

Aspects of Psychodynamic Neuropsychiatry II: Psychical Locality and Biology—Toward the Neurobiology of Psychotherapy

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Abstract: Throughout his career, Freud believed that psychiatry in general and psychoanalysis in particular would one day be rooted in anatomical/biological ground. He felt confident that such ground would replace the psychological understanding on which he had been forced to base most of his clinical theory and practice. He felt confident that one day psychotherapy would be more “scientific.” This article seeks to demonstrate that this day is arriving. A clinical case is presented where assessment and formulation are largely based on neurobiology, where treatment was conducted less in accord with psychodynamic theory than neurodynamic data of anatomy and biology.

I. INTRODUCTION

“I shall entirely disregard the fact that the mental apparatus with which we are here concerned is also known to us in the form of an anatomical preparation, and I shall carefully avoid the temptation to determine psychical locality in any anatomical fashion. I shall remain upon psychological ground” (Freud, 1900, p. 536).

Freud made this statement after having made numerous unsuccessful attempts to determine “psychical locality” and to find biological ground. But despite his abandonment of further efforts to find the anatomical and biological ground of psychotherapy, he often referred back to the fact that he believed one day it would be found. And thus 20 years later he would write, “Biology is truly a land of unlimited possibilities. We may expect it to give us the most surprising information, and we cannot guess what answers it will return in a few dozen years to the questions

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we have put to it. They may be of a kind which will blow away the whole of our artificial structure of hypotheses" (1920, p. 60).

We are now quite "a few dozen years" from when Freud wrote those words. And biology has been delivering, as he had predicted, "the most surprising information," and providing answers that do "blow away" some if not all of the "artificial structures." The intent of this article then, is to carry that idea forward and to present some of the "surprising information" that Freud had anticipated. The intent of this article is to do what Freud foresaw—to find the anatomical and biological ground of a psychotherapy.

II. THE REFERRAL

The patient, a 20-year-old single, female college student* was referred to me by her psychiatrist, who stated that the therapy was at an impasse. "The girl and her mother are in a powerful symbiotic enmeshment," he said. He gave her diagnosis as borderline personality disorder, with affective disorder, depressed type. The patient had been medicated with fluoxetine 60 mg and buspirone 45 mg. She had spent the summer prior to her first year of college (prior to the referral), at home sleeping, drinking, screaming abusively at her parents. Just before going to college she had self-inflicted lacerations to her wrist. "Basically," the doctor confided, "she's a 20-year-old who refuses to grow up, and I don't know how to help her."

I agreed to see the patient.

III. FIRST MEETING

The buzzer rang 30 minutes early. When I answered the door, I was met by an attractive young woman, well groomed with short blond hair, wearing tight jeans, a tight shirt, pink sneakers. When I greeted her, she responded, "I got here real early because I was afraid that I might get lost trying to find your building." I thought that was an interesting beginning but decided not to pursue it. When she came into the office, I said, "Your doctor has been having some trouble helping you and asked me to see you." She smiled. I continued, "Can you tell me a little about what your problems have been?"

*Names have been changed and personal clinical material in this article has been disguised.

“Well I just started college. It’s been a disaster. I got really depressed the end of last summer. I’d been doing nothing except drinking. When I saw my ‘doctor,’ he yelled at me for drinking and raised the dose of Prozac.

“Then it got worse in October when I went home for my birthday. I drank until I got wasted and then I just continued getting wasted three or four times a week. When I went home for Christmas, the same thing happened—all I did was stay in bed, sleep, watch TV. My Mom’d scream at me until she was crying. My Father would yell, ‘look what you’re doing to your Mother.’ The day after Christmas, I cut my wrists. They took me to the ER. My father wanted to leave me there, but the doctor let me go. My mother just kept crying.”

IV. DIAGNOSIS

At this point, my diagnosis was borderline personality disorder with affective disorder, bipolar, type II, and alcohol abuse. I recommended disulfiram 125 mg (and later lamotrigine—up to 125 mg added to fluoxetine, reduced to 20 mg). She readily agreed (only later would I discover that lying and pseudo-compliance were prominent issues in the treatment).

V. TO RETURN TO THE CASE HISTORY—

I asked her about her earliest memories.

“I’m in the hospital in Cleveland. It’s after my first surgery, or one of the early ones. I had Hirshprung’s Disease. You knew that didn’t you?” (The referring psychiatrist had mentioned that she had had many surgeries as a child. Hirshprung’s disease is a congenital lack of innervation of the large bowel resulting in constipation and obstruction of the large bowel).

Tell me more.

“Well I had Hirschprung’s disease and I had a lot of surgeries and after one of them, I remember lying in this hospital room. There was this girl next to me. She was from Germany. She seemed fine. That just made me more really scared.”

Scared?

“Terrified.”

Of what?

“I don’t know. I remember this girl in the next bed. I remember knowing she was gonna be fine. And I remember knowing something terrible was gonna happen to me. And then I started crying and couldn’t stop.”

VI. STRESS RESPONSE 1—THE HPA SYSTEM

The stress response in mammals begins when either an internal or external stressor is received and relayed through the spinal cord predominantly via ascending noradrenergic (NA) pathways (mono-synaptic and poly-synaptic) to the hypothalamus, most specifically to the paraventricular nucleus (PVN). The locus ceruleus (LC) in the pons also connects noradrenergic fibers (NA) to the PVN. Direct NA stimulation of the PVN leads to the release of corticotrophin releasing factor (CRF) and arginine vasopressin (AVP).

The release of CRF in the pituitary causes the release of adrenocortical releasing hormone (ACTH) into the portal circulation which in turn causes the release of cortisol, enkaphalins, and epinephrine into the systemic circulation from the adrenal medulla. These and other inputs initiate and augment the stress response. This system, involving the hypothalamus, the pituitary and the adrenal medulla—the HPA system—is a central feature of the mammalian stress response (Heim & Nemeroff, 1999; Herman & Cullinan, 1997; Sapolsky, 2004; Schafe & LeDoux, 2004; Yehuda et al., 2010).

There are various factors that limit the stress response. There is a direct feedback loop involving cortisol at the PVN where high circulating cortisol lowers the output of CRF. There is a similar inhibitory response mediated through the hippocampus.

The hippocampus has two sets of cortisol receptors, the mineralcorticoid (MC) and the glucocorticoid (GC). The MC receptor has a much higher affinity for cortisol than does the GC receptor and thus under non-stress conditions, the MC receptor is predominantly occupied. However, under stressful conditions when cortisol levels are high, the GC as well as the MC receptor is occupied. When the GC is occupied, there is input from the hippocampus to the PVN to limit the output of CRF and thus to limit the stress response.

Similar limits to CRF output are mediated through the prefrontal cortex (PFC) and through the lateral septal nuclei. The input from the PFC is indirect in that high levels of cortisol and/or noradrenalin cause

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the PFC, especially the ventral medial PFC to dampen excitatory output from the amygdala (Ac) and from the locus ceruleus (LC).

The amygdala's response to stress is different. Like the hippocampus, the amygdala has GC receptors. When the GC receptors at the amygdala are occupied, that is under conditions of high circulating cortisol, cells in the central nucleus of the amygdala (CeA) release CRF not as a neurohormone but as a neurotransmitter at the locus ceruleus (LC). The LC responds to CRF stimulation by releasing NA at the PVN, thus accelerating the stress response. This connection between the amygdala and the LC creates a feed-forward loop that if unopposed accelerates the release of CRF from the PVN, ACTH from the pituitary, and cortisol from the adrenal—that is to say, it is a loop that unopposed could drive the HPA axis until biological exhaustion (Armony & LeDoux, 1997; Cahill, 1996; Cahill & McGaugh, 1996; Conrad, Magarinos, LeDoux, & McEwan, 1999; Maren, 2005; McEwen 2007; McEwan & Sapolsky, 1995; McGaugh, Cahill, & Roozenvaal, 1996; Roozendaal, Quarte, & McGaugh, 1997). The control of cortisol then is pivotal in the allostasis of the stress response.

VII. CASE

Can you tell me more about what you remember of the surgeries?

"I was in and out of the hospital until I was 3 or 4. I remember the children's ward. I remember lying under the surgical lights, with these doctors standing over me. I was crying and screaming, holding my mother, 'don't leave me. Don't leave me.' And my mother crying, 'I'll never leave you.'"

(She begins to cry).

Talking about this . . . ?

"Brings it all back" (she cries).

VIII. STRESS RESPONSE 2—STATE DEPENDENT MEMORY

Powerful emotional events activate the HPA system. Powerful emotional *memories* can also activate the HPA system. This has consequences for the HPA system as well as for the systems that encode, store, and recall emotional memory.

When considering the fate of emotional memory, one must consider at least three possibilities. Emotional memory may be declarative, and is

therefore dependent on the medial temporal lobe, hippocampal memory system. Emotional memory may be conditioned memory (classical and/or operant) and is therefore dependent on the amygdaloid system. Emotional memory may contain aspects of both conditioned and declarative memory and is dependent on the interaction of both memory systems. Which system(s) is (are) activated depends on several factors including whether and to what extent the emotional event (present or remembered) activates the HPA system. This is so because when activated the HPA system affects the levels of cortisol, dopamine, noradrenalin, corticotrophin releasing factor, enkephalin, and other neurotransmitters and neurohormones that have direct effects on the two memory systems and on which one will dominate—either in the encoding of an event or in the retrieval of a memory.

When the hippocampal MC receptor is occupied by cortisol, there is a facilitation of long-term potentiation (LTP)—that is to say, at certain levels, the presence of cortisol at the MC receptor, facilitates the processes that lead to the encoding, consolidation, and potential retrieval of long-term hippocampal dependent memory. It is only when cortisol levels are high that the GC receptor is also significantly occupied. Under such conditions, LTP is inhibited and there is a disinhibition of long-term hippocampal dependent memory. Thus mid-cortisol levels facilitate while low and high cortisol levels impair the encoding, consolidation, and retrieval of long-term hippocampal dependent memory. This inverted U curve also holds true for noradrenalin and dopamine. Hippocampal dependent memory is facilitated by modest levels and is impeded by low or stress levels of cortisol, noradrenalin, and dopamine.

At the amygdala (Ac) the reaction is different. When the GC receptors at the Ac are occupied, there is potentiation of LTP. And thus at the Ac there is memory consolidation when circulating levels of cortisol are elevated. This process of conditioned memory enhancement at the Ac appears to involve the baso-lateral nucleus of the amygdala (BLA), one of the amygdala's primary internal modulating neuronal groups, and not the central nucleus (CeA), the Ac's major outflow path.

Noradrenalin at the Ac also tends to the facilitation of conditioned memory especially as a result of synaptic plasticity involving the dendrites of BLA neurons. Thus high levels of cortisol and noradrenalin facilitate conditioned memory encoding and recall at the amygdala while high levels of cortisol and noradrenalin tend to impair the registration and recall of declarative memory through the hippocampal dependent system. And thus the stress response as mediated through the HPA has opposite effects on these two memory systems.

The impact of the prefrontal cortex (PFC) is also significant and directly impacted by the HPA system. As noted above, under conditions of stress,

the locus ceruleus (LC) as well as the HPA axis are quite active. Under these conditions, the LC releases noradrenalin at the paraventricular nucleus. Through its cortical projections, the LC also releases NA at the PFC. At the PFC there are two classes of noradrenergic receptors, alpha-1 and alpha-2. Alpha-2 receptors have a much higher affinity for NA than do the alpha-1 receptors, and thus under normal conditions the alpha-2 receptors are significantly more occupied than are the alpha-1 receptors. The alpha-2 receptors facilitate LTP and memory storage. Under stress conditions when NA is high, the alpha-1 receptors are also significantly occupied. The response to the alpha-1 receptor is to diminish LTP at the PFC (due to enhanced cellular after-hyperpolarization and a prolongation of the refractory period) and to inhibit the outflow from the PFC to the amygdala. Because the effect of output from the PFC to the amygdala is predominantly inhibitory (via GABA-ergic neurons), the effect of decreasing PFC output to the amygdala is to facilitate the amygdala, and thus to facilitate emotional, conditioned memory at the Ac.

Taken together, the effects of high activation of the HPA system at the amygdala, the hippocampus, and the prefrontal cortex are at the heart of state-dependent memory. State-dependent memory is a concept that refers to a memory that is recalled not as a result of conscious intent (declarative and working memory), but rather to a memory that is recalled as a result of the neurobiologic state that exists at the time of recall. And thus just as memory can activate the HPA system, so can the HPA system activate memory (Arnsten, 1998; Cahill & McGaugh, 1998; deQuervain, Roozendaal, & McGaugh, 1998; deQuervain, Roozendaal, Nitsch, McGaugh, & Hoch, 2000; Ishikawa & Nakamura, 2003; Kaufman, Plotsky, Nemeroff, & Charney, 2000; Lebron, Milad, & Quirk, 2004; Milad & Quirk, 2002; Purcell, Maruff, Kyrios, & Pantelis, 1998; Quirk & Gehlert, 2003; Quirk, Likhtik, Pelletier, & Pare, 2003; Quirk, Russo, Brown, & Lebron, 2000; Rogan & LeDoux, 1996; Tronel, Feenstra, & Sara, 2004).

IX. CASE

"I was first in and out of the hospital from when I was 6 months old until I was 4. I remember flying back and forth to Cleveland. I'd sit on my Dad's lap, hysterically freaking out on the plane. And then later as a kid I'd have to go to the doctor. I'd get in the car, and if my Dad made a right turn, then I knew we were going into town, and it was okay. But if he made a left turn, I knew we were going to the doctor, and I'd freak out."

One of the key components of trauma is predictability and control. A traumatic event is one that occurs unpredictably and over which one

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has little or no control. It was clear that these medical interventions were both necessary and traumatic. I began to reconsider the diagnosis.

X. RE-DIAGNOSIS

Work by Connolly (2004) studied the psychological effect of cardiac transplant surgery on young children. No child in the study had PTSD before surgery. After surgery, 5 children (12% of the sample) met PTSD criteria, and another 5 (12%) had significant symptoms of stress but did not meet criteria for PTSD. The only factor correlated with PTSD was the length of stay in the intensive care unit. And so I asked,

Were you ever in intensive care?

“You mean the place with all those machines and where they never turn out the lights?”

Yes, that place.

“I was there twice.”

And thus I came to question the diagnosis of borderline personality disorder—because it was becoming clear that external traumatic events had a place in determining her behavior, and these needed to be considered as possibly etiologic.

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“I remember another time when I was about 5, with my Mother at the doctor’s and I was watching her talk to him. I was just watching her when she starts to cry. And when I saw that, it freaked me that I’d have to go back and have more surgery or another exam.”

Another exam?

“I kept having to have rectal exams, sigmoid exams. They’d hold me down and put these scopes up me. It was terrifying. And it doesn’t go away.”

What doesn’t?

“The fear. Just the other day, I went to a gynecologist. So much anxiety just being there. I mean just being there I got angry—the whole setting, the room, the examining table and everything, it just got to me, brought back everything.”

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The emotion was overwhelming?

“Yes.”

And did that confuse you?

“How did you know?”

I knew because I was beginning to get the sense that the neurobiology was reacting autonomously, leaving her feeling that her emotional responses and memories were not in her control (not in the control of the declarative memory system) but were state dependent and in the control of the implicit memory system. So my reasoning was that she would periodically be flooded by emotional reactions that were inappropriate either in quality or valence to the context. I reasoned that such a response would be confusing and to a certain degree that she would defend against the awareness of just how inappropriate her responses were. And so I asked,

What made you angry?

XII. STRESS RESPONSE 3—EMOTIONAL MEMORY, VISUAL MEMORY, IMPULSIVITY

One further effect that stress has on memory is that memory, when registered and later recalled under biologic conditions of stress, tends to be more powerful, more visual (eidetic), and more immediate because of the shift toward amygdala facilitated memory—whether that memory is stored wholly in the amygdala (Ac) as implicit memory, or is stored in the cortex as part of the declarative memory system but strengthened by the input of the Ac.

As this shift occurs, memory tends to become more evocative and more immediate, and thus memory tends to become more like the event itself. This shift of memory from the more abstract to the more specific, from the more symbolic to the more concrete has powerful consequences. One of these consequences is that each time the memory is generated, a biologic response is initiated that with each repetition the response to the memory becomes more like the response to the event itself. And thus each time the memory is generated the event seems to be and in certain ways is repeated as well. Another consequence is that with each response, it becomes easier to generate a subsequent response until the point where the full psychological and physiological responses are generated in the absence of any apparent stimuli (Cahill, 1996; Cahill & McGaugh, 1996; Conrad, Magarinos, LeDoux, & McEwan, 1999; McEwan, 2007).

This reinforcement of response and ease of eliciting each subsequent response—by virtue of repetition—is what lies behind the theory of kindling.

XIII. KINDLING

G. V. Goddard, a neurosurgeon, was struck by the fact that some people who suffer head trauma develop a seizure disorder sometimes days, weeks, months, even years after the event. He wondered why. He conducted experiments where rats were subjected to subconvulsant electrical discharge in various parts of the brain. What he noted was that over time and with repeated application the seizure threshold was lowered such that a seizure would be generated by what at the beginning had been a subconvulsant discharge. He called this experimental phenomenon, kindling (Goddard, 1967). And thus while kindling applies to the generation of seizure activity, the same logic has been used to show “evidence of increasing physiological responsivity to the same stimulus over time” (Post & Weiss, 1998, p. 194; Goddard, McIntyre, & Leech, 1969). And so just as a subthreshold electrical current applied to the limbic system of the rat (especially the amygdala or hippocampus) will, if repeated, induce a seizure (kindling), so too a subthreshold cue will, if repeated often enough, induce full blown learning and memory. Goddard in his original work on kindling described this relationship, “It can be argued that the phenomenon described in the present note is analogous to learning . . . It is an appealing notion that deserves the attention of physiologists and psychologists alike”(1967, p. 1021).

And thus in patients with PTSD, a subthreshold cue acting thru the limbic cortex may serve as the sensitizing factor. In this way, there may be an acceleration rather than a diminution of symptoms over time due to the strengthening of the memory, the physiologic response to the memory, and to the ease with which the memory is recalled until such time as when the response may be triggered by cues only vaguely linked to the original event (Bonne, Grillon, Vythilingam, Neumeister, & Charney, 2004; Post & Weiss, 1997; Quirk & Gehlert, 2003).

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What made you angry?

“Just being there (at the gynecologist’s office). Being on the table. The lights. The people looking down at me. Everything all white. And

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while this is going on, I mean I'm saying nothing but this nurse kept asking me all these questions, like was I ever pregnant? How often did I have sex? All this stuff and I mean I tell her I'd never had sex, but she keeps asking me, and then from outta nowhere, these questions keep repeating in my head, and I can't get them to stop, and then the doctor comes in and does the same thing. And I'm still having these thoughts—like do the pains in my stomach mean I'm pregnant? Could I have AIDS? And so I ask him, and he just asks me again if I've ever had sex, and I say 'no', and he says are you sure? As if I'm lying. I mean I'm a fucking virgin. But I just get so confused. And then I scream at him. I mean there I am without any fucking panties and I'm screaming, screaming, 'No. I am not fucking pregnant'."

Because you're so frightened?

"What?"

I don't think you were screaming because you were angry. I think you were screaming because you were frightened.

"Yeah whatever, but he keeps asking me, and my mind begins going in circles and he keeps asking and I just get more and more scared and angry because I don't understand what's going on."

So the fear and anxiety kick in, because of the situation, in a doctor's office, the examining table, the white coats, the nurse, memories start coming back and the emotions start to flood in on you—

"Maybe."

—like when you were much younger and the fear and anxiety kick in making it even harder to think, and the whole thing just leaves you as you say angry, but really underneath terrified and very helpless and confused.

"Yes. My anxiety just kicks in when doctors are standing over me like that—like something really bad is gonna happen. Flashbacks start coming in. And after it was over, all I wanted to do was go out and get drunk. And so that's what I did."

You got wasted?

"That's what I just said."

XV. CHRONIC STRESS AND CHANGES IN CELLULAR MORPHOLOGY

There are further changes that occur as a consequence of repeated stress—whether the repetition be due to ongoing external stressors, internal sensitization, or a combination of the two. In the hippocampus these changes are reflected primarily in the dentate and CA3 gyri.

The dentate gyrus has been hypothesized as the “gatekeeper” to the hippocampus. GABAergic interneurons activated by the mossy cells in the dentate gyrus serve to limit the amount of excitation that passes from the cortex, especially from the parahippocampal gyrus into the hippocampus. “If some of these neurons were to die as a result of repeated stress, then there might be a cumulative effect over time in which repeated bouts of stress might progressively deplete the dentate gyrus of the buffering action that these inhibitory neurons appear to provide” (McEwen & Magarinos, 1997, p. 276).

As a result, there would be a progressive effect, first “at the gate” where the mossy cells’ buffering action is lost, and then further along at the CA3 level where excessive input results in increased intracellular calcium, and increased extracellular glutamate (an excitatory amino acid), cortisol and noradrenalin, leading to increased oxygen demands on these oxygen sensitive cells, which has been shown to result in dendritic atrophy and loss of apical dendrite length in the hippocampal CA3 neurons. These changes have been shown to have detrimental effects on hippocampal dependent learning.

As in the response to acute stress, the amygdala (Ac) responds to chronic stress in quite different ways from the hippocampus. At the Ac stress leads to an increased dendritic arborization in the bed nucleus of the stria terminalis (the BNST is adjacent to and anatomically related to the Ac) and no change in arborization in the central nucleus of the amygdala (CeA). Neurons in the BNST and CeA unlike the CA3 pyramidal neurons do not exhibit dendritic atrophy. On the contrary they remain either unaffected (CeA) or undergo enhanced arborization (BNST).

These changes in the hippocampus and amygdala lead to a shift in what systems will organize, store, and route new data in a stressful situation. The hippocampus is fundamental to the processing and integration of multimodal input into a unified representation. Behavioral decisions mediated through hippocampal processing reflect this multimodal integration of information. Behavioral decisions mediated through the amygdala reflect its unimodal cue strategy, a strategy that can lead to a quicker response that is based on fewer cues.

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Given the dendritic changes found in conditions of chronic stress, there is a physiologic shift that favors processing through the amygdala over the hippocampus, a shift that favors unimodal rather than polymodal integration of data. This shift also favors certain behavioral changes, such as increased emotionality, increased facilitation of fear conditioning, increased (defensive) fighting behavior, increased activation in a familiar environment, increased fear in a novel environment. These are changes in behavior that are all consistent with a shift from hippocampal to amygdala based processing (Bisagno, Ferrini, Rios, Zieher, & Wilinski, 2000; LeDoux, 2000; Liang & Lee, 1988; McEwan, 2000, 2001; McEwan & Magarinos, 1997; McEwan & Sapolsky, 1995; Vyas, Bernal, & Chattarji, 2002; Watanabe, Gould, & McEwan, 1992; Westbrook, 2000).

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"I went home this weekend . . ."

After you got drunk?

"I ah, just wanted to stay there. Yes, I was totally hung-over. I wanted to be with my mother [increased activation in a familiar environment]. When I was younger if there was ever anything to worry about, she'd have all the bases covered. So if there was anything to worry about, she'd be worrying about it already."

And that made it better or worse?

"Worse. Her anxiety would just get passed onto me. So when she was worried, I'd worry. But when she didn't worry, I'd know that everything was okay."

So she was your gauge?

"Yeah."

It sounds a little risky.

"Yeah. I mean if everything was not okay, my anxiety would shoot thru the roof and if not I was always waiting for something bad to happen."

So her fears . . . ?

"Were just passed along. I couldn't get away from my fear."

XVII. EXTINCTION VERSUS GENERALIZATION—1.

Conditioned memories are long lived. Indeed it has been argued that they are just about permanent (LeDoux, 2000). The extinction of conditioned memory requires active learning. Extinction does not refer to the destruction of memory. Rather it refers to the creation of a new memory which is available along with the first. And so extinction creates choice where previously there had only been one option, the conditioned response. And thus by virtue of creating alternatives (and thus by creating freedom, choice, uncertainty) extinction opens a window for learning, for choice, for change.

But there are powerful obstacles to extinction (to new learning) in the context of powerful memory, that is to say, when the underlying memory was generated under conditions of stress. These obstacles are partially summarized by the following:

1. Emotional memories are stronger and more immediate and thus they tend to bring back the whole experience in a vivid and immediate way (eidetic memory).
2. Vivid memory tends to evoke the full emotional response regardless of whether or not the initial stimulus ever recurs. And thus the memory (the conditioned stimulus) tends to recall the entire experience as if it were happening (the unconditioned stimulus). Normally the evocation of the conditioned stimulus, CS, without the unconditioned stimulus, UCS, would lead to extinction, the generation of other possibilities and new learning. And thus in the example of “the boy who cried wolf”—as the boy keeps shouting “Wolf!” eventually people will stop responding to the cue “wolf” (the CS) because an actual wolf (the UCS) never appears, and so people will conclude, “The boy is an attention seeking sociopath” among other conclusions. But in certain situations—such as the boy cries “wolf” and despite the lack of any wolf, there is such a powerful fear response (perhaps because one had been attacked on several occasions by dogs), that the fear response itself is strong enough to enhance the conditioned response (see Eysenck’s important paper). And so too when there is a repeated CS (the sound of a helicopter) without the appearance of the UCS (combat, enemy soldiers), the biological fear response and the memories thereby generated (state dependent memory) may be strong enough to generalize, cross-sensitize and thereby reinforce, rather than extinguish the memory. And thus in these situations, instead of the creation of new learning (it’s just a helicopter, it’s just a sociopathic kid), the old response is

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retained and strengthened (the sound of a helicopter is the prelude to danger, there just might be wolves outside the door).

3. This failure to learn the difference between safe and unsafe stimuli coming in part as a result of the shift in information processing from the hippocampus to the amygdala, is maladaptive and leads to allosteric dysfunction (see below, section XXIII).
4. The ability to distinguish specific aspects of the conditioned stimulus is also part of hippocampal polymodal assessment. This affords the ability to make selective evaluations of a context—and thus a doctor's white coat may or may not be a cause for alarm. The ability to make these distinctions allows for the adjustment of a response depending on such an assessment—leading to extinction of the conditioned response or its strengthening. In contrast when such distinctions cannot be made (i.e., when the presence of a doctor in a white coat is in and of itself overwhelming), there is the generalization of the conditioned response such that one or several aspects of the stimulus are able to elicit the full conditioned response regardless of whether they are still paired with the unconditioned stimulus until finally a situation is reached where neutral stimuli evoke a conditioned-like response, a phenomenon known as cross-sensitization—

“—the whole setting, the room, the examining table, and everything it just got to me, brought back everything. It freaked me out.”

5. This then creates a situation where the stress response is activated in situations that are basically neutral or never fully assessed. This has several consequences. The patient “learns” that danger is potentially anywhere which leads to the condition of inescapable fear—and thus a state of hypervigilance, which requires the participation of the bed nucleus of the stria terminalis. And because the patient's response to danger does not alleviate the internal sense of fear, the patient “learns” that he/she can do nothing to protect him/herself from the experience of danger—leading to undue dependency on others (Bouton, 2002, 2004; Bouton & Moody, 2004; Lovibond, 2004; Phelps, Delgado, Nearing, & LeDoux, 2004; Quirk, 2002, 2004; Richardson, Ledgewood, & Charney, 2004; Santini, Ge, Ren, Pena de Ortiz, & Quirk, 2004).

XVIII. CASE

So you went home this weekend.

“Yeah. I had to be with my mother. I had to hear it from her.”

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You had to hear what from her?

"That I couldn't get pregnant from oral sex."

How old are you?

"I know. I know—it's retarded. I know you can't get pregnant from oral sex. But—"

But what?

"I just needed her to say it."

You needed to hear her say it.

"That's what I said." She moved in her seat, leaned forward, then said, "I mean you can't, right? You can't get pregnant from oral sex. It's like getting AIDS from a toilet seat, right?" She waited no more than ten seconds before asking, "Can you get pregnant from oral sex? I want you to answer. I really want you to answer. Answer me."

XIX. EXTINCTION VERSUS GENERALIZATION—2.

Extinction of a condition learning requires active learning. This process minimally involves the medial prefrontal cortex (mPFC), the amygdala, and the hippocampus. Because it involves new learning, extinction gives the individual greater choice. Obviously there are times when freedom to select among many alternatives is problematic—such as when one's life is in immediate danger and where delay can be fatal. However, in most situations freedom and choice are to be valued. Biologically, greater input from the hippocampus and the mPFC increase choice and complexity by introducing context and by facilitating the recall of extinction learning (more and more complex choices). Conversely decreased input from the hippocampus and mPFC along with increased input from the amygdala tend to facilitate the conditioned response, thereby reducing choice and complexity. The former allows more freedom. The latter leads to behavioral perseveration (Arnesten, 1998; Cain, Blouin, & Barad, 2004; Sotres-Bayon, Busch, & LeDoux, 2004). This helps to explain why once a patient is in this state, his/her behaviors seem compelled to repeat. It is another way of understanding Freud's "repetition compulsion."

XX. CASE

"When it gets bad, I shut down. I just don't function. And it's hard for me to recognize it as fear. I recognize it as anger. Someone has to tell me and then maybe I'll recognize it, but someone has to tell me."

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It feels like anger?

"It feels like anger and that I'm depressed, but really I'm terrified."

It doesn't feel like terror? It feels like anger?

"Yup."

At others? At yourself?

"Both. I mean when I self-mutilate or drink it's at me. But then it's at others too. I'm just telling others to go fuck off. And I look for a fight. I look for ways to be mean to people. But it all feels the same."

You said you shut down.

"I just sleep. I drink. Sometimes I'll go shopping. But I don't do anything. If I go to class, I'm not really there. I won't get dressed for three days and if I do, I just wear the same clothes. I don't shower. I don't brush my teeth."

When you shut down, do you feel afraid?

"No. I don't feel anything."

You feel numb?

"Yup. I don't feel anything. I'll cut myself, and I won't feel anything. I'll be tired but I feel like I have energy. It's the weirdest feeling in the world, and I just get angry because I won't know what's going on."

Can you think when this is happening?

"Nope. Everything's confused. I can't even put sentences together. That gets me all upset. And then I get angry because I don't know why I'm feeling like that. And then I get angry at others because they don't understand it and can't help me. People say I'm behaving like that because I'm spoiled, and when someone says that, I just lose it. I get angry and then I totally lose the ability to think. I can't function. I can't do anything. It's like you're asking me to do something when I can't even brush my teeth. And that's when I just explode and tell everyone to 'fuck off.'"

And that mostly happens between you and your mother?

"Yup."

Because when you go to her for clarification and she can't and all she does is tell you to "brush your teeth," you lose it.

"I lose it."

XXI. TENTATIVE NEURODYNAMIC FORMULATION

Clearly these advances in the understanding of the neurobiology of complex PTSD have blown away some of the “artificial structure of hypotheses”—a result that Freud foresaw. These changes in our understanding have led to changes in the goals of the treatment and in how one attains those goals.

One of the goals is the immediate (or as rapidly as possible) establishment of biologic safety. But the establishment of safety in this context is not a general prescription. It is specific. It has to do with establishing a treatment that facilitates extinction and diminishes the expression of conditioned fear.

Having an understanding of the neurobiology leads to certain very specific approaches to the treatment. The therapy is active, involved, direct. It is not neutral, abstract, metaphoric. One does not wait for understanding. One does not wait for the patient to learn how to establish his/her internal biologic safety. If the patient doesn't get the answer on the first take, then one provides it. The consequences of not “getting it,” of repetition, are too severe to let them continue. And thus one must be more available to the patient. One must educate. One must rescue the patient from his/her reflexive, perseverative patterns. One must not cede control to state dependent memory and consequent loss of cognitive capacities as the patient becomes overwhelmed with affect. One must expect that intense, often irrational abandonment reactions will occur leading to intense expressions of anger that are not part of the “oral rage” of borderline psychopathology, but rather reflect the loss of safety that ensues when the loved and needed object can't restore calm. One must accept the role of that person who like the “good enough parent” restores calm. One must be able to determine how much help the patient needs according to his/her capacities, provide help as necessary, answer seemingly infantilizing questions (“No you cannot get pregnant from oral sex”), so long as by answering one is also increasing his/her safety, all the while figuring how to titrate one's involvement according to the patient's changing level of function and need. One must involve and educate the family. One must take over the role of the helper from family/friends until confident that the patient can involve another without weaving him/her into some interdependency from which there may be no healthy way out. One must always be figuring a way out as one is getting deeper in.

One must use the power of the transference above all to create safety because the patient will need the therapist to be a real, available, and secure “other” until such time as safety can be internalized or safely

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transferred to others (plural). Early on the therapist may be the only safe object. Gradually other safe havens must be established—such as for this patient—Alcoholics Anonymous, same sex friendships, work, athletics, a pet. Limits on family contact must be made until such time as family sessions establish that the family can be a safe and productive support system. Limits on sexual relationships must also be established. The doctor must take on many of the executive functions that the prefrontal cortex would normally perform.

XXII. CASE

“I have this need to have a boyfriend. Actually I have two, in case one leaves me. But dating is a disaster—always has been. The whole thing about allowing a guy to see the scars on my belly that was really hard. But penetration—no way. The idea of sex freaks me out.”

You are a virgin?

“Don’t you listen?”

So sex or attempted penetration would bring back memories?

“I’d get flashbacks. I’d be terrified. And then every time I’d have a date, I’d have to call my Mom—three, four, ten times a day.”

Why?

“Because I’d have all these questions. Like could I be pregnant from oral sex? I know, I know, we’ve already been through that. But it doesn’t go away. I still have to ask. Could I get pregnant from masturbating a guy? Could I get AIDS? And then when I’d ask her these questions she’d get all upset and start asking me, how old is the guy? Where did I meet him? Who are his parents? Where did we go? How much am I drinking? Am I using drugs? And then I just get furious at her and we’re both screaming. Then she’ll hang up or I’ll hang up. And then I’d call her back or she’d call me. And we just start screaming all over again.”

And this happens every time you go out on a date?

“I know it sounds weird but I have to. I need her to know what I’m doing so she can tell me that everything’s going to be okay.”

You can’t tell that to yourself?

“I had to hear it from her (indicating that safety was not internalized, conditioned, state dependent memory was overwhelming her, and

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that she was operating from a point of learned helplessness). She's the only one."

Then in the future I want you to call me.

"You?"

Yes.

"What if it's 3 in the morning?"

Is that when you'd call your mother?

"No. I'd wait to the next day."

Fine, then wait till the next day and then call me.

"You sure?"

Yes, I'm sure. That's what I want you to do.

"Okay, I'll do it."

XXIII. ALLOSTASIS

The stress response obviously is vital to survival. It must be able to activate quickly. It must be maintained until the threat has passed, and then it must turn off. Adjustments, if indicated, must be made. Allostasis is the process of actively maintaining stability under changing circumstances (McEwen, 2007). Obviously a response appropriate to one circumstance might not be appropriate to subsequent circumstances. And furthermore, the baseline that was appropriate before a threat might not be appropriate after a threat had passed. So allostasis is more than a return to the status quo ante. Allostasis includes adaptation. For healthy allostatic growth, the individual must be able to react and change to changing circumstances.

In this patient, there was a clear indication of allostatic dysfunction—a dysfunction that almost certainly was seeded when she was several months old. Repeated, unpredictable trips to the pediatrician, to the gastroenterologist, to the hospital, with multiple surgeries and ICU admissions—created stressors that lead to a broad-based neurobiology of uncertainty and helplessness. The child's sense of safety and control were disrupted from the first few months of her life. This ongoing sense of threat—creating a state of allosteric overload—was evidenced by her opening remark, "I got here real early because I was afraid that I might get lost trying to find your building"—a remark indicating that before she had met me, she was afraid she would lose me, reflecting her active,

biologically based fear of helplessness and abandonment. Her stress response had appropriately turned on when she was a very small girl facing a pediatrician in a white lab coat. We are all afraid on some level of being at the mercy of unknown authorities in lab coats. But her stress response had never turned off—creating allosteric overload.

And this overload had created a myriad of problems. These problems all had a basis in specific neurobiologic interactions—dysfunction and interactions in and among the HPA axis, hippocampus, amygdala, prefrontal cortex, noradrenergic regulation in the locus ceruleus, dopamine regulation in the ventral tegmental area. Obviously these are all interconnected so it is not one brain area that is affected, but rather interconnections among many areas. But the consequences were specific and far reaching—with dysfunction in memory, affect, impulse control, motivation, behavior.

The patient's thinking was overly general. Affect tended to dominate her thinking, overwhelm her decision making, blur specificity. Under the dominance of affect, memory was monotonous—that is, state dependent with a predominant influence of amygdala-based unimodal, conditioned memory at the sacrifice of polymodal hippocampal-based memory. These factors limited new learning. A reliance on old patterns was established. Novelty was avoided. If something were known it was preferred even if the consequences were known and injurious. And thus "risk taking" in this context, for this patient, was in one sense very "safe" because she repeated behaviors that she knew—even if most of them tended to involve alcohol, cocaine, high risk sex (both before and after losing her virginity). So while these choices, these behaviors seemed impulsive and dangerous, they were at base safe by virtue of the fact that these behaviors were known. One of the hallmarks of stress induced allosteric overload is repetition—the challenge to the treatment is to identify what is being repeated and how and why.

All of these problems were due to and further contributed to allosteric overload. Etiologically there had been clear stressors that had driven the stress response system. But the factors that initiated the stress response is just one side of the problem that can lead to allostatic overload. On the other side are the inhibitory systems that failed to turn the system off. In closing I want to address these systems because it is on the side of inhibition where treatment interventions are made.

As was mentioned above, one of the predominant inhibitory pathways of the stress response system is at the hippocampus. When the glucocorticoid receptors at the hippocampus are filled, there is feedback to the hypothalamus to inhibit the secretion of corticotropin releasing factor (CRF) from the paraventricular nucleus (PVN)—and thus an inhibition of the overall HPA stress response. The hippocampus also has a direct

inhibitory influence on the locus ceruleus and the amygdala. But under conditions of allosteric overload, there is dendritic remodeling at the hippocampus with consequent blunting of these inhibitory influences. Dendritic remodeling (loss of length and branching of the apical dendrites) of these hippocampal neurons thus affords greater autonomy to amygdala-based projections to control CRF production and release from the PVN. Projections from the amygdala to the locus ceruleus, the ventral tegmentum, and the raphe nuclei also favor the production and secretion of noradrenalin, dopamine, and serotonin—in other words as allosteric overload persists, there is a tendency for the stress response to gain or at least maintain its strength with or without external provocation. The “threat” then has been internalized as a result of allosteric overload and thus “reality” is viewed as though the threat were lurking. Internal biology is *a priori* defining the external world. Under these conditions the main opposition to this subcortical feed forward loop is inhibitory (GABA) input from the prefrontal cortex.

The medial prefrontal cortex, the orbital prefrontal cortex, and the anterior cingulate cortex are all interconnected with the subcortical structures involved in the stress response. These prefrontal regions have been shown to be critical in restraining the acute stress response and facilitating negative inhibition in the system (Herman & Cullinan, 1997). Treatment is aimed at reinforcing the inhibitory power of these systems.

What exactly does that mean—to reinforce the prefrontal systems?

Treatment goals were first to stop acting-out behaviors. These were not seen (nor interpreted) as transference acting-out but rather as affective explosions. Symptoms had to be controlled. Psychodynamic interpretation of these biologically driven behaviors is counterproductive and to be avoided. Interventions with this patient were based on my understanding of her neurobiology. I explained what she was feeling (almost always anger defending against fear). I explained why she was feeling that way (generalization of affect). I told her what she was afraid of (almost always abandonment). I explained why certain situations were so fearful and recalled flashbacks (affect driven, state dependent memory). I provided comfort when needed (explanations, phone contact, extra sessions). Limit setting was established very early on.

The patient knew that she had no understanding of her thinking nor of her behavior. She just acted. Because of the repetitive quality of her thinking, it was not difficult to predict if not the specific behavior, at least the specific need/fear that she was or would soon act out. And so I would tell her what behaviors I would expect her to engage in. And in the next breath, offer alternatives. Or impose limits. Because I know how her brain worked, I could tell her what she was going to do before

she did it. And I would let her know. And try to get her to stop it. The insistence on Alcoholics Anonymous, frequent phone contact, family sessions, medication (lamotrigine 75 mg, valproate 1,000 mg, fluoxetine 20 mg, disulfiram 125 mg), limiting her access to family, active guidance, active involvement, brief hospitalization. All of these things were part of the treatment plan aimed at helping her prefrontal systems to inhibit conditioned responses—and where necessary to impose those inhibitions/limits.

Does this kind of involvement infantilize the patient? Create undo dependency? Am I being grandiose? Encouraging idealization? Making myself indispensable? Am I forcing myself upon her as a savior?

I think those questions have no place in the early stages of a treatment where the neurodynamic pathology is as clear and as driven as in this woman. I feel it is analogous to asking a neurologist does he/she infantilize an epileptic patient by prescribing Dilantin and thereby stopping the seizures?

By basing the treatment on a biological understanding I try to re-establish safety and free thought for the patient. Once I see that beginning, I move back. But until that point, the treatment is extremely active. I exercise control. I don't want the patient to be in control of his/her life in the early stages of this kind of a treatment because if she/he is in control, it is her/his limbic cortex with state dependent memory and amygdala driven conditioned recall that is dominant. In the early stages of the treatment (and this can last several years), the only way I can offer the patient "an enriched environment," that is to say one that can compensate and provide a counter-weight to the allosteric load, is if I can show the patient that I really do know what is going on in her/his brain, that I can predict the future based on my knowledge of her/his neurodynamics—and help the patient have some choice over the kind of future she/he will have. The transference gives me that power to effect these changes. The neurobiologic frame gives me the confidence to do so.

Because finally Freud was right. He was right about the transference; it is an exquisitely powerful tool—"The psychoanalyst knows that he is working with highly explosive forces and that he needs to proceed with as much caution as a chemist. But when have chemists ever been forbidden, because of the danger, from handling explosive substances?" (1915, p. 179). He was right about anatomy. We can now determine "psychical locality" in an "anatomical fashion." He was right about biology. It has begun to "blow away" the "artificial structure of hypotheses." And finally he was right about psychotherapy. It no longer can remain entirely on "psychological ground."

REFERENCES

- Armory, J. L., & LeDoux, J. E. (1997). How the brain processes emotional information. In R. Yehuda & A. McFarlane (Eds.), *Psychobiology of posttraumatic stress disorder* (pp. 259-270). New York: The New York Academy of Sciences.
- Arnsten, A. F. T. (1998). Catecholamine modulation of prefrontal cortical cognitive function. *Trends in Cognitive Sciences*, 2(11), 436-445.
- Bisagno, V., Ferrini, M., Rios, H., Zieher, L. M., & Wikinski, S. I. (2000). Chronic corticosterone impairs inhibitory avoidance in rats. *Pharmacology Biochemistry and Behavior*, 66(2), 235-240.
- Bonne, O., Grillon, C., Vythilingam, M. V., Neumeister, A., & Charney, D. S. (2004). Adaptive and maladaptive psychobiological responses to severe psychological stress. *Neuroscience and Biobehavioral Review*, 28, 65-94.
- Bouton, M. E. (2002). Context, ambiguity and unlearning. *Biological Psychiatry*, 52, 976-986.
- Bouton, M. E. (2004). Context and behavioral processes in extinction. *Learning and Memory*, 11, 485-494.
- Bouton, M. E., & Moody, E. W. (2004). Memory process in classical conditioning. *Neuroscience and Biobehavioral Reviews*, 28, 663-674.
- Cahill, L. (1996). Neurobiology of memory for emotional events. *Cold Spring Harbor Symposia on Quantitative Biology*, 61, 259-264.
- Cahill, L., & McGaugh, J. L. (1996). Modulation of memory storage. *Current Opinion in Neurobiology*, 6, 237-242.
- Cahill, L., & McGaugh, J. L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends in Neuroscience*, 21, 294-299.
- Cain, C. K., Blouin, A. M., & Barad, M. (2004). Adrenergic transmission facilitates extinction of conditioned fear. *Learning and Memory*, 11, 179-187.
- Connolly, D. (2004). Posttraumatic stress disorder in children after cardiac surgery. *Journal of Pediatrics*, 144, 480-484.
- Conrad, C. D., Magarinos, A. M., LeDoux, J. E., & McEwan, B. S. (1999). Repeated restraint stress facilitates fear conditioning. *Behavioral Neuroscience*, 113(5), 902-913.
- Davis, M. (1998). Are different parts of the extended amygdala involved in fear versus anxiety? *Biological Psychiatry*, 44, 1239-1247.
- deQuevain, D. J., Roozendaal, B., & McGaugh, J. L. (1998). Stress and glucocorticoids impair retrieval of long-term spatial memory. *Nature*, 394, 787-790.
- deQuevain, D. J., Roozendaal, B., Nitsch, R. M., McGaugh, J. L., & Hock, C. (2000). Acute cortisone administration impairs retrieval of long-term declarative memory in humans. *Nature Neuroscience*, 3(4), 313-314.
- Descartes, R. (1650). The passions on the soul. In R. Eaton (Ed.), *Descartes selections*. New York: Scribner's.
- Eysenck, H. (1979). The conditioning model of neuroses. *Behavior and Brain Sciences*, 2, 155-199.
- Freud, S. (1900). The interpretation of dreams. In J. Strachey (Ed. and Trans.) *The standard edition of the complete psychological works of Sigmund Freud* (vol. 4/5). London: Hogarth Press.
- Freud, S. (1915). Transference love. In J. Strachey (Ed. and Trans.) *The standard edition of the complete psychological works of Sigmund Freud* (vol. 12, pp. 159-171). London: Hogarth Press.

PSYCHICAL LOCALITY AND BIOLOGY 309

- Freud, S. (1920). Beyond the pleasure principle. In J. Strachey (Ed. and Trans.) *The standard edition of the complete psychological works of Sigmund Freud* (vol. 18). London: Hogarth Press.
- Goddard, G. V. (1967). Development of epileptic seizures through brain stimulation at low intensity. *Nature*, 214, 1020-1021.
- Goddard, G. V., McIntyre, D. C., & Leech, C. K. (1969). A permanent change in brain function resulting from daily electrical stimulation. *Experimental Neurology*, 25, 295-330.
- Heim, C., & Nemeroff, C. B. (1999). The impact of early adverse experiences on brain systems. *Biological Psychiatry*, 46, 1509-1522.
- Herman, J. P., & Cullinan, W. E. (1997). Neurocircuitry of stress. *Trends in Neuroscience*, 20, 78-84.
- Hyman, S. E. (2009). How adversity gets under the skin. *Nature Neuroscience*, 12, 241-244.
- Ishikawa, A., & Nakamura, S. (2003). Convergence and interaction of hippocampus and amygdalar projections within the prefrontal cortex in the rat. *Journal of Neuroscience*, 23(31), 9987-9995.
- Kaufman, J., Plotsky, P. M., Nemeroff, C. B., & Charney, D. S. (2000). Effects of early adverse experiences on brain structure and function. *Biological Psychiatry*, 48, 778-790.
- Lebron K., Milad, M. R., & Quirk, G. J. (2004). Delayed recall of fear extinction in rats with lesions of ventral medial prefrontal cortex. *Learning and Memory*, 11, 544-548.
- LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience*, 23(1), 155-169.
- Liang, K. C., & Lee, E. H. (1988). Intra-amygdala injections of corticotropin releasing factor facilitate inhibition. *Psychopharmacology*, 96, 232-236.
- Lovibond, P. F. (2004). Cognitive processes in extinction. *Learning and Memory*, 11, 495-500.
- Maren, S. (2005). Building and burying fear memories in the brain. *The Neuroscientist*, 11(1), 89-99.
- McEwan, B. S. (2000). Effects of adverse experiences for brain structure and function. *Biological Psychiatry*, 48, 721-731.
- McEwan, B.S. (2001). Stress, sex hippocampal plasticity. *Clinical Neuroscience Research*, 1, 19-34
- McEwan, B. S. (2007). Physiology and neurobiology of stress and adaptation. *Physiological Reviews*, 87, 873-904.
- McEwan, B. S., & Magarinos, A. M. (1997). Stress effects on morphology and function of the hippocampus. In R. Yehuda & A. McFarlane (Eds.), *Psychobiology of posttraumatic stress disorder* (pp. 259-270). New York: The New York Academy of Sciences.
- McEwan, B. S., & Sapolsky, R. M. (1995). Stress and cognitive function. *Current Opinion in Neurobiology*, 5, 202-216.
- McGaugh, J. L., Cahill, L., & Roozendaal, B. (1996). Involvement of the amygdala in memory storage. *Proceedings of the National Academy of Science, USA*, 93, 13508-13514.
- McNally, R. J. (1997). Implicit and explicit memory for trauma-related information in PTSD. In R. Yehuda & A. McFarlane (Eds.), *Psychobiology of posttraumatic stress disorder* (pp. 219-224). New York: The New York Academy of Sciences.

310 BROCKMAN

- Meaney, M. J. (2010). Epigenetics and the biological definition of gene x environment interactions. *Child Development, 81*, 41-79.
- Milad, M. R., & Quirk, G. J. (2002). Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature, 420*, 70-74.
- Phelps E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans. *Neuron, 43*, 897-905.
- Post, R. M., & Weiss, S. (1997). Kindling versus quenching. In R. Yehuda & A. McFarlane (Eds.), *Psychobiology of posttraumatic stress disorder* (pp. 285-295). New York: The New York Academy of Sciences.
- Post, R. M., & Weiss S. R. B. (1998). Sensitization and kindling phenomena in mood, anxiety, and obsessive-compulsive disorders. *Biological Psychiatry, 44*, 193-206.
- Purcell, R., Maruff, P., Kyrios, M., & Pantelis, C. (1998). Cognitive deficits in obsessive-compulsive disorder on tests of frontal-striatal function. *Biological Psychiatry, 43*, 348-357.
- Quirk, G. J. (2002). Memory for extinction of conditioned fear is long-lasting. *Learning and Memory, 9*, 402-407.
- Quirk, G. J. (2004). Learning not to fear, faster. *Learning and Memory, 11*, 125-126.
- Quirk, G. J., & Gehlert, D. R. (2003). Inhibition of the amygdala. *Annals of the New York Academy of Sciences, 985*, 263-272.
- Quirk G. J., Likhtik, E., Pelletier, J. G., & Pare, D. (2003). Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdalar output neurons. *Journal of Neuroscience, 23*(25), 8800-8807.
- Quirk, G. J., Russo, G. K., Brown, J. L., & Lebron, K. (2000). The role of ventromedial prefrontal cortex in the recovery of extinguished fear. *Journal of Neuroscience, 20*(16), 6225-6231.
- Richardson, R., Ledgerwood, L., & Charney, J. (2004). Facilitation of fear extinction by d-cycloserine: Theoretical and clinical implications. *Learning and Memory, 11*, 510-516.
- Rogan, M. T., & LeDoux, J. E. (1996). Emotion: Systems, cells, synaptic plasticity. *Cell, 85*, 469-474.
- Roozendaal, B., Quarte, G., & McGaugh, J. (1997). Stress-activated hormonal systems and the regulation of memory storage. In R. Yehuda & A. McFarlane (Eds.), *Psychobiology of posttraumatic stress disorder* (pp. 247-258). New York: The New York Academy of Sciences.
- Santini, E., Ge, H., Ren, K., Pena de Ortiz, S., & Quirk, G. J. (2004). Consolidation of fear extinction requires protein synthesis in the medial prefrontal cortex. *Journal of Neuroscience, 24*(2), 5704-5710.
- Sapolsky, R. M. (2004). Stress and cognition. In M. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 1031-1042). Cambridge, MA: MIT Press.
- Schafe, G. E., & LeDoux, J. E. (2004). The neural basis of fear. In M. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 987-1004). Cambridge, MA: MIT Press.
- Sotres-Bayon, F., Busch, D. E., & LeDoux, J. E. (2004). Emotional perseveration: An update on prefrontal-amygdala interactions in fear extinction. *Learning and Memory, 11*, 525-535
- Tronel, S., Feenstra, M. G., & Sara, S. J. (2004). Noradrenergic action in prefrontal cortex. *Learning and Memory, 12*, 453-458.
- Vyas, A., Bernal, S., & Chattarji, S. (2002). Effects of chronic stress on dendritic arborization in the central and extended amygdala. *Brain Research, 965*, 290-294.

PSYCHICAL LOCALITY AND BIOLOGY 311

- Watanabe, Y., Gould, E., & McEwan, B. S. (1992). Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain Research, 588*, 341-345.
- Weiss, S., & Post, R. (1998). Kindling: Separate vs. shared mechanisms in affective disorders and epilepsy. *Neuropsychobiology, 38*(3), 167-180.
- Westbrook, G. L. (2000). Seizures and epilepsy. In E. Kandel, J. Schwartz, & T. Jessell (Eds.), *Principles of neural science* (pp. 910-935). New York: McGraw-Hill.
- Yehuda, R., & Bierer, L. (2009). The relevance of epigenetics to PTSD. *Journal of Traumatic Stress, 22*, 427-434.
- Yehuda, R., Flory, J., Pratchett, L., Buxbaum, J., Ising, M., & Holsboer, F. (2010). Putative biological mechanisms for the association between early life adversity and subsequent development of PTSD. *Psychopharmacology, 212*, 405-417.

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