Mind Control 101

A Recipe For Memory Manipulation

by Richard Fu

Our memory defines who we are: the parenting we received, the skill we acquired, the taste we are habituated to, and the goals we achieved are all products of experiences piled into the apparatus of memory. Experience is transient, and only with memory we are privileged with a continuous narrative, an ongoing story tricking us into purpose and belief. But what would you do if you can go and change something about your almighty script of life? To permanently erase an undesirable event that recurringly hijacks your dreams? To revoke an unchangeable regret that tortures your conscience and steals your happiness? Here is a chance to live out the next Black Mirror episode by the recipes of memory manipulation. Will you seize this opportunity for a new start in life?

Step 1. Locate Your Memory Storehouse: the Hippocampus

Your empirical knowledge may have shown you the wonder of memory. A phone number sequence can barely survive several minutes, yet you can describe the facial features of the thief who snatched your phone within seconds of eye contact. You might not recall what you ate for dinner last Thursday, but the smell of your grandma's home-baked cookies can instantly hydrate your eyes by rekindling your childhood joviality—which now has permanently vanished among adult-life chronic stresses. Memory is stunningly complex, as it synthesizes sensory inputs, spatial data, and temporal valence, along with emotions. It is rapidly updated respecting a personalized priority algorithm that varies individual to individual.[1] The hippocampus is the brain region where all these intricate marvels take place. In a reductionist scope, the memory formation takes three steps: encodement, storage, and retrieval. A single experience consists of multiple sensory inputs that converge at the perforant path to enter the hippocampus at the Dentate Gyrus, where initial encodement starts. Specific groups of neurons are activated upon signal processing at the Dentate Gyrus, and when repeatedly activated along the memory formation, these neuron complexes establish an enduring physical change that enhances their efficiency to communicate together.[2] Until this step, the memory is categorized as short-term memory residing in the hippocampus. The retrieval is triggered by reencountering the same sensory or environmental cues that would reactivate the earlier enhanced neuronal complex. The retrieval process may act as a rehearsal that would relay hippocampal short-term memory to the cortex for consolidated long-term memory that could last indefinitely.[3] The proximity of hippocampus to other brain regions, including the amygdala complex (critical to emotion regulation), explains the coupling of memory with specific emotions upon retrieval.

Step 2. Tidy-Up: Define a Single Episodic Memory

Further, long-term memory is separated into episodic and semantic memories. Episodic memory is what we will target, since it is basically everything pertinent to experience, including the time, place, event, and emotion of a specific past happening.[4] Semantic, on the other hand, involves the comprehension of abstract concepts that do not affiliate with personal experiences. Fear-memory is the most comprehensively studied episodic memory that has proved efficacy with lab animals. The renowned Contextual Fear Conditioning (CFC) is the paradigm widely employed for specific episodic memory assays.[5] Researchers can habituate mice models with a safe environment such as home cage, where they would freely explore with sufficient food and regular social interactions with the friends they grew up with. Later, they will each individually be brought into a new environment where they would receive a fear experience, delivered in the form of very mild foot shocks. At first, they often run around and sniff sporadically, ushered by their natural curiosity to create a contextual impression of this new spot. Upon a physiological trigger of a shock, however, the mice would immediately jump around in fear of the unknown shock, where sensory inputs of the shock causes a rapid response of the sympathetic nervous system (the fight-or-flight response), and the basolateral amygdala simultaneously interprets this situation as fear-raising red alert.

An extended period of freezing would readily follow the alert, where the mice would sit in the corner perfectly still, not knowing what will happen next. But meanwhile, this particular fear memory is encoding while the hippocampus works rigorously to not only synthesize the sensory experience of the shock entering from the perforant path, but to also couple the earlier visual, spatial cues of this new spot and the fear emotion recognized by the basolateral amygdala all together into a neuronal firing pattern (the engram complex).[6] After returning to the home cage for a short while to chat with their pals on how absurd this supernatural experience was, they would again be placed into this (now familiar)

spot but without any mild shock applied. Just upon the entry, they'd freeze in the corner, signalling of memory retrieval. The same contextual cues would instantly reactivate the earlier hippocampal engram pattern to recapitulate the fear experience and the red alert in the basolateral amygdala.

You might question how these poor frozen mice relate to your much more advanced human memories, and the answer would simply be that our hippocampus works pretty much the same. We wouldn't know what the mice would feel exactly on that supernatural foot shock in a box, but the brain activity and behavioral responses draw great parallels. Imagine visiting a haunted house disguised as a regular house and having the most horrific experience where you ran and screamed and found out the door was locked from outside. After a while of futile escape attempts, you ended up at a corner of the basement shielding your face with a dusty rug in shivers. Then magically you returned home where you recounted the experience to everybody, but again woke up in that haunted house; you might skip the running and screaming part to directly hide under the rag while waiting for the magic of a safe return. Even your complexly sorrowful breakup experience follows the similar memory retrieval process to reactivate the engram patterns attributed to the series of love vignettes relaying to amygdala and neocortex and cause further spiral into emo-ness. A customized anniversary mug might act the same as the environmental cues from the shock box.

Step 3. Target the Memory of Your Choice: Find the Engram, Mark the Engram

Although we narrowed the scope of where memory forms to the hippocampus, a relatively smaller section within the brain, there are still millions of neurons to survey. The fact that they work collectively and implicate numerous circuits specialized in sensory processing and emotional mediation only complicates our task. How would we pinpoint a specific memory within the muddle of co-operative biochemical activities? …Markers! A genetic marker would specifically trace the neurons which have just fired after a single episodic memory encodement. The family of immediate-early genes (IEGs) are perfectly suited for this job.[7] They are universal in all cell types and are transiently expressed following the depolarization of the neuron, which is a sign of activation. Ideally, all we need to do is find all these tracer genes right after the specific memory formation. Yet a second challenge arises: how would we limit the group of IEG markers to only the time frame where a single memory encodes instead of everything throughout an extended period of time? A binary system of transgenes using doxycycline as a manipulative tool for conditional inhibition could stop IEGs expression in our favored timeframe.[8] For example, memories were being encoded during safe cage habituation and daily interaction with other mice buddies, and we wouldn't want those IEGs' activity to interfere with the specific engrams we target, and thus doxycycline will be fed to the test mice before and afterthe foot shock to limit the IEGs expression window. With that, we could locate the engram precisely for individual episodic memories.

Step 4. Erase or Incept: You Are the Editor of Your Own Mind.

Now that we are able to lay the target down, it's time for some editing! You ought to be curious about how these IEG-labeled engrams are manipulated and whether the intangible memory can really be altered with just a touch on the engram cells. And let me unfold the suspense. We can install switches onto the targeted engrams and turn the memories on or off, just like TV, but with laser

beams as remote control. Radical as it sounds, it works. The switch is named channelrhodopsin, a light-gated ion channel discovered from green algae photoreceptors that can respond to lasers of various frequencies and result in either cell activation or inhibition. After inserting channelrhodopsin into IEGs-expressing cells via the binary transgene approach, the channelrhodopsin switches would be able to manipulate a comprehensive engram complex specific to one episodic memory.[8] Now back to the mice who were trained with a fear memory at the shock box. After the first memory retrieval to confirm the engram formation, they were treated with optogenetic laser inhibition in vivo., meaning that they would return to the shock box again while the laser beam constitutively inhibiting the activity of the engram pattern of this fear memory coupled to the box. Excitingly, they showed no sign of freezing or fear and explored the shock box as if the first entrance. When the laser was turned off later, the mice would successfully retrieve the fear memory again and would freeze.

The finding supports not only the efficacy of engram manipulation with specific episodic memory, but also the temporal precision that allows flexible alteration of memory.

On the other hand, the activation of the fear engram could associate a memory with unrelated contextual cues. When researchers utilized another laser that would reactivate the earlier labeled fear engrams at a safe context, they immediately froze in the corner as a sign of fear memory retrieval.[9] In this narrative, the recall of a specific memory can be inserted into an irrelevant context or sensory trigger to induce a false memory.

Practical Use?

A series of sci-fi rooted fantasies may pop up your mind just now attempting to paint the future of memory manipulation, and so did scientists—but with baby steps. Extensive research groups across the globe have made significant efforts to advance our knowledge of engram cells. They looked into the neighbors of the hippocampus to map out the circuit of engram activity and further specified the hippocampal dentate gyrus for contextual encodement, the amygdala engram cells which represent the valence information of the emotional ratings, and the sensory cortices' engrams that encode the sensory data. These are all critical to a single episodic memory to fully retrieve an experience.[6] It also reinforces the marvel of recalling a scent or vividly reliving an event with the same excitement or embarrassment, and how they are stored at where they form. Considering that not only the specific episodic memory, but the specific segment of it can be targeted and manipulated, the fantasy to fully remodify the memory script like a playwright may be actualized. But before getting there, we could trace some paths of attempted clinical adaptations following the engram's shaking of the scientific world. These could be the very first practical use.

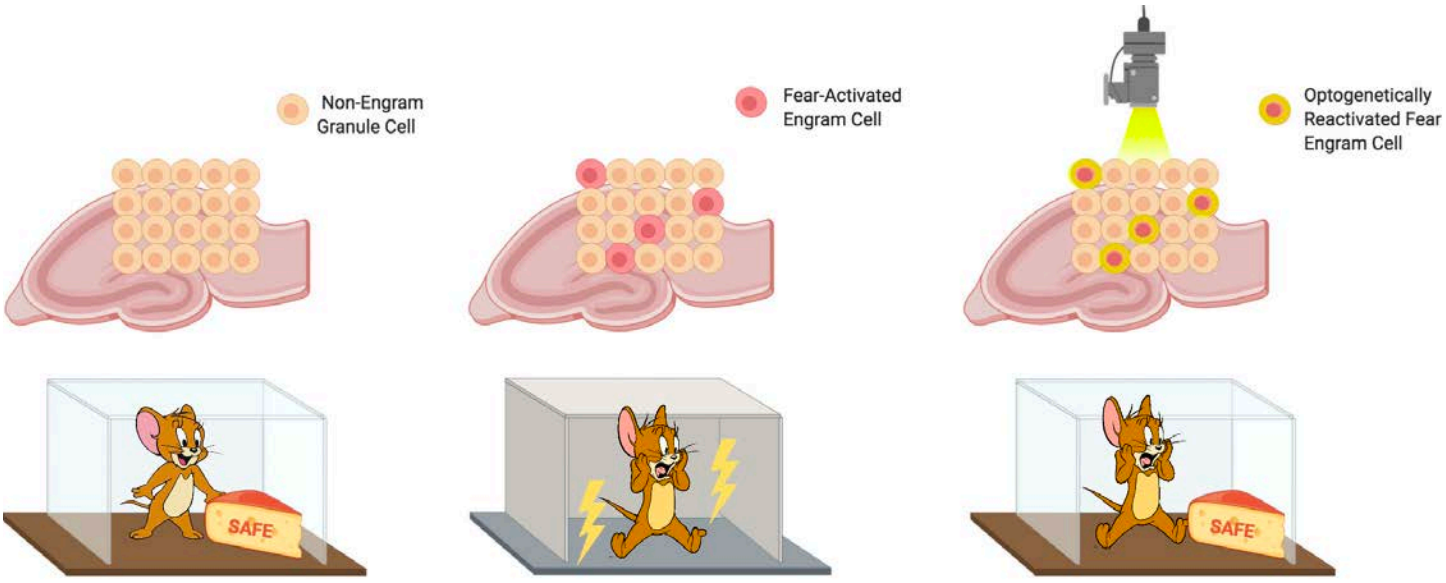

Figure 1. Schematic for engram reactivation. Created in BioRender. Original figure by Richard Fu. Cartoons of Jerry Mouse from Clipart Library.

Mute the Trauma You Don't Deserve

Can you quickly recall the most aversive event you've ever experienced? Then try your best to walk through that experience, reactivating the smallest details and mobilizing your full sensory data. Was it frightening still? Probably causing a slight heart race and shortness of breath? That is the life of 3.5% of U.S. adult population every year and 1 in 11 American adults in their lifetime.[10] We read heart-breaking news of sexual violence, murder, child abuse, and more atrocities where the victims may carry the fault of the wrongdoers for life. PTSD is a debilitating psychiatric disorder often acquired after the exposure to a distressing experience, and the patients may experience involuntary flashbacks, physiological anxiety, frequent arousal by environmental cues, and may develop various mood disorders. The reductionist breakdown of PTSD may be comprehended as the formation of a maladaptive fear memory that is hyperactivated by the traumatic event to the extent that it may not be extinguished.

Consider our mice friend with the foot shock memory again. Suppose the mild foot shock is switched to severe foot shocks lasting several minutes, the hippocampal engram of the mice would reach a hyperactive state along with the engrams in the amygdala and sensory cortex. Not only would this memory become easily retrievable, the transductive communication is also enhanced among the contextual, sensory, and emotional sectors of the engram circuitry. Thus, after the traumatic shock, the mice will freeze at any environment similar to the shock box, and even the sound resemblant of the electric shock can turn them still. The barrier of engram reactivation lowered, while the contextual and sensory cues not exactly same as the original situation (maybe a partial reactivation of the engram pattern) can also retrieve the trauma.[11] We do have a responsive mechanism called extinction, that would put a stop to that hyperactive fear memory. Oftentimes, the cues of a fear memory may reoccur in life in a safer environment, and the fear response shall slowly dissipate as the engrams of new memories related to the same fearful cue may form. These new 'safe engrams' will compete with the fearful engrams to communicate with those often harmless cues, and eventually the trauma does not acutely impose behavioral repercussions.[12] Nonetheless, the PTSD patients often exhibit dysfunctional extinction mechanism that they would descend into extreme fear along with physiological symptoms that push them to avoid any contact with fear-inducing cues. Exposure therapy, a common PTSD treatment, forces the extinction process by asking the patients to recall the traumatic memory with the guidance of the therapist.[13] However, this process is often very long, all while the anxiety can quickly escalate into other health conditions, and the difficulty of even the fundamental activities in life can be too discouraging for the patients.

Given the current limitations with PTSD treatment, the optogenetic fear engram inhibition may perfectly solve the problem. Series of studies individually inhibiting a specific region of the fear memory circuit have shown a strong extinction response.[5] More revolutionarily, a study was able to alter the emotional valence between fear and reward memory.[14] The researchers labeled the amygdala engram patterns of both a fear memory and a reward memory. They later optogenetically activated the reward valence during fear context and fear valence during reward, and successfully rewired the linkage of contextual experience with opposite emotional valence that the mice would tend to choose the fear environment over the reward environment.

Memory Lost & Found

This can be used not just to erase what we don't want in our memory, but to find what has been lost. Alzheimer's disease (AD) is a prevalent neurodegenerative condition that jeopardizes a large proportion of our elderly population and makes up the majority of amnesia.[15] Many families face the gradual dissolution of the memory of their loved ones. The mental degeneration is sometimes romanticized into the philosophical return of the origin, to leave without anything just the way we came. The cause of AD can be diverse and interconnected with factors related to the biological aging of the brain. There are genetic indicators, risk from vascular diseases, and daily lifestyle choices that all contribute to the deterioration of cognitive brain functions. The biological manifestation of AD is the loss of neurons and the connections among them caused by the rise of amyloid plaques and tau proteins, two types of proteins that are considered pathological hallmarks of AD.[16] The overall decay of cognitive function, and specifically the loss of memory can be understood as the engram neurons in key brain regions slowly fall apart, similar to the wires in an old electrical appliance. The episodic memory loss is the key feature of early AD onset, and the cause has been often attributed to hippocampal deficiency that interferes with the encodement of new memories. Nonetheless, some

researchers raised the possibility that maybe the memory can still be synthesized into hippocampal engrams, and it was the retrieval that causes the true episodic amnesia.[17]

AD mice, a genetically modified strain of mice that manifest the biological hallmark of amyloid plaques and tau proteins that also exhibit behavioral deficiencies in memory maintenance, were used in the contextual fear conditioning paradigm. They were treated with a foot shock at the specific shock box, yet when they returned, they didn't show any sign of memory of the shock. Not knowing if this was due to the encodement error or retrieval error, the researchers optogenetically reactivated the earlier labeled engram of this fear memory, and surprisingly, the mice were able to show freezing behavior, a sign of memory retrieval. This means that the memory was successfully encoded in the hippocampus, yet when the AD mice return to the shock box with visual and contextual cues, the sensory inputs fail to reactivate the engram pattern. But when the engrams were artificially reactivated, the memory is retrieved. You might be wondering what causes the engrams to not respond to the sensory cues. An answer is that they start to lose the facilities of communication that allow them receive and send signals. The dendritic spines are the formal names of such facilities. They grow on the wire of the engram neurons that can associate with other neurons to form circuits of transduction. The engram cells of the AD mice show fewer dendritic spines, and that lack of communication facility could be the cause of communication errors. The researchers then conducted several sessions of optogenetic stimulations of this specific engram groups, and observed a steady increase of the dendritic spine density. When the AD mice were sent back to the shock box for a new fear memory, they were able to correctly retrieve the encoded memory without optogenetic aids.

Warranty

Does memory manipulation still sound appealing to you? Will you call us and try it out? Or do you fear that you might end up in the exact same place again? Shall engram manipulation be a chance to test fatalism that we simply can't escape? Or would you be able to handle a revised reality that is equally mediocre, just now without excuses? Stay tuned for more, and maybe see you in a decade or less with the same question but a ready-to-use human approach passing the ethical restraints. ■

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