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Opening The Reconsolidation Window to Extinguish Fear Memories: A New Conceptual Approach to Psychotherapeutics

Memory processes occur in several phases. **Short-term memory is converted to long-term memory by a process of consolidation** that requires the synthesis of new proteins. Transcription factors in the nuclei of hundreds of millions of nerve cells are activated so that specific synapses can be modified for the long term. If protein synthesis is inhibited during a period within a few hours after new learning has occurred, what was learned never gets consolidated and is essentially forgotten. It is thought that this phase of consolidation happens when a memory trace moves from short-term storage in the hippocampus to long-term storage in the cerebral cortex.

Recently a later phase of memory storage called reconsolidation has been identified. **When an old memory is recalled, the reconsolidation window opens, and the memory trace becomes temporarily amenable to change. The reconsolidation window (the period during which the trace can be revised) is thought to begin five minutes after a memory is recalled and last for an hour or possibly two.** New learning that takes place during the reconsolidation window can be more profound than learning that occurs without recall of the related memory or after the reconsolidation window has closed.

Consider the example of a fearful memory created when a person is attacked in a dark alley. If the person repeatedly visits the same alley without being attacked, they can eventually become less afraid of dark places. Repeated viewing of pictures of dark places can also extinguish the fear. These are typical ways in which a fear memory is extinguished. However, the original fear is subject to spontaneous recovery (the fear of dark places returns without provocation) or to reactivation (if another dangerous situation is encountered, the person may renew their fear of dark alleys).

The new findings suggest that if the extinction process (the repeated exposures to the pictures of the dark alley) takes place during the reconsolidation window after the fear memory of being attacked is recalled, the old fear can be permanently reversed (wiped clean, or re-edited such that it appears forgotten) so that it is no longer subject to spontaneous recovery or reactivation.

Editor's Note: To accomplish extinction training within the reconsolidation window, first a person must actively recall the old memory, opening the reconsolidation window. Then, after a 5-minute delay, extinction training (e.g. new learning that the old feared place is now safe) should take place within the next hour. This process has been demonstrated in animal studies and is thought to be clinically relevant for humans in the case of phobic anxiety and post-traumatic stress disorder (PTSD). The psychotherapeutic implications of using the reconsolidation window to better ameliorate PTSD fears, avoidance, and flashbacks are considerable.

Observing the Amygdala's Role in the Extinction of Fear Memory Traces

The amygdala is a crucial part of the learned or conditioned fear pathway. It is activated during fear conditioning and during the recall of cues associated with the fear experience. If the amygdala is removed, conditioned fear does not occur.

A new study published in Science this year by Agren et al. indicates that in humans, the amygdala-based response to conditioned fear can be completely abolished using extinction training within the memory reconsolidation window. Training that took place 10 minutes after the fear memory was activated was successful, while training that took place 6 hours later was not.

On day one of this study, participants were shown a visual cue while receiving a shock 16 times. They began to associate the visual cue with the shock, a process known as fear conditioning.

On day two, the memory of the shock was reactivated by showing the visual cue for two minutes. This was followed by extinction training (presentation of the visual cue without the shock). One experimental group received the extinction training after 10 minutes, i.e. within the memory consolidation window. The other group received the same extinction training 6 hours after seeing the visual cue, when the reconsolidation window had closed.

On day three, participants received a functional magnetic resonance imaging scan (fMRI) while connected to shock electrodes (but not receiving shocks). This revealed activation of the amygdala and related connections

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Also in this issue:

Using the Memory Reconsolidation Window to Extinguish Drug Craving

In the above article we discussed how fearful memories can be changed during the window in which they are reconsolidated (5 minutes to 1 hour after active recall of the long-term memory). **Now the memory reconsolidation window has been used in animals and people to extinguish an addiction to cocaine or heroin.** The results in humans were reported by Xue et al. in the journal *Science* in April 2012.

In a typical recovery scenario, a cocaine addict is repeatedly presented cocaine cues (such as paraphernalia) without the delivery of cocaine, and craving for cocaine becomes extinguished. While the patient stops craving the drug, some biological signs of the addiction remain, such as autonomic hyper-reactivity (e.g. changes in skin conductance, pulse, or blood pressure) in response to the cocaine cues. When the sober cocaine addict leaves the recovery program, he may believe he is no longer subject to cocaine craving even upon the sight of cocaine-related cues, but this craving can return spontaneously or be reactivated by cocaine-related environments or friends who were also users, and he typically relapses.

In order to make the extinction learning more powerful, it must be experienced during the reconsolidation window. In the animal experiments by Xue et al., rodents were trained to press a lever to receive an injection of cocaine or heroin. In the extinction process, the animals were returned for 15 minutes to the same environment where they had learned to press the lever and receive the drug. This was meant to activate memories associated with the drug. Then, after a 10-minute waiting period, a 180-minute extinction training was given. The process was repeated daily for 14 days and resulted in almost complete absence of relapse to drug use with passage of time (spontaneous recovery), exposure to the drug (reinstatement), or exposure to the drug-associated environment (renewal). Moreover, the expected changes in heart rate and blood pressure upon re-exposure to the drug cues were also fully extinguished. Extinction training that began one hour after activation of the memory was also successful.

When the same extinction training was given 6 hours after placing the animal in the drug administration environment, the animal remained prone to drug re-instatement and relapse in the same or different environments or spontaneously. It can be presumed that this occurred because the extinction training took place after the reconsolidation window had closed.

These well-controlled data with both cocaine and heroin self-administration in animals were then taken to the clinic to test their validity in humans.

The same procedure worked in humans addicted to heroin. Two consecutive days of sixty-minute extinction learning within the reconsolidation window, i.e. starting 10 minutes after a 5-minute retrieval of drug-associated memories by watching a video resulted in amelioration of drug craving for at least 184 days, and amazingly, as in the animals, also resulted in the loss of the unconscious biological reactivity in heart rate and to a lesser extent, blood pressure. Patients did not relapse during 6 months of followup. The same extinction process was unsuccessful when it occurred after patients viewed a neutral video without drug cues or when the extinction training occurred outside of the reconsolidation window, i.e. 6 hours after retrieving the drug-related memories.

Editor's Note: These results and the related results about fear conditioning (see page one) could be of considerable potential therapeutic value in a variety of psychiatric illnesses. This process is conceptual breakthrough that has great promise for clinical use. Psychiatrists, psychologists, and patients should become familiar with these data and the principles of exploiting the reconsolidation window for potentially transformational results.

How quickly these principles can be incorporated into mainstream psychotherapeutic encounters remains to be seen. However, clinicians should begin to familiarize themselves with these data and concepts so that they can soon be put to use for more effective clinical treatment of psychiatric conditions involving pathological learning, conditioning, and habits.

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Developing Rapid Onset Antidepressant Drugs That Act at the NMDA Receptor

For several years, researchers have been exploring potential rapid-acting treatments for unipolar and bipolar depression. Intravenous ketamine has the best-replicated results so far. **A slow infusion of ketamine (0.5mg/kg over 40 minutes) produces a rapid onset of antidepressant effects in only a few hours, but the improved mood lasts only 3-5 days.**

Ketamine blocks the receptors of the main excitatory neurotransmitter in the central nervous system, glutamate. Glutamate is released from nerve endings and travels across the synapse to receptors on the next cell's dendrites. There are multiple types of glutamate receptors at the dendrites, and ketamine blocks one called the NMDA receptor, which allows calcium ions to enter the cell.

Some downsides to ketamine are the brief duration of its effectiveness and its dissociative side effects. **The search is on for other drugs that are free from these side effects and that could extend the duration of rapid-onset antidepressant effects.**

At the 2012 meeting of the International Congress of Neuropsychopharmacology (CINP), Mike Quirk of the pharmaceutical company AstraZeneca reviewed data on the intricacies of the glutamate NMDA receptor blockade and discussed the potential of AZD6765, an NMDA receptor blocker he and his colleagues have been researching.

The more the NMDA receptor is blocked, the more psychomimetic it becomes, meaning it produces hallucinations and delusions. For example, phencyclidine (PCP or angel dust) is a potent NMDA receptor blocker and psychosis inducer. For antidepressant purposes, a less complete or less persistent NMDA receptor blockade is desired.

Ketamine enters the NMDA channel on a dendrite when the channel is open (and calcium ions flow in, dragging ketamine with them). When the top of the channel closes, much like the Venus flytrap plant closing and trapping an insect inside, much of the ketamine gets trapped in the channel, and the block persists or builds. Most of the ketamine (82%) is trapped in this way and interferes with normal glutamate functions.

Drugs that block the NMDA receptors vary in the rates at which they get trapped in the channel. Drug researchers would like to find a blocker that gets trapped at a low rate, so that only quickly firing neurons are blocked and normal low-level activity is left unperturbed. Among already developed drugs, ketamine is trapped at 82%, dizocilpine or MK801 (which is not used clinically due to its side effects) at 76%, the anti-Alzheimer's drug memantine at 70%, and the anticonvulsant remacemide at 64%.

In the case of AZD6765, only 52% to 59% of the drug gets trapped in the NMDA receptor. **AZD6765 has rapid-onset antidepressant effects like ketamine, but induces no minor dissociative symptoms or psychosis.** Following initial exploration, it is now being tested in larger, more rigorous placebo-controlled antidepressant trials of 8 and 12 weeks duration, which include multiple infusions.

As a general trend, many large pharmaceutical companies have recently been drastically reducing their research into neuropsychiatric drug development. In the past they often spent hundreds of millions of dollars on the development of a potential central nervous system psychotropic drug that often didn't even make it to market. Now, for example, AstraZeneca has trimmed its central nervous system drug development program from over 300 scientists to about 30. However, the potential of NMDA receptor blockers make this area of drug development appear promising, and Quirk and his remaining colleagues believe they are on the right track with AZD6765.

Extinguishing the Fear Memory Trace in the Amygdala

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in the fear circuit in the 6-hour group. However, the amygdala was not activated in the 10-minute group who had received the extinction training within the reconsolidation window. This suggests that for them, the amygdala-based memory trace was abolished.

On day five, participants received shocks (without the visual cue) and then were re-exposed to the photo. Fear response to the visual cue was measured via skin conductance responses. Participants in the 10-minute extinction group did not show any skin conductance response when they saw the visual cue. The 6-hour group did show skin conductance response to the visual cue, indicating that the fear memory persisted for this group. The 6-hour group also showed greater amygdala activation in response to the visual cue.

Editor's Note: Fear memories can be updated, revised, or abolished when new learning after active memory recall takes place within but not outside of the reconsolidation window. The fear memory trace that is seen by increased blood flow in the amygdala is abolished, and amygdala fear circuit connectivity with other areas of the brain is attenuated only when extinction training occurs within the reconsolidation window after active memory recall (i.e. 5 minutes to one hour after recall).

Agren et al. conclude: "Reactivated fear memories are sensitive to behavioral disruption...and the amygdala proves to be a key neurobiological substrate for this process [in animals and] also in humans." Timing new learning within the reconsolidation window is the key to long-term revision of habits and memories.

How Illness Progresses in the Recurrent Affective Disorders

This editor (RM Post) in collaboration with Jacqueline Fleming and Flavio Kapczinski published the article "Neurobiological mechanisms of illness progression in the recurrent affective disorders" in the *Journal of Psychiatric Research* this year. The article built on several themes about the progression of bipolar illness that had been explored in previous research.

These themes include: 1) the likely acceleration of repeated episodes as a function of the number of prior episodes (episode sensitization), 2) the increased responsivity of the illness to repeated stressors (stress sensitization); and 3) the increased behavioral reactivity to repeated use of psychomotor stimulants such as cocaine (stimulant-induced behavioral sensitization).

Not only are these observations well documented in the scientific literature, but recent observations also suggest that each type of sensitization can show cross-sensitization to the other two types. That is, **individuals exposed to repeated stressors are more likely both to experience affective illness episodes and to adopt comorbid substance abuse. In a similar way, episodes of an affective disorder and stressors may also be associated with the relapse into drug administration in those who have been abstinent**.

In addition to these mechanisms of illness progression in the recurrent affective disorders, the new article reviews the literature showing that the number of affective episodes or the duration of the illness appear to be associated with a variety of other clinical and neurobiological variables.

The number of affective episodes a patient experiences is associated with the degree of cognitive dysfunction present in their bipolar illness, and experiencing more than 4 episodes of unipolar or bipolar depression is a risk factor for dementia in late life. A relative lack of response to most treatments is also correlated with the number of prior episodes, and this holds true for response to naturalistic treatment in general. While most of these data are correlational and the direction of causality cannot be ascertained for certain, it is likely that the number of affective episodes and/or their duration could account for and drive difficulties with treatment and with cognitive function.

If this were the case, one would expect to see a variety of neurobiological correlates with the number of prior episodes or duration of illness, and in the article we summarize those that have been found in unipolar and bipolar disorder. Considerable data indicate that cortical volume and degrees of prefrontal cortical dysfunction can vary as a function of number of prior episodes. There is evidence that increased activity of the amygdala and the nucleus accumbens are also related to episodes or duration of illness. In those with unipolar depression, the volume of the hippocampus is decreased with longer duration of illness.

Some inflammatory markers also increase as a function of number of episodes or duration of illness, and recent studies have indicated that patients with bipolar disorder and other serious mental disorders have shorter life expectancies than the general population, based largely on increases in cardiovascular-related illnesses.

The ratio of short to long telomeres (the segment of DNA at the end of each chromosome), which increases as a function of aging, is significantly higher in bipolar II depressed patients as a function of number of prior depressive episodes. This increase in short telomeres is equivalent to approximately 10 years of premature aging. Stress and its downstream effects on cortisol and other stress hormones as well as inflammatory processes could result in this increased proportion of short chromosomes, but the pathophysiological mechanisms by which this occurs in bipolar II depressed patients have not yet been identified.

There are many reasons why numbers of episodes of depression could relate to degree of neurobiological abnormality, based on the findings that each episode of depression is associated with increases in inflammatory factors and oxidative stress and the production of free radicals, as well as decreases in neuroprotective factors such as brain derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF).

Recurrent episodes may increase the number of factors toxic to neurons and glial cells in the relative absence of neuroprotective factors. This would provide a plausible set of mechanisms to explain the relationship of number of episodes to brain and somatic system abnormalities. However, it again must be cautioned that it is also possible that greater degrees of these abnormalities are associated with a greater vulnerability to episode recurrence, and the direction of causality remains to be further ascertained.

Nonetheless, preventing episodes is a goal that has considerable merit in its own right, as this would decrease the suffering and dysfunction associated with manic and depressive episodes even if it did not mitigate the neurobiological abnormalities and slow the progressive course of the affective disorder.

Thus the clinical message of this research into illness progression is that there is a great need for early intervention and long-term prevention in the recurrent affective disorders, to prevent morbidity and mortality from these illnesses, but also to lessen the risk of illness progression and deterioration.

Prevent episodes, protect the brain is our new motto.

Patients with Bipolar Depression Have a Higher Mortality Rate From Suicide, Especially if They Also Have Cardiovascular Disease

In a large longitudinal study of depressed patients in Taiwan that was published in the Journal of Psychiatric Research this year, Chang et al. found that after 10 years, patients with bipolar depression (N=1,542) had significantly higher mortality rate than those with other types of depression (N=17,480). **Patients with bipolar depression were twice as likely to have died from suicide or accidental death than were patients who had other types of depression.** When cardiovascular disease was also present in both groups, patients with bipolar disorder were also four times more likely to have died from suicide or accidental death than those with other types of depression.

Editor's Note: These data again emphasize the critical importance of patients with bipolar disorder carefully looking after their medical and cardiovascular health both early on and throughout the entire course of their illness.

Much of the excess medical mortality in bipolar disorder is attributed to cardiovascular disease, and now those with cardiovascular disease also appear more prone to suicide. This should be a call to action to improve the long-term treatment of both bipolar disorder and its common comorbidity, cardiovascular disease.

Get your medical illness treated!

It will improve your health and longevity.

Especially treat these signs of the metabolic syndrome, a major risk factor for cardiovascular disease:

Cholesterol
Increase "good" cholesterol (high-density lipoproteins or HDLs) to over 50 mg/dL for women or over 40 mg/dL for men

High Triglycerides
Triglycerides should be below 150 mg/dL

Blood Pressure
Aim for 130/85 mmHg or lower

Blood Sugar
Fasting blood sugar (glucose) should stay below 100 mg/dL

Overweight & Obesity
Keep waist circumference under 40" for men or 35" for women

Exercise is good for all of these!

The Impact of Obesity on the Brain and on Cognitive Abilities

In an abstract presented at the 5th Biennial Conference of the International Society for Bipolar Disorders, K. Sim and colleagues discussed the impact of increased body mass index on the integrity of white matter in the brain during a first episode of mania. **The researchers found significant abnormalities in white matter integrity in the temporal pole and occipital brain regions in overweight and obese patients compared to patients of normal weight.** These data highlight the need to clarify the neural mechanisms that link obesity and poorer functional outcomes in bipolar disorder.

Other investigators have reported that bipolar patients with obesity have a less robust response to naturalistic treatment compared to those of normal weight. At least one study suggested that patients with overweight and obesity experience more cognitive difficulties.

Editor's Note: The pathophysiological mechanisms involved in the relationship between weight and brain function are not yet clear, although one possibility is that in obese patients, some fat cells in the abdominal area become too big to survive and are scavenged by other cytokine-producing cells. These inflammatory cytokines are then able to cross the blood-brain barrier, enter the brain, and affect neuronal functioning. Whether a mechanism like this is at play in relation to these particular findings remains for further investigation.

Nonetheless, these data suggest the importance of good diet, exercise, and other means of maintaining a good body weight in order to attempt to avoid some of the adverse associations of obesity with deficits in cognition, white matter integrity, and treatment outcome.

Exercise and Brain Health: Some Good Points to Remember

In a review article in the Neuroscientist published in February of this year, Kirk I. Erickson and collaborators wrote that "[m]ajor depressive disorder is considered a risk factor for Alzheimer's dementia and memory impairment and is associated with less BDNF and greater hippocampal atrophy, possibly through a BDNF pathway. However, **exercise and effective treatment for geriatric depression increases BDNF levels, increases serotonin fibers, is associated with greater hippocampal volumes, and reduces the risk for Alzheimer's dementia**."

Editor's note: Not a bad set of benefits from exercise! The researchers suggest that exercise is extremely important in reversing the decreases in brain-derived neurotrophic factor (BDNF) associated with depression, helping to improve depressed mood, increasing cardiovascular fitness, and maintaining healthy cognition.

Hippocampal volume and BDNF levels in blood both decrease with age. Yet exercise increases both BDNF and the formation of new neurons (neurogenesis) in animals. New data in humans suggest that aerobic fitness is associated with the size of the hippocampus, both in both children and adults. It is not clear yet whether this increase in hippocampal volume is directly driven by increases in BDNF and/or neurogenesis. However, since a smaller hippocampus is a risk factor both for depression and for mild cognitive impairment progressing to Alzheimer's dementia, attempting to enhance hippocampal volume in any way possible is probably a good idea.

Methods of increasing hippocampal volume include treatment with antidepressants or with lithium. In the 2012 paper Erickson and collaborators also wrote, "Anaerobic exercise enhances executive and memory function and reduces hippocampal atrophy in late adulthood, and this may be partially mediated through a BDNF pathway."

Erickson and collaborators conducted a longitudinal study published in 2010 that quantified the amount of physical activity subjects engaged in by calculating the total number of blocks walked per week. Individuals reporting greater amounts of physical activity at the beginning of the study had, upon examination nine years later, greater gray matter volume in several parts of the brain, including the hippocampus. This effect was "dose-dependent," meaning that only those individuals who walked at least 72 blocks per week (roughly equivalent to 1 mile per day) had significant sparing of brain tissue nine years later. The study found increased gray matter volume in the prefrontal cortex and in the temporal lobe.

After a further follow-up of four more years, greater gray matter volume with physical activity was associated with a two-fold reduced risk of cognitive impairment. The researchers concluded that "physical activity patterns earlier in life were linked to brain volume and cognitive impairment later in life."

There are a number of important points to remember about cognitive impairment. One is that increasing hippocampal volume and preventing its decrement with aging may help prevent age-related memory loss and potentially the rapidity at which mild cognitive impairment progresses.

A second point is that it is critically important to prevent depressive episodes, since having more prior depressions is associated with experiencing more cognitive dysfunction, and there is some evidence that it may also be associated with decreasing volume of the hippocampus.

A third point is that several different modes of helping protect hippocampal volume are available.

1) Antidepressants: Researcher Yvette Sheline has shown that unipolar depressed patients on antidepressants more of the time compared to less of the time do not experience hippocampal volume loss with aging. These data converge with others that indicate that antidepressants either increase hippocampal volume or prevent its decrement, likely through by increasing BDNF and neurogenesis.

2) Lithium: Lithium increases hippocampal volume in patients with bipolar disorder and is also known to increase BDNF and neurogenesis. Preliminary data from a large population of patients studied in a Danish case registry also suggest that patients who renew their lithium prescriptions are less likely to receive a diagnosis of dementia in old age. A small study published by Forlenza et al. in the British Journal of Psychiatry in 2011 indicated that treatment with lithium at 150mg/day compared to placebo over a period of one year decreased the rate of cognitive decline in psychiatrically well patients in the general population who had mild cognitive impairment (MCI).

3) Long-term maintenance: Long-term preventative treatment is important in both unipolar and bipolar depression. Antidepressants in unipolar patients not only help prevent depressions (and the associated decreases in BDNF in the brain and the blood), but also protect hippocampal volume. In bipolar patients, effective mood stabilizers for adequate long-term prophylaxis are critically important. These drugs are able to increase BDNF. Lithium in particular also increases hippocampal volume.

4) Exercise: Now it seems that including exercise as part of one's regular approach to maintaining good health might also lead to benefits in

Getting Motivated for Exercise During a Depression

maintaining hippocampal volume and associated memory function with aging. While the literature is mixed about the role of exercise as an antidepressant, a sufficient number of positive controlled studies have indicated that it can be helpful. Exercise-induced increases in BDNF may be important both in helping to ward off depression and preventing hippocampal volume loss with aging.

Previously we have suggested a mantra for long-term prevention of mood disorders: "Prevent episodes, protect the brain." To this mantra we might add a new one: **"Exercise protects the heart and the brain."** Not only is exercise a way of increasing cardiovascular fitness, which itself is associated with increases in hippocampal volume, but exercise has many other potential benefits as well, particularly in the cardiovascular arena. In addition, exercise directly increases BDNF and neurogenesis, and also increases the ratio of beneficial or high-density lipoproteins to problematic or low-density lipoproteins.

Enhancing Motivation For Exercise During A Depression

One common problem for depressed patients is lack of motivation to exercise, even in those who enjoy exercise and are highly committed to it when euthymic. Approaching exercise in small steps may be helpful. A walk around the block may be a good first step, and the distance can gradually be increased. Walking, bicycling, sports, or other forms of exercise that can be done with a friend may increase motivation to exercise while also providing social support. In patients who like dogs, having a dog that insists on a regular walking routine may also be helpful.

Exercise also has benefits in the realm of weight control. Patients who are depressed tend to move less and gain weight accordingly. Exercise, as well as good dietary habits, can be a key element in helping to maintain one's weight during depression or to reduce it during periods of planned dieting in those who are overweight.

There is another potential benefit to exercise, this one neurobiological. Since exercise helps in the generation of new neurons, it may also increase some higher-level cognitive processes that require fine discrimination between choices. Animal studies by Fred Gage and colleagues have revealed that newly formed cells in the hippocampus are more excitable than older neurons. Older neurons are adequate for discriminating objects that are markedly different, but young neurons can differentiate between two closely related objects or concepts thanks to their hyperexcitability, and this may be an asset in some types of demanding cognitions.

In summary, exercise is good for: the hippocampus, cognition, depression, cardiovascular health, and weight maintenance.

Modern modes of transportation like cars, planes, trains, escalators, moving sidewalks, and even flights of imagination from the sofa while watching TV or from the desk chair while using the internet make it too easy to avoid exercise. Building exercise into one's general health regimen (or therapeutic regimen in those with depression or mild cognitive impairment) may be a way of overcoming the unintended negative consequences of modern life. So "A mile a day keeps memory loss away" may be a good thought for those of us who want to protect our brains and bodies for as long as possible.

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