

Manipulating Hippocampus-dependent Memories: To Enhance, Delete or Incept?

Hugo J. Spiers*, William de Cothi and Daniel Bendor*

Institute of Behavioural Neuroscience, Department of Experimental Psychology, Division of Psychology and Language Sciences, 26 Bedford Way, University College London, London, WC1H 0AP, UK.

* To whom correspondence should be addressed. E-mail: h.spiers@ucl.ac.uk and d.bendor@ucl.ac.uk. The authors contributed equally to this review.

“In a sense, he thought, all we consist of is memories. Our personalities are constructed from memories, our lives are organized around memories, our cultures are built upon the foundation of shared memories that we call history and science. But now to give up a memory, to give up knowledge, to give up the past... His entire being rebelled against the idea of forgetting.”, *Sphere*, Michael Crichton

In his novel *Sphere*, Michael Crichton’s protagonists are faced with the dilemma of whether or not to wipe their memories in order to save others from danger. The lead character, Harry, realises in this moment just how important his memories are to him. Science fiction has continually played with memory enhancement, memory erasure and memory implantation (inception) (see Groes et al., 2016). Recent years have seen science ‘fiction’ translate to science ‘reality’.

The capacity to manipulate memories offers the potential for huge benefits. In the medical domain, being able to treat patients with memory problems such as Alzheimer’s dementia by enhancing their memory carries the possibility for treating their catastrophic memory loss problems. While for such patients memory enhancement is helpful, for others memory removal may be needed. Patients suffering from post-traumatic stress disorder (PTSD), phobias, or anxiety disorders suffer from memory problems that may be elevated by dampening memory retrieval. Weighed against these potential benefits is the dark side of memory manipulation. Over the decades films have provided a continual warning about the dangers of unbridled meddling with memories (see Appendix). With the rise of new technologies a number of authors have provided careful consideration of the ethics surrounding memory manipulation (Liao and Sandberg, 2008; Mohamed and Sahakian, 2012; Ragan et al., 2013). Despite the need for caution, research in this domain continues apace.

In this chapter we provide an overview of recent research on memory manipulation. This review extends a recent review on this topic (Spiers and Bendor 2014). We will cover studies that manipulate memories for which the hippocampus is thought to be required, including those defined as spatial, episodic, relational, or declarative (Eichenbaum, 2004; Moscovitch et al., 2006; Squire et al., 2004; Spiers 2012). Psychologists have studied memory manipulation through stimuli at length (e.g. Loftus and Palmer 1974). Here we focus on memory manipulation using invasive interventions or with cuing during sleep states. In table 1 we summarise each of the main methods currently used to target memory, which include: optogenetics, chemogenetic tools, transcranial stimulation,

deepbrain stimulation and pharmacological agents. We will also discuss results arising from recording neural activity during memory manipulation, giving an insight into the mechanisms by which the intervention may affect memory (see e.g. Bendor and Wilson 2012; Hauner et al. 2013).

Table 1: A brief summary of the main methods covered in this review that are currently used to manipulate memories.

| | |
|--|---|
| Transcranial stimulation | A magnetic field generator is held externally to the head and used to stimulate brain tissue. The magnetic field passes through the skull and electromagnetically induces small, electrical currents in the regions of the brain that are within the vicinity of the field. |
| Deep brain stimulation | Electrodes are surgically implanted into the brain so that small electric currents can stimulate targeted brain areas via a battery pack (called a neurostimulator). |
| Optogenetics | Using light to stimulate <i>in vivo</i> neurons that have been genetically modified to express light-gated ion channels. |
| Designer receptors exclusively activated by designer drugs (DREADDs) | A chemogenetic tool that utilises G-protein-coupled-receptors to achieve spatiotemporal control over neural stimulation. A 'designer drug' (such as Clozapine-N-Oxide) is used stimulate neurons expressing a 'designer receptor' (such as hM ₃ D _q). |
| Propranolol | A medication mainly used to treat various cardiovascular conditions. It is being investigated as a potential treatment for post-traumatic stress disorder and phobias as it is thought it may block the reconsolidation of fear memories (Brunet, Poudjia, et al., 2011; Kindt et al., 2009). |

Improving memory

Much like strength is an asset for physical activities, mental tasks are facilitated by having a better memory. While generally not recommend due to the health-related side-effects, drugs such as steroids can be used to artificially accelerate the process of adding muscle tone. Is there the equivalent of "mental steroids", that can be used to artificially improve your memory?

While several putative "cognitive enhancers" have in fact been developed (e.g. Kaplan and Moore, 2011; Rodríguez et al., 2013), there is simply no substitute for our brain's natural approach to memory enhancement - a good night of sleep. During sleep, memories are normally consolidated, a process whereby labile memory traces are strengthened for long-term storage in memory (Stickgold and Walker 2013, Frankland and Bontempi, 2005; Squire and Alvarez, 1995). Thus, through this process the brain sifts through what is to be retained and sheds the memory traces that are less behaviourally or motivationally useful. In particular, non-REM sleep plays a critical role in the consolidation of hippocampus-dependent memories, such as word pairings and spatial associations (Dudai, 2004; Frankland and Bontempi, 2005; Squire and Alvarez, 1995, Diekelmann and Born 2012). While there are clear benefits from a good night of

sleep, manipulations that have the potential to make this process more efficient and specific memories could theoretically lead to further memory enhancement.

One strategy for doing this is to manipulate a number of different “brain waves”, including slow wave oscillations and thalamocortical spindles, that occur only during non-REM sleep (Buzsaki 2009). Slow wave oscillations are large amplitude, low frequency (<1 Hz) variations in the local field potential (LFP) and are a by-product of neocortical up and down states (Buzsaki et al. 2012). Thalamocortical spindles are brief oscillations in the thalamocortical pathway (7-14 Hz) - generated by the thalamic reticular nucleus (Steriade et al. 1993). Since spindles and slow-wave oscillations are thought to be critical for memory consolidation, boosting either their quantity or amplitude during non-REM sleep could provide an avenue to strengthening memory. In order to boost slow wave oscillations, Marshall and colleagues applied a slow time-varying transcranial stimulation (0.75 Hz) to the frontal cortex of sleeping human subjects (Marshall et al 2006). One unexpected effect of the low frequency transcranial stimulation was an increase in spindle power. Following training on a hippocampus-dependent task involving word-pair associations, subjects went to sleep and received either transcranial stimulation or sham stimulation as a control. Once the subjects had awoken, those that had received the transcranial stimulation performed better on the task than the control subjects. Since both slow-wave oscillations and spindles were affected in this experiment, the underlying mechanism (i.e. which type of oscillation) responsible for this memory enhancement is still unclear. Optogenetics may provide an approach for disambiguating the roles of slow wave oscillations and spindles during memory consolidation. Using optogenetic techniques, Halassa and colleagues artificially generated thalamocortical spindles in rodents (Halassa et al. 2011). However, whether optogenetically boosting spindle production during sleep leads to better memory consolidation has not yet been demonstrated, nor is optogenetics currently viable for human subjects.

Another type of oscillation that is observed during non-REM sleep is the sharp-wave ripple; a brief, high frequency (140-220 Hz) oscillation generated within the hippocampal complex that co-occurs with a large “sharp wave” deflection in the LFP. Sharp-wave ripples also have been observed to co-occur with the cortico-thalamic spindle oscillations (Siapas and Wilson 1998, Sirota et al. 2003).. During sharp-wave ripples, sequential neural patterns linked to a previous behavioural experience reactivate spontaneously in both the hippocampus and neocortex in a phenomenon commonly referred to as “replay” (Wilson and McNaughton 1994, Lee and Wilson 2002, Ji and Wilson 2006). Replay events are a neural memory trace of a previous experience and by replaying these memory traces repeatedly, the brain could reinforce and gradually consolidate memories. Sharp-wave ripples can be suppressed by using the preceding sharp wave signal to trigger stimulation of the ventral hippocampal commissure. This disruption in replay activity leads to a memory deficit (Girardeau et al 2009, Ego-Stengel and Wilson 2010), suggesting that memory consolidation requires hippocampal replay (or at least sharp-wave ripples). If memory consolidation depends on hippocampal sharp-wave ripples and replay, can these be manipulated to enhance memories? One approach of modifying what is replayed during a sharp-wave ripple event is to use Targeted Memory Reactivation (TMR); where a sensory cue that has previously been paired with a behavioural task is repeatedly presented to a sleeping subject. For example, after rats have received a training session for an auditory-spatial association task, playing a task-related sound cue during non-REM sleep will bias replay events towards the spatial locations associated with that cue (Bendor and Wilson 2012). Therefore, biasing replay

towards reactivating a specific memory in turn strengthens the consolidation of that memory. In both rodents and humans, the presentation of task related cues during non-REM sleep improves performance in a post-nap test, compared to control conditions in which no cue is presented (Barnes and Wilson 2014, Rasch et al. 2007, Rudoy et al. 2009, Diekelmann et al. 2011, Rolls et al. 2013). This method of targeted memory reactivation (Oudiette and Paller 2013) is specific to non-REM sleep and presenting task related cues during either the awake state or REM sleep does not provide any improvement in memory consolidation (Rasch et al. 2007, Diekelmann et al. 2011).

Rather than directly targeting the sensory component of a memory with a cue, a second strategy for modifying memories during sleep is to target the emotional valence of an experience. For mice performing a spatial task, optogenetic stimulation of the Ventral Tegmental Area (VTA), a reward center in the brain, results in enhanced sleep replay activity and improved subsequent performance of the task (McNamara et al. 2014). Meanwhile, when electrical stimulation of the VTA in rats is precisely timed to the reactivation of a single hippocampal place cell, it results in a new place preference for the rat matching the neuron's place field (de Lavilleon et al. 2015). Thus stimulation of the VTA can be used to artificially manipulate the valence of an experience during behaviour, or of a reactivated experience during sleep, leading to an enhanced memory.

While the above examples all take advantage of the brain during non-REM sleep, recent studies have shown memory enhancement can also be achieved during wakefulness. One such approach is deep brain stimulation (DBS), where electrical current is applied to the nuclei or fibre tracks of targeted brain structures via surgically implanted electrodes. This approach has been used in multiple applications, including the treatment of Parkinson's disease, depression, severe dementias and obesity. More recently, DBS of the fornix and hypothalamus has been reported to enhance associative and episodic memory recollection (Hamani et al., 2008), as well as slowing down the rate of cognitive decline in patients with Alzheimer's disease (Laxton et al., 2010). Furthermore, DBS of the entorhinal cortex has been shown to improve spatial memory (Suthana et al., 2012). While DBS may provide a route to memory enhancement, a less invasive alternative could be high-frequency, repetitive transcranial magnetic stimulation (rTMS). Using rTMS to target an area of the lateral parietal cortex with strong connectivity to the hippocampus, Wang and colleagues observed a long-lasting improvement in patients' performance of an associative memory task (Wang et al. 2014), with effects lasting to 15 days (Wang and Voss, 2015).

To summarise, brain stimulation and targeted memory reactivation are two different approaches that have been used to enhance the consolidation process of hippocampus-dependent memories. It is worth noting that while statistically significant, these effects typically mild (~10% improvement). Manipulating coordinated brain rhythms (e.g. ripple-spindle interactions) and more precisely targeting the neural circuits storing a particular memory (Liu et al 2012) may strengthen memory consolidation even further.

Removing unwanted memories

Not all memories are helpful. Some memories we might want to forget. The lead characters in the film *The Eternal Sunshine of the Spotless Mind* take advantage of a new technology that can delete selected autobiographical memories from their brain. They use this to forget their unhappy relationship, however the technology turns out to

be too good to be true and they face the problem of piecing their memories together. Such technology does not currently exist, and based on current evidence seems unlikely to work. While frontotemporal dementia can give rise to amnesia for personally known individuals (Thompson et al., 2004), it is highly unlikely that it would be possible to selectively erase all the memories associated with a specific person. This is because semantic memories appear to be widely distributed in the neocortex (Martin and Chao, 2001; McClelland and Rogers 2003). By contrast, editing hippocampus-dependent memories for a single event or learned association is not so inconceivable. Indeed, rather than something to be feared, memory removal may prove helpful in the treatment of phobias, PTSD and anxiety disorders.

While there appear to be specific endogenous mechanisms in the brain for degrading memories (Anderson et al. 2004; Frankland, Köhler, & Josselyn, 2013; Hardt, Nader, & Nade, 2013; Hulbert et al. 2016), the search for drugs that can aid this process has been topic of recent interest. Pharmacological treatment of the persistent involuntary memory retrieval that accompanies PTSD has been explored in numerous studies (see e.g. Steckler and Risbrough, 2012; de Kleine, Rothbaum, & van Minnen, 2013 for review). The unwanted memory retrieval in PTSD is highly disruptive to the patient's health. They may suffer distraction at work from involuntary flash backs and 'night terrors' while sleeping. While psychological interventions have shown impressive advancement in recent years, attempts to treat the condition with drugs has been on the rise. In both clinical and laboratory settings, a wide variety of pharmacological agents have explored, with particular emphasis on disrupting fear-related memories (Kaplan & Moore, 2011). These have focused on glucocorticoid (e.g. (de Bitencourt, Pamplona, & Takahashi, 2013), glutamatergic (Kuriyama, Honma, Yoshiike, & Kim, 2013), GABAergic (Rodríguez et al., 2013) adrenergic (Kindt, Soeter, & Vervliet, 2009), cannabinoid (Rabinak et al., 2013), serotonergic (Zhang et al., 2013) and glycine (File, Fluck, & Fernandes, 1999) receptors.

In animal models the study of memory manipulation has predominately focused on Pavlovian fear conditioning in rodents, in which an electrical shock is delivered through the floor of the test cage. The dominance of this approach is due to the rapid memory formation, and the robustness of the expression of this memory in the form of freezing behaviour. 'Auditory fear conditioning' involves initial exposure to the repeated pairings of an electrical shock with a neutral tone. With time, the tone alone evokes a fear memory revealed in observed freezing behaviour (Maren 2001). In 'contextual fear conditioning' the animal is exposed to a novel environment in which it receives one or more electric shocks, eliciting a learned association between the environmental context and the potential for more shocks (Kim and Fanselow, 1992). Recent contextual fear memories can be suppressed by hippocampal inactivation, however this effect is not specific to a single memory (Varela et al. 2016). However, repeated exposure to the tone or context alone leads to a natural reduction in freezing, suggesting a weakening of the memory. This is referred to as extinction. When fibroblast growth factor 2 (an agent affecting neural cell development and neurogenesis) is infused into the amygdala immediately after extinction, it strongly increases the likelihood that the fear memory will not re-surface (Graham and Richardson, 2011). It has been demonstrated that the extinction of conditioned fear memories can be boosted via reactivation of the memories during non-REM sleep. For example, Hauner and colleagues conditioned humans to expect a shock when viewing certain faces, where the presentation of the faces associated with the shocks was also paired with certain odours. Subsequently, during non-REM sleep subjects were re-exposed to the odours associated with half of the

feared faces. After sleep and during fMRI, conditioned responses to the faces associated with the odours that were represented during sleep were ameliorated in comparison to the faces paired with odours that were not (Hauner et al. 2013). This effect was observed in a reduced BOLD signal in the hippocampus, as well as a reorganisation of activity patterns in the amygdala when pre- and post- sleep conditioning periods were compared. Although these results might appear to go against the memory-enhancing effects of cued-reactivation during non-REM sleep (Rasch et al. 2007, Rudoy et al. 2009, Rolls et al. 2013), the extinction of a fear memory is not necessarily caused by memory removal. Contrary, it is likely that extinction involves the active suppression of a still intact fear memory by regions of the brain distinct from where the original fear memory is stored (Milad and Quirk 2002). Furthermore, recent work by Schriener and colleagues has shown that the memory benefits of cued reactivation during sleep are lost if the memory cue is immediately followed by other auditory stimulation. Sleeping patients were presented with reactivation cues in the form of Dutch vocabulary, immediately followed by either a correct or incorrect translation into German vocabulary (mother tongue), or a neutral tone. The reactivation effect caused by the initial cue was diminished by the subsequent auditory stimulus, and this was also observed via EEG as the disruption of the neural oscillations associated with learning (Schriener et al., 2015).

Applying drugs or selective cueing during sleep provides one means of disrupting memories, another approach is to manipulate the brain at a much later point in time, potentially many weeks later. Memories are thought to require restabilising after reactivation, a process known as reconsolidation (Misanin et al., 1968; Sara, 2010; Dudai 2004). In an influential study by Nader and colleagues, an infusion of protein synthesis inhibitors was found to disrupt fear conditioned memories when applied during periods following the reactivation of the memory (Nader et al 2000). Oral application of the adrenergic modulator propranolol has been used to study reconsolidation in humans, with an emphasis on preventing the reactivation of fear conditioned memories (Brunet, Poundja, et al., 2011; Kindt et al., 2009). It is thought that propranolol is able to block the reconsolidation of fear memories, providing a potential treatment for PTSD and phobias. However, because propranolol must be administered before the reactivation to have an effect, there has been some debate as to whether reconsolidation processes have been specifically targeted (Brunet, Ashbaugh, et al., 2011) or not (Schiller & Phelps, 2011).

The study of long-term potentiation (LTP) has been important for research on memory manipulation. LTP is an activity-dependent, persistent form of synaptic plasticity and provides a key model for memory storage at the cellular level (Bliss and Collingridge 1993, Malenka and Bear 2004). LTP is a complex topic beyond the scope of this review, but in a simplified model it is thought synapses that have been active during an experience become strengthened to form a memory of that experience. Whether the memory persists depends on the continued maintenance of LTP in the relevant synapses. Prior work has suggested that persistent phosphorylation by PKM ζ (protein kinase M zeta) is needed for this maintenance (Ling et al. 2002). An injection of synthetic ζ -pseudosubstrate inhibitory peptide (ZIP) to the hippocampus inhibits PKM ζ , and consequently causes disruption to LTP (Serrano et al. 2005). One day after rats have been trained in an active place avoidance task, specific injection of ZIP into their hippocampus disrupts their performance (Pastalkova et al. 2006). Furthermore, injection of ZIP at different neuroanatomical sites can also help to delete other memory types; deletion of a taste-aversion memory stored in the insula can be achieved by ZIP injection to the insula (Shema et al. 2007). Another approach to disrupting PKM ζ has been the

lentivirus-induced overexpression of a dominant-negative PKM ζ mutation in insular cortex. This also blocks taste-aversion memory (Shema et al. 2011). Interestingly, enhancement of taste aversion can be achieved by overexpression of PKM ζ in the insular cortex (using the same lentiviral approach) (Shema et al. 2011). However, recent evidence suggests that the relationship between ZIP, PKM ζ and LTP maintenance may be more complicated than previously thought. If PKM ζ was essential for memory, then transgenic knockout mice lacking PKM ζ should have impaired memory function, but they do not (Volk et al. 2013, Lee et al. 2013). Since ZIP is still effective in erasing memories in PKM ζ null mice, ZIP does not need PKM ζ to function and kinases other than PKM ζ may be crucial for LTP maintenance. Indeed, a recent study found that an enzyme closely related to PKM ζ , named PKC ι/λ (protein kinase C iota/lambda), substitutes for PKM ζ in the transgenic knockout mice (Tsokas et al. 2016) and is similarly inhibited by ZIP but at higher concentrations (Ren et al., 2013). Additionally, another recent explanation for how ZIP disrupts memories is that ZIP triggers cell death in hippocampal cells (Sadeh et al., 2015). However it should be noted, Sadeh and colleagues reported the majority of these cell deaths at ZIP concentrations far higher than the doses often used to impair memory. As well as this, similar cell deaths were reported for the same concentrations of scrambled ZIP (scr-ZIP); a control peptide known to not affect long-term memory retention (Pastalkova et al. 2006, Shema et al. 2007).

Incepting Memories

In the movie *The Matrix* (see Appendix), Neo has the knowledge of kung fu “downloaded” directly into his brain. How close are we to artificially creating or “incepting” new memories into our brain? Like the sleep-specific manipulations discussed previously that can be used to enhance memories, similar approaches can be used to artificially create new memories. One approach used by Arzi and colleagues was to present paired auditory-olfactory cues (e.g. a high frequency tone with an unpleasant odour) to human subjects while they were sleeping (Arzi et al. 2012). Because larger sniff volumes are evoked by pleasant odours than unpleasant odours, the sniff volume when a sound is presented in the absence of an odour provides a proxy for the expectation of the odour (that is normally paired to the sound). After these auditory-olfactory pairings were conditioned during a pre-test, non-REM sleep, Arzi and colleagues observed that sounds associated with pleasant odours had larger sniff volumes than sounds associated with unpleasant odours. The results provide a new method for unconsciously storing new memories, albeit limited to associations between sensory cues.

Next-generation molecular-genetic methods are now being used to more directly target and manipulate the neurons encoding memories - referred to as memory engram cells. In a c-Fos-tTA transgenic mouse, the tetracycline transactivator (tTA) is under the control of the immediate early gene c-Fos, which in turn is driven by recent neural activity. Additionally, the presence of doxycycline inhibits the binding of tTA to its target. Thus, the combination of c-Fos and tTA allows the spatial and temporal restriction of gene expression to be limited to the neural circuit involved in encoding a single recent experience. Using the strategy of cFos/tTA-driven transcription with either channelrhodopsin-2 (ChR2) or the hM $_3$ D $_q$ DREADDs receptor (designer receptor exclusively activated by designer drug) (Liu et al. 2012, Garner et al. 2012), mice underwent a fear conditioning protocol. After doxycycline was removed from the diet, allowing c-Fos-tTA gene transcription to function normally, mice received several mild

shocks in a novel context to create a new contextual fear memory. As a result, using either light (for ChR2 mice) or an intraperitoneal injection of Clozapine-N-Oxide (for hM₃D_q mice), activity in the neural circuit storing the newly formed fear memory could be induced, observable by the freezing behaviour of the mouse. While these two methods successfully reactivated the fear memory, it is difficult to determine if the neural circuit storing this memory was directly targeted. The ChR2 approach only targeted the dentate gyrus (Liu et al. 2012), thus it is unclear whether the actual fear memory is stored in the ChR2 expressing neurons, or if it resides further downstream in the neural cascade that produces the freezing response (e.g. CA3 and CA1 of the hippocampus). Additionally, although the hM₃D_q approach (Garner et al. 2012) targeted multiple brain regions, it is likely that the memory is only stored in a subset of the neurons expressing hM₃D_q. Therefore, it is probable that the neural circuit encoding the fear memory is not uniquely targeted by the Clozapine-N-Oxide.

To take this one step further and artificially create an entirely new memory, Ramirez and colleagues used c-Fos-tTA mice expressing ChR2 to identify memory engram cells in the hippocampus corresponding to the memory of a novel context. Using light stimulation, they then paired the reactivation of this memory with a fear conditioning (shocks) in a different, unrelated context (Ramirez et al 2013). Upon returning the mice to the original context, the mice showed elevated freezing levels despite never having been actually shocked in this context. Hence, the mice were artificially fear conditioned by pairing the reactivation of the contextual memory with a shock, thus creating a new fear association into their memory. Extending this method even further, Redondo and colleagues (2014) succeeded in changing the valence of a contextual memory stored in the hippocampus of mice. By incorporating the optogenetic reactivation of a fearful engram within a rewarding context, the negative valence of this memory was decreased (Redondo et al. 2014). It is important to note that this approach, as well as the cue-pairing during sleep approach described previously, only creates a new association between previous experiences. Although we are still far away from the ability to download complex procedural memories (i.e. kung fu) into our brains, we have taken a giant step in this direction, with the “inception” of new hippocampus-dependent, associative memories.

Conclusion

In this chapter, we have discussed the different approaches and methods for modifying hippocampus-dependent memories. These fall under the approaches of enhancing memories, deleting memories and implanting false memories (inception). Related to these topics is the idea that it could one day be possible ‘read’ peoples thoughts. Whilst seemingly deep into the realms of science fiction, it is an area of considerable interest to domains such as law and marketing. In a recent study, Uncapher and colleagues went a step closer to determining whether ‘mind reading’ could be viable technique in an eyewitness identification context. They conducted a study whereby participants were shown a series of previously studied and novel faces whilst undergoing fMRI scanning. Using multivariate pattern analysis (MVPA) on the fMRI data, they were able to reliably classify whether a presented face was previously known or novel to the participant. However, when the participants were asked to conceal their true memory state (i.e. pretend a novel face was known and vice versa), the ability to decode that memory state using MVPA was lost, and in some cases even reversed (Uncapher et al. 2015). Hence, it may be that mind reading techniques based on neuroimaging are never robust enough for use in a court of law.

An approach taken by many of the studies covered in this chapter is to manipulate memories during sleep, when they are more malleable (Diekelmann and Born 2010, Oudiette and Paller 2013). A second strategy has been to targeting specific neurons using molecular-genetic techniques, allowing control over the neural circuits regulating the encoding of a memory (Liu et al. 2012, Garner et al. 2012). Finally, a third strategy has been to manipulate the synaptic processes involved in memory maintenance (Pastalkova et al. 2006). Looking to the future, combining these three approaches may lead to a more powerful means of controlling memory. Researchers will continue to enhance, delete, and incept memories; whether on day science will be able to emulate all the concepts that science fiction has to offer remains to be seen.

Appendix: Movies about memory enhancement, deletion, and inception

The following appendix is an updated version of the appendix appearing in Spiers and Bendor 2014.

Lucy (2015): After getting overdosed with a new experimental drug that unlocks the “unused” portion of the brain, the main character develops super cognitive abilities, including telekinesis and metamorphosis. According to the movie, we use only 10% of our brain. This is a scientific “urban legend” that is completely false. The only person that uses 10% of their brain was perhaps the writer of this movie.

The Bourne Identity (2002): *A highly-trained spy with no episodic memory, but all his procedural memory intact. Essentially James Bond with dementia and without the NHS.*

Eternal Sunshine of the Spotless Mind (2004): After breaking up with his girlfriend, the main character has a procedure performed- while he sleeps, a machine zaps and deletes all the memories of his ex-girlfriend. This technology replaces more established gustatory-driven methods of recovering from a break-up, like eating several cartons of ice cream.

Inception (2010): Using a “shared dream” technology, the main character and his team attempt to implant false memories (inception) in an unsuspecting target. The larger question is how did they get all that “dream-hacking” equipment through airport security?

Limitless (2011): The main character takes a mystery pill (NZT) that substantially enhancing his cognitive abilities. The movie demonstrates some of the downsides of “genius withdrawal”.

The Manchurian Candidate (1962, 2004 (remake)): A soldier captured by the enemy is “programmed” to become an assassin. After receiving the trigger (a queen of diamonds playing card), the soldier unconsciously carries out any instruction (such as assassinating a target), after which he forgets everything related to these actions. With the “queen of diamonds” as the trigger, best to avoid playing poker with this guy...

The Matrix Trilogy (1999, 2003): The year is 2199. After a war between humans and computers, humans now live inside a virtual reality environment called “the Matrix”, where humans still think it is 1999, and are unaware of what has happened. The few humans that have managed to leave the Matrix are staging a revolution, and must re-enter the Matrix to fight the computers. As the Matrix is essentially software, computer

code structured by rules, humans find that it is possible to “download” new skills and learn to bend or even break the rules of physics. The writers also decide to break the rules of physics by ignoring the first law of thermodynamics, suggesting that humans within the Matrix are used as energy sources (producing more energy than they require to survive).

Total Recall (1990): Implanting a false memory of a vacation to Mars has bizarre consequences for the main character, unlocking a suppressed memory of his true identity- a secret agent. Could this movie have been the inspiration behind Newt Gingrich’s plan to build a space colony on Mars?

Total Recall (2012 (remake)): A poorly done remake of the 1990 Total Recall movie. After watching this, you may want to look into some memory deletion technology (see *Eternal Sunshine of the Spotless Mind*)

See Baxendale (2004) for a review of movies exploring memory-related themes

References

Anderson, M. C., Ochsner, K. N., Kuhl, B., Cooper, J., Robertson, E., Gabrieli, S. W., Glover, G.H., Gabrieli, J. D. E. (2004). Neural systems underlying the suppression of unwanted memories. *Science*, 303(5655), 232-235.

Antony, J. W., Gobel, E. W., O'Hare, J. K., Reber, P. J., & Paller, K. A. (2012). Cued memory reactivation during sleep influences skill learning. *Nature neuroscience*, 15(8), 1114-1116.

Arzi, A., Shedlesky, L., Ben-Shaul, M., Nasser, K., Oksenberg, A., Hairston, I. S., & Sobel, N. (2012). Humans can learn new information during sleep. *Nature Neuroscience*, 15(10), 1460-1465.

Barnes, D. C., & Wilson, D. A. (2014). Slow-wave sleep-imposed replay modulates both strength and precision of memory. *The Journal of Neuroscience*, 34(15), 5134-5142.

Baxendale, S. (2004). Memories aren't made of this: amnesia at the movies. *BMJ: British Medical Journal*, 329(7480), 1480.

Bendor, D., & Wilson, M. A. (2012). Biasing the content of hippocampal replay during sleep. *Nature neuroscience*. 15, 1439–1444.

Bliss, T. V. P., & Collingridge, G. L. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*, 361(6407), 31-39.

Buzsáki, G. (2009). *Rhythms of the Brain*. Oxford University Press.

Buzsáki, G., Anastassiou, C. A., & Koch, C. (2012). The origin of extracellular fields and currents—EEG, ECoG, LFP and spikes. *Nature Reviews Neuroscience*, 13(6), 407-420.

De Bitencourt, R.M., Pamplona, F.A., Takahashi, R.N., (2013). A current overview of cannabinoids and glucocorticoids in facilitating extinction of aversive memories: potential extinction enhancers. *Neuropharmacology* 64, 389–395.

De Kleine, R. A., Rothbaum, B. O., van Minnen, A., (2013). Pharmacological enhancement of exposure-based treatment in PTSD: a qualitative review. *Eur. J. Psychotraumatology* 4.

de Lavilléon, G., Lacroix, M. M., Rondi-Reig, L., & Benchenane, K. (2015). Explicit memory creation during sleep demonstrates a causal role of place cells in navigation. *Nature neuroscience*, 18(4), 493-495.

Diekelmann, S., & Born, J. (2010). The memory function of sleep. *Nature Reviews Neuroscience*, 11(2), 114-126.

Diekelmann, S., Büchel, C., Born, J., & Rasch, B. (2011). Labile or stable: opposing consequences for memory when reactivated during waking and sleep. *Nature neuroscience*, 14(3), 381-386.

Dudai, Y. (2004). The neurobiology of consolidations, or, how stable is the engram?. *Annu. Rev. Psychol.*, 55, 51-86.

Eichenbaum, H. (2004). Hippocampus: cognitive processes and neural representations that underlie declarative memory. *Neuron* 44, 109–120.

Ego-Stengel, V., & Wilson, M. A. (2010). Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. *Hippocampus*, 20(1), 1-10.

File, S.E., Fluck, E., Fernandes, C. (1999). Beneficial effects of glycine (bioglycin) on memory and attention in young and middle-aged adults. *J. Clin. Psychopharmacol.* 19, 506–512.

Frankland, P.W., Bontempi, B. (2005). The organization of recent and remote memories. *Nat. Rev. Neurosci.* 6, 119–130.

Frankland, P. W., Köhler, S., Josselyn, S. A. (2013). Hippocampal neurogenesis and forgetting. *Trends in Cognitive Sciences*, 36(9).

Garner, A. R., Rowland, D. C., Hwang, S. Y., Baumgaertel, K., Roth, B. L., Kentros, C., & Mayford, M. (2012). . *Science*, 335(6075), 1513-1516.

Girardeau, G., Benchenane, K., Wiener, S. I., Buzsáki, G., & Zugaro, M. B. (2009). Selective suppression of hippocampal ripples impairs spatial memory. *Nature neuroscience*, 12(10), 1222-1223.

Graham, B. M., & Richardson, R. (2011). Intraamygdala infusion of fibroblast growth factor 2 enhances extinction and reduces renewal and reinstatement in adult rats. *The Journal of Neuroscience*, 31(40), 14151-14157.

Groes (2016) *Memory in the Twenty-First Century New Critical Perspectives from the Arts, Humanities, and Sciences*. Palgrave MacMillan.

- Halassa, M. M., Siegle, J. H., Ritt, J. T., Ting, J. T., Feng, G., & Moore, C. I. (2011). Selective optical drive of thalamic reticular nucleus generates thalamic bursts and cortical spindles. *Nature neuroscience*, 14(9), 1118-1120.
- Hamani, C., McAndrews, M. P., Cohn, M., Oh, M., Zumsteg, D., Shapiro, C. M., ... & Lozano, A. M. (2008). Memory enhancement induced by hypothalamic/fornix deep brain stimulation. *Annals of Neurology*, 63(1), 119-123.
- Hardt, O., Nader, K., Nader, L. (2013) Decay happens: the role of active forgetting in memory. *Trends in Cognitive Sciences*, 17(3).
- Hauner, K. K., Howard, J. D., Zelano, C., & Gottfried, J. A. (2013). Stimulus-specific enhancement of fear extinction during slow-wave sleep. *Nature neuroscience*.
- Hulbert, J. C., Henson, R. N., Anderson, M. C. (2016). Inducing amnesia through systematic suppression. *Nature Communications*, 7, 11003.
- Ji, D., & Wilson, M. A. (2006). Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nature neuroscience*, 10(1), 100-107.
- Kaplan, G.B., Moore, K.A. (2011). The use of cognitive enhancers in animal models of fear extinction. *Pharmacol. Biochem. Behav.* 99, 217–228.
- Kim, J. J., & Fanselow, M. S. (1992). Modality-specific retrograde amnesia of fear. *Science*, 256(5057), 675-677.
- Kindt, M., Soeter, M., Vervliet, B. (2009). Beyond extinction: erasing human fear responses and preventing the return of fear. *Nat. Neurosci.* 12, 256–258.
- Kuriyama, K., Honma, M., Yoshiike, T., Kim, Y. (2013). Valproic acid but not D-cycloserine facilitates sleep-dependent offline learning of extinction and habituation of conditioned fear in humans. *Neuropharmacology* 64, 424–431.
- Laxton, A. W., Tang - Wai, D. F., McAndrews, M. P., Zumsteg, D., Wennberg, R., Keren, R., ... & Lozano, A. M. (2010). A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. *Annals of Neurology*, 68(4), 521-534.
- Lee, A. K., & Wilson, M. A. (2002). Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron*, 36(6), 1183-1194.
- Lee, A. M., Kanter, B. R., Wang, D., Lim, J. P., Zou, M. E., Qiu, C., ... & Messing, R. O. (2013). Prkcz null mice show normal learning and memory. *Nature*.
- Liao, S. M., & Sandberg, A. (2008). The normativity of memory modification. *Neuroethics*, 1(2), 85-99.
- Ling, D. S., Benardo, L. S., Serrano, P. A., Blace, N., Kelly, M. T., Crary, J. F., & Sacktor, T. C. (2002). Protein kinase M ζ is necessary and sufficient for LTP maintenance. *Nature neuroscience*, 5(4), 295-296.

- Liu, X., Ramirez, S., Pang, P. T., Puryear, C. B., Govindarajan, A., Deisseroth, K., & Tonegawa, S. (2012). Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature*, *484*(7394), 381-385.
- Loftus, E. F., & Palmer, J. C. (1974). Reconstruction of automobile destruction: An example of the interaction between language and memory. *Journal of verbal learning and verbal behaviour*, *13*(5), 585-589.
- Malenka, R. C., & Bear, M. F. (2004). LTP and LTD: an embarrassment of riches. *Neuron*, *44*(1), 5-21.
- Maren, S. (2001). Neurobiology of Pavlovian fear conditioning. *Annual review of neuroscience*, *24*(1), 897-931.
- Martin, A., Chao, L.L. (2001). Semantic memory and the brain: structure and processes. *Curr. Opin. Neurobiol.* *11*, 194–201.
- Marshall, L., Helgadóttir, H., Mölle, M., & Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. *Nature*, *444*(7119), 610-613.
- McClelland, J. L., & Rogers, T. T. (2003). The parallel distributed processing approach to semantic cognition. *Nature Reviews Neuroscience*, *4*(4), 310-322.
- McNamara, C. G., Tejero-Cantero, Á., Trouche, S., Campo-Urriza, N., & Dupret, D. (2014). Dopaminergic neurons promote hippocampal reactivation and spatial memory persistence. *Nature neuroscience*.
- Milad, M. R., & Quirk, G. J. (2002). Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature*, *420*(6911), 70-74.
- Misanin, J.R., Miller, R.R., Lewis, D.J. (1968). Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. *Science* *160*, 554–555.
- Mohamed, A.D., Sahakian, B.J. (2012). The ethics of elective psychopharmacology. *Int. J. Neuropsychopharmacol. Off. Sci. J. Coll. Int. Neuropsychopharmacol. CINP* *15*, 559–571.
- Moscovitch, M., Nadel, L., Winocur, G., Gilboa, A., Rosenbaum, R.S. (2006). The cognitive neuroscience of remote episodic, semantic and spatial memory. *Curr. Opin. Neurobiol.* *16*, 179–190.
- Nader, K., Schafe, G. E., & Le Doux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature*, *406*(6797), 722-726.
- Oudiette, D., & Paller, K. A. (2013). Upgrading the sleeping brain with targeted memory reactivation. *Trends in Cognitive Sciences*, *17*(3).

- Pastalkova, E., Serrano, P., Pinkhasova, D., Wallace, E., Fenton, A. A., & Sacktor, T. C. (2006). Storage of spatial information by the maintenance mechanism of LTP. *Science*, 313(5790), 1141-1144.
- Rabinak, C.A., Angstadt, M., Sripada, C.S., Abelson, J.L., Liberzon, I., Milad, M.R., Phan, K.L. (2013). Cannabinoid facilitation of fear extinction memory recall in humans. *Neuropharmacology* 64, 396–402.
- Ragan, C.I., Bard, I., Singh, I. (2013). What should we do about student use of cognitive enhancers? An analysis of current evidence. *Neuropharmacology* 64, 588–595.
- Ramirez, S., Liu, X., Lin, P. A., Suh, J., Pignatelli, M., Redondo, R. L., ... & Tonegawa, S. (2013). Creating a False Memory in the Hippocampus. *Science*, 341(6144), 387-391.
- Rasch, B., Büchel, C., Gais, S., & Born, J. (2007). Odour cues during slow-wave sleep prompt declarative memory consolidation. *Science*, 315(5817), 1426-1429.
- Redondo, R. L., Kim, J., Arons, A. L., Ramirez, S., Liu, X., & Tonegawa, S. (2014). Bidirectional switch of the valence associated with a hippocampal contextual memory engram. *Nature*. 513(7518), 426-430.
- Ren, S. Q., Yan, J. Z., Zhang, X. Y., ... & Lu, W. (2013). PKC λ is critical in AMPA receptor phosphorylation and synaptic incorporation during LTP. *The Embo Journal*. 32(10), 1365-1380.
- Rodríguez, M.L.C., Campos, J., Forcato, C., Leiguarda, R., Maldonado, H., Molina, V.A., Pedreira, M.E. (2013). Enhancing a declarative memory in humans: the effect of clonazepam on reconsolidation. *Neuropharmacology* 64, 432–442.
- Rolls, A., Makam, M., Kroeger, D., Colas, D., de Lecea, L., Heller, H.C. (2013) Sleep to forget: interference of fear memories during sleep. *Mol. Psychiatry* 18, 1166–1170.
- Rudoy, J. D., Voss, J. L., Westerberg, C. E., & Paller, K. A. (2009). Strengthening individual memories by reactivating them during sleep. *Science*, 326(5956), 1079-1079.
- Sadeh, N., Verbitsky, S., Dudai, Y., & Segal, M. (2015). Zeta Inhibitory Peptide, a Candidate Inhibitor of Protein Kinase M ζ , Is Excitotoxic to Cultured Hippocampal Neurons. *The Journal of Neuroscience*, 35(36), 12404-12411.
- Sara, S. J. (2010). Reactivation, retrieval, replay and reconsolidation in and out of sleep: connecting the dots. *Frontiers in behavioural neuroscience*, 4, 185. doi:10.3389/fnbeh.2010.00185.
- Schreiner, T., Lehmann, M., & Rasch, B. (2015). Auditory feedback blocks memory benefits of cueing during sleep. *Nature communications*, 6.
- Serrano, P., Yao, Y., & Sacktor, T. C. (2005). Persistent phosphorylation by protein kinase M ζ maintains late-phase long-term potentiation. *The Journal of neuroscience*, 25(8), 1979-1984.

- Shema, R., Sacktor, T. C., & Dudai, Y. (2007). Rapid erasure of long-term memory associations in the cortex by an inhibitor of PKM ζ . *Science*, 317(5840), 951.
- Shema, R., Haramati, S., Ron, S., Hazvi, S., Chen, A., Sacktor, T. C., & Dudai, Y. (2011). Enhancement of consolidated long-term memory by overexpression of protein kinase M ζ in the neocortex. *Science*, 331(6021), 1207-1210.
- Siapas, A. G., & Wilson, M. A. (1998). Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron*, 21(5), 1123-1128.
- Sirota, A., Csicsvari, J., Buhl, D., & Buzsáki, G. (2003). Communication between neocortex and hippocampus during sleep in rodents. *Proceedings of the National Academy of Sciences*, 100(4), 2065-2069.
- Spiers H.J. (2012) Hippocampal Formation. In: V.S. Ramachandran (ed.) *The Encyclopedia of Human Behaviour*, vol. 2, pp. 297-304. Academic Press.
- Spiers, H. J., & Bendor, D. (2014). Enhance, delete, incept: Manipulating hippocampus-dependent memories. *Brain research bulletin*, 105, 2-7.
- Squire, L.R., Alvarez, P. (1995). Retrograde amnesia and memory consolidation: a neurobiological perspective. *Curr. Opin. Neurobiol.* 5, 169–177.
- Squire, L.R., Stark, C.E.L., Clark, R.E. (2004). The medial temporal lobe. *Annu. Rev. Neurosci.* 27, 279–306.
- Steckler, T., & Risbrough, V. (2012). Pharmacological treatment of PTSD—established and new approaches. *Neuropharmacology*, 62(2), 617-627.
- Steriade, M., McCormick, D. A., & Sejnowski, T. J. (1993). Thalamocortical oscillations in the sleeping and aroused brain. *Science*, 262(5134), 679-685.
- Stickgold, R., & Walker, M. P. (2013). Sleep-dependent memory triage: evolving generalization through selective processing. *Nature neuroscience*, 16(2), 139-145.
- Suthana, N., Haneef, Z., Stern, J., Mukamel, R., Behnke, E., Knowlton, B., & Fried, I. (2012). Memory enhancement and deep-brain stimulation of the entorhinal area. *New England Journal of Medicine*, 366(6), 502-510.
- Thompson, S. A., Graham, K. S., Williams, G., Patterson, K., Kapur, N., & Hodges, J. R. (2004). Dissociating person-specific from general semantic knowledge: roles of the left and right temporal lobes. *Neuropsychologia*, 42(3), 359-370.
- Tsokas, P., Hsieh, C., Yao, Y., Lesburguères, E., ... Fenton, A. A., & Sacktor, T. C. (2016). Compensation for PKM ζ in long-term potentiation and spatial long-term memory in mutant mice. *Elife*, 5.
- Uncapher, M. R., Boyd-Meredith, J. T., Chow, T. E., Rissman, J., Wagner, A. D. (2015). Goal-Directed Modulation of Neural Memory Patterns: Implications for fMRI-Based Memory Detection. *The Journal of Neuroscience*, 35(22), 8531-8545.

Varela, C., Weiss, S., Meyer, R., Halassa, M., Biedenkapp, J., Wilson, M. A., Goosens K.A., Bendor, D. (2016). Tracking the Time-Dependent Role of the Hippocampus in Memory Recall Using DREADDs. *PLoS one*, 11(5), e0154374.

Volk, L. J., Bachman, J. L., Johnson, R., Yu, Y., & Huganir, R. L. (2013). PKM- ζ is not required for hippocampal synaptic plasticity, learning and memory. *Nature*, 493(7432), 420-423.

Wang, J. X., Rogers, L.M., Gross, E. Z., Ryals, A.R., Mehmet, D. E., Brandstatt, K. L., Hermiller, M. A., Voss, J. L. (2014). Targeted enhancement of the cortical-hippocampal brain networks and associative memory. *Science*, 346(6200), 1054-1057.

Wang, J. X., & Voss, J. L. (2015). Long-lasting enhancements of memory and hippocampal-cortical functional connectivity following multiple-day targeted noninvasive stimulation. *Hippocampus*, 25(8), 877-883.

Wilson, M. A., & McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science*, 265(5172), 676-679.

Zhang, G., Ásgeirsdóttir, H.N., Cohen, S.J., Munchow, A.H., Barrera, M.P., Stackman, R.W. (2013). Stimulation of serotonin 2A receptors facilitates consolidation and extinction of fear memory in C57BL/6J mice. *Neuropharmacology* 64, 403–413.