Can negative memories be altered into positive memories?

Judith Radersma (S3477207)

University College Groningen

Final Thesis

Dr Chris May

June 2020

ABSTRACT

Memory engrams are the neurons that are involved in one specific memory. They are activated during the consolidation and recall of the memory. Research in rodents has shown that through artificial activation of those engrams, negative or fearful memories can be altered into positive memories. Researchers reactivated the engram of a negative memory while putting the rat in a positive environment. When reactivating the engram after this manipulation, the rats responded with approach behaviour where they showed freeze behaviour previously. This thesis deals with the question whether it is possible to achieve this in humans. Based on the current literature, the human engram is not yet found on a cell-level, which is necessary to perform artificial manipulations on the engram. Alternative experiments are proposed which rely on a natural reactivation of memories. The general idea of reactivating negative memories in a positive environment could be used for therapeutic interventions. Further research in locating engrams and behavioural manipulations are needed before this approach could be used.

CONTENTS

INTRODUCTION

The process of storing a memory in the brain involves physical changes in brain cells or neurons (Josselyn, Köhler, & Frankland, 2015). During this process, the connection between different neurons is strengthened. When this connection is strong enough, the memory can easily be retrieved. During retrieval, the memory becomes temporarily fragile. During this time, the memory is susceptible to change. The main consequence of this timeframe is that the memory becomes less reliable over time. This happens, for example, in eyewitness testimonies (Loftus & Zanni, 1975). People might be very uncertain about what the perpetrator looked like or become surer over time because they keep repeating, and therefore recalling, the memory.

In clinical psychology, many forms of therapy with people suffering from post-traumatic stress disorder (PTSD) rely on the fact that memory is susceptible to change. For people suffering from PTSD, certain negative memories become so traumatic that they cannot cope well (Yehuda, 2002). Eye Movement Desensitisation and Reprocessing (EMDR), for example, is based on the principle that memories can change after retrieval. In EMDR, a traumatic memory is recalled while the patient is presented with a fast-moving object that they must follow with their eyes. The idea is that their mind is occupied with following the movement and has less space for re-encoding all the details of the traumatic memory. This has the consequence that the memory is re-encoded as less emotional and traumatic.

Most of the clinical research that is currently available is based on decreasing the emotional arousal. Not much research has been conducted regarding changing the valence of a memory, i.e. changing a negative memory into a positive memory or vice versa. In this paper, I will investigate whether it is possible to alter the emotional component of a consolidated memory in humans. More specifically, is it possible to manipulate a memory experience in such a way that a negative memory is changed into a positive memory?

The existing research regarding this topic is mostly conducted in rodents. Studies in rats have shown that it is possible to alter a memory in such a way that a negative memory becomes positive (Redondo, Kim, & Arons, 2014). In this paper, negative memorise are defined as memories associated with avoidance behaviour. Fearful memories are an example of negative memories. Positive memories, on the other hand, are associated with approach behaviour. I will first discuss what a memory is, how memory consolidation works, and which brain areas are involved in memory consolidation and retrieval. Then, I will investigate influences on how well a memory is consolidated. Furthermore, the difference between positive and negative memories will be discussed as well as different manners in which a memory can be manipulated. The last part of the paper will be focused on an experimental proposal, in which I will investigate whether it is possible to change negative memories into positive ones in humans.

WHAT IS A MEMORY?

MEMORY ENGRAMS

Memory engrams can be seen as the physical representation of a memory (Josselyn & Tonegawa, 2020). Engrams consist of a group of brain cells or neurons that contain a certain experience. When an engram is reactivated, a certain memory is recalled. There are three different phases to forming an engram cell (Josselyn & Tonegawa, 2020). First, engram cells start to develop during a learning experience, when a specific group of neurons is activated. This, then, leads to a physical alteration of these neurons because of the learning experience. Lastly, memory retrieval occurs when these cells are activated later. Retrieval cues can guide the retrieval of certain memories (Josselyn & Tonegawa, 2020). Retrieval cues are often stimuli that are were also present during the learning experience. Seeing a flower can for example trigger the retrieval of a memory that occurred in a flower field. This explains why memories are recalled better when the circumstances are similar during encoding and retrieval – a phenomenon called state-dependent learning. If people are studying for a test, for example, they can aid retrieval by keeping the environment as similar as possible to the test environment.

While studies in humans have been coming closer to locating engrams over the past decades, the exact location of engrams is yet to be found (Eichenbaum, 2016). Studies in rodents, on the other hand, have showed that the concept of engram cells does seem to exist. Different studies in rats showed that certain cells in a range of different brain areas are active both during encoding and retrieval (Josselyn & Tonegawa, 2020). These cells are not activated during activities that are unrelated to the encoded experience. When those cells were removed, the learning experience also disappeared. This also works the other way around. The retrieval of a memory can be artificially induced when the engram cells are activated even when there are no retrieval cues in the environment (Josselyn & Tonegawa, 2020). While the exact engram in humans is yet to be found, the concept behind it could also work in humans.

MEMORY CONSOLIDATION

Memory consolidation is the process through which new and unstable memories are changed into stable long-term memories. Right after a learning experience, a memory is susceptible to disruptions that prevent the memory from being stored long-term (Ryan, Roy, Pignatelli, Arons, & Tonegawa, 2015). One way in which a memory can be disrupted is protein synthesis inhibition. Protein synthesis is necessary for the consolidation of memories and if this is blocked, that person will suffer from graded retrograde amnesia. This means that people will lose fragile memories that occurred before the event. Memories that are more prone to being lost are memories that did not go through a training phase yet. Protein synthesis inhibition blocks the training phase, in which the memory will be rehearsed. The training phase is necessary for a memory to become long-term. Protein synthesis inhibition does not block the learning of tasks or experiences. This observation suggests that there are two distinct phases of memory: a learning phase and a training phase. Hebb and Gerard first proposed this as the dual-trace theory of memory (McGaugh, 2000).

When memories have gone through a training phase, the synaptic strength of the memory engrams has increased. This means that the different neurons in the engram have a stronger connection than before.

In retrograde amnesia, the synaptic strength of the cells involved has not changed. This means that the cells have been somewhat strengthened, because they have gone through a learning phase. However, since the cells have not completed the training phase, the connection between the cells are not strong enough to be activated naturally. The memories can still be artificially activated, though, suggesting that the memory engram is still there (Ryan, Roy, Pignatelli, Arons, & Tonegawa, 2015). This further proves that there are at least two different phases in the consolidation of memory – a training phase and a learning phase (Ryan, Roy, Pignatelli, Arons, & Tonegawa, 2015).

RECONSOLIDATION

Every time that a memory is recalled, the memory cells become temporarily fragile again. This process during which memories are strengthened again after they are retrieved is called reconsolidation. During this time, the memory is susceptible to changes (Besnard, Caboche, & Laroche, 2012). Consolidation and reconsolidation are two very similar processes. They are both dependent on protein synthesis. A memory can only be reconsolidated if it is directly activated. This process is specific to the memory that was activated. Other memories, even if they are closely associated to the activated memory remain unchanged.

After a memory is retrieved, there are two different possible scenarios. The memory can either extinguish and disappear or the memory can be reconsolidated (Besnard, Caboche, & Laroche, 2012). For people who suffer from post-traumatic stress disorder, or PTSD, it is important that the exact mechanisms influencing whether a memory is reconsolidated or extinguished are investigated. This might be able to help them to alter the traumatic memory in such a way that it is not as traumatising anymore.

WHICH BRAIN AREAS ARE INVOLVED IN MEMORIES?

AMYGDALA

One area that is involved in the processing and encoding of emotional memories is the amygdala (Janak & Tye, 2015). The function of the amygdala has been investigated across many different species, both mammalian and non-mammalian (Janak & Tye, 2015). Environmental stimuli are first processed by a range of different brain areas. These areas forward the information to the amygdala. After the amygdala processes this information, it sends back signals to the different sensory areas.

The most important function of the amygdala is its involvement in fear conditioning. Fear conditioning is the process during which two unrelated stimuli are linked to each other, because they are repeatedly presented at the same time (Lonsdorf, et al., 2017). For example, an electrical shock might relate to the sound of a bell. The fearful stimulus is called the unconditioned stimulus and the innocent stimulus becomes the conditioned stimulus (Lonsdorf, et al., 2017). If the combination of stimuli is strong enough, humans and animals show fear reactions even when they are presented with the conditioned stimulus alone. This mechanism plays a crucial role in post-traumatic stress disorder. In this case, the conditioned stimulus triggers a response to the traumatic experience, even when there is no actual danger (Lonsdorf, et al., 2017).

The process of fear conditioning is partly mediated through synaptic plasticity (Bocchio, Nabavi, & Capogna, 2017). Synaptic plasticity is the ability of different neurons to strengthen or weaken during a longer period. This happens as a result from higher or lower activity. If certain neurons are activated often, the connection between the neurons will strengthen because of the higher activity. What happens during the process of fear conditioning is that the amygdala develops an increased sensitivity to conditioned stimuli. This increased sensitivity is necessary for the formation and maintenance of fear memories (Bocchio, Nabavi, & Capogna, 2017).

The amygdala does not directly impair the functioning of declarative, or conscious, memory (Buchanan & Adolphs, 2004). However, the amygdala can influence the consolidation of material that was previously learned by either strengthening or weakening their interconnections. The effect of the amygdala on memory is largely dependent on different stress hormones. Increased epinephrine levels enhance memory performance for a specific memory, for example. People whose amygdalae are removed or significantly decreased in size have more trouble with encoding and recalling emotional memories (Buchanan & Adolphs, 2004).

MEDIAL TEMPORAL LOBE

The medial temporal lobe is mainly involved in forming and consolidating declarative memories (Buchanan & Adolphs, 2004). Declarative memories or explicit memories comprise all facts and events that people consciously have. The medial temporal lobe is located in the middle of the bottom of the brain. The hippocampus is one of the areas that falls under the medial temporal lobe.

How the hippocampus influences memories depends on how recent the memory is. Evidence for this is found in the observation that hippocampal damage has a larger impact on recent memories compared

to more distant memories (Hasselmo, 1999). This suggests that there are different stages that a memory can go through. Right after a learning experience, there is a window in which the memory is most susceptible to changes. Memories that have been consolidated for a longer time are not as susceptible to disruptions. The second phase of consolidation usually occurs during slow-wave sleep and quiet waking, but it can also take place when someone is actively trying to rehearse a certain memory (Hasselmo, 1999). During sleep, the representations of certain memories are activated. When a memory engram is activated, the signal spreads to adjacent neurons. This results in a stronger connection between the engram and other neurons. In general, how stronger a memory is embedded in a network of different memories, the easier it is to recall that memory.

During the first phase of memory consolidation, the hippocampus plays an important role. When a memory is not yet consolidated, both areas in the cortex and the hippocampus are activated during the recall of a new experience (Goldstein & Van Hooff, 2008). During consolidation new connections are formed that connect different areas in the cortex to each other. The hippocampus can be seen as a sort of transfer station that connects different cortical areas to each other in the first stages of memory consolidation. After consolidation, retrieval is not dependent on the hippocampus anymore. While there is much support for this theory, there is no complete consensus yet about whether this theory of consolidation is the most accurate theory of consolidation (Goldstein & Van Hooff, 2008). For distant semantic memories, also called factual memories, the hippocampus is mostly active at earlier stages of consolidation, but the activity for episodic memories, the memory for events, shows activation of the hippocampus even for remote memories.

The involvement of the hippocampus might also depend on the exact type of episodic memory. In a study by Eldridge et al. (2000), memories were divided into two different types. There are memories that are specifically linked to a time and a place and there are memories that only carry a feeling of familiarity. Activity in the hippocampus increased mainly when the person could consciously recall where they had first made that memory compared to “familiar” memories. In the study, they looked at the activity during retrieval, suggesting that the hippocampus does play a role in the retrieval of memories in which the learning experience was recalled.

PREFRONTAL CORTEX

The prefrontal cortex is located at the front of the head and is involved in higher-order tasks, such as planning and motivation (Goldstein & Van Hooff, 2008). Additionally, the prefrontal cortex plays a role in emotional memories. In rodents, engram cells were found in the prefrontal cortex. A recent study by Kitamura et al. (2017) showed that these engram cells already exist from the first day of training. The cells remain activated both throughout the whole cycle of creating a memory, both in the learning and the training phase. Hippocampal cells, on the other hand, were mostly active during the first phase of training. These cells lose their activity once the engram cells in the prefrontal cortex are matured.

Moreover, the prefrontal cortex is active during the retrieval of emotional memories. In a study in which participants had to listen to recordings of memories of their own life, activity in the right prefrontal

cortex increased significantly (Fink, et al., 1996). The activity increased especially in the case of emotional memory.

The prefrontal cortex forms a strong connection with the amygdala. The amygdala is involved in arousing emotions and activity in the prefrontal cortex also increases in arousing contexts. This occurs even when neutral words are presented in an arousing context. In a study by Maratos & Rugg (2001), a neutral sounding words, like "corn", was presented in either a neutral sentence or an arousing sentence. An example of an arousing sentence is "The farmer was shredded when he fell into the corn grinder". During arousing sentences, activity in specific parts of the prefrontal cortex was significantly higher.

NEUROTRANSMITTERS

Neurotransmitters are chemicals that are used as messengers to spread information from one neuron to another (Sasikumar, 2016). In the process of consolidation and memory, multiple neurotransmitters are involved (Myhrer, 2003). Neuronal receptors respond to one type of neurotransmitters, which allows for high specialisation in how messages are transmitted. During the process of consolidation, the activity of different types of neurotransmitters increased. This is critical for the development of new memories.

Acetylcholine is one of the neurotransmitters that plays a role in consolidation. The level of acetylcholine is dependent on the circadian rhythm (Hasselmo, 1999), During the day, acetylcholine levels are high. It is suggested that acetylcholine suppresses the spreading activation between neurons, which eases initial encoding of new memories without interference of consolidated memories. During sleep and relaxation, acetylcholine levels are lower. This allows for a spread in activity in the hippocampus and from the hippocampus to the cortex (Hasselmo, 1999).

BRAIN NETWORKS

It is important to realise that different brain regions do not act in isolation, but that they are largely dependent on the connection they have with other brain regions (Pessoa, 2018a). Emotional experience cannot be created by one brain area alone. (Pessoa, 2018a). The systems that are involved in emotional processing are not very different from the systems that involve motivation and cognition (Pessoa, 2018b).

Different specific memories can be characterised by specific activity patterns in the brain (Josselyn, Köhler, & Frankland, 2015). It is suggested that the engram cells in humans for specific memories consist of up to millions of neurons. This can be contrasted with studies in rodents where a group of engram cells can consist of less than one hundred cells (Redondo, Kim, & Arons, 2014). Because it is fairly difficult to monitor the activity of single cells in humans, it might be an outcome to look at activity patterns to connect memories to their corresponding brain activity. If such research can be conducted successfully, a memory could theoretically be activated artificially by stimulating that specific pattern of brain activity.

FACTORS INFLUENCING MEMORY

MEMORY AND STRESS

Stressful experiences are often characterised by a lack of control (Buchanan & Adolphs, 2004). As opposed to other emotions which are meant to prepare us for action – "fight or flight" – stress has a more prolonged effect, which might mean that it affects memory in a different way compared to other emotions. The effect of stress on memory can be compared to the shape of an inverted U (Buchanan & Adolphs, 2004). A medium amount of stress has beneficial effects on memory, but if the stress is too much, these effects are nullified.

Stress also impacts if and how emotional memories are stored (Diamond, Park, & Woodson, 2004). Stress can impair recently learned information. Long-term potentiation, or LTP, happens when the connection between two neurons is strengthened because of increased recent activity. LTP has the characteristic that it does not spread to other neurons. This means that LTP is input-specific and if one memory undergoes LTP, this does not necessarily happen to other neurons (Engert & Bonhoeffer, 1997). LTP is sensitive to salient cues, meaning that extreme or unexpected stimuli are more likely to be strengthened. Stress has a positive effect on LTP, strengthening the sensitivity to salient cues. This can also be illustrated by the so-called "weapon focus effect". The weapon focus refers to the observation that victims in a crime tend to be very focused on the weapon of the perpetrator, which is the most stressful stimulus in situations like this (Tooley, Brigham, Maass, & Bothwell, 1987). This also means that victims tend to forget other details, such as what the perpetrator looked like, which makes eyewitness testimonies less reliable.

While moderate stress levels do have a positive effect on the ability to retrieve a memory, stress can also cause memories to be the source of anxiety (Roozendaal, McEwen, & Chattaji, 2009). As a result of a stressful events, the neurotransmitter noradrenaline is released in the amygdala (Roozendaal, McEwen, & Chattaji, 2009). Noradrenaline is responsible for a better consolidation of stressful experiences. Noradrenaline also mediates the release of other neurotransmitters that play a role in consolidation. If a memory is too stressful, it can result in permanent changes in the amygdala. This can be the cause of post-traumatic stress disorders, PTSD, in which a traumatic event is constantly re-experienced. PTSD is often accompanied with avoidance of stimuli that are related to the traumatic event (Roozendaal, McEwen, & Chattaji, 2009).

MEMORY AND DEPRESSION

People who suffer from depression sometimes have trouble with recalling memories (Kizilbash, Vanderploeg, & Curtiss, 2000). People with depression have more difficulty with recalling new information. If they also experience anxiety, many individuals also experience problems with retention and recall.

Memory can also positively suppress depressive symptoms. In a study by Ramirez, et al. (2015), the researchers artificially activated engram cells that were active during a positive experience. This resulted in higher activity in the hippocampus, amygdala, and nucleus accumbens. The latter plays an important

role in positive memories. In people who suffer from depression, activity in these areas is significantly lower. The activation of the positive memories led to a decrease in stress-related behaviours. This suggests that memory engrams can be useful in therapeutic interventions for depressions.

In a study by Moffitt, Singer, Nelligan, Carlson, & Vyse (1994), depressed and non-depressed participants had to write down a personally significant and emotional memory. They were asked to write down either a positive or a negative memory. Participants who scored high on depression tended to write down more general memories than individuals who scored lower on depression. This effect can be explained because individuals with depression tend to overgeneralise. They have difficulty with remembering or encoding specific positive memories. This overgeneralisation is a state marker, meaning that once people have recovered from their depressive episode, they show less overgeneralisation (Brittlebank, Scott, Mark, Williams, & Ferrier, 1993).

CHANGING MEMORY VALENCE IN RATS

There has not yet been a lot of research on changing negative memories into positive ones in humans but there is some work done in rodents. A study by Redondo et al. (2014) showed that it is possible to alter the emotional component of memories in rats. Their research was based on the idea that the valence of memories is stored in the amygdala and that the hippocampus – the dorsal dental gyrus (DG) specifically – provides contextual information for the memory (Redondo, Kim, & Arons, 2014). For example, if a happy experience occurred in a park, the context (i.e., the park) is encoded in the hippocampus and the valence (i.e., the positivity of the experience) is encoded in the amygdala. Using this distinction, the researchers divided the rats into one group in which the hippocampus was manipulated and another group in which they manipulated the amygdala.

This experiment used optogenetics to artificially manipulate cells. Optogenetics is a method used to artificially manipulate cells (Deisseroth, 2011). The main idea behind optogenetics is that light is used to artificially excite or inhibit the connection between two different neurons. By using a specific form of blue light, neurons can be excited, while yellow light inhibits the neuron. For optogenetics to work properly, neurons are first genetically modified in such a way that they become sensitive for light. This method is mainly used in rodents because it requires genetic modification. This allows for the localisation and labelling of cells that are related to a specific memory or experience.

In the experiment, rats were first placed in either a fear condition or a reward condition. In the fear condition, rats were put into an environment where they heard a tone, while they were shocked. After several trials, the rats were classically conditioned, in such a way that they would freeze when they heard the tone, even if the shock were absent. In the reward condition, the rats interacted with a female mouse, while a tone played. The degree to which the conditioning was successful was measured by the fear response and appetitive response of the rat.

As a second stage of the experiment, the rats in the fear condition were put in the rewarding environment and vice versa. In this phase, the rats did not go through the conditioning process, but they were just in a positive or negative environment. During the second stage, the experimenters activated the firing neurons from the first stage using optogenetics. In half of the rats the amygdala cells were activated and in the other half the hippocampus cells. The manipulation technique was used to find out whether activation of specific cells outside of the original context can change the valence of the original memory (i.e., make a previously negative memory positive and vice versa).

The researchers found that the valence of the memory was indeed switched in the hippocampus group, but not in the amygdala group. This was measured by putting the rats in the first environment. The experimenters, then, measured whether the rats still showed a fearful or an appetitive response. When the hippocampus was stimulated, the rats showed an opposite response to what would be expected based on the conditioning. This means that rats who went through fear conditioning showed an appetitive response in the fearful environment and vice versa.

This means that conditioned responses elicited by the activation of certain cells in the hippocampus can be reversed. If the memory engram is re-associated with a new stimulus with an opposite valence, a previously negative memory can be changed into a positive memory. To make it more concrete, a rat who previously experienced fear in environment A, showed an appetitive response in the same environment, after the experiment. When neurons linked to a negative memory are activated during a pleasant experience, this can change the previous negative memory into a positive one. This can also occur in the opposite direction.

This study can help us to gain an insight on how a memory can be altered. While the memory system in rats works differently from the human memory system, the two do resemble each other to some extent. The rat's memory system is less complex than the human system, which makes it easier to manipulate cells in rats (Axmacher, 2016). While engrams of rats consist of a relatively small number of cells, engrams in humans can consist of up to millions of cells. This means that one single memory is represented by an enormous number of neurons. In rats, only a part of the cells involved with a specific memory need to be activated before the whole memory is activated. If this is also the case in humans, engrams could be activated in a similar way as they are in rodents.

REWARD AND PUNISHMENT

Memories associated with reward and punishment are processed differently in the brain. This has to do with the difference between rewarding and punishment behaviour. There are two areas in the brain that are mainly responsible for this difference: the nucleus accumbens and the centromedial amygdala (Namburi, et al., 2015). The nucleus accumbens plays an important role in intense, positive experiences, like passion and motivation (Salamone, Correa, Mingote, & Weber, 2005). It is also important in addiction and falling in love. The centromedial amygdala, on the other hand, is important in punishment behaviour and conditioned fear. Moreover, rats with centromedial amygdala lesions are less sensitive to rewards than rats without lesions (Kawasaki, Glueck, Annicchiarico, & Papini, 2015).

In the basolateral amygdala, there are different projection pathways. Some cells project onto the nucleus accumbens, these are called NAc projectors. Cells projecting onto the centromedial amygdala are called CeM projectors. If NAc projectors are artificially stimulated, positive reinforcement is strengthened (Namburi, et al., 2015). Positive reinforcement happens, for example, when dogs receive treats when they perform a trick. This works the other way around for CeM projectors; if these cells are stimulated, negative reinforcement is strengthened (Namburi, et al., 2015). Negative reinforcement means that a behaviour is strengthened because there is something removed from the situation. Positive reinforcement can be associated with approach behaviour. Negative reinforcement, on the other hand, is associated with flight behaviour.

This research gives more insight in how rewarding and punishing memories are processed differently. There seem to be different neural structures involved. This might also have consequences when looking at whether memories associated with approach behaviour can be changed into memories associated with flight behaviour. It could be worthwhile, for example, to investigate activating the reward system, while a negative memory is activated.

ENGRAMS IN HUMANS

TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation or TMS is a non-invasive way of brain stimulation (Hallett, 2000). Through using a magnetic field, an electrical current is created at a specific part of the brain. The current that is created can either excite or inhibit that part of the brain. TMS can help with finding how a brain area works exactly without harming the brain. Additionally, TMS is also used in patients suffering from clinical depression to alleviate symptoms.

TMS is mostly used to excite or inhibit parts of the brain that lie directly under the skull. Most of the parts that are important in the formation and retrieval of memories lie deeper into the brain. That does not mean that there are no options for TMS though. It can still be used to indirectly excite or inhibit the hippocampus by targeting another area. In a study by Tambina, Nee, and D'Esposito (2018), the researchers targeted an area in the parietal cortex that is closely related to the hippocampus. Consequently, the function of the hippocampus was enhanced; meaning that certain items were encoded better after manipulation through TMS. This also works for other areas that lie deeper in the brain (Zangen & Hyodo, 2002)

EPILEPSY PATIENTS

Patients suffering from severe forms of epilepsy sometimes undergo brain surgery as a way to alleviate the symptoms (Axmacher, 2016). In patients suffering from epilepsy, memory engrams can be artificially activated (Josselyn, Köhler, & Frankland, 2015). In early studies, electrical stimulation was used to induce memory retrieval (Penfield & Perot, 1963). Nowadays, a technique called deep brain stimulation is used to treat seizures. Electrodes are placed in parts of the brain that can suppress certain epilepsy symptoms. The downside of deep brain stimulation is that it is not used in healthy participants, because the method is very invasive. Deep brain stimulation can only be used when the patient requires brain surgery for another condition.

Another method that can be used in epilepsy patients is implanting cells with microwires (Axmacher, 2016). These microwires can track the activity of individual cells, something that is not possible yet using non-invasive methods. Cells in the hippocampus can be activated, for example, by a specific location or through seeing the picture of a specific person. This corresponds with the findings of engram cells in rodents. One important characteristic of neurons is that a single hippocampal cell can be part of different specific memories. Memory engrams are also a part of a much larger network. A single concept can be represented by up to millions of different neurons.

LOCALISATION OF MEMORY ENGRAMS

Most research in finding memory engrams in humans is done through functional neuroimaging. The most common method of neuro-imagining is Functional Magnetic Resonance Imaging, of fMRI (Gage & Baars, 2018). fMRI measures the oxygen level of blood circulation in the different brain areas, the so-called BOLD level. The idea behind fMRI is that neurons consume oxygen when they are firing, after which they will need oxygenated blood. Brain areas in which many neurons are firing need more blood.

This means that the fMRI signal will go up for that area. The main advantage of fMRI is that the spatial resolution is very high; it is very accurate in locating which parts of the brain are activated. The main downside is that fMRI has a relatively low temporal resolution (Gage & Baars, 2018).

fMRI studies in humans have found that activity patterns that are found during learning are also found during the slow-wave sleep (Josselyn, Köhler, & Frankland, 2015). The level of replaying activity corresponds with how well a memory can be retrieved. If a memory is reactivated in the hippocampus during sleep more often, it is more likely that that memory will be successfully consolidated. The engram of a specific memory can also be activated without contextual or retrieval cues. Furthermore, the ability to recall a certain memory can be predicted by how often a memory was spontaneously activated. The activity pattern of brain areas can be used to detect a specific memory. For every specific event that is consolidated, a different specific activity pattern emerges when the memory is reactivated.

The main problem with the memory engram in humans is that it is not yet possible to localise memory engrams at the cell level, but only at the level of brain regions or networks (Josselyn, Köhler, & Frankland, 2015). It is possible, for example, to artificially induce the retrieval of a random memory through stimulating certain cells, but it is unpredictable which memory will be activated. However, since there is a very large number of cells involved in one single concept that is stored in memory, it might also be possible to define and manipulate engrams at the level of brain regions or networks. The number of cells that are involved in a specific memory can be up to millions (Axmacher, 2016). Every single memory can be characterised by a specific pattern of activity.

HOW CAN A MEMORY BE MANIPULATED?

PROTEIN SYNTHESIS

A relatively new way of regulating emotion is based on the blocking of reconsolidation (Hartley & Phelps, 2010). This relies on the idea that every time a memory is recalled, the memory engram becomes fragile again. This allows for an opportunity to disrupt and change the memory. After retrieval, protein synthesis is necessary for producing new proteins and to complete the reconsolidation. When this cannot happen – because of the injection of a protein synthesis inhibitor for example – the original memory disappears. Research in rats showed that an experimentally induced memory can be erased using this technique (Hartley & Phelps, 2010). The memory cannot be reactivated over time or through using contextual cues, but an inhibitor can only erase one very specific memory. This might complicate erasing memories if there are many different memories. In that case, every memory should be erased separately.

PROPRANOLOL

While protein synthesis inhibitors is not feasible in humans, research has shown that propranolol, a beta blocker used for lowering blood pressure, can block reconsolidation (Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2013). If propranolol is administered immediately after a memory is reactivated, the fear-conditioned memory is consequently not reconsolidated. It is not sure how exactly propranolol blocks the reconsolidation. It might be the case that propranolol receptors in the brain regulate protein synthesis (Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2013). Protein synthesis, in return, regulates long-term memory. This might be very important in treating patients with PTSD, since propranolol can not only block consolidation if it is taken right after a potential traumatic experience takes place, but also when it is administered after a longer period.

BEHAVIOURAL MANIPULATIONS

Apart from pharmacological manipulations, there might also be behavioural manipulations that can prevent reconsolidation. Monfils et al. (2009) designed a study in which rodents went through an extinction training during reconsolidation. After the memory was reactivated in rats, through repeating the tone, the rats went through a period of extinction training. During this period, the conditioned stimulus (i.e., the tone) is repeatedly presented without the unconditioned stimulus (i.e., the shock). When the extinction training occurred shortly after the reactivation of the memory, the rats were less sensitive to the fear conditioning afterwards. The researchers showed that this worked significantly better for extinguishing fear than extinction training without reactivation or extinction training after reactivation.

Extinction training means that the conditioned stimulus is presented without the occurrence of the unconditioned stimulus (Hartley & Phelps, 2010). This results in a decrease in the conditioned response. Someone might, for example, get anxiety when they see cars because they were in a car accident. In this case, seeing the car is the conditioned stimulus, and the car accident the unconditioned stimulus. The conditioned response is the anxiety. When the person is repeatedly confronted with an environment in which they are exposed to a car, the anxiety will slowly decrease.

EYE MOVEMENT REPROCESSING AND DESENSITISATION

Eye Movement Reprocessing and Desensitisation (EMDR) is a therapeutic intervention mainly used for people suffering from post-traumatic stress disorder (PTSD) (Cuijpers, Van Veen, Sijbrandij, Yoder, & Christea, 2020). The goal of EMDR is that traumatic memories can lose some of their emotionality through eye movements. The patient is asked to relive their traumatic memory, while following rapid movements. EMDR is based on the fact that memories become labile during recall (Van den Hout, Eidhof, Verboom, Littel, & Engelhard, 2014). During that time, memories are temporarily "moved back" to the working memory. The idea behind EMDR is that the working memory is taxed with another task, which does not leave enough room for the memory to be reconsolidated as vividly and emotional as before. When a memory is changed during recall, future memory recall has also changed, meaning that when the patient remembers the traumatic event in the future, it is not as intense and emotional as before.

In a study by Van den Hout et al. (2014), researchers examined whether EMDR also works for positive and neutral memories. They asked all participants to write down a neutral memory and an emotional memory. One of the memories was recalled while the working memory was taxed with eye movements and the other was recalled without eye movements. For both positive and negative memories, the emotionality of the memories decreased, while the vividness of the memories remained the same. The neutral memories did not change after EMDR. This suggests that it might be the case that there is something specific about emotional memories that non-emotional memories do not have.

EXPERIMENT PROPOSAL

INTRODUCTION

The research so far has been able to artificially change the valence of a memory in rodents. More specifically, fear behaviour in rats can be changed into approach behaviour and vice versa (Redondo, Kim, & Arons, 2014). This is not yet possible in humans. Before an engram could be manipulated artificially, it would first be necessary to be able to localise the engram precisely. It might also be sufficient to find a smaller number of cells that are associated with a certain memory. In rodent studies, only a part of the cells associated with an engram need to be activated in order for the memory to be reactivated (Redondo, Kim, & Arons, 2014). This might also be the case for humans. In this case, only part of the cells involved in an engram need to be identified before an engram could be activated artificially.

It is also possible to naturally activate a human engram. An engram is activated when the memory that it is associated with, is recalled. It is also possible for humans to recall a memory without artificial interventions. As mentioned before, memories are context-specific, meaning that they can be activated when a person is in a similar context to when the memory was created (Josselyn, Köhler, & Frankland, 2015). After recall, there is a window in which the memory is more fragile, and it is possible for that memory to be altered.

In this section, I will propose several hypotheses that could test whether the valence of a memory can be altered in humans. Redondo et al. (2014) have managed to successfully alter memories in rats by artificially activating cells with negative associations during a positive event. Rats in which memories were successfully altered showed approach behaviour in a situation in which they previously showed fear behaviour. If this is also possible in humans, it might be feasible to alter engram cells of traumatic memories in such a way that it might lose the traumatic value for people. This would be an addition to the mostly behavioural interventions that already out there. These mechanisms focus on extinguishing fear response, whereas this would focus on altering the fear component altogether, which might lead to even stronger results.

Since there are multiple possibilities in which this could be achieved, several different approaches towards this problem will be discussed. First of all, a replication of the experiment by Redondo et al. (2014) on humans will be discussed. Secondly, it might be a possibility to activate the reward system through transcranial magnetic stimulation. Lastly, the idea of activating a negative memory in a positive environment might also change the memory.

IDENTIFICATION OF ENGRAMS

Since memories can be altered even when they are activated naturally, it might not be necessary to locate the cells in an engram to manipulate the memory associated with these cells. However, localising and subsequently being able to control a specific engram might have an advantage, because in this case it would be possible to control one specific memory. Currently, the only method out there that allows for the monitoring of specific cells is through brain surgery. Because of how invasive this method is, it is not

used on healthy patients, which would restrict studies to epilepsy patients who undergo surgery for the treatment of their seizures. Using micro-wires, it is possible to monitor the activity of single cells (Josselyn, Köhler, & Frankland, 2015). In this way, it might be possible to locate a specific engram and to subsequently activate that memory. Using deep brain stimulation, memories could be activated artificially. This would mean that it might be possible to replicate the experiment that was conducted by Redondo et al. (2014) on humans.

Assuming that it is possible to localise and activate a memory engram, research in humans can show whether it is possible to change a negative memory into a positive one. In this section, I will propose how the experiment that originally was conducted on rodents could be replicated with human participants. As mentioned in more detail above, rats were first placed in a fear conditioning environment in this experiment. Afterwards, the rats were placed in a "rewarding" environment during which the engram from before was activated. This was enough to change the original memory into a positive memory. When the rats were placed in the original environment, they behaved similarly to rats that had only been in the reward situation.

In rats, fear conditioning is usually achieved by pairing electrical shocks with loud tones (Redondo, Kim, & Arons, 2014). The extent to which the fear conditioning was successful is measured by how much the rat freezes after hearing the tone without being shocked. The reward condition in this study was created by placing a female mouse in the same environment as the tested rat in combination with the playing of a tone. This led to approach behaviour, which was visible even if the tone played without the presentation of the female mouse.

For practical reasons, there are some changes to be made before the research in rodents could be replicated in humans. This does not mean, however, that it is completely impossible to condition humans. In fear conditioning, it is important to identify the conditioned and unconditioned stimuli and the conditioned response. As mentioned earlier, the unconditioned stimulus (US) is the fear-inducing stimulus and the conditioned stimulus is the stimulus is paired with the unconditioned stimulus to create a conditioned response (CR). Studies in humans often rely on visual conditioned stimuli (CS), such as pictures with different colours or shapes (Lonsdorf, et al., 2017). The degree to which the fear conditioning is successful depends on how salient the CS is. Another possibility is to have a non-neutral CS, such as a picture of a spider or angry face. This can lead to more rapid fear learning. The downside is that there are more individual differences, because not everyone will have the same sensitivity to non-neutral CSs (Lonsdorf, et al., 2017). Because of this downside, it would be preferable to choose for a more neutral CS with the consequence that the fear learning will take longer.

For the unconditioned stimulus (US), there are different possibilities as well. Small pain signals are used most often (Lonsdorf, et al., 2017). This is usually achieved through giving small shocks to the skin. There are also options out there that are less unpleasant, which is even more important when the study is conducted with clinical patients, like epilepsy patients. As described earlier, research in epilepsy could be conducted earlier, because in that case it would be possible to perform an experiment while the patient is in surgery. There are several different auditory stimuli that can also be employed, including

loud noise and screams. The level of the US depends on how strong the individual experiences it. This is normally tested before starting with the experiment.

Besides the fearful environment, the study also created a rewarding environment. For rats, the manipulation was being put in the same environment as a single female rat for two hours (Redondo, Kim, & Arons, 2014). There are different possibilities of how to apply reward conditioning in humans. In one study, appetitive conditioning was used (O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003). Reward conditioning can also be manipulated through other modalities. Pleasant music can, for example, be used to generate a feeling of reward (Blood, Zatorre, Bermudez, & Evans, 1999). If the music is presented together with a visual CS, the feeling of reward can also arise without the presentation of the music.

It is best to use the same modality for both the positive and the negative experience. In this case, there are fewer confounding variables. A study by Rolls et al. (2003) differentiated between pleasant and unpleasant touch. In this study, the pleasant touch was the feeling of soft velvet against the skin of the hand. The unpleasant touch was the feeling of a pointed stylus against the skin. A major advantage of this method is, that it can be applied even if the participant is restricted in how freely they can move. This is the case for participants undergoing deep brain stimulation. Since the participants are in surgery at the time of the experiment, the manipulation should be feasible, even when the participant is lying still.

In the original experiment, rats were divided into two groups, where in one of the groups a negative memory switched to a positive memory and the other way around for the second group. The most interesting finding in replicating such a study with humans would be to see whether it is possible to change a negative memory into a positive one. This has higher practical value, since it might be a solution for many people who suffer from traumatic memories. For this reason, it is more important to focus on the group that underwent a change in memory from negative to positive.

In this experiment, participants would have to be divided into two groups. In one of the groups, the engrams of the fear memory are activated in a rewarding environment. In the other group, the engram is activated in a neutral environment. If the group in the rewarding environment would respond more positively to the reactivation of the engram, this would suggest that it is possible to change a negative memory into a positive one in humans.

TRANSCRANIAL MAGNETIC STIMULATION

Since it is not yet possible to locate a human memory engram, it is also worthwhile to investigate other options concerning changing the valence of a memory. The main principle behind the study in rodents is that a negative memory is reactivated while the rat undergoes a positive experience. This principle could, theoretically, also be applied to humans without artificially reactivating a memory. A memory engram can also be naturally reactivated when it is recalled. Retrieval can be guided using retrieval cues (Josselyn, Köhler, & Frankland, 2015). After retrieval, there is a window of time in which the memory is susceptible to changes. This window could be used to test whether negative memories could theoretically be changed to positive memories.

One way of testing this could be by activating the reward system while recalling a negative memory. The reward system is associated with positive memories and could have a similar effect to being in a positive environment. The idea would be similar to the experiment that was conducted by Redondo et al. (2014). In the experiment, the rat's negative memory was activated while the rat was in a positive environment. This relies on the same principle of the activation of a negative memory while experiencing something positive.

The most important area in the reward system is the nucleus accumbens. This area is active, for example, when a person experiences passion and longing (Salamone, Correa, Mingote, & Weber, 2005). Activity in this area is also systematically lower in individuals who suffer from depression. People who suffer from depression generally have a lower feeling of reward, which leads to a range of different symptoms (Kizilbash, Vanderploeg, & Curtiss, 2000). There are different treatment forms for depression that are reliant on activating the reward system. One way of achieving this is through using transcranial magnetic stimulation (TMS). TMS is a non-invasive method that can be used to activate or inhibit a brain area through a magnetic field around the skull (Hallett, 2000). TMS can only directly be applied to areas that lie directly under the skull.

TMS can also be applied as a form of treatment for individuals suffering from depression (Zangen & Hyodo, 2002). In this treatment, part of the frontal lobes is activated. This leads to higher activity in the nucleus accumbens, important in the reward system. The nucleus accumbens, in turn, releases higher levels of dopamine. A release of dopamine in the nucleus accumbens is associated with a feeling of reward (Zangen & Hyodo, 2002).

It might be possible to use this method to test whether negative memories can change into positive memories. If a person is asked to recall a negative, or fearful, memory and undergoes transcranial magnetic stimulation afterwards, during the window in which the memory is fragile, it might be possible to alter the memory. In this case, the person experiences a feeling of reward while remembering a negative memory, which could have similar effects to the study that was conducted in rats. To test whether a memory was manipulated successfully, it is important to compare the reaction to the memory before and after manipulation. In rodents, this can be done, for example, by the extent to which a rat shows freezing or approach behaviour after being put in the conditioned environment. In humans, this can be measured through eye blinks, pupil dilations or heart rates (Lonsdorf, et al., 2017).

This experiment could be conducted by conditioning participants with fear. This could be achieved in a manner that is similar to the one mentioned above. After that, participants would be divided into two groups in which one of the groups reactivates the fear conditioning memory while undergoing TMS. In the other group, the memory could be reactivated without TMS. A difference between the two groups would indicate that memories could be altered with this manipulation. More specifically, if the fear reaction would disappear completely and be replaced with approach behaviour, this would show that it is possible to change the valence of a memory in humans.

RECALLING A NEGATIVE MEMORY IN A POSITIVE ENVIRONMENT

A more general replication of the study by Redondo et al. (2014) could be achieved by recalling a negative memory in a positive environment. A positive environment could be achieved by putting participants in an environment in which they experience pleasant music or when they are able to eat pleasant foods. If they then recalled a negative memory in that situation, this would create a similar situation to the study by Redondo et al. (2014). Instead of artificially activating the negative memory, the memory would then be recalled through retrieval cues. After successful fear conditioning, for example, the memory is recalled when the unconditioned stimulus is presented without the conditioned stimulus.

This could be achieved when participants are presented with a fear conditioning situation in which a tone is linked to an unpleasant stimulus, such a small electrical shock. If, consequently, the tone is presented as a retrieval cue in a different, pleasant environment, it could be tested whether this influences the original memory experience. If there is an effect on the original memory, the participant would react differently when they would be put in the original environment again, and when they are presented with the tone.

DISCUSSION

Based on the literature that is already out there, I believe that it would eventually be possible to manipulate an existing human engram in such a way that the valence of the memory changes. It is proven to be possible to manipulate a memory in rodents. Cells in the hippocampus related to a negative memory that are artificially activated during a positive experience can help with this. In rats, a technique was used which allowed researchers to label certain cells that are active during a specific experience. It is also possible to reactivate those cells in rats.

In humans, this is not possible yet. Especially in healthy participants, where non-invasive methods must be used, it is not possible to do perform a study in which a group of cells is monitored and manipulated. A study with patients who are undergoing brain surgery would be a possible outcome because it is possible to monitor the activity of single cells in these types of experiments. There are different methods that might be useful for monitoring and localising engrams. In epilepsy patients, there is the possibility of using microwires to monitor the activity of single cells. In this way, it would be possible to monitor whether a cell is a part of a group of engram cells. Alternatively, the hypothesis could be tested using behavioural manipulations to reactivate a negative memory in a positive environment.

This research is relevant because it might help people who suffer from traumatic or extremely negative memories. If techniques like this one can be developed, there would be a wider range of possibilities that can be used to help people with PTSD and related symptoms. Extinguishing fear behaviour is something that is widely used within PTSD treatments but changing the fear behaviour into approach behaviour has not been researched in humans yet. This might lead to better results than fear extinguishing. There is also a limitation here. Fear reactions can also be adaptive and should not always be erased. It is important that this type of research, if available, should only be used in cases of maladaptive fear reactions.

Furthermore, this type of research can also be used in other clinical groups of patients, such as patients suffering from anxiety or depressive disorders. Through creating more positive associations with memories, this might lead to more approach behaviour instead of fear behaviour in anxiety patients. Avoidance behaviour is an important symptom in anxiety patients, and it might be alleviated when negative memories can be altered into positive memories. In depressive disorders, activating the reward system using TMS is already used as an intervention. This effect could be strengthened if negative memories are recalled during this manipulation.

In conclusion, engram research is coming closer and closer to the moment where we can manipulate the cells of which a memory consists. As proven to be possible in rats, it might then also a possibility to change a negative memory into a positive memory or vice versa. Alternative behavioural manipulations are also worthwhile to investigate.

REFERENCES

Axmacher, N. (2016). In search of the human engram. *e-Neuroforum, 7*, 31-36.

Besnard, A., Caboche, J., & Laroche, S. (2012). Reconsolidation of memory: a decade of debate. *Progress in neurobiology, 99*(1), 61-80.

Blood, A. J., Zatorre, R. J., Bermudez, P., & Evans, A. C. (1999). Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. *Nature neuroscience, 2*(4), 382-387.

Bocchio, M., Nabavi, S., & Capogna, M. (2017). Synaptic plasticity, engrams, and network oscillations in amydgala circuits for storage and retrieval of emotional memories. *Neuron, 94*(4), 731-743.

Brittlebank, A. D., Scott, J., Mark, J., Williams, G., & Ferrier, I. N. (1993). Autobiographical memory in depression: state or trait marker? *The British Journal of Psychiatry, 162*(1), 118-121.

Buchanan, T., & Adolphs, R. (2004). The Neuroanatomy of Emotional Memory in Humans. In D. Reisberg, & P. Hertel, *Memory and Emotion* (pp. 43-68). Oxford: Oxford University Press.

Cuijpers, P., Van Veen, S., Sijbrandij, M., Yoder, W., & Christea, I. (2020). Eye movement desensitization and reprocessing for mental health problems: a systematic review at meta-analysis. *Cognitive Behaviour Therapy*, 1-16.

Deisseroth, K. (2011). Optogenetics. *Nature methods, 8*(1), 26-29.

Diamond, D., Park, C., & Woodson, J. (2004). Stress generates emotional memories and retrograde amnesia by inducing an endogenous form of hippocampal LTP. *Hippocampus, 14*(3), 281-291.

Eichenbaum, H. (2016). Still searching for the engram. *Learning & behavior, 44*(3), 209-222.

Eldridge, L., Knowlton, B., Furmanski, C., Bookheimer, S., & Engel, S. (2000). Remembering episodes: a selective role for the hippocampus during retrieval. *Nature neuroscience, 3*(11), 1149-1152.

Engert, F., & Bonhoeffer, T. (1997). Synapse specificity of long-term potentiation breaks down at short distances. *Nature, 388*(6639), 279-284.

Fink, G., Markowitsch, H., Reinkemeier, M., Bruckbauer, T., Kessler, J., & Heiss, W. (1996). Cerebral representation of one's own past, neural networks invovled in autobiographical memory. *Journal of Neuroscience, 16*, 4275-4282.

Gage, N., & Baars, B. (2018). Observing the Brain. In *Fundamentals of Cognitive Neuroscience: A Beginner's Guide* (pp. 53-97). Oxford: Elsevier.

Goldstein, B., & Van Hooff, J. (2008). Long-Term Memory: Basic Principles. In *Cognitive psychology: Connecting mind, research and everyday experience* (pp. 176-234). Wadsworth Cengage Learning.

Goldstein, B., & Van Hooff, J. (2008). Short-Term and Working Memory. In *Cognitive psychology: Connecting mind, research and everyday experience* (pp. 135-175). Wadsworth Cengage Learning.

Hallett, M. (2000). Transcranial magnetic stimulation and the human brain. *Nature, 406*(6792), 147-150.

Hartley, C., & Phelps, E. (2010). Changing fear: the neurocircuitry of emotion regulation. *Neuropsychopharmacology, 35*(1), 136-146.

Hasselmo, M. (1999). Neuromodulation: acetylcholine and memory consolidation. *Trends in cognitive sciences, 3*(9), 351-359.

Janak, P. H., & Tye, K. M. (2015). From circuits to behaviour in the amygdala. *Nature, 517*(7534), 284-292.

Josselyn, S., & Tonegawa, S. (2020). Memory engrams: Recalling the past and imagining the future. *Science, 367*(6473).

Josselyn, S., Köhler, S., & Frankland, P. (2015). Finding the engram. *Nature Reviews Neuroscience, 16*(9), 521-534.

Kawasaki, K., Glueck, A., Annicchiarico, I., & Papini, M. (2015). Function of the centromedial amygdala in reward devaluation and open-field activity. *Neuroscience, 303*, 73-81.

Kitamura, T., Ogawa, S., Roy, D., Okuyama, T., Morrissey, M., Smith, L., . . . Tonegawa, S. (2017). Engrams and Circuits Crucial for Systems Consoldiation of a Memory. *Science, 356*(6333), 73-78.

Kizilbash, A., Vanderploeg, R., & Curtiss, G. (2000). The effects of depression and anxiety on memory performance. *Archives of clinical neuropsychology, 17*(1), 57-67.

Loftus, E., & Zanni, G. (1975). Eyewitness testimony: The influence of the wording of a question. *Bulletin of the Psychonomic Society, 5*(1), 86-88.

Lonsdorf, T., Menz, M., Andreatta, M., Fullana, M., Golkar, A., Haaker, J., . . . Merz, C. (2017). Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. *Neuroscience and Biobehavioral Reviews, 77*, 247-285.

Maratos, E., & Rugg, M. (2001). Electrophysiological correlates of the retrieval of emotional and non-emotional contex. *Journal of Cognitive Neuroscience, 13*, 877-891.

McGaugh, J. L. (2000). Memory--a century of consolidation. *Science, 287*(5451), 248-251.

Moffitt, K., Singer, J., Nelligan, D., Carlson, M., & Vyse, S. (1994). Depression and memory narrative type. *Journal of Abnormal Psychology, 103*(3), 581-583.

Monfils, M., Cowansage, K., Klann, E., & LeDoux, J. (2009). Extinction-reconsolidation boundaries: key to persistent attenuation of fear memories. *Science, 324*, 951-955.

Myhrer, T. (2003). Neurotransmitter systems involved in learning and memory in the rat: a meta-analysis based on studies of four behavioral tasks. Brain Research Reviews. *Brain Research Reviews, 41*(2-3), 268-287.

Namburi, P., Beyeler, A., Yorozu, S., Calhoon, G., Halbert, S., Wichmann, R., . . . Tye, K. (2015). A Circuit Mechanism for Differentiating Positive and Negative Associations. *Nature, 520*(7549), 675-678.

O'Doherty, J., Dayan, D., Friston, K., Critchley, H., & Dolan, R. (2003). Temporal difference models and reward-related learning in the human brain. *Neuron, 38*(2), 329-337.

Penfield, W., & Perot, P. (1963). The brain's record of auditory and visual experience. A final summary discussion. *Brain, 86*, 595-696.

Pessoa, L. (2018a). Understanding emotion with brain networks. *Current opinion in behavioural sciences*, 19-25.

Pessoa, L. (2018b). Emotion and the interactive brain: Insights form comparative neuroanatymy and complex systems. *Emotion Review, 10*(3), 204-216.

Ramirez, S., Liu, X., MacDonald, C., Moffa, A., Zhou, J., Redondo, R., & Tonegawa, S. (2015). Activating positive memory engrams suppresses deppression-like behaviour. *Nature, 522*(7556), 335-339.

Redondo, R., Kim, J., & Arons, A. (2014). Bidirectional switch of the valence associated with a hippocampal contextual memory engram. *Nature, 513*(7518), 426-430.

Rolls, E., O'Doherty, J., Kringelbach, M., Francis, S., Bowtell, R., & McGlone, F. (2003). Representations of pleasant and painful touch in the human orbitofrontal and cingulate cortices. *Cerebral Cortex, 13*(3), 308-317.

Roozendaal, B., McEwen, B., & Chattaji, S. (2009). Stress, memory and the amygdala. *Nature Reviews Neuroscience, 10*(6), 423-433.

Ryan, T., Roy, D., Pignatelli, M., Arons, A., & Tonegawa, S. (2015). Engram cells retain memory under retrograde amnesia. *Science, 348*(6238), 1007-1013.

Salamone, J., Correa, M., Mingote, S., & Weber, S. (2005). Beyond the reward hypothesis: alternative functions of nucleus accumbens dopamine. Current opinion in pharmacology. *Current opinion in pharmacology, 5*(1), 34-41.

Sasikumar, N. (2016). Influence of neurotransmitters on memory and learning. *Conflux: Journal of Education, 3*(9), 2-8.

Tambini, A., Nee, D. E., & D'Esposito, M. (2018). Hippocampal-targeted theta-burst stimulation enhances associative memory formation. *Journal of cognitive neuroscience, 30*(10), 1452-1472.

Tooley, V., Brigham, J., Maass, A., & Bothwell, R. (1987). Facial Recognition: Weapon Effect and Attentional Focus 1. *Journal of Applied Social Psychology, 17*(10), 845-859.

Van den Hout, M., Eidhof, M., Verboom, J., Littel, M., & Engelhard, I. (2014). Blurring of emotional and non-emotional memories by taxing working memory during recall. *Cognition and emotion, 28*(4), 717-727.

Yehuda, R. (2002). Post-traumatic stress disorder. *New England journal of medicine, 346*(2), 108-114.

Zangen, A., & Hyodo, K. (2002). Transcranial magnetic stimulation induces increases in extracellular levels of dopamine and glutamate in the nucleus accumbens. *Neuroreport, 13*(18), 2401-2405.