing, as a decrease in memory ability and lessened neuroplasticity are a normal effect of ageing in the elderly\textsuperscript{[8]}. The question remains on what exactly a cure for AD would entail. The ideal scenario would not only mean finding a way to prevent AD, but to remedy the already existing cases in the world, which, as of 2017, numbered around 50 million people\textsuperscript{[9]}. This would have to include a way not only to preserve existing neuronal health, but for lost neural connections to be restored, landing us at the problem of the previous paragraph. Neurons sometimes have connections to a whole different region of the brain. There are whole branches of modern science dedicated to researching the cellular and molecular factors that determine how neuronal axons manage to find the right destination in the brain. It would be an enormous undertaking to find these out, and to apply them to live human subjects. Rebuilding lost neural connections would not mean restoring lost memories, as memories are known to be essentially a collection of molecular connections in the neocortex\textsuperscript{[10]}. Molecular and pharmacological therapies might be in order to achieve this goal.

Despite all that I have just mentioned: the cost, the amount of time and effort that would go into finding a way to restore lost neural connections, I believe that it would be a worthwhile effort. It would open the door to curing not only AD, but a whole range of other diseases. Additionally, in the introduction I already mentioned the tremendous cost of AD treatment in the world, which is only bound to increase. As of now, the global cost of treating AD is estimated to be at \textdolar{818}\textsuperscript{[11]}. Yearly. AD incidence is projected to increase even more drastically in the future, from 5.5 million in 2010 to 13.8 million sufferers in 2050 in the US alone\textsuperscript{[12]}. AD already takes a tremendous financial and emotional toll on society, a cost which we shouldn’t have to bear.
To summarize, the current knowledge we have on ACh and its roles in memory, plasticity and rhythms is something that, in and of itself, has little to add to potential research. Our newly uncovered knowledge on the interaction between ACh and non-neuronal cells has some major implications for new research, and could very well be the key to finding a more potent remedy for one of the major risks to our health in the modern era.

References.


xxvii Ackermann S, Rasch B. Differential Effects of Non-REM and REM Sleep on Memory Consolidation?. Current Neurology and Neuroscience Reports. 2014;14(2).


