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Prevention of recurrent affective episodes using extinction training in the reconsolidation window: A testable psychotherapeutic strategy

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ABSTRACT

Stressors may initially precipitate affective episodes, but with sufficient numbers of recurrences, episodes can occur more autonomously. It is postulated the memory engram for these recurrent depressions moves from the conscious representational memory system to the unconscious habit memory system encoded in the striatum. If this were the case, cognitive behavior therapy targeted toward extinction of habit memories could be an effective maneuver for helping reverse the automaticity of affective episode recurrence. Extinction training in the reconsolidation window (which opens about 5 min to 1 h after active memory recall) can revise, reverse, or eliminate the long term memories associated with PTSD and other anxiety disorders and with drug abuse craving. We hypothesize that similar cognitive behavioral work in the reconsolidation window could inhibit stress-induced and spontaneous affective episodes. Some initial formulations of possible therapeutic strategies are presented and discussed, as well as caveats. It is hoped that preliminary exposition of this theoretical approach to recurrences in the affective disorders based on principles dependent on work in the reconsolidation window will lead to more detailed elaboration of the therapeutic maneuvers most likely to be successful and ones that can be specifically tested for their clinical efficacy.

1. Introduction

1.1. Background on memory formation, consolidation, and reconsolidation

Memory formation goes through successive stages of encoding. Hippocampally-based short term memory has long been known to require consolidation into long term memory in the cerebral cortex by a process that requires gene expression and new protein synthesis. In 2000, Nader et al. (2000, 2013) discovered a new later phase in memory storage called reconsolidation. Reconsolidation occurs after a long term memory is actively recalled and the old memory is reprocessed in such a way that it again requires new protein synthesis (Fig. 1). In addition to memory recall, there must be novel information or context for opening of the reconsolidation window (Agren, 2014; Ecker, 2015). Fig. 2.

During this phase of reconsolidation, the memory trace becomes labile and subject to long term revision by psychological processes occurring within the reconsolidation window which lasts approximately 5 min to 1 h (and possibly up to 5 h) after the active memory recall. The original memory trace can either be further strengthened with each

new reconsolidation experience or modified and revised if the circumstances and requirements for new learning are met. Ecker (2015) describes “reconsolidation as having two biological functions: (a) It preferentially strengthens recent learnings that are most frequently reactivated and destabilized, and (b) it allows new learning experiences to update (strengthen, weaken, modify, or nullify) an existing learning.”

In this manuscript we review some of the pertinent clinical and preclinical data on the use of new learning within the reconsolidation window to alter conditioned fear and memories of positive drug experiences that drive addiction. How these concepts might then be utilized in psychotherapy to attempt to prevent the recurrences of depression are preliminarily outlined, and how these effects could be potentiated by medications is discussed. The potential for exacerbation as well as positively modifying emotional learning is also described. Thus, it is hoped that the current exposition of the role of reconsolidation memory in the psychotherapeutic process will provide further background information for clinicians and investigators wanting to utilize these concepts in the development of more systematic approaches to preventing depressive episodes in the recurrent mood disorders.

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Opening the Reconsolidation Window Renders a Long Term Memory Trace Labile and Subject to Permanent Revision

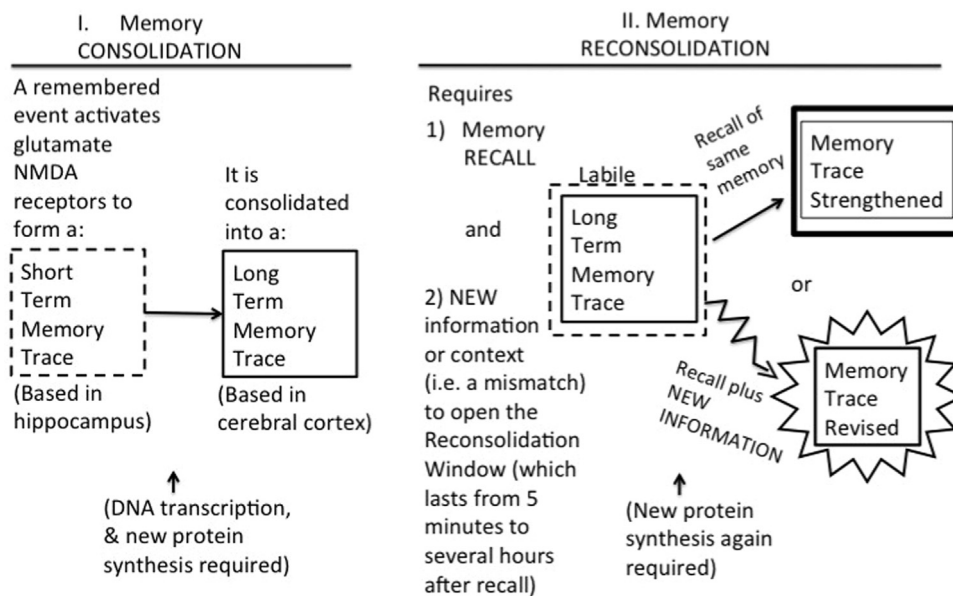


Fig. 1. There are two phases of memory consolidation. Short term memory requires new protein synthesis for I. CONSOLIDATION into long term memory. Active recall of the long term memory in the presence of new information (what has been called mismatch prediction error) activates a phase of II. RECONSOLIDATION, which renders the old memory amenable to revision during a window of about 5 min to several hours after recall. It again requires new protein synthesis. In the RECONSOLIDATION phase the memory can either remain intact and be strengthened (if there is no mis-match) or revised in the presence of new information.

1.2. Conditioned fear: erasure in the reconsolidation window

The memory trace of a conditioned fear association in humans (Agren et al., 2012) can essentially be erased if extinction training occurs in the reconsolidation window, but not at 6 h after recall (by which time the reconsolidation window has closed). In the study of Agren et al. (2012), the appearance of a specific photograph (the conditioned stimulus, cs) that was repeatedly associated with a mild

shock (the unconditioned stimulus, ucs) acquired conditioned stimulus properties and the picture itself came to evoke a fear response. Sight of the picture was also associated with activation of the amygdala as seen on functional magnetic resonance imaging (fMRI) and with changes in skin conductance even when no shock is given.

However, after active recall of the memory linking the picture with the shock, the conditioned fear memory trace could be revised by extinction training within the re-consolidation window, ie the repeated

DISRUPTION of RECONSOLIDATION ERASES AMYGDALA FEAR MEMORY TRACE in HUMANS (Agren et al 2012)

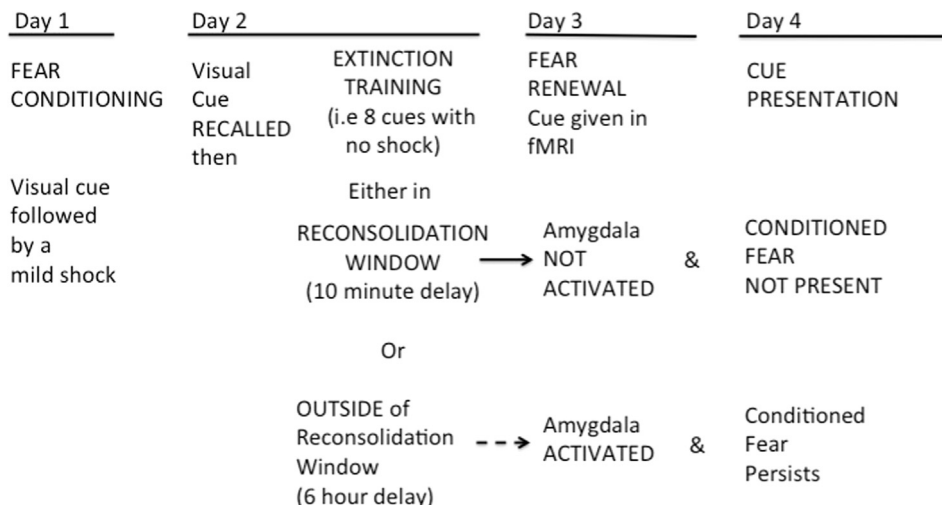


Fig. 2. This study of Agren et al. (2012) shows that in normal volunteers extinction training within the reconsolidation window (the 10 min group) reduces conditioned fear and eliminates the associated amygdala activation seen on the fMRI. These positive results do not occur if the same extinction training is conducted outside of the re-consolidation window (the 6 h delay group).

exposure to the picture not followed by the shock. The specific picture eventually ceases to evoke fear subjectively or objectively as measured by the changes in skin conductance previously seen. Remarkably, the fMRI study reveals that the amygdala activation which had previously occurred upon presentation of the picture (the former conditioned stimulus) also no longer occurs.

If however the exact same extinction training is conducted 6 h after active recall of the cs-ucs pairing, the conditioned fear response remains intact along with changes in skin conductance and the amygdala activation persists. Thus, both active memory recall is required to open the re-consolidation window and the extinction training (new information or expectancy mis-match) must take place in the 5 min to several hour time frame. The active recall renders the memory trace labile and subject to long term if not permanent revision and the amygdala-based memory trace is taken off line (Agren et al., 2012).

Ecker (2015) and Sevenster et al. (2013) emphasize that it is not just active recall and memory reactivation that is sufficient to open the reconsolidation window, but a new set of expectancies must be present as well, which Ecker labels as mismatch prediction error. The expectancy is that the conditioned stimulus will be followed by a shock and when this does not occur there is new information that is at odds or mismatched with the prior learning. Viewed from this perspective, when there is no mismatch, memory is reconsolidated and the fear memory persists.

It is noteworthy that the procedures and their temporal sequence involved in Eye Movement Desensitization and Reprocessing (EMDR) which has been used for rapid treatment of post traumatic stress disorder (PTSD) would appear to make implicit use of the same principles of active trauma memory recall followed by reworking of the memory in the re-consolidation window (Hogberg et al., 2008). However, in EMDR eye movement tracking is also employed and some, but not all literature supports the potential importance of this added ingredient. Similar therapeutic work in the re-consolidation window (without associated eye tracking) has been used in the treatment of anxiety disorders and PTSD (Schwabe et al., 2013, 2014), and even more remarkably in the treatment of animal and human addictions as noted below. Ecker (2015) emphasizes: “In a juxtaposition experience, the client lucidly experiences *both* the problematic original learning or schema *and* a contradictory, disconfirming new learning in the same field of awareness—not just the desired new experience by itself.”

1.3. Revision of addiction memories and decreased proneness to relapse

For example, Xue et al. (2012) and Sartor and Aston-Jones (2014) showed that cocaine re-instatement in the rodent (frantic pressing a bar that had previously delivered cocaine, but no longer does) could be prevented by extinction training in the re-consolidation window, but not outside of it. Xue et al. (2012) took these preclinical findings into the human arena and validated that these procedures work in patients who were addicted to heroin and cocaine. Normally when an addicted individual undergoes traditional therapy and abstinence in a hospital or jail, they are at very high risk for relapse when they are re-exposed to the environment where they typically used drugs, see drug paraphernalia or other drug cues, or ingest tiny amounts of drug.

However, in humans addicted to heroin (Xue et al., 2012), the extinction training immediately after active recall of the positive drug experience (while watching an appealing drug-related video) resulted in long lasting (up to 180 days) decreases in subjective drug craving, an absence of relapse, and a lack of the blood pressure increases (mediated by the autonomic nervous system) that had previously accompanied exposure to drug cues (Fig. 3). All of the same procedures after watching a neutral video (which fails to open the re-consolidation window) resulted in prominent relapses and blood pressure changes upon cue presentation. Saladin et al. (2013) also showed that post-

retrieval propranolol could transiently alter re-consolidation memory for craving in cocaine dependent patients.

2. Conceptual formulation of the recurrent affective disorders

2.1. Successive stages of evolution of recurrent affective illness based on sensitization to stressors, episodes, and substances of abuse

We now ask how and whether these clinical data and concepts of extinction training in the re-consolidation window might be applied for therapeutic intervention in the recurrent affective disorders. Kraepelin (1921) originally observed that initial episodes of affective disorder were often triggered by psychosocial stressors, but with enough recurrences they could begin to occur with more minor stressors, mere anticipation of stressors, or more automatically with no stressors at all. We have reviewed the literature which is largely consistent with these observations and further codified them in the frame work of the kindling and sensitization model of the recurrent affective disorders (Post, 1992, 2007, 2008, 2010, 2013, 2016a, 2016b).

The findings of episode sensitization (faster recurrences as a function of number of prior episodes) has been most clearly validated in the reviews and work of Kessing et al. (Kessing and Andersen, 2001; Kessing et al., 1998). Stress sensitization (increased reactivity to recurrence of stressor) has been validated in multiple types of laboratory (Antelman, 1988; Kalivas and Stewart, 1991) and clinical studies. For example Caspi et al. (2003) showed that stressors in adulthood precipitated depression only in the context of prior childhood adversity, particularly with greater number or severity of the stressors. There has been some ambiguity about the consistency of the gene-environment interaction that is specifically related to the short form of the serotonin transporter that Caspi et al. (2003) and others have observed. However, meta-analyses clearly support the basic proposition that childhood stressors and traumas sensitize to adult stressors in precipitating depressions (Risch et al., 2009; Rutter, 2008).

Similarly, Shonkoff and Garner (2012) emphasize how childhood traumas and their accumulation provide the fertile soil for later emergence in adulthood of not only major psychiatric problems such as depression and suicidality, but also multiple physical illnesses as well. These data help bridge the conceptual gap that childhood traumas not only are vulnerability factors to the later occurrence of PTSD, but also of depression and many other difficulties. The type of trigger in adulthood may be relevant to the different outcomes, with traumas associated with the threat of loss of life or limb resulting in PTSD, while those related to psychological and relationship losses more likely to result in depression. Ecker (2015) describes a case example of a child repeatedly traumatized by frightening anger from his parents where the subsequent vulnerability to depression can be a learned process occurring outside of the child's awareness. He states: “This learning can occur with no representation in conscious thoughts or conceptualization, entirely in the implicit learning system”.

The sensitization to stressors has been systematically demonstrated clinically in recurrent depressed patients by Kendler et al. (2000, 2001) and Slavic et al. (2011). They showed that the first 5–7 episodes of recurrent unipolar depression were linked to the occurrence of psychosocial stressors, but thereafter episodes began to appear more autonomously or without the need for obvious psychosocial triggers. This point is of importance, as some have suggested that the persistent triggering of new episodes by stressors or continued occurrences of stressors late in the course of illness is evidence against a sensitization process (Bender and Alloy, 2011; Hammen and Gitlin, 1997). However, this is what would be expected from the sensitization perspective; patients would be more, not less, sensitive to stressors (and their precipitation of depression), but with sufficient numbers of recurrences such triggers would no longer be necessary and autonomous episodes would also begin to emerge as well. Other ambiguities in

EXTINCTION of HEROIN (or Cocaine) ADDICTION IN THE RECONSOLIDATION WINDOW (Xue et al 2012)

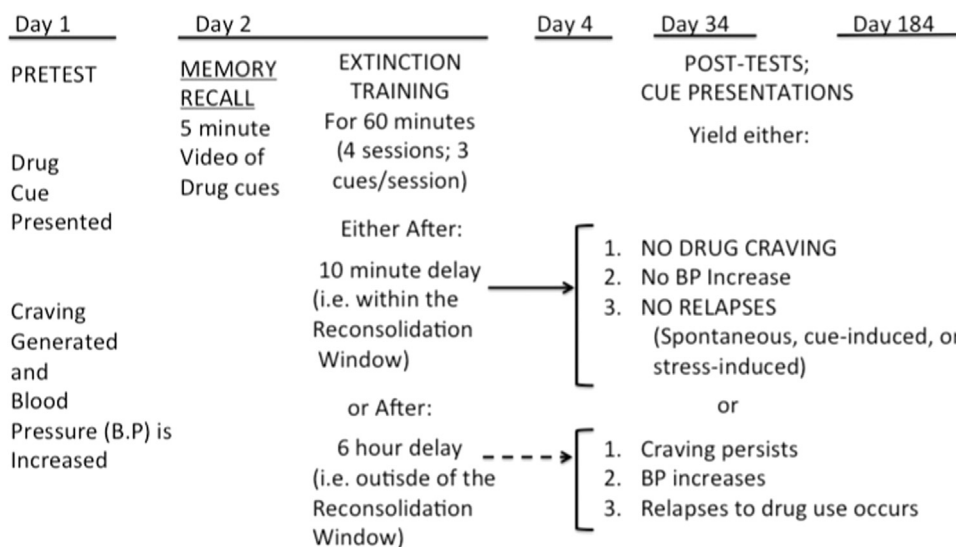


Fig. 3. Patients addicted to cocaine or heroin do not experience drug craving, blood pressure changes, or spontaneous or cued relapse for up to 6 months when extinction training is conducted within, but not outside of, the reconsolidation window after active memory recall (viewing a video of drug cues), but not after a 6 hour delay.

the data and critiques of the sensitization/kindling hypothesis are comprehensively discussed by [Bender and Alloy \(2011\)](#).

These observations are analogous to the temporal sequence of behaviors occurring in electrical kindling of seizures following daily stimulation of the amygdala ([Goddard et al., 1969](#)). Initially once daily, 1 s stimulations of the amygdala that are subthreshold for behavioral response begin to evoke increasingly more complex, first unilateral forepaw involvement, then bilateral full-blown major motor seizures with rearing and falling. Following enough of these stimulation-induced triggered episodes, seizures also begin to occur spontaneously ([Pinel, 1983](#)).

[Goddard and Douglas \(1975\)](#) envisioned the kindling process as behavioral evidence of a learning and memory process taking place at a molecular level, such that memory of prior stimulations resulted in increased physiological and behavioral responsiveness over time. While prolonged affective episodes in humans are not in any way homologous with brief (usually about 1 min) seizure episodes in kindling, the progressive evolution to full blown episodes following repeated stimuli and the subsequent transition from triggered to spontaneous episodes share a temporal sequence and evolution that may be a useful in conceptualizing some of the underlying memory-like processes mediating these phenomena.

Thus, kindling is a non-homologous model for the progression of the stages of stressors beginning to trigger affective episodes, then regularly triggering episodes, and finally episodes occurring in the absence of stressors. Effective treatment in the initial development phase of amygdala kindling delays the onset of full-blown episodes, and early intervention against full-blown seizures makes them less prone to develop tolerance to anticonvulsant drugs and precludes the emergence of the late, spontaneous episodes. These data in the kindling paradigm suggest the possibility that early intervention may also be helpful in heading off later stages of affective illness development.

Sensitization to episode recurrence could also be conceptualized more directly from the perspective of the reconsolidation process. Each new trigger and associated affective episode could be viewed as opening the reconsolidation window in a new set of circumstances and environmental cues and therefore lead to further generalization and

reconsolidation rather than attenuation of the recurrence process ([Hogberg et al., 2008](#)). In this formulation each new depression would bring new experiences into the depressive engram via layering and re-layering of memory in the reconsolidation window, which could ultimately result in stimulus generalization and the more automatic emergence of depressions without obvious psychosocial precipitants. Conversely, as discussed below, following memory recall, therapeutic maneuvers in the reconsolidation window could theoretically attenuate this automaticity.

2.2. Cross sensitization among stressors, mood episodes, and substances of abuse

Animals also show sensitization (increased reactivity) upon repetition of stressors and bouts of cocaine abuse, and these altered responses necessarily must be based on a prior learning or neural encoding of the previous experience ([Antelman, 1988; Esparza et al., 2012; Kalivas and Stewart, 1991](#)). Moreover, sensitization to stressors can cross sensitize to cocaine sensitization and episode sensitization, creating a vicious positive feedback cycle where relapses and recurrences in one domain can enhance the others and drive illness progression ([Post et al., 2013; Post and Kalivas, 2013](#)). It appears that with repetition, each type of sensitization becomes more automatic and based in the striatum ([Kalivas, 2008](#)).

We originally postulated ([Post, 1992](#)) that with repetition, the neural substrates encoding stress, episode, and substance abuse sensitization increasingly moved from those involved in the conscious representational memory system of the medial temporal lobe (amygdala and hippocampus) which is subject to conscious recall to the habit memory system of the striatum which can occur on a non-conscious basis ([Mishkin and Appenzeller, 1987](#)). This type of habit memory is typified by the procedural learning involved in learning to ride a bicycle, which becomes increasingly automatic and is never forgotten ([Kalivas and Kalivas, 2016](#)). This transition into the habit memory system of the striatum is clearly the case for cocaine sensitization which involves increases in BDNF in the ventral striatum (nucleus accumbens), and then comes to involve the dorsal striatum.

Interestingly, in mice, defeat stress-induced depressive-like behaviors, such as social avoidance and not seeking sweet or rewarding substances, are also associated with increases in brain derived neurotrophic factor (BDNF) in the ventral striatum, and clinical depression in humans is also associated with increases in BDNF in the same area. Since BDNF is critical to the generation and persistence of long term memory, one way of viewing these convergent biochemical findings would be to consider stress sensitization, cocaine sensitization, and depressive episode sensitization as manifestations of over-learned pathological habits occupying the dopamine-based reward systems of the ventral striatum, and with increasing repetition, involving the dorsal striatum (Kalivas and Kalivas, 2016; Post and Kalivas, 2013). As discussed below, each type of sensitization appears to have an epigenetic basis, as blockade of DNA methylation or other epigenetic mechanisms, inhibits the behavioral sensitization to recurrent stressors, cocaine use, or defeat stress-induced depression (Post, 2016a).

In Ecker's (2015) example of the boy who repeated experiences frightening anger from his parents and then develops depression, anxiety, withdrawal, and other negative behaviors, he states "the neural circuits encoding these learnings are mainly in subcortical regions of implicit memory that store implicit, tacit, emotionally urgent, procedural knowledge, not mainly in neocortical regions of explicit memory that store conscious, episodic, autobiographical, declarative knowledge."

2.3. N-acetylcysteine as a possible example of a single therapeutic approach having therapeutic effects in multiple habits

The cross sensitization among stressors, affective episodes, and cocaine implies some mechanisms in common are involved, such as the BDNF increases in the striatum. However, common mechanisms also suggest the possibility of common pharmacological or psychological approaches to all three types of sensitization. One possible drug example, is N-acetylcysteine (NAC) which is readily-available (from health food stores). There are preliminary data that NAC has positive effects in depression and anxiety in bipolar disorder (Berk et al., 2008) and may decrease a variety of addictions (including cocaine, gambling, marijuana, alcohol, and nicotine), and habits such as trichotillomania, obsessive compulsive disorder, and stereotypy in autism (reviewed in Kalivas and Kalivas (2016) and Post (2016a)). However, not all studies are positive and further systematic study of each syndrome is required. While NAC has multiple mechanism of action as an anti-oxidant, a glutathione precursor, and an anti-inflammatory substance, it has one action that could account for its positive effects across a range of sensitized behaviors and habits. NAC decreases hyperactive glutamate signaling in the accumbens induced by multiple habits by increasing the number of glutamate transporters on glial cells, which pull glutamate out of the synapse. This lowers the intensity of the striatal habit system, allowing greater volitional cerebral cortical control (Kalivas and Kalivas, 2016; Post and Kalivas, 2013).

Kalivas at MUSC found that cocaine addiction in animals markedly increased glutamate signaling in the ventral striatum, ie the nucleus accumbens (or reward area of the brain) and hypothesized that NAC would decrease the glutamate signal and prevent cocaine re-instatement in addicted animals (Kalivas and Volkow, 2011). In some but not all subsequent studies, NAC decreased craving and relapse clinically in addicted individuals (Kalivas and Kalivas, 2016; LaRowe et al., 2013).

Cocaine addicted animals lose the ability of the cortex to modulate the activity of the nucleus accumbens as cocaine impairs the molecular mechanisms of learning, memory, and plasticity of long term potentiation (LTP) and long term depression (LTD) in the pathway from cortex to accumbens (Moussawi et al., 2009, 2011). In cocaine addicted animals, treatment with NAC restores LTP and LTD, allowing new learning and flexible responses to environmental contingencies. Similar dampening of the glutamate signaling in the striatum could underlie the ability of NAC to help overcome other urges and habits in

trichotillomania, compulsions, PTSD, and a variety of addictions in humans (Kalivas and Kalivas, 2016). The findings that extinction training in the reconsolidation window also can inhibit drug seeking in humans (Agren et al., 2012) and intrusive thinking in PTSD and related disorders (Ecker, 2015; Nader et al., 2013), further suggests some commonalities in the ability to alter habits by either pharmacological or neuropsychological approaches.

3. Therapeutic work in the re-consolidation window for prevention of recurrent depression

Based on the observations that extinction learning in the reconsolidation window can decrease PTSD and related trauma memories as well as the craving and relapse proneness of heroin and cocaine addicts as noted above, we postulate that related work in the reconsolidation window would be effective in dealing with the sensitization to and automaticity of recurrent depressions. While stressors are often the initial triggers for affective episodes early in the course of illness, the more automatic emergence of episodes following multiple repetitions may nonetheless be amenable to attenuation by work in the reconsolidation window in a fashion similar to the automaticity of drug craving and its associated autonomic increases in blood pressure (Xue et al., 2012). In PTSD and dysfunctional fear-memory reactions, Hogberg (2011) states: "The goal of the treatment is to change a reliving intruding memory into a more distant episodic memory." In parallel the aim of treatment in the recurrent affective disorders would be a reworking of the triggering experience and a rendering of the depressive experience as less harsh, severe, self-defeating (guilt-inducing).

The neural substrates mediating sensitization to stress and cocaine evolve over time and the effectiveness of pharmacological intervention differs as a function of initial development versus later expression of sensitized behavior (Post et al., 1988). Likewise, since the different stages of kindling evolution and progression involve a spatio-temporal spread of neural activity and gene expression that is initially confined to the amygdala to new brain areas such as hippocampus and then cortex (Clark et al., 1991; Rosen et al., 1992, 1993), it is again not surprising that effective pharmacological interventions differ as a function of the stage of kindling evolution. This is illustrated in Fig. 4 where some drugs are effective in A. the initial developmental stage of kindling, but not B. the midphase of fully developed, major motor triggered seizures. Other drugs do not block A. kindling development, but are potent against B. the full-blown kindled seizures. Remarkably there is a double dissociation in the anticonvulsant effects of phenytoin and diazepam where phenytoin becomes effective in the prevention of C. the late spontaneous seizures, while diazepam shows the opposite effect (Pinel, 1983).

In a somewhat parallel fashion, we are hypothesizing that pharmacological and psychotherapeutic approaches might differ in different stages of evolution of the recurrent disorders from: A. the early developmental stage of stressors triggering minor depressive episodes; to B. the mid phase of full-blown triggered depressive episodes; and C. the late stage of spontaneous episodes (Figs. 4 and 5). While there are only preliminary clinical data supporting this proposition, perhaps the most clear-cut example is lithium and many other pharmacological agents becoming less effective after multiple recurrences (Post et al., 2012). In a similar vein, one could hypothesize that psychodynamic and insight-oriented therapies would be most helpful in dealing with initial and stress-related affective episodes, but with stressor and affective episode recurrence, interpersonal and cognitive behavioral techniques may be required for reducing perceived stress and increasing cortically based adaptive coping mechanisms. However, with the transition to late spontaneous episodes and their automaticity of recurrence, even more habit and implicit memory oriented techniques might be necessary. The data of Scott et al. (2006) are partially supportive of this view. They found cognitive behavioral therapy

Differential Pharmacology as a Function of Stage of Amygdala Kindled Seizure Development

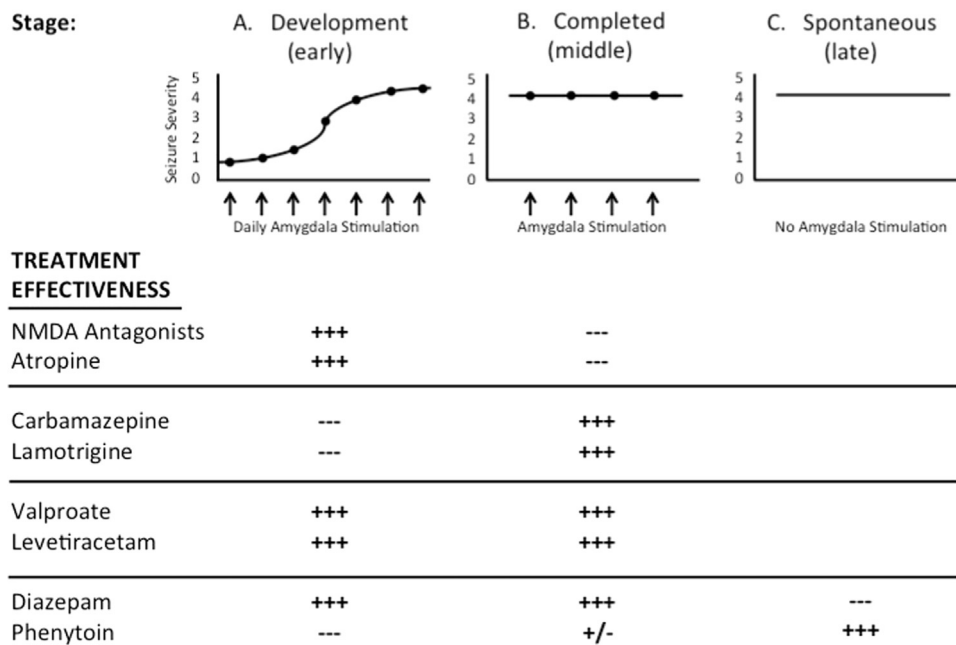


Fig. 4. The different stages of amygdala kindled seizure development are schematized: A. Stimulations evoke seizure of increasing complexity; B. Stimulations regularly trigger full-blown seizures; and C. Seizure emerge in the absence of amygdala stimulation. The first 2 drugs block A. the Development but not B. Completed (fully kindled) seizures, while carbamazepine and lamotrigine show the opposite pattern of efficacy. In contrast, valproate and levetiracetam are effective in inhibiting seizures in both the Development and Completed phases. Phenytoin and diazepam are noteworthy for their double dissociation. Diazepam is effective in A. Early and B. Mid phases of kindling, but not on the late spontaneous seizures, while phenytoin essentially shows the opposite pattern. These data raise the question of whether different pharmacological agents may differ in their efficacy as a function of stage of illness evolution in the affective disorders, as schematized in Fig. 5.

(CBT) helped in bipolar patients early in their course of illness, but in those with a great many prior episodes (presumably in the late phases of spontaneous episodes), CBT not only was not effective, but appeared to be counter productive.

Thus, in this later phase of illness evolution involving spontaneous episodes, different techniques may again be required, one of which could involve altering habit memory by work in the reconsolidation window. In partial contrast to this view of different therapeutic approaches as a function of the course of illness, Lane et al. (2015) see work in the reconsolidation window being amenable to all types and stages of memory mechanisms as noted below. How work in the

reconsolidation window could be best applied to those with recurrent affective episodes would have to be assessed with initial exploratory work in individual patients and in proof of principal studies before more large-scale clinical trials were attempted. An example or two of how these techniques could be conceptualized and applied are preliminarily outlined.

The longitudinal history of an individual's course of illness would be taken in detail to assess early (distal) stressors and traumatic events in childhood, and the history of more adult difficulties and (proximal) stressors that may be involved in the acute precipitation of depression. Finally, in those with highly recurrent episodes, acute stressors if any,

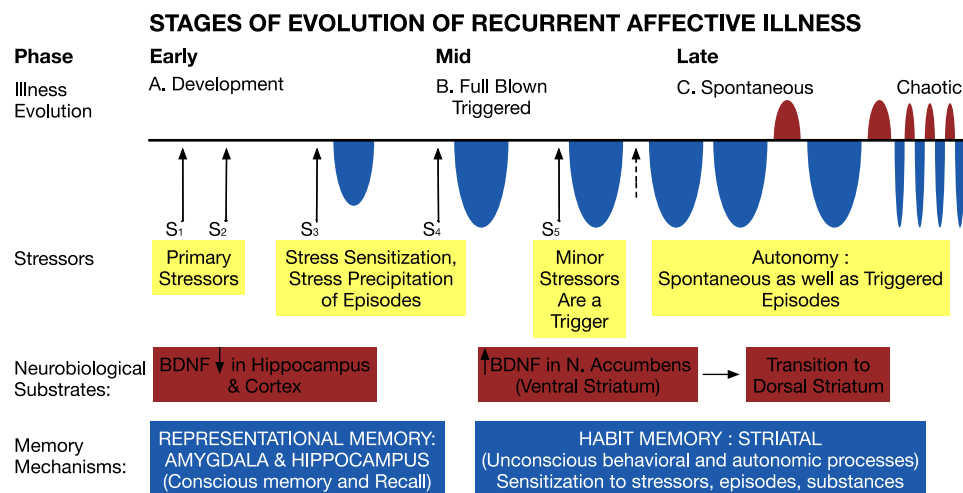


Fig. 5. As in the stages of kindled seizure evolution; A. full-blown affective episodes (in blue) emerge with repeated stressors (in yellow, S 1–3), then B. Full-blown episodes are regularly triggered by stressors (S 3, 4), and finally in C. Spontaneous episodes can occur in the absence of triggers. The neurobiological and anatomical substrates (in red) and memory mechanisms (in blue) may also differ and evolve as a function of these stages of illness progression. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

would need to be further explored, as would the most current episodes potentially occurring more spontaneously without obvious triggers. Once this longitudinal evaluation has been completed, one would have to decide which types of stressors were, or previously had been, the most important triggers. One might then try to work in the re-consolidation window opened by the evocation of the most prominent and emotionally laden memories, be they from childhood, early adulthood, or the most recent epoch.

Alternatively, as a starting point it may be most advantageous to initially work with patients who have identified stressors as critical triggers of their depressive episodes, and only after seeing success in this domain begin to work with patients who have entered the phase of automaticity of episodes. However, even in this latter instance, it might be most expeditious to work with patients who had previously recognized the role of stressors as precipitants prior to episodes becoming more automatic.

One might then proceed by having the patient evoke the memory and its associated emotion as part of the recall procedure in order to renew the lability (amenability to change) of this memory trace in the re-consolidation window. The evocative recall could then be immediately followed by a re-working of the traumatic memory from multiple perspectives and in the safe environment of the therapeutic relationship. These might include: reframing the traumatic memory, emphasizing the adaptive components of the response, the youth of the child (if this were the case), addressing any guilt associated with participation in the behavior, and many of the other techniques described in literature on traumatic memories and psychotherapy. Hogberg et al. (2011) suggests that activating positive affect in the work in the reconsolidation window involves increasing parasympathetic tone, which “can be achieved by relaxation exercises: breathing and meditation, safe-place imagery, perhaps walking on a treadmill or bicycling on a spinning cycle.”

In addition to traumatic memory, similar work in the reconsolidation window could proceed in relationship to the depressive experience itself and the patients overwhelming negative view of the self and the future. Lane et al. (2015) make the case that work in the reconsolidation window could target all of the components of what they call the integrated memory structure, which would include: emotional responses (using behavior therapy); episodic memory (using psychodynamic psychotherapy); and semantic structures (using cognitive-behavioral therapy). In each of these approaches, the therapist is attempting to help the patient in “updating of prior emotional memories through a process of reconsolidation that incorporates new emotional experiences... into these reactivated memories via the process of reconsolidation”. The Lane et al. (2015) article merits careful reading for the wealth of information and insights into how work in the reconsolidation window mediates change in psychotherapy and can be utilized in multiple therapeutic domains. Ecker (2015) concludes that “profound unlearning and cessation of acquired behaviors and states of mind occurs through the process of memory reconsolidation.”

3.1. What is different in this exposition

One might criticize this approach to recurrent depression utilizing the reconsolidation window as not novel and that it is merely using techniques already used in many existent therapies. While this view has some merit, what is novel here is the specifics of the procedure involving active memory recall to open the reconsolidation window in the presence of a mismatch of expected outcomes, and then attempting in therapy to more permanently modify the emotional and associative impact of the memory and its potential for triggering new episodes. Some of the variables that could result in further exacerbation or reconsolidation of the original emotional memory are also made more explicit as discussed below. Moreover, the potential of enhancing the positive effects with adjunctive physiological or pharmacological approaches, including those making use of information about the role of

epigenetic mechanisms in normal memory processes is also new.

The link of memory to re-triggering of affective episodes also opens new possibilities of therapeutic work in multiple temporal domains of illness evolution. These might include those related to childhood and adolescent adversities as well as those related to triggering of depressions in, early and late adulthood. This exposition also puts a new set of principles based on more precise preclinical and clinical experience into the equation that then can be tested in individuals and modified as new experience is gained. The paradigm would also be further informed by the ongoing clinical, laboratory, and conceptual work on this phase of memory re-consolidation, and as new insights and information are gleaned from the basic and clinical neuropsychiatric literature, the procedures most pertinent to the affective disorders could be further modified and adapted accordingly.

3.2. Conundrums for future study

As noted above, one of the many questions that emerges from this formulation regarding stressor desensitization and extinction is whether the work in the re-consolidation window should focus on the original traumas (in childhood) or on the more proximal stressors, which initially triggered mood episodes in adulthood. Manic episodes could also be the target of such work with their positive reward-engendering characteristics similar to cocaine-induced craving and euphoria and dysphoria. Depressive feeling and cognitions could also be a target for the extinction procedures even after they have started to appear autonomously. Thus how to sequence the extinction procedures for optimal therapeutic results and apply them to the appropriate phase of illness evolution would be a major theme for study in the clinical development of this strategy.

Another unanswered question is for which patients this technique would be most appropriate and which other types of patients would be most unlikely to benefit. We would surmise that those patients who readily recognized the role of stressors in triggering their episodes early in their course of illness would be among the best candidates with whom to begin work. However, strategies designed to elicit emotions and amygdala activation associated with an individual's unique sense of threat to status, autonomy, or relationships may provide a template for work in the reconsolidation window in an individual who has not yet fully identified his areas of vulnerability.

Ecker (2015), Agren (2014), and Lane et al. (2015) all make the point that work in the reconsolidation window is appropriate for a whole range of types of learning and memory from declarative to appetitive memories, procedural memories, and fear memories. To this extent, work in the reconsolidation window may be pertinent to many stages of affective illness evolution. The research directions suggested in this manuscript are thus very much in line with others' work and ideas about therapy. Ecker (2015) explicitly states that it is a misconception to believe that work in the reconsolidation window is pertinent only to fear-based learning, and clinicians already have enough information to begin to apply this concept to “a wide range of clinical conditions (that) also are rooted in and driven by implicit memory.”

One would also have to pay careful attention to the possibility that the memory recall could further kindle pathological emotional responses rather than help extinguish them. This caution is discussed further by Nader et al. (2013) and Schwabe et al. (2013), and others in the PTSD literature have approached this problem with techniques to minimize this possibility. These include: graded recall, blunting the emotional recall with propranolol, etc., but whether such attempts would impair the ability of the recall to actively open the re-consolidation window would have to be assessed. Other attempts have also been made to reduce the stress with the beta noradrenergic antagonist propranolol (Otis et al., 2015; Pitman et al., 2012) and mineralocorticoid receptor blockade with spironolactone which prevents stress from promoting striatum-based learning at the expense of hippocampus-

based declarative learning (Schwabe et al., 2013). One study with propranolol showed that different memory traces of learned fear do not necessarily undergo reconsolidation simultaneously as propranolol reduced fear-potentiated startle, but not skin conductance responses, or the subjective anticipation of fear (Soeter and Kindt, 2012).

Additionally, how this work on extinction in the re-consolidation window could be enhanced by the principles of cognitive training and rehabilitation would be another area for productive exploration. Vinogradov et al. (2012) emphasize how increases in lower level cognitive training can yield positive results on higher level cognitive operations and how work on implicit learning can result in positive effects on explicit learning. Vinogradov et al. (2012) also emphasize the importance of repetition and number of trials, as well as immediacy of reward to maintain motivation in cognitive training. In this fashion it might be considered how (passive) extinction training in the re-consolidation window could be augmented with (active) new learning of adaptive responses to stressful triggers in order to minimize threats to the self in attempts to optimize the possibility of preventing affective episode recurrence. Listing, recalling, and rehearsing potential adaptive alternative responses to perceived threats followed by immediate reward and encouragement of the therapist may add new elements of learning positive ways of responding to the task of extinction training rather than just the re-working of old stimulus-response habit memories.

3.3. Possible augmentation strategies

How psychological work in the re-consolidation window could be integrated with other therapeutic modalities that have already been studied in humans might be an additional fruitful topic of future research. For example, D-cycloserine is a partial agonist at glutamate NMDA receptors and its augmentation of glutamatergic tone has been shown in some studies to enhance the new learning required for extinction of clinical phobias and other anxiety disorders (Gupta et al., 2013; Norberg et al., 2008; Ressler et al., 2004), although a recent study of its effects as augmentation of CBT in OCD was not positive (Storch et al., 2016). Additionally, the D-cycloserine effects are short lived and subject to tolerance development. One could look for other modalities that could generate a D-cycloserine-like enhancement of new learning, such as methylene blue, which enhances fear extinction in claustrophobia (Telch et al., 2014), increases mitochondrial cytochrome oxidase in neurons that are the most active, and improves residual symptoms in bipolar depression (Alda et al., 2016).

Another candidate would be repeated transcranial magnetic stimulation (rTMS), which regionally stimulates neurons and increases the release of glutamate and BDNF, as well as dopamine in the striatum. We have postulated that high frequency (10–20 Hz) rTMS which induces LTP in the hippocampus and increases regional brain activity measured in patients with O15 positron emission tomography (PET) scans in a long lasting fashion might be optimal for enhancing new learning needed for extinction in structures such as the medial prefrontal cortex (Post and Speer, 2007; Speer et al., 2000, 2009). Therapeutic work during the rTMS would be postulated to enhance experience dependent neuroplasticity. Conversely, low frequency (1–5 Hz) rTMS induces LTD, and it decreases regional brain activity that might be helpful in taking emotional memory off line. How such opposing physiological processes could be best integrated into the neuropsychological work with extinction training would require further specific exploration and testing.

Another option worthy of future exploration is the co-administration of a drug such as valproate (Depakote) with the extinction work within the reconsolidation window. This clinically available and widely used drug has so far only been used in preclinical models of learning and memory. Valproate is a potent histone de-acetylase inhibitor which has been shown to increase the specific BDNF variant - BDNF exon IV mRNA expression - needed for extinction learning (Bredy et al., 2007).

Valproate has also been shown to enhance extinction learning in animal models.

The potential use of valproate as a histone de-acetylase inhibitor to enhance extinction also raises the whole issue of how a range of epigenetic mechanisms (such as DNA methylation, histone modifications, and micro RNA) which have been intimately implicated in learning, memory, and the mood disorders (Nestler, 2013, 2014; Zovkic and Sweatt, 2013) could be further exploited for enhancement of new learning and extinction procedures. Post (2016a) has reviewed the evidence that epigenetic alterations are critically involved in sensitization to recurrent stressors, mood episodes, and bouts of substance abuse. The elucidation of how the processes of reconsolidation interact with or are mediated by specific epigenetic mechanisms will be a very exciting area of future investigation.

The studies of Bredy and Barad (2008) on valproate also raise a series of important issues about the competing processes for either memory enhancement (re-consolidation) or extinction of conditioned fear, and that according to the “strength dominance hypothesis” the strength and duration of the stimulus at the time of reactivation as well as the inter-trial interval of the extinction training determines which type of memory (re-consolidation or extinction) is reactivated. When they gave valproate with seven massed trials (5 s apart), the original context dependent fear memory was further enhanced. When valproate was given with seven spaced trials (20 min apart), extinction memory was not only enhanced but became context-independent. This study thus further clarifies the critical nature of the characteristics and timing of the extinction protocol for achieving the desired lessening of the fear or drug memory versus further re-consolidating it. Valproate, based on its histone de-acetylase inhibition effects, can thus enhance either one of the competing memory traces of re-consolidation or extinction. Bredy and Barad (2008) conclude: “Perhaps administering VPA in combination with brief, spaced cue exposures may yield a more effective and more generalized therapeutic result.”

Ketamine administered intravenously has recently been shown to be acutely (within 2 h) effective in relieving refractory depression and its accompanying suicidality (Murrough et al., 2013). It has also had some success in the treatment of PTSD (Feder et al., 2014). Ketamine's behavioral antidepressant-like effects in chronically stressed rodents are accompanied (also within 2 h) by a return from immature, spike-shaped dendritic spines to mature mushroom-shaped dendritic spines (Li et al., 2011). Thus, ketamine's ability to restore normal synaptic structure may be a way of enhancing new learning in the reconsolidation window, or conversely work in the reconsolidation window may be a way of extending the duration of the antidepressant effects of iv ketamine which usually last only 3–5 days.

3.4. Further caveats

As noted above, one would have to pay careful attention to the temporal characteristics of the recall of the traumatic or euphoric affect (and the hoped-for extinction learning trials) so that the recall does not provide a counter-productive new kindling-like experience or a further sensitizing stimulus rather than new extinction learning. Schwabe et al. (2014) describe uncertainty about the boundary conditions that affect re-consolidation, such as: the age and strength of the memories, the reminder structure, the context and frequency of the reactivation, the presence of new information at the time of reactivation, the experience of stress after memory reactivation, and even the length of the reconsolidation window. As many of these questions are better answered in the future with new clinical and preclinical data, they will further guide the development of the optimal paradigms for extinguishing fear, drug craving, and as discussed here, the possibility of stress-induced precipitation of affective episodes or their automaticity.

One might raise the concern that attempts at memory revision and erasure or memory erasure drugs are problematic from an ethical perspective. However, we and others do not believe that the drugs

described are memory erasure drugs, but drugs that facilitate new learning. Ecker (2015) states: “When a learned, unwanted emotional reaction is erased, there is no loss of memory of events in one’s life”. Therefore we would hope that this work would fall under the rubric of many other types of psychotherapy that attempt to reduce unwanted and unproductive emotional and behavioral reactions, rather than memory erasure per se.

It is also unclear how to best focus efforts at extinction learning on stressors as a function of temporal evolution of affective episodes from those earliest in childhood (which may not be accompanied by an episode); to stressors in adulthood that are regularly associated with episode occurrence, or on the late, presumably, conditioned stress responses that yield episodes that appear un-triggered. For example, it is possible that work on extinction of the stress-related triggering of initial affective episodes may be more productive than later work once the phase of spontaneity has been reached. Moreover, it is possible that extinction work early in the phase of triggered episodes could pre-empt the later more rapidly-recurring, triggered episodes as well as their conversion to the spontaneous variety in parallel to the effects seen preventing amygdala kindled seizures. In this fashion, early intervention for triggered episodes could be viewed as an attempt at secondary and tertiary prevention of subsequent illness recurrence and progression.

4. Conclusions

Given this multiplicity of unanswered questions, the current formulation about using therapeutic maneuvers in the reconsolidation window to attempt to prevent depressive recurrences is far from complete. It is hoped, nonetheless, that it will provide an initial framework for further exploration and development of psychotherapeutic approaches specifically aimed at revisions of automatic habit-based learning associated with affective episode occurrence and progression to spontaneity.

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