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NEUROETHICS

Psychopharmacology and memory

W Glannon

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Psychotropic and other drugs can alter brain mechanisms regulating the formation, storage, and retrieval of different types of memory. These include “off label” uses of existing drugs and new drugs designed specifically to target the neural bases of memory. This paper discusses the use of beta-adrenergic antagonists to prevent or erase non-conscious pathological emotional memories in the amygdala. It also discusses the use of novel psychopharmacological agents to enhance long term semantic and short term working memory by altering storage and retrieval mechanisms in the hippocampus and prefrontal cortex. Although intervention in the brain to alter memory as therapy or enhancement holds considerable promise, the long term effects of experimental drugs on the brain and memory are not known. More studies are needed to adequately assess the potential benefits and risks of these interventions.

capacity of long term semantic and short term working memory. It is because they are used to strengthen a capacity considered normal that these drugs are a form of enhancement. These interventions hold considerable promise; but they may also involve pitfalls. Both classes of drugs are experimental in the sense that they are being developed and used for “off label” purposes for which they were not originally designed. Because they are experimental, the long term effects of these novel forms of psychopharmacology are unknown. I will discuss some of the potential beneficial and harmful effects of psychopharmacology on memory.

THERAPEUTIC PSYCHOPHARMACOLOGY

Adrenaline is a hormone released by the adrenal medulla in situations requiring effort to fight against or flee from a perceived or real threat. It is closely related to the other stress hormone, cortisol. Adrenaline is released when the adrenal gland receives a signal from the amygdala in the brain when this structure senses an external threat to a human organism. The amygdala is part of the brain's limbic system, which regulates emotions.^{1 2} It is one of the most primitive parts of the brain and plays a critical role in our capacity to avoid threats and survive. One effect of adrenaline is to embed non-conscious emotional memories of fearful or threatening events in the amygdala. If emotional memory is embedded too strongly in the amygdala, however, it can produce a heightened fear response to external events that is out of proportion to the actual nature of the problems at hand. Because emotional memories stored in the amygdala are out of our conscious control, they can be difficult to eradicate or modulate and can adversely influence the nature and content of our beliefs, feelings, and other conscious mental states. Events perceived as stressors or threats can trigger a chronic fear response that puts the brain, body, and mind on a constant state of alert. This describes the pathology and pathophysiology of some forms of depression, anxiety, and the emotionally disturbing flashback memories of traumatic events that characterise PTSD.

Some researchers have raised the possibility of using a beta-adrenergic antagonist, specifically the drug propranolol, to treat PTSD. This drug blocks the effects of the hormone norepinephrine, levels of which rise in the brain in response to adrenaline. The aim of using propranolol would be to prevent the embedding of pathological unconscious emotional memories of fearful events in the amygdala. Brian Strange and

Memory is critical to both human survival and personal identity. Non-conscious emotional memory of fearful or threatening events enables us to recognise and respond appropriately to real threats in the natural and social environment. Episodic memory of events involving personal experience is necessary for the psychological connectedness and continuity that gives one the feeling of persisting through time as the same person. Other forms of memory include non-conscious procedural memory, which enables us to perform basic motor skills and tasks of daily life, and semantic memory, which enables us to recall and use concepts and facts. Semantic and episodic memory are two forms of declarative memory, which enables us to consciously recall facts and events. Working memory is a short term version of declarative memory and is involved in such complex cognitive tasks as reasoning and decision making.

Recent advances in psychopharmacology are enabling researchers to intervene in emotional, semantic, and working memory systems. In the first type of intervention, existing drugs are being used to block or reverse the process through which non-conscious fearful memories of traumatic events become pathological and cause post-traumatic stress disorder (PTSD) and similar debilitating mental illnesses. It is because they are used to treat mental disorders that these drugs are a form of therapy. In the second type of intervention, drugs are being designed to enhance the formation, storage, and retrieval

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colleagues have conducted experiments, the results of which appear to support this hypothesis.³ The key is to intervene in a way that blocks the mechanisms through which these memories are formed and stored. This involves the process of consolidation, whereby an event that one has experienced is first registered by certain neural correlates and is then translated into a permanently stored memory in the brain. Adrenaline appears to play a role in consolidation, ensuring that an emotional memory is strengthened and becomes firmly embedded in the amygdala. If it takes days or weeks for a memory to consolidate and become embedded and stored in the amygdala, and if this process depends on a certain level of adrenaline, then conceivably a sufficient dose of propranolol could block adrenaline and prevent the memory from forming.

This was the hypothesis of Harvard University psychiatrist Roger Pittman, who conducted a study of 40 patients admitted to the emergency room of the Massachusetts General Hospital for various traumatic injuries.^{4,5} Subjects in the study took propranolol or a placebo for 19 days immediately after the traumatic event. The idea was to test whether the drug could prevent the consolidation of negative emotional memories of the event by blocking the action of adrenaline and other stress hormones and their effects in the brain. Pittman's hypothesis also rested on the fact that memories that have already formed are vulnerable to erasure over time and need to be reconsolidated. Since many of the same biological mechanisms involved in consolidation are also involved in re-consolidation, it is conceivable that the use of propranolol or other beta-adrenergic antagonists could reverse the mechanisms of consolidation and erase a pathological memory that had already formed. Alternatively, these drugs could be given to people going into harm's way as a form of prevention. They could prevent an excessive release of adrenaline and thereby prevent the formation of heightened fear inducing memories in the amygdala. Such drugs could be given to soldiers before going into battle, or to paramedics just before responding to a medical disaster. In the light of a recent study showing that about one in six soldiers returning from the war in Iraq have had symptoms of PTSD, anxiety, and major depression, this type of intervention could prevent significant harm to many people.⁶

One possible consequence of using these drugs for this purpose would be the blunting of the natural fear response. This response is adaptive because it offers us a survival advantage in protecting us from external threats. It becomes maladaptive when it puts our bodies and minds on a constant state of high alert and is out of proportion to the real nature of external events. Could we ensure that a betablocker designed to prevent a pathological state of fear did not have the extreme opposite effect, weakening our natural fear response to the point of making us vulnerable to real threats? Could we ensure that erasing some harmful memories would not result in the erasure of beneficial memories as well? Even if these drugs were given in carefully calibrated doses, could we accurately weigh the potential benefit against the potential harm in using them for the therapeutic or preventive purposes that I have described?

PROPRANOLOL AND PTSD

Suppose that soldiers in the Iraq war were given propranolol as a form of prevention before combat. The aim would be to ensure that no traumatic experience would become embedded in the amygdala as non-conscious emotional memory. This memory could result in a chronic hyperactive fear response when triggered by certain stimuli long after combat. Administering the drug could modulate the fear response. Soldiers would respond appropriately to threatening

events but would not form pathological emotional memories of them. Yet if the drug blunted this response too much, then soldiers could end up being wounded or killed because they would have lost their normal fight or flight response. What was intended as a prophylactic intervention to prevent harm could unwittingly result in harm.

Alternatively, suppose that some of these soldiers already had these pathological memories and were diagnosed with PTSD. The drug would be administered shortly after they returned from combat and ideally would weaken or erase the memories from their storage site in the amygdala. This would be a way of treating the veterans of the war who returned home with the disorder. Here too it is possible that the people treated would develop inappropriate responses to fear inducing stimuli and would become vulnerable to threats in everyday life. Furthermore, although the amygdala regulates non-conscious emotional memory and the hippocampus regulates conscious episodic memory, it is unclear whether a drug aimed at altering the first type of memory would have any effect on the second. The amygdala and hippocampus are both parts of the limbic system, which regulates general emotional processing and therefore are not entirely independent of each other. The action of the drug would have to be very specific, and it would be difficult to predict that the drug would not have any adverse effects on other memory systems. There is no guarantee that targeting negative emotional memories in the amygdala would not result in collateral damage to episodic memories in the hippocampus. Indeed, the results from the experiments by Strange and colleagues seem to confirm this fear. Different memory systems are interconnected to some degree through complex neural pathways. These findings suggest that the benefits of beta-adrenergic blockade or modulation of negative emotional memories may entail costs to the encoding of episodic memories, as well as the potential loss of these memories in retrograde amnesia.

The primary use of beta-adrenergic antagonists such as propranolol is to block or diminish the cardiovascular excitatory response to the stress hormones adrenaline and noradrenaline. Propranolol has been used as a first line antihypertensive and antiarrhythmic agent. This and other betablockers are generally classified as antiarrhythmic drugs because they can correct heart rhythm abnormalities by blocking beta-adrenergic receptors in the heart. In some cases, these drugs can have the opposite effect and exacerbate arrhythmias. Presumably, propranolol would not have this effect because of the way it acts on autonomic brain functions. Still, it is not known what effects the chronic use of this drug might have on all the systems involved in the stress response. Specifically, it is unclear whether the intended blocking effect to treat PTSD could be limited to the amygdala.

Perhaps the main problem with beta-adrenergic blockade of stress hormones is that not all people who experience trauma are susceptible to PTSD or to related psychiatric disorders. The initial response is not predictive of who will develop a full blown disorder. Some people who experience a traumatic event may have sleeping difficulties, nightmares, or obsessive thoughts; but these often disappear not long after the event. In these cases, people would be given a putative therapeutic medication they did not need and would be exposed to its potential risks. One of these risks could be the loss of positive episodic and emotional memories. This could occur if these drugs affected multiple memory systems regulated by multiple cortical/limbic pathways in the brain. These brain pathways include not only the regions that compose the limbic system, but also the prefrontal cortex and its projections to and from such limbic structures as the amygdala and the hippocampus. On the other hand, failure

to intervene in those who are susceptible could mean losing the opportunity to prevent or effectively treat the disorder. Imaging studies indicate that people with PTSD have smaller hippocampi than those without the disorder. It is not known, however, whether this is a marker of susceptibility to the disorder, or an effect of it. Even if magnetic resonance imaging (MRI) or other brain scans could identify those who were at risk, it would not be feasible to scan the brain of every patient admitted to the emergency room following an accident.

Nevertheless, if propranolol could dampen or erase the pathological memories symptomatic of PTSD, then its use could be justified on the ground that a life of psychic suffering is worse than the loss of some positive emotional or episodic memory. The potential benefits of the drug therapy would outweigh the potential risks, significant though they may be. A combination of cognitive/behavioural therapy and anti-anxiety or antidepressant medication has been the conventional treatment for PTSD. Unfortunately, in many cases these interventions have not been effective in treating the disorder. When a condition is intractable to other interventions, when it severely affects one's quality of life, and when it poses a significant risk of harm to oneself and to others, considerations of immediate efficacy can override considerations of long term safety.

In its most recent report, the United States President's Council on Bioethics warned against the psychopharmacological manipulation of memories.^{7,8} It expressed concern about the possibility of therapeutic forgetting on the ground that it could subtly reshape who we are. Unpleasant memories are a necessary imperfection in our human nature. Preventing or eliminating memories would be an undesirable and inherently immoral alteration of our humanity. This position fails, however, to draw the critical distinction between conscious episodic memories that are merely unpleasant and non-conscious negative emotional memories that are pathological. The second type is at the core of psychiatric disorders such as PTSD and severe depression and causes considerable disability and suffering in the people affected by them. Treating these disorders with beta-adrenergic antagonists or other psychopharmacological agents is not meant to alter a normal self, but rather to restore a sick self to a normal healthy state. Even if these drugs significantly altered the brain and mind, it seems preferable to alter the self by erasing pathological memories than to retain the self associated with these memories. A substantial alteration of psychological properties might preclude a comparison of earlier and later selves and prevent us from saying that the earlier self was made better off and thus benefited from the alteration. Such a comparison might not be possible if the alteration disrupted psychological connectedness and continuity and thus disrupted personal identity through time. Still, the effect of possibly altering personal identity and the self seems better than the alternative, for intuitively it is preferable to eliminate pathological states of mind than to retain them.

The therapeutic use of drugs targeting emotional memory in mental disorders such as PTSD is very different from the therapeutic use of a distinct class of drugs targeting memory in neurodegenerative disorders such as Alzheimer's disease. Drugs used to treat Alzheimer's aim to prevent additional loss of episodic and semantic memory, especially in the early stages of the disease—for example, donepezil and memantine are designed to do this by preventing further neuronal loss and atrophy in the hippocampus, which is the main brain region implicated in the disease. Propranolol for PTSD aims to erase or prevent pathological emotional memories from forming in the amygdala. These are two distinct interventions with distinct aims involving different memory systems.

The long term effects of propranolol and similarly acting drugs on non-conscious emotional memory are not known. In particular, it is not known what dosage of the drugs, or when to administer them, would be optimal for preventing pathological fear responses while retaining normal responses to fear inducing stimuli. In addition, it is not known what effects erasure of these memories would have on other memory systems. It could result in the loss of episodic or other memories that are critical to personal identity through time. The potential side effects of preventing pathological memories from forming could be just as harmful to an individual as the potential side effects of erasing existing pathological memories. While erasing episodic memories could disrupt the psychological connectedness between one's present awareness and awareness of one's past, preventing new episodic memories from forming could disrupt the psychological connectedness between one's present awareness and one's anticipation of the future. This could adversely affect one's ability to learn new things and to plan and undertake new projects. Thus the potential side effects of memory erasure and prevention are equally metaphysically and morally significant. All of these considerations indicate that more studies like those of Strange and Pittman are needed to accurately assess the safety and efficacy of these drugs.

MEMORY ENHANCEMENT

An even more exciting area of psychopharmacology is the use of drugs to enhance different mechanisms of memory. Unlike the use of beta-adrenergic antagonists to inhibit the formation of, or to erase, pathological emotional memories, these drugs would enhance the storage and retrieval of normally functioning semantic memory and its connection to working memory. As noted earlier, working memory can be characterised as short term form of declarative memory, which consists of episodic and semantic memory. Working memory is regulated by the prefrontal cortex, which retrieves semantic and episodic memory of facts and events from a long term storage site in the hippocampus for short term use. Drugs that are already under development aim to increase memory storage by acting on the transcription factor cyclic adenosine monophosphate (AMP) and the protein that it modulates, CREB (cyclic AMP response element binding protein). This protein is responsible for switching on and off the genes involved in long term memory formation and storage. Memory enhancing drugs would activate CREB through a series of molecular interactions. The drugs would stimulate the neurotransmitter glutamate at the synapses connecting neurons, which would then activate the NMDA (N-methyl-D-aspartate) receptor and increase the supply of CREB inside neurons and thereby strengthen memory consolidation in the pathway between the hippocampus and prefrontal cortex.

Memory enhancement could benefit individuals by enabling them to access a broader base of factual and conceptual information, as well as to process this information more effectively in decision making and other cognitive tasks. It could promote greater opportunity for individuals to have better education and more lucrative employment. This in turn could benefit society as a whole by creating a more informed population with a higher standard of living.

Some famous cases of people with traumatic brain injuries suggest that different memory systems in the brain operate independently and that damage to them is highly selective. In one case, a person experienced retrograde amnesia and lost episodic memory of the past. He did not, however, experience anterograde amnesia, or the ability to form new memories. In a different case, a person experienced both retrograde and anterograde amnesia, yet he retained semantic and

procedural memory.⁹ These examples suggest that CREB boosting drugs could enhance the storage and retrieval of semantic or working memory without adversely affecting conscious episodic memory or non-conscious procedural and emotional memory. If memory systems operate independently of each other, then we should be able to use “smart drugs” to target and enhance one system without having to worry about any collateral damage to other systems.^{10–12}

There is, however, some disagreement within the research community about the presumed independence of memory systems. Some believe that, despite reported cases of selective damage to different memory systems, these systems are interconnected through various pathways in the brain.^{13–15} The hippocampus and its projections to the prefrontal cortex may, for example, play a critical role in both episodic and semantic memory. If memory systems are interconnected, then could enhancing the mechanisms of one system impair the mechanisms of others? In particular, could enhancing the storage capacity of semantic memory impair the capacity of working memory to retrieve information?

These questions are motivated by an evolutionary interpretation of memory. The limits we have in our capacity to remember only so many facts or events may be part of a natural design that is critical for our survival. Each memory system may have optimal levels of formation, storage, and retrieval, in which case trying to increase the storage capacity of memory in a particular system could have deleterious effects on formation or retrieval in that system or in other systems. Ideally, we would want to use drugs that both increased memory formation and storage and made memory retrieval more efficient across all memory systems. A more rapid rate of memory retrieval might, however, affect the brain’s ability to form and store memories. Moreover, increased storage would not necessarily mean quicker retrieval. More facts stored in the brain might result in an overloaded short term working memory, which could impair the ability to execute cognitive tasks and to learn new things, which depends on a certain degree of forgetting. This makes good evolutionary sense. It is advantageous for us to recall facts and events, or to learn new facts, to the extent that they enable us to perform cognitive and physical tasks of daily life that are necessary for our survival. It is not obvious that storing many memories beyond what is useful in helping us to carry out these tasks could benefit us in this regard or any other.

CREB BOOSTING DRUGS

These considerations suggest that there may be an optimal amount of CREB in our brains for memory. Too much CREB could result in an overproduction and oversupply of memory, which could result in our brains and minds becoming cluttered with memories of facts and events that served no purpose. This memory overload could impair our ability to perform complex cognitive tasks, which ironically would defeat the aim of using these drugs. CREB boosting drugs could also overstimulate glutamate. Too much glutamate can kill neurons and thus inhibit the formation of new memories or even eliminate memories that already have been formed and stored in the brain. Admittedly, this is speculative. Yet if there is an optimal balance between remembering and forgetting, then it seems plausible to hypothesise that increased semantic memory storage and decreased forgetting could result in impaired semantic memory retrieval. Neuroscientist Martha Farah supports this point: “We understand very little about the design constraints that were being satisfied in the process of creating a human brain. Therefore, we do not know which ‘limitations’ are there for a good reason...normal forgetting rates seem to be optimal for information retrieval.”^{16–17} Farah further warns of “hidden

costs” of trying to enhance memory, and that evolutionary considerations should make us wary of the prospect of general cognitive enhancement as a “free lunch”. We should be wary of making the inference that if a certain amount of memory is good, then more memory is better. This point was made by J. McCaugh in his testimony before the US President’s Council on Bioethics.⁷

The potential problem of memory overload that I have described could be avoided by separating retrieval of recent memory from retrieval of remote memory. Presumably, researchers could avoid any adverse effects by using smart drugs enhancing the storage and retrieval of recent memory while allowing normal forgetting rates of remote memory. Nevertheless, even recent memory can involve many trivial details that could clutter the mind, and it is unclear how specially designed drugs could effectively weed out recent memory of trivial facts from recent memory of useful facts. Nor is it clear that quicker retrieval would not have any untoward effects on the formation and storage of useful semantic memory. Again, the idea of an optimal balance within and among memory systems serving an adaptive purpose seems intuitively plausible. It is unclear how artificial manipulation of naturally designed memory systems that have served us so well could improve these systems. More importantly, it is unclear whether this could be done without any short or long term risks to these systems. There is no “memory bank” in the brain corresponding to computer memory. Memory systems in the human brain could not easily be upgraded or expanded by activating neurons with certain drugs, unlike replacing or adding silicon chips in computers to upgrade or increase computer memory. Human memories are not encoded in specific neuronal connections, but are distributed across multiple neural pathways. Because of the complexity of these pathways, it would be difficult to design drugs that could effectively and safely target specific functions of specific memory systems without adversely affecting other functions of other memory systems.¹⁸

A different worry is that altering regions of the brain that control memory and other cognitive functions might disrupt emotional functions. Cognitive and emotional processing are part of an interconnected system in the mind, which is regulated by interconnected cortical/limbic pathways in the brain. Because of these interactions, trying to enhance cognitive processing could impair emotional processing. A drug that made one “smarter” might also make one emotionally flat by blunting one’s affective capacities. Even the therapeutic use of psychopharmacological agents to treat cognitive deficits could have this effect. Anecdotal evidence suggests that dextro-amphetamine (Adderall), which is in the same class of drugs as methylphenidate (Ritalin), can have adverse effects on mood. One woman taking this drug to improve attention, memory, and other cognitive abilities that had become impaired due to an earlier series of concussions noted: “I worked like a demon, but I found myself disconnected. At the computer I was entirely focused, but off duty, certain pleasures, like wandering around aimlessly in my own mind, were no longer available to me.”¹⁹ It is also possible that, given the connection between cognition and emotion, too much of one and too little of the other could impair some forms of reasoning. In psychopathy—for example, there appears to be a correlation between the inability to experience certain emotions and the inability to rationally consider the long term consequences of action.^{20–22} The constellation of psychological effects of cognitive enhancement might not be so desirable.

No one knows what the long term cognitive, affective, or conative effects of memory enhancing drugs would be. Chronic use of psychotropic drugs could lead to the remodelling of synapses and changes in neural circuitry,

and it is not known whether this would all be salutary or benign. To be sure, this concern is not unique to enhancement drugs but applies to therapeutic drugs as well. Still, it is one thing for a physician to prescribe a drug with potential adverse effects for therapeutic treatment of a mental disorder. It is quite another thing for a physician to prescribe a drug with potential adverse effects to enhance normal mental functions. Until there is a better understanding of any risks of using drugs for cognitive enhancement, the potential harm from long term use of these drugs justifies limiting them to short term use in special circumstances and only when there is a compelling reason to use them.

CONCLUSION

Psychopharmacology can be used therapeutically to prevent or erase pathological emotional memory. It can also be used non-therapeutically to enhance the normal formation, storage, and retrieval capacity of semantic and working memory. Each of these interventions raises a different set of medical, metaphysical, and ethical questions. Because off label and other novel uses of psychotropic and other drugs to alter the neurobiological substrate of memory are experimental, there is still considerable uncertainty about their effects on memory. Accordingly, more longitudinal studies involving a significant number of people are needed to accurately assess the risks and benefits of these drugs. These studies will determine how safe and effective the drugs are, which in turn will influence physicians' decisions regarding whether to prescribe them and individuals' decisions regarding whether to take them.

Memory is essential to our experience of persisting through time and is in this respect an essential component of personal identity, the self, agency, and responsibility. It is also critical to our survival in enabling us to recognise and respond appropriately to threats in the natural and social environment. There are different memory systems serving different biological and psychological functions. Some of these systems and functions may independently, whereas others seem to be interdependent. The psychological importance of memory and its neurobiological complexity make it clear that a better understanding of the effects of psychopharmacology on

memory is needed before we can argue that this type of intervention in the brain could be justified as a general practice.

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