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Neural plasticity and emotional memory

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Abstract
Posttraumatic stress disorder is the pathological replay of emotional memory formed in response to painful, life-threatening, or horrifying events. In contrast, depression is often precipitated by more social context-related stressors. New data suggest that different types of life experiences can differentially impact biochemistry, physiology, anatomy, and behavior at the level of changes in gene expression. Repeated separation of neonatal rat pups from their mother results in many long-lasting alterations in biology and behavior paralleling that in depression, including hypercortisolism. The role of the amygdala in modulating emotional memory is highlighted, as well as some of its unique properties such as metaplasticity (i.e., the differential direction of long-term adaptation, either potentiation or depression) in response to the same input as a function of the prior history of stimulation. The implications of these emerging data on the physiological and molecular mechanisms underlying emotional memory emphasize the particular importance of prevention and early intervention.

Posttraumatic stress disorder (PTSD) is the paradigmatic example of pathological emotional memory. We know that normal processes of learning and memory, if subjected to sufficient repetitions, or if they are of enough intellectual interest or special relevance, can last a lifetime. Emotion appears to play a unique role in conveying permanence to memories. This can be either of a positive nature, with particularly happy or joyful occasions being carried throughout life, or conversely, negative or traumatic experiences imbuing an immanence and immediacy of memory for many decades, if not the entire life span of the individual.

We are beginning to glimpse only the barest outlines of how such memories are formed on a neurobiological basis. Nonetheless, we will present elements of this organizing structure for PTSD as the clearest example of emotional memory. We assume from the outset that this map will change both in pattern and detail with the acquisition of new knowledge in this rapidly expanding field. However, such an initial exposition of the preliminary data base may assist not only in tests of these formulations, but also in arriving at new potential interventions and therapeutic approaches to PTSD.

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The Evolution of PTSD

As depicted in Figures 1 and 2, PTSD, by definition, involves a traumatic stressor of sufficient emotional significance that it carries a threat to an individual's life or limb (i.e., having an element of real or potential catastrophic significance). Given this stressor of sufficient magnitude and, by definition, emotional intensity, a cascade of psychological and neurobiological events are set in motion. The initial acute phase of impact may be associated with pain, horror, fear, and terror and may be of such magnitude that it leads to dis-

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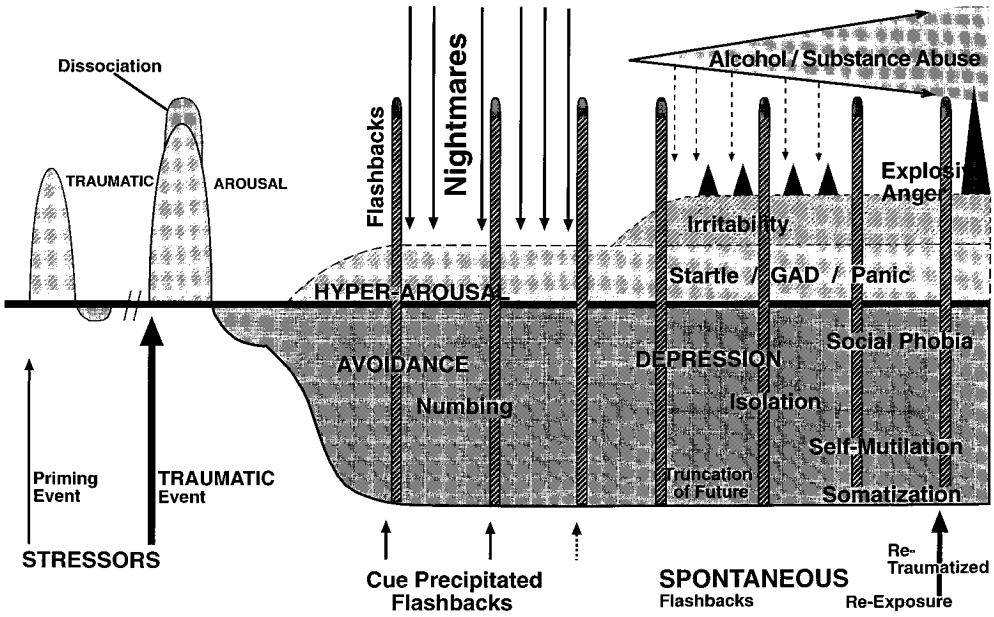


Figure 1. Schematic illustration of emerging symptoms of posttraumatic stress disorder. GAD, generalized anxiety disorder.

sociative elements that are highly predictive of the development of subsequent PTSD. Following this acute phase, there may be a period of numbing, dulling, or disbelief, perhaps periodically interrupted by recrudescence of the initial emotion, either through visual memories or actual reexperiencing phenomena should an individual have, for example, to identify the body of a dead relative or revisit the scene of the trauma, etc. Even after the attenuation of this initial swing in the direction of depression and dulling, paroxysmal events will be triggered by actual reminders or cues in the environment, or internally by evocative memory and recall, precipitating flashbacks and other emotionally laden reexperiencing phenomena. Nightmares are often a substantial accompaniment, and each of these elements occurs from a new baseline of hyperarousal evident in daytime-related hyperstartle and nighttime-related profound sleep disturbance.

In the resolving phase of PTSD, all of these elements may dissipate, leaving only the memory of the event intact, with an attenuation of the baseline hyperarousal and the paroxysmal components of flashbacks and nightmares as well. However, given an initial trauma of sufficient magnitude or, even more importantly, of sufficient repetition, occurring at times of critical developmental vulnerability, the PTSD syndrome may evolve into a relatively intractable form for years and decades, if not for a person's entire life span.

Elsewhere, we have discussed how the learning and memory analogies with amygdala-kindled seizures and sensitization may be related to processes that could be occurring in the memory circuits of PTSD (Post, Weiss, & Smith, 1995; Post, Weiss, Smith, Li, & McCann, 1997). In this fashion, we think there is considerable heuristic value in considering PTSD as an ictal disorder in which, rather than motor seizures of epilepsy, affective seizures are the sine qua non, which periodically and paroxysmally emerge from more chronic altered neuroadaptive set points of hyperarousal on the one hand and depression, withdrawal, and dulling on the other. In the kindling model of epilepsy, sufficient repetitions of triggered motor seizures (Goddard, McIntyre, & Leech, 1969) can ultimately lead to the emergence of untriggered seizures mirroring those in spontaneous epilepsy (Wada & Sato, 1974). We postulate that, given sufficient repetitions of externally and internally triggered flashbacks, these would also begin to occur in an autonomous form, with an impact and

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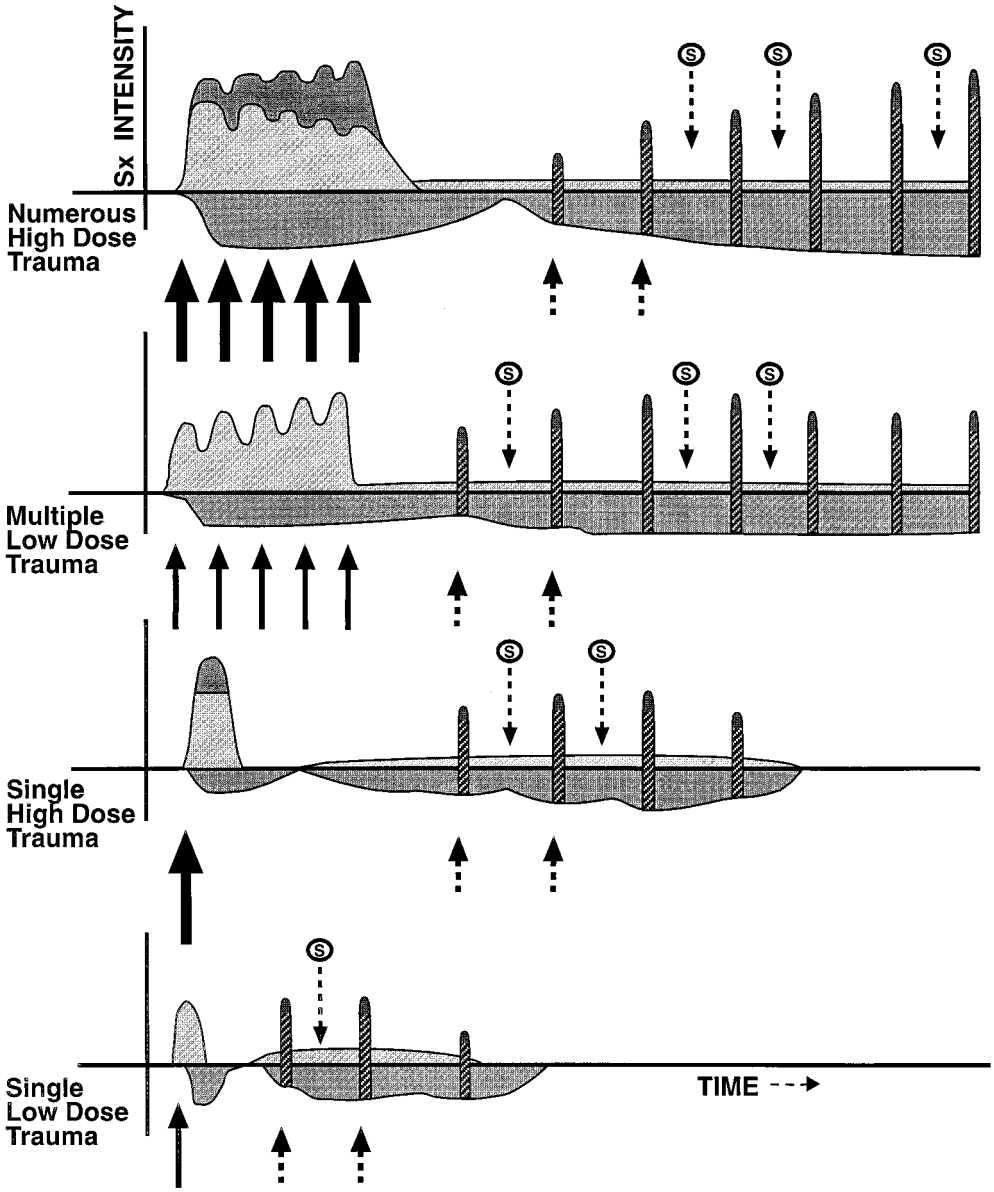


Figure 2. Schematic illustrating the postulated relation of severity and persistence of PTSD symptomatology (Sx) to the intensity and frequency of the inducing traumatic events. As in Figure 1, the arrows on the left indicate single (↑) or multple (↑↑↑) stressors; hatched arrows to the right indicate cue-precipitated flashbacks; shaded areas above the line (hyperarousal and dissociation) and below the line (avoidance and depression) correspond to Figure 1 as well. Ⓢ, sleep-related reexperiencing phenomena and nightmares.

disruption to life functioning not dissimilar to that of the motor seizure variety. This reformulation and reconceptualization has several strategic advantages, including providing a model of memory formation that can easily be assessed and upon which therapeutic interventions can be evaluated (see Figure 3).

Kindling

A single epileptic seizure, whether or not it is treated prophylactically, may or may not develop into full-blown epilepsy. However, once a number of seizures occur, whether triggered or untriggered, the likelihood of their

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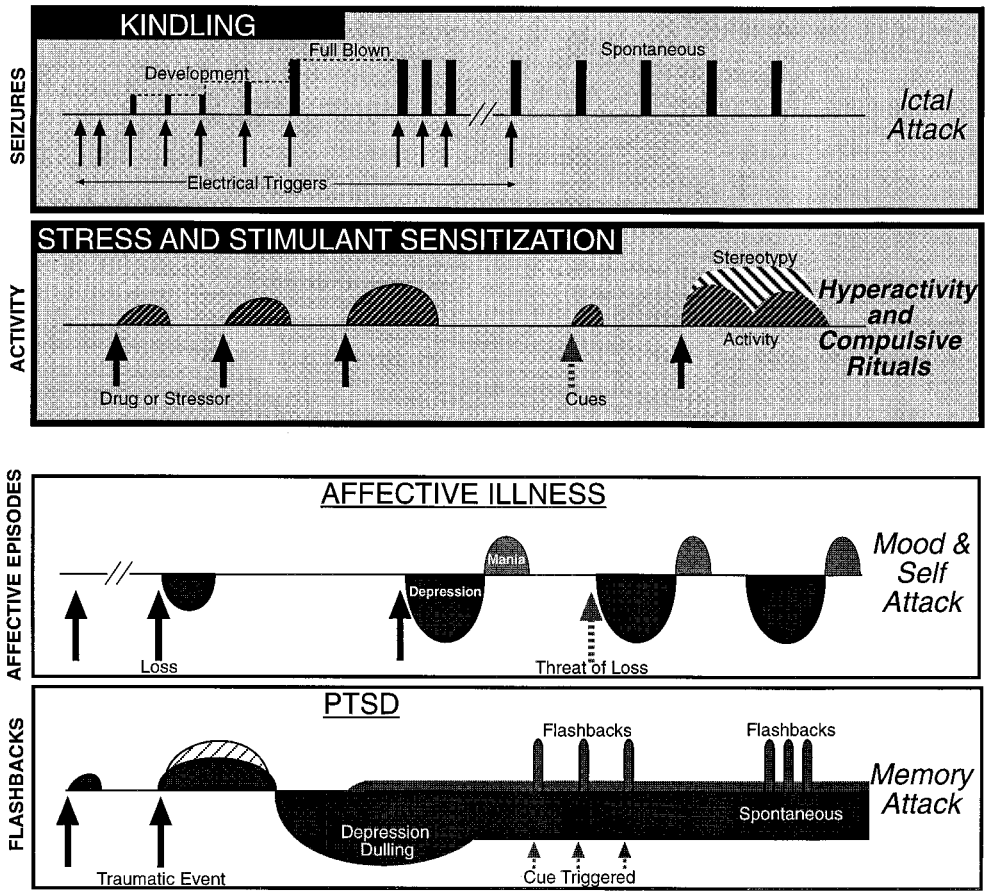


Figure 3. Sensitization and kindling-like progression of components of several neuropsychiatric syndromes.

progressing to a full-blown autonomous seizure disorder greatly increases. With sufficient repetitions, the patient may be at higher risk for the development of treatment resistance. Moreover, given the potentially severe consequences of motor seizures and the importance of early intervention (Reynolds, 1987), it would, in a parallel fashion, place the experiencing and reexperiencing of the affective seizures of PTSD in the category of a medical emergency—one to be evaluated, diagnosed, and treated with the same care as the motor variety. There is such a standard of care for motor seizures in neurology. Similarly, an evolving standard of care should be enunciated and revised as further information about the adequacy and efficacy of early and late interventions in PTSD becomes clear from a systematic clinical-trials literature.

The model of kindled seizure evolution gives us a variety of preliminary neurobiological structures to consider for their potential relevance to the evolution of PTSD and other pathological disorders of affective memory. We know that kindling requires repetition of amygdala stimulations of such magnitude as to produce afterdischarges which themselves convey long-term neurobiological consequences (Goddard, McIntyre, & Leech, 1969; Racine, 1978). Sutula and colleagues (Golarai & Sutula, 1996; Sutula, 1991; Sutula, Cavazos, & Woodard, 1994) have demonstrated that amygdala afterdischarges, even short of inducing a full-blown seizure, are ca-

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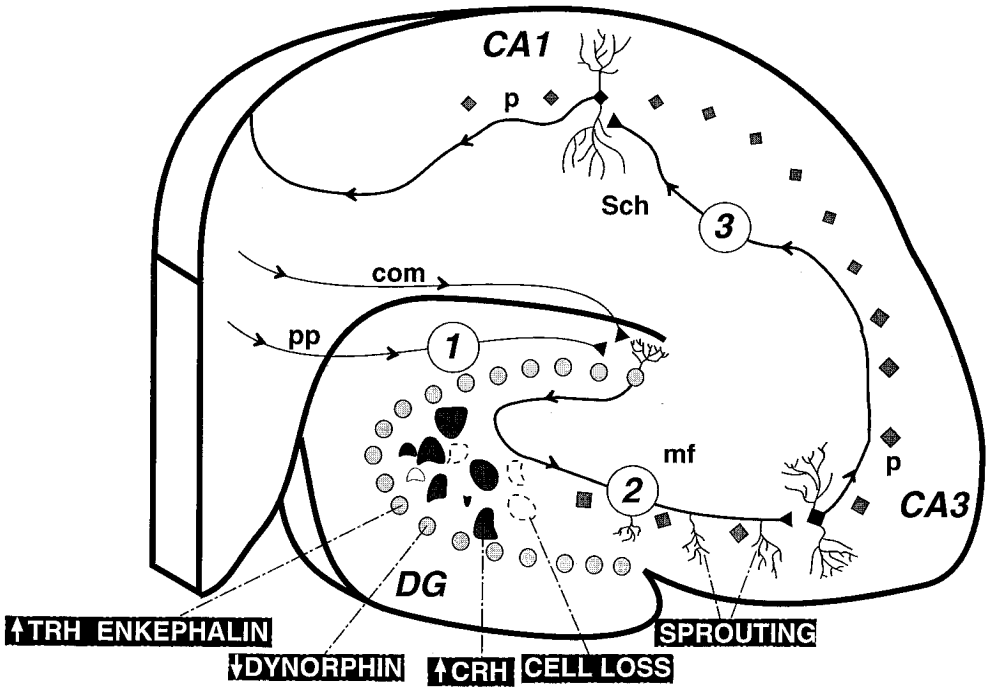


Figure 4. Schematic illustration of a hippocampal slice from any amygdala-kindled animal showing some of the changes in gene expression and microanatomy that have been described in the literature. Mossy fiber (mf) sprouting is shown in the CA3 region; cell loss is indicated in the hilar cells. Increases in gene expression for thyrotropin releasing hormone (TRH), enkephalin, and corticotropin-releasing hormone (CRH) are found in the dentate gyrus (DG) along with decreases in dynorphin. sch, Schaeffer collaterals; pp, perforant path; com, commissural pathway; p, pyramidal cells.

pable of inducing neuronal sprouting in dentate granule cells and also perhaps apoptosis (i.e., preprogramed cell death) in the distant structures of the dentate gyrus of the hippocampus, particularly in the hilar region.

An exquisite change in the neurochemistry and neuroanatomy of hippocampal synapses based on kindled seizure evolution is now apparent (see Figure 4). Not only is there sprouting of dentate granule cells and increased expression of thyrotropin-releasing hormone (TRH) (Rosen, Cain, Weiss, & Post, 1992; Rosen, Kim, & Post, 1994), but expression of corticotropin-releasing hormone (CRH) (Smith et al., 1991) and cell death in the cells of the dentate hilar region as well (Zhang, Smith, Li, Weiss, & Post, 1998). These alterations also involve dramatic changes in neurotrophic factor gene expression, such as increases in brain-derived neurotrophic factor (BDNF) (Smith, Makino, Kim, & Kvetnansky, 1995) and decreases in neurotrophin-3 (NT3) in the hippocampus, but increases in other areas of brain (Smith, Makino, Kvetnansky, & Post, 1995).

BDNF may be a neurotrophic factor of particular significance because, in animals that have no BDNF expression due to gene knockout strategies, elementary forms of learning and memory such as long-term potentiation (LTP) of the hippocampal slice are impaired, as are actual learning and memory as evidenced by an inability of animals to negotiate a Morris swim maze (Korte, Staiger, Griesbeck, Thoenen, & Bonhoeffer, 1996). In the kindling model, BDNF and other neurotrophic factors may help explain the sprouting of the dentate granule cells and the expression of

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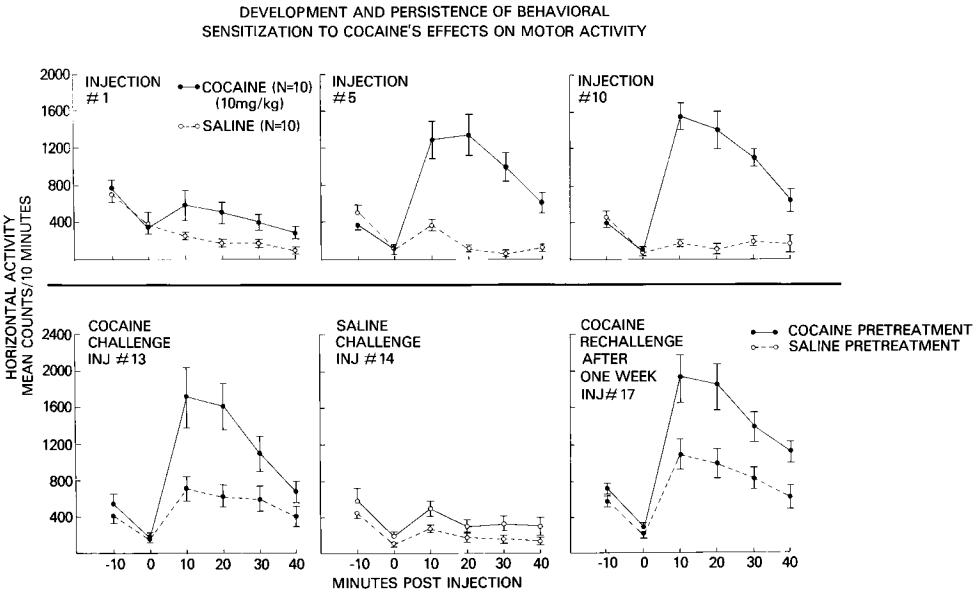


Figure 5. Rats treated with cocaine (10 mg/kg) show increases in motor activity following repeated injections (injection 10 vs. 1) and increased responses to cocaine compared to saline-pretreated controls (injections 13 and 17). A small but significant conditioned response to a saline injection (14) was also apparent in the cocaine compared to saline-pretreated animals (which had received only one prior cocaine injection).

CRH and other early changes in biochemical signature of a neuron or events in the sequence leading to cell death.

Stimulant and Stress-Induced Behavioral Sensitization

Stimulant sensitization

Behavioral sensitization to the psychomotor stimulants amphetamine and cocaine consists of increased behavioral reactivity to repeated administration of the same dose over time. This is essentially the opposite of tolerance and, of necessity, involves a memory-like mechanism. Although stimulant-induced behavioral sensitization differs greatly from electrophysiological kindling in terms of the inducing variables, biochemical pathways involved, and physiological and behavioral endpoints, they both share the property of having a memory-like component as evidenced by increased behavioral or convulsive responsivity (Post, 1992; Post, Weiss, & Leverich, 1994) (see Figure 5). Analogous to the situation in amygdala kindling, a preliminary map is available of some of the neurobiological pathways involved in stimulant-induced behavioral sensitization. Dopamine pathways, particularly those in the midbrain or ventral tegmental area, appear to be highly implicated in the initiation of sensitization, but other pathways become involved with the maintenance phases (see Figure 6). Similarly, there are a host of changes in immediate early and late effector genes leading to a virtual reprograming of much of the striatal, thalamic, cortical, and limbic pathways involved in the modulation of motor activity (Post, 1992) (see Figure 7).

In addition, there is a prominent conditioned component to cocaine-induced behavioral sensitization, such that animals that become sensitized to a drug in a specific environmental context (usually the setting in which they receive their drug) do not show this same enhanced cocaine response in a different environment (see Figure 8). This context dependency indicates that sensitization can involve associative learning; in this case, cues from the environment can either allow or inhibit expression of the enhanced drug re-

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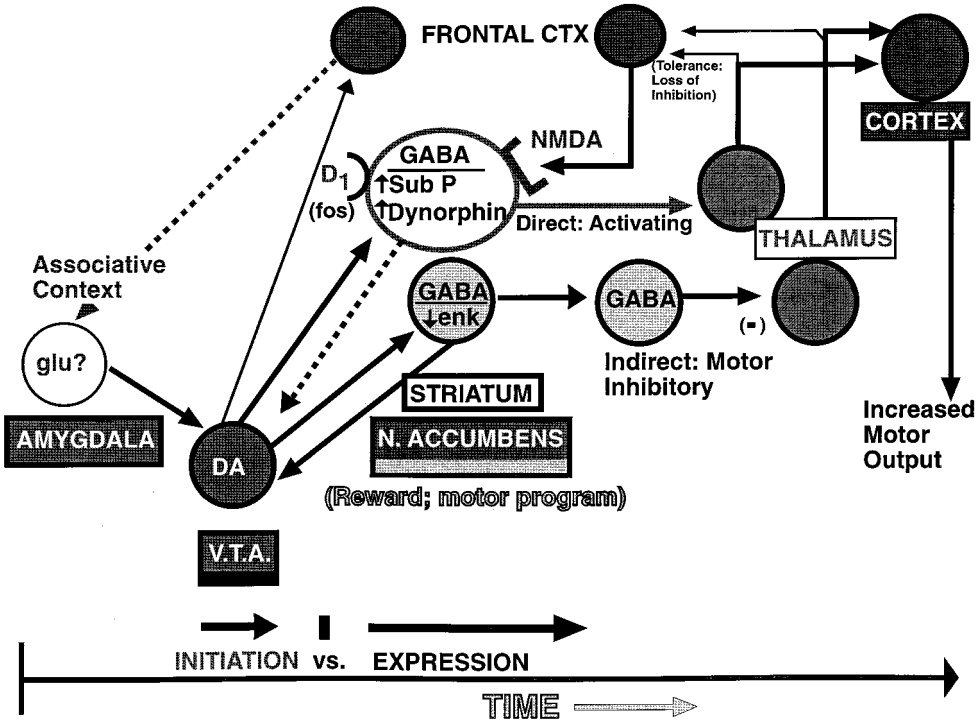


Figure 6. Progression in the neural substrates mediating cocaine-induced behavioral sensitization. The schematic illustrates the brain structures, neurotransmitters, and peptides thought to be involved in cocaine sensitization. The VTA is critical to the initial development of sensitization, whereas the nucleus accumbens and more distal structures may be involved in its expression. The amygdala may play a role in the initial associative components of sensitization. The ventral pallidum and motor cortex are important for the motor output. Dopamine is implicated in the VTA and n. accumbens, as well as glutamate, which may also be important for the context-dependent component of sensitization (Figure 8). GABA, gamma aminobutyric acid; Sub P, substance P; DA, dopamine; D_1, dopamine receptors; enk, enkephalin; VTA, ventral tegmental area; glu, glutamate; NMDA, *N*-methyl-D-aspartate.

sponse. This may also be relevant for sensitization to other types of stimuli (e.g., stressors). Thus, not only could a traumatic experience elicit an acute stress reaction, but, by association, specific environmental cues would also become capable of contributing to or eliciting subsequent, possibly sensitized, stress responses.

Stress sensitization

There is abundant evidence of cross-sensitization between psychomotor stimulants and stresses in both directions (Antelman, Eichler, Black, & Kocan, 1980; Kalivas & Duffy, 1989; Kalivas, Richardson–Carlson, & Van Orden, 1986; Piazza, Deminiere, LeMoal, & Simon, 1990; Sorg & Kalivas, 1991). Although all paradigms do not invariably show cross sensitization, a multitude of evidence indicates that at least some of the pathways are common and that one type of sensitization can facilitate the other. Therefore, the notion that repeated intermittent experiences of stresses can lead to behavioral sensitization rather than tolerance, begins to put the multiple classes of intermittent stressors into a new light. They, as well as cocaine-induced behavioral sensitization and kindling, can leave behind neurobiological memory traces at the level of gene expression, such that, upon rechallenge later in life, an increased rather than decreased reactivity will be evident. Even a single stressor may have sensitization components that grow

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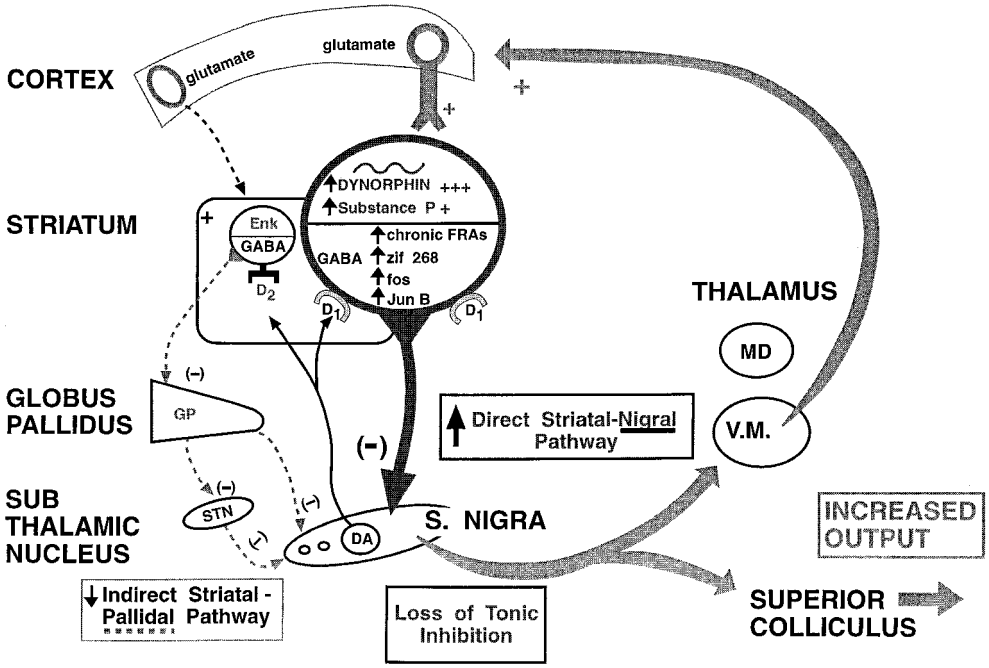


Figure 7. Cocaine reprograms the genetic machinery of the direct striatal output pathway leading to increased motor behavior. GABA, γ-aminobutyric acid; DA, dopamine; D_1, D_2, dopamine receptors; enk, enkephalin; glu, glutamate; MD, medial dorsal nucleus of the thalamus; VM, ventromedial nucleus of the thalamus; s. nigra, substantia nigra.

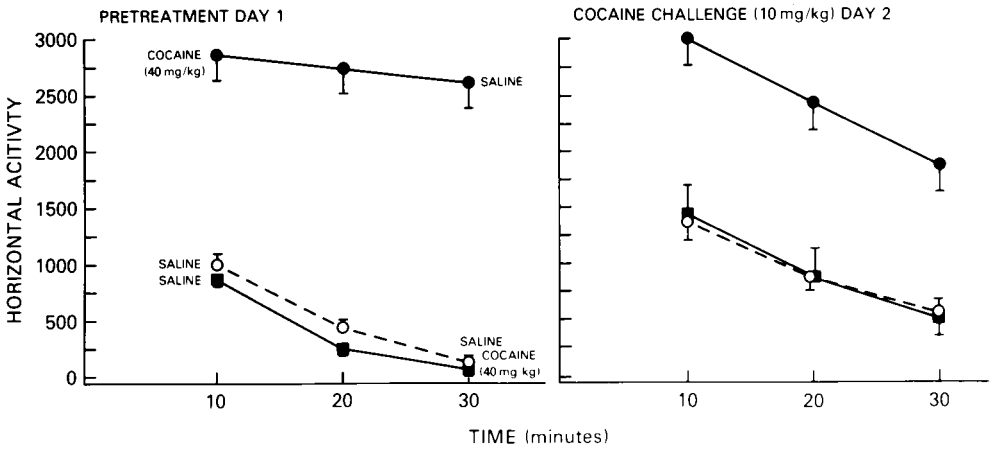


Figure 8. Cocaine-induced behavioral sensitization depends on the environmental context. The left panel illustrates the mean horizontal activity of rats ($n = 10$/group) that received the following treatment on day 1: (●) cocaine (40 mg/kg, IP) in the activity chamber and saline in the home cage, (■) saline in the test chamber and cocaine in the home cage, and (○) saline in both environments. The right panel illustrates horizontal activity for these three groups following a cocaine challenge (10 mg/kg, IP) on day 2. Only the rats that received cocaine in the test chamber on day 1 showed sensitization to cocaine on day 2.

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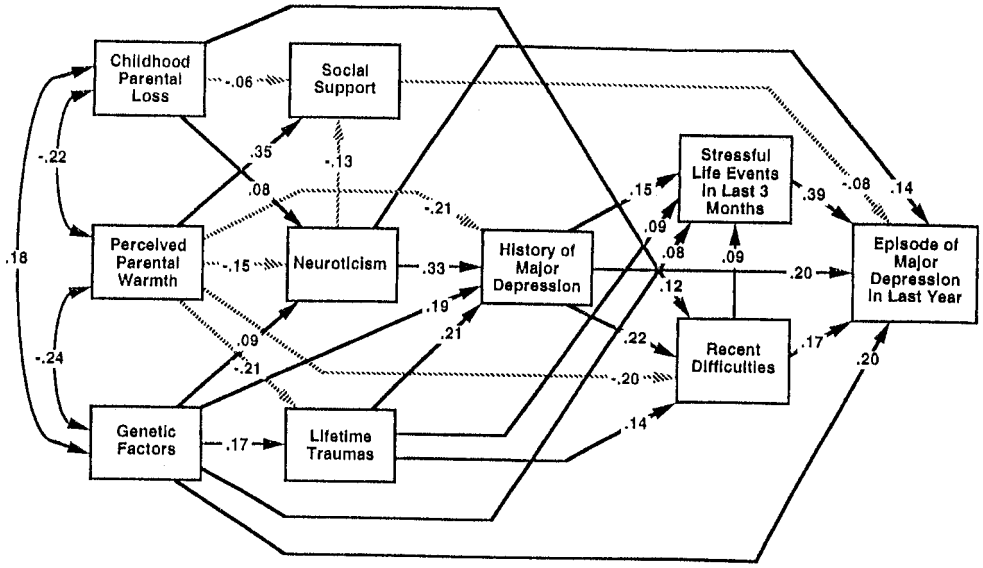


Figure 9. Kendler's path estimates of the best-fitting model of prediction of major depression in 1,360 female twins. Early and recent life events (left, top two boxes) interacting with genetic vulnerability (left, bottom box) predispose to early mild symptoms and episodes (Neuroticism box) and more major depression (middle box and last box on right). Episode occurrence further increases vulnerability to recurrence (middle box to last box on right). The values along the double-headed arrows between the independent variables (at the left side of the figure) are correlation coefficients. The values along the single-headed arrows are path or standarized regression coefficients indicating the weight of the relationships. The black single-headed arrows represent positive path coefficients. Negative path coefficients are depicted by striped paths (see Kendler et al., 1993, for details). Reprinted with the permission of Kendler et al.

with the passage of time (Antelman et al., 1988).

This becomes of profound importance for stress-sensitive psychiatric syndromes, most paradigmatically, PTSD, but also those involving a prominent role for stressors at least early in the course of development of the unipolar (Kendler, Neale, Kessler, Heath, & Eaves, 1992) (see Figure 9) and bipolar affective disorders (Post, 1992) . In this latter instance, there is considerable evidence from the literature (Post, 1992), as well as new studies (Nierenberg et al., 1998), that confirm the notion that stressors are more likely involved in the initial episodes of affective illness but, with sufficient recurrences, episodes begin to appear more autonomously. It is not that stressors are not capable of precipitating the later episodes; it is only that they are less essential to the emergence of new episodes.

Thus, like kindled seizures, in which the precipitated ones self-organize to the point that they can occur autonomously, a similar transition appears to occur with affective episodes, with sufficient recurrence revealing their increasing automaticity as well. These data are convergent with those of Kessing, Andersen, Mortensen, and Bolwig (1998), indicating that the number of prior depressive hospitalizations is directly proportional to the latency and likelihood of relapse for both unipolar and bipolar depressions. Thus, it would appear that not only is there stress-sensitization, but additional episode sensitization (i.e., the experience of episodes themselves is capable of inducing long-lasting vulnerabilities that enhance the likelihood of recurrence).

Developmental and Neurobiological Substrates for Vulnerability to Depression and PTSD

Elsewhere, (see figure 1 in Post & Weiss, 1997) we have outlined some of the essential

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differences between the neurobiology of PTSD and affective disorders. Perhaps the most striking contrast is in neuroendocrine regulation, in which affectively ill patients are hypercortisolemic with a deficiency of glucocorticoid receptors, whereas the converse is true for PTSD. In this latter instance, there is a wealth of literature indicating that PTSD patients are, paradoxically, hypocortisolemic with increased glucocorticoid receptor expression. Moreover, whereas depressed patients tend to be hypometabolic or hypoperfused in the frontal cortical regions (left greater than right), patients with PTSD, particularly when they are engaged in recall of traumatic memories, show a pattern of right frontal corticolimbic hyperactivity (Rauch et al., 1996; Semple et al., 1993; Shin et al., 1997; van der Kolk, Burbridge, & Suzuki, 1997). The timing, magnitude, and qualitative aspects of the stressful life experiences that seem to predispose to these two illnesses also differ. Separation, loss, and threat in the social context and to the self seem far more involved in depressive precipitants than do the more horrific events characteristic of PTSD. Therefore, one would expect differential neurochemical mechanisms at the level of gene expression with such different life experiences. This is, in fact, what is demonstrable in animal models (see Figure 10).

Meaney, Plotsky, and colleagues (Meaney, Aitken, Van Berkel, Bhatnagar, & Sapolsky, 1988; Plotsky & Meaney, 1993) have compared the differential effects of separation stress in the neonatal rat pup on a variety of behavioral and neuroendocrine endpoints pertinent to the development of depression. The repeated experience of 3 hr of maternal separation to neonatal rat pups in the first weeks of life yields an animal that is permanently hypercortisolemic and more prone than its littermate controls to alcohol and cocaine self-administration. These effects are reversible by a serotonin-selective antidepressant (Plotsky, Eisler, & Anand, 1996; Plotsky, 1997); however, when the drug is discontinued, the hypercortisolemia and proneness to drug self-administration returns.

Interestingly, 15 min of maternal separation appeared to immunize the rat pups against age-related memory decline (Meaney et al., 1988) and hippocampal defects (Plotsky & Meaney, 1993). Recently, the mechanism for this effect has been revealed to be the increased attention and grooming by the mother in response to the foreign smell that occurs with the brief handling of her neonates (Liu et al. 1997). These data highlight the substantial differential impact of deprivation versus enrichment of maternal care behavior in the neonate as it pertains to long-term behavioral and endocrine consequences. The relative permanence of these effects is striking in terms of the regulation of both the hypothalamic-pituitary-adrenal axis and in the prevention of late-life related memory decline based on such early life experiences.

Investigators in our group working in collaboration with Dr. Seymour Levine have further examined the impact of 24 hr of maternal separation in the 10- to 14-day-old rat pup (Zhang, Xing, Levine, Post, & Smith, 1997; Zhang, Dent et al., 1998). Strikingly, this single manipulation doubles the rate of programed cell death (apoptosis) in the brain as measured by apoptag. Moreover, there is an increase in the mRNA for the cell death gene *BAX*, as well as increases in *c-jun*, and significant decrements in the neurotrophic factor BDNF in the hippocampus. Increases in nerve growth factor (NGF) are also observed in widespread areas of brain.

Upon visual inspection, it is apparent that many of the apoptag-labeled cells are undergoing classic apoptosis, as opposed to necrosis, with the characteristic pattern of nuclear condensation, membrane blebbing, and desolution without associated inflammatory process or marked glial infiltration. Striking increases in apoptosis also were revealed in the external germinal layer of the cerebellum, a structure that eventually disappears in the adult animal.

Thus, taken together, these series of studies from different laboratories indicate that there are profound biochemical, endocrinological, and, potentially, neuroanatomical consequences of single or repeated stresses based on maternal deprivation in the neonatal rat. Many of these changes appear to mirror the neurobiological concomitants of depression

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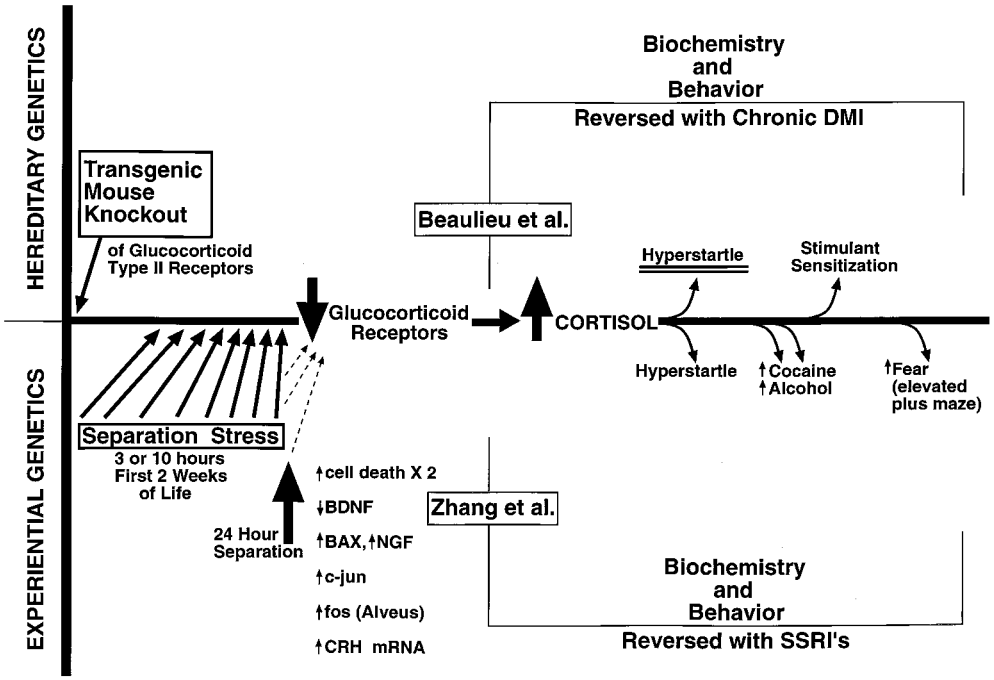


Figure 10. Convergent genetic and environmental models of depression. Either heredity or experiential genetics may lead to compounding behavioral and biochemical end points similar to those seen in depression and reversible by antidepressants. DMI, desipramine; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; CRH, corticotropin-releasing hormone; SSRIs, serotonin selective reuptake inhibitors.

occurring clinically in the adult, including hypercortisolemia and relative memory defects, and even an increased vulnerability to substance abuse. Partial validation of this model is also evident with the amelioration by serotonin-selective antidepressants and their requirement for maintenance treatment. In patients who respond to acute antidepressant treatment, the statistical significance of the differential rate of relapse of continuation of this prophylaxis versus placebo substitution is 10^{-34} (Davis, Wang, & Janicak, 1993), further indicating the need for sustained pharmacoprophylaxis in patients vulnerable to recurrent affective illness (Post, Leverich et al., 1997).

Hubel and Wiesel (1979) won the Nobel Prize for demonstrating the physiological and anatomical consequences of the deprivation of visual input. Based on the initial studies described above, as well as those in primates (Harlow, Dodsworth, & Harlow, 1965; Suomi, DeLizio, & Harlow, 1976; Young, Suomi, Harlow, & McKinney, 1973), and confirmatory studies regarding the differential effect of group versus isolation rearing of Robbins et al. from England (Geyer, Wilkinson, Humby, & Robbins, 1993; Jones, Marsden, & Robbins, 1990; Jones, Marsden, & Robbins, 1991), one is beginning to see that equally profound effects of deprivation of normal maternal input may also occur in neural substrates critical to the development of cognitive, emotional, and affiliative behavior.

Again, these studies are further validated by the effects in the opposite direction of environmental enrichment being able to enhance a variety of behavioral, physiological, and even anatomical endpoints (Comery, Shah, & Greenough, 1995; Fuchs, Montemayor, & Greenough, 1990; Wallace, Kilman, Withers, & Greenough, 1992). Most striking are the recent data of Gage and colleagues indicating that environmental enrichment, even in mature animals, is capable of increasing the number of progenitor cells going on to become neurons, as opposed to glial cells

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(Kempermann, Kuhn, & Gage, 1997, 1998). Thus, there appears to be both early developmental and late ongoing alterations in the balance of biochemistry and microneuroanatomy based on environmental impact.

These data bespeak the futility of the exclusive nature versus nurture argument, which has prominently resurfaced with the new neurobiology of molecular genetics. Somehow, it is assumed that the genetic vulnerabilities that are inherited are more valid or cogent than those induced by environmental circumstances. This assumption prevails despite the fact that a family history of bipolar illness or schizophrenia is evident in half or less of the cases of the illness, and nongenetic factors are most definitely implicated (Gershon, Hamovit, Guroff, & Nurnberger, 1987; Goodwin & Jamison, 1990). This assumption has driven an imbalance in the field that deserves correction (even more so in the field of psychiatry than in neurology because of the polygenic heredity influences in its illnesses) and the wealth of data indicating that environmental experience can affect virtually all levels of neurobiology. The dichotomy between hereditary and experiential molecular genetics thus appears artificial and evocative of a biased approach to the evaluation of quality research (Cicchetti & Tucker, 1994).

With the new ability to create transgenic animals, researchers have been able to model hypercortisolemia of depression by decreasing glucocorticoid receptor number (Beaulieu, Rousse, Gratton, Barden, & Rochford, 1994). Related findings also have been acquired by the group headed by Holsboer (see, e.g., Dijkstra et al. 1998; Karanth et al., 1997; Stec, Barden, Reul, & Holsboer, 1994). At the same time, long-lasting and persistent hypercortisolemia can be induced through an experiential impact on molecular genetics, particularly if it occurs in crucial phases of development, as described above. Thus, behaviorally relevant alterations in biochemistry can be imparted by either hereditary or experiential molecular genetics (see Figure 10) and it is likely that there will be an exquisite interplay between genetic and experiential vulnerability in determining many of the prominent major psychiatric illnesses.

That the division between hereditary and experiential molecular genetics is highly artificial is also illustrated by the recent advances in molecular biology that allow the experimenter to determine the exact timing of the onset of a genetic defect. Since the manipulation can now be induced later in life rather than from its outset, the effects of the gene on development can be parceled out from its effects in a mature animal. This has been elegantly documented in the studies of Rotenberg and colleagues (Rotenberg, Mayford, Hawkins, Kandel, & Muller, 1996) in which they demonstrated that genetic alteration of calcium-calmodulin kinase in the adult rat was associated with loss of spatial and navigational memory skills, and this was specifically related to a loss of the ability of place cells in the hippocampus to code prior information from the environment. Thus, molecular biologists are now beginning to create models that are more pertinent to the time course of experiential impact on gene expression, permitting exploration of the consequent changes in neurochemistry, enzyme activity, and behavior. Such modulation late in life also will likely be shown to have profound effects on learning and memory.

It appears that environmental experience of a specific quality or quantity, particularly when it occurs in crucial phases of development, may be capable of exerting profound effects on neural organization and anatomy (Cicchetti & Tucker, 1994; Eisenberg, 1995; Nelson & Bloom, 1997). Much work remains to delineate the critical periods for such impact and windows of opportunity for ameliorative manipulations. Taking this as a given, it is also pertinent to discuss neural plasticity in adulthood to ascertain the potential implications of ongoing experience for learning, memory, and the neurobiology of the brain.

LTP and Long-Term Depression (LTD)

Preliminary insights into the neurobiology of learning and memory reveal extremely exciting data on the extraordinary plasticity of neurons and their synaptic connectivity in adulthood. Perhaps the best studied and most accepted model of neuronal learning and

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memory is that achievable in the hippocampal slice preparation (Bliss & Lomo, 1973; Malenka, 1995). Here, the precise anatomical connections of the trisynaptic excitatory synapses of the hippocampus are well delineated and one is able to stimulate and record from precisely targeted areas of brain. LTP occurs when brief high-frequency stimulation produces a long-lasting pathway specific enhancement of strength in synaptic transmission. More recently, phenomena of LTD have begun to be studied wherein low frequency and more extended stimulation (often 10–15 minutes) is utilized to produce long-lasting decrements in the strength of specific synaptic inputs.

The studies of Malenka and colleagues (Oliet, Malenka, & Nicoll, 1996) have further demonstrated that there is bidirectional plasticity wherein the same synapse can either be potentiated or depotentiated depending on the input characteristics of brief, high-frequency stimulation alone, or followed by more sustained low-frequency stimulation to reverse the impact of the high frequency train on cellular function (see Figure 11). Glutamate receptors are necessary for the induction of LTP and these changes have now been traced to a cascade of events involving alterations in gene expression at the level of the nucleus. Thus, second messenger systems such as calcium and cyclic-AMP, kinases and phosphatases, as well as neurotrophins and other transcriptional regulators, are all implicated in such cascades modulating the strength of the specific synapses based on neuronal activity.

The *N*-methyl-D-aspartate (NMDA)-type glutamate receptor is necessary for the induction of LTP, but the AMPA-type glutamate receptor is thought to be involved in its maintenance (Muller, Joly, & Lynch, 1988). This is of particular interest in relationship to the modulation of AMPA receptors by phosphorylation, based on the differential calcium influx through the NMDA receptor, as illustrated in Figure 11. That is, brief, high-frequency bursts of neural activity are associated with large calcium influxes which then differentially affect calmodulin and CaCM-kinase II in the direction of phosphorylation of the AMPA receptor. In contrast, with low-frequency firing in a more chronic and sustained fashion, phosphatases predominate and phosphate groups are removed from AMPA receptors, decreasing the response to glutamate release. This paradigm is pertinent to the CA-1 area of the hippocampus, but there are also LTP and LTD mechanisms in the synapses between the dentate gyrus granule cells and the CA-3 pyramidal cells that are not dependent on NMDA receptors. Thus, there appear to be diverse molecular mechanisms involved in learning and memory formation at different synapses; to some extent these may reflect differences in function or type of memory mechanism, as illustrated in Figure 12.

LTP and LTD in the amygdala slice preparation

Dr. He Li and colleagues have been able to establish similar paradigms for inducing LTP and LTD in the amygdala slice preparation (Li, Weiss, Chuang, Post, & Rogawski, 1998), which we think is particularly pertinent to the type of amygdala-based learning and memory that may take place in a variety of psychiatric disorders, including disorders of emotion and anxiety modulation. The amygdala has been implicated as a major anatomical substrate for connecting cues in the environment with anxiety and other affective behaviors (Davis, 1997; Gloor, Olivier, Quesney, Andermann, & Horowitz, 1982; LeDoux, 1992; Rolls, 1992). There also is clinical evidence based on structural and functional brain imaging that amygdala function may be disordered in patients with affective illness (George, Ketter, & Post, 1993; Ketter et al., 1994). Examining amygdala neuroplasticity at the level of cortical input to basolateral amygdala synapses may thus reveal mechanisms pertinent to emotional memory and its similarities and differences from other types of learning and memory, such as those revealed in the hippocampus.

Principles of emotional neuroplasticity derived from the amygdala slice preparation

Dr. He Li, in collaboration with Dr. M. Rogawski, has been able to develop a new prepa-

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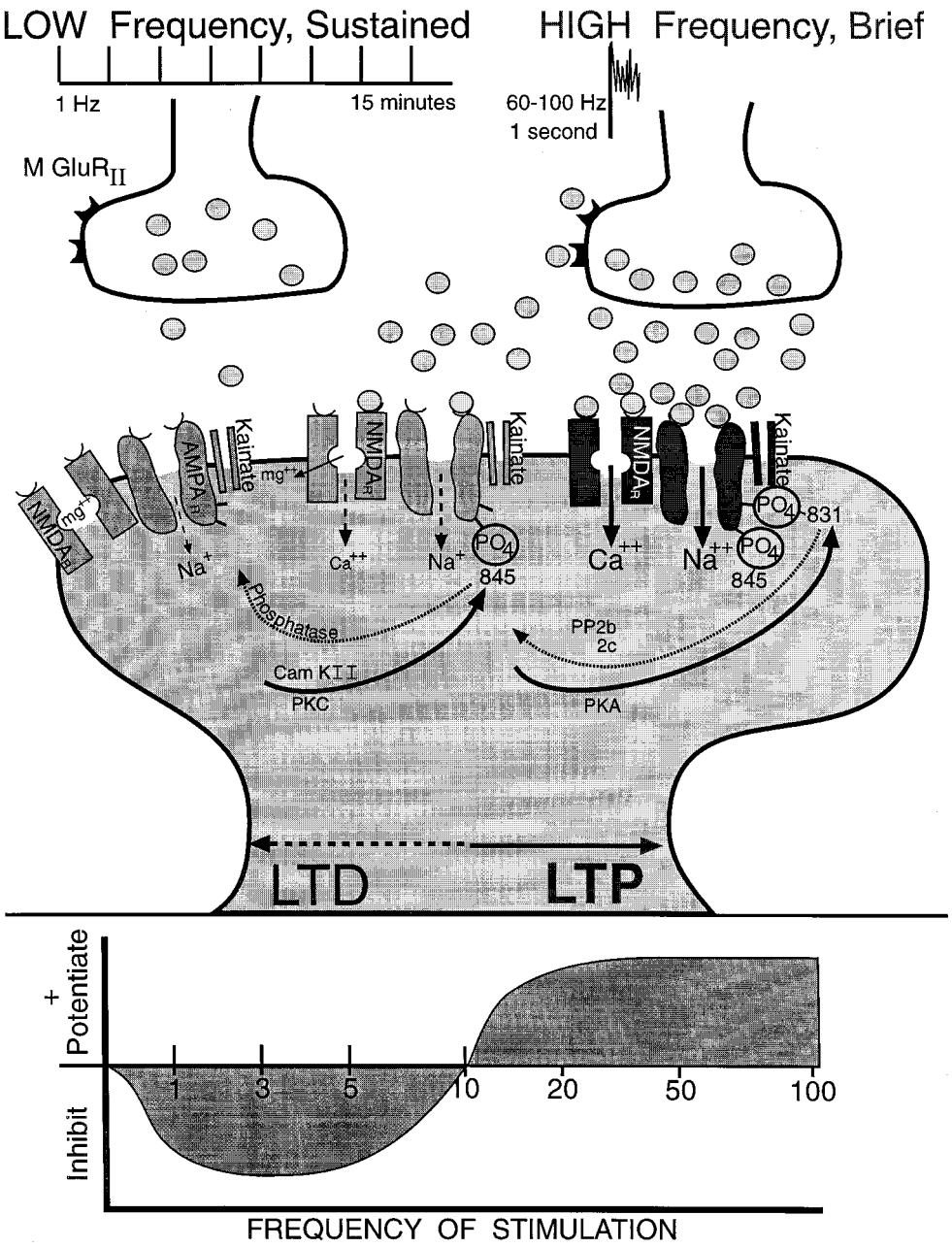


Figure 11. Schematic illustration showing the bidirectional modification in synaptic excitability as a function of frequency of stimulation (top and bottom) and putative cellular components (middle) of long-term depression (LTD) and long-term potentiation (LTP). LTD occurs following low frequency, sustained stimulation (e.g., 1 Hz for 15 min, top left) and may involve increased phosphatase activity leading to dephosphorylation of the AMPA receptors. LTP occurs following brief high frequency stimulation (e.g., 100 Hz for 1 s, top right) and involves relatively large increases in calcium flux through the NMDA receptor and increases in kinase activity leading to increased phosphorylation of the AMPA receptors. The bottom illustrates the frequency dependence of these two phenomena with lower frequency stimulation (1–5 Hz) producing relative synaptic inhibition and higher frequency stimulation (20–100 Hz) producing potentiation. Adapted from Malenka (1995), Dudek and Bear (1992), and Li et al. (1998).

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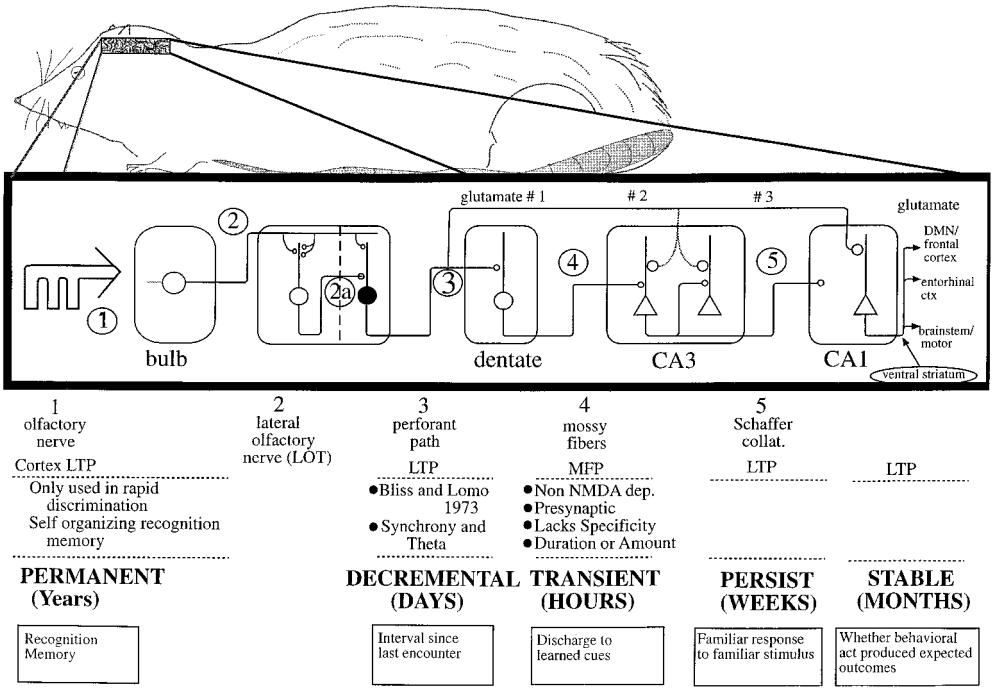


Figure 12. Anatomy of olfactory discrimination (cortex to hippocampus) linking past experience with current environment. This figure illustrates the various forms of LTP that have been demonstrated in the different regions of the olfactory bulb and hippocampus leading to long-term olfactory learning. In addition to the regional differences noted on the figure, there are also distinct temporal qualities to each form of synaptic plasticity allowing for functional specialization of each part of the pathway. LTP, long-term potentiation; NMDA, *N*-methyl-D-aspartate; MFP, mossy fiber potentiation; DMN, dorsal medial nucleus of the thalamus. Adapted from Lynch and Granger (1992).

ration for recording from single neurons in the basolateral nucleus of the amygdala and stimulating these neurons either rostrally from the external capsule or basally from the basal nucleus of the amygdala. In contrast to the hippocampus in which a single high frequency stimulation leads to long-term potentiation, in the basolateral nucleus of the amygdala it leads to only short-term potentiation and a second high-frequency stimulation is required for LTP (see Figure 13). This would appear to be a conservative break on the permanence of emotional memory formation, with the notion that only with a second repetitive stimulation would one want to code amygdala-relevant stimuli into long-term memory.

However, if amygdala stimulation is accompanied by noradrenergic potentiation with the beta-adrenergic agonist isoproterenol, the amplitude of basolateral nucleus responsivity is extraordinarily enhanced (see Figure 14). Thus, a variety of potentiating mechanisms are available for maximizing emotional memory formation, and these data are convergent with the recent evidence from McGaugh, Cahill, and Roozendaal (1996) that β blockers are able to attenuate emotional memory while leaving other types of memory relatively intact.

History-dependent modulation of amygdala excitation: Metaplasticity in vitro

If basolateral neurons of the amygdala are given a single high frequency stimulation sufficient to produce short-term potentiation, and the synaptic strength returns to baseline, then low frequency stimulation (1 Hz for 15 min) is capable of inducing LTD. However, in previously unstimulated basolateral amygdala

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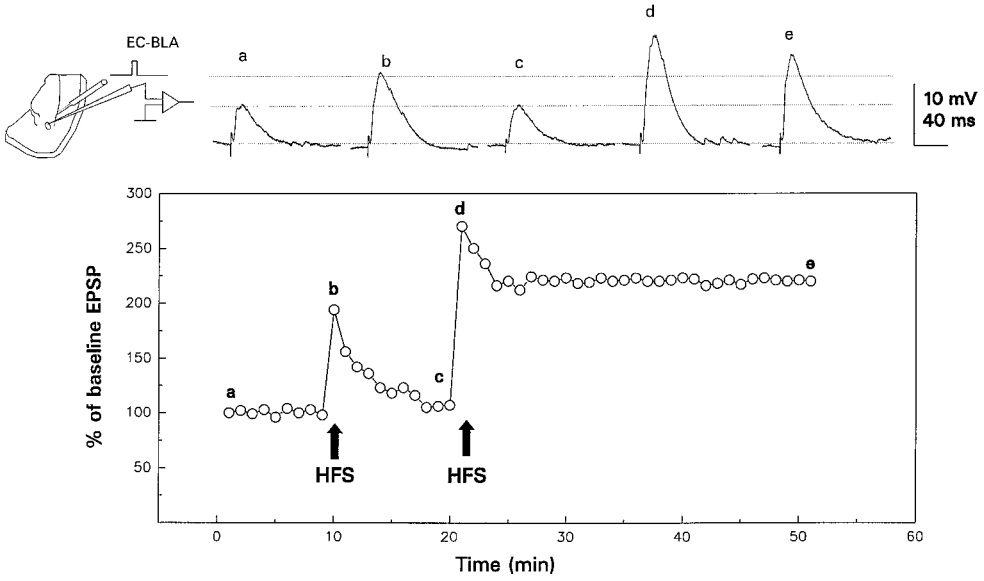


Figure 13. Two spaced, high frequency stimulations (HFS) of the external capsule induce long-term potentiation in a basolateral amygdala neuron. The top figure shows traces sampled from intracellularly recorded synaptic responses in a basolateral amygdala neuron evoked by stimulation of the external capsule: (a) the baseline response; (b) the response 1 min following the first HFS (100 Hz for 1 s); (c) the response 10 min following the first HFS; (d) the response 1 min following the second HFS; and (e) the response 30 min following the second synaptic response. The bottom figure shows the time course of the synaptic response as a percent of the baseline. The filled arrows indicate the timing of the HFS. The picture at the top left (Figures 12–14) is a schematic representation of the brain slice stimulation and recording configuration showing the site of the intracellular recording electrode in the basolateral amygdala (BLA) and the site of the stimulating electrode in the external capsule (EC).

nucleus neurons, the same 1-Hz stimulation produces LTP (see Figure 15). These data provide evidence for history-dependent metaplasticity (i.e., the direction of the long-term adaptation to a given frequency of stimulation depends on the prior history and stimulation characteristics of the neuron).

Dr. He Li has gone on to establish this phenomenon of metaplasticity, not only in separate groups of stimulated and unstimulated neurons, but also in the same neuron that originally showed LTP with its initial 1-Hz stimulation but subsequently showed LTD when the low frequency stimulation followed a high-frequency burst. This will likely represent just one of a series of phenomena revealing the exquisite adaptive and regulatory mechanisms involved in differential responsivity in amygdala neurons, dependent on the prior history of the organism. These investigators have demonstrated that this switch process from LTP to LTD is dependent on metabotropic type-2 glutamate receptors (Li, Weiss, Chuang, Post, & Rogawski, 1998), thus providing a new potential target of therapeutics for regulating long-term synaptic strength through this type of glutamate receptor, in addition to the other types (NMDA, AMPA, and kainate receptors) described above.

These data may also be relevant for the therapeutics of PTSD, because the ability to stimulate the brain transcranially with repeated transcranial magnetic stimulation (rTMS) (George et al. 1995; George et al., 1997; Post et al., 1997) allows manipulation of the frequency of stimulation from 1 Hz (or lower) up to 20–25 Hz. In this fashion it is possible that low frequency stimulation may be able to selectively depress synaptic transmission that

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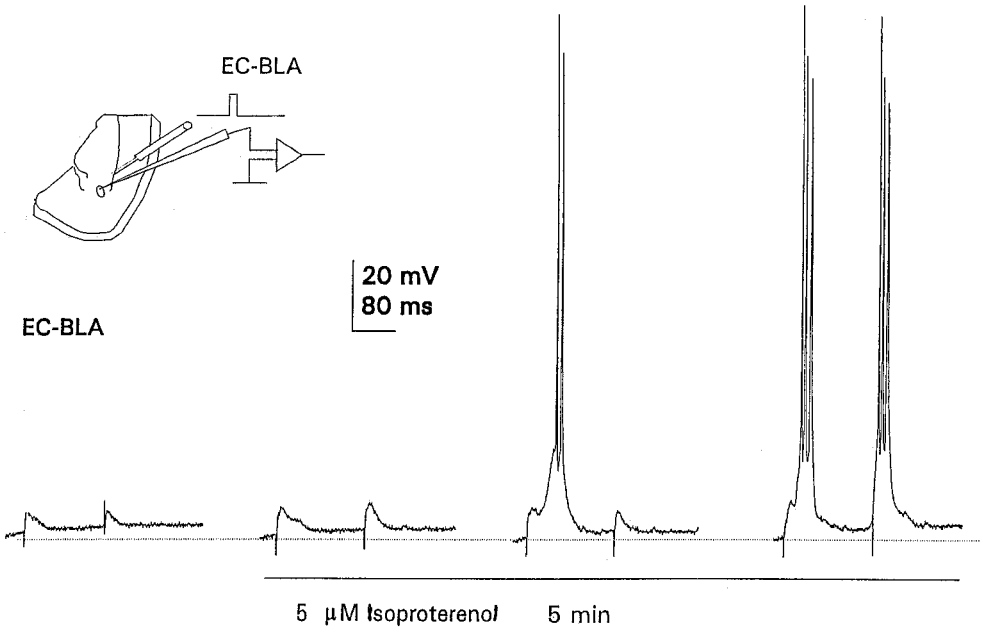


Figure 14. Application of a β-adrenergic receptor agonist (isoproterenol), massively enhances synaptic transmission in the basolateral amygdala (BLA). This is a trace of synaptic response in the BLA to external capsule stimulation in the absence (left) and presence (right) of isoproterenol. Note the marked potentiation of the first BLA response after 5 min and of responses to both pulses after 10 min of β-receptor stimulation. This provides a potential mechanism in vivo for conveying the strong impact of arousal in potentiating and cementing emotional memory.

has been made hyperexcitable based on prior experience, such as in a patient with PTSD (McCann et al., 1998).

Differential Effects of rTMS on Brain Activity Measured by Positron Emission Tomography (PET): Implications for Clinical Therapeutics in Humans

In fact, there is converging evidence that 1 Hz stimulation with rTMS is capable of decreasing glucose utilization in normal volunteers, not only bilaterally in the frontal cortex following stimulation over the right prefrontal cortex, but also contralaterally into the striatum and left amygdala (Kimbrell et al. 1997). One Hz versus 20 Hz rTMS also produces opposite effects on activity measured by blood flow with PET using O^{15} labeled H_2O (Speer et al., 1998). These data raise the possibility that the neurophysiological plasticity at the level of amygdala and its role in emotion modulation may ultimately be accessible to therapeutic maneuvers utilizing rTMS.

In this regard, another phenomenon of activity-dependent neural plasticity becomes particularly relevant. There is considerable preclinical evidence that only synapses that are actively being stimulated are capable of responding to selected molecular mechanisms which enhance excitability, such as neurotrophic factors. That is, in the context of neural firing, neurotrophic factors such as BDNF are capable of enhancing synaptic activity, but in the absence of this neuronal firing, BDNF does not change the background set point (Marty, Berzaghi, & Berninger, 1997). Thus, with the ability of stimulating the awake human brain while patients are engaged in a variety of clinical neuropsychologic or psychotherapeutic tasks comes the possibility of enhancing or suppressing pathways selectively involved in neural networks particularly pertinent to given themes in PTSD or other

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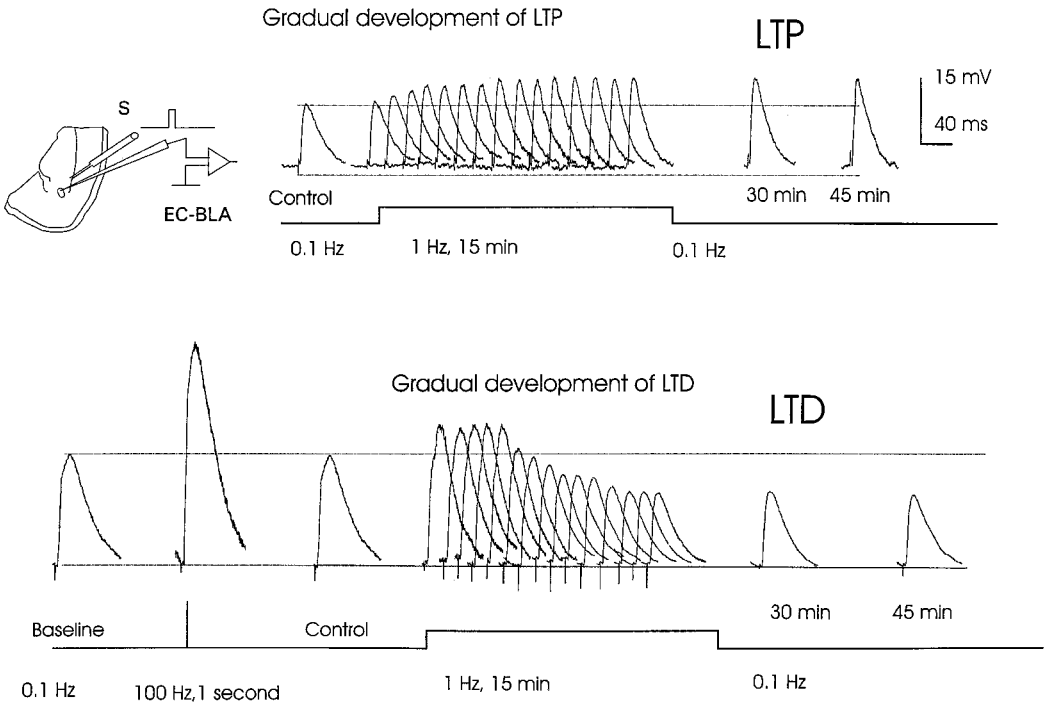


Figure 15. History-dependent bidirectional modulation of synaptic transmission by low frequency stimulation of external capsule. Traces were intracellularly recorded synaptic responses evoked by stimulation of external capsule. (Top panel) Low frequency stimulation (LFS, 1 Hz for 15 min) induces a gradual development of synaptic LTP lasting for more than 30 min after the termination of LFS. (Bottom panel) Low-frequency stimulation 10 min after conditioning HFS induces an initial transient synaptic facilitation followed by enduring synaptic LTD lasting for more than 30 min after the termination of LFS. LTP, long-term potentiation; LTD, long-term depression.

areas of affective sensitivity. Thus, we would postulate that 1 Hz stimulation of patients with PTSD may either be more effective or long-lasting in the context of recall of traumatic material pertinent to their PTSD, compared with merely stimulating in the baseline resting state. Such a differential hypothesized outcome based on the interactions of stimulation and nature of the ongoing activity can be readily tested with the available tools and, in part, validated with appropriate rating and brain-imaging techniques.

Obviously, much work is required to ascertain what stimulation characteristics are most pertinent to developing a long-term resetting of amygdala excitability of potential clinical and biological relevance. Current studies with 1 Hz stimulation in patients with PTSD do not reveal sustained alterations in PTSD symptomatology and patients appear to relapse relatively quickly following the termination of 1 Hz stimulation (see Figures 16 and 17) (McCann et al. 1998). Nonetheless, with the ability to induce longer term changes with LTP and LTD at the level of the amygdala slice preparation, one would hope that ultimately the optimal parametrics of stimulation and experimental clinical research designs can be found, so that rTMS would be capable of inducing longer-lasting changes in neural excitability for the therapeutics of PTSD and related anxiety disorders, if not a permanent resetting of the threshold for reexperiencing phenomena or panic attacks.

Amygdala and Cortical Plasticity in Emotional Memory

Thus, the type of metaplasticity described by Dr. Li and his colleagues clearly indicates a

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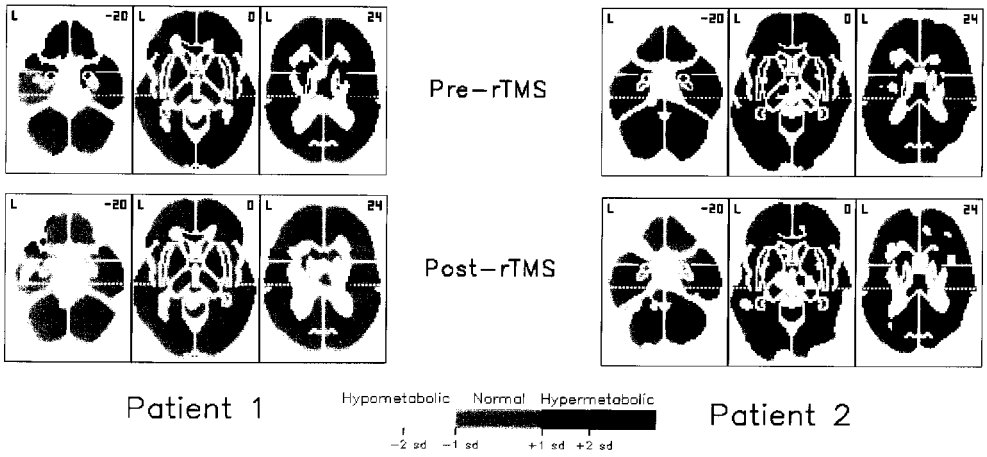


Figure 16. Effect of 1-Hz rTMS over right frontal cortex on rCMRglu. Compared to normal age-matched controls, these patients with PTSD showed enhanced glucose metabolism in the right frontal and temporal areas of the brain before rTMS and relatively more normal patterns of glucose utilization following 1 month of 1-Hz rTMS in association with modest clinical improvement (see Figure 17). rTMS, repeated transcranial magnetic stimulation; rCMRglu, regional cerebral metabolic rate for glucose.

very different effect of low frequency stimuli as a function of prior environmental experience. Some of the emerging details of amygdala plasticity revealed in the slice preparation may also be pertinent to an understanding of different aspects of the PTSD syndrome. LTP achieved either with this low frequency repetitive stimulation or several high frequency bursts is capable of inducing increased excitability in synaptic inputs other than the original synapse stimulated (heterosynaptic LTP). These data may be important in relation to the increased excitability that is induced in a long-lasting fashion in PTSD to not only trauma-related input, but to other environmental stimuli as well. For example, in addition to flashbacks and trauma-related memories, there is increased arousal and hyperstartle in other circuits, based on appropriate or inappropriate cues in the environment. The phenomenon of heterosynaptic LTP thus could provide a basis for understanding how information in one pathway to a neuron could affect the responsivity in another unrelated pathway that also synapses on the same amygdala neuron.

Moreover, Smith et al. (1995) observed that even mild stressors were capable of inducing NT3 gene expression in the locus coeruleus. Thus, given the appropriate emotion-arousing stimuli, it becomes possible to conceptualize how there might be long-term changes in excitability in the anxiety-arousal system mediated by the noradrenergic locus coeruleus which modulates amygdala and hippocampal excitability in a bidirectional fashion (Pickel, Segal, & Bloom, 1974; Segal & Bloom, 1976). Therefore, the general level of hyperarousal could occur either at the level of midbrain neurotransmitter amine arousal mechanisms (related to the basic mechanisms of the reticular formation), or at the level of the amygdala and its crucial role in linking past experience with emotion modulation, or both. Moreover, with each successive emotional "hit," as discussed in the kindling and sensitization models of PTSD (Post & Weiss, 1997; Post et al., 1996), there may be an accumulation and cementing of these alterations at levels of anatomic, synaptic, and molecular adaptations.

We are now aware that the hippocampus is critical to the laying down of new memories, but it is not the place in which they are stored (Mishkin & Appenzeller, 1987; Squire, 1986; Squire & Zola–Morgan, 1988; Squire & Zola–Morgan, 1991). (Storage is probably accomplished in the cerebral cortex.) It is likely

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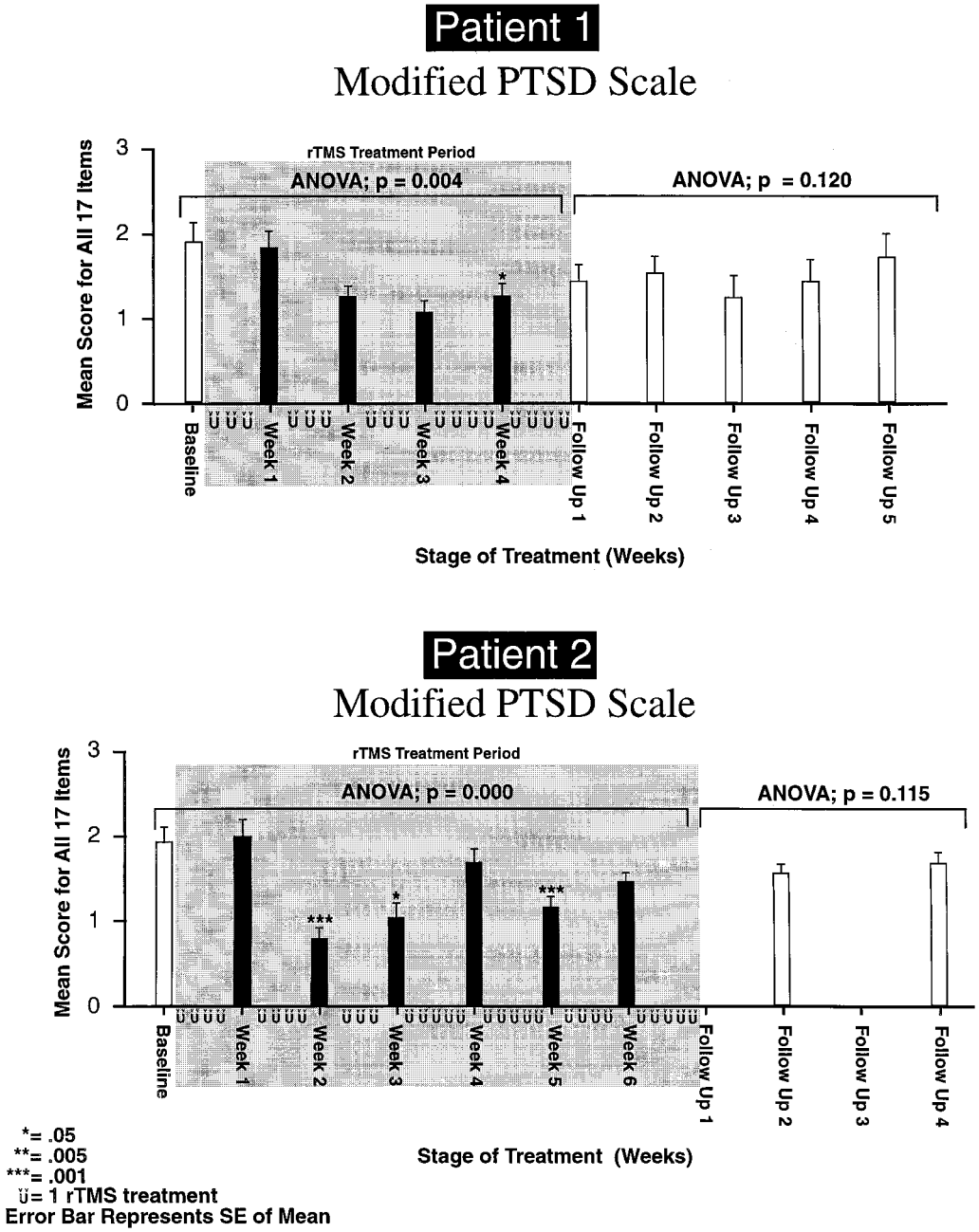


Figure 17. PTSD symptoms during 1-Hz rTMS over right frontal cortex. rTMS, repeated transcranial magnetic stimulation; PTSD, posttraumatic stress disorder.

that the amygdala associative processes are crucial for linking emotion and memory, but they also may not be the location in which emotional memories are stored (LeDoux, 1994). It is believed that these involve much wider circuits throughout the cerebral cortex. Recent neurophysiological discoveries in animals, now confirmed by PET, have revealed how the properties of objects are synthesized in very different neuronal pathways before arriving at the final process of object recognition (Haxby et al., 1991; Haxby, Grady, Un-

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gerleider, & Horwitz, 1991; Ungerleider et al., 1998). For example, shape and color are imparted to objects at various stations in the occipital temporal stream encoding vision, whereas texture of the object is imparted by somatesthetic cells in the sensory cortex of the parietal lobe, and sound and taste in yet other pathways; smell components may come in through the olfactory system which is more directly related to the amygdala.

Reediting Emotional Memory over the Life Span: Redefining the Emotional Homunculus

The amygdala is thought to be involved with imparting the emotional significance to an object and linking it to other memory systems initially imparted by the hippocampus but then subserved by other complex cerebral pathways potentially involving many hundreds of thousands if not millions of synapses. Just the way the properties of objects are synthesized convergently by different pathways, we can surmise that the historical and emotional significance of objects are likewise "synthesized," but also edited, updated, and revised based on new experiences. In this fashion, the more complex associative experiential properties and cues may be attached to critical objects in the environment, such as one's parents, siblings, and even the concept of oneself. We know that cortical representations of tactile sensory maps can be modulated by experience even in adult primates (Manger, Woods, & Jones, 1996; Pons et al., 1991; Pons, Garraghty, & Mishkin, 1988), and we surmise that a similar or greater degree of neuroplasticity is involved in secondary and tertiary order association areas related to an individual's history and laying down of cognitive and emotional memory.

The representation in space of neurons in the hippocampus are reprogramed according to experience (Rotenberg, Mayford, Hawkins, Kandel, & Muller, 1996; Tongiorgi, Righi, & Cattaneo, 1997) and one would postulate that similar plasticity is involved in the construction of emotional environmental maps and the pathways through which one must navigate in relation not only to the more basic survival drives of food and sex, but also the more complex subtle aspects of rewards based on social interactions, stressful experiences successfully negotiated or not, and the like.

Given this conceptualization, one would imagine that the neural representations of the mother, for example, assume a major portion of cortical representations in the newborn and young infant, but then, with increasing experience and maturation, others in the environment become differentiated including the father, siblings, and others intimately associated with rewards and punishments and experience of everyday life. With different stages of development, in rough parallel with those described by Freud and Erikson (Meyersburg & Post, 1979), the size, shape, complexity, and interactional matrix of these representations would change accordingly. For example, some of the network space as well as individual neurons and synapses reserved for and selectively tuned to signals from the parent or parents may be transferred to that of a spouse and then sequentially one's children.

Central nervous system (CNS) remodeling in grief reactions and PTSD

Such remodeling over the course of the life span could even be the basis for one's being overcome with waves of ideation and emotion related to the death of a loved one in the typical process of mourning and grieving. The usual pathways, representations, and networks that have traditionally been linked to an individual would suddenly, dramatically be altered by the absence of that individual until a new set of networks and cognitive-emotional processes was reestablished. Thus, we are postulating that there is an actual physiologicalanatomical component to the grief reaction, much like that which occurs in relevant neurotransmitter pathways following the withdrawal of a chronically used drug. Pathways and receptors occupied are suddenly deprived of their normal input. Although obviously not a complete or sufficient model, we suggest that there are many analogous processes at the psychological and physiological levels that constitute such reworking and neural plasticity of the grief reaction. This would be only

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one of the more dramatic examples of an ongoing process of change in evolution and representation of the environment and its associated emotional valences that occur continuously throughout one's entire life.

Based on such a rough model, one would envision strikingly different impacts of similar types of experience at different stages of an individual's psychological and physiological evolution. As noted above, deprivation related to neglect and the converse (that related to physical, sexual, or verbal abuse) in early childhood may affect the basic and emerging organization of the central nervous system and its sculpting by early life experience (Cicchetti, 1996; Cicchetti & Tucker, 1994). These same phenomena later in life may be associated with a different impact, because they are occurring on a more fully developed CNS and one is more likely to have functional rather than major anatomical and biochemical pathway effects. Recovery capability would also differ as a function not only of severity, duration, and repetition of the stressor, but also of the timing or stage of insult as well (cf. Manly, Cicchetti, & Barnett, 1994).

Nonetheless, just as some types of learning and memory can last a lifetime, it also is apparent that some types of stressful life experiences in adulthood can leave eidetic images intact and evolve into the pathological aspects of PTSD with triggered and autonomous flashbacks and nightmares, as well as hyperarousal, hyperstartle, and a sense of dulling and depression (Rodriguez, Ryan, Rowan, & Foy, 1996; Yehuda, Kahana, Schmeidler et al., 1995). Interestingly, for the current thesis regarding early neural substrates and repetition of stressors, much evidence is beginning to emerge that prior experiences serve as vulnerability factors in determining which group of subjects develops PTSD compared to which group is relatively protected. That is, prior and early experiences of severe stressors and traumas before the initial inciting PTSD event are, in fact, strong illness predictors (Bremner, Southwick, Johnson, Yehuda, & Charney, 1993; Yehuda, Giller, Southwick, Lowy, & Mason, 1991; Yehuda, Kahana, Binder–Brynes et al., 1995; Yehuda, Kahana, Schmeidler et al., 1995). Thus, there may be residual neuroendocrine, biochemical, and neuronal pathway vulnerabilities left from these earlier episodes that remain subthreshold until a more full-blown syndrome is triggered by a stressful recurrence.

Stages in the evolution of PTSD: Differences in therapeutics

In instances where the basic wiring of the CNS has not been impacted early in childhood by deprivational or traumatic life events and environmental circumstances, one should have a much greater chance at ameliorating the hyper- and hypoexcitabilities of the PTSD syndrome that emerges from trauma experienced only in adulthood. What the appropriate therapeutic interventions are, however, even for the "uncomplicated" PTSD of adulthood are not yet fully articulated. The unfolding nature of the PTSD syndrome would suggest the possibility that different interventions may vary in efficacy as a function of stage of PTSD development. As noted above, a particular focus of investigation should be the methods of treating the individual in the immediate posttraumatic period in order to prevent the consolidation of the kinds of emotional memory traces with an intensity that is likely to predispose to long-term sequellae of the sort observed in PTSD. In addition to these types of prevention trials, early intervention at the beginning of symptom development may also be more useful than allowing the full-blown syndrome to emerge with increasing repetition and ferocity. Finally, some late interventions may be effective, as suggested by recent reports of cognitive behavioral interventions (Chemtob, Novaco, Hamada, & Gross, 1997), as well as eye movement desensitization and reprocessing (EDMR) of traumatic memories (Carlson, Chemtob, Rusnak, Hedlund, & Muraoka, 1998; Forbes, Creamer, & Rycroft, 1994), which remain to be confirmed by further controlled studies.

Edelman argues that it is the unique expansion of the cerebral cortex in humans that allows one not only such specific flexibility

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in learning and memory, but also enables abstract and conceptual thought, planning for the future, and even the concept of free will (Edelman, 1992). Thus, the exquisite evolutionary mechanisms brought to bear in conveying the human capabilities of learning, memory, planning, and choice may also have some costs and liabilities. The ability to transmit culture across the generations may also make humans particularly vulnerable to the pathological overreplay of actions and memories observed in a variety of neuropsychiatric syndromes, most particularly, PTSD.

Epilogue

With further dissection of what now is only the first glimpse into the fundamental mechanisms of learning and memory in the mammalian CNS, it is hoped that this knowledge will be used for good and in the service of therapeutic interventions in deficient syndromes of learning and memory, as well as those of its hyperactivation in PTSD. One could even hope, however slim the chances, that revisions in our fundamental conception of these types of human potentialities will ultimately also help in a shift in the balance of sadistic to altruistic thoughts and actions. Many religions forecast such days of judgement and redemption and one can only hope that some breakthrough in understanding CNS processes helps in this shift. We certainly hope that our capabilities derived from 10 billion neurons, 20–30 billion glial cells, 100,000 or more synapses per neuron, and a wealth of intracellular machinery tuned to recording and benefitting from past experiences, will ultimately give us the wisdom to find and choose such a pathway.

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