Disorders of memory and plasticity in psychiatric disease

Christopher Pittenger, MD, PhD

Introduction

The capacity for plastic change is a fundamental characteristic of the nervous system and underlies innumerable aspects of development, homeostasis, learning, and memory. Plasticity is essential for the recovery of the nervous system after injury, stroke, and other pathological processes and can permit remarkable functional recovery even after devastating damage, especially in a young and otherwise healthy brain. However, the very mechanisms of plasticity that permit development, learn-

Plasticity is found throughout the nervous system and is thought to underlie key aspects of development, learning and memory, and repair. Neuroplastic processes include synaptic plasticity, cellular growth and remodeling, and neurogenesis. Dysregulation of these processes can contribute to a variety of neuropsychiatric diseases. In this review we explore three different ways in which dysregulation of neuroplastic and mnemonic processes can contribute to psychiatric illness. First, impairment of the mechanisms of plasticity can lead to cognitive deficits; this is most obvious in dementia and amnesia, but is also seen in more subtle forms in other conditions. We explore the relationship between stress, major depression, and impaired neuroplasticity in some detail. Second, enhanced memories can be pathogenic; we explore the example of post-traumatic stress disorder, in which intrusive trauma associated memories, accompanied by hyperactivity of the normal fear learning circuitry, are core aspects of the pathology. Third, impaired modulation of the relationship between parallel memory systems can contribute to maladaptive patterns of behavior; we explore the bias towards inflexible, habit-like behavior patterns in drug addiction and obsessive-compulsive disorder. Together, these examples illustrate how different abnormalities in the mechanisms of neuroplasticity and memory formation can contribute to various forms of psychopathology. It is hoped that a growing understanding of these relationships, and of the fundamental mechanisms underlying neuroplasticity in the normal brain, will pave the way for new understandings of the mechanisms of neuropsychiatric disease and the development of novel treatment strategies.

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Author affiliations: Yale OCD Research Clinic, Yale University School of Medicine, New Haven, Connecticut, USA

Address for correspondence: Dr Christopher Pittenger, 34 Park Street, W315, New Haven, Connecticut, CT 06519, USA
(e-mail: christopher.pittenger@yale.edu)

ing, resilience, and recovery can also contribute to behavioral dysfunction and to psychopathology. Disruption of memory, and of plastic processes in general, is a common theme in the emerging neurobiological understanding of several disparate neuropsychiatric conditions. In this review we explore several illustrative examples of this theme.

The disruption of mnemonic processes can contribute to pathology in a variety of ways. The most obvious is the case in which fundamental mechanisms of memory formation are disrupted, either at the cellular or systemic level. This leads to conditions in which a memory deficit is the cardinal and defining symptom. For example, in Alzheimer's disease, which is covered in detail elsewhere in this volume (p 445), cellular pathology affects both the integrity of the hippocampus-centered explicit memory system and the cellular processes within it whereby information is stored, leading to prominent explicit memory deficits early in the disease course.[1] In amnesia secondary to ischemic, infectious, or physical damage to medial temporal lobe structures, dense deficits in episodic memory may be observed in the context of otherwise normal brain function.[2]

Abnormalities in mnemonic processes can contribute to psychopathology in a variety of more subtle ways. Disruption of explicit memory capacity is seen in a number of stress-associated disorders, such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD); chronic stress produces a number of abnormalities in brain circuitries that are required for explicit memory function, such as the hippocampus and dorsolateral prefrontal cortex, which provides a probable mechanism for these effects.[3] Pathologically enhanced memories contribute to acute stress disorder and PTSD, in which excessively strong associations with traumatic events lead to their disruptive recall and generalization. Pharmacological treatments that directly manipulate synaptic plasticity have shown promise in the treatment of such pathological memories.[4] Pathologically enhanced memories also contribute to substance abuse, in which drug-associated cues take on enhanced salience, to the exclusion of other cues and natural rewards[5]; the interaction of drugs of abuse with plasticity-related molecular processes is addressed in detail elsewhere in this volume (p 431). Finally, disruption of the balance or interplay between parallel memory systems may contribute to psychopathology in some conditions; this idea has been particularly well developed in the study of drug addiction,[6] but recent data suggest that it may also be the case in obsessive-compulsive disorder (OCD)[7] and other conditions.

Stress, depression, and neuroplasticity

Cognitive impairment is a core endophenotype of MDD[8]; difficulty with concentration is one of the defining criteria of the disorder.[9] In addition to these deficits in concentration and attention, patients with major depression can exhibit difficulties with explicit memory, especially recollection memory.[10-12]

Over the past 20 years, a startling parallel has emerged between the mechanisms implicated in various forms of neuroplasticity—synaptic plasticity, neuronal remodeling, and neurogenesis—and those implicated in stress-associated neuropsychiatric conditions, such as MDD.[3] The parallels, on multiple levels of analysis, have become sufficiently striking as to suggest that there is a deep connection between neuroplasticity and mood regulation, although why this should be so remains to be elucidated.[13]

Stress, especially when it is chronic and uncontrollable, produces a depression-like behavioral profile in animal models[14,15] and is thought to be a trigger for the development of major depression in genetically vulnerable individuals.[16] Chronic stress has numerous effects on plasticity-associated processes throughout the brain in rodent models.[3,14,17] In the hippocampus, chronic stress produces dendritic atrophy, especially in the CA3 region[18]; prolonged pharmacological elevation of glucocorticoids, the principle adrenal stress hormones, can lead to cell death.[19] Severe stress can also inhibit long-term potentiation (LTP)[20] and enhance long-term depression in the hippocampus.[21]

Similar effects are seen in the frontal cortex in rodents: both chronic behavioral stress and corticosteroid agonists lead to atrophy of the apical dendrites of layer 5 pyramidal cells in the frontal cortex[22] and to reduced dendritic spines in the medial prefrontal cortex.[23,24] Stress also inhibits some forms of synaptic LTP of synapses onto prefrontal pyramidal cells.[24]

Brain plasticity also occurs at the level of neurogenesis: the production of new neurons, particularly in the dentate gyrus of the hippocampus, and their integration into the functional circuitry. This is another form of neuroplasticity that may contribute to memory formation.[25-27] Chronic stress impairs neurogenesis in the dentate gyrus.[28,29]

These effects of stress and stress hormones on the substrates and mechanisms of plasticity are, unsurprisingly, paralleled by cognitive impairments after stress in animal models. Transient mild stress can actually enhance learning and memory; this may represent an adaptive response to threatening situations.[30] More extended stress, however, disrupts hippocampus-dependent memory in experimental animals.[31] Corticosteroid treatment has similar effects.[32,33]

What is the relevance to human psychopathology of these effects of stress on plasticity and on mnemonic processes in experimental animals? Neuroimaging and postmortem studies in humans indicate that structural changes are seen in MDD, supporting the parallel between the effects of experimental stress and the pathophysiology of mood disorders. Structural MRI studies have revealed reduced hippocampal volume in individuals with depression,[34,35] reminiscent of the experimentally documented effects of chronic or severe stress.[18] This effect appears to correlate with the number of depressive episodes; as these episodes are themselves extremely stressful events, this pattern can be interpreted as further evidence for a role for stress in the observed volumetric effects.[34] Thinning in the prefrontal cortex has also been described[36,37]; postmortem analyses show a concomitant reduction in the dendritic complexity, but not the number, of cortical pyramidal cells.[38] These effects recapitulate those seen in experimental animals after chronic stress.

Studies in animals of the mechanistic effects of antidepressant drugs have further strengthened the connection between the effects of stress and the pathophysiological abnormalities associated with depression, and have added significant molecular detail. A particularly prominent example of this is the role of brain-derived neurotrophic factor (BDNF) in both processes. BDNF is well established as playing an important role in several forms of synaptic plasticity, especially translation-dependent long-lasting synaptic plasticity (eg, ref 39,40) and BDNF signaling through the tropomycin kinase B (TrkB) receptor is required for normal hippocampus-dependent learning.[41,42] BDNF also critically regulates the survival of newborn neurons in the adult dentate gyrus.[43] It is therefore striking that BDNF is also suppressed by stress[44] and is induced by antidepressant drugs.[45] Indeed, dysregulation of BDNF, and consequent disruption of normal neurogenesis, forms the heart of a prominent pathophysiological theory of depression.[46]

Another convergence of well-established mechanisms of plasticity and of antidepressant effects is the transcription factor c-AMP response element-binding protein (CREB), which is both a regulator and a target of BDNF.[3,47] CREB has been shown in numerous experimental systems to be a critical regulator of long-lasting synaptic plasticity (eg, ref 3,48,49). It is again striking that it is equally well established to be upregulated by antidepressant treatment.[50]

A particularly striking convergence of antidepressant effects and the mechanisms of plasticity derives from recent work on the rapid antidepressant effects of the N-methyl-D-aspartate (NMDA) receptor blocker ketamine.[51] At subanesthetic doses, ketamine produces a rapid, but transient, antidepressant effect in up to 70% of individuals with depression, even when it has proven refractory to more conventional chemical antidepressants.[52,53] It similarly reverses depression-like behaviors in animals exposed to a chronic stress paradigm.[54] At these doses, ketamine produces a rapid and substantial increase in glutamate in the frontal cortex and induces morphological and electrophysiological synaptogenesis in the frontal cortex.[55] This apparently direct connection engenders optimism that other treatments—focused directly on the enhancement of plasticity—may lead to novel avenues for the treatment of depression.[13]

Excessive memory formation in the pathophysiology of trauma-associated disorders

Excessively strong memory formation can also lead to psychopathology. This is well illustrated by trauma-associated disorders—paradigmatically, PTSD. PTSD develops when a constitutionally susceptible individual is exposed to a traumatic event associated with overwhelming fear, helplessness, or horror.[9] Re-experiencing a deeply ingrained memory of the traumatic effect, in the form of flashbacks and nightmares, is one of the cardinal symptoms of PTSD; the other symptoms consist of generalized emotional numbing and avoidance, and hypervigilance. PTSD affects approximately 5% of the population, with the incidence increasing dramatically with the frequency of traumatization.[56] People exposed to a violent or horrifying event are not, however, uniformly susceptible to the development of PTSD; genetics, early life experience, and perhaps other factors syn-

ergize to determine an individual's susceptibility to the development of psychopathology in response to a traumatic experience (eg, ref 57).

The initiating pathology of PTSD can be conceptualized as fear conditioning gone terribly wrong. In fear conditioning, as studied in controlled settings in experimental animals, an innocuous sensory stimulus, such as an auditory tone, is paired with an inherently aversive stimulus such as a footshock; the tone subsequently triggers a fear response, as quantified by freezing, fear-potentiated startle, or some other experimental metric.[58] Fear conditioning critically involves the amygdala; the association between the tone and shock is thought to be formed in the basolateral nucleus of the amygdala, while the species-characteristic fear response is coordinated by the central nucleus.[56,58] Manipulation of synaptic plasticity within this circuitry, and of the electrophysiological properties of different classes of neurons that compose it, can enhance or attenuate fear conditioning.[59,60] Contextual conditioning, or learned fear associated with the context in which training occurred rather than with a discrete cue, additionally involves the dorsal hippocampus, in which spatial representations can be formed.[61]

How might this process be subverted to lead to the pathological memories that characterize PTSD? The animal literature suggests several possibilities. A breakdown in the specificity of the learned associations may lead to untoward stimulus generalization, whereby the associations initially made with the training stimulus bleed over into other, nonassociated cues and contexts. Under normal circumstances the repeated recall of a fearful association in the absence of adverse consequences results in extinction; however, in susceptible individuals a traumatic memory may lead to sensitization, whereby repeated recall leads to an enhanced, rather than attenuated, fear response.[56]

Several lines of evidence suggest that this fear circuitry elaborated in studies in animals is conserved in humans and is dysregulated in PTSD. In functional neuroimaging studies, fear-inducing stimuli, especially fearful faces, lead to robust amygdala activation in healthy subjects.[62] Individuals with amygdala damage show attenuated fear learning.[63] In individuals with PTSD, the amygdala response to fear-inducing stimuli is exaggerated.[64] The hippocampus and portions of the prefrontal cortex, which normally modulate amygdala activity, are also dysregulated in individuals with PTSD.[65]

The implication of hippocampal dysfunction may be of particular relevance here. As noted above, the dorsal hippocampus is critical for contextual conditioning—the association of a fear response with the particular context in which training occurred.[61] The faithful encoding and recall of the training-associated context is likely to be critical to prevent promiscuous generalization of the fear response to other, innocuous contexts. Reduced recruitment or dysfunction of the hippocampus—such as may occur after intense or chronic stress[31]—may lead to reduced efficacy of contextual encoding, and thus set the stage for untoward contextual generalization.

This association of normal fear learning mechanisms with the pathophysiology of PTSD holds promise for the development of new therapeutic strategies.[56] Core cognitive-behavioral therapy (CBT) techniques for the treatment of PTSD rely on extinction learning: the repeated pairing of fear-associated stimuli or contexts with innocuous outcomes, leading over time to a new set of associations that, it is hoped, will occlude the fear-associated pairings. Extinction is an active form of learning that depends on the NMDA receptor and a suite of downstream plasticity-associated pathways. Pharmacological enhancement of NMDA signaling during extinction training using D-cycloserine has been shown to accelerate extinction-based CBT in several anxiety disorders (eg, ref 66,67). A recent trial suggests that this approach may be useful in PTSD.[68]

Interference with the mechanisms of trauma-associated learning may be possible in the window hours or days after a traumatic event, during the process of consolidation—the collection of molecular, cellular, and systems-level processes whereby memories are converted from a labile state to a more robust, long-lasting form. Interference with a number of different molecular mechanisms associated with consolidation has been shown to disrupt long-term fear learning in animals.[58] In humans, the logistical challenges of delivering a pharmacological intervention after a trauma, which is inherently an unpredictable and disruptive event, have limited rigorous studies of this strategy towards secondary prevention of the development of PTSD; however, this remains an exciting potential area of therapeutic development.[56]

Substantial interest has focused, in recent years, on the phenomenon of reconsolidation in the context of fear memories. The importance of reconsolidation was not widely appreciated until about a decade ago.[69] The key insight underlying this phenomenon is that under certain circumstances, the recall of a memory transiently puts it

into a labile state. Reconsolidation is the process whereby this newly labile memory is again transformed into a stable state; its mechanisms overlap with, but are distinct from, the mechanisms of consolidation after initial learning.[70] Disruption of reconsolidation, through either pharmacological intervention or behavioral manipulations, prevents this stabilization and thus weakens or even erases the underlying memory.[56,58,69,71]

This is, in theory, a potentially more efficacious way to attenuate the excessive fear memories in PTSD than extinction: whereas extinction learning attempts to overlay a set benign memory on top of the traumatic one, disruption of reconsolidation holds the potential to actually erase the underlying traumatic associations. It remains to be seen whether this will prove to be an efficacious strategy for the treatment of trauma-associated disorders; data from animals indicating that older, stronger memories are less susceptible to labilization during recall[72,73] suggest that such an intervention may be useful only as secondary prevention in the aftermath of a traumatic event, and not as treatment after PTSD is well established.

Imbalance between memory systems

The multiple memory systems model, now widely accepted, posits that anatomically distinct mnemonic circuits in the mammalian brain subserve qualitatively different types of learning, specialized for a different type of environmental contingency or context.[74] In a complex environment these systems are engaged in parallel and may interact synergistically or, under some circumstances, compete with one another for the control of the organism's behavior.[74-76]

Two of these systems, the spatial/contextual memory system containing the dorsal hippocampus and the fear learning system centered on the basolateral amygdala, have figured prominently in the preceding discussion. An additional system that has been documented to interact with these two in a variety of circumstances is the striatal habit system. In rodents, the dorsolateral striatum is essential for the acquisition and execution of inflexible patterns of behavior that automate routine responses to common circumstances.[77,78] In certain contexts, habit-driven stimulus-response behaviors compete with more flexible, goal-directed behaviors. This has been shown, for example, in a water maze navigation task, in which disruption of the hippocampus, which is essential for flexible spatial navigation, actually enhances cue-based habit-like learning, while disruptions of striatal function enhance spatial learning.[76]

An implication of the multiple interacting memory systems is that clinically significant disruptions in adaptive behavior may derive not only from dysfunction or pathological hyperfunction of one or another memory system, but from an imbalance or disrupted regulation of the balance between systems. Recent data and theoretical advances suggest that this is indeed the case in several neuropsychiatric conditions. We close this review with a discussion of two of these.

Addiction is a complex disorder that involves pathological alterations to many parts of the brain. Ultimately, however, it can be conceptualized, with some risk of oversimplification, as a perversion of the normal action-selection mechanisms, such that behaviors geared towards acquisition and consumption of a drug are chosen in preference to more adaptive behaviors, even in the face of adverse consequences. Drugs of abuse are thought to produce this aberrant and maladaptive behavioral state by hijacking normal neuronal processes involved in motivated behavior, reinforcement, and plasticity.[79]

From the perspective of multiple memory systems, there may be multiple pathways to the addicted state. Maladaptive drug-associated patterns of behavior may derive, for example, from enhanced motivational power of the drug or reduced motivational power of other, naturalistic rewards, or from an increased reliance on inflexible habitual patterns of learned behavior or a reduced capacity of more flexible control systems. This view has recently been developed at length in an enumeration of 10 major vulnerabilities in the mechanisms underlying normal decision-making, exploitation of any one of which by a drug may lead to an addicted state.[6]

Addiction is characterized by enhanced use of rigid habit-like patterns of drug-associated behavior. One can envision such a pattern deriving from enhancement of the habit learning system described above, through repeated drug exposure and reinforcement of acquisition and consumption-related behaviors.[80] However, in light of the multiple memory systems model, one can also envision over-reliance on habitual modes of learned behavior deriving from impairment or inhibition of potentially competing learning systems and behaviors. A shift from habits to more flexible forms of behavior is thought to

require top-down regulation of action selection by prefrontal cortex (eg, ref 81). Inhibition or dysfunction of this cortical capacity may inappropriately leave behavior in a habit-guided mode, predisposing towards the inflexible behavior patterns that characterize the addicted state.[6] There is evidence that alcohol, amphetamine, and cocaine can all induce such a bias towards habitual control of behavior and a reduced capacity to recruit the prefrontal cortex to regulate it.[82,83]

OCD is also characterized by maladaptive inflexible patterns of behavior.[84] Increased activation of the basal ganglia circuitry is well established in this condition, as is pathology of the prefrontal cortex.[85] This raises the question of whether dysregulation of striatum-dependent habit learning, or the balance between habit learning and more flexible forms of behavioral regulation, may contribute to OCD, as well as to drug addiction.

Recent work suggests just such a dysregulation. Subjects were trained in behavioral paradigms in which their choices could be guided by an outcome-dependent strategy or a more automatic, habitual strategy. With overtraining, individuals with OCD showed a greater tendency to rely on inflexible habit-like behavioral routines. Such findings suggest that enhancement of the habit learning system, or dysregulation of the top-down mechanisms that would normally regulate the balance between habit and goal-directed systems, may contribute importantly to the development of OCD.[7,86]

These findings in drug addiction and OCD beg an important question; if both conditions can be explained, at least in part, by an enhancement of habit-like learning or a dysregulation of the balance between learning systems, then why are they so manifestly different from a clinical perspective? This is an important question for further study.

Conclusion

In this brief review, we have sought to illustrate several instances in which dysregulation of mnemonic processes and the mechanisms of neuroplasticity contribute to prevalent neuropsychiatric diseases. As illustrated in the foregoing discussion, reduced, enhanced, and imbalanced plasticity can all potentially lead to psychopathology.

This discussion has by no means been comprehensive—there are other disorders that might be chosen to illustrate the connections between neuroplasticity and psychopathology, and each of the individual topics sketched above could be an ample focus for a lengthy review in its own right. The reader is directed to the various recent references provided for more detail. However, these examples serve to illustrate that advances in the basic science of synaptic plasticity, neurogenesis, memory systems, and related processes may lead very directly to new insight into a number of psychiatric diseases and, potentially, to new therapeutic strategies. ❑

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Trastornos de la memoria y la plasticidad en la patología psiquiátrica

La plasticidad se encuentra en todo el sistema nervioso y se cree que subyace a aspectos clave del desarrollo, del aprendizaje y la memoria, y de la reparación. Los procesos neuroplásticos incluyen la plasticidad sináptica, el crecimiento y la remodelación celular, y la neurogénesis. La falta de regulación de estos procesos puede contribuir a una variedad de enfermedades neuropsiquiátricas. En este artículo se revisan tres maneras diferentes en las que la falta de regulación de los procesos neuroplásticos y nemotécnicos puede contribuir a la enfermedad psiquiátrica. En primer lugar, el deterioro de los mecanismos de plasticidad puede llevar a déficit cognitivo, lo que es muy obvio en la demencia y la amnesia, pero también se observa de manera más sutil en otras condiciones. Se revisa con algún detalle la relación entre estrés, depresión mayor y deterioro de la neuroplasticidad. En segundo lugar, ya que las memorias aumentadas pueden ser patogénicas, se explora el ejemplo del trastorno por estrés postraumático, en el cual las memorias invasoras asociadas con el trauma, acompañadas de la hiperactividad del circuito normal de aprendizaje del miedo constituyen aspectos centrales de esta patología. En tercer lugar, ya que una modulación deteriorada de la relación entre sistemas de memoria en paralelo puede contribuir a patrones conductuales de mala adaptación, se examina la propensión hacia patrones conductuales rígidos, tipo hábitos, en la adicción a drogas y en el trastorno obsesivo compulsivo. Se espera que una creciente comprensión de estas relaciones y de los mecanismos fundamentales que subyacen a la neuroplasticidad en el cerebro normal facilitará el camino para nuevas comprensiones de los mecanismos de la enfermedad neuropsiquiátrica y el desarrollo de nuevas estrategias terapéuticas.

Troubles de la mémoire et de la plasticité dans les maladies psychiatriques

La plasticité fait partie intégrante du système nerveux et serait au cœur des phénomènes de développement, d'apprentissage, de mémoire et de réparation. La plasticité synaptique, la croissance cellulaire, le remodelage et la neurogenèse font partie des processus neuroplastiques. Leur dérèglement contribue à de nombreuses maladies neuropsychiatriques. Nous analysons dans cet article trois voies différentes de dérèglements des processus neuroplastiques et mnésiques contribuant aux troubles mentaux. Premièrement, une altération des mécanismes de plasticité peut entraîner des déficits cognitifs, plus évidents dans la démence et l'amnésie, mais qui peuvent aussi se voir dans des formes plus subtiles d'autres pathologies. Nous étudions en détail les liens entre le stress, la dépression caractérisée et l'altération de la neuroplasticité. Deuxièmement, une exacerbation de la mémoire peut être pathologique ; dans l'état de stress post-traumatique, des souvenirs intrusifs associés au traumatisme s'accompagnent d'une hyperactivité du circuit d'apprentissage normal de la peur, deux aspects centraux de la pathologie. Troisièmement, une modulation défectueuse des relations entre des systèmes de mémoire parallèle peut contribuer à des schémas mal adaptés de comportement ; nous étudions la tendance à établir des comportements rigides et routiniers dans la toxicomanie et les troubles obsessionnels compulsifs. Tous ces exemples illustrent la façon dont différents mécanismes anormaux de neuroplasticité et de formation de la mémoire peuvent participer à différentes formes de psychopathologie. Nous espérons qu'une meilleure compréhension de ces interactions et des mécanismes fondamentaux de la neuroplasticité cérébrale normale ouvrira la route à de nouvelles connaissances des mécanismes des pathologies neuropsychiatriques et au développement de nouvelles stratégies thérapeutiques.

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